SYNTHESIS OF SOME 4-QUINOLONES AND RELATED STRUCTURES FOR EVALUATION AS POTENTIAL ANTIMALARIAL AGENTS

Adria C. Casey

Bridgeport University

Prepared for:

Army Medical Research and Development Command

30 November 1974

AD_____

ANNUAL REPORT NUMBER 2

SYNTHESIS OF SOME 4-QUINOLONES AND RELATED STRUCTURES FOR EVALUATION AS POTENTIAL ANTIMALARIAL AGENTS

FINAL SCIENTIFIC REPORT

by

Adria C. Casey

November 30, 1974

Supported by

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D. C. 20314

Contract No. DAMD-17-74C-4044

University of Bridgeport
Bridgeport, Connecticut 06877

DOCUMENT CONTROL DATA - R & D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1 ORIGINATING ACTIVITY (Corporate author)
University of Bridgeport
Department of Chemistry
Bridgeport, Connecticut 06602

2a. REPORT SECURITY CLASSIFICATION
Unclassified

2b GROUP
None

3 REPORT TITLE
Synthesis of Some 4-Quinolones and Related Structures for Evaluation as Potential Antimalarial Agents

4 DESCRIPTIVE NOTES (Type of report and inclusive dates)
Final Report, May 1, 1973 - November 30, 1974

5 AUTHOR(S) (First name, middle initial, last name)
Adria C. Casey

6 REPORT DATE
November 30, 1974

7a. TOTAL NO OF PAGES
45

7b. NO OF REFS
7

8a. CONTRACT OR GRANT NO
DAMD17-74-C-4044

b. PROJECT NO
---

c.

d.

9a. ORIGINATOR'S REPORT NUMBER(S)
None

9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
---

10 DISTRIBUTION STATEMENT
Approved for public release; distribution unlimited.

11 SUPPLEMENTARY NOTES
---

12. SPONSORING MILITARY ACTIVITY
U. S. Army Medical Research and Development Command
Washington, D. C. 20314

13 ABSTRACT

Our aim was to synthesize and submit for antimalarial evaluation new compounds related to either endochin (2-methyl-3-heptyl-7-methoxy-4(1H)-quinolone) or the 3-carbomethoxy-4(1H)-quinolones that had shown moderate to good antimalarial activity. A total of 31 new compounds, 16 of these target compounds, were synthesized and submitted for antimalarial evaluation.

Compound BD26235 (N-hydroxy-4-oxo-2-methyl-3-n-heptyl-7-methoxyquinolone, endochin-N-oxide), when tested against sporozoite-induced P. gallinaceum infection in chicks, cured 2 out of 5 chicks at a dose of 30 mg/Kg; 3 out of 5 chicks at a dose of 120 mg/Kg and 5 out of 5 chicks at a dose of 480 mg/Kg with no toxicity at any dose level. Apparently introduction of an N-hydroxy group in the endochin molecule, which resulted in increased water solubility, produced a compound with greater absorption and thus improved antimalarial activity. Compound BE11382 (3-carboethoxy-6-n-butyl-7-phenoxyethylmercapto-4(1H)-quinolone) was found to increase the mean survival time of the treated animals over that of the control group (ΔST) by 3.5 days at a dose of 320 mg/Kg and by 5.3 days at a dose of 640 mg/Kg with no toxicity when tested in the blood-induced P. berghei mouse test. The activity of this compound suggests that a sulfur substituent at the 7 position of the 3-carboethoxy-4-quinolones [illegible] of benefit in attempting to increase antimalarial activity in this se[illegible]

14 KEY WORDS	LINK A		LINK B		LINK C	
	ROLE	WT	ROLE	WT	ROLE	WT
Endochin						
4(1H)-quinolones						
1,8-naphthyrid-4-ones						
P. berghei						
P. gallinaceum						
P. cynomolgi						

ANNUAL SCIENTIFIC REPORT

NUMBER 2

on

SYNTHESIS OF SOME 4-QUINOLONES AND RELATED STRUCTURES FOR EVALUATION AS POTENTIAL ANTIMALARIAL AGENTS

to

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND

Contract No. DAMD-17-74C-4044

from

University of Bridgeport

by

Adria C. Casey

November 30, 1974

SUMMARY

The aim of our investigation was to synthesize and submit for prophylactic and therapeutic antimalarial evaluation new compounds related to either endochin (2-methyl-3-heptyl-7-methoxy-4(1H)-quinolone) or the 3-carbomethoxy-4(1H)-quinolones that had shown moderate to good antimalarial activity. Our target compounds were so designed as to include substituents that would increase the water solubility of the poorly absorbed 4(1H)-quinolones and also substituents that hopefully would increase the antimalarial activity of the compounds without a concomitant increase in toxicity.

A total of 31 new compounds, 16 of these target compounds, were synthesized and submitted for antimalarial evaluation.

Compound BD26235 (N-hydroxy-4-oxo-2-methyl-3-n-heptyl-7-methoxyquinolone, endochin-N-oxide), when tested against sporozoite-induced P. gallinaceum infection in chicks, cured 2 out of 5 chicks at a dose of 30 mg/Kg; 3 out of 5 chicks at a dose of 120 mg/Kg and 5 out of 5 chicks at a dose of 480 mg/Kg with no toxicity at any dose level. Apparently introduction of an N-hydroxy group in the endochin molecule, which resulted in increased water solubility, produced a compound with greater absorption and thus improved antimalarial activity.

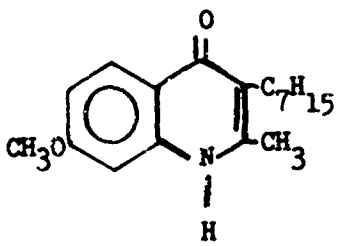
Compound BE 11382 (3-carboethoxy-6-n-butyl-7-phenoxyethylmercapto-4-(1H)-quinolone) was found to increase the mean survival time of the treated animals over that of the control group (ΔST) by 3.5 days at a dose of 320 mg/Kg and by 5.3 days at a dose of 640 mg/Kg with no toxicity when tested in the blood-induced P. berghei mouse test. The activity of this compound suggests that a sulfur substituent at the 7 position of the 3-carboethoxy-4-quinolones may be of benefit in attempting to increase antimalarial activity in this series.

TABLE OF CONTENTS

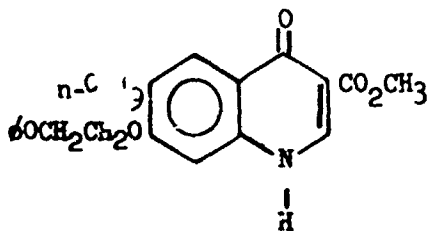
LIST OF TABLES

Introduction and Background

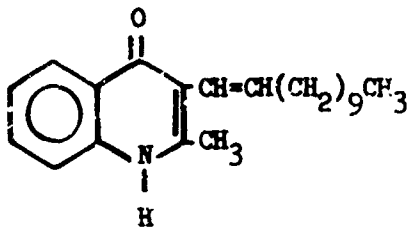
Some 4-quinolones such as endochin (I), ICI-56780 (II) and AY-85164 (III) have been reported to exhibit moderate to excellent antimalarial activity in several animal models.[1-3] *Compound I was reported to have excellent prophylactic activity in avian malaria, and II was reported as having protected mice challenged with P. berghei sporozoites and, more importantly, rhesus monkeys against P. cynomolgi sporozoite infection.[2]



I



II



III

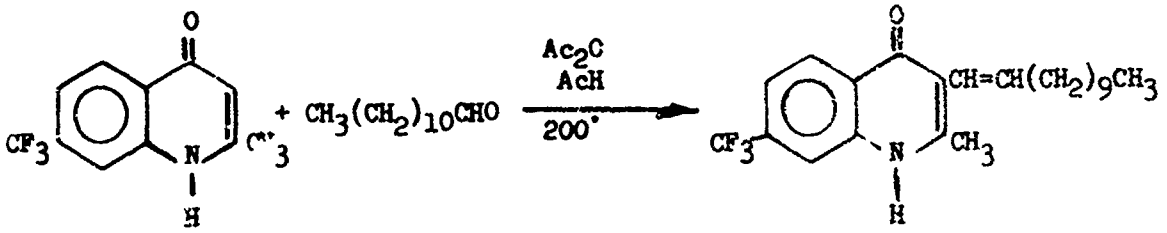
*It was not until mid-1974 and when this investigation was well in progress, that endochin was found to be inactive in the rhesus monkey prophylactic test.[4] This test is at present the model of choice for evaluation of prophylactic antimalarial activity.

With the need for less toxic and more effective prophylactic agents for the treatment of plasmodial infections in humans, it became desirable to synthesize and evaluate for antimalarial activity a series of new 4-quinolones and 1,8-naphthyrid-4-ones structurally related to I and II. Proper modification of the ring nucleus and side chain attachments would hopefully provide useful antimalarial agents.

Chemistry

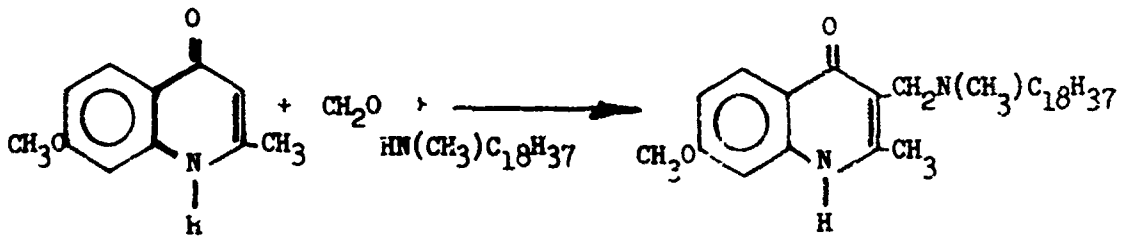
1. 4(1H)-Quinolones related to endochin

Compounds IV was prepared by the reaction of dodecyl aldehyde with 2-methyl-7-trifluoromethyl-4(1H)-quinolone using a slight modification of the general procedure described earlier.[3] An excess of the aldehyde (4:1) was used in this reaction in order to obtain an homogeneous reaction mixture. With the successful preparation of IV, the reaction of aliphatic aldehydes with 2-methyl-4(1H)-quinolones to give the 3(1-alkenyl) derivatives proved its generality, since it proceeds when both electron withdrawing and electron donating groups are present in the benzene portion of the quinolone moiety.



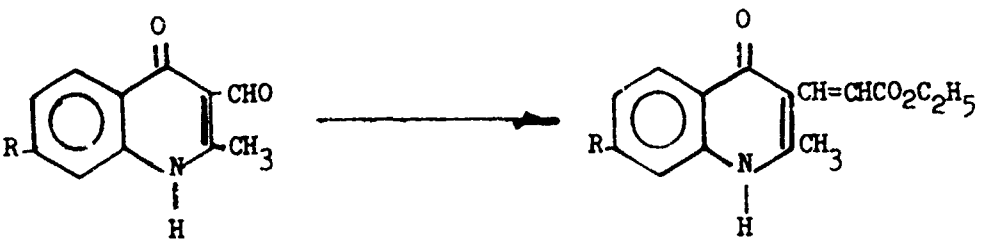
IV

Compound V was prepared by the Mannich reaction of 2-methyl-7-methoxy-4(1H)-quinolone and N-methyl-N-octadecylamine, in good yields. This facile reaction indicates, once more, the activated nature of the 3 position in the (1H)-quinolone ring system.



