peroxide by the procedure previously described for hexyl diphenylphosphinate.

Hexyl Diphenylphosphinodithioate.—This material was prepared from 30.2 g. (0.1 mole) of hexyl diphenylphosphinothioite and 3.2 g. (0.1 mole) of sulfur by the procedure described previously for hexyl diphenylphosphinothionate. The crude product, a crystalline solid, was purified by recrystallization from naphtha.

Acknowledgment.—The authors wish to thank Mr. Rudolph Greenwald who prepared some of the starting materials and Mr. Harry Ferber who carried out all analytical determinations.

CLEVELAND, OHIO

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

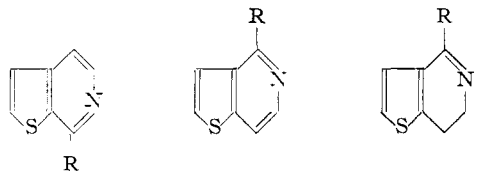
Sulfur Analogs of Isoquinolines. IV. The Pictet–Gams Reaction and Attempts to Prepare Analogs of Papaverine[1,2]

BY WERNER HERZ AND LIN TSAI

RECEIVED DECEMBER 18, 1954

The Bischler–Napieralski and Pictet–Gams reactions in the thiophene series have been found to proceed satisfactorily. However, attempts to prepare papaverine analogs were not successful. Introduction of a methoxy group into the thiophene ring in order to facilitate cyclization resulted in demethylation; the resulting compounds appear to exist in the thiolactone form.

The feasibility of preparing analogs of isoquinolines in which the benzene moiety is replaced by a thiophene nucleus has been demonstrated.[2,3] Earlier work indicated that the Bischler–Napieralski and the Pomeranz–Fritsch reactions could be applied successfully to derivatives of thiophene to give thieno(2,3-c)- (I) and thieno(3,2-c)pyridines (II). The present paper describes our attempts to extend this work, particularly to the preparation of analogs of papaverine, in order to produce compounds whose pharmacological properties would be of interest.



I II III

Because 2-(2-thienyl)-ethylamine is the key intermediate in the synthesis of compounds of type II by the Bischler–Napieralski reaction, attempts were made to improve its preparation from 2-thienylacetonitrile. These are described in the experimental part. A significant improvement in the yield obtained by reduction by means of lithium aluminum hydride was observed when the contact time with the basic medium was shortened. For the synthesis of 3,4-dihydro(3,2-c)pyridine (III, R = H) the amine was formylated by ethyl formate.[4] Cyclization with polyphosphoric acid–phosphorus oxychloride, the best procedure found, gave only an 8% yield of III (R = H), whereas the cyclization of N-formyl-2-phenylethylamine reportedly furnishes 31% of 3,4-dihydroisoquinoline.[5]

With the purpose of synthesizing a sulfur analog resembling papaverine, N-homoveratroyl-2-(2-thienyl)-ethylamine was prepared, but all attempts to cyclize the amide were fruitless. This was not entirely surprising since Kondo[6] failed to obtain 1-veratryl-3,4-dihydroisoquinoline under similar conditions. Bischler–Napieralski cyclizations of N-homoveratroyl derivatives appear to be successful only when the phenyl ring is activated by the presence of one or more hydroxy or alkoxy substituents.[7]

A route to the desired papaverine analog which in view of previously published reports[7] offered greater prospects of success, while avoiding the dehydrogenation step which lowers the yield of 1-alkylthieno-(3,2-c)pyridines,[3] is the method of Pictet and Gams. Its several modifications utilize a 2-hydroxy- or 2-methoxy-2-phenylethylamide whose cyclization leads directly to an isoquinoline derivative. Although 2-hydroxy-2-(2-thienyl)-ethylamine was not accessible through adaptations of standard methods,[8] the corresponding methoxy derivative was prepared in fair yield by reaction of β-2-nitrovinylthiophene with sodium methoxide followed by reduction with lithium aluminum hydride.

The acetyl derivative of this amine was subjected to widely varied cyclization conditions. After extensive experimentation, 1-methylthieno(3,2-c)pyridine (II, R = CH_3) was prepared in an over-all yield of 22.5%, based on the amine. The cyclization was favored by mild conditions (phosphorus oxychloride at room temperature for 30 days). This thienopyridine has previously been prepared in lower yield by aromatization of 1-methyl-3,4-dihydrothieno(3,2-c)pyridine (III, R = $-CH_3$).[3] Since we were also interested in developing a synthetic method for the preparation of 1,2,3,4-tetrahydrothienopyridines, the methiodide of the latter compound was reduced[9] to 1,2-dimethyl-1,2,3,4-tetra-

(1) Supported in part by grant RC-3097 from the United States Public Health Service, Department of Health, Education and Welfare.

(2) Previous paper, W. Herz and L. Tsai, THIS JOURNAL, **75**, 5122 (1953).

(3) W. Herz, *ibid.*, **73**, 351 (1951).

(4) This derivative was reported by G. Barger and A. P. T. Easson, *J. Chem. Soc.*, 2100 (1938), but no analysis was given. The authors stated that they were unable to cyclize this amide.

