Anal. Calcd. for $C_{24}H_{22}N_4O_4$: C, 66.96; H, 5.15; N, 13.02. Found: C, 66.65; H, 5.02; N, 13.30.

The **oxime** crystallized from petroleum ether (b. p. 60–75°) in fine colorless needles; m. p. 179.5–180.5°.

Anal. Calcd. for $C_{18}H_{19}NO$: C, 81.47; H, 7.22; N, 5.28. Found: C, 81.27; H, 7.50; N, 5.80.

The *sym.* **trinitrobenzene complex** crystallized from ethanol in orange yellow needles; m. p. 155–156°.

Anal. Calcd. for $C_{24}H_{21}N_3O_7$: C, 62.20; H, 4.57. Found: C, 61.86; H, 4.37.

Epimerization of *d*-Desoxyequilenin (I).—A mixture of 8 mg. of *d*-desoxyequilenin (I) and 8 mg. of 5% palladium on charcoal was heated at 250° under an atmosphere of nitrogen for eight minutes. The product was separated from the catalyst by filtration of a benzene solution. After evaporation and crystallization from petroleum ether (b. p. 60–75°), *d*-desoxyisoequilenin (I) was obtained in colorless prisms; m. p. 106–107° alone and when mixed with a sample obtained by another synthesis (m. p. 107.5–108.5°).[5]

Summary

The application of the Bucherer reaction to *d*-equilenin yielded *d*-3-aminodesoxyequilenin, which represents a new type of steroid amine. Diazotization of the amino group and hydrolysis regenerated *d*-equilenin, while reduction of the diazonium chloride with hypophosphorous acid afforded *d*-desoxyequilenin, which has recently been isolated from the urine of pregnant mares. *d*-Desoxyequilenin was converted into *d*-desoxyisoequilenin by epimerization with palladium.

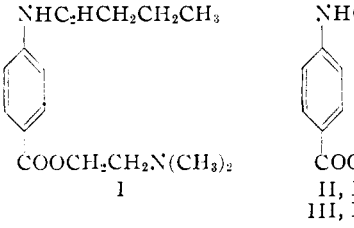
ANN ARBOR, MICHIGAN RECEIVED JULY 14, 1949

[CONTRIBUTION FROM THE STERLING–WINTHROP RESEARCH INSTITUTE]

Dialkylaminoalkyl 4-Alkylaminobenzoates

BY R. O. CLINTON, U. J. SALVADOR, S. C. LASKOWSKI AND J. S. BUCK

In spite of the high local anesthetic activity observed with tetracaine[1] (I), very few basic esters of this type have been investigated. Rab-



I

II, R = $CH_2CH_2CH_2$

III, R = $C(CH_3)_2$

inovich, Konavalova and Uretskaya[2] prepared the tropine, pseudotropine and N-β-hydroxyethylnortropidine esters of 4-butylaminobenzoic acid, and Mndzhoyan[3] has similarly recorded the synthesis of several 1,3-bisdialkylamino-2-propyl 4-butylaminobenzoates. Homologous series (*e. g.*, 2 - diethylaminoethyl 4 - propylaminobenzoate) have also been investigated by Eisleb[4] and by Reasenberg and Goldberg.[5] However, in the latter types the local anesthetic activity is less than that of the corresponding 4-butylaminobenzoates.[1a] In the 4-butylaminobenzoate series, the only simple basic esters reported are tetracaine[1] and the corresponding 2-diethylaminoethyl analog.[6]

In the present work we have prepared a number of dialkylaminoalkyl 4-butylaminobenzoates for the purpose of determining the effect of ester side-chain variance upon activity and toxicity. The investigation was extended to include several dialkylaminoalkyl 4-(5-hydroxyamylamino)-benzoates, (II), and a dialkylaminoalkyl 4-(2,2-dimethyl-3-hydroxypropylamino)-benzoate, (III), in order to evaluate the effect of a hydroxyl group in the 4-alkylamino chain upon the therapeutic index. These types of tetracaine analog have not been previously prepared.

