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SYNTHESIS OF SPIROCYCLIC DERIVATIVES RELATED TO THE BUTYROPHENONE NEUROLEPTICS

by

Leon J. Schiff
Patrick J. Mudd

February 1972

DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Chemical Laboratory
Edgewood Arsenal, Maryland 21010

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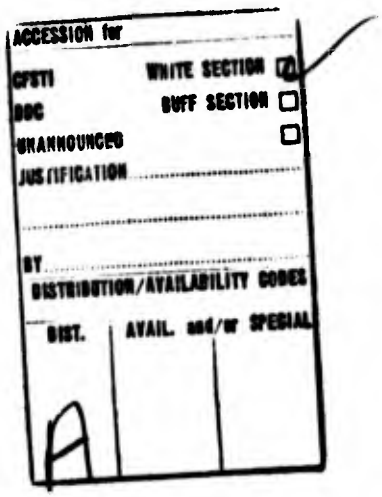

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13. ABSTRACT

(U) A number of analogs related to haloperidol were synthesized and submitted for biological evaluation. In the course of our studies, we were able to develop two novel synthetic procedures: (1) the preparation of ketones by addition of acid chlorides to organocopper compounds, and (2) the two-step preparation of secondary amines from tertiary benzyl amines having a divalent sulfur atom in the molecule.

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SYNTHESIS OF SPIROCYCLIC DERIVATIVES RELATED TO THE BUTYROPHENONE NEUROLEPTICS

by

Leon J. Schiff
Patrick J. Mudd

Chemical Research Division

February 1972

Task 1B562602AD1201

DEPARTMENT OF THE ARMY
EDGEWOOD ARSENAL
Chemical Laboratory
Edgewood Arsenal, Maryland 21010

FOREWORD

The work described in this report was performed under Task 1B562602AD1201, Incapacitating Agent Investigations. The experimental data are contained in notebooks 8100, 8111, and 8344. The work was begun 6 January 1969 and completed 2 March 1970.

In conducting the research described in this report, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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We wish to thank the following members of the branches of Chemical Research Division, Chemical Laboratory, Edgewood Arsenal, who assisted the authors in the performance and interpretation of the work presented in this report:

Organic Chemistry Branch: Mr. W. J. Lennox for the mouse screening data.

Analytical Chemistry Branch for providing elemental analyses.

Physical Chemistry Branch: Mr. H. Klapper and Mrs. L. Szafraniec for NMR spectral determinations, and Mr. L. Daasch and Mr. J. Weber for mass spectral determinations.

DIGEST

A number of analogs related to haloperidol were synthesized and submitted for biological evaluation.

In the course of our studies, we were able to develop two novel synthetic procedures: (1) the preparation of ketones by addition of acid chlorides to organocopper compounds and (2) the two-step preparation of secondary amines from tertiary benzyl amines having a divalent sulfur atom in the molecule.

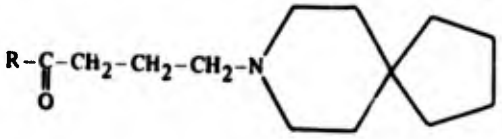
CONTENTS

SYNTHESIS OF SPIROCYCLIC DERIVATIVES RELATED TO THE BUTYROPHENONE NEUROLEPTICS

I. INTRODUCTION.

The butyrophenone series of neuroleptic drugs originated in the laboratories of P.A.J. Janssen, Belgium.[1] Our goal was to modify the butyrophenone skeleton so that the biological activity of these compounds would be greatly enhanced.

Most of the potent compounds in this series possess the general structure, I,

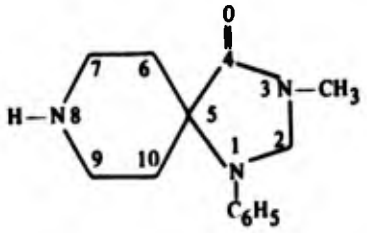


I

in which R is p-fluorophenyl (4-F-C_6H_4) or 2-thienyl () and the five-membered ring of the spirocyclic fragment usually contains at least one carbonyl group along with two other heteroatoms, one of which is a nitrogen atom. The work that is presented in this report is a summary of our efforts to alter the nature of the R group and the five-membered ring of structure I.

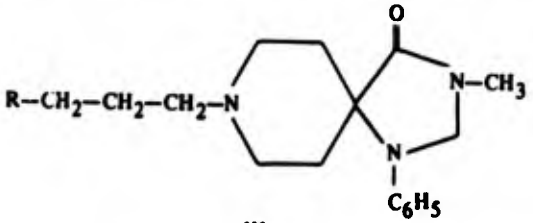
II. PROCEDURES AND RESULTS.

Our initial efforts were concerned with the synthesis of compounds containing the commercially available (Aldrich Chemical Company) 3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro-[4.5]decane fragment II.

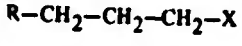


II

Products having the basic structural unit III were prepared by condensation of II with compounds having the general structure IV, where X is a halogen atom.



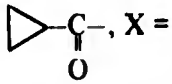
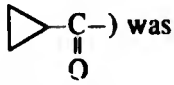
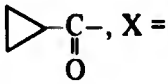
III



IV

[1] Janssen, P.A.J. Haloperidol and Related Butyrophenones in Medicinal Chemistry. Vol 4. Part II. p 199. Gordon, M., ed. Academic Press, New York, New York. 1967.