(5) H. R. Snyder and F. Y. Werber, THIS JOURNAL, **72**, 2962 (1950).

(6) J. Kondo, *J. Pharm. Soc. Japan*, No. 519, 429 (1925).

(7) Pertinent work on this and related subjects is reviewed by W. M. Whaley and T. R. Govindacharl, as well as by W. J. Gensler in "Organic Reactions," Vol. VI, John Wiley and Sons, Inc., New York, N. Y., 1951, pp. 74, 151 and 191.

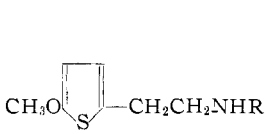
(8) The nitrosation of 2-acetylthiophene has been recorded[4] but we were not able to reduce this compound successfully to the β-hydroxyethylamine. Similarly we were unable to prepare the cyanohydrin of 2-thiophenealdehyde whose reduction was expected to lead to the desired compound.

(9) H. Schmid and P. Karrer, *Helv. Chim. Acta*, **32**, 960 (1949).

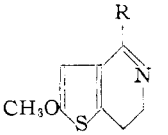
hydrothieno(3,2-c)pyridine in 61% yield. The postulated structure of this compound is supported by the identity of its ultraviolet absorption spectrum (λ_{max} 234–236 mμ, log ε 3.8 in 95% ethanol) with that of 2,3-dimethylthiophene.[10]

Extension of the cyclization studies to N-homoveratroyl-2-methoxy-2-(2-thienyl)-ethylamine furnished in several instances a small amount of basic material whose picrate had the analytical values calculated for the picrate of II (R = 3,4-dimethoxybenzyl). The assignment of this structure receives support from a consideration of the ultraviolet absorption spectrum of its hydrochloride. The first maximum (235 mμ, log ε 4.5) is identical in position as well as intensity with the corresponding band in the spectrum of 1-methylthieno(3,2-c)pyridine methiodide. The second band (266–274 mμ, log ε 4.35) corresponds approximately to a composite of the spectra of the above methiodide and 4-methylveratrole[11] in this region.

It was expected that the cyclization of alkoxy thiophenes might yield substances more closely related to the isoquinoline alkaloids. 5-Methoxy-2-thiophenealdehyde[12] was condensed with nitromethane and the resulting substance was reduced to 2-(5-methoxy-2-thienyl)-ethylamine (IV, R = H). Alkylation with methyl iodide furnished the crystalline trimethylammonium iodide; the formyl derivative (IV, R = CHO) on reduction gave the partially methylated N-methyl-2-(5-methoxythienyl)-ethylamine (IV, R = $-CH_3$). In an effort to improve the over-all yield of these amines from 2-methoxythiophene, the lithium derivative of the latter substance was treated with ethylene oxide. However the conversion of the resulting alcohol to the tosylate and thence to the desired amines was not successful.

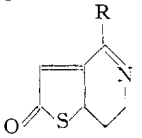


IV



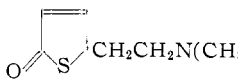
V

Cyclization of N-benzoyl-2-(5-methoxy-2-thienyl)-ethylamine (IV, R = benzoyl) gave a solid base whose analysis was in harmony with the empirical formula $C_{13}H_{11}ONS$ instead of the expected $C_{14}H_{13}ONS$ based on structure V (R = phenyl). A similar substance of analogous formula was obtained in very low yield from the N-acetyl derivative (IV, R = acetyl). This indicates that cyclization is accompanied by demethylation; evidence which led to the assignment of structure VI rather than the alternative tautomeric forms is given in the experimental part.



VI

The ease with which the methoxy group of 2-methoxythiophenes is cleaved under acidic conditions[13] is further illustrated by the observation that demethylation occurred when an attempt was made to apply the Eschweiler–Clark reaction to 2-(5-methoxy-2-thienyl)-ethylamine. Chemical and spectroscopic evidence indicated that the resulting substance existed in the α,β-unsaturated thiobutenolide form VII.



VII

Several of the compounds described in this report are being tested pharmacologically. We wish to thank the Monsanto Chemical Company for the gift of chemicals.

Experimental[14]

2-2-Thienylethylamine.—The best procedure is a modification of the method of Crowe and Nord.[15] A solution of 12.3 g. of 2-thiopheneacetonitrile[16] in 100 ml. of anhydrous ether was added very rapidly (within five or six minutes) to a solution of 4 g. of lithium aluminum hydride in 100 ml. of ether which was cooled by an ice-bath. The mixture was stirred in the cold for an additional 30 minutes, decomposed by addition of 100 ml. of wet ether, followed by 2 ml. of water, 2 ml. of 20% sodium hydroxide solution and finally 10 ml. of water. On working up in the usual way there was obtained 6.8 g. (55%) of 2-(2-thienyl)-ethylamine, b.p. 95–97° (10 mm.), $n^{26}D$ 1.5530.

