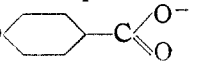
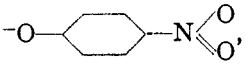
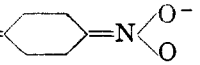
which provides further evidence that the azo group contributes to the interaction with the antibody.

A small amount of inhibition was observed for sulfate ion and for phosphate ion.

The similarity in shape of the *p*-hydroxybenzoate ion  and the *p*-nitrophenolate ion  ,  suggested that *p*-nitrophenol might be an effective inhibitor for the anti-benzoic acid system at *p*H 8; experimental test, however, showed that it is not.

This investigation was carried out with the aid of a grant from The Rockefeller Foundation. We wish to thank Professor Dan H. Campbell for advice during the course of the work and Dr. W. B. Renfrow, Jr., and Mr. Carol Ikeda for the preparation and analysis of several substances.

Summary

A quantitative study has been made of the serological properties of anti-X serum, prepared by injecting rabbits with beef serum coupled with diazotized *p*-aminobenzoic acid. It was found that this antiserum gives specific precipitation with a simple substance containing two *p*-azobenzoic acid groups (substance XXXV), made by coupling diazotized *p*-(*p*-aminophenylazo)benzoic acid to chromotropic acid, but not with any one of six other polyhaptenic substances, in which the haptenic groups are closer together than in XXXV. The antiserum also precipitates X-ovalbumin, made by coupling *p*-aminobenzoic acid with ovalbumin.

The dependence on the *p*H of the system of the amount of precipitate formed by anti-X serum with XXXV and with X-ovalbumin was studied.

The effect of each of 56 haptens in inhibiting precipitation was also investigated, and the data were interpreted with use of a quantitative theory based on the assumed heterogeneity of the antiserum. It was found that the order of activity of the haptens is nearly the same for the two precipitating antigens, XXXV and X-ovalbumin. The order of activity of groups in para-substituted benzoic acids is $CH_3CONH > OHC_6H_4NN > NH_2C_6H_4NN > NO_2 > CH_3O > Br > Cl > CH_3 > COOH > OH > F > H > NH_2$. In general the meta-substituted benzoic acids are weak inhibitors, and the ortho-substituted benzoic acids are still weaker, presumably as the result of steric hindrance. An exception is *o*-aminobenzoic acid, which exerts a strong inhibiting action, which may be connected with the presence of the hydrogen bond between the amino group and the carboxyl group. The effects of two or more substituents in benzoic acid are roughly additive in the free energy of interaction with antibody.

The precipitation of antigen XXXV with anti-X serum was found to be enhanced by moderate amounts of weak haptens, including substances other than substituted benzoic acids. This phenomenon was not observed for X-ovalbumin.

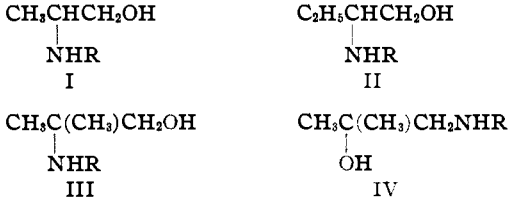
PASADENA 4, CALIFORNIA RECEIVED JUNE 15, 1944

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

Monoalkylaminopropanols and Butanols and their Esters

BY EVELYN M. HANCOCK[1] AND ARTHUR C. COPE

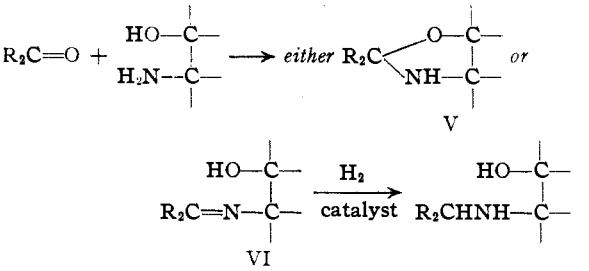
In previous papers[2] practical methods have been described for preparing and esterifying 2-alkylaminoethanols and 1-alkylamino-2-propanols. This paper describes the preparation and esterification of 2-alkylamino-1-propanols (I), 2-alkylamino-1-butanols (II), 2-alkylamino-2-methyl-1-propanols (III) and 1-alkylamino-2-methyl-2-propanols (IV).