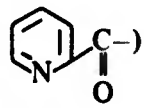
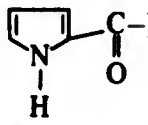
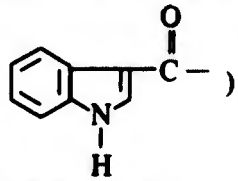
The compounds, EA 5167, 8-[3-carbethoxypropyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]-decane (III, R = $COOC_2H_5$), and EA 5194, 8-[3-cyanopropyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane (III, R = CN), were synthesized by the reaction of II with the commercially available ethyl 4-bromobutyrate (IV, R = $CO_2C_2H_5$, X = Br) and 4-bromobutyronitrile (IV, R = CN, X = Br), respectively. The reaction of diethylamine with 4-chlorobutyryl chloride readily afforded N,N-diethyl-4-chlorobutyramide (IV, R = $-\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2$, X = Cl), which upon condensation with II provided EA 5211, 8-[3-(N,N-diethylcarbamoyl)propyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane (III, R = $-\overset{O}{\overset{\|}{C}}-N(C_2H_5)_2$).

The addition of 4-chlorobutyronitrile to the Grignard reagent derived from cyclopropyl bromide resulted in the formation of 4-chlorobutyrylcyclopropane (IV, R =  , X = Cl). The product, EA 5225, 8-[3-(cyclopropylcarbonyl)propyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro-[4.5]decane, (III, R = ) was isolated from the reaction of IV (R =  , X = Cl) with II.

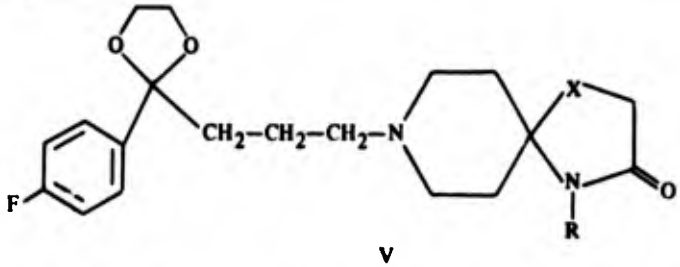
The presence of an aromatic fluorine substituent (e.g., III, R = $4-F-C_6H_4-\overset{O}{\overset{\|}{C}}-$) in some of the more active compounds in this series[1] made us feel that the incorporation of a trifluoromethyl (CF_3) group or additional fluorine atoms into the aromatic nucleus should produce a more effective chemical agent. Accordingly, addition of 4-chlorobutyryl chloride (IV, R = $\overset{O}{\overset{\|}{C}}-Cl$, X = Cl) to p-trifluoromethylphenyl copper ($4-CF_3-C_6H_4Cu$), prepared from p-trifluoromethyl magnesium bromide ($4-CF_3-C_6H_4MgBr$) and cuprous iodide, readily afforded p-(4-chlorobutyryl)benzotrifluoride (IV, R = $4-CF_3-C_6H_4-\overset{O}{\overset{\|}{C}}-$, X = Cl). The identical reaction of the acid chloride with pentafluorophenyl copper (C_6F_5Cu) provided 4-chlorobutyrylpentafluorobenzene (IV, R = $C_6F_5-\overset{O}{\overset{\|}{C}}-$, X = Cl). Prior to its reaction with II, it was necessary to convert the carbonyl group of 4-chlorobutyrylpentafluorobenzene to an ethylene ketal derivative (IV, R = $C_6F_5-\overset{O}{\overset{O}{\diagdown\diagup}}C-$, X = Cl) with ethylene glycol. This step was taken to prevent the nucleophilic displacement of ring substituted ortho and para fluorine atoms by secondary amines, when a carbonyl group is in direct conjugation with an aromatic ring.[2] In order to preclude any unexpected side reactions with II, p-(4-chlorobutyryl)benzotrifluoride (IV, R = $4-CF_3-C_6H_4-\overset{O}{\overset{\|}{C}}-$, X = Cl) was also converted into an ethylene

[2]Bader, H., Hansen, A. R., and McCarty, F. J. Nucleophilic Displacements of Activated Fluorine in Aromatic Compounds. J. Org. Chem. *31*, 2319 (1966).

ketal derivative (IV, R = 4–CF_3–C_6H_4–  , X = Cl). Subsequent condensation of these ketals with II gave EA 5340, 8-[4-(pentafluorophenyl)-4,4-ethylenedioxy-1-butyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane (III, R = C_6F_5–  , and EA 5309, 8-[4-(p-trifluoromethylphenyl)-4,4-ethylenedioxy-1-butyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane (III, R = 4–$CF_3C_6H_4$– ).

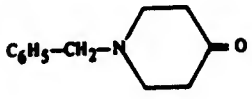
Other attempts to introduce heterocyclic nuclei into compounds of type III were uniformly unsuccessful. Our repeated failure to prepare the required precursors IV in which R would be 2-pyridoyl (), 2-pyrroyl (), or 3-indoloyl () made us abandon this approach toward the modification of the basic butyrophenone structure.

Another aspect that had been under investigation was the alteration of the nature and position of the heteroatoms in the five-membered ring of the spirocyclic fragment in structure I. Our efforts were directed toward the synthesis of materials that possess the structure V in which R may be a hydrogen atom or an alkyl or aryl substituent and X may be an oxygen, sulfur, or substituted nitrogen atom.

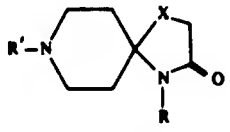


V

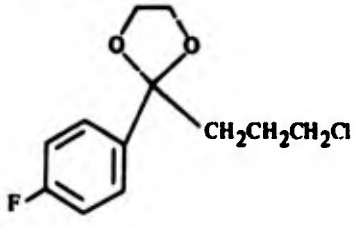
The synthetic scheme began with the reaction of 1-benzyl-4-piperidone (VI) with a number of different compounds to produce the spirocyclic skeleton VII (R′ = C_6H_5–CH_2–). Debenzylation by catalytic hydrogenolysis resulted in VII (R′ = H), which was then condensed with the ethylene ketal of γ-chloro-p-fluorobutyrophenone (VIII) to give compounds with the structure V.