Bouveault-Blanc reduction of the nitrile gave only a 9% yield of the amine. Because Kotake and Sakan[17] reported the electrolytic reduction of 3-thianaphtheneacetonitrile to β-3-thianaphthene-ethylamine in 60% yield, an improvement on the yield obtained by reduction with lithium aluminum hydride, a number of attempts were made to reduce 2-thienylacetonitrile electrolytically. With a lead oxide or nickel black cathode at various amperages for periods of time varying from one to 24 hours, using the general procedure of Swann,[18] the yield of amine was at best 25% accompanied by a neutral fraction consisting largely of starting material.

The stepwise conversion of the nitrile to the amine was also investigated. A mixture of 2.1 g. of 2-thienylacetonitrile, 3 g. of IRA-400 resin and 60 ml. of water was heated under reflux with stirring for 11 hours. Removal of the solvent at reduced pressure gave 1.1 g. (45%) of the amide, m.p. 147° (lit.[19] 148°, 35% yield using hydrogen peroxide and sodium hydroxide[21]). Four grams of the amide on reduction with lithium aluminum hydride by the Soxhlet method gave 2.1 g. (58%) of amine.

N-Formyl-2-(2-thienyl)-ethylamine.—A mixture of 20 g. (0.16 mole) of the amine and 150 ml. (135 g., 1.8 moles) of ethyl formate was heated at 100° in a sealed tube for two hours. The solvent was removed at reduced pressure and the residue was distilled *in vacuo*. A low-boiling fraction, b.p. 50–75° (0.3–0.5 mm.), wt. 9.3 g., consisted of starting material and unidentified neutral by-products. The formyl derivative distilled at 135–145° (0.4 mm.), $n^{25}D$ 1.5580, wt. 14 g. (58%).

Anal. Calcd. for C_7H_9ONS: N, 9.0. Found: N, 8.9.

3,4-Dihydrothieno(3,2-c)pyridine.—The N-formyl derivative (2.7 g., 0.018 mole) was added to 68 g. of polyphosphoric acid and 2.6 of phosphorus oxychloride under vigorous stirring. The mixture was heated at 100–105° for 15 minutes, poured into ice-water and the aqueous solu-

(10) H. D. Hartough, "Thiophene and Its Derivatives," Interscience Publishers, Inc., New York, N. Y., 1952, p. 105.

(11) E. A. Braude, *Ann. Repts.*, **42**, 123 (1945).

(12) J. Sice, THIS JOURNAL, **75**, 3697 (1953).

(13) 2-Methoxyfuran (M. P. Cava, C. L. Wilson and C. J. Williams Jr., *Chemistry and Industry*, 17 (1955)) appears to be even more acid sensitive (private communication from Dr. Cava).

(14) Melting points and boiling points are uncorrected unless noted otherwise. Analyses by Clark Microanalytical Laboratory, Urbana, Illinois, and by Drs. Weiler and Strauss, Oxford.

(15) B. F. Crowe and F. F. Nord, *J. Org. Chem.*, **15**, 71 (1950).

(16) F. F. Blicke and F. Leonard, THIS JOURNAL, **68**, 1934 (1946).

(17) H. Kotake and T. Sakan, *J. Inst. Polytech., Osaka City Univ., Ser. C*, **2**, No. 1, 25 (1951).

(18) S. Swann in "Technique of Organic Chemistry," Vol. II, Interscience Publishers, Inc., New York, N. Y., 1948, pp. 170–172.

(19) P. Cagniant, *Bull. soc. chim.*, [5] **16**, M847 (1949).

tion was washed with chloroform. It was then made basic with concentrated sodium hydroxide solution, saturated with ammonium sulfate and extracted exhaustively with chloroform. The chloroform extracts were dried and the solvent was removed at reduced pressure. Distillation of the residue *in vacuo* in a sublimation apparatus gave 0.2 g. of an amorphous solid, m.p. 123–126°. Two further sublimations at 100° furnished a white powder, m.p. 133–135° (cor.).

Anal. Calcd. for C_7H_7NS: C, 61.28; H, 5.14; N, 10.21. Found: C, 61.18; H, 5.95; N, 10.4.

The methiodide, after two recrystallizations from absolute ethanol, melted at 141–142° (cor.).

Anal. Calcd. for $C_8H_{10}NSI$: C, 34.42; H, 3.61. Found: C, 35.45; H, 3.45.

The assigned structure is supported by the similarity of the ultraviolet spectra of the base (λ_{max} 223, 228, 262 mμ, log ϵ_{max} 4.2, 4.15, 3.7, λ_{min} 226, 240 mμ, log ϵ_{min} 4.15, 3.35) and of its methiodide (λ_{max} 222, 293 mμ, log ϵ_{max} 4.4, 3.9, λ_{min} 252 mμ, log ϵ_{min} 3.05) to the spectra of 1-methyl-3,4-dihydrothieno(3,2-c)pyridine (λ_{max} 223, 228, 257 mμ, log ϵ_{max} 4.25, 4.2, 3.68, shoulder at 263 mμ, log ϵ 3.66, λ_{min} 226, 240 mμ, log ϵ_{min} 4.19, 3.4) and its methiodide (λ_{max} 220, 223, 282 mμ, log ϵ_{max} 4.5, 4.48, 4.0, λ_{min} 222, 250 mμ, log ϵ_{min} 4.47, 3.67).