The dialkylaminoalkyl 4-nitrobenzoates were prepared in the conventional manner from 4-nitrobenzoyl chloride and an ω-dialkylaminoalkanol. The 4-nitrobenzoates were readily reduced by any of the standard methods to the 4-aminobenzoates. The 4-alkylaminobenzoates were prepared from the parent 4-aminobenzoates by reductive alkylation with an aldehyde (or ω-hydroxyaldehyde) in the presence of zinc dust and acetic acid.[7] Contrary to the observations of Shapiro,[1b] in our hands this method gave better yields than the alternative routes from 4-butylaminobenzoyl chloride hydrochloride[2,3,8] or alkylation with an alkyl halide and an alkali carbonate.[1b,4] The new compounds in the above series are listed in Table I.

Preliminary testing[9] of the dialkylaminoalkyl 4-butylaminobenzoates indicated for certain members of the series a higher local anesthetic activity than that of tetracaine, both topically and by infiltration. However, in general, this greater activity was accompanied by a proportionate increase in toxicity. Apparently no member of the series possessed a therapeutic index greatly exceeding that of tetracaine.

The inclusion of a hydroxyl group in the 4-

(1) (a) Eisleb, German Patent 582,715, U. S. Patent 1,889,645; (b) Shapiro, *J. Soc. Chem. Ind.*, **64**, 177 (1945).

(2) Rabinovich, Konavalova and Uretskaya, *J. Gen. Chem. (U. S. S. R.)*, **9**, 41 (1939) [*Chem. Abstr.*, **33**, 6323 (1939)].

(3) Mndzhoyan, *ibid.*, **16**, 1033 (1946) (*Chem. Abstr.*, **41**, 2737 [1947]).

(4) Eisleb, German Patents 431,166 and 437,976 (*Frdl.*, **15**, 1440, 1442 (1925-1927)), U. S. Patent 1,550,350.

(5) Reasenberg and Goldberg, THIS JOURNAL, **67**, 933 (1945).

(6) Skita and Stühmer, German Patent 716,668 (*Chem. Abstr.*, **38**, 2345 (1944)).

(7) (a) German Patent 491,856 (*Frdl.*, **16**, 356 (1927)); (b) Clinton, Salvador, Laskowski and Suter, THIS JOURNAL, **70**, 950 (1948).

(8) Graf and Langer, *J. prakt. Chem.*, **148**, 161 (1937).

(9) Complete results will be published at a later date by Dr. F. P. Luduena of these laboratories.

