and particularly with the two dimensional theory of Moore and Eyring. The theory indicates a general correspondence between our value of k', in the equation

$$\log \sigma = \log \sigma_0 + k'f$$

and their value a/kT, where k' is a constant. If k is the Boltzmann constant then in absolute units $a/kT = 0.054$, while k' varies in our work from 0.022 to 0.076.

CHICAGO, ILLINOIS RECEIVED FEBRUARY 23, 1939.

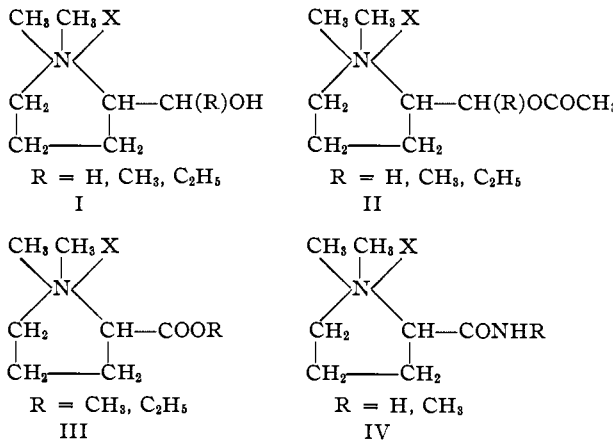
[CONTRIBUTION FROM THE NICHOLS CHEMICAL LABORATORY OF NEW YORK UNIVERSITY]

Pyrrolidinium Analogs of Choline and Betaine. Onium Compounds. XXI

BY R. R. RENSHAW[1] AND W. E. CASS[2]

The work described in this paper represents a continuation of previous investigations on the synthesis[3] and pharmacology[4] of nitrogen heterocyclic onium compounds having a substituent on the cyclic carbon atom. The preparation of certain pyrrolidinium derivatives is described here.[5] In these compounds the carbon chain of choline or betaine is contained partly in the heterocyclic ring. On this basis compounds, which may be considered analogous to choline, β-methyl choline and β-ethyl choline, I, the acetylated derivatives of these cholines, II, the methyl and ethyl esters of betaine, III, and the amide and methyl amide of betaine, IV, have been obtained. Certain tertiary pyrrolidine salts, closely related to these compounds, also have been prepared.

CHART I



Choline and Acetylcholine Analogs.—(1-Methylpyrrolidyl-2)-methanol was obtained by the reduction of the ethyl ester of hygric acid (1-methyl pyrrolidine-2-carboxylic acid) with sodium and alcohol. (A new synthesis for hygric acid will be described below.) Methyl iodide added readily to this substance in dry ether with the production of the choline analog (I, R = H). Treatment of (1-methylpyrrolidyl-2)-methanol in dry ether with acyl halides yielded hydrohalide salts of esters of this tertiary amino alcohol.

In the preparation of the remaining members of this series (I, R = CH_3, C_2H_5), 2-pyrrolidyl methyl and ethyl methanols were obtained by the reduction of 2-acetyl- and 2-propionylpyrroles with sodium and alcohol, according to the method of Hess.[6] It was found advisable to modify the procedure of Hess by using larger amounts of carefully dried alcohol and a stirring technique which favored more rapid reaction. The yields of pyrrolidine alcohols were 25–30%. The onium derivatives of these pyrrolidine alcohols were obtained by treating the secondary bases in alcohol solution with an excess of methyl iodide in the presence of an excess of barium hydroxide.

The acetylcholine analogs (II) were obtained in all cases by heating the quaternary alcohols (I) at 100° in a sealed tube with a large excess of acetic anhydride for five to ten hours. The crude onium derivatives were precipitated from the acetic anhydride by the addition of dry ether.

Betaine Ester and Amide Analogs.—Compounds in this group are all derivatives of hygric acid. This substance has been synthesized by Willstätter and Ettlinger[7] in several steps from malonic ester. Hygric acid was here prepared by a method involving the catalytic hydrogenation of 1-methylpyrrole-2-methylcarbonamide, a

(1) This paper is being published, following the death of Professor Renshaw, by his collaborator.

(2) This paper has been constructed from a thesis presented by W. E. Cass, June, 1938, for the degree of Doctor of Philosophy at New York University.

(3) Renshaw and Conn, THIS JOURNAL, **59**, 297 (1937); Renshaw, Ziff, Brodie and Kornblum, *ibid.*, **61**, 638 (1939).

(4) Hunt and Renshaw, *J. Pharmacol.*, **35**, 75 (1929); **37**, 177 (1929).