1-Methyl-3,4-dihydrothieno(3,2-c)pyridine Methiodide.—Six grams (0.047 mole) of 2-(2-thienyl)-ethylamine was converted to the acetyl derivative which was subsequently cyclized by the procedure reported previously.[3] The basic product was dissolved in 20 ml. of dry benzene, treated with Darco, filtered and mixed with 20 ml. of methyl iodide. After standing in the refrigerator overnight, 4.0 g. (29% based on amine) of brown crystalline methiodide was collected. Four recrystallizations from absolute ethanol afforded an analytical sample, m.p. 157–157.5° (cor.).

Anal. Calcd. for $C_9H_{12}NSI$: N, 4.78. Found: N, 4.80.

1,2-Dimethyl-1,2,3,4-tetrahydrothieno(3,2-c)pyridine.—The crude methiodide (4.4 g., 0.015 mole), after having been dried at room temperature over phosphorus pentoxide in a vacuum, was added to a slurry of 0.8 g. (0.02 mole) of lithium aluminum hydride in 100 ml. of dry ether with cooling and stirring. After one hour of stirring at room temperature, the mixture was decomposed in the usual way and filtered through Hyflo-supercel. The residue was thoroughly washed with ether, the ether filtrate and washings were combined, dried and distilled. The product boiled at 62–65° (0.3 mm.), yield 1.5 g. (61%). Redistillation in a Fraenkel distillation apparatus gave a colorless liquid, b.p. 66–67° (0.4 mm.), $n^{24}D$ 1.5530.

Anal. Calcd. for $C_9H_{13}NS$: C, 64.62; H, 7.83; N, 8.37. Found: C, 64.74; H, 7.88; N, 8.15.

The picrate crystallized in bright yellow short needles, m.p. 166.0–166.8° (cor.).

Anal. Calcd. for $C_{15}H_{16}O_7N_4S$: C, 45.45; H, 4.07. Found: C, 45.45; H, 4.13.

The methiodide was obtained by treating 0.2 g. of the base with 5 ml. of methyl iodide in 5 ml. of absolute ethanol. Concentration of the solution and recrystallization of the product furnished fine, colorless needles, m.p. 164.6–165.4° (cor.).

Anal. Calcd. for $C_{10}H_{16}NSI$: C, 38.84; H, 5.22; N, 4.53. Found: C, 39.22; H, 5.03; N, 4.55.

N-Homoveratroyl-2-(2-thienyl)-ethylamine.—Homoveratroyl chloride, prepared from 10.2 g. of acid and 10.2 g. of phosphorus oxychloride, was mixed with 7.0 g. of the amine by the usual Schotten–Baumann method.[20] The amide, wt. 8.4 g. (50%), was recrystallized three times from chloroform–petroleum ether and then melted at 96.5–97° (cor.).

Anal. Calcd. for $C_{16}H_{19}O_3NS$: C, 62.91; H, 6.27. Found: C, 62.72; H, 6.34.

One-gram samples of the amide were subjected to cyclization with phosphorus pentoxide–phosphorus oxychloride in boiling xylene, with phosphorus oxychloride in boiling xylene or in boiling benzene, and with phosphorus pentachloride in chloroform at room temperature. Traces of basic intractable resin were obtained, but attempts to isolate a homogeneous product were unsuccessful.

1-Methoxy-1,2-thienyl-2-nitroethane.—To a suspension of 7.8 g. (0.05 mole) of finely powdered ω-nitrovinylthiophene[21] in 75 ml. of methanol cooled to 2–5° by an ice–salt-bath, a solution of sodium methoxide, prepared by treating 1.5 g. (0.065 atom) of metallic sodium with 15 ml. of methanol, was added rapidly with vigorous stirring. The temperature of the reaction mixture rose to 10–20° and the suspension turned brown. Stirring was continued for four minutes. The solution was acidified with 6 ml. of acetic acid and diluted with 200 ml. of water. A red oil separated. The mixture was extracted with ether until the extract was colorless. The combined ethereal extracts were washed with water, dried and concentrated. The residue was distilled *in vacuo* and a pale yellow oil was collected at 92–95° (0.7 mm.), yield 4.2 g. (45%). An analytical sample was obtained by redistillation, b.p. 93–95° (0.7 mm.), $n^{25}D$ 1.5249.

Anal. Calcd. for $C_7H_9O_3NS$: C, 44.91; H, 4.86; N, 7.48. Found: C, 45.36; H, 4.94; N, 7.36.

2-Methoxy-2-(2-thienyl)-ethylamine.—A solution of 42 g. (0.22 mole) of 1-methoxy-1,2-thienyl-2-nitroethane in 300 ml. of anhydrous ether was added dropwise to 17 g. of lithium aluminum hydride in 800 ml. of ether with stirring. After six hours the mixture was decomposed and worked up by the method of Amundsen and Nelson.[22] The amine boiled at 63–66° (0.7 mm.), $n^{25}D$ 1.5291, yield 24.4 g. (70%).

