and mixed m. p.) with a sample prepared from the amino-alcohol and hydrochloric acid.

Anal. Calcd. for $C_9H_{22}ONCl$: Cl, 18.11. Found: Cl, 18.09.

Addition of pentane to the alcohol–ether filtrate gave a precipitate from which 1.5 g. (4%) of the *p*-nitrobenzoate hydrochloride of 1-isoamylamino-2-methyl-2-propanol was obtained by recrystallization. The properties of this salt are described in Table IV.

The ester-amide described above, m. p. 127–128°, was characterized by a quantitative hydrogenation in the presence of palladinized charcoal in dilute alcohol containing hydrochloric acid; 97% of the theoretical quantity of hydrogen was absorbed. In a similar hydrogenation 3.1 g. of the ester-amide dissolved in 300 cc. of 30% alcohol was hydrogenated in the presence of 1.7 cc. of 6 *N* sulfuric acid. The product, the *p*-aminobenzoate sulfate of N-*p*-aminobenzoyl-1-isoamylamino-2-methyl-2-propanol was recrystallized from alcohol; yield 2.4 g., m. p. 184–185° (dec.).

Anal. Calcd. for $C_{23}H_{31}O_4N_3 \cdot H_2SO_4$: N, 8.48. Found: N, 8.51.

The ester-amide was also prepared by refluxing a chloroform solution of 1.04 g. of the *p*-nitrobenzoate hydrochloride and 0.56 g. of *p*-nitrobenzoyl chloride for forty-three hours. The solvent was removed *in vacuo* and the residue crystallized from alcohol, yielding 0.7 g. of the ester-amide.

Pharmacological.—Pharmacological data recorded in Tables III, IV and V were obtained at the Merck Institute for Therapeutic Research and will be published elsewhere by Albert O. Seeler and Samuel Kuna. The method of testing is outlined in ref. 2b.

Summary

A number of monoalkylaminopropanols and butanols have been prepared by condensing a ketone (or an aldehyde) with an aminopropanol or aminobutanol and hydrogenating, the two steps being carried out either simultaneously or successively. The monoalkylaminopropanols and butanols which are primary alcohols were esterified by reaction of their hydrochlorides with *p*-nitrobenzoyl chloride in chloroform solution. *p*-Aminobenzoate hydrochlorides were prepared from the *p*-nitrobenzoate hydrochlorides by catalytic hydrogenation.

1-Alkylamino-2-methyl-2-propanols (IV), which are tertiary alcohols, were esterified successfully by an indirect method. Reaction with acid chlorides in the presence of aqueous sodium hydroxide converted them into amides, which were isomerized to esters by heating with alcoholic hydrochloric acid for a short time.

$$(CH_3)_2C(OH)CH_2NHR \xrightarrow{R'COCl} (CH_3)_2C(OH)CH_2N(R)COR' \xrightarrow{HCl} R'COOC(CH_3)_2CH_2NHR \cdot HCl$$

The local anesthetic activity of a number of the monoalkylaminoalcohol esters has been examined.

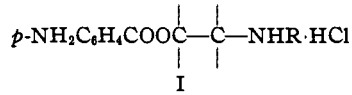
NEW YORK, N. Y. RECEIVED MARCH 23, 1944

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF BRYN MAWR COLLEGE AND COLUMBIA UNIVERSITY]

Aminoalcohols and their Esters

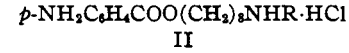
BY EVELYN M. HANCOCK,[1] ELIZABETH M. HARDY, DOROTHEA HEYL, MARY ELIZABETH WRIGHT AND ARTHUR C. COPE

A number of *p*-aminobenzoates of aminoalcohols containing secondary amino groups recently have been found to have pronounced local anesthetic activity.[2] These esters correspond to the general formula I, in which R has been varied widely, while the substituents on the ethanol fragment have been hydrogen, methyl and ethyl.

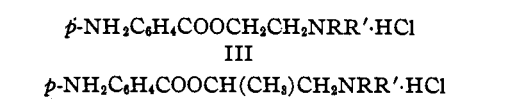


I

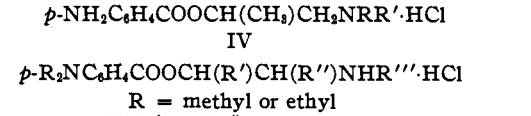
In order to determine the effect on local anesthetic properties, the structures of some of the promising compounds previously described have been modified by preparing analogous esters of 3-alkylamino-1-propanols, II, esters containing *tertiary* amino groups (III and IV), and *p*-dialkylaminobenzoates (V, VI and VII).



