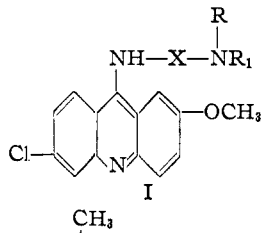
[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

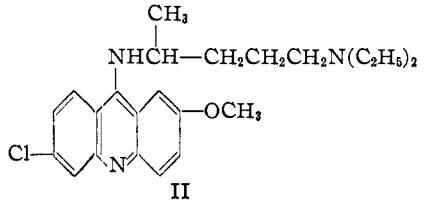
2-Methoxy-6-chloro-9-(N-substituted-amino)-acridines. II. Compounds Derived from Cyclic Secondary Amines[1]

BY JOSEPH CORSE, J. T. BRYANT[2] AND H. A. SHONLE

In a recent paper[3] we described a number of 2-methoxy-6-chloro-9-(dialkylaminoalkylamino)-acridines (I), related to quinacrine (II), but de-



I



II

rived from unsymmetrical secondary amines. We now report some products in which R and R_1 are replaced by a heterocyclic nucleus.

For the most part, the side chain (—X—) is propyl. The 3-*t*-aminopropylamines were made by the reduction of 3-substituted propionitriles, which were made from the cyclic secondary amines and acrylonitrile.[3,4]

The cyclic secondary amines were obtained from Eastman Kodak Company or prepared by catalytic reduction[5] of the aromatic analogs in a bomb with Raney nickel catalyst. Some of the substituted piperidines reacted with great vigor with acrylonitrile and gave excellent yields. "Triton B"[6] was necessary to catalyze the reaction in other cases.

4-(α-Methylpiperidino)-2-butylamine was prepared by reduction of the oxime of 4-(α-methylpiperidino)-2-butanone. This ketone was made by the Mannich reaction between α-methylpiperidine hydrochloride and acetone.[7]

2,1′,2′,3′,4′-Tetrahydroquinolinoethylamine was made by Gabriel's method from 2-bromoethylphthalimide and tetrahydroquinoline. The substituted phthalimide was hydrolyzed with hydrazine hydrate.[8]

The *t*-aminoalkylamines were condensed with 2-methoxy-6,9-dichloroacridine and the reaction product was worked up according to Knunyantz, Chelintzev, Benevolenska, Osetrova and Kursonova.[9]

Pharmacological studies of these compounds were made by Mr. C. L. Rose and Dr. K. K. Chen of these laboratories and will be reported elsewhere.

Experimental[10]

3-Substituted Acrylonitriles.—The secondary amine used was added in small portions through a reflux condenser to an excess of acrylonitrile. If "Triton B" was used, it was then added, and the reaction mixture was heated on a steam-bath overnight. The products were separated by distillation *in vacuo*.

3-Substituted Propylamines.—When reduced catalytically, the nitriles were dissolved in one and one-half volumes of ether and placed in a bomb pre-cooled with Dry Ice. Then 5–10 ml. of liquid ammonia was added, and the reduction was carried out at 1400 to 1800 p.s.i. in normal fashion after the addition of Raney nickel catalyst.

If the nitriles were reduced with sodium, 0.2 mole was dissolved in 400 ml. of hot absolute alcohol and 30 g. of sodium was added rapidly. The alcohol was removed by steam distillation and the residual diamine was separated, dried over potassium hydroxide and distilled.

4-α-Methylpiperidino-2-butylamine.—A mixture of 67.7 g. of α-methylpiperidine hydrochloride, 290 g. of acetone, 160 ml. of water and 90 ml. of 37% formalin was refluxed on a steam-bath overnight. The excess acetone was removed by distillation, and the residue was cooled and made alkaline with sodium hydroxide solution. The resulting oil was extracted with ether and dried over magnesium sulfate. Distillation under reduced pressure gave 47.5 g. of 4-α-methylpiperidino-2-butanone, b. p. 87–91° (17–18 mm.).

Anal. Calcd. for $C_{10}H_{20}ON_2$: N, 15.20. Found: N, 14.92.

Thirty-three and eight-tenths grams of the above ketone was added to a solution of 15.4 g. of hydroxylamine hydrochloride in 20 ml. of water. Then 12.3 g. of sodium carbonate was added and the mixture was heated for three and one-half hours on the steam-bath. Ether extraction and vacuum distillation yielded 25.5 g. of 4-α-methylpiperidino-2-butanone oxime, b. p. 116–120° (2 mm.).

Thirty grams of sodium was added to 25 g. of 4-α-methylpiperidino-2-butanone oxime dissolved in 250 ml. of absolute alcohol. After the reaction was completed, the alcohol was removed by steam distillation and the residual oil was separated and dried. Nine grams of 4-α-methylpiperidino-2-butylamine, b. p. 113–116° (26 mm.), was obtained.