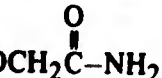
VI



VII



VIII

By continuously removing the water that was formed in the reaction between hydroxyacetamide () and VI, we were able to isolate 8-benzyl-1-oxa-4,8-diazaspiro[4.5]decan-3-one (VII, R′ = $C_6H_5CH_2$, R = H, X = O). Removal of the benzyl group gave VII, R = R′ = H, X = O), which was converted to EA 5310, 8-[4-(p-fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-oxa-4,8-diazaspiro[4.5]decan-3-one (V, R = H, X = O).

In a similar reaction, VI was condensed with mercaptoacetic acid ($HSCH_2CO_2H$) and ammonium carbonate to form 8-benzyl-1-thia-4,8-diazaspiro[4.5]decan-3-one (VII, $R' = C_6H_5CH_2$, $R' = H$, $X = S$). Catalytic hydrogenolysis of the benzyl group of this molecule was ineffective since the presence of a sulfur atom had apparently poisoned the palladium catalyst. The alkyl group was subsequently removed by a two-step procedure in which the benzyl group was first displaced by a carbobenzyloxy group (VII, $R' = C_6H_5CH_2-O-\overset{O}{\overset{\|}{C}}-$, $R = H$, $X = S$) in a reaction with benzyl chloroformate $C_6H_5CH_2O-\overset{O}{\overset{\|}{C}}-Cl$).[3] Treatment of the carbobenzyloxy derivative with triethylsilane, a reagent that selectively replaces carbobenzyloxy groups with hydrogen,[4] gave the desired intermediate VII ($R = R' = H$, $X = S$) which was condensed with VIII to give EA 5320, 8-[4-(p-fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-thia-4,8-diazaspiro[4.5]decan-3-one (V, $R = H$, $X = S$).

Compounds possessing the 1,4,8-triazaspiro[4.5]decan-3-one skeleton (VII, $R = H$, $R' = C_6H_5CH_2-$, $X = NR''$) were prepared by the reaction of VI with an appropriately substituted aminoacetonitrile (IX) in the presence of a base.[5]

$$R-NH-CH_2-CN$$

IX

Aminoacetonitrile (IX, $R = H$) and N-methylaminoacetonitrile (IX, $R = CH_3$) were obtained by neutralization of their respective hydrochloride salts, while anilinoacetonitrile (IX, $R = C_6H_5$) was prepared by treating aniline with cyanomethyl p-toluenesulfonate.[6] N,N-dimethyl-N'-cyanomethylhydrazine (IX, $R = -N(CH_3)_2$) was formed in the reaction of N,N-dimethylhydrazine with aqueous formaldehyde and potassium cyanide.[7] The spirocyclic derivatives 8-benzyl-1,4,8-triazaspiro[4.5]decan-3-one (VII, $R = H$, $R' = C_6H_5-CH_2-$, $X = -NH$), 8-benzyl-1-methyl-1,4,8-triazaspiro[4.5]decan-3-one (VII, $R = H$, $R' = C_6H_5-CH_2-$, $X = -NCH_3$), 8-benzyl-1-phenyl-1,4,8-triazaspiro[4.5]decan-3-one (VII, $R = H$, $R' = C_6H_5-CH_2-$, $X = -NC_6H_5$), and 8-benzyl-1-dimethylamino-1,4,8-triazaspiro[4.5]decan-3-one (VII, $R = H$, $R' = C_6H_5-CH_2-$, $X = N-N(CH_3)_2$) were readily isolated from the condensation of the ketone VI with the various nitriles (IX). Hydrogenolysis afforded the debenzylated methyl (VII, $R = R' = H$, $X = NCH_3$ and the debenzylated phenyl (VII, $R = R' = H$, $X = NC_6H_5$) derivatives. We were unable to obtain the unsubstituted or dimethylamino compounds by this reaction. Displacement of the chlorine atom of VIII by the secondary amines (VII, $R = R' = H$, $X = NCH_3$ or NC_6H_5) produced adequate amounts of EA 5355, 8-[4-(p-fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-methyl-1,4,8-triazaspiro[4.5]decan-3-one (V, $R = H$, $X = NCH_3$), and EA 5360, 8-[4-(p-fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-phenyl-1,4,8-triazaspiro[4.5]decan-3-one (V, $R = H$, $X = NC_6H_5$).

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[3] Wright, W. B., and Brabender, H. J. Debenzylation of Tertiary Benzyl Amines With Ethyl Chloroformate. J. Org. Chem. *26*, 4057 (1961).

[4] Birkofer, L., Bierwirth, E., and Ritter, A. Decarbobenzoxylation with Triethylsilane. Chem. Ber. *94*, 821 (1961).

[5] Davis, A. C., and Levy, A. L. The Interaction of α-Aminonitriles and Aldehydes and Ketones. J. Chem. Soc., 3479 (1951).

[6] Grudzinski, S. Application of Cyanomethyl Benzenesulfonate as a New Cyanomethylating Agent. II. Cyanomethylation of Primary Aliphatic and Aromatic Amines. Acta Pol. Pharm. *24*, 1 (1967); C.A.: 67, 73112f.

[7] Masuda, K., and Imashiro, Y. Sydnonimine Derivatives. US Patent 3,312,690. 4 April 1967.

III. DISCUSSION.

Most of the synthetic procedures that have been described in the preceding section are well documented and do not require further elaboration. However, there are some reactions about which a few comments are in order. In particular, one should note the preparation of ketones in respectable yields from the reaction of an acid chloride with an organocopper reagent. The generally prescribed method for this conversion, which utilizes an organocadmium intermediate, failed to provide any of the desired products. The fact that cuprous iodide is less hygroscopic and has a longer shelf life than cadmium chloride seems to offer a reasonable explanation for this difference in behavior. These results suggest that the addition of acid chlorides to organocopper compounds is a very reliable method for the preparation of ketones.