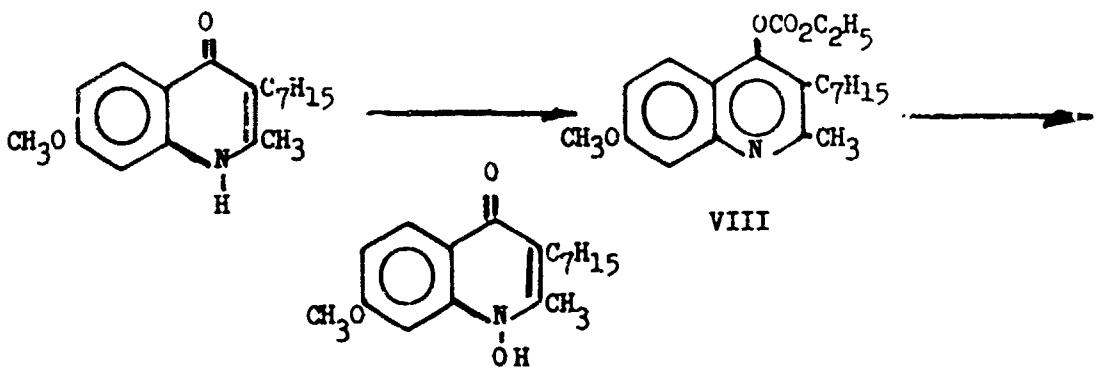
V

Since a double bond conjugated with the quinolone ring (as in III) seemed to provide the molecule with interesting antimalarial properties, the synthesis of VI (R=OCH_3) designed as to have present those two groups was attempted. The aldehyde VII (R=H) was prepared as model compound by the Reimer-Tiemann reaction of 2-methyl-4(1H)-quinolone with chloroform and alcoholic KOH.[5] However Perkins condensation of VII (R=H) with potassium acetate and acetic anhydride failed as did the modified Wittig reaction of VII (R=H) with triethylphosphonoacetate and NaH. The thiosemicarbazone of VII (R=H) was then prepared in order to test the reactivity of the formyl group. The derivative was obtained in high yields. We cannot explain at this time the failure of VII (R=H) to react under Wittig or Perkin conditions to give VI (R=H).



VII VI

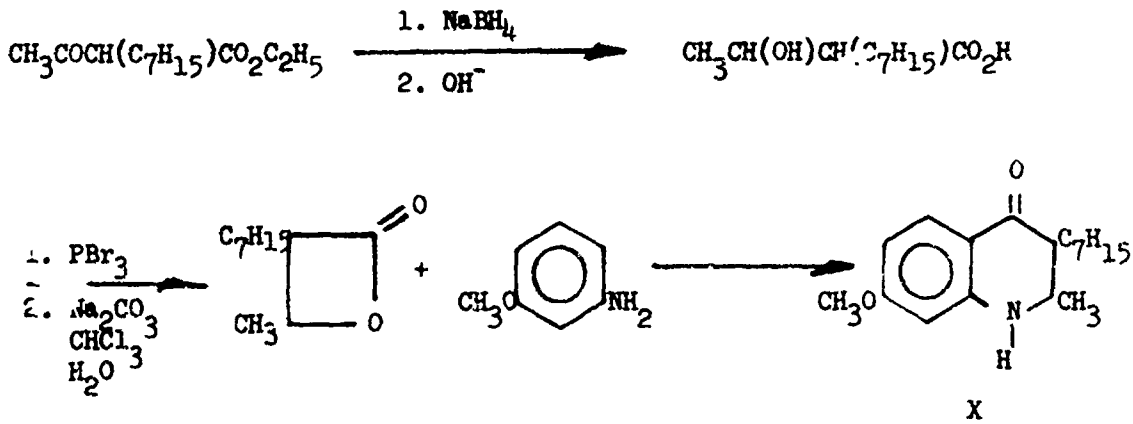
Since 4-quinolones are poorly absorbed through the gut due to their low water solubility,[2] it became of interest to prepare some derivative of endochin (I) with substituents that would hopefully enhance the solubility and thus the absorption of the compound. Endochin-N-oxide (IX) was prepared in a 2-step synthesis since 4-quinolones cannot be oxidized directly to the N-oxide. 2-Methyl-3-heptyl-4-ethylcarbonyldioxy-7-methoxyquinoline (VIII) was prepared by the reaction of endochin with ethyl chloroformate in the presence of NaH. Compound VIII is quite hygroscopic and its synthesis requires completely anhydrous conditions. The carbonate VIII was then oxidized with m-chloroperbenzoic acid, followed by basic hydrolysis to give IX. Endochin-N-oxide seems to exist predominantly in the N-hydroxy-4-oxo form since it gives a positive Tollen's test.



VIII

IX

Another endochin congener of interest was X, tetrahydroendochin. Several attempts to prepare X by catalytic hydrogenation of endochin failed. The alternative path, shown on Scheme 1, was then followed. 2-n-Heptyl-3-hydroxybutanoic acid was prepared by the sodium borohydride reduction, followed by hydrolysis of ethyl 2-n-heptylacetoacetate. The hydroxy acid was then reacted with PBr_3 and the bromo acid was used crude (decomposes on distillation) for the synthesis of the β-lactone. Spectrophotometric and elemental analysis data indicated that the lactone was indeed obtained. However it seems to exist in equilibrium with the hydroxyacid, with the latter as the predominant form.

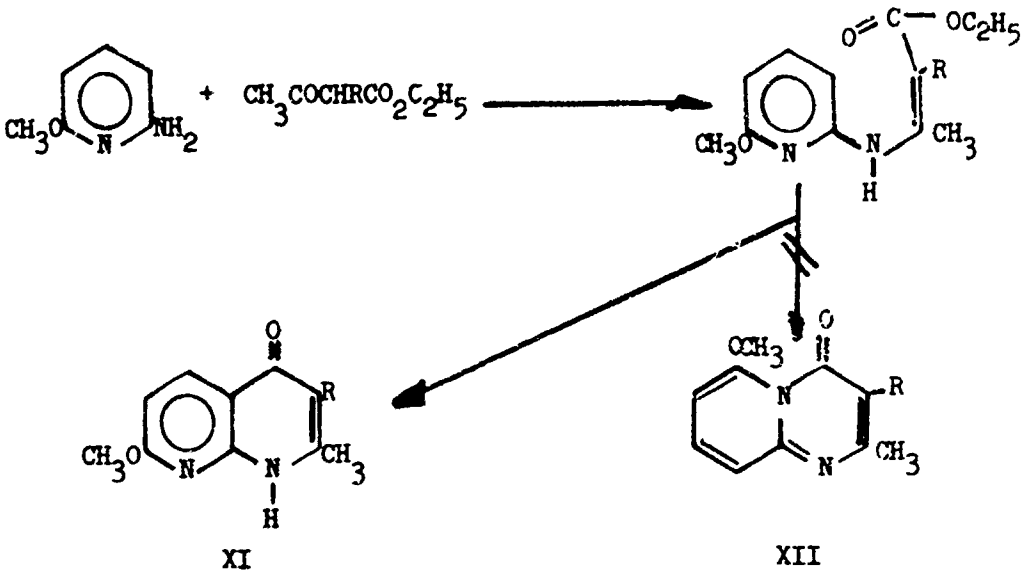


SCHEME 1

Further preparation of endochin analogs was discontinued when it was found that endochin had shown no activity in the rhesus monkeys prophylactic test.[4]

2. 1,8-Naphthyrid-4-ones related to endochin

Compounds XIa (R=-C_7H_{15}), XIb (R=-$[CH_2CH{=}C(CH_3)CH_2]_2H$) and XIc (R=-$CH_2CH{=}C(CH_3)[(CH_2)_3CH(CH_3)]_3CH_3$ were prepared by the Conrad Limpach method as shown on Scheme 2. The appropriate α-substituted ethyl acetoacetates were prepared as reported earlier. That the products of these reactions were the desired 1,8-naphthyrid-4-ones and not the products of cyclization on nitrogen (pyrido[1,2,a]pyrimidine-4-one, XII) was demonstrated by nmr analysis. Only 2 aromatic protons were observed in the spectra of compounds XI. These results were expected, since 2-aminopyridines carrying electron donating groups in position 6 have been reported to give 1,8-naphthyrid-4-ones with ethyl ethoxymethylenemalonate (EMME).[6]



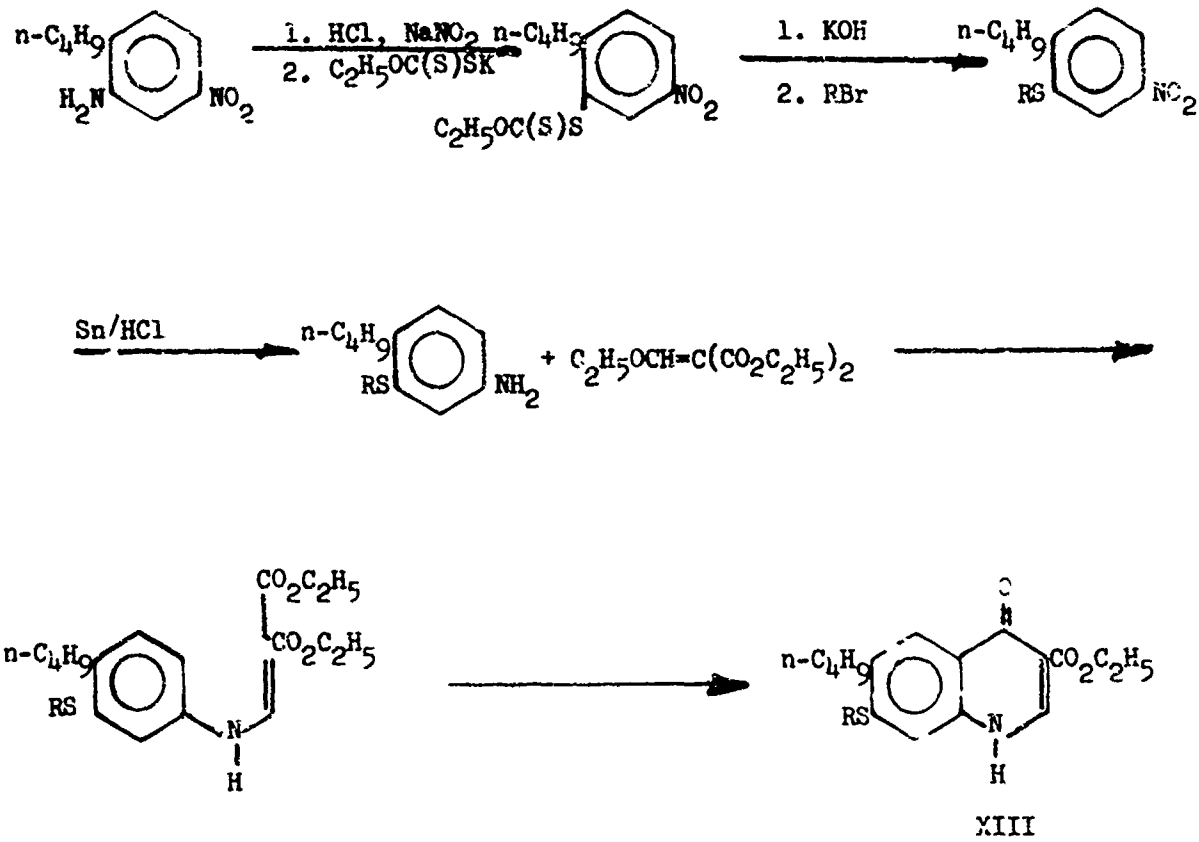
XI XII

SCHEME 2

3. 4(1H)-Quinolones related to ICI-56780(II)

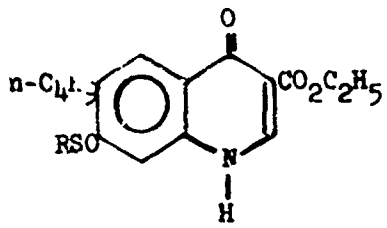
Several sulfur containing compounds are undergoing preclinical and clinical evaluation (i.e., WR158122, WR159412),[4] others such as WR174179 have shown promising activity in rhesus monkeys challenged with P. cynomolgi sporozoites.[4] Consequently compounds related to II, but having an S instead of an O at position 7, became of interest for synthesis and antimalarial evaluation.

