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Synthesis of some 6-aralkyl-2, 4-diamino-5,6,7,8-tetrahydropyrimido (4,5-d) pyrimidines

ANNUAL REPORT

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Aralkyloxyamines

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

Exploratory investigations in several series of amines were conducted with the view of obtaining optimum conditions as well as representatives examples for biological screening. Difficulties encountered with either the reactivity of some of the amines or the stability of some of the products prevented completion of this initial goal. Where such areas of difficulty arose further work will be required. A series of 6-(substituted benzyl)-2,4-diamino-5,6,7,8-tetrahydropyrimido (4,5-d) pyrimidines has been prepared and is in the process of being submitted for screening.

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SUMMARY

This work was based on the proposition that a one-step synthesis of 6-substituted-2, 4-diamino-5,6,7,8-tetrahydropyrimido (4,5-d) pyrimidines could be accomplished from a variety of amines and 2,4,6-triaminopyrimidine under Mannich reaction conditions. The chemical rationale for this class of compound was based on similarities to existing active antimalarial agents in both the antifolic acid and the reduced s-triazine series. The possibility that such a chemical class could interfere at two distinct sites in the folic acid metabolic pathway served as the primary biological rationale.

Using either commercially available amines or synthesizing those which were not otherwise available we subjected these to Mannich reaction conditions. In all cases 2,4,6-triaminopyrimidine was used as the substrate. Formalin, paraformaldehyde or trioxymethylene constituted the third ingredient. Variations in solvent, temperature, p^H of the medium, time of reaction and order of addition were some of the main points explored in these reactions in an attempt to optimize the reaction.

Our results to date indicate that the smoothest reaction occurred when a series of benzylamines were employed. Considerable experimental difficulties attended the use of the arylamines, the arylethylamines, the aryloxyethyl hydroxyamines and the benzyloxyamines. In these cases either very poor yields or no desired products were obtained.

On the basis of this rather preliminary information it appears that the stability and/or reactivity of the Schiff base derived from the amine and formaldehyde is the most significant factor in the results obtained thus far.

FOREWARD

Due to the unusual delay in commencing actual work on this project, the annual summary report covers a period of only five months. One full-time investigator (Dr. Salah M. Sami) conducted the major portion of the work being reported. The principal investigator and author of this report (Thomas J. Delia) was supported twenty-five percent.

At the outset we attempted to explore one or two examples in each series originally proposed. This was done to discuss any difficulties and to provide representative examples in each series for screening. The difficulties were discovered while the screening goal was not realized. But this approach most certainly has saved considerable laboratory time in that we are alerted to inherent problems in each class.

The authors are indebted to Ms. Theresa Higgins for competent technical assistance and to Central Michigan University for general support and specifically for providing the services of Ms. Higgins.

TECHNICAL REPORT

I. Statement and Background of the Problem

One of the chief difficulties with many antimalarial agents today is the fact that the parasite ultimately develops a tolerance to them. Consequently, there is an interest in an agent which would be more resistant to this effect or which could be used in conjunction with existing agents.

Our approach to this problem has been to propose a series of 6-substituted -2,4-diamino-5,6,7,8-tetrahydropyrimido (4,5-d) pyrimidines as likely candidates for effective antimalarial chemotherapy. The rationale for this series is based on both chemical and biological information. For example this series is very similar in structure to the antifols which are active antimalarials (1,2) in which there is a simple reversal of the carbon and nitrogen atoms at the 5 and 6 positions. The tetrahydroquinazolines (3,4,5) is another series which shows good antimalarial activity. Consequently, one of the heterocyclio rings is shown in the reduced form. The substituents chosen were taken from several studies of which those by Elslager et al. (6) and Laing (7) are typical.