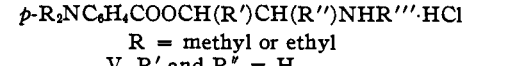
II



III



IV



R = methyl or ethyl
V, R′ and R″ = H
VI, R′ = methyl, R″ = H
VII, R′ = H, R″ = ethyl

The 3-alkylamino-1-propanol derivatives required for the synthesis of the esters (II) were prepared by hydrogenation of a mixture of a ketone with 3-amino-1-propanol, or by hydrogenating the anhydro compound formed by condensation of the ketone and aminoalcohol. These procedures, which are analogous to the methods used in preparing monoalkyl derivatives of ethanolamine,[3] led to 78 to 98% yields of the aminoalcohols described in Table I. The nature of the intermediate anhydro compounds in this synthesis is of interest, since they may be either tetrahydro-1,3-oxazines (VIII) or Schiff bases (IX). Anhydro

(1) Sharp and Dohme Research Associate.

(2) (a) Cope and Hancock, THIS JOURNAL, **66**, 1448 (1944); (b) **66**, 1453 (1944); (c) Hancock and Cope, *ibid.*, **66**, 1738 (1944).

(3) Cope and Hancock, *ibid.*, **64**, 1503 (1942).

TABLE I

3-ALKYLAMINO-1-PROPANOLS, $RNH(CH_2)_3OH$

	Alkyl group	Yield, %	Boiling point, °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction, Calcd.	Found
1	2-Heptyl	90	147–148	28	1.4504	0.8767	53.52	53.31
2	4-Heptyl	98	140–141	25	1.4498	.8761	53.52	53.29
3	2-Octyl	90	153–154	22	1.4521	.8733	58.14	58.03
4	4-(2,6-Dimethylheptyl)	93	147–148	23	1.4497	.8660	62.76	62.63
5	Cyclohexyl	78	144–145 (solidified, m. p. 71–72°)	19				

	Formula	Nitrogen, % Calcd.	Found	Picrates[a] M. p., °C.	Formula	Nitrogen, % Calcd.	Found
1	$C_{10}H_{23}ON$	8.08	8.03	70–72	$C_{16}H_{26}O_8N_4$	13.92	13.78
2	$C_{10}H_{23}ON$	8.08	8.05	88–89	$C_{16}H_{26}O_8N_4$	13.92	13.88
3	$C_{11}H_{25}ON$	7.47	7.35	62.5–64	$C_{17}H_{28}O_8N_4$	13.46	13.45
4	$C_{12}H_{27}ON$	6.96	6.81	114–115	$C_{18}H_{30}O_8N_4$	13.02	13.03
5	$C_9H_{19}ON$	8.91	8.78	121–122	$C_{15}H_{22}O_8N_4$	14.50	14.49

[a] Prepared by reaction of equivalent quantities of aminoalcohols and picric acid and recrystallized to constant melting point from alcohol or alcohol and water.

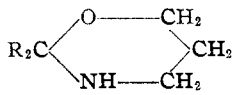
TABLE II

p-NITRO AND *p*-AMINOBENZOATE HYDROCHLORIDES OF 3-ALKYLAMINO-1-PROPANOLS, *p*-NO_2 (OR *p*-NH_2)$C_6H_4COO(CH_2)_3NHR\cdot HCl$

	Alkyl group	*p*-Nitrobenzoate hydrochloride, formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Found
1	2-Heptyl	$C_{17}H_{27}O_4N_2Cl$	80	122–124[a]	9.88	9.95
2	4-Heptyl	$C_{17}H_{27}O_4N_2Cl$	75	110–111[a]	9.88	9.94
3	2-Octyl	$C_{18}H_{29}O_4N_2Cl$	90	123–124[b]	9.51	9.46
4	4-(2,6-Dimethylheptyl)	$C_{19}H_{31}O_4N_2Cl$	54	167–168[b]	9.16	9.25
5	Cyclohexyl	$C_{16}H_{23}O_4N_2Cl$	72	237–238.5[c]	10.34	10.40

	p-Aminobenzoate hydrochloride, formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Found	Anesthetic activity Topical, × cocaine	Infiltration, × procaine	Toxicity, subcutaneou LD_{50}, mg./kg.s
1	$C_{17}H_{29}O_2N_2Cl$	100	114–116[d]	10.78	10.70	2.5	2.5	125
2	$C_{17}H_{29}O_2N_2Cl$	90	112–113.5[d]	10.78	10.70	2	2.5	100
3	$C_{18}H_{31}O_2N_2Cl$	100	89–90[e]	10.34	10.34	0.5	2	150
4	$C_{19}H_{33}O_2N_2Cl$	81	153–154[d]	9.93	9.93	5	4	75
5	$C_{16}H_{25}O_2N_2Cl$	84	196.5–197.5[d]	11.33	10.97	1	2	200

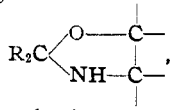
[a] Crystallized from absolute alcohol and ether. [b] From absolute alcohol. [c] From 95% alcohol. [d] From acetone and ether. [e] Isolated as the dry salt by concentrating *in vacuo* the solution obtained by catalytic reduction of the *p*-nitrobenzoate hydrochloride.