Compounds XIIIa (R=-C_8H_{17}), XIIIb (R=-$C_{18}H_{37}$) and XIIIc (R=-$CH_2CH_2O\phi$) were prepared as shown on Scheme 3. Diazotization of 4-nitro-2-amino-n-butylbenzene, followed by reaction of the diazonium salt with ethyl potassium xanthate gave the intermediate aromatic xanthates. Attempts to purify the xanthates resulted only in decomposition. Thus they were hydrolyzed crude in basic medium followed by reaction with the desired alkyl halide. Reduction with Sn and HCl of the nitro derivatives prepared in this manner gave the appropriate 2-mercapto-4-amino-n-butylbenzenes. Condensation of the amines with diethyl ethoxymethylenemalonate (EMME) gave the corresponding diethyl 3-alkylmercapto-4-butylanilinomethylene malonates in good yields. Cyclization of the latter in refluxing Dowtherm A gave the desired 4-quinolones. Compounds of type XIII are very intractable and are only soluble in hot DMSO.

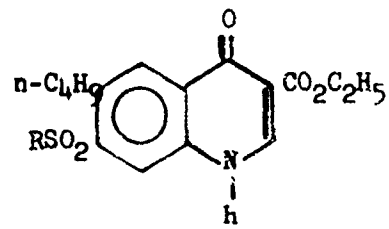


SCHEME 3

Compounds of type XIV and XV were also of interest for antimalarial evaluation. A seemingly reasonable approach to their syntheses was the oxidation of the corresponding sulfides (XIII) with oxidizing agents known to convert sulfide groups to sulfinyl or sulfonyl derivatives (i.e., $KMnO_4$; H_2O_2 in acetic acid; 1,4-diazabicyclo[2,2,2]octane (DABCO): bromine, etc.). However, all these oxidation procedures failed, probably due to the insolubility of compounds of type XIII in the solvents used for these reactions.



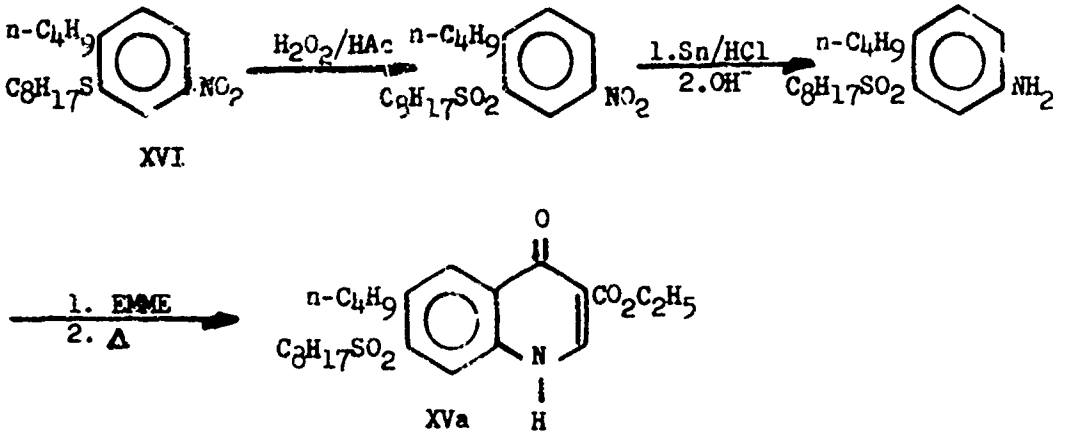
XIV



XV

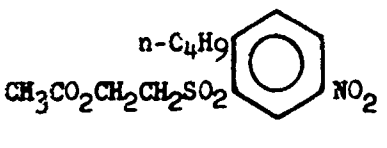
It was then decided to approach the synthesis of XIV and XV by the oxidation of the sulfide group at an earlier stage of the synthetic path leading to the 4-quinolones, namely at either the nitro or the amino derivative stage (see Scheme 3).

After several unsuccessful approaches XVa (R=-C_8H_{17}) was prepared as shown on Scheme 4. The key step in this synthetic scheme was the reduction of the nitro sulfonyl derivative with Sn and HCl. The fact that the sulfonyl group remained intact during the reduction step allowed the synthesis of XVa.

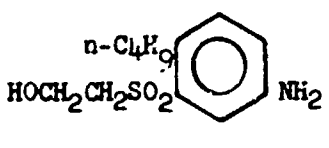


SCHEME 4

Attempts to prepare XVc (R=-$CH_2CH_2O\phi$) by a synthetic path similar to the one shown on Scheme 4 failed. Oxidation of the nitrosulfide XVIc (R=-$CH_2CH_2O\phi$) with H_2O_2/HAc led not to the sulfonyl derivative as expected but instead to XVII, where the phenyl group had been displaced by an acetyl group. Compound XVII was identified by infrared, nmr as well as elemental analysis. Moreover, Sn/HCl reduction of XVII led to XVIII where presumably the ester grouping was hydrolyzed during the reaction. These results cannot be explained at present since the phenyl group is not an easily leaving group and would not have been expected to be displaced by an acetyl group.

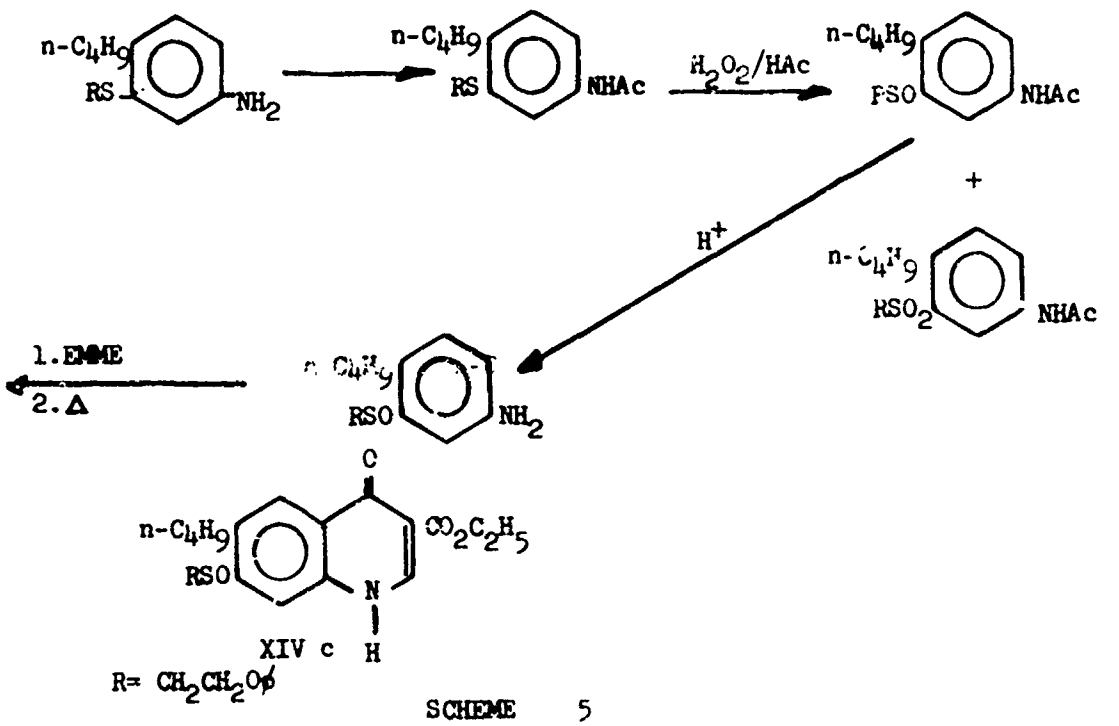


XVII



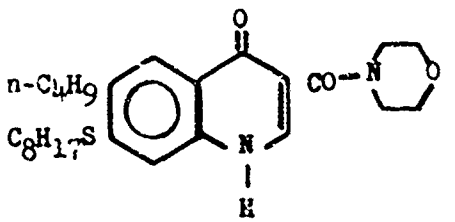
XVIII

The synthesis of XIVc (R=-$CH_2CH_2O\phi$) was approached by the route shown on Scheme 5. Protection of the amino group by acetylation, followed by oxidation of the acetyl derivative with H_2O_2/HAc gave a mixture of the sulfonyl and sulfinyl derivatives which was separated by fractional crystallization with mixed solvents. The sulfinyl derivative was then reacted with EMME followed by cyclization to give what seemed the desired product XIVc (infrared). However elemental analysis after repeated purifications did not give values corresponding to those calculated for XIVc.