II. Approach to the Problem

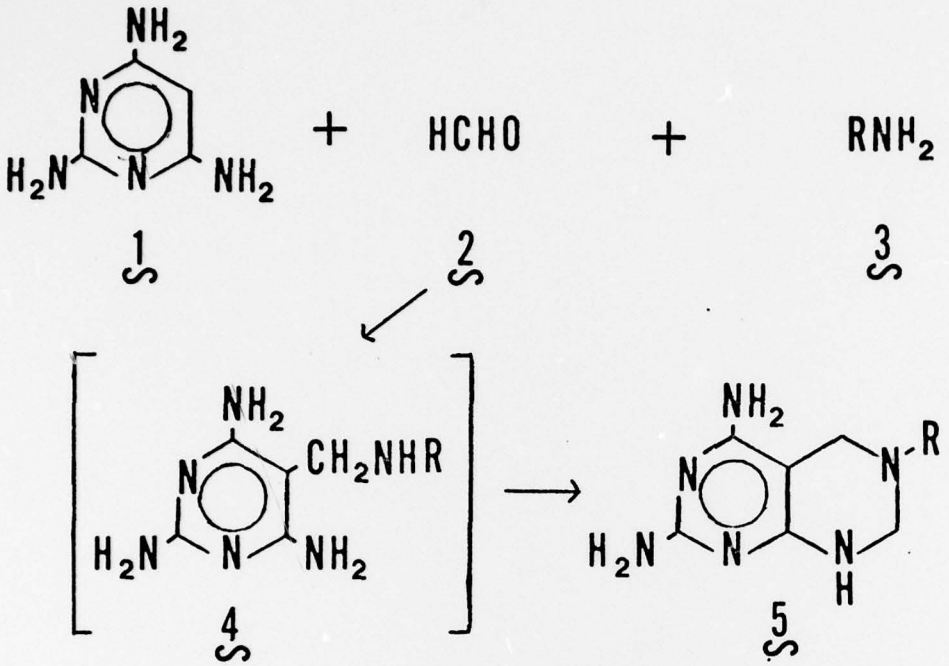
We have proposed the synthesis of the desired tetrahydropyrimidopyrimidines (5) by applying the conditions of the Mannich reaction to 2,4,5,-triaminopyrimidine (1), as shown in Figure 1. We have put emphasis on the synthesis of compounds that could be obtained from 1 and 3 where 3 may be arly and aralkylamines derivatives, O-aryl, O-aralkyl and O-aryloxyhydroxylamines. Each of these may contain one or more halogen atoms (Cl or F) attached either directly or indirectly. In this report we describe the attempts and the results achieved towards the synthesis of these compounds.

III. Discussion of Results

A. Reactions with Phenylethylamine (3a)

The reaction of 1 with amines under the Mannich conditions as well as the yield of the reaction depends largely on the structure of the amine used, molar ratio of the reactants, temperature, pH of the media, solvent, reaction time, and other conditions affecting the course of the reaction. In our preliminary experiments we investigated the reaction using a variety of combinations of these parameters with the commercially available phenylethylamine (3a) as a model. Experiments were performed over a temperature range of 0-80^{o}C, a variety of molar ratios of 1:3:2 including 1:1:1, 1:1:2, 1:2:2 and using water, aqueous ethanol or absolute ethanol as solvent. 1 and the amine were added into the reaction as either the free bases or in the form of their hydrochloride salts. In some cases the reaction was carried out with the free bases in the presence of a few drops of conc HCl (pH≈4). In some experiments the Schiff base of the amine or its hydrochloride

FIGURE 1



WHERE R MAY BE:

A = PHENYLETHYL

B = 4-CHLOROPHENOXYETHYLOXY

C = 3,4-DICHLOROBENZYL

D = 4-CHLOROBENZYL

E = 2,4-DICHLOROBENZYL

F = 3-TRIFLUOROMETHYLBENZYL

G = 2,6-DICHLOROBENZYL

H = 2,6-DICHLOROBENZYLOXY

I = 4-CHLOROPHENYLETHYL

J = 2,4-DICHLOROPHENYLETHYLOXY

K = 4-CHLOROPHENYL

L = 2-CHLOROPHENYL

M = 2,4-DICHLOROPHENYL

was first prepared in situ, then allowed to react with 1. In all experiments with the exception of those which were carried out at 0°C and are still under investigation neither intermediate 4 nor desired product 5 could be detected or isolated. The main reaction products were either unidentifiable solids (the majority of which were insoluble in most common solvents but dissolve in some organic acids like formic, acetic and lactic acids) or unreacted starting materials along with other minor components. Table 1 provides a summary of these experiments with phenylethylamine and the results obtained.