(1) Sharp and Dohme Research Associate.

(2) (a) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942); (b) **66**, 1448 (1944); (c) **66**, 1453 (1944).

Each of the aminoalcohols was prepared by condensing a ketone (or an aldehyde) with an aminoalcohol containing a primary amino group and hydrogenating, the two steps being carried out either simultaneously or successively.



Steric hindrance of either the carbonyl or the amino group slowed these reactions. The hydrogenation of ketones with 2-amino-2-methyl-1-pro-

panol in the presence of platinum or Raney nickel catalyst failed to give the alkyl derivatives (III). Anhydro compounds which proved to be oxazolidines (type formula V, above; Table II) were prepared by condensing this aminoalcohol with methyl ethyl ketone, methyl amyl ketone, cyclohexanone and isovaleraldehyde. The oxazolidine derived from the aldehyde could be hydrogenated in the presence of platinum catalyst; the oxazolidines derived from ketones were not hydrogenated under these conditions, but were reduced with Raney nickel catalyst at higher temperatures. These oxazolidines were also less sensitive to hydrolysis than oxazolidines derived from ethanolamine and isopropanolamine. Two of the oxazolidines listed in Table II were converted into stable picrates. Attempts to prepare other oxazolidine picrates[2c] have resulted in hydrolysis and formation of the picrate of the original aminoalcohol.

It was necessary to prepare the anhydro compounds from diisobutyl ketone and 2-amino-1-propanol and 2-amino-1-butanol before hydrogenation to prepare the corresponding alkyl derivatives, I and II. As in the ethanolamine[2a] and isopropanolamine series,[2c] the physical properties of the anhydro compounds prepared from this hindered ketone indicated that they existed predominantly in the Schiff base rather than the oxazolidine form (type formula VI rather than V). Hydrogenations of ketones with 1-amino-2-methyl-2-propanol, in which the amino group is not hindered, proceeded rapidly and gave high yields of the alkyl derivatives (IV). The properties of all of the aminoalcohols are described in Table I.

p-Nitrobenzoate hydrochlorides of the aminoalcohols I, II and III, which are described in Table III were prepared by the reaction of the aminoalcohol hydrochlorides with *p*-nitrobenzoyl chloride in chloroform solution. Amide formation was effectively blocked under these conditions, and the pure ester hydrochlorides were isolated in 51 to 84% yield. *p*-Aminobenzoate hydrochlorides (also described in Table III) were prepared by hydrogenation of the nitro compounds.

In contrast to the results obtained with these aminoalcohols which are primary alcohols (I–III), as well as other primary and secondary alcohols,[2b,c] reaction of the hydrochlorides of the aminoalcohols (IV) containing tertiary hydroxyl groups with *p*-nitrobenzoyl chloride gave mixtures of products resulting from partial substitution of the secondary amino groups. Reaction of 1-isoamylamino-2-methyl-2-propanol hydrochloride with *p*-nitrobenzoyl chloride, for example, gave a mixture from which was isolated 40% of the original aminoalcohol hydrochloride, 17% of the ester-amide (VII), and 4% of the *p*-nitrobenzoate hydrochloride, VIII.