VIII

$R_2C{=}N(CH_2)_3OH$

IX

compounds in the series previously studied have proved to be either oxazolidines,  , or Schiff bases. In general, the anhydro compounds derived from reactive, unhindered ketones were oxazolidines, while the condensation products of certain hindered ketones were Schiff bases.[2,3] On the basis of physical properties (boiling point and molecular refraction), the anhydro compound derived from cyclohexanone and 3-amino-1-propanol is a tetrahydro-1,3-oxazine, while the dipropyl ketone and diisobutyl ketone condensation products are largely in the Schiff base form.

Hydrochlorides of the 3-alkylamino-1-propanols were esterified by reaction with *p*-nitrobenzoyl chloride in chloroform solution under conditions found to be satisfactory for other alcohols containing secondary amino groups.[2b] The *p*-nitrobenzoate hydrochlorides were converted into *p*-aminobenzoate hydrochlorides by catalytic hydrogenation. Both classes of esters are described in Table II.

Aminoalcohols containing *tertiary* amino groups (Table III) were prepared from the corresponding secondary amino derivatives, which have been described previously, by alkylation with methyl iodide or ethyl sulfate. The aminoalcohols (Table III) were converted into *p*-nitrobenzoate hydrochlorides by reaction with *p*-nitrobenzoyl chloride in boiling benzene. The *p*-nitrobenzoate hydrochlorides were hydrogenated to *p*-aminobenzoate hydrochlorides (III and IV, Table IV) in the usual manner.

TABLE III

DIALKYLAMINOALCOHOLS

	Alkyl groups, R and R′	Yield, %	Boiling point, °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction, Calcd.	Found
	2-Dialkylaminoethanols, $RR'NCH_2CH_2OH$							
1	2-Octyl, methyl	20	142–143	28	1.4469	0.8656	58.48	57.98
2	2-Octyl, ethyl	33	148–149.5	29	1.4452	.8562	63.10	62.80
3	Cyclohexyl, methyl[a]	24	127–129	26	1.4786	.9606	47.04	46.56
4	Cyclohexyl, ethyl[a]	53	127–130	20	1.4727	.9372	51.66	51.41
	1-Dialkylamino-2-propanols, $RR'NCH_2CHOHCH_3$							
5	4-(2,6-Dimethylheptyl), methyl	49	128–129	24	1.4372	0.8418	67.72	67.26
6	4-(2,6-Dimethylheptyl), ethyl	65	134–134.5	25	1.4373	.8387	72.34	71.91
7	Cyclohexyl, methyl	55	130–131	28	1.4658	.9283	51.66	51.23
8	Cyclohexyl, ethyl	62	128–129	22	1.4624	.9148	56.28	55.90

	Formula	Nitrogen, % Calcd.	Found	Picrates: M. p., °C.	Formula	Nitrogen, % Calcd.	Found
1	$C_{11}H_{25}ON$	7.48	7.49	[b]			
2	$C_{12}H_{27}ON$	6.95	6.92	65–67[c]	$C_{18}H_{30}O_8N_4$	13.01	13.03
3	$C_9H_{19}ON$			115.5–116[d]	$C_{15}H_{22}O_8N_4$	14.49	14.46
4	$C_{10}H_{21}ON$			[a]			
5	$C_{13}H_{29}ON$	6.50	6.52	106–107[e]	$C_{19}H_{32}O_8N_4$	12.60	12.70
6	$C_{14}H_{31}ON$	6.10	6.00	63–65[c]	$C_{20}H_{34}O_8N_4$	12.22	12.19
7	$C_{10}H_{21}ON$	8.17	8.16	105–106[e]	$C_{16}H_{24}O_8N_4$	13.99	13.96
8	$C_{11}H_{23}ON$	7.56	7.47	92–94[d]	$C_{17}H_{26}O_8N_4$	13.51	13.43

[a] Prevously reported by Wedekind and Bruch, ref. (6). [b] A crystalline picrate was not obtained. [c] Recrystallized from ether. [d] From alcohol and water. [e] From alcohol.