TABLE I

DIALKYLAMINOALKYL 4-ALKYLAMINOBENZOATES

R_2	n	Derivative	M. p., °C.	Formula	Analyses, % Nitrogen Calcd.	Nitrogen Found	Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
				4-Nitrobenzoates, $NO_2C_6H_4COO(CH_2)_nNR_2$						
C_4H_8[a]	2	Picrate	234.5–235.5	$C_{19}H_{19}N_5O_{11}$	2.83[b]	2.85	46.25	46.46	3.88	3.92
C_5H_{10}[c]	2	Picrate	232–234	$C_{20}H_{21}N_5O_{11}$	2.76[b]	2.82	47.34	47.47	4.17	4.23
C_5H_{10}[c]	3	Picrate	204.0–205.5	$C_{21}H_{23}N_5O_{11}$	2.68[b]	2.68	48.37	48.20	4.44	4.76
C_6H_{12}[d]	2	Base	63.5–65.0	$C_{16}H_{20}N_2O_4$	4.79[b]	4.76	...	...	..	..
C_6H_{12}[d]	2	Picrate	224.5–225.5	$C_{21}H_{23}N_5O_{11}$	2.68[b]	2.70	...	...	..	..
C_6H_{12}[d]	3	Picrate	196.0–197.0	$C_{22}H_{25}N_5O_{11}$	2.61[b]	2.62	49.34	49.43	4.70	4.97
C_6H_{12}[e]	2	Picrate	193.0–194.0	$C_{21}H_{23}N_5O_{11}$	2.68[b]	2.70	48.37	48.29	4.44	4.70
C_6H_{12}[e]	3	Picrate[f]	202.0–203.0	$C_{22}H_{25}N_5O_{11}$	2.61[b]	2.64	49.34	49.41	4.70	4.61
C_7H_{14}[g]	2	Base	103.5–104.5	$C_{16}H_{22}N_2O_4$	4.57[b]	4.59	62.72	62.65	7.24	7.42
C_7H_{14}[g]	2	Picrate	208.6–209.8	$C_{22}H_{25}N_5O_{11}$	2.61[b]	2.65	49.34	49.39	4.70	4.92
				4-Aminobenzoates, $NH_2C_6H_4COO(CH_2)_nNR_2$						
C_4H_8[a]	2	Picrate[h]	168.0–169.0	$C_{19}H_{21}N_5O_9$	6.05[b]	5.93	...	...	..	..
C_5H_{10}[c]	2	[i]	.....	.....	....	...	...	...	..	..
C_5H_{10}[c]	3	Base	Oil	$C_{15}H_{22}N_2O_2$	10.68	10.47	68.67	68.60	8.45	8.34
C_5H_{10}[c]	3	Picrate	161.5–162.5	$C_{21}H_{25}N_5O_9$	5.70[b]	5.57	...	...	..	..
C_6H_{12}[d]	2	Base	107.5–109.0	$C_{15}H_{22}N_2O_2$	10.68	10.64	68.67	68.92	8.45	8.39
C_6H_{12}[d]	2	Dipicrate	160.0–161.0	$C_{27}H_{28}N_8O_{16}$	3.88[b]	3.87	...	...	..	..
C_6H_{12}[d]	3	Base	Oil	$C_{16}H_{24}N_2O_2$	10.14	10.11	69.45	69.45	8.75	8.64
C_6H_{12}[d]	3	Picrate	143.0–144.0	$C_{22}H_{27}N_5O_9$	5.55[b]	5.47	...	...	..	..
C_6H_{12}[e]	2	Base	84.5–86.5	$C_{15}H_{22}N_2O_2$	10.68	10.59	68.67	68.85	8.45	8.67
C_6H_{12}[e]	2	Dipicrate	119.0–120.0	$C_{27}H_{28}N_8O_{16}$	3.88[b]	3.86	...	...	..	..
C_6H_{12}[e]	3	Base[j]	Oil	$C_{16}H_{24}N_2O_2$	10.14	10.26	69.53	69.86	8.75	8.90
C_6H_{12}[e]	3	Dipicrate	167.0–168.5	$C_{28}H_{30}N_8O_{16}$	3.81[b]	3.91	...	...	..	..
C_7H_{14}[g]	2	Base	101.9–103.4	$C_{16}H_{24}N_2O_2$	10.14	10.20	69.53	69.81	8.75	8.95
C_7H_{14}[g]	2	Dipicrate	171.0–172.0	$C_{28}H_{30}N_8O_{16}$	3.81[b]	3.57	...	...	..	..
				4-Butylaminobenzoates, $C_4H_9NHC_6H_4COO(CH_2)_nNR_2$						
C_4H_8[a]	2	Base	61.5–62.5	$C_{17}H_{26}N_2O_2$	9.64	9.48	70.30	70.61	9.02	8.95
C_4H_8[a]	2	Hydriodide[k]	154.0–155.0	$C_{17}H_{27}IN_2O_2$	6.69	6.55	48.81	48.95	6.50	6.40
C_4H_8[a]	2	Picrate	123.5–124.5	$C_{23}H_{29}N_5O_9$	5.38[b]	5.18	...	...	..	..
C_5H_{10}[c]	2	Base	Oil	$C_{18}H_{28}N_2O_2$	9.20	9.03	71.02	71.36	9.27	9.52
C_5H_{10}[c]	3	Base	Oil	$C_{19}H_{30}N_2O_2$	8.79	8.67	71.66	71.79	9.49	9.59
C_6H_{12}[d]	2	Base	Oil	$C_{19}H_{30}N_2O_2$	8.79	8.66	71.66	71.70	9.49	9.39
C_6H_{12}[d]	3	Base	Oil	$C_{20}H_{32}N_2O_2$	8.42	8.27	72.24	72.29	9.70	9.72
C_6H_{12}[d]	3	Picrolonate	143.0–144.0	$C_{36}H_{40}N_6O_7$	4.68[b]	4.48	...	...	..	..
C_6H_{12}[e]	2	Base	Oil	$C_{19}H_{30}N_2O_2$	8.79	8.55	71.66	71.80	9.49	9.50
C_6H_{12}[e]	2	Flavianate	184.5–185.5	$C_{29}H_{36}N_4O_{10}S$	2.21[b]	2.26	...	...	..	..
C_6H_{12}[e]	3	Base	Oil	$C_{20}H_{32}N_2O_2$	8.42	8.39	72.24	72.63	9.70	9.49
C_7H_{14}[g]	2	Base	81.2–82.4	$C_{20}H_{32}N_2O_2$	8.42	8.34	72.24	72.32	9.70	9.48
				4-(5-Hydroxyamylamino)-benzoates, $HO(CH_2)_5NHC_6H_4COO(CH_2)_nNR_2$						
$(CH_3)_2$	2	Base	65.6–66.8	$C_{16}H_{26}N_2O_3$	9.52	9.27	65.27	65.50	8.90	8.90
$(CH_3)_2$	2	Flavianate[l]	167.4–168.6	$C_{26}H_{32}N_4O_{11}S$	2.30[b]	2.27	...	...	..	..
$(CH_3)_2$	2	Phosphate	128.8–130.2	$C_{16}H_{29}N_2PO_7$	7.14	6.94	48.97	48.77	7.45	7.45
$(C_2H_5)_2$	2	Flavianate[m]	143.5–144.5	$C_{28}H_{36}N_4O_{11}S$	2.20[b]	2.14	...	...	..	..
$(C_2H_5)_2$	2	Phosphate[n]	136.0–136.8	$C_{18}H_{33}N_2PO_7$	6.66	6.64	...	...	..	..
C_6H_{12}[d]	2	Base	Oil	$C_{20}H_{32}N_2O_3$	8.04	8.23	68.93	69.04	9.25	9.30
C_6H_{12}[d]	3	Base	Oil	$C_{21}H_{34}N_2O_3$	7.73	8.00	69.56	69.74	9.45	9.23
C_7H_{14}[g]	2	Base	Oil	$C_{21}H_{34}N_2O_3$	....	...	69.56	69.47	9.45	9.26
C_7H_{14}[g]	2	Dipicrate	174.0–176.2	$C_{33}H_{40}N_8O_{17}$	3.41[b]	3.69	...	...	..	..

