funnel, and reflux condenser, protected from moisture with a soda lime tube, were placed 8 g. of lithium aluminum hydride and 500 ml. of anhydrous ether. When solution had been effected a solution of 14.8 g. (0.066 mole) of *N*-dimethylaminopropyl-3-azabicyclo[3.2.1]octane-2,4-dione in 200 ml. of anhydrous ether was added over a period of 10 min. The reaction mixture was stirred for 3 hr. and then decomposed by slow addition of water. A slight excess of water was added, the mixture stirred for 0.5 hr., and inorganic solids filtered off. The solid cake was well washed with ether. The ethereal solutions were combined and dried over sodium sulfate, the ether stripped off, and the resultant oil distilled *in vacuo* to yield 9.6 g., 74%, of base boiling at 60°/0.3 mm., n_D^{20} 1.4772. The *dihydrochloride*, prepared in the usual manner by treating an isopropyl alcohol solution with ethanolic-HCl, melted after recrystallization from methanol-ether at 280–282°. The *dimethiodide* was not formed by refluxing the base with excess methyl iodide in methanol. The following procedure was employed. Into a bomb tube were placed 4 g. of the base, 20 ml. of absolute methanol, and 10 ml. of methyl iodide. The tube was sealed and heated at 100° for 4 hr. On cooling much crystalline material separated. The tube was opened and the crystalline residue dissolved in boiling methanol, filtered, and refrigerated. Most of the bis-quaternary salt precipitated on cooling. The remainder was precipitated with ether. After recrystallization from methanol-ether it melted at 270–272° dec.

WASHINGTON, D. C.

[CONTRIBUTION FROM THE CHEMICAL RESEARCH LABORATORY OF A. H. ROBINS COMPANY, INC.]

Preparation of 4-Amino-1-butanols and Some Derivatives of Pharmacological Interest

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Received February 18, 1957

The 4-alkylamino and 4-dialkylamino-1-butanols are prepared in good yields by lithium aluminum hydride reduction of the reaction product of equimolar amounts of butyrolactone and a primary or secondary amine. The use of two moles of amine results in the formation of *N,N'*-symmetrically substituted putrescines. The 3-aminopropanols are prepared in a similar manner by the substitution of propiolactone for butyrolactone. The 3,4,5-trimethoxybenzoates, the diphenylacetates, and the benzhydryl ethers of several of the aminobutanols and of *N*-3-hydroxypropylpiperidine and their quaternary salts have been prepared and their pharmacological activity examined.

In view of the fact that the reserpine structure contains a hydroxyl group esterified with 3,4,5-trimethoxybenzoic acid separated from a tertiary amino group by four carbon atoms it seemed of interest to examine several derivatives of the 4-dialkylamino-1-butanols for pharmacological activity. A similarly inspired investigation[1] has recently led to the synthesis of aminoethyl-, aminopropyl-, and aminomethylcyclohexyl-3,4,5-trimethoxybenzoates. Although little interest has been directed toward the 4-amino-1-butanol system some derivatives have been reported to possess pharmacological activity. For example, the diphenylacetate of 4-morpholinebutanol[2] has been reported to be 60% as effective as papaverine in its antispasmodic action on the isolated guinea pig ileum. In addition, it has been reported that tests in laboratory animals indicated the *p*-aminobenzoate of 4-diethylamino-1-butanol[3] to be a more effective local anesthetic than cocaine.

The present work is concerned with the synthesis of the 3,4,5-trimethoxybenzoate and diphenylacetate esters as well as the benzhydryl, and *p*-chlorobenzhydryl ethers of some of the 4-dialkylamino-1-butanols. The detailed pharmacology of the compounds will be the subject of separate communications.[4]

The *N*-substituted 4-amino-1-butanols have generally been prepared by (1) the alkylation of amines with 4-halo-1-butanol[2,5] or its esters[6] and (2) by the lithium aluminum hydride reduction of *N,N*-dialkylsuccinamates[7] or succinamic acids.[8] Catalytic hydrogenation of β-carbethoxypropionylpiperidine to 4-piperidinobutane-1-ol has also been successful.[9]

The disadvantages of the alkylation method are obvious since mixtures are usually obtained. By an adaptation of the reduction method it has been found that the 4-dialkylamino-1-butanols are easily prepared in yields of the order of 60% from the readily available starting materials: butyrolactone,

(1) F. M. Miller and M. S. Weinberg, Abstracts, Atlantic City Meeting, AMERICAN CHEMICAL SOCIETY, p. 11N (1956).