TABLE IV

p-NITRO AND *p*-AMINOBENZOATES OF DIALKYLAMINOALCOHOLS

	Alkyl groups, R and R′	*p*-Nitrobenzoate hydrochloride, formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Found
	p-Nitro and *p*-Aminobenzoate Hydrochlorides of 2-Dialkylaminoethanols p-NO_2 (or p-NH_2)$C_6H_4COOCH_2CH_2NRR'\cdot HCl$					
1	2-Octyl, methyl	$C_{18}H_{29}O_4N_2Cl$	80	133.5–134[a]	9.51	9.58
2	2-Octyl, ethyl	$C_{19}H_{31}O_4N_2Cl$	80	99–100[a]	9.16	9.08
3	Cyclohexyl, methyl	$C_{16}H_{23}O_4N_2Cl$	88	193–194 (dec.)[b]	10.34	10.31
4	Cyclohexyl, ethyl	$C_{17}H_{25}O_4N_2Cl$	88	143.5–144.5[c]	9.94	9.89
	p-Nitro and *p*-Aminobenzoate Hydrochlorides of 1-Dialkylamino-2-Propanols p-NO_2 (or p-NH_2)$C_6H_4COOCH(CH_3)CH_2NRR'\cdot HCl$					
5	Cyclohexyl, methyl	$C_{17}H_{25}O_4N_2Cl$	94	179.5–180.5[c]	9.94	9.99
6	Cyclohexyl, ethyl	$C_{18}H_{27}O_4N_2Cl$	48	109–111[a]	9.56	9.48

	p-Aminobenzoate hydrochloride, formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Found	Anesthetic activity: Topical, × cocaine	Infiltration, × procaine	Toxicity, subcutaneous LD_{50}, mg./kg.
1	$C_{18}H_{31}O_2N_2Cl$	81	131.5–133[a]	10.34	10.38	2.5	2	300
2	$C_{18}H_{33}O_2N_2Cl$	86	150.5–152[c]	9.93	9.97	2.5	2	>300
3	$C_{16}H_{25}O_2N_2Cl$	79	196–198 (dec.)[c]	11.33	11.20	1	4	300
4	$C_{17}H_{27}O_2N_2Cl$	95	210–212 (dec.)[d]	10.85	10.85	2	2	450
5	$C_{17}H_{27}O_2N_2Cl$	88	184.5–186.5[c]	10.85	10.95	1	2	200
6	$C_{18}H_{29}O_2N_2Cl$	88	180.5–181.5[c]	10.40	10.49	1	2	250

[a] Recrystallized from acetone and ether. [b] From absolute alcohol. [c] From absolute alcohol and ether. [d] From absolute alcohol and acetone.

p-Dialkylaminobenzoate hydrochlorides (V, VI and VII, Table V) of several of the aminoalcohols whose *p*-aminobenzoates had good local anesthetic properties were prepared by reaction of the aminoalcohol hydrochloride with the acid chloride of *p*-dimethylaminobenzoic acid and *p*-diethylaminobenzoic acid, in chloroform solution. These acid chlorides are very sensitive to hydrolysis and it proved to be inadvisable to isolate them. It was necessary to exercise care in removing the last traces of the excess thionyl chloride employed in their preparation, because the aminoalcohols

TABLE V

p-DIALKYLAMINOBENZOATE HYDROCHLORIDES OF AMINOALCOHOLS

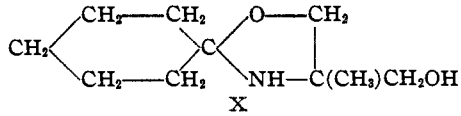
	p-Alkyl groups, R	Alkyl group, R′	Yield, %	M. p., °C.
	p-Dialkylaminobenzoate Hydrochlorides of 2-Alkylaminoethanols, *p*-$R_2NC_6H_4COOCH_2CH_2NHR'\cdot HCl$			
1	Diethyl	2-Octyl	29	70–71[b]
2	Dimethyl	Cyclohexyl	69	229.5–230[c]
3	Diethyl	Cyclohexyl	57	165.5–166.5[d]
	p-Dialkylaminobenzoate Hydrochlorides of 1-Alkylamino-2-propanols, *p*-$R_2NC_6H_4COOCH(CH_3)CH_2NHR'\cdot HCl$			
4	Dimethyl	4-(2,6-Dimethylheptyl)	11	154.5–155[b]
5	Diethyl	4-(2,6-Dimethylheptyl)	24	152.5–153[b]
6	Dimethyl	Cyclohexyl	29	223–224 (dec.)
7	Diethyl	Cyclohexyl	60	149–151[f]
	p-Dialkylaminobenzoate Hydrochlorides of 2-Alkylamino-1-butanols, *p*-$R_2NC_6H_4COOCH_2CH(C_2H_5)NHR'\cdot HCl$			
8	Dimethyl	Cyclohexyl	55	199–199.5[d]
9	Diethyl	Cyclohexyl	65	171–171.5[d]