$$p\text{-}NO_2C_6H_4COOC(CH_3)_2CH_2N(C_5H_{11})COC_6H_4NO_2$$
VII

$$p\text{-}NO_2C_6H_4COOC(CH_3)_2CH_2NH(C_5H_{11})\cdot HCl$$
VIII

It was found possible to esterify the tertiary alcohols (IV) indirectly by first converting them to amides (IX), which were then rearranged to ester hydrochlorides (X) by heating with hydrochloric acid. The amides (IX), which are described in Table IV, were prepared in 81 to 95% yield by reaction of the aminoalcohols (IV) with *p*-nitrobenzoyl chloride in a two-phase system containing aqueous sodium hydroxide and methylene chloride. These conditions proved to be advantageous because the products were protected from hydrolysis by extraction into the methylene chloride, while refluxing the methylene chloride maintained a suitable reaction temperature. The ester hydrochlorides (X), which are also described in Table IV, were obtained in 69 to 93% yield by boiling solutions of the amides in absolute alcohol with a 50 to 75% molar excess of concd. hydrochloric acid for five minutes. They were converted into *p*-aminobenzoate hydrochlorides (Table IV) in the usual manner by hydrogenation.

$$p\text{-}NO_2C_6H_4CON(R)CH_2C(CH_3)_2OH \xrightarrow{HCl}$$
IX

$$p\text{-}NO_2C_6H_4COOC(CH_3)_2CH_2NHR\ HCl$$
X

Although the tertiary esters (X) are most readily prepared by rearrangement of the amides, direct esterification of the aminoalcohol hydrochlorides is preferable for primary and secondary alcohols. This was established by applying the indirect procedure to 2-cyclohexylaminoethanol and 1-cyclohexylamino-2-propanol. The amides were obtained by reaction with *p*-nitrobenzoyl chloride by the procedure outlined above in relatively poor yield (21 and 36%, respectively), because the more reactive primary and secondary hydroxyl groups present in these alcohols reacted with the acid chloride. The rearrangement of the two amides gave yields of 53 and 62% of the corresponding ester hydrochlorides, respectively, under conditions which gave better yields (69 to 93%) of the tertiary ester hydrochlorides (X).

A number of esters of 1-cyclohexylamino-2-methyl-2-propanol were prepared by rearrangement of the corresponding N-acyl derivatives in the presence of hydrochloric acid; both the esters and amides are described in Table V. The N-benzoyl and cinnamoyl derivatives rearranged as readily as the N-*p*-nitrobenzoyl compound. The N-diphenylacetyl derivative rearranged much more slowly, presumably because of steric hindrance. The corresponding phenylurea was also rearranged into the phenylurethan hydrochloride. In order to avoid hydrolysis this rearrangement was carried out in the presence of dry hydrogen chloride in chloroform solution.

In two recent publications, the products obtained by reaction of aminoalcohols with *p*-nitro-

TABLE I

AMINOALCOHOLS

Alkyl group	Yield, %	Boiling point, °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular Calcd.
						2-Alkylamino-1-propanols,
3-Pentyl	64[a]	106-107	26	1.4454	0.8839	44.28
4-Heptyl	84[a]	115-116	15	1.4461	.8728	53.52
5-Nonyl	72[a]	140.5-141	17	1.4500	.8683	62.76
4-(2,6-Dimethylheptyl)	93[b]	127.5-128	15	1.4459	.8616	62.76
Cyclohexyl[f]	82[c]	123-124 (m. p. 57-59)	15	1.4803[i]		
						2-Alkylamino-1-butanols,
Isopropyl	93[a]	69.5-70 (m. p. 48-50)	8	1.4412[i]		
3-Pentyl	94[d], 73[b]	92-92.5	7.5	1.4472	0.8816	48.90
4-Heptyl	91[d], 70[b]	112-112.5	7.5	1.4488	.8717	58.14
5-Nonyl	50[a]	148-151	19	1.4498	.8692	66.38
4-(2,6-Dimethylheptyl)	83[b]	121-121.5	8	1.4483	.8603	67.38
Cyclohexyl	68[a]	128-129 (m. p. 50-52)	12	1.4785[i]		
						2-Alkylamino-2-methyl-1-porpanols,
s-Butyl[n]	74[e]	74-75.5	8.5	1.4460	0.8873	44.28
2-Heptyl	64[e]	114-115 (m. p. 35.5-37)	10	1.4500[i]		
Cyclohexyl	47[d]	116-118 (m. p. 78-78.5)	12			
Isoamyl[g]	80[b]	100-103 (m. p. 75.5-76.5)	13			
						1-Alkylamino-2-methyl-2-propanols,
Isopropyl[h]	96[c]	64-65	20	1.4248	0.8469	39.66
3-Pentyl	96[c]	91-92	20	1.4328	.8523	48.90
2-Heptyl	98[c]	119.5-120.5	19	1.4372	.8475	58.14
2-Octyl[o]	98[c]	137.5-139.5	25	1.4393	.8472	62.76
Cyclohexyl	87[c]	103.5-104	8	1.4645	.9263	51.32
Isoamyl[h]	89[c]	104-105	25	1.4331	.8481	48.90