(2) L. C. Cheney and W. G. Bywater, *J. Am. Chem. Soc.*, **64**, 970 (1942).

(3) M. G. Kartvelishvili, *Farmakol. i. Toksikol.*, **8**, No. 3, 32 (1945); *Chem. Abstr.* **40**, 6683 (1946).

(4) The pharmacological studies were carried out by Hazleton Laboratories, Inc., Falls Church, Va., and by Doctor J. M. Little and associates, Department of Pharmacology and Physiology, The Bowman-Gray School of Medicine, Winston-Salem, N. C., and will be the subject of separate communications.

(5) E. Wilson and M. Tishler, *J. Am. Chem. Soc.*, **73**, 3635 (1951).

(6) (a) E. Szarvasi, *Bull. soc. chim. France*, 647 (1949); (b) L. M. Smorgonskii and Y. L. Gol'dfarb, *J. Gen. Chem. (USSR)*, **10**, 1113 (1940); *Chem. Abstr.*, **35**, 4011 (1941).

(7) A. W. D. Avison, *J. Applied Chem. (London)*, **1**, 469 (1951).

(8) R. E. Holmen and D. D. Carroll, *J. Am. Chem. Soc.*, **73**, 1859 (1951).

(9) J. C. Sauer and H. Adkins, *J. Am. Chem. Soc.*, **60**, 402 (1938).

the dialkylamine, and lithium aluminum hydride. The method appears to be general and can also be used for the preparation of the monoalkylaminobutanols, although in our hands the yields have averaged slightly lower than is the case for the dialkyl derivatives. However, the yields compare favorably with those reported for previous methods.

The method consists of the reaction of butyrolactone with an amine to give the γ-hydroxybutyramide (I)[10] and probably the γ-aminobutyric acid (II), and the reduction of the crude reaction mixture to the aminobutanol (III).

Spath[10] has isolated γ-hydroxybutyramides from the reaction of butyrolactone and amines by distillation; however, the reaction mixture must also contain some of the amino acid, possibly in equilibrium with the hydroxyamide *per se* or through the intermediate *N*-alkylbutyrolactam, because when an excess of amine is used there is also formed the γ-dialkylaminobutyramide (IV). The evidence for the presence of IV is the formation of the tetrasubstituted putrescine (V) when the mixture is reduced with lithium aluminum hydride. Tetramethylputrescine and 1,4-bis(1-piperidino)butane have been prepared in this manner. A general method is thus provided for the preparation of *N,N,N',N'-tetrasubstituted putrescines.*

The 3-aminopropanols may be prepared in a similar manner by the substitution of propiolactone for butyrolactone. 3-Hydroxypropylpiperidine was prepared in 68% overall yield from propiolactone, piperidine, and lithium aluminum hydride.

The aminobutanols prepared by this method and their properties are given in Table I.

The diphenylacetates and 3,4,5-trimethoxybenzoates were prepared from the amino alcohol and the acid chloride; the benzhydryl ethers, from the amino alcohol and the benzhydryl halide. These compounds and their properties are given in Tables II and III.

PHARMACOLOGY[4]

The benzhydryl ether of 4-hydroxybutylpiperidine and the diphenylacetate of 3-hydroxypropylpiperidine completely relaxed the histamine-induced contraction of the isolated guinea pig tracheal chain at a dilution of 1:100,000, and the citrate salt of the *p*-chlorobenzhydryl ether of diethylaminobutanol was active at the same concentration against egg white-induced contraction. The other tertiary aminobenzhydryl ethers and diphenylacetates were essentially devoid of antihistaminic or bronchodilator activity. The most significant activity of the quaternary salts of these compounds was the enhancement of the adrenalin response in the anesthetized dog.

The trimethoxybenzoates were devoid of any reserpine-like activity as indicated by their failure to prolong the hexobarbital sleeping time in mice and their failure to effect the fall-off time of rats from a rotating rod.

EXPERIMENTAL[11]

The 4-amino-1-butanols were all prepared in essentially the same manner. A typical procedure is illustrated by the synthesis of *4-dibutylamino-1-butanol.* A mixture of 68.8 g. (0.8 mole) of butyrolactone and 104 g. (0.8 mole) of di-*n*-butylamine was heated at 150° for 4 hr. The resulting mixture, usually a sirup, was dissolved in ether and added dropwise to a stirred solution of 25.1 g. (0.68 mole) of lithium aluminum hydride in 300 ml. of ether. After complete addition the reaction mixture was stirred and refluxed for 1 hr. The excess hydride was decomposed with water, and the mixture was filtered. The filtrate was concentrated, and the residue was fractionally distilled at reduced pressure. Yield 97.4 g. (62%); b.p. 172–175° (40 mm.).