	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found	Anesthetic activity: Topical, × cocaine	Anesthetic activity: Infiltration, × procaine	Toxicity, subcutaneous LD_{50}, mg./kg.
1	$C_{21}H_{37}O_2N_2Cl\cdot H_2O$[a]	62.58	62.62	9.75	9.84	8.79	9.16	[g]	2	>400
2	$C_{17}H_{27}O_2N_2Cl$	62.46	62.22	8.33	8.18	10.85	10.80	2	2	>200
3	$C_{19}H_{31}O_2N_2Cl$	64.29	64.29	8.80	9.04	9.99	9.97	1	2	>400
4	$C_{21}H_{37}O_2N_2Cl$	65.51	65.60	9.69	9.55	9.21	9.11	2.5	2	>200
5	$C_{23}H_{41}O_2N_2Cl$	66.88	66.97	10.01	10.07	8.58	8.57	2.5	0.3	>100
6	$C_{16}H_{29}O_2N_2Cl$	63.42	63.23	8.57	8.50	10.40	10.48	2	2	>200
7	$C_{20}H_{33}O_2N_2Cl$	65.06	65.32	9.01	9.24	9.61	9.53	2	2	>200
8	$C_{19}H_{31}O_2N_2Cl$	64.29	64.37	8.80	8.77	9.99	9.98	2.5	2	>100
9	$C_{21}H_{35}O_2N_2Cl$	65.86	65.53	9.21	9.19	9.26	9.33	2.5	2	>100

[a] Water of crystallization determined by drying to constant weight at 78° (1 mm.). Calcd.: H_2O, 4.47. Found: H_2O, 4.49. [b] Recrystallized from a mixture of acetone, ether and pentane. [c] From dilute alcohol. [d] From absolute alcohol and acetone. [e] From a mixture of ethyl acetate, ether and pentane. [f] From methyl ethyl ketone. [g] Produced irritation.

were converted readily into alkylaminoalkyl chlorides by any thionyl chloride retained in the acid chlorides.

2-Amino-2-methyl-1,3-propanediol has been condensed with cyclohexanone, yielding an anhydro compound which proved to be the oxazolidine, X. The amino-diol prepared by hydrogenation of X, and its *p*-nitrobenzoate hydrochloride, are described in the Experimental Part.



X

Experimental Part[4]

3-Alkylamino-1-propanols.—The aminoalcohols described in Table I, with the exception of 3-[4-(2,6-dimethylheptyl)-amino]-1-propanol, were prepared as follows. 3-Amino-1-propanol was prepared by Kremer's modification of a procedure used by Putochin.[5] A solution of 0.3 mole of 3-amino-1-propanol and 0.4 mole of ketone in 50 cc. of absolute alcohol was added to a suspension of 0.5 g. of freshly reduced platinum oxide catalyst in 15 cc. of absolute alcohol. The mixture was shaken under hydrogen at one to two atmospheres pressure. The hydrogenations were usually sufficiently rapid to be exothermic; they required three to nine hours for completion. The dipropyl ketone reaction mixture was heated to 50 to 60° in order to obtain a rapid reduction. 3-[4-(2,6-Dimethylheptyl)-amino]-1-propanol (Table I) was prepared by hydrogenation of a solution of 31.5 g. of 3-[4-(2,6-dimethylheptylidene)-amino]-1-propanol (described below) in 35 cc. of absolute alcohol under similar conditions. Eight hours were required to complete the hydrogenation at 50 to 60°.

Spiro-[cyclohexane-1,2′-tetrahydro-1′,3′-oxazine].—A solution of 15 g. of 3-amino-1-propanol and 26.5 g. of cyclohexanone in 100 cc. of benzene was refluxed under a constant water separator for six hours, during which time a water layer of 3.5 cc. was collected. The benzene solution was distilled through a Widmer column, and yielded 25 g. (80%) of the anhydro compound; b. p. 119–120° (29 mm.); $n^{25}D$ 1.4864. The liquid product crystallized rapidly to a solid, m. p. 44–45°. It crystallized so readily that it was impossible to determine the density (and consequently the molecular refraction) of the supercooled liquid. The low b. p. of the anhydro compound, however, compared to the corresponding aminoalcohol obtained from it by hydrogenation (b. p. 144–145° (19 mm.)), is good evidence that the compound has the structure of a tetrahydro-1,3-oxazine rather than a Schiff base.

Anal. Calcd. for $C_9H_{17}ON$: N, 9.02. Found: N, 9.12.

3-(4-Heptylideneamino)-1-propanol.—A solution of 15 g. of 3-amino-1-propanol and 30.8 g. of dipropyl ketone in 100 cc. of benzene was boiled under a constant water separator for nine hours, while 3.5 cc. of water collected. Distillation through a Widmer column yielded 29 g. (85%) of 3-(4-heptylideneamino)-1-propanol; b. p. 139–140°

(4) All melting and boiling points are uncorrected. We are indebted to John R. Taylor for semi-micro Kjeldahl determinations and to Saul Gottlieb for micro carbon-hydrogen analyses.