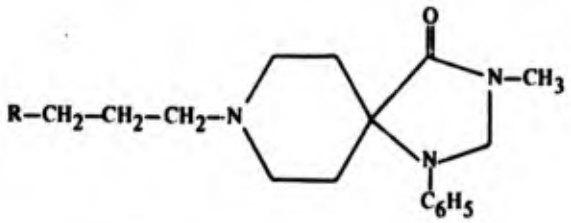
The two-step transformation of a tertiary benzylamine (VII, R = H, R′ = C_6H_5-CH_2-, X = S) into a secondary amine (VII, R = R′ = H, X = S) is a new synthetic procedure that we have developed. Benzyl groups are normally removed from nitrogen by catalytic hydrogenolysis, but the presence of a divalent sulfur atom in the molecule destroys the activity of the catalyst and renders this method ineffective. Since ethyl chloroformate had been found to displace benzyl groups from tertiary benzyl amines,[3] we believed that benzyl chloroformate would behave in a similar fashion. Not only did the reaction with benzyl chloroformate proceed in a facile manner but the near quantitative yield (98%) came as a very pleasant surprise. Benzyl chloroformate is preferred in this reaction sequence because of the relative ease in replacing carbobenzyloxy groups with hydrogen. By refluxing in triethylsilane, we were able to convert the carbobenzyloxy amide into a secondary amine.[4] This procedure should find application in other sulfur-containing tertiary benzyl amines where removal of the benzyl group is desired.

Structure elucidation of the various compounds that have been described was achieved with the aid of infrared (IR), nuclear magnetic resonance (NMR), and mass spectroscopy (MS). The IR spectra of compounds of types III and V have an absorption band in the 2820 cm^{-1} region, which is characteristic of a tertiary amine group. The presence of two triplets and a multiplet each integrating for two protons in the NMR spectra of the butyrophenone intermediates IV was strong evidence for a structure with three adjacent methylene groups flanked by a carbonyl group and a chlorine atom. A two-proton singlet that was attributed to a methylene group situated between a carbonyl group and a heteroatom was found in the spectra of the spirocyclic intermediates VII and the butyrophenone products V.

All the compounds having structures III and V were submitted for pharmacological evaluation. Table I summarizes the toxicity screening data for type III compounds, and table II summarizes the screening data for type V compounds.

A survey of the screening data in tables I and II reveals that while most of the compounds tested had some effect upon the behavior of the animal, none was sufficiently potent to merit further consideration as potential incapacitating agents.

Table I. Toxicity Screening Data for Compounds With the General Structure



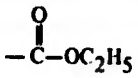
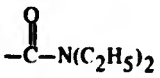
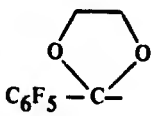
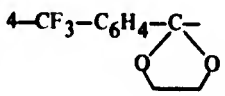
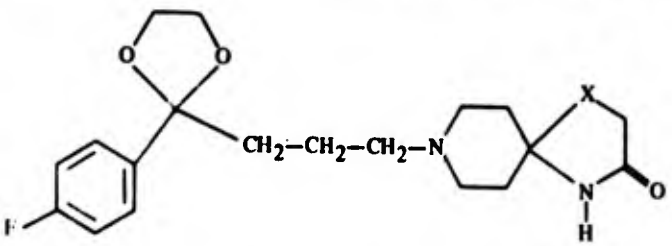
EA No.	R	Toxicity, iv, mice		Type activity
		LD50	MED50	
		mg/kg		
5167		32.0	0.56	Decreased activity
5194		>20.0	5.6	Decreased activity
5211		14.0	1.8	Decreased activity
5225		10.0	0.56	Decreased activity
5340		>20.0	1.0	Catalepsy
5309		14.0	1.8	Decreased activity

Table II. Toxicity Screening Data for Compounds With the General Structure



EA No.	X	Toxicity, iv, mice		Type activity
		LD50	MED50	
		mg/kg		
5310	O	>20.0	>20.0	No effect
5320	S	>20.0	5.6	Decreased activity
5355	$-NCH_3$	>20.0	>20.0	No effect
5360	$-NC_6H_5$	>10.0	0.56	Decreased activity

IV. EXPERIMENTATION.

The IR spectra were recorded on a Perkin-Elmer Infracord Model 237B. The NMR spectra were obtained on a Varian A-60 spectrometer. Chemical shifts are reported in δ parts per million (ppm) relative to tetramethylsilane as an internal standard. Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E spectrometer.

Melting points were taken on a Thomas-Hoover melting point apparatus and are uncorrected.

Elemental analyses were performed in the Micro Analytical Laboratory, Analytical Chemistry Branch, Chemical Research Division, Chemical Laboratory, Edgewood Arsenal.

8-[3-Carbethoxypropyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane, EA 5176

A mixture of 2.82 gm (0.0100 mole) of 3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5] decane hydrochloride, 1.95 gm (0.0100 mole) of ethyl 4-bromobutyrate, 3.18 gm (0.0300 mole) of sodium carbonate, and a few crystals of potassium iodide in 100 ml of 4-methyl-2-pentanone was placed under reflux for 69 hr. After cooling, the reaction mixture was filtered, and the filtrate was washed twice with 50 ml of water and once with 75 ml of saturated salt solution and dried ($MgSO_4$). The drying agent was filtered off, and the solvent was evaporated under reduced pressure. The residual oil was crystallized by adding 10 ml of petroleum ether (bp 30-60°C) and cooling in a dry ice-acetone bath. Recrystallization from petroleum ether, which included treatment with charcoal, gave 2.30 gm (64.1%) of the white solid product, mp 76.5° to 77.5°C.

Anal. Calcd for $C_{20}H_{29}N_3O_3$: C, 66.8; H, 8.1; N, 11.7.

Found: C, 66.7; H, 7.9; N, 11.6.