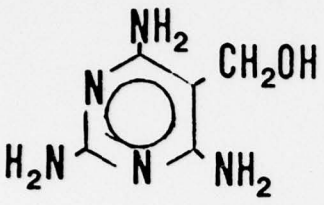
B. Reactions with p-Chlorophenoxyethylhydroxylamine (3b)

Since the reaction with phenylethylamine seemed to be somewhat sensitive and led only to unwanted products, we decided to explore the reaction with other amine series. Consequently, p-chlorophenoxyethylhydroxylamine (3b), representing the aryloxyhydroxylamines, was prepared and allowed to react with 1 under different conditions. In some experiments the oxime was first formed from the amine hydrochloride and formalin in aqueous pyridine which produced, by a buffering effect, a pH close to neutral or alternatively from the hydroxylamine base and formalin in boiling ethanol- aq. NaH_2PO_4 mixture which gives the same pH value. These experiments and the results obtained are described in Table 2. As shown in Table 2 in no case were we able to isolate or detect any amount of either of the desired compounds 4b or 5b. The failure to obtain the desired compounds in either of the cases described under the conditions used led us to conclude that the reaction products resulting from 1 and these amines may not be stable under these conditions.

C. Reactions with Benzylamine Derivatives (3_{c-g})

We undertook next the examination of the reaction with the benzylamine and 1-benzylhydroxylamine series. When 1 was allowed to react with 3c (3,4-dichlorobenzylamine hydrochloride) and polyoxymethylene in a molar ratio 1:1:1, respectively, with boiling ethanol as solvent, the main isolable products were a yellow insoluble solid, unreacted 1 and unreacted amine (3c). In boiling acetic acid with the same molar ratio of the reactants but using the benzylamine base instead of the salt the reaction led to the formation of insoluble yellow solid, unreacted amine and a very poor yield of the tetrahydropyrimidopyrimidine 5c. When the reaction with the hydrochloride salt of the amine was carried out in the same manner as in the first case but with a molar ratio 1:1:2 and without prior formation of the Schiff base we obtained after 24 h. refluxing a mixture of insoluble yellow solid and 5c in nearly equal amounts. In basic medium the reaction seemed to favor tetrahydropyrimidopyrimidine formation. Thus, equimolor quantitites of 1 and the Schiff base of 3,4-dichlorobenzylamine (prepared from equimolar amounts of the amine and formalin) reacted within 24 h. refluxing in ethanol to give a mixture of 5c (≃30%) and 5-hydroxymethyl-2,4,6-triaminopyrimidine (6) (Figure 2) (≃50%). However, the best results were obtained when this experiment was repeated in the same manner employing a molar ratio of 1 to the Schiff base of 1:2. In this case 1 reacted smoothly without the formation of side products to give nearly a quantitative yield of compound 5c. Compounds 5d-g as well as their hydrochloride salts were prepared

FIGURE 2



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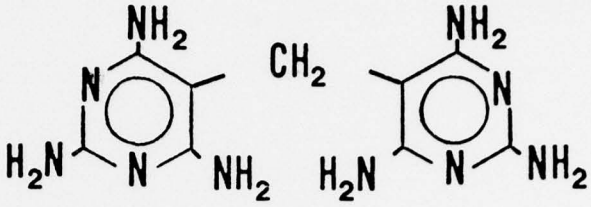

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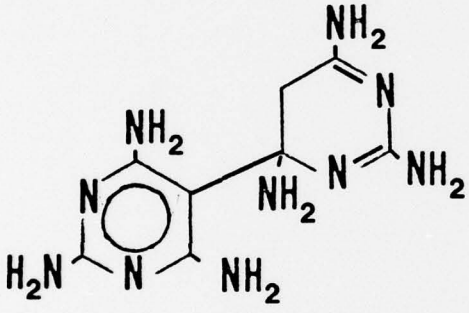