(5) Kremer, THIS JOURNAL, 61, 1321 (1939); Putochin, *Ber.*, 59, 628 (1926).

(25 mm.); $n^{25}D$ 1.4587; d^{25}_{25} 0.8962; MD calcd. 52.92, found 52.37 (calcd. for the tetrahydro-1,3-oxazine structure 51.44).

Anal. Calcd. for $C_{10}H_{21}ON$: N, 8.17. Found: N, 8.12.

3-[4-(2,6-Dimethylheptylidene)-amino]-1-propanol.—A solution of 22.5 g. of 3-amino-1-propanol and 56.8 g. of diisobutyl ketone in 100 cc. of benzene was refluxed under a constant water separator for ten hours, while a water layer of 6.0 cc. collected. The Schiff base was obtained by distillation through a Widmer column; yield 44 g. (73%); $n^{25}D$ 1.4588; d^{25}_{25} 0.8822; MD calcd. 62.16, found 61.92 (calcd. for the tetrahydro-1,3-oxazine structure 60.68).

Anal. Calcd. for $C_{13}H_{25}ON$: N, 7.03. Found: N, 6.88.

3-Alkylamino-1-propanol Esters.—The *p*-nitrobenzoate and *p*-aminobenzoate hydrochlorides described in Table II were prepared by procedures previously outlined for the corresponding 1-alkylamino-2-propanol esters.[2b]

Dialkylaminoalcohols.—Several of the aminoalcohols containing secondary amino groups which have been described recently[2,3] were methylated and ethylated by a method similar to a procedure described by Wedekind and Bruch.[6] The preparation of 1-cyclohexylmethylamino-2-propanol is cited as typical of the procedures employed in preparing the compounds listed in Table III.

A mixture of 31.5 g. (0.2 mole) of 1-cyclohexylamino-2-propanol and 42.5 g. (0.3 mole) of methyl iodide was stirred and heated in a bath maintained at 50–54° for eighteen hours. The mixture was cooled, made strongly alkaline with aqueous potassium hydroxide, and extracted with ether. The ether was removed by distillation and the residual oil dissolved in 30 cc. of three normal sulfuric acid. A concentrated solution of 7.4 g. of sodium nitrite was added and the mixture was heated on a steam-bath for one-half hour. After cooling, enough dilute sulfuric acid was added to make the mixture acid to congo red. The nitroso derivative of the unreacted secondary amino compound was removed by extraction with ether. Ten cc. of six normal sulfuric acid was added to the aqueous acid solution of the tertiary amino compound, and the mixture was refluxed for two hours in order to decompose any nitrous acid ester of the aminoalcohol which might be present.[7] The acid solution was then made strongly basic by adding saturated potassium hydroxide solution. The product was extracted with ether and distilled; yield 19 g. (Table III).

The tertiary amino compounds substituted by ethyl groups described in Table III were prepared from the secondary amino derivatives and a 20% excess of ethyl sulfate. The tertiary amino compounds are less associated and boil lower than the secondary amino compounds from which they were prepared. Picrates were prepared from them as solid derivatives by reaction with an equivalent quantity of picric acid in boiling alcohol.

Dialkylaminoalcohol Esters.—The *p*-nitrobenzoate hydrochlorides described in Table IV were prepared by refluxing a solution of approximately 0.05 mole of each aminoalcohol with an equivalent quantity of *p*-nitrobenzoyl chloride in 75 to 100 cc. of dry benzene for one to four hours. The hydrochlorides which separated on cooling were recrystallized to constant melting point. The *p*-aminobenzoate hydrochlorides were prepared by the procedure described in ref. 2b.

***p*-Dialkylaminobenzoate Hydrochlorides.**—*p*-Dimethylaminobenzoic acid was prepared by the reaction of phosgene and dimethylaniline[8] in 51% yield, m. p. 232.5–233°. *p*-Diethylaminobenzoic acid was synthesized from diethylaniline in the same way, yield 73%, m. p. 191.5–192.5°. The preparation of the *p*-diethylaminobenzoate hydrochloride of 2-cyclohexylaminoethanol is described as a typical example of the preparation of the esters listed in Table V.