(5) The physiological activity of these compounds is being determined in coöperation with Drs. Green and Brodie at the Department of Pharmacology, College of Medicine, New York University, and will be reported elsewhere.

(6) Hess, *Ber.*, **46**, 3123 (1913).

(7) Willstätter and Ettlinger, *Ann.*, **326**, 91 (1903).

compound first prepared by Bell.[8] The pyrrole cycle in this substance was reduced to the pyrrolidine cycle both over platinum oxide in acid solution and over Raney nickel under high pressure of hydrogen. Hygric acid methyl amide resulting from the reduction was either used directly for the preparation of amidic derivatives or hydrolyzed to hygric acid. The yield of hygric acid hydrochloride was 70–90% on the basis of the pyrrole amide.

From the hydrochloride of hygric acid the methyl[9] and ethyl[7] esters were obtained, following the method of Fischer[10] for the esterification of amino acids. The yields in this procedure were 60–65%. The amide of hygric acid was obtained in good yield from the methyl ester by the use of methyl alcoholic ammonia.

Most of the onium derivatives of these compounds were obtained in a straightforward manner. The quaternary salts were prepared by treating the free bases in dry ether with an excess of methyl iodide and allowing the solution to stand for several hours at room temperature. The hydrochloride salts of the amides were obtained by passing dry hydrogen chloride into dry ethereal solutions of the free bases. The hydrochloride salts of the esters, prepared in a similar manner, were found too hygroscopic to work with and tended to form oily, rather than crystalline, precipitates. The preparation of the hydroiodide of the ethyl ester of hygric acid was attempted by treating proline[11] ethyl ester in toluene with an equivalent amount of methyl iodide. An oily precipitate resulted from which only the quaternary derivative was isolated. By neutralizing the free hygric esters in alcohol with a dried solution of hydrobromic acid in alcohol, the hydrobromides were obtained and were precipitated in crystalline condition by the addition of dry ether.

Experimental Part

(1-Methylpyrrolidyl-2)-methanol.—A solution of 13.3 g. (0.085 mole) of the ethyl ester of hygric acid (b. p. 74–76° at 12 mm.) in 100 cc. of ethanol (dried with magnesium methylate) was placed in a one-liter, three-necked, round-bottomed flask, fitted with two reflux condensers and a mechanical stirrer. The solution was heated to boiling and then 12 g. (0.52 atom) of sodium was added as rapidly as possible with constant stirring. The solution was heated to 130° on an oil-bath and stirred vigorously until all of the sodium was dissolved and 25 cc. more alcohol was added to prevent the precipitation of sodium ethylate. The solution was allowed to cool and 100 cc. of cold water was added. The basic solution was steam distilled into a slight excess of dilute hydrochloric acid until the steam distillate was no longer basic. The acidic solution was evaporated under reduced pressure at 40–50° until the volume was about 25 cc. The residue was layered with 150 cc. of ether and cooled in an ice–salt bath. The base was liberated with 20% potassium hydroxide solution and then an excess of solid potassium hydroxide was added. The base was extracted with three additional 100-cc. portions of ether and the combined ether extracts were dried, first with potassium carbonate and then with barium oxide. After the removal of the ether through a short bead column, the residue was distilled under reduced pressure. There was obtained 5.1 g. (52%) of a clear, basic-smelling oil of b. p. 67–70° (12 mm.). Most of this substance redistilled at 67–68° (12 mm.).

Anal. Calcd. for $C_6H_{13}ON$: C, 62.57; H, 11.38; N, 12.17. Found: C, 62.74; H, 11.16; N, 11.94.

Chloroaurate.—Yellow powdery precipitate from dilute hydrochloric acid; m. p. 203–207° (dec.) (corr.).

Anal. Calcd. for $C_8H_{14}ONAuCl_4$: Au, 43.32. Found: Au, 43.27, 43.44.

Picrate.—This substance formed with ethereal picric acid solution and was recrystallized from alcohol as fine yellow needles; m. p. 173–174° (dec.) (corr.).

Anal. Calcd. for $C_{12}H_{16}O_8N_4$: C, 41.86; H, 4.68; N, 16.28. Found: C, 41.72, 41.83; H, 4.46, 4.48; N, 16.10.

Reduction of Pyrryl Ketones.—The procedure of Hess[6] was modified as follows: 0.2 mole of 2-acetyl- or 2-propionylpyrrole in 350 cc. of ethanol (dried with magnesium methylate) was placed in a two-liter, three-necked flask, fitted with two large bore reflux condensers and a mechanical stirrer. The solution was heated to boiling and 66 g. (2.9 atoms) of sodium was added as rapidly as possible with constant stirring. Occasionally it was found necessary to cool the flask to moderate the vigor of the reaction. The flask was then heated to 130° on an oil-bath and the solution stirred vigorously until all of the sodium had reacted. About 350 cc. more alcohol was added in several portions to prevent the precipitation of sodium ethylate. Water (400 cc.) was added, the base was steam distilled into a slight excess of hydrochloric acid, and the distillate (2 l.) was evaporated to 50 cc. at 40–50° on a water-bath. The product was isolated as described in the preceding section for (1-methylpyrrolidyl-2)-methanol. The yield was 25–30%.