2-Methoxy-6-chloro-9-[2′-(1″,2″,3″,4″-tetrahydroquinolino)-ethylamino]-acridine Dihydrochloride.—A mixture of 20 g. of 1,2,3,4-tetrahydroquinoline, 25 ml. of "Methyl Cellosolve,"[11] 2 g. of potassium iodide and 28.1 g. of 2-bromoethylphthalimide was heated overnight on a steam-bath. The solvent was evaporated *in vacuo* from the dark

(1) Presented at the 108th meeting of the American Chemical Society, September 11 to 15, 1944, New York, N. Y.

(2) Deceased December 30, 1943.

(3) Corse, Bryant and Shonle, THIS JOURNAL, **68**, 1905 (1946).

(4) British Patents 404,744 and 457,621.

(5) Homer Adkins, "Reactions of Hydrogen with Organic Compounds over Copper-Chromium Oxide and Nickel Catalysts," The University of Wisconsin Press, Madison, Wisconsin, 1937, pp. 64–68.

(6) "Triton B," a 37% solution of benzyltrimethylammonium hydroxide, was obtained from Röhm and Haas Company, Philadelphia.

(7) Mannich, *Arch. Pharm.*, **255**, 261 (1917).

(8) Ing and Manske, *J. Chem. Soc.*, 2348 (1926).

(9) (a) Knunyantz, Chelintzev, Benevolenska, Osetrova and Kursonova, *Bull. acad. sci. U. R. S. S.*, 165 (1934). (b) Burckhalter, Jones, Holcomb and Sweet, THIS JOURNAL, **65**, 2012 (1943).

(10) The melting points were determined on a Fisher–Johns block.

(11) "Methyl Cellosolve" was obtained from The Carbide and Carbon Chemicals Corporation.

TABLE I

3-SUBSTITUTED PROPIONITRILES

3-Substituent	Yield, %	B. p., °C.	Mm.	Derivative	Formula	M. p., °C.	Analyses, % N Calcd.	Found
Pyrryl[c]	86[a]	135–150	8–10		$C_7H_8N_2$		23.32	23.77
Pyrrolidino	81	110–112	28	Flavinate	$C_{18}H_{18}O_8N_4S$	140–145	12.78	12.69
Piperidino	74	125–130	27		$C_8H_{14}N_2$		20.27	20.43
2-Methylpiperidino	99	137–140	30		$C_9H_{16}N_2$		18.40	18.54
3-Methylpiperidino	97	126–128	28		$C_9H_{16}N_2$		18.40	18.57
4-Methylpiperidino	87	127–130	27–28		$C_9H_{16}N_2$		18.40	18.06
2,3-Dimethylpiperidino	99[b]	140–142	35		$C_{10}H_{18}N_2$		16.85	17.23
2,4-Dimethylpiperidino	68[b]	130–133	29		$C_{10}H_{18}N_2$		16.85	16.89
2,6-Dimethylpiperidino	82	121–125	26–28		$C_{10}H_{18}N_2$		16.85	17.04

[a] Sodium methoxide was added as a catalyst. [b] "Triton B" was added as a catalyst. [c] Clemo and Ramage, *J. Chem. Soc.*, 49 (1931).

TABLE II

3-SUBSTITUTED PROPYLAMINES

3-Substituent	Yield, %	B. p., °C.	Mm.	Derivative	Formula	M. p., °C.	Analyses, % Calcd.	Found
Pyrryl	86[a]	117–120	30	Picrate	$C_{18}H_{19}O_{14}N_8$	135–137	19.3	19.6
Pyrrolidino	71[b]	85–87	26	Picrate	$C_{19}H_{22}O_{14}N_8$	219–231 dec.	19.12	19.1
Piperidino	77[b]	110–115	31	Picrate	$C_{20}H_{24}O_{14}N_8$	195–204 dec.	18.66	19.03
2-Methylpiperidino	45[b]	163–170	755	Picrate	$C_{21}H_{26}O_{14}N_8$	212–215	18.23	18.17
3-Methylpiperidino	85[b]	110–112	27	Picrate	$C_{21}H_{26}O_{14}N_8$	185–187	18.23	18.2
4-Methylpiperidino	74[b]	90–92	18	Picrate	$C_{21}H_{26}O_{14}N_8$	212–212	18.23	18.23
				Phenylthiourea	$C_{16}H_{25}N_3S$	140–141	14.43	14.15
2,3-Dimethylpiperidino	62[a]	114–115	22	Picrate	$C_{22}H_{28}O_{14}N_8$	208–210	17.83	17.62
2,4-Dimethylpiperidino	52[b]	120–122	34	Picrate	$C_{22}H_{28}O_{14}N_8$	203–205	17.83	17.8
2,6-Dimethylpiperidino	38[b]	122–130	31–32	Picrate	$C_{22}H_{28}P_{14}N_8$	206–208	17.83	18.13

[a] Catalytic reduction in bomb in ether and liquid ammonia at 100–125°. [b] Sodium and alcohol reduction.