Five grams (0.026 mole) of *p*-diethylaminobenzoic acid was placed in a 200-cc. round-bottom flask attached to a small distilling column, receiver and drying tube. Thionyl chloride (15 cc.) was added with cooling. There was an immediate reaction, and the acid dissolved to give a clear solution. After the solution stood at room temperature for twenty minutes, the excess thionyl chloride was removed by distillation *in vacuo*, while the flask was heated in a warm water-bath. In order to remove the last traces of thionyl chloride, dry benzene was added to the residue and removed by distillation under diminished pressure. The process was repeated several times with benzene and once with dry ether. A solution of 3.7 g. (0.023 mole) of 2-cyclohexylaminoethanol in 15 g. of chloroform was saturated with hydrogen chloride and rinsed into the flask containing the acid chloride with 15 g. of chloroform. The solution was heated at 50–60° for ninety hours. The solvent was removed by distillation *in vacuo* and the residue was dissolved in a small volume of alcohol. Several volumes of water were added and the solution was extracted several times with benzene. A large portion of the colored impurities was removed by this process. The aqueous solution was made alkaline with sodium carbonate and the ester was extracted with benzene. The benzene solution was washed with a small amount of water and brought to *p*H 5 to 6 by the addition of alcoholic hydrogen chloride.[9] The solvent was removed by distillation and the hydrochloride was recrystallized from a mixture of alcohol and acetone.

It was necessary to remove the last traces of excess thionyl chloride in these preparations, in order to avoid the formation of alkylaminoalkyl chloride hydrochlorides. In one case, for example, the product isolated from 1-cyclohexylamino-2-propanol was 1-cyclohexylamino-2-chloropropane hydrochloride, m. p. 219–220° (dec.).

Anal. Calcd. for $C_9H_{19}Cl_2N$: C, 50.89; H, 9.02; ionic Cl, 16.71. Found: C, 50.88; H, 8.86; ionic Cl, 16.71.[10]

The same chloro compound was prepared by reaction of 1-cyclohexylamino-2-propanol hydrochloride and thionyl chloride in methylene chloride solution.

The *p*-dialkylaminobenzoate hydrochlorides (Table V) were soluble in water only to the extent of 0.3 to 1.0%.

4'-Methyl-4'-hydroxymethyl-spiro-[cyclohexane-1,2'-oxazolidine] (X).—A solution of 52.5 g. of 2-amino-2-methyl-1,3-propanediol (Commercial Solvents Corp., recrystallized) and 59 g. of cyclohexanone in 100 cc. of benzene was refluxed under a constant water separator for five hours. The solution was fractionated through a Widmer column, and yielded 83.5 g. (90%) of X; b. p. 147–147.5° (16 mm.), $n^{25}D$ 1.4895; d^{25}_{25} 1.0706; MD calcd. 50.76, found 50.14 (calcd. for the Schiff base structure, 52.24). On standing the oxazolidine crystallized; m. p. 56–57°.

Anal. Calcd. for $C_{10}H_{19}O_2N$: N, 7.56. Found: N, 7.62.

2-Cyclohexylamino-2-methyl-1,3-propanediol.—An attempt to reduce the above oxazolidine in the usual manner in the presence of Adams platinum catalyst was unsuccessful. A solution of 29 g. of X in 45 cc. of absolute alcohol was hydrogenated in the presence of 2 g. of Raney nickel at 150° and 100–130 atmospheres pressure. 2-Cyclohexylamino-2-methyl-1,3-propanediol was isolated by crystallization from a mixture of absolute alcohol and ether; yield 16 g. (54%), m. p. 123–125°.

Anal. Calcd. for $C_{10}H_{21}O_2N$: N, 7.48. Found: N, 7.61.

Di-*p*-nitrobenzoate Hydrochloride of 2-Cyclohexylamino-2-methyl-1,3-propanediol.—The above aminoalcohol (8.5 g.) in 75 g. of chloroform was saturated with hydrogen chloride and heated with 16.7 g. of *p*-nitrobenzoyl chloride at 55 to 60° for one hundred and eight hours. After removal of the solvent and crystallization from dilute

(6) Wedekind and Bruch, *Ann.*, **471**, 73 (1929).

(7) *Cf.* Ladenburg, *ibid.*, **301**, 137 (1898).

(8) Meisenheimer, Budkewicz and Kananow, *Ann.*, **423**, 89 (1921).

(9) When an excess of hydrochloric acid was added, an unstable dihydrochloride was isolated, m. p. 186.5–187.5° (dec.).

(10) Gravimetric chlorine analysis was slightly high if a considerable excess of silver nitrate was used.

alcohol, the ester hydrochloride was obtained in yield of 9.5 g. (40%); m. p. 177–178° (dec.).

Anal. Calcd. for $C_{24}H_{28}O_3N_3Cl$: N, 6.79. Found: N, 6.75.

Pharmacological.—Pharmacological data included in Tables II, IV and V were obtained at the Merck Institute for Therapeutic Research, and will be published elsewhere by Albert O. Seeler and Samuel Kuna. The method of testing is outlined in ref. 2a.