1-(2-Pyrrolidyl)-ethanol-1 (from 2-Acetylpyrrole).—Oil, b. p. 97–102° (21 mm.) or 188–196° (760 mm.) (Hess,[6] 187–193° at 759 mm.).

Picrate.—This substance was formed with ethereal picric acid solution and was very soluble in water and alcohol; recrystallized from benzene, plus a small amount of absolute alcohol, as small yellow prisms; m. p. 122–130° (corr.).

(8) Bell, *Ber.*, **10**, 1861 (1877).

(9) Trier, *Z. physiol. Chem.*, **67**, 328 (1910).

(10) E. Fischer, *Ber.*, **34**, 433 (1901).

(11) Proline was prepared by the method of Signaigo and Adkins, THIS JOURNAL, **58**, 1122 (1936). In this connection it was found that the reduction of 1,2-dicarbethoxypyrrolidine could also be carried out satisfactorily over platinum oxide in alcohol solution containing a slight excess of hydrochloric acid under 3 atm. of hydrogen.

TABLE I

PYRROLIDINIUM DERIVATIVES

1,1-Dimethyl-(−)-pyrrolidinium iodide	Crystal form[a,b]	Yield, %	M. p., °C. (corr.)	Formula	Iodine, % Calcd.	Found	
2-Hydroxymethyl	Crystalline powder	90	283–284[c]	$C_7H_{16}ONI$	49.36	49.15	49.21
2-Acetoxymethyl	Slightly yellow needles	95	127–128	$C_9H_{18}O_2NI$	42.43	42.20	42.27
2-(α-Hydroxyethyl)[d]	Thick, pointed needles	60	111–123	$C_8H_{18}ONI$	46.81	46.88	46.86
2-(α-Hydroxyethyl)[d]	Triangular plates		127–138	$C_8H_{18}ONI$	46.81	46.84	46.67
2-(α-Acetoxyethyl)[d]	Fine needles or thin plates	95	129–140	$C_{10}H_{20}O_2NI$	40.52	40.35	40.40
2-(α-Hydroxypropyl)[d]	Clumps of needles	50	106–113	$C_9H_{20}ONI$	44.51	44.29	44.40
2-(α-Acetoxypropyl)[d]	Leaflets and needles[e]	25	166–170	$C_{11}H_{22}O_2NI$	38.79	38.79	38.89
2-Carbomethoxy	Clusters of prisms	90	103.5–104	$C_8H_{16}O_2NI$	44.51	44.40	44.41
2-Carbethoxy[f]	Clusters of prisms	90	88–89	$C_9H_{18}O_2NI$	42.43	42.30	
2-Carbamyl	Rhombic crystals	90	133–135	$C_7H_{15}ON_2I$	46.98	46.82	46.90
2-Methylcarbamyl	Cubic crystals	90	130–132.5	$C_8H_{17}ON_2I$	44.67	44.58	44.61

[a] All substances recrystallized from ethyl alcohol–ethyl acetate or by layering alcohol solutions with dry ether. [b] All substances colorless except where otherwise noted. [c] Uncorr. dec. [d] Diastereoisomeric mixture. [e] An oily fraction also obtained. From low yield possibly only one diastereoisomer acetylated readily. [f] First prepared by Willstätter and Ettlinger[7] (m. p. 88–89°).

TABLE II

TERTIARY PYRROLIDINE SALTS

1-Methyl-(−)-pyrrolidine	Crystal form[a,b]	Yield, %	M. p., °C. (corr.)	Formula	Halogen, % Calcd.	Found	
2-Acetoxymethyl, HCl	Clusters of needles[c,d]	80	73–74	$C_8H_{16}O_2NCl$	18.31	18.47	18.52
2-Acetoxymethyl, HBr	Clusters of needles[c,d]	80	74–75	$C_8H_{16}O_2NBr$	33.56	33.92	33.97
2-Benzoxymethyl, HCl	Fine needles	90	162–163	$C_{13}H_{18}O_2NCl$	13.86	13.92	13.94
2-Carbomethoxy, HBr	Glistening prisms[d]	90	108–109.5	$C_7H_{14}O_2NBr$	35.66	35.56	35.58
2-Carbethoxy, HBr	Crystalline powder[c,d]	80	83.5–85	$C_8H_{16}O_2NBr$	33.56	33.90	33.99
2-Carbamyl, HCl	Soft, small plates	95	192–193	$C_6H_{13}ON_2Cl$	21.54	21.50	21.51
2-Methylcarbamyl, HCl	Long needles	95	146.5–148	$C_7H_{15}ON_2Cl$	19.85	19.84	19.85

[a] All substances purified by precipitation from alcohol solution with dry ether. [b] All substances colorless. [c] Tended to precipitate in oily condition. [d] Hygroscopic.