TABLE III

2-METHOXY-6-CHLORO-9-AMINOACRIDINE DIHYDROCHLORIDES

9-Substituent	M. p., °C.	Formula	Analyses, % N Calcd.	Found
3-Pyrrylpropylamino	210–213	$C_{21}H_{22}ON_3Cl_3$	9.58	10.4
3-Pyrrolidinopropylamino	228–230	$C_{21}H_{26}ON_3Cl_3$	9.49	9.50
3-Piperidinopropylamino	245–247	$C_{22}H_{28}ON_3Cl_3$	9.19	9.24
3-(2′-Methylpiperidino)-propylamino	255–257	$C_{23}H_{30}ON_3Cl_3$	8.92	9.03
3-(3′-Methylpiperidino)-propylamino	241–242 dec.	$C_{23}H_{30}ON_3Cl_3$	8.92	8.78
3-(4′-Methylpiperidino)-propylamino	256–257 dec.	$C_{23}H_{30}ON_3Cl_3$	8.92	8.79
3-(2′,3′-Dimethylpiperidino)-propylamino	238–240	$C_{24}H_{32}ON_3Cl_3$	8.67	8.65
3-(2′,4′-Dimethylpiperidino)-propylamino	234–236	$C_{24}H_{32}ON_3Cl_3$	8.67	8.72
3-(2′,6′-Dimethylpiperidino)-propylamino	239–241	$C_{24}H_{32}ON_3Cl_3$	8.67	8.61
3-(1′,2′,3′,4′-Tetrahydroquinolino)-ethylamino	156–158	$C_{25}H_{26}ON_3Cl_3$	8.56	8.67
4′-(α-Methylpiperidino)-3′-butylamino	247–248 dec.	$C_{24}H_{32}ON_3Cl_3$	8.67	8.57
2′,4′(or 5′)-Imidazolethylamino	250–255	$C_{19}H_{19}ON_4Cl_3$	13.16	13.3

reaction product and the residue was dissolved in dilute hydrochloric acid, filtered from insoluble material and then made alkaline with sodium carbonate solution. The resulting 2-(1′,2′,3′,4′-tetrahydroquinolino)-ethylphthalimide was recrystallized from aqueous alcohol; m. p. 131–133°.

Anal. Calcd. for $C_{19}H_{18}O_2N_2$: N, 9.14. Found: N, 9.11.

Twelve and two-tenths grams of the phthalimide above was suspended in 50 ml. of absolute alcohol and 2.4 g. of 85% hydrazine hydrate was added. After warming gently five hours, an excess of dilute hydrochloric acid was added and the mixture was filtered after standing an hour. An excess of 12.5 *N* sodium hydroxide was added to the filtrate and the small amount of oil, 2-1(1′,2′,3′,4′-tetrahydroquinolino)-ethylamine, was taken up in methyl acetate. After drying and removing the solvent from the diamine, 10 g. of 2-methoxy-6,9-dichloroacridine and 30 ml. of phenol was added. This reaction mixture was heated on a steam-bath for one hour. The 2-methoxy-6-chloro-9-[2′-(1″,2″,-3″,4″-tetrahydroquinolino)-ethylamino]-acridine was separated by means of its acid solubility and converted into its dihydrochloride salt; m. p. 156–158°.

2-Methoxy-6-chloro-9-[2′-(4″ or 5″-imidazoly)-ethylamino]-acridine Dihydrochloride.—A mixture of 7 g. of 2-methoxy-6,9-dichloroacridine, 30 ml. of phenol, 3.5 g. of potassium carbonate and 4.5 g. of histamine dihydrochloride was stirred and heated on a steam-bath for four and one-half hours. The mass was poured into dilute sodium hydroxide solution and allowed to stand several days after acidification with acetic acid. The solid which formed was then extracted with dilute hydrochloric acid. The product which precipitated with acetone and concentrated hydrochloric acid on chilling was collected on a filter and washed with acetone. There resulted a small yield of the desired 2-methoxy-6-chloro-9-[2′-(4″ or 5″-imidazoyl)-ethylamino]-acridine dihydrochloride; m. p. 250–255°.

We wish to thank Mr. W. L. Brown, Mrs. Shirley Caper and Mr. H. L. Hunter for the microanalyses reported in this paper.

Summary

A number of cyclic secondary amines, pyrrole, pyrrolidine, piperidine, the three monomethylpiperidines, three dimethylpiperidines, 1,2,3,4-tetrahydroquinoline, and imidazole have been used to prepare side chains for 2-methoxy-6-chloro-9-(N-substituted amino)-acridines related to quinacrine.