When the starting amine boiled below 150° the reaction with butyrolactone was carried out at reflux until the pot temperature reached 150° where it was maintained for 4 hr. When the starting amine was dimethylamine or diethylamine the reaction was run in a sealed tube at 150°. The properties of the aminobutanols thus prepared are given in Table I.

N,N,N',N'-Tetramethylputrescine.[12] A mixture of 172 g. (2.0 mole) of butyrolactone and 180 g. (4.0 mole) of dimethylamine was heated in two sealed tubes at 200° for 4 hr. The resulting reaction mixture was heated to 125° *in vacuo*, and reduced with 125 g. of lithium aluminum hydride, as described above. There was obtained 86 g. (30%) of *N,N,N',N'*-tetramethylputrescine, b.p. 78–80° (28 mm.); n_D^{25} 1.4261; d^{27} 0.7864.

Anal. Calcd. for $C_8H_{20}N_2$: C, 66.60; H, 13.97. Found: C, 66.78; H, 13.95.

The dipicrate melted 203–205° (Lit.[12] 198°).

Anal. Calcd. for $C_{20}H_{26}N_8O_{14}$: C, 40.17; H, 4.35. Found: C, 40.35; H, 4.26.

(10) E. Spath and J. Lintner, *Ber.*, 69*B*, 2727 (1936).

(11) All melting points are corrected. Carbon and hydrogen analyses by Schwarzkopf Microanalytical Laboratory, 56-19 37th Avenue, Woodside 77, New York.

(12) R. Willstätter and W. Huebner, *Ber.*, **40**, 3869 (1907).

TABLE I

4-DIALKYLAMINO-1-BUTANOLS, $RR'NCH_2CH_2CH_2CH_2OH$

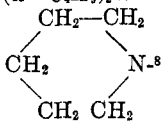
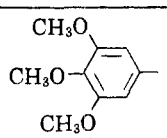
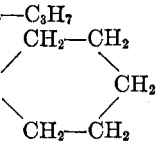
R, R′	B.P., °C.	Mm.	Yield, %	n_D^{25}	d^t	Formula	ANALYSIS N Calcd.	N Found	C Calcd.	C Found	H Calcd.	H Found
C_4H_9NH-[3]	80–80.5	0.2	44	1.4503	0.8900^{28}	$C_8H_{19}NO$	9.64	9.30	66.15	66.25	13.18	12.98
$C_6H_5CH_2NH$	137–140	0.8	56	1.5288		$C_{11}H_{16}NO$	7.81	7.90	73.70	73.48	9.56	9.57
$(CH_3)_2N$-[6]	98	22	56	1.4390	0.8798^{25}	$C_6H_{15}NO$			61.49	61.58	12.90	12.84
$(C_2H_5)_2N$-[6]	83–85	0.8	80	1.4460	0.8653^{27}	$C_8H_{19}NO$	9.64	9.93	66.15	66.37	13.18	13.22
$(n—C_3H_7)_2N$-	114	4.3	77	1.4472	0.8723^{26}	$C_{10}H_{23}NO$	8.08	7.90	69.31	69.22	13.88	13.50
$(n—C_4H_9)_2N$-	135	0.3	62	1.4502	0.8616^{27}	$C_{12}H_{27}NO$	6.96	7.02	71.58	71.69	13.52	13.44
	75	0.2	71	1.4733	0.9471^{27}	$C_9H_{19}NO$	8.91	8.72	68.74	68.53	12.18	12.01