Anal. Calcd. for $C_{12}H_{16}O_8N_4$: N, 16.28. Found: N, 16.10.

1-(2-Pyrrolidyl)-propanol-1 (from 2-Propionylpyrrole).—White crystalline solid; b. p. 96–102° (18 mm.); m. p. 48–50° (Hess,[6] 95–98° at 17 mm. and 50°).

Picrate.—Formed and recrystallized as in the preceding case; short yellow needles; m. p. 124–130° (corr.).

Anal. Calcd. for $C_{15}H_{18}O_8N_4$: N, 15.64. Found: N, 15.83.

Onium Formation from Secondary Amines.—Five-hundredths mole of pyrrolidine alcohol in 40 cc. of alcohol was refluxed for three hours with 0.5 mole of methyl iodide in the presence of 0.1 mole of barium hydroxide. The solution was filtered and barium chloride precipitated by the addition of dry hydrogen chloride. After refiltration the solution was evaporated to dryness in a vacuum desiccator. The crude product was either recrystallized from ethyl alcohol–ethyl acetate or precipitated from its alcohol solution with dry ether.

Catalytic Reduction of 1-Methylpyrrole-2-Methylcarbonamide.[8] **(A) Platinum Oxide Catalyst.**—Reductions were carried out in 20–50% alcohol–water solutions containing a slight excess over the theoretical amount of hydrochloric acid. When absolute alcohol–hydrochloric acid solutions or alcohol–water solutions containing a 100% excess of hydrochloric acid were used, less favorable results were obtained. The use of glacial acetic acid as a solvent gave negative results. Absorption of hydrogen was at all times slow and coagulation of the catalyst was rapid and very marked. The addition of gum arabic solution did not prevent this coagulation. The catalyst was not appreciably reactivated by shaking with air or oxygen; in fact, this procedure seemed to increase coagulation. It was necessary to add small portions of fresh catalyst from time to time to cause absorption of hydrogen to proceed. Fourteen grams (0.1 mole) of the pyrrole amide in 120 cc. of water, 30 cc. of alcohol and 10 cc. of concentrated hydrochloric acid was reduced in the presence of 0.4 g. of platinum oxide under 3 atm. hydrogen in thirty hours. The product was identified as hygric acid methyl amide, a compound obtained by Willstätter[7] in the synthesis of hygric acid, by its chloroaurate (m. p. 148–150°), chloroplatinate (m. p. 197–198°) and picrate (m. p. 214–216° (dec.)).

(B) Nickel Catalyst.—1-Methylpyrrole-2-methylcarbonamide (34.5 g., 0.25 mole) made up to 100 cc. volume with ethanol was hydrogenated over 5 g. of Raney nickel at 150–160° under 130–150 atm. hydrogen in fifteen to twenty hours. The product was identified by its picrate (m. p. 214–216°) as hygric acid methyl amide.

The yield in both cases, figured on the basis of the hygric acid hydrochloride formed by the hydrolysis of the amide, was 70–90%.

Hygric Acid.—The procedure of Willstätter[7] was modified as follows: the solution of the hydrochloride of hygric acid methyl amide was evaporated on a steam-bath and the oily residue hydrolyzed by heating at 125° in a

sealed tube for five hours with a large excess of concentrated hydrochloric acid. The excess hydrochloric acid was evaporated on a steam-bath and the residue made basic with sodium hydroxide. The methylamine was removed by steam distillation. The solution was treated with decolorizing charcoal, acidified with hydrochloric acid, and again evaporated on a steam-bath. Sodium chloride was separated by treating the residue with alcohol and filtering. On evaporation of the alcohol the crude hydrochloride of hygric acid was obtained. This was dried and purified by precipitation from its alcohol solution with either. From alcohol the material crystallized as colorless rhombic plates of m. p. 182–186°.

By treating the hydrochloride with silver carbonate and hydrogen sulfide, hygric acid was obtained and recrystallized from chloroform as white needles of m. p. 168–170° (dec.) (Willstätter,[7] 169–170°). The copper and gold salts of this substance melted at 208–209° and 190–197°, respectively.