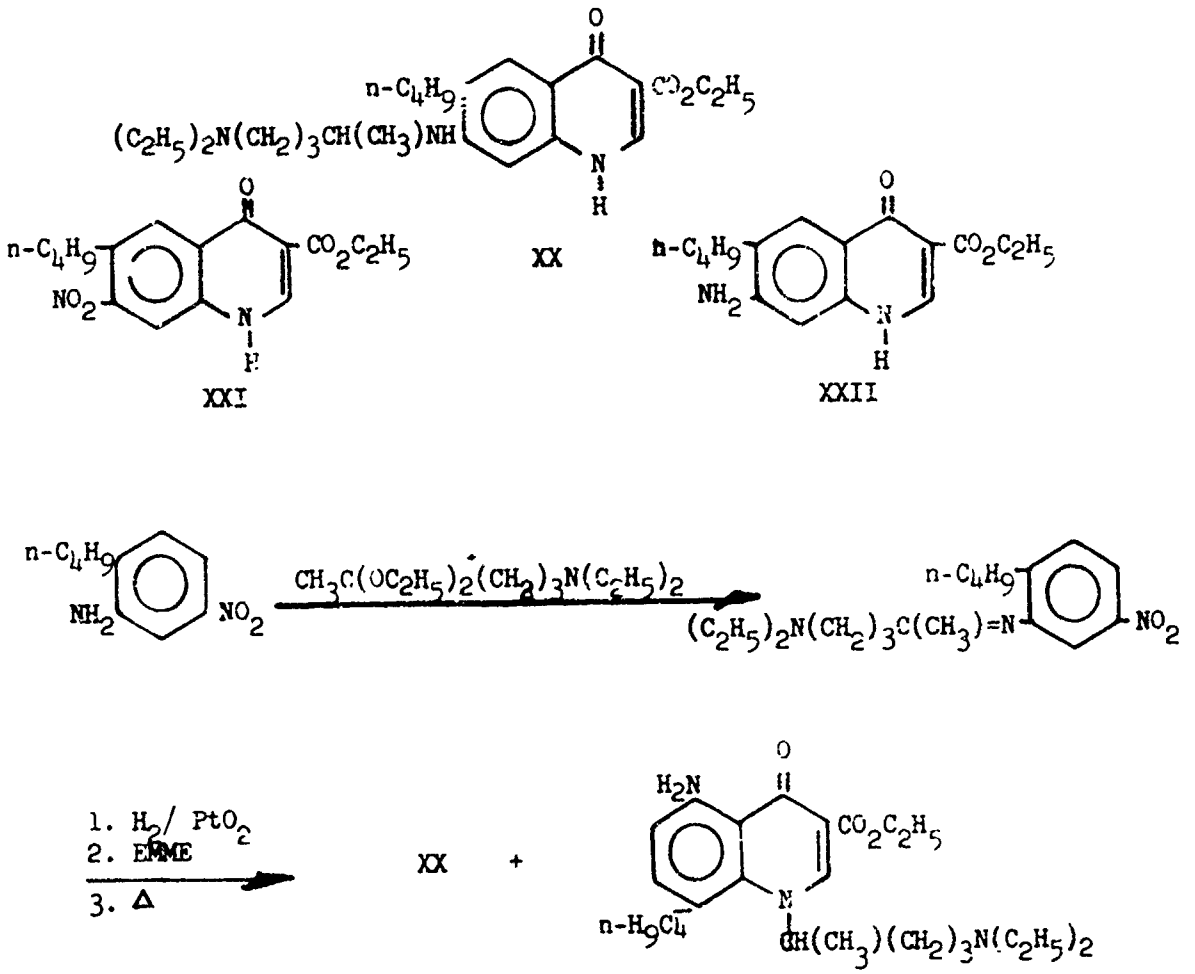
SCHEME 5

It was of interest to investigate the effect of an amide function at position 3 of the 4-quinolones instead of the usual carbethoxy function in both the solubility as well as the antimalarial activity of the compound. Compound XIX was prepared by reacting XIIIa (R=-C_8H_{17}) with morpholine and it was found that water solubility had greatly increased. However the compound showed no biological activity.



XIX

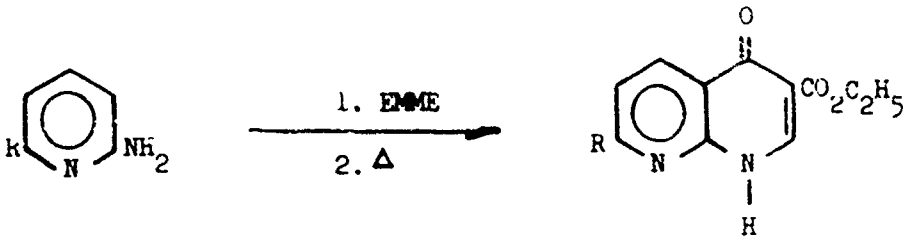
Compound XX was also of interest for antimalarial evaluation and for this reason XXI was synthesized from 4-amino-2-nitro-n-butylbenzene by the EMME method, since XXII, the corresponding amine, would be an ideal starting material for XX. Catalytic hydrogenation of XXI was impossible due to its insolubility in most common solvents used for these purposes (XXI is only soluble in hot DMSO). Alternative paths were then sought and the one shown on Scheme 6 on a small scale run allowed the preparation of XX. However in a large scale run the separation of the isomeric quinolones was impossible (preparative TLC, column chromatography and fractional crystallization) and the method was abandoned.



SCHEME 6

4. 1,8-Naphthyrid-4-ones related to ICI-56780(II)

Compounds XXIIIa (R=-CH_3) and XXIIIb (R=-OCH_3) were prepared as shown on Scheme 7 by an EMME reaction.



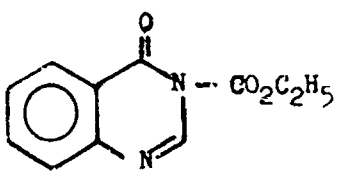
XXIII

SCHEME 7

5. 3-Carbethoxy-4-quinazolone.

The structural relationship between XXIV (3-carbethoxy-4-quinazolone) and the 4-quinolones of the ICI-56780 type (II) is apparent. Consequently the synthesis of XXIV was investigated since the compound could possess interesting antimalarial properties.

Reaction of the sodium salt of 4-quinazolone with ethyl chloroformate gave a crude product whose infrared spectrum corresponded to XXIV (2 CO absorption at 1750 and 1725 cm^{-1}, respectively, vs. 1725 cm^{-1} only for the starting material). TLC analysis indicated that the crude product also contained starting material. Repeated crystallization from a variety of solvents led to a highly pure product that in 4-5 hours would again give 2 spots on TLC: starting material and the blue fluorescent spot of the product, indicating the very unstable nature of the material. This result was not completely surprising. The N-acetyl derivative of 4-quinazolone has also been reported to be unstable.[7] Apparently the imide functionality imposes too much strain in the molecule to allow for stability.

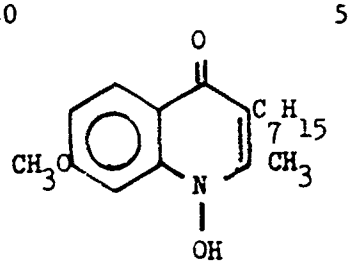


XXIV

Biological results

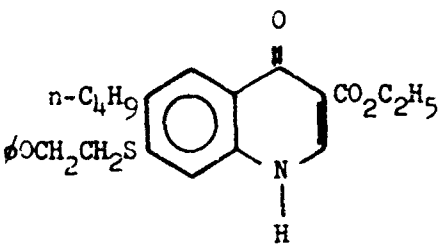
Compound BD-26235, endochin-N-oxide, showed the following antimalarial activity against P. gallinaceum (sporozoite-induced infection) in chicks.

Dose (mg/Kg)	Cures	Toxicity
30	2 out of 5	0
120	3 out of 5	0
480	5 out of 5	0



Compound BE11382 was found to increase the mean survival time of the treated animals over the mean survival time of the control group (ΔST) in P. berghei in mice as follows:

Dose (mg/Kg)	ΔST (days)	Toxicity
160	1.7	0
320	3.5	0
640	5.3	0



None of the other compounds submitted for evaluation showed antiralarial activity.

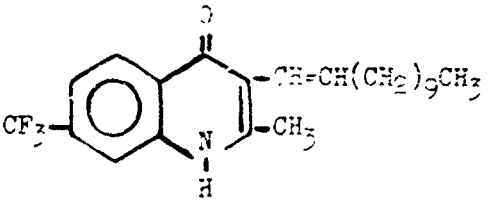
One can conclude from our results that proper modification of the side chain attachments of the 4-quinolones and 1,8-naphthyrid-4-one ring systems to provide for higher water solubility would indeed increase the antimalarial activity of these types of compounds.

Experimental

All melting points (Thomas-Hoover)are uncorrected. Elemental analysis: Baron Consulting Company, Orange, Connecticut. IR (potassium bromide pellet for solids, neat for liquids): Perkin-Elmer 137 spectrophotometer. NMR: Hitachi-Perkin-Elmer R-24. Mass spectral analysis: MS-109.

2-Methyl-3-(1'-dodecenyl)-7-trifluoromethyl-4(1H)-quinolone

BD 23181
Submitted 1.06 g

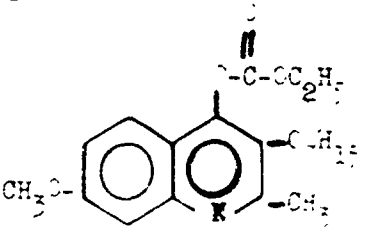


The general method of Casey[3] was used except that a 4:1 molar ratio of aldehyde to quinolone was employed in this preparation. A tan solid, mp 218-220° (d) was obtained in 27% yield. Recrystallization from aqueous ethanol gave a white solid, mp 220-222° (d).
Anal. Calculated for $C_{24}H_{30}NOF_3$: C, 70.20; H, 7.68; N, 3.56.

Found: C, 70.44; H, 7.87; N, 3.47.

2-Methyl-3-heptyl-4-ethylcarbonyldioxy-7-methoxyquinoline

BD 26226
Submitted 1.85 g



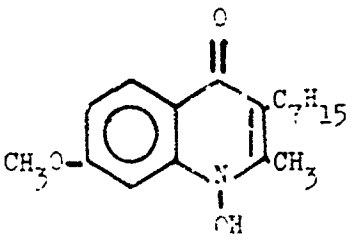
All glassware was flamed, prior to use, in order to remove moisture. In a round-bottomed 3-necked flask and under a nitrogen atmosphere, 0.23 g (5.5 mmoles) of 57% sodium hydride dispersed in oil was suspended in 5 ml of dimethylformamide

(dried over molecular sieves) and stirred for 15 minutes. To this mixture was added in small portions 1.44 g (5.0 mmoles) of endochin (dried at 100° overnight). This produced a slight dark coloration. An additional 5 ml of DMF was added and the mixture was stirred for 15 more minutes at room temperature. Ethyl chloroformiate (97%;45 ml, 5 mmoles) in 5 ml of dried DMF was added dropwise to the reaction mixture. Stirring was continued for 3 h. The sodium chloride which precipitated was filtered and washed with methylene chloride. Evaporation of the filtrate gave a white solid which was washed with anhydrous ethyl ether. Removal of the ether at room temperature gave a white solid, mp 45-47° (100% yield). Recrystallization from hexane produced white crystals, mp 47.5-48.5°.
Anal. Calculated for $C_{21}H_{29}NO_4$: C, 70.17; H, 8.13; N, 3.90.

Found: C, 69.93; H, 8.24; N, 4.15.

1-Hydroxy-2-methyl-3-heptyl-7-methoxy-4-quinolone

BD 26235
Submitted 1.40 g

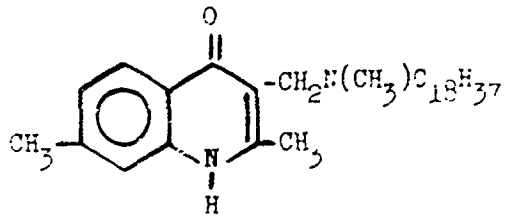


To a stirred solution of 180 mg (0.50 mmoles) of 2-methyl-3-heptyl-4-ethylcarbonyldioxy-7-methoxy-quinoline in 7 ml of chloroform was added dropwise 200 mg (1.00 mmoles) of 85% m-chloroperbenzoic acid in 5 ml of chloroform. The yellow homogeneous solution was heated under reflux for 1.5 hr. After cooling the solution was washed twice with a 3% sodium carbonate solution and once with water. Evaporation to dryness gave 234 mg of an amber-colored oil. The oil was dissolved in 3 ml of absolute ethanol and hydrolyzed by the addition of 3 ml of 2N KOH at room temperature. The resulting dark-brown mixture was filtered and the cooled filtrate acidified to litmus paper to give 123 mg (82% yield) of an off-white solid, mp 166-168°. Recrystallization from acetone gave a white solid, mp 175-175.5°.
Anal. Calculated for $C_{18}H_{25}NO_3$: C, 71.25; H, 8.31; N, 4.62.