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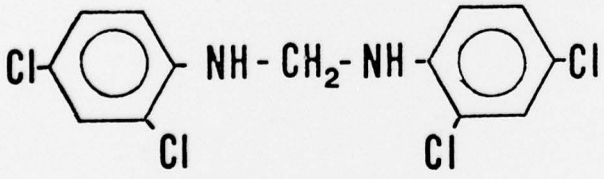

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successfully in a similar manner. Table 3 gives a summary of these experiments and the results obtained with the benzylamine series. Note should be made to the fact that in all these experiments we were unable to detect the existence of 4d-g among the products.

D. Reactions with 2,6-Dichlorobenzylhydroxylamine (3h)

Where the Mannich reaction of 1 with the benzylamine series is acid-base catalyzed the reaction of 1 with benzylhydroxylamines and formalin proceeds only under acid catalyzed conditions. Thus, when we reacted 1 with 2,6-dichlorobenzylhydroxylamine (3h) and formalin in a molar ratio 1:2:2, respectively, and with prior formation of the oxime we isolated only side products and unreacted starting materials. However, carrying out the reaction under the same conditions using 3h as the hydrochloride we obtained within 24 h. refluxing compounds 5h in 42% yield together with some unreacted 1. Increasing the reaction time did not improve the yield. Table 4 provides a summary of these experiments.

E. Reactions with p-Chlorophenylethylamine (3i) and O-(2-(2,4-Dichlorophenoxy)ethyl hydroxylamine (3j)

After the conditions of the reaction with the benzylamine and benzylhydroxylamine were established we returned to the reaction of 1 with the phenylethylamine and aryloxyhydroxylamine series. We tried to apply the same conditions which worked out well with the benzylamine series to the reaction of 1 with p-chlorophenylethylamine (3i) and those used with the benzylhydroxylamine to the reaction of 1 with O-(2-(2,4-dichlorophenoxy)ethyl hydroxylamine (3j). In the case of 3i the reaction proceeded without the formation of any undesired insoluble materials and we obtained mainly one reaction product in excellent yield, together with unreacted amine. The reaction product was converted into the hydrochloride salt which was crystallized from methanolic hydrogen chloride. The PMR spectrum of the salt (DMSO-d_6) did not indicate any NH or NH_2 protons attributable to the pyrimidine moiety. However, ring-CH_2 protons as well as phenyl and CH_2 protons of the phenylethylamine moiety are indicated. It seems that the product is not stable and probably undergoes decomposition during the process of crystallization since the PMR spectrum of the first crop of crystals is different than that of the second crop isolated. To date no definite conclusion can be drawn concerning the Mannich reaction of 1 with the phenylethylamine series and further work is needed. With 3j the reaction led to the formation of a mixture from which we failed to isolate and detect any amount of the desired compounds.

F. Reactions with Clorinated Anilines (3_{k-m})

We have also investigated the Mannich reaction of 1 with aromatic amines, namely p-chloroaniline (3k) o-chloroaniline (3l) and 2,4-dichloroaniline (3m). These reactions are carried out under the same conditions that worked so well with the benzylamine series. Among these amines only 3b reacted in the desired direction.

We succeeded in isolating compound 5b in poor yield (18%) from the reaction product which consisted mainly of unreacted amine and a large amount of an unidentifiable solid insoluble in most common solvents: 3l gave a large amount of unidentifiable yellow solid which is also insoluble in all solvents tried together with unreacted amine while 3m gave, besides these two products, a compound thought to be either 7 or 8 (Figure 2). In neither case could we detect even traces of the desired compounds. When the reaction was repeated with 3l and 3m under the same conditions mentioned above but using a Molar ratio of 1:3:2 of 1:4:4 we obtained essentially the same results. Additionally from the reaction of 3m we obtained the methylene bis 2,4-dichloroaniline (9) (Figure 2) as well as another product which was shown by PMR, probably arose as a result of substitution in the aromatic nucleus followed by cyclization into a condensed bicyclic compound.