Hygric Acid Amide.—Fifteen grams of the methyl ester of hygric acid (b. p. 64–67° at 9 mm.) was dissolved in 100 cc. of methanol–ammonia (saturated at 0°). The solution was let stand overnight in a pressure bottle and then heated to 70–80° for twenty hours. Methyl alcohol and excess ammonia were removed by evaporation in a vacuum desiccator. A white crystalline residue remained. The yield was 12 g. or 90%. The compound was very soluble in water and in most organic solvents except ether, petroleum ether and benzene. It was recrystallized from benzene as fine white needles of m. p. 135.5–137° (corr.).

Anal. Calcd. for $C_6H_{12}ON_2$: C, 56.22; H, 9.44; N, 21.86. Found: C, 56.32, 56.19; H, 9.11, 9.05; N, 21.75, 21.77.

Chloroaurate.—Yellow crystalline precipitate from dilute hydrochloric acid; m. p. 173–174° (corr.) (softens lower).

Anal. Calcd. for $C_6H_{13}ON_2AuCl_4$: Au, 42.12. Found: Au, 41.89.

Chloroplatinate.—Fine orange needles and plates from 50% alcohol; very soluble in water; m. p. 196–197° (dec.) (corr.).

Anal. Calcd. for $C_{12}H_{26}O_2N_4PtCl_6$: Pt, 29.30. Found: Pt, 28.93.

Picrate.—Small yellow prisms or needles from alcohol; m. p. 132.5–133.5° (corr.).

Anal. Calcd. for $C_{12}H_{15}O_8N_5$: N, 19.60. Found: N, 19.52.

Summary

1. A synthesis for hygric acid, involving the catalytic reduction of a pyrrole compound, has been described.

2. Hygric acid amide and (1-methylpyrrolidyl-2)-methanol have been prepared.

3. Several tertiary pyrrolidine and quaternary pyrrolidinium derivatives have been prepared for pharmacological testing.

NEW YORK, N. Y. RECEIVED MARCH 13, 1939

[CONTRIBUTION FROM THE TECHNICAL DIVISION, SHARP & DOHME, INC.]

Substituted Sulfanilamides. I. N^4-Acyl Derivatives[1]

BY ELLIS MILLER, HENRY J. ROCK AND MAURICE L. MOORE

Following the announcement of Domagk[2] that certain sulfonamide compounds were specific remedies in the treatment of experimental streptococcic infections, a large number of derivatives and analogs of sulfanilamide have been prepared and tested in the search for other compounds which would be effective as chemotherapeutic agents.[3–9]

Fourneau, *et al.*,[10] and others have indicated that the antistreptococcic activity of sulfanilamide was reduced greatly by the introduction of an acyl group, such as the formyl or acetyl, on the 4-amino nitrogen. We have found, however, that the N^4-*n*-caproyl derivative of sulfanilamide is as active as the parent compound itself, but much less toxic, in the protection of mice against B. hemolytic streptococci. This paper describes the preparation of a series of N^4-acyl derivatives of sulfanilamide, and other analogs, some of which have been found to be very active as anti-streptococcal agents.

The monocarboxylic acid derivatives were prepared, preferably by the action of the desired acid chloride on a suspension of sulfanilamide in an inert solvent, with or without the presence of an organic base such as pyridine, or by condensing the appropriate 4-acylaminobenzenesulfonyl chloride with ammonia or ammonium carbonate, according to the following equations

(1) In naming these compounds, we have followed the nomenclature described by Crossley, Northey and Hultquist[3] which was suggested by Austin M. Patterson.

(2) Domagk, *Deut. med. Wochschr.*, **61**, 250 (1935).

(3) See Crossley, Northey and Hultquist, THIS JOURNAL, **60**, 2217 (1938), for references to the previous literature on these derivatives; also Crossley, *et al.*, *ibid.*, **60**, 2222, 2225 (1938).

(4) Choudhury, *et al.*, *J. Ind. Chem. Soc.*, **14**, 733 (1937); *C. A.* **32**, 4150 (1938).

(5) Whitby, *Lancet*, **1**, 1210 (1938).

(6) Smyth and Carpenter, *Science*, **87**, 350 (1938).

(7) Kolloff, THIS JOURNAL, **60**, 950 (1938).

(8) Stuart, U. S. Patent 2,117,260; *C. A.*, **32**, 5160 (1938).

(9) Webster and Powers, THIS JOURNAL, **60**, 1553 (1938).

(10) Fourneau, *et al.*, *Compt. rend. soc. biol.*, **122**, 258 (1938).