Anal. Calcd. for $C_7H_{11}ONS$: C, 53.48; H, 7.05. Found: C, 53.71; H, 6.95.

N-Acetyl-2-methoxy-2-(2-thienyl)-ethylamine.—To a suspension of 25.5 g. of the amine in 250 ml. of 20% sodium hydroxide solution was added 75 ml. of acetic anhydride in portions with shaking and intermittent cooling. The mixture was allowed to stand at room temperature for four hours and was then thoroughly extracted with benzene. The benzene extracts were dried and concentrated. Ligroin (b.p. 65–110°) was added to the concentrated solution until a slight turbidity appeared and the mixture was then chilled in a Dry Ice–acetone bath. The solid which separated, wt. 25.3 g. (82%), was recrystallized repeatedly in a similar manner to give an analytical sample, m.p. 49.5–50.5° (cor.).

Anal. Calcd. for $C_9H_{13}O_2NS$: C, 54.22; H, 6.57. Found: C, 54.51; H, 6.82.

1-Methylthieno(3,2-c)pyridine.—The best procedure is described below. Ten grams of 2-methoxy-2-(2-thienyl)-ethylamine was converted to the acetyl derivative which was taken up in 250 ml. of dry chloroform. Twenty-five grams of phosphorus pentachloride was added and the mixture was allowed to stand at room temperature with exclusion of moisture for 30 days. The excess reagent was decomposed by pouring the mixture cautiously into ice-water. The aqueous layer was made basic under cooling and extracted with ether. The dried ether yielded an oil, b.p. 78–80° (0.5 mm.), $n^{25}D$ 1.6097, wt. 2.15 g. (22.5% based on amine). The picrate melted at 241° dec., lit.[3] 245–246°.

The methiodide melted at 163–165°.

Anal. Calcd. for $C_9H_{10}NSI$: C, 37.12; H, 3.46. Found: C, 37.50; H, 4.05.

N-Homoveratroyl-2-methoxy-2-(2-thienyl)-ethylamine.—Homoveratroyl chloride prepared from 5 g. of homoveratric acid was added in small portions to 1 g. of the amine in 20 ml. of 20% sodium hydroxide solution as above. The yellow oil which separated was extracted with ether. The ether solution was dried and the ether removed at reduced pressure. The residue was taken up in 8 ml. of dry benzene and ligroin (b.p. 65–110°) was added to incipient turbidity. Chilling produced a yellow precipitate which was recrystallized from chloroform–petroleum ether, yield 1.5 g. (70%). The analytical sample melted at 72–73.5° (cor.).

Anal. Calcd. for $C_{17}H_{21}O_4NS$: C, 60.87; H, 6.31. Found: C, 61.04; H, 6.33.

1-Veratrylthieno(3,2-c)pyridine.—The procedure given below represents the best of many experiments. A mixture of 1 g. of the amide, 3 g. of phosphorus pentachloride and 30 ml. of dry chloroform was allowed to stand at room temperature for eight days. It was worked up as in the case

(20) R. L. Shriner and R. C. Fuson, "The Systematic Identification of Organic Compounds," Third ed., John Wiley and Sons, Inc., New York, N. Y., 1948.

(21) W. J. King and F. F. Nord, *J. Org. Chem.*, **14**, 405 (1948).

(22) L. H. Amundsen and L. S. Nelson, THIS JOURNAL, **73**, 242 (1951).

of the 1-methyl analog, but the yield of basic oil was too small to permit isolation of a homogeneous product. It was taken up in 1 ml. of ethanol and mixed with picric acid solution. The precipitate weighed 120 mg. Two recrystallizations from acetone furnished yellow platelets, m.p. 181.2–182.6° (cor.); 190–192° (Kofler stage, with shrinking at 184°).

Anal. Calcd. for $C_{22}H_{18}O_9N_4S$: C, 51.36; H, 3.53; N, 10.89. Found: C, 51.53; H, 4.05; N, 10.7.

An alcoholic solution of the hydrochloride was prepared by decomposing a solution of the pure picrate with concentrated hydrochloric acid. The ultraviolet absorption spectrum of this solution exhibited maxima at 235 and 286–274 mμ (log ε 4.5 and 4.35) and minima at 222 and 249 mμ (log 4.35 and 4.2).

5-Methoxy-2-(β-nitrovinyl)-thiophene.—A mixture of 60 g. (0.42 mole) of 2-methoxythiophenealdehyde, 26.5 ml. (30 g., 0.5 mole) of nitromethane and 4 ml. of *n*-amylamine was allowed to stand at room temperature in the dark for six days. The yellow crystals were filtered, washed with a small amount of ether and weighed 42.5 g. (54%). Several recrystallizations from methanol gave an analytical sample of m.p. 129.6–130.0° (cor.).

Anal. Calcd. for $C_7H_7O_3NS$: C, 45.41; H, 3.81; N, 7.57. Found: C, 45.30; H, 4.25; N, 7.36.

The yields using benzylamine were comparable, but experiments employing triethylamine or aqueous sodium hydroxide were unsatisfactory.