IV. Conclusions

1. 2,4,6-triaminopyrimidine (1) reacts under the Mannich conditions with benzylamines to give quantitative yield of the tetrahydropyrimidopyrimidines 5 c-g and with benzylhydroxylamines to give satisfactory yields of compounds of type 5h. With the benzylamines the reaction is acid-base catalyzed whereas with the benzylhydroxylamines it is acid catalyzed.

2. The Mannich reaction of 1 with 3a and its analogs in acid medium or in the absence of excess of Schiff base leads mainly to side products. However, under the conditions that worked out successfully with benzylamines it seems that the reaction proceeds with the formation of the corresponding tetrahydropyrimidopyrimidines (5a). It is likely that these products have low stability and undergo decomposition easily. Therefore, they require special treatment.

3. Attempts to prepare the tetrahydropyrimidopyrimidines of the type 5b and 5j via the Mannich reaction of 1 with the appropriate amine were unsuccessful. Further investigation of this problem has yet to be performed.

4. The tetrahydropyrimidopyrimidine 5k was synthesized by allowing 1 to react with 3k and formalin. Attempts to involve other aromatic amines namely 3l and 3m in a similar reaction were unsuccessful. Further study of the reaction is necessary in order to establish the proper conditions that favor the tetrahydropyrimidopyrimidine formation from 1 and halogenated aromatic amines.

TABLE 1

SUMMARY OF REACTIONS WITH PHENYLETHYLAMINE (3a)

Expt. No.	Forms of Reactants			Molar Ratio 1:3a:2	Procedural Notes	Temp. (in °C)	*Time	Solvent	Product and Result
	1	3a	2						
1	free base	HCl Salt	Trioxy-methylene	1:1:2	Mixed all together	80	Total 9 days	aq. EtOH	Major -Unidentifiable yellow solid insoluble in most common solvents, but dissolves in some organic acids like CH_3COOH, HCOOH, Lactic. Minor -Oil from the reaction filtrate (not characterized)
2	free base	free base	Formalin	1:1:2	Few drops of conc. HCl added to solution of the reactants in EtOH (pH ≃ 4)	80	2 days	aq. EtOH	Major (from reaction filtrate) -Unreacted 1 hydrochloride. -Unreacted 3a hydrochloride. Minor -Unidentifiable yellow solid crystallized from water.
3	free base	HCL Salt	polyoxy-methylene	1:1:1	†The Schiff base was first formed in situ by refluxing the amine hydrochloride with polyoxymethylene in absolute EtOH. It was then treated with a solution of the substrate in EtOH.	room temp 50 80	24 hrs. 24 hrs. 5 days	abs. EtOH abs. EtOH aq. EtOH	Major (from reaction filtrate) -Unreacted 3a. Minor -Unidentifiable solid insoluble in most common solvents (separated only upon refluxing).

TABLE 1 (Cont'd)

Expt. No.	Forms of Reactants			Molar Ratio	Procedural Notes	Temp. (in °C)	*Time	Solvent	Product and Results
	1	3a	2	1:3n:2					
4	HCl Salt	HCl Salt	Formalin	1:1:2	Mixed all together	room temp.	††total 11 days		Major -Unidentifiable white solid gradually changes into a rubber like material upon standing in air.
5	HCl Salt	free base	Formalin	1:1:1	†Schiff base was first formed in situ by shaking the amine with formalin at room temp. for 15 min.	0 room temp.	7 days several weeks	water water & EtOH	Under both conditions the main product is a new substance which is still under investigation.
6	free base	free base	Formalin	1:1:2	†The Schiff base was first formed in situ by refluxing the amine with formalin in EtOH then treated with a solution of the substrate in EtOH	80	3 days	aq. EtOH	Major -Colorless solid from the reaction filtrate. The PMR of which showed only phenyl and CH_2 protons. Minor -Unidentifiable solid insoluble in most common solvents but dissolves in boiling ethanolic HCl from which it was recovered as an oil.
7	free base	free base	Formalin	1:2:2	†The Schiff base was first formed in situ at room temp. then treated with the substrate	room temp.	several weeks	aq. EtOH	-The major product is a new substance which is still under investigation.