[a] Pyrrolidyl-1. [b] Basic amino nitrogen, by titration with perchloric acid in glacial acetic acid solution. [c] 2-Methylpyrrolidyl-1. [d] 2-Methylpiperidyl-1. [e] 3-Methylpiperidyl-1. [f] The hydrochloride, m. p. 190–192°, has been reported by McElvain, THIS JOURNAL, 49, 2835 (1927), U. S. Patent 1,784,903. [g] 2,6-Dimethylpiperidyl-1. [h] The base melted at 100–101°; Blicke and Blake, THIS JOURNAL, **53**, 1015 (1931), reported m. p. 98–100°. [i] A crude crystalline base, m. p. 74–77°, was obtained, but it could not be purified or characterized by a derivative. [j] The hydrochloride, m. p. 158–160°, has been reported by McElvain, footnote *f*. [k] Calcd.: HI, 30.58. Found: HI, 30.80. [l] Calcd.: S, 5.27. Found: S, 5.23. [m] Calcd.: S, 5.04. Found: S, 5.07. [n] Calcd.: H_3PO_4, 23.32. Found: H_3PO_4, 23.42.

alkylamino chain greatly decreased both activity and toxicity. The dialkylaminoalkyl 4-(ω-hydroxyalkylamino)-benzoates showed a therapeutic index slightly lower than that of procaine.

Experimental[10]

2-(3-Methylpiperidyl-1)-ethanol.—The reaction between two moles of 3-methylpiperidine[11] and one mole of ethylene chlorohydrin in aqueous solution gave a 46% yield (based on the chlorohydrin) of product: colorless, somewhat viscous oil, b. p. 98.0° (15.0 mm.); $n^{25}D$ 1.4708.

Anal. Calcd. for $C_8H_{17}NO$: N, 9.77. Found: N, 9.68.

The **picrate** formed canary yellow needles from absolute alcohol, m. p. 133.5–134.5°.

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: N, 3.76. Found: N,[12] 3.74.