2-(5-Methoxy-2-thienyl)-ethylamine.—Because of the relatively low solubility of the nitrovinyl compound in ether, 15 g. of the finely powdered solid was added as rapidly as possible to 9 g. of fresh lithium aluminum hydride in 600 ml. of anhydrous ether cooled in an ice-bath. Stirring was continued for 30 minutes at room temperature and the mixture was worked up in the usual way. The amine boiled at 77–88° (0.3 mm.), yield 7.6 g. (60%). The analytical sample distilled at 78–80° (0.6 mm.), $n^{25}D$ 1.5410, but the carbon values remained somewhat low, possibly due to formation of the carbonate.

Anal. Calcd. for $C_7H_{11}ONS$: C, 53.47; H, 7.05; N, 8.91. Found: C, 52.79; H, 7.30; N, 9.15.

The ultraviolet spectrum in 95% ethanol showed a maximum at 252 mμ (ε 6800), a minimum at 214 mμ (ε 1900) and a cut-off near 284 mμ (ε 100).

The N-formyl derivative was prepared by heating 5 g. of the amine and 45 ml. of ethyl formate in a sealed tube for two hours. The product boiled at 145–155° (0.4 mm.), yield 4.3 g. (72%). The analytical sample had a b.p. of 152–155° (0.4 mm.), $n^{24}D$ 1.5495, bands in the infrared spectrum (carbon tetrachloride solution) at 1680 (C=O), 3470 and 3320 (free and bonded –OH), 1210 and 1160 cm.$^{-1}$ (arylalkyl ether).

Anal. Calcd. for $C_8H_{11}O_2NS$: C, 51.87; H, 5.99; N, Found: C, 51.64; H, 6.04; N, 7.72.

The acetyl derivative was prepared by the Schotten–Baumann method and purified by distillation, b.p. 151–154° (0.5 mm.), m.p. 37°, yield quantitative.

Anal. Calcd. for $C_9H_{13}O_2NS$: C, 54.24; H, 6.58; N, 7.03. Found: C, 53.84; H, 6.08; N, 7.15.

The benzoyl derivative was prepared by the Schotten–Baumann reaction. The oil which separated did not solidify in the cold and was extracted with benzene. The dried benzene extracts were concentrated at reduced pressure; the oily residue was crystallized from acetonitrile at −15°. Two crops weighing 2.7 g. (82%) were obtained from 2.2 g. of starting material. Further crystallizations from acetonitrile at −15° gave a sample melting at 68.4–69° (cor.).

Anal. Calcd. for $C_{14}H_{15}O_2NS$: C, 64.34; H, 5.79; N, 5.4. Found: C, 64.47; H, 6.04; N, 5.6.

N,N,N-Trimethyl-2-(5-methoxy-2-thienyl)-ethylammonium Iodide.—To a solution of 1.1 g. (0.007 mole) of the amine in 30 ml. of dry methanol, 2 ml. of methyl iodide and 1.0 g. of powdered anhydrous potassium carbonate was added in succession. The mixture was stirred and refluxed for 22 hours, 2 ml. of methyl iodide was added and stirring at reflux was continued for another ten hours. On cooling, filtering, concentrating to 10 ml. and allowing to cool, two crops totalling 1.58 g. (70%) were obtained. Recrystallization from dry methanol furnished colorless needles, m.p. 212–213° dec.

Anal. Calcd. for $C_{10}H_{18}ONSI$: C, 36.70; H, 5.54; N, 4.28. Found: C, 36.85; H, 5.51; N, 4.33.

An attempt to methylate 2-(5-methoxy-2-thienyl)-ethylamine completely by heating it with formic acid and formalin for eight hours at 120° produced considerable carbon dioxide evolution, but the basic product, b.p. 85–86° (0.4 mm.), wt. 1.4 g. from 3 g. of amine, $n^{24}D$ 1.5482, did not have the expected formula. It solidified on long standing. Repeated recrystallization from benzene–petroleum ether at −15° raised the m.p. to 40.5–41.5°.

Anal. Calcd. for $C_8H_{11}ONS$: C, 56.79; H, 6.55; N, 8.3. Found: C, 56.47; H, 6.41; N, 8.0.

Treatment of this compound with methyl iodide in absolute ethanol gave a quantitative yield of N,N,N-trimethyl-2-(5-methoxy-2-thienyl)-ethylammonium iodide. The infrared spectrum exhibited bands at 1700 and 1615 cm.$^{-1}$, but no –OH or –NH absorption nor the peaks near 1210 and 1150 cm.$^{-1}$ characteristic of 2-methoxythiophenes and arylalkyl ethers.[23] Its ultraviolet spectrum in 95% ethanol (λ_{max} 219, 269 mμ, log ε 4.05, 3.45, λ_{min} 246 mμ, log ε 3.29) was remarkably similar to the spectrum of 2-thienol.[24] It is concluded that cleavage of the methoxy group occurred and that the substance exists in the α,β-unsaturated thiolactone form, VII.

N-Methyl-2-(5-methoxy-2-thienyl)-ethylamine.—Reduction of 4.0 g. of the N-formyl derivative with lithium aluminum hydride gave a colorless liquid, b.p. 78–80° (1 mm.), yield 2.6 g. (71%). The analytical sample had $n^{24}D$ 1.5269.