* In all experiments except those which were carried out at 0° the course of the reaction has been followed by TLC. The first TLC spots have usually been taken ≈ 2 hr. after starting the reaction. In experiments wich involve the formation of insoluble solids TLC was performed only on the reaction solution.

† The formation of Schiff base was identified by TLC.

†† In this experiment the white solid which separated out after stirring for 24 hr. was filtered. The filtrate after stirring for 10 days was basified and the resulting white solid obtained was filtered. Both solids were unstable in air at room temperature.

TABLE 2

SUMMARY OF REACTIONS WITH p-CHLOROPHENOXYETHYLHYDROXYLAMINE (3b)

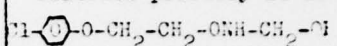
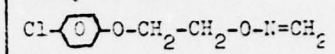
Expt. No.	Forms of Reactants			Molar Ratio 1:3b:2	Procedural Notes	Temp. (in °C)	*Time	Solvent	Product and Results
	1	3b	2						
1	free base	HCl Salt	polyoxy-methylene	1:1:1	All mixed Together	80	Total 7 days	EtOH	Major -Unreacted pyrimidine from the reaction filtrate). -Oil from the reaction filtrate probably it is  or the decomp. product of the reaction filtrate probably of the amine. Minor -Small amount of pale yellow solid from the reaction filtrate probably it is  -Yellow solid insol. in EtOH but dissolves in boiling EtOH-H_2O. It did not receive attention.
2	free base	HCl Salt	Formalin	1:1:1	oxime first formed in situ by refluxing the aryloxyhydroxylamine hydrochloride with formalin in pyridine for 5 hrs. It was then allowed to react with the pyrimidine	temp. of boiling pyridine EtOH mix	Total 7 days	Pyridine (2mL) and EtOH (8mL)	Major -Oil from the reaction filtrate that dissolves in pet. ether (63-75°); it did not receive attention. Minor -Yellow solid insoluble in common solvents. -Pale yellow solid from the reaction filtrate. It's structure is not settled yet.

TABLE 2 (Cont'd)

Expt. No.	Forms of Reactants			Molar Ratio 1:3b:2	Procedural Notes	Temp. (in °C)	Time	Solvent	Product and Results
	1	3b	2						
3	free base	free base	Formalin	1:1:2	Formation of oxime first by refluxing the amine with formalin in a solution of 1.5g NaH_2PO_4 in 5 ml H_2O.	boiling point of a mix EtOH-H_2O containing 1.5g NaH_2PO_4 (1:1)	Total 10 days	EtOH-H_2O combining 1.5g NaH_2PO_4 (1:1)	-Yellow solid not characterized yet. -Small amount of pale yellow solid from the reaction filtrate which showed CH_2 protons only in its NMR spectra.
4	free base	free base	Formalin	1:1:1	All mixed together	80/ under N_2	Total 9 days	EtOH	-2,4,6-triamino-5-hydroxymethylene pyrimidine the amount of which increases with refluxing time. -Unreacted pyrimidine -Unreacted amine or its decomposition product.
5	free base	free base	Trioxymethylene	1:1:2	All mixed together	80/ under N_2	Total 2 days	EtOH	This experiment has not been worked up yet.

TABLE 3

SUMMARY OF REACTIONS WITH BENZYLAMINES (3_{c-g})

Expt. No.	Forms of Reactants			Molar Ratio	Procedural Notes	Temp. (in °C)	*Time	Solvent	% Yield	Products and Result
	1	3	2							
1	free base	3c·HCl	polyoxy-methylene	1:1:1	First formation of the Schiff base by refluxing the amine hydrochloride with the aldehyde for 1½ hrs.	120	Total 8 days	AcOH	---	Major -Insoluble yell solid and pale yellow oil which were not characterized. The yellow soli formed only after 19 hrs. refluxing. Minor -Very poor yiel of 5c.
2	free base	3c	polyoxy-methylene	1:1:1	Formation of Schiff base first by re-fluxing the amine with polyoxymethyl-ene in AcOH for 24 hrs.	80	4 days	EtOH	---	-Insoluble yello solid which di not receive attention. -Unreacted py-rimidine. -Unreacted amin
3	free base	3c·HCl	polyoxy-methylene	1:1:2	Mixed all together	80	24 hrs.	EtOH	--- ≈30%	-Yellow solid i soluble in mos common solvent -5c
4	free base	3c	Formalin	1:1:1	**	80	Total 5 days	EtOH	50 30	-5-Hydroxymethy 2,4,6 -triaminopyrimi dine -5c