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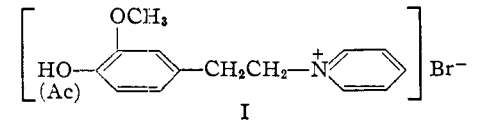
Pyridinium Analogs of the Pressor Amines. II. The Guaiacol Series[1]

BY BYRON RIEGEL AND HAROLD WITTCOFF[2]

The desire for more complete physiological data for correlative purposes prompted the preparation of a series of pyridinium analogs of the pressor amines similar to those described in the preceding paper[3] save that the aromatic nuclei were substituted so as to relate them to guaiacol. Formulas I–IV indicate the products synthesized; compounds I, II and IV having been obtained not as the free phenols, but as the acetates.



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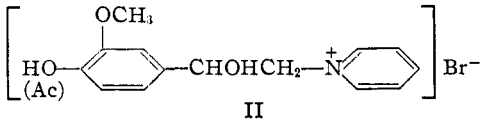

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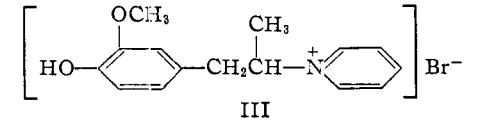

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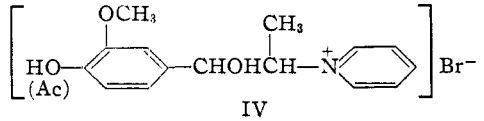

IV

β - (3 - Methoxy - 4 - acetoxyphenyl) - ethylpyridinium bromide (I) resulted from the interaction of anhydrous pyridine with β-(3-methoxy-4-acetoxyphenyl)-ethyl bromide in dry benzene. The bromide, whose structure was deduced indirectly, was obtained by the non-Markownikoff addition of hydrogen bromide to 4-vinylguaiacol acetate according to the conditions which previously had effected a similar reaction with styrene.[4] 4-Vinylguaiacol acetate resulted from the decarboxylation of acetylferulic acid according to the procedure outlined by Reichstein[5] for the preparation of 4-vinylguaiacol. Evidence for reverse hydrobromination derived from the fact that formation of the pyridinium salt required steam-bath temperatures. If the bromide were of secondary nature, the pyridinium salt would have formed only with great difficulty as examples in this and the preceding paper indicate. Indeed, it is known that secondary halides in which the halogen is adjacent to a phenyl nucleus are unstable oils which undergo dehydrohalogenation readily with pyridine to yield the parent vinyl compound.[6] Our attempts to prepare β-(3-methoxy-4-hydroxyphenyl)-ethyl bromide are described in the experimental part.

β - (3 - Methoxy - 4 - acetoxyphenyl) - β - hydroxyethylpyridinium bromide (II) was formed by the high pressure catalytic reduction of 3-methoxy-4-acetoxyphenacylpyridinium bromide. Although the procedure was similar to that used for the successful reduction of phenacylpyridinium bromide,[3] the yield was vitiated by the formation of a by-product, the piperidinium salt of 4-bromoacetylguaiacol acetate which was identified by comparison with an authentic sample.

A desire to prepare β-(3-methoxy-4-hydroxyphenyl)-β-hydroxyethylpyridinium bromide occasioned the preparation of 3-methoxy-4-hydroxyphenacylpyridinium bromide. This material, however, proved too insoluble to be amenable to catalytic reduction.

4-Bromoacetylguaiacol, necessary for the preparation of 3-methoxy-4-acetoxyphenacylpyridinium bromide, was synthesized in 75% yield by the direct interaction of bromoacetyl bromide and guaiacol in a Friedel–Crafts type of reaction. At low temperatures the reaction proceeded smoothly and was not accompanied with demethylation. The direct haloacylation of guaiacol has not previously been described, although similar compounds have been prepared by the simultaneous acylation and demethylation of veratrole.[7] The structure of the brominated ketone was proved by the reductive removal of the halogen atom according to the method of Pratt and Robinson[7] to obtain 4-acetylguaiacol, identified by its phenylhydrazone.

The preparation of 4-(α-hydroxy-β-bromoethyl)-guaiacol acetate, which on reaction with

(1) From the Ph.D. thesis by Harold Wittcoff, June, 1943.

(2) Present address: General Mills, Inc., Minneapolis, Minn.

(3) B. Riegel and H. Wittcoff, THIS JOURNAL, **68**, 1805 (1946).

(4) C. Walling, M. S. Kharasch and F. R. Mayo, *ibid.*, **61**, 2693 (1939).

(5) T. Reichstein, *Helv. Chim. Acta*, **15**, 1450 (1932).

(6) R. Quelet, *Compt. rend.*, **202**, 956 (1936).

(7) D. D. Pratt and R. Robinson, *J. Chem. Soc.*, **123**, 745 (1923).