Anal. Calcd. for $C_8H_{13}ONS$: C, 56.10; H, 7.65; N, 8.18. Found: C, 56.24; H, 7.55; N, 7.88.

The infrared spectrum in carbon tetrachloride solution exhibited a broad band at 3400 cm.$^{-1}$ (bonded –NH) and peaks at 1210 and 1156 cm.$^{-1}$ (arylalkyl ether). The methiodide was identical with a sample of the methiodide prepared from the primary amine.

Cyclization of N-Benzoyl-2-(5-methoxy-2-thienyl)-ethylamine.—A number of variations of the Bischler–Napieralski reaction were investigated. All resulted in the same product but the following procedure gave the best yield. A solution of 1.16 g. of the amide in 180 ml. of dry toluene was refluxed with 12.5 ml. of phosphorus oxychloride for two hours, care being taken to exclude moisture. The solvent and excess reagent were removed by distillation at reduced pressure. The resinous residue was taken up in cold 5% hydrochloric acid and washed with ether, made basic with ammonia and the curdy precipitate which separated was filtered and dried, wt. 0.77 g., m.p. 115–120°. Sublimation gave an almost colorless amorphous solid, m.p. 122.8–123.8° (cor.). Recrystallization was not satisfactory and the analysis indicated that the sample was not entirely pure.

Anal. Calcd. for $C_{13}H_{11}ONS$: C, 68.09; H, 4.84; N, 6.11; S, 14.0. Found: C, 67.36; H, 5.01; N, 5.85; S, 14.3.

The picrate after three recrystallizations from ethanol melted at 162.4–163.8° (cor.).

Anal. Calcd. for $C_{19}H_{14}O_8N_4S$: C, 49.78; H, 3.08; N, 12.22. Found: C, 49.28; H, 3.14; N, 11.85.

The compound was soluble in dilute hydrochloric acid, soluble in ether, moderately soluble in ethanol and benzene and insoluble in water, petroleum ether and cold alkali. It dissolved upon warming in dilute alkali and could not be recovered upon neutralization. It decolorized a solution of bromine in carbon tetrachloride and an alcoholic solution of potassium permanganate. Attempted condensation with benzaldehyde led to intractable material. Hydrolysis with potassium carbonate or potassium hydroxide gave a basic fraction which did not yield a crystalline picrate; hydrogen sulfide was liberated on acidification as well as on treatment with warm 4% hydrochloric acid. Hydrogenation with excess palladium–black gave a resinous basic material from which no well-defined fractions could be isolated. Dehydrogenation under mild conditions did not effect any changes. Desulfurization by the method of Papa and co-workers[25] gave mixtures from which no homogeneous material could be isolated. Treatment with diazomethane had no effect on the substance.

(23) H. Tschamler and R. Leutner, *Monatsh.*, **83**, 1502 (1952).

(24) C. D. Hurd and R. L. Kreuz, THIS JOURNAL, **72**, 5545 (1950).

(25) D. Papa, E. Schwenk and H. F. Ginsberg, *J. Org. Chem.*, **14**, 723 (1949).

The ultraviolet spectrum of the substance (solvent ethanol) exhibited only one broad maximum at 238–244 mμ (log ε 3.95) instead of the two maxima shown by 3,4-dihydrothieno(3,2-c)pyridines. The band was considerably stronger and broader than a similarly located band of 2-methoxythiophene.[24] In the infrared it absorbed strongly at 1695 cm.$^{-1}$, but there was no hydroxyl band and the peaks at 1212 and 1155 cm.$^{-1}$ characteristic of arylalkyl ethers[23] were missing (*cf.* the spectrum of 2-thienol[24] which has these bands and an intense band at 1670 cm.$^{-1}$, presumably due to a thiolactone band). Consideration of the spectra and the chemical evidence cited earlier suggest that the base exists in form VI.[26]

Cyclization of N-Acetyl-2-(5-methoxy-2-thienyl)-ethylamine.—A mixture of 3.2 g. of the acetyl derivative, 1 g. of phosphorus pentoxide and 30 ml. of phosphorus oxychloride in 230 ml. of dry toluene was refluxed, with stirring, under a nitrogen atmosphere. The solvent and excess oxychloride was removed at reduced pressure and the resinous residue was taken up in ice-cold dilute hydrochloric acid, washed with ether, filtered through Hyflo-supercel, cautiously made basic with ammonium hydroxide under cooling and thoroughly extracted with ether. The dried ether extracts were concentrated at reduced pressure. The residue was distilled *in vacuo* at a bath temperature of 80–90°. The light yellow oil, wt. 0.1 g., was converted to a picrate, m.p. 171.2–171.6° (cor.) after three recrystallizations from ethanol.

Anal. Calcd. for $C_{14}H_{12}O_8N_4S$: C, 42.42; H, 3.05. Found: C, 42.79; H, 3.10.