Found: C, 71.08; H, 8.29; N, 4.66.

2-Methyl-3-(N,N-methyloctadecylaminomethyl)-7-methoxy-4(1H)-quinolone

BD 09485
Submitted 2.00 g

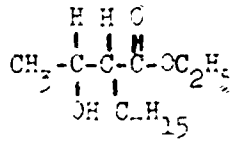


In 7 ml of refluxing ethanol 0.33 g (0.0033 mole) of paraformaldehyde and 11 g (0.039 mole) of N-methyl-N-octadecylamine were dissolved. 2-Methyl-7-methoxy-4 (1H)-quinolone (1.89 g, 0.01 mole) was added and refluxing was continued for 3 h. On cooling 2.53 g (51% yield) of the product was obtained. Recrystallization from ethanol gave white solid, mp 166-167°.
Anal. Calculated for $C_{31}H_{52}N_2O_2$: C, 76.80; H, 10.81; N, 5.78.

Found: C, 77.05; H, 10.85; N, 5.80.

Ethyl 2-heptyl-3-hydroxybutanoate

Not submitted

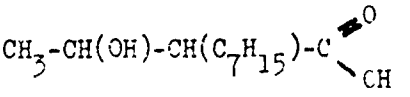


To a solution of ethyl 2-heptylacetoacetate (2.2 g; 0.01 mole) in 25 ml of ethanol, 0.19 g. (5 mmole) of sodium borohydride was added while stirring and keeping the mixture at 0°. After 4 h the reaction mixture was acidified, concentrated in a rotary evaporator and 50 ml of ethyl ether was added. The etherial solution was washed twice with 25 ml of water and then dried over sodium sulfate. Evaporation of the solvent gave 2.0 g (87% yield) of an oil. Vacuum distillation gave a colorless liquid, bp 85°/0.15 mm.
Anal. Calculated for $C_{13}H_{26}O_3$: C, 67.78; H, 11.38.

Found: C, 67.90; H, 11.66.

2-Heptyl-3-hydroxybutanoic acid

BD 26262
Submitted. C 5 g

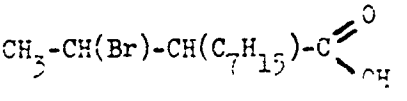


A mixture of 17.3 g (0.07 mole) of ethyl 2-heptyl-3-hydroxybutanoate in 100 ml of 10% NaOH solution was refluxed for 2 h. After cooling the solution was acidified and extracted three times with 30 ml portions of ethyl ether. The combined ethereal extracts were dried over sodium sulfate and the solvent evaporated. The oily residue was distilled under reduced pressure to give a colorless liquid, bp 139°/0.3 mm in 40% yield.
Anal. Calculated for $C_{11}F_{22}O_3$: C, 65.31; H, 10.96.

Found: C, 65.03; H, 10.70.

2-n-Heptyl-3-bromobutyric acid

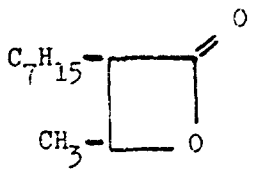
Not submitted



A solution of 10.85 g (0.054 mole) of 2-n-heptyl-3-hydroxyacetoacetic acid and 2.4 ml of pyridine in 40 ml of anhydrous ether was cooled to -5°C. To this cooled solution 4.4 ml (0.046 mole) of phosphorus tribromide in 30 ml of ether was added dropwise over a 40 minute period. After stirring for one additional hour at -5°C the mixture was allowed to warm to room temperature. After adding 100 ml of ice-water, the organic phase was washed three times with water until neutral. Drying (Na_2SO_4), followed by removal of the solvent under reduced pressure, gave an oil which gave a positive Beilstein test and was used without further purification.

2-Heptyl-3-methylpropiolactone

Not submitted

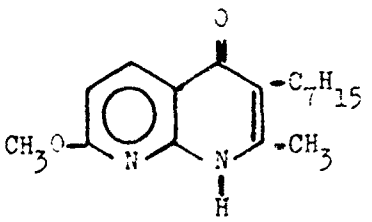


To a mixture of 12.55 g (0.047 mole) of 2-heptyl-3-hydroxybutyric acid, 50 ml of water and 50 ml of chloroform was added 5.94 g of sodium carbonate. After stirring for 1 h the chloroform layer was separated and replaced by a fresh portion. The combined chloroform extracts were dried ($MgSO_4$) and the solvent removed under reduced pressure. The remaining yellow oil was distilled to give 79% yield of a colorless liquid, bp 70°/0.35 mm.
Anal. Calculated for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94.

Found: C, 71.42; H, 10.99.

2-Methyl-3-heptyl-7-methoxy-1,8-naphthyrid-4-one

BD 27849
Submitted. 2.08 g



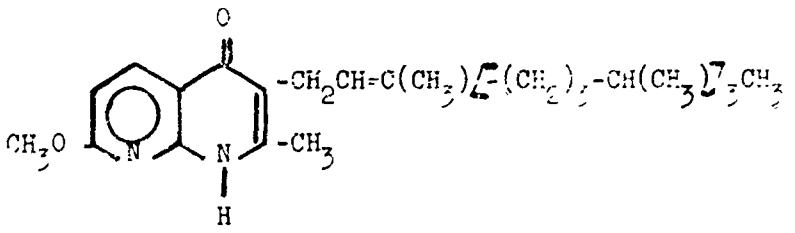
A mixture of 0.025 mole of 2-amino-6-methoxypyridine, 0.025 mole of ethyl 2-heptylacetoacetate and 40 ml of benzene was refluxed until no more water separated in a Dean and Stark condenser. The benzene was then evaporated and the residue used for cyclization without further purification.

The crude anilinocrotonate was added to refluxing Dowtherm A (50 ml) and stirring and refluxing was continued for 15 min. On cooling a solid separated which was filtered and washed with petroleum ether. A colorless solid was obtained in 22% yield. Recrystallization from ethanol gave white solid, mp 255-256° (d).
Anal. Calculated for $C_{17}H_{24}N_2O_2$: C, 70.80; H, 8.39; N, 9.71.

Found: C, 70.75; H, 8.37; N, 9.94.

2-Methyl-3-phytyl-7-methoxy-1,8-napthyrid-4-one

BD 27867
Submitted: 1.87 g



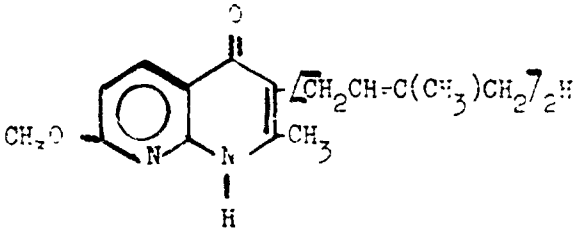
A mixture of 0.025 mole of 2-amino-6-methoxypyridine, 0.025 mole of ethyl 2-phytylacetoacetate and 40 ml of benzene was refluxed until no more water separated in a Dean and Stark condenser. The benzene was then evaporated and the residue used for cyclization without further purification.

The crude anilinocrotonate was added to refluxing Dowtherm A (50 ml) and stirring and refluxing was continued for 15 min. On cooling a solid separated which was filtered and washed with petroleum ether. A colorless solid, recrystallized from ethanol, obtained in 18% yield. Mp 183-185°.
Anal. Calculated for $C_{30}H_{48}N_2O_2$: C, 76.89; H, 10.3; N, 5.97.

Found: C, 76.59; H, 10.15; N, 5.70.

2-Methyl-3-geranyl-7-methoxy-1,8-napthyrid-4-one

BD 27858
Submitted: 0.9 g



A mixture of 0.025 mole of 2-amino-6-methoxypyridine, ethyl 2-geranylacetoacetate and 40 ml of benzene was refluxed until no more water separated in a Dean and Stark condenser. The benzene was then evaporated and the residue used for cyclization without further purification.

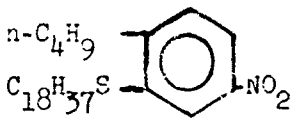
The crude anilinocrotonate was added to refluxing Dowtherm A (50 ml) and stirring

and refluxing was continued for 15 min. On cooling a solid separated which was filtered and washed with petroleum ether. A colorless solid, obtained in 21% yield. Mp 238-240° (d).
Anal. Calculated for $C_{20}H_{26}N_2O_2$: C, 73.58; H, 8.03; N, 8.58.

Found: C, 73.34; H, 8.01; N, 8.52.

Octadecyl 2(1-n-butyl-4-nitro)phenyl

BD 57516
Submitted: 0.5 g

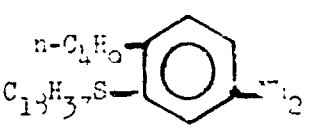


A cold solution of 7.4 g of sodium nitrite in 17 ml of water was added dropwise to a mixture of 20 g (0.102 mole) of 2-amino-4-nitro-n-butylbenzene, 22 ml of concentrated HCl and 22 ml of water while stirring and keeping the temperature 0-10°C for 0.5 h. The cold, filtered diazonium salt solution was poured into a solution of 0.064 mole of potassium ethyl xanthate in 26 ml of water kept at 75°C. A vigorous evolution of gas took place and a reddish brown oil separated on cooling. The oily xanthate layer was separated and hydrolyzed by refluxing for 1.5 h with 50 ml of a 20% solution of potassium hydroxide in 70% ethanol. The resulting solution was alkylated by the gradual addition of 33.9 g (0.102 mole) of octadecylbromide and refluxing for 3 h. A solid was obtained upon addition of ethanol to the crude dark brown oil. This was recrystallized from ethanol-hexane affording 37% of pale yellow solid, mp 48-49°.
Anal. Calculated for $C_{28}H_{49}NSO_2$: C, 72.57; H, 10.58; N, 3.02; S, 6.91.

Found: C, 72.74; H, 10.43; N, 2.74; S, 6.72.

3-n-Octadecylmercapto-4-n-but, aniline

Not submitted



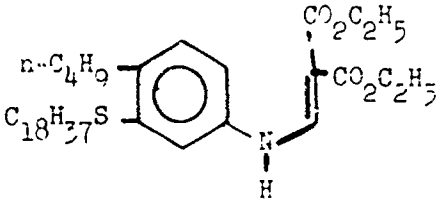
A mixture of 1.21 g (0.0026 mole) of 3-n-octadecylmercapto-4-n-butylnitrobenzene, 5 ml of ethanol and 2 g of tin in 6 ml of concentrated HCl was refluxed for one-and-a-half hours. The solid residue remaining in the ethereal solution was filtered and discarded. The solvent was removed in vacuum and the residue was triturated with benzene. A solid separated (1.7 g; 55% yield) which was recrystallized first from DMSO and followed by recrystallization CH_2Cl_2 to give white crystals, mp 91-93°.
Anal. Calculated for $C_{56}H_{104}N_2SCl_6Sn$: C, 50.03; H, 8.33; N, 2.33.

Found: C, 50.41; H, 8.04; N, 2.34.

The solid $SnCl_2$ double salt was treated with 25% NaOH solution, followed by extraction of the free amine with ether. Evaporation of the solvent gave free amine, mp 38-40°.