TABLE II

$RCOOCH_2CH_2CH_2CH_2\overset{+}{N}R''(R')_2\ X^-$

R	R′	R″	X^-	M.P., °C.	Yield, %[a]	Formula	Analysis, Halogen Calcd.	Found
	CH_3	H	Cl	122–124[b]	75	$C_{16}H_{25}NO_5 \cdot HCl$	10.20	10.17
"	C_2H_5	H	Cl	140–141[b]	97	$C_{18}H_{29}NO_5 \cdot HCl$	9.44	9.42
"	C_2H_5	CH_3	I	142.5–144[c]	78	$C_{18}H_{29}NO_5 \cdot CH_3I$	26.40	26.10
"	$n—C_3H_7$	H	Cl	118–119[d]	35	$C_{20}H_{33}NO_5 \cdot HCl$	8.78	8.44
"	$n—C_3H_7$	CH_3	I	115–117[d]	37	$C_{20}H_{32}NO_5 \cdot CH_3I$	24.95	24.67
"		H	Cl	156.5–157[d]	83	$C_{19}H_{29}NO_5 \cdot HCl$	9.14	9.17
"	"	CH_3	I	171–173[c]	35	$C_{19}H_{29}NO_5 \cdot CH_3I$	25.73	25.79
$(C_6H_5)_2CH—$	"	H	Cl	148–150[b]	53	$C_{23}H_{29}NO_2 \cdot HCl$	9.15	9.13
"	"	CH_3	I	69–72[e]	34	$C_{23}H_{29}NO_2 \cdot CH_3I$	25.77	25.55
"	"	CH_3	Br	144–146[e]	61	$C_{23}H_{29}NO_2 \cdot CH_3Br$	17.93	17.90

[a] The yields reported are generally the results of a single trial; [b] recrystallized from isopropyl alcohol; [c] absolute ethanol; [d] absolute ethanol–ether; and [e] butanone.

There was also obtained a higher boiling fraction which proved to be 4-dimethylamino-1-butanol (60 g., 25.5%); b.p. 103–105° (28 mm.).

1,4-Bis(1-piperidino)butane. In a manner similar to that described for the tetramethylputrescine, 17.2 g. (0.2 mole) of butyrolactone, 34.0 g. (0.4 mole) of piperidine, and 11.4 g. (0.3 mole) of lithium aluminum hydride were used to make 25 g. (56%) of 1,4-bis(1-piperidino)butane; b.p. 117–118° (0.3 mm.).

Anal. Calcd. for $C_{14}H_{28}N_2$: Neut. Equiv. 112 mg./m. eq. Found: Neut. Equiv. 114 mg./m. eq.

The hydrochloride was prepared by addition of ethereal hydrogen chloride to the base. It melted above 300°.

Anal. Calcd. for $C_{14}H_{28}N_2 \cdot HCl$: Cl^-, 23.85. Found: Cl^-, 23.75.

1-Piperidinepropanol. Propiolactone 28.4 g. (0.40 mole) was added dropwise to 34.0 g. (0.40 mole) of piperidine with continuous stirring and ice bath cooling so that the temperature was maintained at 5–10°. Near the end of the addition the mixture was allowed to warm to 20°. The resulting sirup was dissolved in 100 ml. of tetrahydrofuran, and the solution was reduced with 11.4 g. (0.30 mole) of lithium aluminum hydride in the usual manner. The excess hydride was decomposed with water, and the mixture was filtered. The filtrate was concentrated, and the residue was fractionally distilled at reduced pressure. Yield 31 g. (68%); b.p. 117–122° (25 mm.); n_D^{25} 1.4750; d_{25}^{29} 0.9585 (Lit.[13] b.p. 108–109°) (20–21 mm.); n_D^{25} 1.4742; d_{25}^{25} 0.9529.

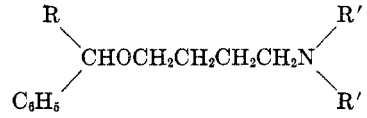
The preparation of the benzhydryl ethers of the 4-dialkylamino-1-butanols. A typical synthesis is illustrated by the following:

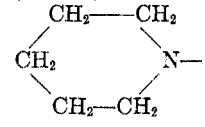
N-(4-Benzhydryloxybutyl)-N,N-di-n-propylamine. A solution of 49.3 g. (0.20 mole) of benzhydryl bromide and 69.2 g. (0.40 mole) of 4-di-*n*-propylamino-1-butanol in 200 ml. of toluene was refluxed 15 hr., concentrated *in vacuo*, and partitioned between 5% sodium hydroxide and ether. The ethereal extract was extracted with 5% hydrochloric acid. This was made alkaline with 20% sodium hydroxide and extracted with ether. This ethereal extract was washed with water, dried over sodium sulfate, and concentrated, and the residue was distilled. Thirty-nine grams of dipropylaminobutanol were recovered. The yield of the benzhydryl ether was 26 g. (38.4%); b.p. 175–177° (1.5 mm.).

Anal. Calcd. for $C_{23}H_{33}NO$: C, 81.36; H, 9.80; N, 4.13. Found: C, 81.12; H, 10.03; N, 4.10.

(13) O. A. Barnes and R. Adams, *J. Am. Chem. Soc.*, **49**, 1307 (1927).