8-[3-Cyanopropyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane, EA 5194

A mixture of 28.2 gm (0.100 mole) of 3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]-decane hydrochloride, 14.8 gm (0.100 mole) of 4-bromobutyronitrile, 31.8 gm (0.300 mole) of sodium carbonate, and a few crystals of potassium iodide in 500 ml of 4-methyl-2-pentanone was placed under reflux for 88 hr. The reaction mixture was worked up in a manner identical to that of EA 5167 (see above). Evaporation of the solvent left an oil, which crystallized on standing. Recrystallization from methylene chloride-hexane afforded 24.7 gm (79.2%) of the solid product, mp 117° to 120°C.

Anal. Calcd for $C_{18}H_{24}N_4O$: C, 69.2; H, 7.7; N, 17.9.

Found: C, 69.4; H, 8.0; N, 17.9.

N,N-Diethyl-4-chlorobutyramide

A solution of 14.6 gm (0.200 mole) of diethylamine in 10 ml of ether was added dropwise to an ice-cooled solution of 14.1 gm (0.100 mole) of 4-chlorobutyryl chloride in 50 ml of ether. After the addition was complete, the reaction mixture was filtered and the salt was washed

with ether. The filtrate and washings were combined and washed with 50 ml of 0.1 N hydrochloric acid, 50 ml of saturated sodium bicarbonate solution, and twice with 50 ml of water and dried ($MgSO_4$). The drying agent was removed by filtration, and the solvent was evaporated under reduced pressure. The residual oil was distilled to give 11.0 gm (61.9%) of the desired product, bp 92° to 96°C (0.3 mm) (bp 101° to 103°C (3 mm)[8]). The IR spectrum was consistent with the proposed structure.

8-[3-(N,N-Diethylcarbamoyl)propyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]-decane, EA 5211

A mixture of 7.14 gm (0.0401 mole) of N,N-diethyl-4-chlorobutyramide, 11.3 gm (0.0401 mole) of 3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane, 8.50 gm (0.0802 mole) of sodium carbonate, and a few crystals of potassium iodide in 250 ml of 4-methyl-2-pentanone was placed under reflux for 69 hr. The reaction mixture was worked up in a manner identical to that of EA 5167 (see above). The dark oily residue was purified by chromatography on neutral alumina (Woelm Activity 1). The product was eluted with benzene and recrystallized from hexane to give 6.30 gm (40.6%) of white crystals, mp 106° to 109°C.

Anal. Calcd for $C_{22}H_{34}N_4O_2$: C, 68.4; H, 8.9; N, 14.5.

Found: C, 68.7; H, 8.8; N, 14.2.

4-Chlorobutyrylcyclopropane

A solution of 14.5 gm (0.120 mole) of cyclopropyl bromide in 100 ml of dry ether was added dropwise to 2.60 gm (0.107 gm-at.) of magnesium turnings in a nitrogen atmosphere over a 1-hr period. After refluxing for 2 hr, the reaction mixture was cooled to room temperature, and a solution of 10.4 gm (0.100 mole) of 4-chlorobutyronitrile in 25 ml of ether was added dropwise over 15 min. Refluxing was continued for an additional 3 hr. The mixture was decomposed at room temperature by the addition of 2.5 ml of saturated ammonium chloride solution. The solids were filtered, and the filtrate was dried over magnesium sulfate. The drying agent was removed, and the solvent evaporated under reduced pressure. The residual oil was distilled and 3.10 gm (21.2%) of the desired product, bp 43° to 46°C (0.25 mm), was collected. The IR and NMR spectra were consistent with the proposed structure.

8-[3-(Cyclopropylcarbonyl)propyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]-decane, EA 5225

A mixture of 5.6 gm (0.020 mole) of 3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]-decane hydrochloride, 2.9 gm (0.020 mole) of 4-chlorobutyrylcyclopropane, 6.2 gm (0.040 mole) of sodium carbonate, and a few crystals of potassium iodide in 150 ml of 4-methyl-2-pentanone was refluxed for 22 hr. The reaction mixture was worked up in the same way as EA 5167 (see above). The residual dark oil was chromatographed on neutral alumina (Woelm Activity 1). Elution with

[8]Schlesinger, A. H., and Prill, E. J. N-Substituted Amides. J. Amer. Chem. Soc. *78*, 6123 (1956).

benzene gave a crystalline material. Recrystallization from benzene-hexane produced 3.2 gm (45%) of the product as white needles, mp 129° to 131°C.

Anal. Calcd for $C_{21}H_{29}N_3O_2$: C, 71.0; H, 8.2; N, 11.8.

Found: C, 70.7; H, 7.9; N, 11.8.

4-Chlorobutyrylpentafluorobenzene

Into a 3-neck round-bottom flask kept under nitrogen were introduced 1.2 gm (0.050 gm-at.) of magnesium turnings, 25 ml of dry tetrahydrofuran (THF), and about 6 drops of 1,2-dibromoethane. When the solution became cloudy, it was cooled in an ice bath, and a solution of 12.4 gm (0.0500 mole) of bromopentafluorobenzene in 10 ml of dry THF was added dropwise, with stirring. After 2 hr of stirring, 11.4 gm (0.0600 mole) of cuprous iodide was added, and the reaction was allowed to warm to room temperature over a 1-hr period. To this dark solution, a solution of 7.1 gm (0.050 mole) of 4-chlorobutyryl chloride in 10 ml of dry THF was added. Stirring was continued for 90 min, and the reaction was decomposed by addition of 10 ml of saturated ammonium chloride solution. The solids were removed by filtration through Celite, and the filtrate was washed with 25 ml of dilute ammonia, three 50-ml portions of water, and 50 ml of saturated salt solution. After drying, the solution was filtered to remove the drying agent, and the solvent was evaporated under reduced pressure to leave a dark oil which was distilled to give 9.3 gm (68%) of the slightly yellow liquid product, bp 82° to 85°C (0.005 mm). The IR and NMR spectra were consistent with the proposed structure.

p-(4-Chlorobutyryl)benzotrifluoride

Utilizing virtually the same procedure as that for the pentafluorophenyl derivative (see above), a Grignard reagent was prepared from 45 gm (0.20 mole) of p-bromobenzotrifluoride and 4.8 gm (0.20 gm-at.) of magnesium in 100 ml of THF in a 250-ml round-bottom flask. Cuprous iodide (38 gm, 0.20 mole) and 4-chlorobutyryl chloride (28 gm, 0.20 mole) were added, with cooling. The mixture was decomposed with 25 ml of ammonium chloride solution and worked up in a manner identical to that of the pentafluorophenyl compound. Distillation produced 12 gm (24%) of the desired product, bp 100° to 108°C (0.015 mm). The IR and NMR spectra were consistent with the proposed structure.