Diethyl 3-Octadecylmercapto-p-butylanilinomethylenemalonate

BD 58120
Submitted: 0.5 g

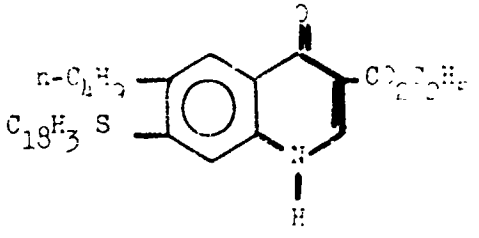


A solution of the amine (0.023 mole) and diethyl ethoxymethylenemalonate (0.026 mole) in 50 ml of isopropyl alcohol was refluxed for 24 h. On cooling a solid was obtained. Recrystallization from ethanol gave a white feathery solid, mp 56°; yield 94%.
Anal. Calculated for $C_{36}H_{61}NSO_4$: C, 71.64; H, 10.12; N, 2.34.

Found: C, 71.62; H, 9.86; N, 2.39.

Ethyl 6-Butyl-4-oxo-7-octadecylmercapto-3-quinolin-4(1H)carboxylate

BD 57963
Submitted: 1.8 g

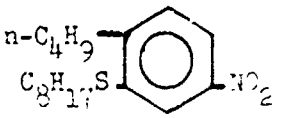


Diethyl 3-octadecylmercapto-p-butylanilinomethylenemalonate (0.003 mole) was added portionwise to 10 ml of refluxing Dowtherm A. After 10 min at 255° the mixture was cooled and 4 volumes of petroleum ether added. The solid obtained was filtered and washed thoroughly with petroleum ether. Recrystallization from dimethyl sulfoxide gave a light yellow solid, mp 198-199°; yield 47%.
Anal. Calculated for $C_{34}H_{55}NSO_3$: C, 73.25; H, 9.87; N, 2.51.

Found: C, 73.51; H, 9.89; N, 2.68.

Octyl 2(1-n-butyl-4-nitrophenyl) Sulfide

BD 58148
Submitted: 0.5 g

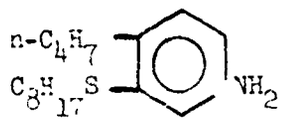


A cold solution of 7.4 g of sodium nitrite in 17 ml of water was added dropwise to a mixture of 20 g (0.102 mole) of 2-amino-4-nitro-n-butylbenzene, 22 ml of concentrated HCl and 22 ml of water while stirring and keeping the temperature 0-10°C for 0.5 h. The cold, filtered diazonium salt solution was poured into a solution of 0.064 mole of potassium ethyl xanthate in 26 ml of water kept at 75°C. A vigorous evolution of gas took place and a reddish brown oil separated on cooling. The oily xanthate layer was separated and hydrolyzed by refluxing for 1.5 h with 50 ml of a 20% solution of potassium hydroxide in 70% ethanol. The resulting solution was alkylated by the gradual addition of 0.102 mole of octylbromide and refluxing for 3 h. The reaction mixture was diluted with water and extracted with ethyl ether. After evaporation of the solvent, the crude residue was distilled under high vacuum affording 24% of yellow liquid, bp 175° (0.1 mm).
Anal. Calculated for $C_{18}H_{29}NSO_2$: C, 66.87; H, 3.98; N, 4.33.

Found: C, 66.66; H, 9.10; N, 4.53.

3-n-Octylmercapto-4-n-butylaniline

Not submitted

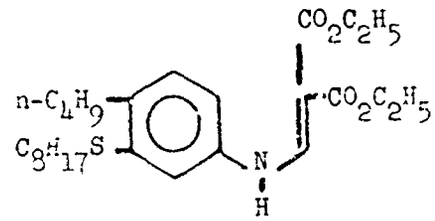


A mixture of 4.19 g (0.013 mole) of 3-n-octylmercapto-4-n-butylnitro-benzene, 20 ml of ethanol and 12 g of tin in 40 ml of concentrated HCl was refluxed for one-and-a-half hours. The upper liquid layer was separated and extracted with pentane. The viscous oil left was made strongly basic with 30% NaOH solution and the liberated amine extracted with several 30 ml portions of ether. Evaporation of the ether gave an oil that was distilled under vacuum, to give a colorless liquid, bp 135° (0.005 mm), 3.3 g (80%).
Anal. Calculated for $C_{18}H_{31}NS$: C, 73.72; H, 10.58; N, 4.78.

Found: C, 73.46; H, 10.62; N, 4.71.

Diethyl 3-Octylmercapto-p-butylanilinomethylenemalonate

BD 59707
Submitted: 0.7 g

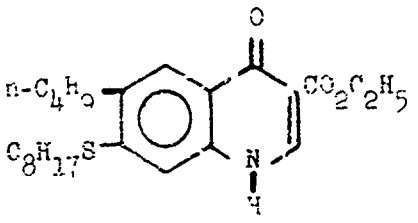


A solution of the amine (0.023 mole) and diethyl ethoxymethylenemalonate (0.026 mole) in 50 ml of isopropyl alcohol was refluxed for 24 h. On cooling a solid was obtained. Recrystallization from cold ethanol gave a white solid, mp 46°; yield 70%.
Anal. Calculated for $C_{26}H_{41}NSO_4$: C, 67.39; H, 8.86; N, 3.02.

Found: C, 67.11; H, 8.84; N, 2.77.

Ethyl 6-Butyl-4-oxo-7-octylmercapto-3-quinolin-4(1H)carboxylate

BD 59716
Submitted: 2.05 g

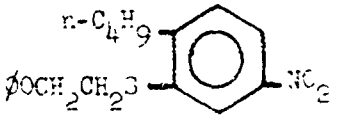


Diethyl 3-octylmercapto-p-butylanilinomethylenemalonate (0.003 mole) was added portionwise to 10 ml of refluxing Dowtherm A. After 10 min at 255° the mixture was cooled and 4 volumes of petroleum ether added. The solid obtained was filtered and washed with petroleum ether. Recrystallization from dimethyl sulfoxide gave a light yellow solid, mp 222-223; yield 69%.
Anal. Calculated for $C_{24}H_{35}NSO_3$: C, 69.06; H, 8.39; N, 3.36.

Found: C, 69.33; H, 8.12; N, 3.60.

Phenoxyethyl 2(1-n-butyl-4-nitrophenyl Sulfide

BD 58139
Submitted: 0.5 g



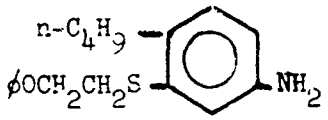
A cold solution of 7.4 g of sodium nitrite in 17 ml of water was added dropwise to a mixture of 20 g (0.102 mole) of 2-amino-4-nitro-n-butylbenzene, 22 ml of concentrated HCl and 22 ml of water while stirring and keeping the temperature 0-10°C for 0.5 h. The cold, filtered diazonium salt solution was poured into a solution of 0.064 mole of potassium ethyl xanthate in 26 ml of water kept at 75°C. A vigorous evolution of gas took place and a reddish brown oil separated on cooling. The oily xanthate layer was separated and hydrolyzed by refluxing for 1.5 h with 50 ml of a 20% solution of potassium hydroxide in 70% ethanol. The resulting solution was alkylated by the gradual addition of 0.102 mole of phenacyl bromide and refluxing for 3 h. The reaction mixture was diluted with water and extracted

with ethyl ether. After evaporation of the solvent, the crude product was fractionally distilled under high vacuum affording 2.9 g (18%) of yellow liquid, bp 185° (0.025 mm)
Anal. Calculated for $C_{18}H_{21}NSO_3$: C, 65.26; H, 6.34; N, 4.23.

Found: C, 65.46; H, 6.09; N, 4.25.

3-n-Phenoxyethylmercapto-4-n-butylaniline

Not submitted

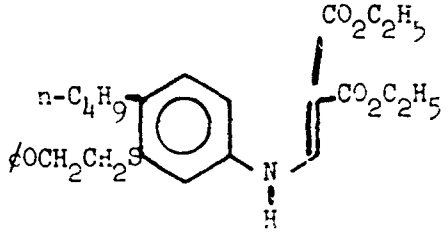


A mixture of 1.7 g (0.007 mole) of 3-n-phenoxyethylmercapto-4-n-butylnitrobenzene, 5 ml of ethanol and 3 g of tin in 13 ml of concentrated HCl was refluxed for one-and-a-half hours. The aqueous layer was washed with pentane and the water evaporated to give an oil. The residue was made strongly basic with 30% NaOH solution and the liberated amine was extracted 4 times with 30 ml portion of ether. The ethereal solution was dried over Na_2CO_3. Removal of the ether gave an oil that was distilled under vacuum to give a colorless liquid, bp 183° (0.05 mm) in 25% yield.
Anal. Calculated for $C_{18}H_{23}NSO$: C, 71.76; H, 7.64; N, 4.65.

Found: C, 72.02; H, 7.91; N, 4.65.

Diethyl 2-phenoxyethylmercapto-4-butylanilinomethylenemalonate

BE 11391
Submitted: 0.5 g

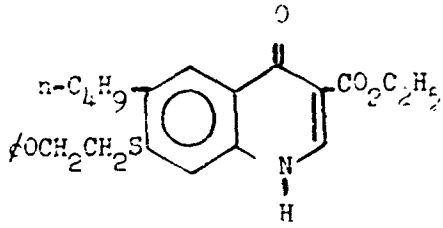


A solution of 4.74 g (0.015 mole) of 3-n-phenoxyethylmercapto-4-n-butylaniline and 3.56 g (0.0165 mole) of diethyl ethoxymethylenemalonate in 25 ml of isopropanol was refluxed for 24 h. On cooling a dark solid separated. Recrystallization from ethanol gave an off-white solid, mp 66° in 47% yield (3.35 g).
Anal. Calculated for $C_{26}H_{33}NSO_5$: C, 66.24; H, 7.01; N, 2.97.

Found: C, 65.99; H, 6.92; N, 3.03.

Ethyl 6-butyl-7-phenoxyethylmercapto-4-oxo-4(1H)-quinolin-3-carboxylate

BE 11382
Submitted: 2.0 g

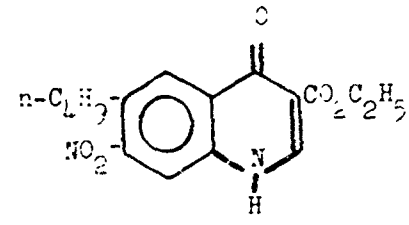


To Dowtherm A (10 ml per 0.003 mole of malonate derivative) at 240° was added portionwise the appropriate amount of aminomethylenemalonate with stirring. The resulting solution was maintained at this temperature for 15 min. On cooling acetone was added. The solid that separated in 74% yield was recrystallized from DMSO to give solid, mp 236-237°.
Anal. Calculated for $C_{24}H_{27}NSO_4$: C, 67.76; H, 6.35; N, 3.29.

Found: C, 67.49; H, 6.26; N, 3.16.

Ethyl 6-butyl-7-nitro-4-oxo-4(1H)-quinolin-3-carboxylate

BD 57507
Submitted: 0.5 g



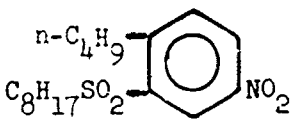
A solution of 10 g (0.051 mole) of 4-amino-2-nitrobutylbenzene and 12.1 g (0.056 mole) of diethyl ethoxymethylenemalonate in 100 ml of isopropanol was refluxed for 24 h. On cooling a solid separated which was recrystallized from hexane (98%, mp 70-71°).