When the compound was prepared by the reaction of 3-methylpiperidine with ethylene oxide in aqueous solution, there was obtained a 62% yield of 2-(3-methylpiperidyl-1)-ethanol, $n^{25}D$ 1.4705.

2-(2,6-Dimethylpiperidyl-1-)-ethanol.—The condensation of 2,6-dimethylpiperidine[11] with ethylene oxide in water gave a 53% yield of product. When the reaction was carried out in methanol[13] there was obtained a 67% yield of product. The condensation was very slow and required long refluxing for completion. The steric effects of the two α-methyl groups were probably responsible for the much lower yield in comparison to that obtainable with 2-methylpiperidine under similar conditions.[14] The pure compound boiled at 69.0° (0.20 mm.), $n^{25}D$ 1.4820.

Anal. Calcd. for $C_9H_{19}NO$: N, 8.90. Found: N, 8.91.

The **picrate** crystallized from alcohol in long, slender yellow needles, m. p. 146.5–147.5°.

Anal. Calcd. for $C_{15}H_{22}N_4O_8$: N[12], 3.63. Found: N[12], 3.63.

The **hydrochloride** formed white needles from isopropyl alcohol–ethyl acetate, m. p. 211.0–212.0°.

Anal. Calcd. for $C_9H_{20}ClNO$: Cl, 18.30. Found: Cl, 18.01.

The **benzoate hydrochloride** crystallized in white needles from acetone–absolute alcohol, m. p. 188.6–189.8°.

Anal. Calcd. for $C_{16}H_{24}ClNO_2$: C, 64.52; H, 8.12; Cl, 11.91. Found: C, 64.69; H, 7.96; Cl, 11.81.

3-(2-Methylpyrrolidyl-1)-propanol.—The reaction between equimolecular proportions of 2-methylpyrrolidine[14] and trimethylene chlorohydrin in the presence of aqueous sodium hydroxide[15] gave a 51% yield of product: colorless mobile oil, b. p. 86.5° at 6.0 mm., $n^{25}D$ 1.4671.

Anal. Calcd. for $C_8H_{17}NO$: N, 9.78; OH, 11.87. Found: N, 9.66; OH, 11.84.

The **picrate** crystallized from alcohol in canary-yellow needles, m. p. 77.5–78.5°.

Anal. Calcd. for $C_{14}H_{20}N_4O_8$: N, 11.29. Found: N,[16] 11.30.

The **picrolonate** formed yellow needles from alcohol, m. p. 159.0–160.0°.

Anal. Calcd. for $C_{18}H_{25}N_5O_6$: N, 6.88. Found: N,[16] 7.17.

2-(2-Methylpyrrolidyl-1)-ethanol,[14] 2-(2-methylpiperidyl-1)-ethanol[11] and 3-(3-methylpiperidyl-1)-propanol[11] were prepared by literature methods. 2-(**Pyrrolidyl-1**)-**ethanol**[17] was obtained in 17–25% yields by the reaction between ethanolamine and 1,4-dichlorobutane in the presence of sodium hydroxide.[18]

The **cinnamate hydrochloride** formed white cottony needles from acetone–absolute alcohol–ether, m. p. 164.4–166.0°.

Anal. Calcd. for $C_{15}H_{20}ClNO_2$: C, 63.94; H, 7.11; N, 4.97; Cl, 12.58. Found: C, 63.96; H, 7.11; N, 5.12; Cl, 12.50.

Dialkylaminoalkyl 4-Nitrobenzoates.—These compounds were readily prepared in the usual manner from 4-nitrobenzoyl chloride and an ω-dialkylaminoalkanol in dry benzene, with subsequent conversion of the hydrochloride to the free base by means of sodium hydroxide solution. This method, however, often gave a colored base, which was purifiable only with difficulty. The use of the sodium bicarbonate–water–chloroform procedure, previously applied only to amines,[7b] gave excellent yields of pure bases. The nitro bases were generally pale yellow, mobile oils, which yielded crystalline derivatives only with difficulty. These compounds are listed in Table I.