2-(3-Chloropropyl)-2-(pentafluorophenyl)dioxolane

In a 200-ml round-bottom flask fitted with a Dean-Stark water separator were placed 2.74 gm (0.0100 mole) of 4-chlorobutyrylpentafluorobenzene and 4 ml (0.002 mole) of ethylene glycol in 100 ml of trichloroethylene. Boron trifluoride etherate (1 ml) was added, and the mixture was allowed to stir at reflux for 48 hr or until gas chromatography showed that the ketal was the major component. The reaction mixture was cooled and then washed with 100 ml of saturated sodium bicarbonate solution, two 100-ml portions of water, and 100 ml of saturated salt solution. The solution was dried over magnesium sulfate, and the solvent was removed under reduced pressure. The residue was distilled to give 2.78 gm (87.6%) of the liquid product, bp 104° to 106°C (0.004 mm). The IR and NMR spectra were consistent with the proposed structure.

2-(3-Chloropropyl)-2-(p-trifluoromethylphenyl)dioxolane

A 200-ml round-bottom flask was charged with 2.5 gm (0.040 mole) of ethylene glycol and 0.150 gm of p-toluenesulfonic acid in 100 ml of benzene. After refluxing for an hour under a Dean-Stark trap, 5.9 gm (0.020 mole) of p-(4-chlorobutyryl)benzotrifluoride was added and the mixture was refluxed for an additional 48 hr or until gas chromatography showed that the ketal was the major component. The reaction mixture was worked up in a manner identical to that of the pentafluorophenyl compound (see above). Distillation afforded 4.9 gm (82%) of the liquid product, bp 100° to 103°C (0.002 mm). The IR and NMR spectra were consistent with the proposed structure.

8-[4-(p-Trifluoromethylphenyl)-4,4-ethylenedioxy-1-butyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane, EA 5309

A mixture of 2.94 gm (0.0100 mole) of 2-(3-chloropropyl)-2-(p-trifluoromethylphenyl) dioxolane, 2.82 gm (0.0100 mole) of 3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane hydrochloride, 1.66 gm (0.0100 mole) of potassium iodide, and 3.20 gm (0.0200 mole) of potassium carbonate in 30 ml of dry dimethylformamide was heated at 90° for 24 hr. The reaction mixture was cooled and filtered, and the filtrate was poured into a separatory funnel containing 100 ml of water and 100 ml of methylene chloride. The organic layer was separated, washed with two 50-ml portions of water, and 50 ml of a saturated salt solution, and dried over magnesium sulfate. Removal of the drying agent, followed by evaporation of the solvent under reduced pressure, left a dark oil, which was chromatographed on neutral alumina (Woelm Activity 1). Elution with ether afforded a crystalline product. Recrystallization from methylene chloride-hexane gave 1.0 gm (20%) of the product as white needles, mp 123° to 124°C.

Anal. Calcd for $C_{27}H_{32}F_3N_3O_3$: C, 64.4; H, 6.4; F, 11.3; N, 8.4.

Found: C, 64.2; H, 6.5; F, 11.3; N, 8.2.

8-[4-Pentafluorophenyl-4,4-ethylenedioxy-1-butyl]-3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane, EA 5340

A mixture of 1.27 gm (4.00 mmole) of 2-(3-chloropropyl)-2-pentafluorophenyldioxolane, 1.13 gm (4.00 mmole) of 3-methyl-4-oxo-1-phenyl-1,3,8-triazaspiro[4.5]decane hydrochloride, 0.664 gm (4.00 mmole) of potassium iodide, and 1.28 gm (9.00 mmole) of potassium carbonate in 15 ml of dry dimethylformamide was kept at 100° for 17 hr. The reaction mixture was worked up in a manner identical to that of EA 5309 (see above). The oily residue was chromatographed on neutral alumina (Woelm Activity 1) and a small amount of product was eluted with methylene chloride. Recrystallization from methylene chloride-hexane gave 0.13 gm (6.2%) of a white solid product, mp 114° to 116°C. A mass spectral analysis indicated a molecular weight of 525 (calcd molecular weight, 525).

Anal. Calcd for $C_{26}H_{28}F_5N_3O_3$: C, 59.4; H, 5.4; F, 18.1; N, 8.0.

Found: C, 59.5; H, 5.5; F, 18.3; N, 7.8.

8-Benzyl-1-oxa-4,8-diazaspiro[4.5]decan-3-one

Into a 500-ml round-bottom flask fitted with a Soxhlet apparatus containing a thimble filled with calcium chloride were introduced 38.0 gm (0.200 mole) of 1-benzyl-4-piperidone, 15.0 gm (0.200 mole) of hydroxyacetamide (prepared according to Gucker and Ford[9] in 74% yield), 11.2 ml (0.400 mole) of concentrated sulfuric acid, and 350 ml of chloroform. The contents were stirred at reflux for 24 hr. After cooling, the mixture was washed twice with 250-ml portions of saturated sodium bicarbonate solution, two 250-ml portions of water, and 250 ml of a saturated sodium chloride solution. The mixture was dried over magnesium sulfate and, after removal of the drying agent, the solvent was evaporated under reduced pressure to leave a crude solid. This material was taken up in 100 ml of ethanol and treated with activated charcoal. Recrystallization from benzene-hexane gave 27 gm (70%) of the white solid product, mp 147° to 149°C. The IR and NMR spectra were consistent with the proposed structure.