Summary

Several 3-alkylamino-1-propanols have been prepared by hydrogenating ketone-3-amino-1-propanol mixtures, or by hydrogenating the anhydro compounds formed by condensation of ketones with 3-amino-1-propanol. *p*-Nitro and *p*-aminobenzoate hydrochlorides have been synthesized from the 3-alkylamino-1-propanols by methods previously used for preparing similar alkylaminoethanol derivatives.

Several new *p*-aminobenzoate hydrochlorides of 2-dialkylaminoethanols and 1-dialkylamino-2-propanols have been prepared for comparison with similar monoalkylamino derivatives.

p-Dimethylaminobenzoate and *p*-diethylaminobenzoate hydrochlorides of representative 2-alkylaminoethanols, 1-alkylamino-2-propanols and 2-alkylamino-1-butanols have been synthesized.

These esters have been examined for local anesthetic activity.

NEW YORK, N. Y. RECEIVED MARCH 23, 1944

[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

The Action of Platinum on Cholesterol in Acetic Acid Solution

BY HERBERT S. ANKER[1] AND KONRAD BLOCH

In the preparation of deuterio cholesterol in this Laboratory[2] by treatment of cholesterol with deuterium-containing acetic acid, heavy water and active platinum at elevated temperatures, it was observed that other compounds besides deuterio cholesterol were formed in the reaction. The amount of cholesterol recovered was dependent on the length of the treatment, the concentration of acetic acid and the amount of catalyst present. The conditions which favored the introduction of deuterium into the sterol molecule also favored its decomposition. Preliminary tests indicated that the products formed were of the nature of steroid ketones and hydrocarbons. As these products arise in the absence of any oxidizing or reducing agents they must have been formed by intermolecular hydrogen transfer.

In order to identify the products formed, cholesterol was subjected to the same conditions which had led to the formation of deuterio cholesterol, except that ordinary dilute acetic acid was used. Moreover, the products isolated from the experiment carried out in an isotopic medium were analyzed for deuterium in order to obtain some information on the mechanism of the reactions.

The free alcohol group of the cholesterol molecule appears to be necessary for the introduction of deuterium and for the occurrence of chemical changes since cholesteryl chloride and *i*-cholesteryl methyl ether remain unchanged on such treatment.[2] The influence of the double bond on the nature of the chemical changes and the exchange reaction was studied by analogous treatment of dihydrocholesterol.

Experimental

Action of Platinum and Dilute Acetic Acid on Cholesterol

Fifty grams of cholesterol purified via the dibromide[3] was shaken for one hundred hours at 127° in sealed flasks with 240 ml. of 50% acetic acid and platinum obtained by the reduction of 6 g. of platinum oxide. The reaction mixture was dissolved in ether, filtered, washed several times with 0.5% sodium bicarbonate solution, then with water and dried. The ether was then removed.

Acids.—In order to saponify the partially acetylated reaction products the residue was dissolved in 1.3 liters of 2% ethanolic potassium hydroxide. After three days at room temperature the reaction mixture was diluted with water and extracted with ether. The alkaline layer on acidification yielded 0.69 g. of acidic material. By titration in ethanol with sodium hydroxide an equivalent weight of 330 ± 10 was found. After esterification with diazomethane determination of the molecular weight by the micro method of Rast gave a value of 406 ± 40. No attempt was made further to characterize this small fraction.

Ketones.—The neutral fraction (42 g.), on treatment with *p*-hydrazinobenzoic acid yielded 32 g. of hydrazones. According to Anchel and Schoenheimer[4] the *p*-carboxyphenylhydrazones of α,β-unsaturated ketones are not split by formaldehyde, but are by pyruvic acid. Advantage was taken of this method to separate the ketones into a saturated and an unsaturated fraction.

Saturated Ketones.—On hydrolysis with formaldehyde[4] the total hydrazones yielded 12.7 g. of saturated ketones, which on fractional crystallization from ethanol and ether–methanol yielded a less soluble fraction which melted at 113–124°, and after adsorption on activated aluminum oxide and fractional elution with benzene was identified as cholestanone. A more soluble fraction had m. p. 78–79° unchanged on repeated recrystallization from ethanol, ether–methanol and acetone–ethanol. This

(1) This report is from a dissertation submitted by Herbert S. Anker in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the Faculty of Pure Science, Columbia University.

(2) Bloch and Rittenberg, *J. Biol. Chem.*, **149**, 505 (1943).

(3) Schoenheimer, Behring, Hummel and Schindel, *Z. physiol. Chem.*, **192**, 73 (1930).

(4) Anchel and Schoenheimer, *J. Biol. Chem.*, **114**, 539 (1936).