To 45 ml of refluxing Dowtherm A was added 5 g of the crude solid and the temperature kept at 255° for 15 min. On cooling a solid was obtained that was washed with petroleum ether. Recrystallization from dimethyl sulfoxide gave a gray solid, mp >300°; yield 46%.
Anal. Calculated for $C_{16}H_{18}N_2O_5$: C, 60.38; H, 5.66; N, 8.80.

Found: C, 60.11, H, 5.77; N, 8.77.

4-n-Butyl-3(n-octylsulfonyl)nitrobenzene

BE 13028
Submitted: 0.6 g

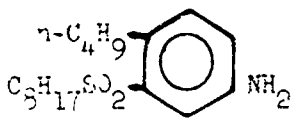


A solution of 4-n-butyl-3(n-octylmercapto)nitrobenzene(2 g, 0.0062 mole) in 40 ml of glacial acetic acid and 24 ml of H_2O_2 was warmed at 60° with stirring for 4 days. The solution was neutralized with 30% NaOH solution and extracted three times with 50 ml portions of ether. After drying the solvent was evaporated to give solid, 1.93 g (87% yield). Recrystallization from 75% ethanol gave mp 41-42°.
Anal. Calculated for $C_{18}H_{29}NSO_4$: C, 60.85; H, 8.17; N, 3.94.

Found: C, 60.62; H, 7.92; N, 4.16.

3-n-Octylsulfonyl-4-n-butylaniline

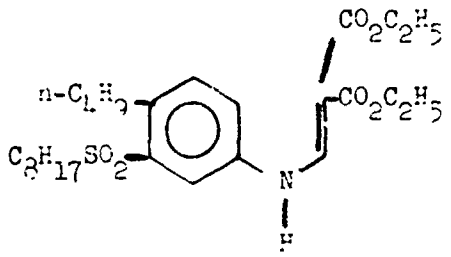
Not submitted



A mixture of 0.5 g (0.0014 mole) of 3-n-octylsulfonyl-4-n-butylnitrobenzene, 3 ml of ethanol and 0.7 g of tin in 2.5 g of concentrated HCl was refluxed for one-and-a-half hours. After this time the reaction mixture was poured into ice and made strongly basic by the addition of 15 ml of a 50% NaOH solution. Extraction with ether gave after drying and removal of the solvent, 0.2 g (50% yield) of the amine which was used without further purification.

Diethyl 3-n-octylsulfonyl-4-butylanilinomethylinemalonate

BE 13037
Submitted: 0.75 g

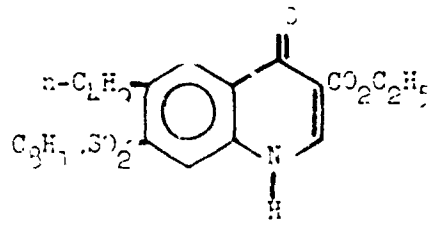


A solution of 1.6 g (0.005 mole) of 3-n-octylsulfonyl-4-butylaniline and 1.08 g (0.005 mole) of diethyl ethoxymethylenemalonate in 15 ml of isopropanol was refluxed for 24 hours. After cooling the solvent was evaporated in vacuum and the residue was triturated with petroleum ether to give 2.0 g (82%) of a cream white solid, mp 69-70°. Recrystallization from hexane gave mp 69-70°.
Anal. Calculated for $C_{26}H_{41}NSO_6$: C, 63.03; H, 8.28; N, 2.83.

Found: C, 62.79; H, 8.30; N, 2.70.

Ethyl 6-n-butyl-7-n-octylsulfonyl-4-oxo-4(1H)-quinolin-3-carboxylate

BE 13046
Submitted: 2.1 g

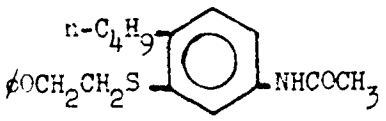


To 10 ml of Dowtherm A at 250° was added portionwise 1.25 g (0.0025 mole) of the anilinomethylenemalonate derivative. After the addition, stirring at 250° was continued for 10 min. Acetone was added after cooling and the solid that separated was filtered, 0.5 g (48%). Recrystallization from DMSO gave mp 251-252°. Anal. Calculated for $C_{24}H_{35}NSO_5$: C, 64.14; H, 7.80; N, 3.12.

Found: C, 64.12; N, 7.76; H, 3.40.

3-[β-Phenethyl]mercapto-4-n-butylacetanilide

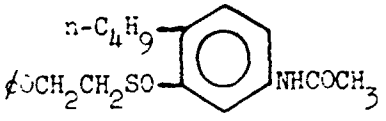
Not submitted



To a solution of 7.95 g (0.0246 mole) of 4-amino-3-[β-phnethyl]mercapto-n-butylbenzene in 10 ml of glacial acetic acid, 8 ml of acetic anhydride was added gradually with stirring. The solution was refluxed for one hour and then poured into 350 ml of ice-water. The gummy solid was filtered and washed thoroughly with water. Recrystallization from aqueous ethanol gave white crystals, mp 86° in 32% yield. Infrared spectrum: 1670 cm^{-1}(s).

3-[β-Phenethyl]sulfinyl-4-n-butylacetanilide

Not submitted



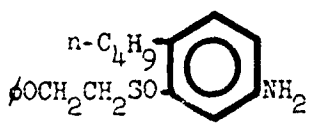
A solution of 0.5 g (0.00145 mole) of 3-[β-phenethyl]mercapto-4-n-butylacetanilide in 6.5 ml of glacial acetic acid and 3.5 ml of hydrogen peroxide was stirred at room temperature for 5 h. It was then poured into 100 ml of ice-water and the precipitate that separated was filtered and washed with water (90% yield). TLC (50:50, $CHCl_3$-benzene) showed two spots, R_F 0.1 and 0.2 respectively, different

from starting material. Fractional crystallization from acetone-petroleum ether (x6) gave pure lower R_F material in 30% of the total crude product. Infrared spectrum: 1050 cm^{-1}(s); mp 105-106°.
Anal. Calculated for $C_{20}H_{25}NSO_3$: C, 66.85; H, 6.96; N, 3.90.

Found: C, 66.73; H, 6.94; N, 3.98.

3-[β-Phenethyl]sulfinyl-4-n-butylaniline

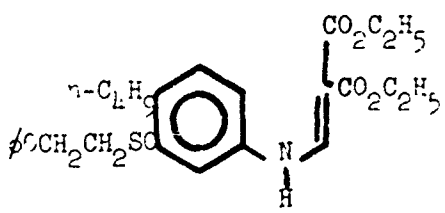
Not submitted



A suspension of 0.75 g (0.0021 mole) of 3-[β-phenethyl]sulfinyl-4-n-butylacetanilide in 3 ml of concentrated hydrochloric acid and 5 ml of water was refluxed for 2 h. During this time the solid went into solution and then reprecipitation occurred. After cooling the solid was filtered, and treated with 4 ml of a 50% solution of Na_2CO_3. Extraction with ether and evaporation of the solvent gave almost quantitative yield of the free amine. It was used without further purification.

Diethyl [3-(β-phenethyl)sulfinyl-4-butylanilinomethylene]malonate

Not submitted

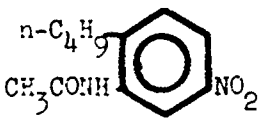


A solution of 0.57 g (0.00173 mole) of diethyl ethoxymethylenemalonate in 5 ml of 150 propanol was refluxed for 24 h. After cooling the solvent was evaporated in vacuum to give 0.8 g of white solid (95%). Recrystallization from ethanol-hexane gave white needles, mp 104.
Anal. Calculated for $C_{26}H_{33}NSO_6$: C, 64.07; H, 6.78; N, 2.87.

Found: C, 64.20; H, 6.85; N, 2.85.

3-Nitro-6-n-butylacetanilide

BE 16898
Submitted: 0.6 g

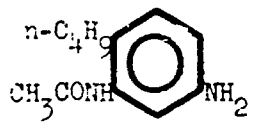


A suspension of 9.7 g (0.05 mole) of 3-nitro-6-n-butylaniline in 20 ml of glacial acetic acid and 16 ml of acetic anhydride was refluxed for 2 h. The solution was poured into 150 ml ice-water and the precipitate filtered and washed with water. After drying 12.1 g (100%) of the acetanilide was obtained. Recrystallization from ethanol gave white needles, mp 146-147°.
Anal. Calculated for $C_{12}H_{16}N_2O_3$: C, 61.00; H, 6.82; N, 11.85.

Found: C, 61.02; H, 6.98; N, 11.71.

3-Amino-6-n-butylacetanilide

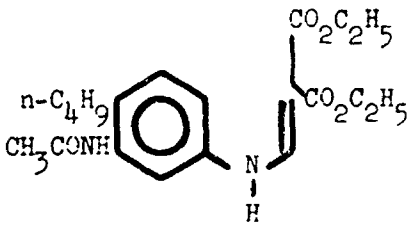
Not submitted



A solution of 2 g (0.0084 mole) of 3-nitro-6-n-butylacetanilide in 250 ml of ethyl acetate was hydrogenated at 71 psi using 0.01 g PtO_2 as catalyst. After the theoretical amount of hydrogen was used the catalyst was filtered and the solvent evaporated to give 1.37 g (71%) of white solid, mp 160-161°. Recrystallization from $CHCl_3$ gave mp 161-162°.

Diethyl (3-acetylamino-4-n-butylanilinomethylene)malonate

BE 17973
Submitted: 0.69



A solution of 0.9 g (0.0041 mole) of 3-amino-6-n-butylacetanilide and 1 g (0.0041 mole) of diethyl malonate in 15 ml of isopropanol was refluxed for 24 h. Evaporation of the solvent gave fluffy white solid (68%). Recrystallization from ethanol gave mp 170-171.
Anal. Calculated for $C_{20}H_{28}N_2O_5$: C, 63.81, H, 7.49; N, 7.43.

Found: C, 64.06; H, 7.76; N, 7.69.

5-Diethylamino-2-pentanone diethylketal

Not submitted

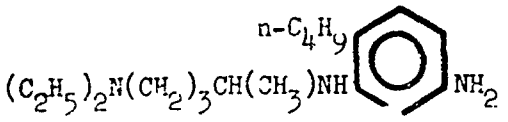
$$CH_3C(OC_2H_5)_2(CH_2)_3N(C_2H_5)_2$$

To a flask containing 15 ml of concentrated hydrochloric acid, 15.7 g (0.1 mole) of 5-diethylamino-2-pentanone was added while stirring. Evaporation of the solvent gave a brown oil which was further dried by azeotropic evaporation with benzene. A brown solid was obtained which when recrystallized from acetone-ethyl ether gave white crystals, mp 73-74°, of the amine hydrochloride.

A mixture of triethyl orthoformate (5.5 g, 0.037 mole), the amine hydrochloride previously obtained (6.19 g, 0.031 mole), and catalytic amounts of NH_4NO_3 (0.11 g) in 5 ml of ethanol was refluxed for 2.5 h. After cooling the solution was neutralized with a sodium ethoxide in ethanol solution followed by addition of water. Extraction with ethyl ether (3x100 ml) and evaporation of the ethereal solution after drying gave an oil whose infrared spectrum lacked carbonyl absorption. The desired ketal was obtained after distillation, bp 130° (15 mm).