1-Oxa-4,8-diazaspiro[4.5]decan-3-one

A solution of 13 gm (0.050 mole) of 8-benzyl-1-oxa-4,8-diazaspiro[4.5]decan-3-one in 125 ml of ethanol along with 1.2 gm of a 5% palladium on carbon catalyst was placed under a hydrogen atmosphere of 55 psig at 60° in a Paar apparatus. After shaking overnight, the catalyst was removed, and the solvent was evaporated under vacuum to leave a crystalline residue. The crystals were washed with methylene chloride, and 5.1 gm (61%) of product, mp >200° (decomposition), was collected on a filter. The IR and NMR spectra were consistent with the proposed structure.

8-[4-(p-Fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-oxa-4,8-diazaspiro[4.5]decan-3-one, EA 5310

A mixture of 1.22 gm (5.00 mole) of 2-(3-chloropropyl)-2-(p-fluorophenyl)dioxolane, 0.780 gm (5.00 mmole) of 1-oxa-4,8-diazaspiro[4.5]decan-3-one, 0.830 gm (5.00 mmole) of potassium iodide, and 1.28 gm (8.00 mmole) of potassium carbonate in 30 ml of dry dimethylformamide was kept at 100° for 67 hr. The reaction mixture was worked up in a manner similar to that of EA 5309 (see above). Evaporation of the solvent left a crystalline residue, which was recrystallized from methylene chloride-hexane to give 0.32 gm (18%) of the desired product, mp 123° to 125°C.

Anal. Calcd for $C_{19}H_{25}FN_2O_4$: C, 62.6; H, 6.9; F, 5.2; N, 7.7.

Found: C, 62.6; H, 6.8; F, 5.2; N, 7.5.

8-Benzyl-1-thia-4,8-diazaspiro[4.5]decan-3-one

In a 250-ml round-bottom flask equipped with a Dean-Stark trap were placed 18.9 gm (0.100 mole) of 1-benzyl-4-piperidone, 7.5 ml (0.10 mole) of mercaptoacetic acid, and 6.0 gm (0.050 mole) of ammonium carbonate in 150 ml of benzene. The mixture was stirred at reflux for 48 hr and worked up in a manner identical to that of the oxygen-substituted analog (see above). Recrystallization from acetone afforded 6.5 gm (70%) of the desired product, mp 179° to 180°C. The IR and NMR spectra were consistent with the proposed structure.

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[9]Gucker, F. T., and Ford, W. L. The Apparent and Partial Molal Heat Capacities and Volumes of Glycine and Glycolamide. J. Phys. Chem. *45*, 309 (1941).

8-Carbobenzyloxy-1-thia-4,8-diazaspiro[4.5]decan-3-one

A solution of 13.1 gm (0.0500 mole) of 8-benzyl-1-thia-4,8-diazaspiro[4.5]decan-3-one and 10.2 gm (0.0600 mole) of benzyl chloroformate in 250 ml of dry toluene was refluxed for 48 hr. The mixture was cooled and washed with 100 ml of saturated sodium bicarbonate solution, 100 ml of water, and 100 ml of saturated salt solution. After drying ($MgSO_4$), the solvent was removed under vacuum. The solid residue was washed with hexane to give 15 gm (98%) of the desired product, mp 127° to 128°C. The IR and NMR spectra were consistent with the proposed structure.

1-Thia-4,8-diazaspiro[4.5]decan-3-one

A mixture of 15.3 gm (0.0500 mole) of 8-carbobenzyloxy-1-thia-4,8-diazaspiro[4.5]decan-3-one, 56.6 gm (0.400 mole) of triethylsilane, 250 mg of palladium chloride, and 10 drops of triethylamine was refluxed for 70 hr. After cooling, 50 ml of methanol was added and all volatiles were removed under reduced pressure. The solid residue was recrystallized from methanol to give 6.0 gm (68%) of the desired product, mp 225° to 227°C. The IR spectrum was consistent with the proposed structure. Mass spectral molecular weight, 172 (calcd molecular weight, 172).

8-[4-(p-Fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-thia-4,8-diazaspiro[4.5]decan-3-one, EA 5320

A mixture of 4.89 gm (0.0200 mole) of 2-(3-chloropropyl)-2-(p-fluorophenyl)dioxolane, 3.44 gm (0.0200 mole) of 1-thia-4,8-diazaspiro[4.5]decan-3-one, 3.32 gm (0.0200 mole) of potassium iodide, and 4.14 gm (0.0300 mole) of potassium carbonate in 60 ml of dry dimethylformamide was kept at 125°C for 69 hr. The workup was identical to that of EA 5309 (see above). The dark solid residue was chromatographed on neutral alumina (Woelm Activity 1). The product was eluted with ether and recrystallized from methylene chloride-hexane to give 2.17 gm (29.4%) of a white solid, mp 147° to 149°C.

Anal. Calcd for $C_{19}H_{25}FN_2O_3S$: C, 60.0; H, 6.6; N, 7.4; S, 8.4.

Found: C, 59.8; H, 6.9; N, 7.1; S, 8.3.

8-Benzyl-1,4,8-triazaspiro[4.5]decan-3-one

A mixture of 3.8 gm (0.068 mole) of aminoacetonitrile and 12.8 gm (0.0680 mole) of 1-benzyl-4-piperidone was cooled to 0°C and treated with 1 ml of a solution prepared from 0.5 gm of sodium and 5 ml of methyl alcohol. After 5 min, acetone was added and the crude product was crystallized. Recrystallization from methylene chloride-hexane afforded 9.5 gm (57%) of the desired product, mp 173° to 175°C. The IR and NMR spectra were consistent with the proposed structure.