TABLE III



R	R′ N— R′	Salt	B.P., °C. (M.P., °C.)	Mm	Yield, %[a]	Formula	Analysis Calcd.	Found
C_6H_5	$(C_2H_5)_2N$—		202–205	1.4	68	$C_{21}H_{27}NO$	N, 4.51	4.52
C_6H_5	$(C_2H_5)_2N$—	HBr	(109–111.5)[b]			$C_{21}H_{27}NO\cdot HBr$	Br, 20.38	20.53
C_6H_5	$(C_2H_5)_2N$—	CH_3Br	(120–121)[b]		81	$C_{21}H_{27}NO\cdot CH_3Br$	Br, 19.68	19.68
C_6H_5	$(n\text{-}C_3H_7)_2N$—		175–177	1.5	38	$C_{23}H_{33}NO$[d]	N, 4.13	4.10
C_6H_5	$(n\text{-}C_4H_9)_2N$—		192–194	1.5	38	$C_{25}H_{37}NO$[e]	N, 3.82	3.86
C_6H_5			217–220	2.0	46	$C_{22}H_{29}NO$		
C_6H_5		HCl	(135.5–137)[b]			$C_{22}H_{29}NO\cdot HCl$	Cl, 9.85	9.80
C_6H_5		CH_3I	(126–126.5)[b]		73	$C_{22}H_{29}NO\cdot CH_3I$	I, 27.28	27.30
p-ClC_6H_4-	$(C_2H_5)_2N$—	Citrate	(123–124)[c]		62	$C_{21}H_{28}ClNO\cdot C_6H_8O_7$[f]	N, 2.60	2.75

[a] The yields reported are generally the results of a single trial; [b] recrystallized from butanone and [c] absolute ethanol. [d] Calcd.: C, 81.36: H, 9.80. Found: C, 81.12; H, 10.03. [e] Calcd.: C, 81.69; H, 10.15. Found: C, 81.59; H, 9.97. [f] Calcd.: C, 60.27; H, 6.74. Found: C, 60.35; H, 6.66.

The preparations of the 3,4,5-trimethoxybenzoic acid and diphenylacetic acid esters were accomplished by the reaction of the acid chloride with the aminoalcohol and are illustrated by the following:

4-Dimethylaminobutyl 3,4,5-trimethoxybenzoate hydrochloride. To a cooled solution of 23 g. (0.10 mole) of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of chloroform was added 11.7 g. (0.10 mole) of 4-dimethylamino-1-butanol in several portions and the solution was refluxed 2 hr. and concentrated. The residue was partitioned between dilute hydrochloric acid and ether. The acid extract was made alkaline with 20% sodium hydroxide and extracted with ether. This ethereal extract was washed with water, dried over sodium sulfate, filtered, and acidified with ethereal hydrogen chloride. The oil which separated was crystallized from isopropyl alcohol or butanone. Yield 26 g. (75%); m.p. 122–124°.

Anal. Calcd. for $C_{16}H_{25}NO_5\cdot HCl$: Cl^-, 10.20. Found: Cl^-, 10.17.

The quaternary salts of both the esters and the ethers were prepared by the addition of methyl iodide or methyl bromide to an ethereal solution of the base. When crystallization did not occur spontaneously the ether was decanted and the oil was crystallized from a suitable solvent.

The following derivatives of 1-piperidinepropanol were prepared in the same manner as has been described for the aminobutanols.

3-(1-Piperidino)propyl 3,4,5-trimethoxybenzoate hydrochloride. Yield 51%; m.p. 169–171° when crystallized from absolute ethanol-ether.

Anal. Calcd. for $C_{18}H_{27}NO_5\cdot HCl$: Cl^-, 9.48. Found: Cl^-, 9.63.

3-(1-Piperidino)propyl diphenylacetate nitrate. Yield 90%; m.p. 115–116° when crystallized from water.

Anal. Calcd. for $C_{22}H_{27}NO_2\cdot HNO_3$: N, 7.00. Found: N, 7.04.

3-(1-Piperidino)propyl diphenylacetate methiodide. M.p. 144.5–146° when crystallized from absolute ethanol.

Anal. Calcd. for $C_{22}H_{27}NO_2\cdot CH_3I$: I^-, 26.48. Found: I^-, 26.50.

3-(1-Piperidino)propyl diphenylacetate methobromide. M.p. 165–166° when crystallized from isopropyl alcohol.

Anal. Calcd. for $C_{22}H_{27}NO_2\cdot CH_3Br$: Br^-, 18.50. Found: Br^-, 18.50.

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