4-Butyl-3[4-diethylamino-1-methylbutyl)amino]aniline

BE 16878
Submitted: 0.6 g



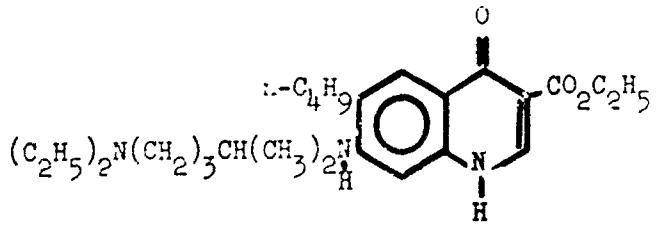
A mixture of 0.58 g (0.003 mole) of 2-amino-4-nitrobutylbenzene and 1.12 g (0.0048 mole) of the diethylketal of 5-diethylamino-2-pentanone in the presence of catalytic amounts of p-toluensulfonic acid (0.02 g) was heated at 150-160° for 2 h. It was poured into 20 ml of water and neutralized with 10% NaOH solution. Extraction with ether followed by evaporation of the solvent after drying ($MgSO_4$) gave an oil that was used without further purification.

Catalytic hydrogenation of the crude Schiff's base in 150 ml of ethanol was carried out in the presence of PtO_2 at 35 psi. After the theoretical amount of H_2 was absorbed, the solution was filtered and the solvent evaporated. The oily residue was distilled under vacuum to give 80%, bp 157° (0.05 mm) of the desired aniline.
Anal. Calculated for $C_{19}H_{35}N_3$: C, 74.75; H, 11.48; N, 13.77.

Found: C, 74.90; H, 11.36; N, 13.89.

3-Carbethoxy-6-butyl-7[(4-diethylamino-1-methylbutyl)amino]-4(1H)-quinolone

Not submitted



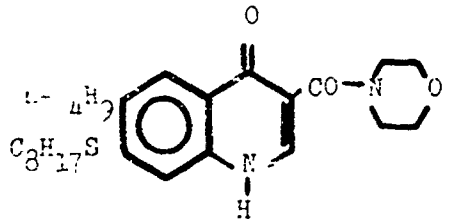
A solution of 6.41 g (0.02 mole of 4-butyl-3[(4-diethylamino-1-methylbutyl)amino] aniline and 4.9 g (0.023 mole) of diethyl ethoxymethylenemalonate in 35 ml of isopropanol was refluxed for 24 h. Avter evaporation of the solvent the oily residue showed twoalmost adjacent spots on TLC (10:90; MeOH:$CHCl_3$). This crude oil 9 g, 87%) was used without further purification.

To 20 ml of Dowtherm A at 230° was added 2.5 g (0.0052 ml) of the malonate derivative. After 15 min at this temperature the mixture was cooled and the gummy solid that separated was triturated with petroleum ether (1.2 g, 53%). Extraction of the solid with hot iso-octane gave a yellow solid, mp 142-144.
Anal. Calculated for $C_{25}H_{39}N_3O_3$: C, 69.93; H, 9.09; N, 9.79.

Found: C, 70.09; H, 9.17; N, 9.72.

3-Carbomorpholine-6-butyl-7-octylmercapto-4(1H)-quinolone

BE 16887
Submitted: 0.6 g

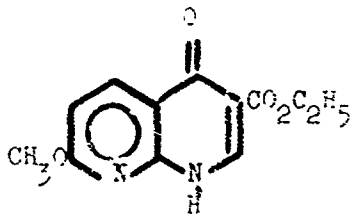


A solution of 1.96 g (0.0051 mole) of 3-carbethoxy-6-butyl-7-octylmercapto-4(1H)-quinolone in 25 ml of morpholine was refluxed for 4 h. The excess morpholine was distilled off and the residue triturated with petroleum ether. The solid was recrystallized from aqueous ethanol to give an off-white solid (36%) mp 174-175°.
Anal. Calculated for $C_{26}H_{38}N_2O_3S$: C, 68.18; H, 8.35; N, 6.10.

Found: C, 68.18; H, 8.07; N, 6.29.

3-Carbethoxy-7-methoxy-1,8-naphthyrid-4-one

BE 17964
Submitted: 1.85 g



A solution of 2-amino-6-methoxypyridine (6.9 g, 0.056 mole) and diethylethoxymethylenemalonate (12.1 g, 0.056 mole) in 100 ml of isopropanol was refluxed for 24 h. After evaporation of the solvent the oily residue was triturated with

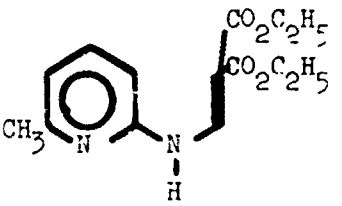
absolute ethanol to give an off-white solid (95%) mp 56-57°. Recrystallization from absolute ethanol gave mp 58-59°.

To 100 ml of refluxing Dowtherm A (255°) 5 g (0.017 mole) of the previously prepared malonate derivative was added and the temperature held for 15 min. On cooling and addition of 4 times the volume of petroleum ether a white solid separated in 58%. Recrystallization from ethanol gave mp 255-256°.
Anal. Calculated for $C_{12}H_{12}N_2O_4$: C, 58.05; H, 4.87; N, 11.28.

Found: C, 58.31; H, 4.60; N, 11.00.

3-Carbethoxy-7-methyl-1,8-naphthyrid-4-one

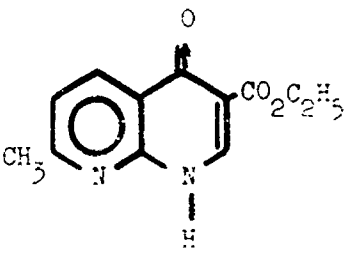
BE 17946
Submitted: 1.5 g



A solution of 2-amino-6-methylpyridine (20 g, 0.185 mole) and diethyl ethoxymethylenemalonate (40 g, 0.185 mole) in 200 ml of isopropanol was refluxed for 24 h. After evaporation of the solvent the solid residue was recrystallized from ethanol (91% yield, mp 104-106°).
Anal. Calculated for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.51; N, 10.06.

Found: C, 60.11; H, 6.40; N, 10.22.

BE 17955
Submitted: 0.8 g



To 100 ml of refluxing Dowtherm A (255°C) 10 g (0.016 mole) of the previously prepared malonate derivative was added and the temperature held for 45 min. On cooling and adding 4 volumes of petroleum ether a yellow solid separated in 50% yield. Recrystallization from ethanol gave mp 268-270°.
Anal. Calculated for $C_{12}H_{12}N_2O_3$: C, 62.05, H, 5.21; N, 12.06.

Found: C, 61.67; H, 5.15; N, 11.98.

Publications in preparation

A. C. Casey and J. Marone, Some 4-Quinolones related to endochin as antimalarial agents.

A. C. Casey and S. Abidi, Some 7-Mercapto substituted 4-quinolones as antimalarial agents.

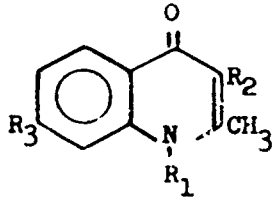
Personnel

A. Lee, B.S.
J. T. Marone, Ph.D.
S. Abidi, Ph.D.
S. Palermo, B.S.
A. C. Casey, Ph.D.

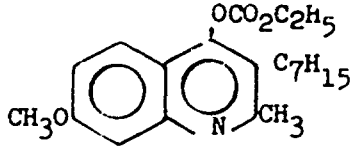
TABLE 1

Summary Table

Structure



R_1	R_2	R_3	WRAIR Number	Reference
H	$CH{=}CH(CH_2)_9CH_3$	CF_3	BD 23181	p 15
H	$CH_2N(CH_3)C_{18}H_{37}$	CH_3	BD 09485	p 16
OH	C_7H_{15}	OCH_3	BD 26235	p 16



	BD 26226	p 15
$CH_3CH(OH)CH(C_7H_{15})CO_2H$	BD 26262	p 18

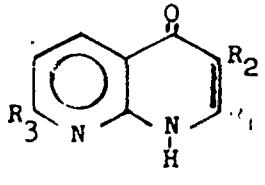
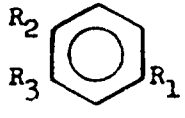


TABLE 1

Summary Table

Structure			WRAIR Number	Reference
R_1	R_2	R_3		
CH_3	C_7H_{15}	OCH_3	BD 27849	p 19
CH_3	phytyl	OCH_3	BD 27867	p 20
CH_3	geranyl	OCH_3	BD 27858	p 20
H	$CO_2C_2H_5$	OCH_3	BE 17964	p 35
H	$CO_2C_2H_5$	CH_3	BE 17955	p 36

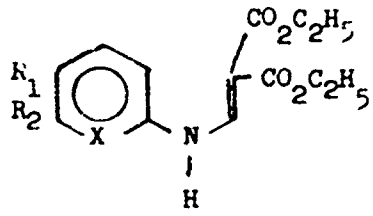


R_1	R_2	R_3		
NO_2	n-butyl	$SC_{18}H_{37}$	BD 57516	p 21
NO_2	n-butyl	SC_8H_{17}	BD 58148	p 23
NO_2	n-butyl	$SCH_2CH_2O\phi$	BD 58139	p 25
NO_2	n-butyl	$SO_2C_8H_{17}$	BE 13028	p 28
NO_2	n-butyl	$NHCOCH_3$	BE 16898	p 32
NH_2	n-butyl	$NH(CH_3)CH(CH_2)_3N(C_2H_5)_2$	BE 16878	p 34

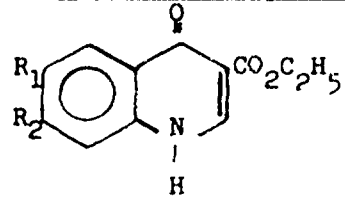
TABLE 1

Summary Table

Structure



X	R_1	R_2	WRAIR Number	Reference
CH	n-butyl	$SC_{18}H_{37}$	BD 58120	p 22
CH	n-butyl	SC_8H_{17}	BD 59707	p 24
CH	n-butyl	$SCH_2CH_2O\phi$	BE 11391	p 26
CH	n-butyl	$SO_2C_8H_{17}$	BE 13037	p 29
CH	n-butyl	$NHCOCH_3$	BE 17973	p 33
N	H	CH_3	BE 17955	p 36



R_1	R_2		
n-butyl	$SC_{18}H_{37}$	BD 57963	p 22

LITERATURE CITED

(1) BIOS, final report, N. 116, item No. 24, pages 10 and 14.

(2) J. Ryley and W. Peters. Ann. Trop. Med. Parasitol., 64, 209 (1970).

(3) A. C. Casey, J. Med. Chem., 17, 255 (1974).

(4) Personal communication from WRAIR.

(5) M. Conrad and L. Limpach, Ber., 21, 1965 (1888).

(6) G. R. Lappin, J. Am. Chem. Soc., 70, 3348 (1948).

(7) R. Mirza, Nature, 186, 716 (1960).