** Preliminary formation of Schiff base by shaking the amine with formalin at room temperature for 15 minutes.

TABLE 3 (Cont'd)

Expt. No.	Forms of Reactants			Molar Ratio	Procedural Notes	Temp. (in °C)	*Time	Solvent	Yield	Products and Results
	1	3	2							
5	free base	3c	Formalin	1:2:2	**	80	24 hrs.	EtOH	98	-5c
6	free base	3d	Formalin	1:2:2	**	80	24 hrs.	EtOH	97	-5d
7	free base	3e	Formalin	1:2:2	**	80	24 hrs.	EtOH	92	-5e
8	free base	3f	Formalin	1:2:2	**	80	24 hrs.	EtOH	98	-5f
9	free base	3g	Formalin	1:2:2	**	80	24 hrs.	EtOH	43	-5g

** Preliminary formation of Schiff base by shaking the amine with formalin at room temperature for 15 minutes.

† In all experiments the course of the reaction was followed by TLC four hours after beginning of reflux.

†† The structures for Compounds 5_{c-g} are based on the NMR Data. Analytical data of Compound 5e is consistent with the analized structure.

TABLE 4

SUMMARY OF REACTIONS WITH 2,6-DICHLOROBENZYLHYDROXYLAMINE (3h)

Expt. No.	Forms of Reactants			Molar Ratio	Procedural Notes	Temp. (in °C)	*Time	Solvent	% Yield	Products and Resul
	1	3h	2							
*1	free base	free base	Formalin	1:2:2	Formation of oxime first by stirring the amine with formalin in EtOH	80	Total 2 days	EtOH	---	-A white solid has not been characterized. Probably it is the 5-methyl-hydroxy 2,4,6-triaminopyrimidine. -Unreacted pyrimidine -Unreacted amin or its side product
2	free base	HCl Salt	Formalin	1:2:2	Formation of oxime first by stirring the amine slat with formalin in EtOH	80	24 hrs. or 2 days or 4 days or 7 days	EtOH	---	In all expts. the Major products are -pale yellow oi according to N it is a reacti product contai ing the amine moiety only. -Pale yellow solid which showed only CH protons in NMR -Comp. 5h Minor -Unreacted pyrimidine

*When the product from this experiment was treated with the calculated amount of conc. HCl and refluxing was continued for 5 days, the reaction proceeded with the formation of 5h. Another substance appeared on TLC with R_f value lower than that of 5h. Further work on this experiment is continuing.

LITERATURE CITED

1. J. B. Hynes, W. T. Ashton, H. G. Merriman III, and F. C. Walker III, J. Med. Chem. 17, 682 (1974).

2. J. B. Hynes and W. T. Ashton, J. Med. Chem. 18, 263 (1975).

3. K. E. Kinnamon, A. L. Ager and R. W. Orchard, Experimental Panesitology, 40, 95 (1976).

4. F. I. Carroll, B. Berrang and C. P. Linn, Chem. and Industry, 477 (1975).

5. A. Markovac, M. P. LaMontagne, P. Blumbergs, A. B. Ash, and C. L. Stevens, American Chemical Society, 163rd National Meeting, April 1972.

6. E. F. Elslager, O. D. Bird, J. Clarke, S. C. Perricone, D. F. Worth and J. Davoll, J. Med. Chem. 15, 1138 (1972).

7. A. B. G. Laing, Transactions of the Royal Society of Tropical Medicine and Hygiene, 68, 133 (1974).

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