The ultraviolet spectrum of the base in 95% ethanol exhibited a maximum at 224–228 mμ (log ε 3.5) superimposed on a broad band whose maximum could not be determined but which appears as a shoulder near 260 mμ (log ε approximately 3).

2-(5-Methoxy-2-thienyl)-ethanol.—2-Methoxythiophene (16.5 g., 0.145 mole) was added with stirring to a solution of phenyllithium prepared from 1.92 g. of lithium and 14.5 ml. of bromobenzene in 100 ml. of anhydrous ether under a nitrogen atmosphere. After an hour, the flask was cooled in an ice–salt-bath and the nitrogen inlet was replaced by a tube leading to a flask containing 11.0 g. of ethylene oxide. The oxide was slowly vaporized and introduced under the surface of the mixture with stirring and cooling. Stirring was continued at room temperature for eight hours and the mixture was worked up in the usual way. Two fractions were obtained: a low-boiling fraction, b.p. 64–69°, $n^{24}D$ 1.5309, wt. 11.7 g., whose ultraviolet and infrared spectrum indicated that it contained about 50% of unchanged methoxythiophene, and a higher-boiling material, b.p. 95–105° (0.4 mm.), wt. 10 g. 87–89° (0.3 mm.), $n^{23}D$ 1.5384.

Anal. Calcd. for $C_7H_{10}O_2S$: C, 53.14; H, 6.37. Found: C, 53.00; H, 5.80.

The infrared spectrum (film and CCl_4 solution) exhibited bands at 3690 and 3520 cm.$^{-1}$ (free and bonded OH); the characteristic C–O band of primary alcohols[28] was at 1050 cm.$^{-1}$.

The naphthylurethan was recrystallized from ligroin (b.p. 65–110°), m.p. 107.8–108° (cor.).

Anal. Calcd. for $C_{18}H_{17}O_3NS$: N, 4.28. Found: N, 4.23.

(26) The carbonyl absorption of α,β-butenolides (1750 cm.$^{-1}$) is approximately the same as that of an acyclic ester (1735–1755 cm.$^{-1}$). This is explained by assuming that the hypsochromic shift on passing from an acyclic to a cyclic system is compensated by a bathochromic shift due to the conjugative effect of α,β-unsaturation. Similarly one expects the carbonyl absorption of an α,β-unsaturated thiobutenolide to be approximately the same as that of an acyclic thioester (1680 cm.$^{-1}$).[27] Hence the 1695 cm.$^{-1}$ band in the spectrum of the base may be due to the α,β-thiobutenolide structure VI.

(27) H. T. Clark, J. R. Johnson and R. Robinson (ed.), "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, pp. 382–415.

(28) H. H. Zeiss and M. Tsutsui, THIS JOURNAL, **75**, 897 (1953).

TALLAHASSEE, FLORIDA

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF IRWIN, NEISLER & CO.]

Bis-ammonium Salts. Unsymmetrical Derivatives of Some β-Carbolines[1]

BY ALLAN P. GRAY, ERNEST E. SPINNER, DOROTHY C. SCHLIEPER AND CHESTER J. CAVALLITO

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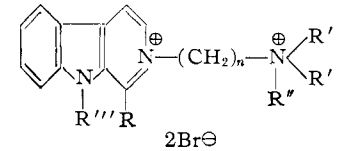
A series of unsymmetrical bisammonium salts has been prepared in which a small cationic head is attached through an alkyl chain to either the Py–N or Ind–N of a β-carboline. Included in this series are derivatives of norharman, harman, Ind-N-methylharman, Py–N-methyltetrahydroharman, and, for comparison, α-carboline. The derivatives in which the chain is linked at the Ind-N were synthesized by alkylation with the appropriate dialkylaminoalkyl chlorides in the presence of sodamide. A number of the Py-N-substituted β-carboline bis salts, in particular those in which the charged groups are separated by a three carbon chain, display intense hypotensive activity, not necessarily associated with strong ganglionic blocking properties. Structure–activity relationships are discussed.

A program concerned with the synthesis and biological examination of a variety of bis-ammonium salts has, for some time, been in progress in these laboratories. In the course of these investigations some symmetrical bis-carboline salts[2] were observed to be hypotensive agents of relatively short duration in comparison with the more potent ganglion blocking "methoniums." It thus became of interest to examine the pharmacological properties of compounds having a large, charged carboline structure and a small cationic (*i.e.* "methonium" type) head attached at either end of a carbon chain. The first compound prepared (VI) showed markedly greater hypotensive activity than could be ascribed to ganglionic blockade, and this prompted the synthesis of a large number of related unsymmetrical bis-ammonium salts. The present paper deals with the preparation of carboline derivatives, *viz.*



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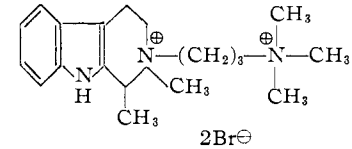

2Br⊖

XII

(1) Presented in part before the Division of Medicinal Chemistry at the 127th National Meeting of The American Chemical Society, March 29–April 7, 1955.

(2) A. P. Gray, E. E. Spinner and C. J. Cavallito, THIS JOURNAL, **76**, 2792 (1954).