8-Benzyl-1-methyl-1,4,8-triazaspiro[4.5]decan-3-one

To a mixture of 7.00 gm (0.100 mole) of N-methylaminoacetonitrile and 18.9 gm (0.100 mole) of 1-benzyl-4-piperidone kept at 0° was added 1 ml of a solution prepared from 0.5 gm of sodium and 5 ml of methanol. There was a sudden rise in temperature, and the product began to crystallize. Recrystallization from methanol afforded 19.7 gm (76.2%) of the desired product, mp187° to 189°C. The IR and NMR spectra were consistent with the proposed structure.

8-Benzyl-1-phenyl-1,4,8-triazaspiro[4.5]decan-3-one

To a mixture of 5.0 gm (0.038 mole) of N-phenylaminoacetonitrile and 6.5 gm (0.035 mole) of 1-benzyl-4-piperidone kept at 0° was added 1 ml of a solution prepared from 0.5 gm of sodium and 5 ml of methanol. The reaction was allowed to warm to room temperature and then was heated at 90° for 15 min. After cooling, the solid was collected on a filter and recrystallized from methanol to give 2.1 gm (20%) of the desired product, mp 215° to 219°C. Mass spectral molecular weight, 321 (calcd molecular weight, 321). The IR spectrum was consistent with the proposed structure.

8-Benzyl-1-dimethylamino-1,4,8-triazaspiro[4.5]decan-3-one

To a mixture of 9.5 gm (0.050 mole) of 1-benzyl-4-piperidone and 5.0 gm (0.050 mole) of N,N-dimethylamino-N′-cyanomethylhydrazine was added 1 ml of a sodium methoxide solution (0.5 gm of sodium in 5 ml of methanol). A spontaneous rise in temperature occurred, and the reaction mixture was heated on a steam bath for 5 min. After cooling, ether was added, and 2.0 gm (14%) of the desired product, mp 145° to 147°C, was collected on a filter. The IR and NMR spectra were consistent with the proposed structure.

1-Methyl-1,4,8-triazaspiro[4.5]decan-3-one

A solution of 5.18 gm (0.0200 mole) of 8-benzyl-1-methyl-1,4,8-triazaspiro[4.5]-decan-3-one in 75 ml of methanol along with 250 mg of a 10% palladium on carbon catalyst was placed under a 50 psig atmosphere of hydrogen on a Paar apparatus. After shaking for 24 hr, the catalyst was filtered, and the solvent evaporated under reduced pressure. Recrystallization of the residue from methanol-ether afforded 2.85 gm (84.4%) of the desired product, mp 180° to 182°C. The IR and NMR spectra were consistent with the proposed structure.

1-Phenyl-1,4,8-triazaspiro[4.5]decan-3-one

A solution of 5.13 gm (0.0160 mole) of 8-benzyl-1-phenyl-1,4,8-triazaspiro[4.5]decan-3-one in 1 liter of methanol was divided into 5 equal portions. To each portion was added 300 mg of a 10% palladium on carbon catalyst. Each solution was placed on a Paar apparatus under 50 psig of hydrogen. After shaking for 20 hr, the catalyst was filtered and the solvent evaporated under vacuum to leave a solid residue. The combined solids were washed with ether and collected on a filter to give 2.52 gm (68.3%) of the desired product, mp 196° to 198°C. Mass spectral molecular weight, 231 (calcd molecular weight, 231). The IR spectrum was consistent with the proposed structure.

8-[4-(p-Fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-methyl-1,4,8-triazaspiro[4.5]decan-3-one, EA 5355

A mixture of 3.38 gm (0.0200 mole) of 1-methyl-1,4,8-triazaspiro[4.5]decan-3-one, 4.89 gm (0.0200 mole) of the ethylene ketal of 4-chloro-p-fluorobutyrophenone, 4.14 gm (0.0200 mole) of potassium carbonate, and 3.32 gm (0.0200 mole) of potassium iodide in 80 ml of dry dimethylformamide was heated at 90° for 6 hr. The workup was identical to that of EA 5309 (see above). Recrystallization of the solid residue from methanol-ether gave 5.7 gm (76%) of the desired product, mp 145° to 147°C. The IR and NMR spectra were consistent with the proposed structure.

Anal. Calcd for $C_{20}H_{28}FN_3O_3$: C, 63.6; H, 7.5; N, 11.1.

Found: C, 63.2; H, 7.5; N, 10.3.

8-[4-(p-Fluorophenyl)-4,4-ethylenedioxy-1-butyl]-1-phenyl-1,4,8-triazaspiro[4.5]decan-3-one, EA 5360

A mixture of 1.16 gm (5.00 mmole) of 1-phenyl-1,4,8-triazaspiro[4.5]decan-3-one, 1.22 gm (5.00 mmole) of the ethylene ketal of 4-chloro-p-fluorobutyrophenone, 1.38 gm (10.0 mmole) of potassium carbonate, and 0.830 gm (5.00 mmole) of potassium iodide in 100 ml of dry dimethylformamide was kept at 125°C for 24 hr. The workup was identical to that of EA 5309 (see above). Recrystallization from methanol gave 0.90 gm (41%) of the desired material, mp 202° to 204°C. The IR and NMR spectra were consistent with the proposed structure.

Anal. Calcd for $C_{25}H_{30}FN_3O_3$: C, 68.3; H, 6.9; N, 9.6.

Found: C, 67.3; H, 7.0; N, 9.4.

V. CONCLUSION.

Our efforts to prepare butyrophenone type molecules with enhanced biological activity failed to produce any compounds that possessed the desired properties.

During the course of this work, we were able to develop two new synthetic procedures. The first was the synthesis of ketones by the addition of acid chlorides to organocopper intermediates. We believe this method offers a distinct advantage over the preparation of ketones from acid chlorides and organocadmium compounds or the addition of nitriles to Grignard reagents. A second new synthetic procedure that was found was the removal of benzyl groups from tertiary benzyl amine molecules having a divalent sulfur atom by treatment of the amine first with benzyl chloroformate followed by triethylsilane.

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