Dialkylaminoalkyl 4-Aminobenzoates.—The reduction of the dialkylaminoalkyl 4-nitrobenzoates was readily carried out with ferrous sulfate–ammonia,[7b] by West's method,[19] or by catalytic reduction with platinum oxide or Raney nickel. The yields, by any of these methods, were high. The dialkylaminoalkyl 4-aminobenzoates were viscous, pale yellow oils, which did not readily yield crystalline derivatives. One noteworthy property of the compounds was observed in the preparation of picrates. In all cases, the base was treated with an excess of alcoholic picric acid; with about one-half of the compounds a monopicrate was obtained, while the others gave dipicrates. The results are best explained on steric grounds. The new 4-aminobenzoates and their derivatives are listed in Table I.

Dialkylaminoalkyl 4-Butylaminobenzoates.—Reductive alkylation of the dialkylaminoalkyl 4-aminobenzoates with butyraldehyde, zinc dust and acetic acid[7] gave nearly quantitative yields of the desired bases. In most cases the bases were mobile, pale yellow oils, which did not yield crystalline salts. The bases were purified by transference from the base to the hydrochloride several times in solution, followed by removal of the solvent at 80° and 0.01 mm. These compounds are listed in Table I.

Dialkylaminoalkyl 4-(5-Hydroxyamylamino)-benzoates, II.—These compounds were obtained in high yield by the procedure cited above, using 5-hydroxypentanal[14,20] in place of butyraldehyde. Reductive alkylation of ethyl 4-aminobenzoate with 5-hydroxypentanal gave an 85% yield of **ethyl 4-(5-hydroxyamylamino)-benzoate**; white prisms from benzene–Skellysolve B, m. p. 61.6–62.6°.

Anal. Calcd. for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.73; H, 8.20; N, 5.48.

Hydrolysis with aqueous-alcoholic sodium hydroxide solution gave a quantitative yield of **4-(5-hydroxyamylamino)-benzoic acid**, m. p. 126.2–127.4°.

Anal. Calcd. for $C_{12}H_{17}NO_3$: N, 6.27. Found: N, 6.14.

2-Dimethylaminoethyl 4-(2,2-Dimethyl-3-hydroxypropylamino)-benzoate, III.—The reductive alkylation of 2-dimethylaminoethyl 4-aminobenzoate with 2,2-dimethyl-3-hydroxypropionaldehyde afforded an 80% yield of pure base, white prisms from ethyl acetate–Skellysolve B, m. p. 87.0–88.0°.

Anal. Calcd. for $C_{16}H_{26}N_2O_3$: C, 65.27; H, 8.90; N, 9.52. Found: C, 65.09; H, 8.95; N, 9.36.

The **flavianate** crystallized from alcohol in orange needles, m. p. 173.4–174.7°.

Anal. Calcd. for $C_{26}H_{32}N_4O_{11}S$: S, 5.27. Found: S, 5.29.

The **hydrochloride** formed white prisms from absolute alcohol, m. p. 192.0–193.7°.

(10) All melting and boiling points are corrected. The authors are indebted to Mr. Morris E. Auerbach and staff for the analyses.

(11) McElvain and Carney, THIS JOURNAL, **68**, 2592 (1946).

(12) Basic amino nitrogen by titration with perchloric acid in acetic acid solution.

(13) *Cf.* Pollard, THIS JOURNAL, **57**, 1988 (1935).

(14) Clinton, Salvador and Laskowski, *ibid.*, **71**, 3366 (1949).

(15) *Cf.* Adams, *et al.*, *ibid.*, **59**, 2249 (1937).

(16) Nitro nitrogen by titration with titanous chloride.

(17) v. Braun, Braunsdorf and Räth, *Ber.*, **55**, 1666 (1922).

(18) Unpublished work by Dr. A. W. Ruddy of these laboratories.

(19) West, *J. Chem. Soc.*, **127**, 494 (1925).

(20) Woods and Sanders, THIS JOURNAL, **68**, 2111 (1946).

Anal. Calcd. for $C_{16}H_{27}ClN_2O_3$: N, 8.47; Cl, 10.72. Found: N, 8.40; Cl, 10.48.

Summary

A series of dialkylaminoalkyl 4-butylamino-benzoates, 4-(5-hydroxyamylamino)-benzoates, and intermediates in their preparation have been described. The 4-alkylamino compounds showed marked local anesthetic activity in most cases.

RENSSELAER, N. Y. RECEIVED JULY 20, 1949

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

Synthesis of the Branched Chain 5-Isopropylaminoamyl and 4-Isopropylaminobutyl Ethers and of the Bromides Derived from Them[1,2]

BY ROBERT C. ELDERFIELD, BURNETT M. PITT AND IRIS WEMPEN

The series of drugs comprising derivatives of 8-aminoquinoline carrying an alkylaminoalkylamino or aminoalkylamino side chain in the 8-position is unique in that the members of the group are the only drugs presently known which possess the property of effecting a high percentage of permanent cures of relapsing vivax malaria when administered in conjunction with quinine. Despite the impressive amount of work which has been done along synthetic lines in the exploitation of this group of substances, several gaps remain to be filled in before a complete understanding of the relationship between structure and antimalarial action can be achieved.[3] While the most effective 8-aminoquinoline drugs presently known carry a methoxyl group in the 6-position of the quinoline ring, the effect of other substituents in the aromatic portion of the drug molecules is incompletely understood and forms the basis for separate investigations both in these laboratories and elsewhere.

In the 6-methoxy-8-aminoquinoline series, available data on the effect of branching the carbon side chain between the two nitrogen atoms is scanty if one excludes the familiar 1-methyl-4-alkylaminobutylamino configuration present in such drugs as pamaquin and isopentaquin. Indeed only two drugs embracing such variations have been reported in the literature, namely, SN-13,355 and SN-13,371.[3] Available pharmacological data on these two drugs are summarized in Table I together with similar data for pamaquin as a point of reference.[3] In addition to the data of Table I, SN-13,355 showed about one-half the toxicity of pamaquin in the monkey.

An analysis of the meager data available (Table I) indicates that in SN-13,355 in which the alkyl side chain is branched at the 4- rather than at the 1-carbon atom, both specificity to the host and to the test species of malaria have disappeared as compared to pamaquin. In SN-13,371 in which branching of the alkyl side chain occurs both at the 1- and 4-carbon atoms, such species and/or host specificity is partially restored. Further, the reported toxicity of SN-13,355 compares at worst not unfavorably with that of pamaquin.

In the light of the above data, it appeared to be worth while to undertake a systematic study of the effect of branching of the alkyl side chain of such drugs other than at the 1-carbon atom. In order to limit the scope of the investigation certain limitations have been imposed. The terminal amino group of the side chain has been restricted to the isopropylamino group because of the apparently unique effectiveness of this group on general curative antimalarial action and toxicity.[3,4] Further, the number of carbon atoms in the straight chain connecting the two nitrogen atoms of the side chain of the drugs has been limited to 4 and 5 and the total number of carbon atoms between the two nitrogens of the side chain has been limited to 5 and 6. The basis for this rather arbitrary choice is found in the pharmacology of a number of 8-aminoquinoline derivatives in which such variations are taken into account.[3] The arrangements selected appear to be the optimum ones.

As defined by the above restrictions, the 6-methoxy-8-aminoquinoline drugs selected for synthesis as candidate antimalarials are shown in Table II.

The most convenient procedure for the preparation of 8-aminoquinoline drugs consists in the alkylation of an 8-aminoquinoline with an appropriate amino halide.[5] In the present work the synthesis of the isopropylamino ethers XI–XIX and of the amino halides derived from them by cleavage of the ethers is described. The yields, properties and analytical data for the isopropylamino ethers are tabulated in Table III and the salts prepared for characterization of several of them are also listed in this table.

(1) This work was done with the aid of a grant from the National Institutes of Health to Columbia University.

(2) A portion of the work here described forms part of a dissertation submitted in partial fulfillment of the requirements for the degree of Doctor of Philosophy by Burnett M. Pitt at Columbia University.

(3) For a survey of existing data on such substances see Wiselogle, "Survey of Antimalarial Drugs," Edwards Bros., Ann Arbor, Mich., 1946.

(4) Private communications from Dr. Leon Schmidt, Christ Hospital Institute for Medical Research, Cincinnati, Ohio, and Dr. Alf Alving, University of Chicago.

(5) See THIS JOURNAL, August, 1946, for a number of papers dealing with this.