[a] By procedure (a) described in the experimental part. [b] By procedure (b). [c] By procedure (c). [d] By procedure (d) [e] By procedure (e). [f] Prevously described by Skita and Keil, *Ber.*, **61**, 1682 (1928). [g] Reported in ref. 4. [h] Reported in ref. 3. [i] Determined on the supercooled liquid. [j] Micro Dumas analysis. Nitrogen determinations by the semi-

benzoyl chloride have been assumed to be *p*-nitrobenzoates rather than N-*p*-nitrobenzoyl derivatives without evidence which would differentiate the two classes. Goldberg, Ringk and Spoerri[3] have prepared a series of compounds stated to be *p*-nitrobenzoates by reaction of 1-alkylamino-2-methyl-2-propanols (IV, R = primary alkyl) with *p*-nitrobenzoyl chloride in the presence of aqueous sodium hydroxide. Following their procedure with 1-isoamylamino-2-methyl-2-propanol, we obtained the neutral amide, *p*-$NO_2C_6H_4CON(C_5H_{11})CH_2C(CH_3)_2OH$, XI, m. p. 114–115° (identical with this amide described in Table IV). Their product, m. p. 112–113°, was no doubt this same amide, and it is highly probable that each of the compounds which they describe as a *p*-nitrobenzoate is in fact the corresponding N-*p*-nitrobenzoyl derivative. We have prepared the *p*-nitrobenzoate hydrochloride (VIII, described in Table IV) from this amide by heating it with hydrochloric acid; in addition, the neutral and acid sulfates of the *p*-nitrobenzoate have been made by rearrangement of the amide in the presence of sulfuric acid. Hydrogenation of the *p*-nitrobenzoate hydrochloride and sulfate yielded the crystalline *p*-aminobenzoate hydrochloride (Table IV) and sulfate, respectively. The m. p. of the latter (150–152°) is close to the m. p. of 146–148° quoted for this compound by Goldberg, Ringk and Spoerri. In their reduction procedure, their "*p*-nitroesters" (actually the amides, IX) are treated with tin and hydrochloric acid, after which the mixtures are made alkaline and the *p*-amino compounds are isolated. It is uncertain whether these *p*-amino derivatives, which they consider to be esters, are actually esters or amides. Rearrangement from amide to ester (IX to X) might occur in the acid reduction media. However, when the mixtures are made alkaline, the reverse rearrangement to a *p*-amino-amide would be expected to occur. We have observed that the *p*-nitrobenzoate hydrochloride VIII rearranges very rapidly to the amide XI as soon as its solutions are made alkaline. In the process of preparing the sulfate of the *p*-amino compound, however, rearrangement could yield the *p*-aminobenzoate sulfate, provided the reactants were heated, even if the parent base were the *p*-amino-amide. The correspondence in melting points noted above suggests that in this case their sulfate was the *p*-aminobenzoate sulfate.

Kremer and Waldman[4] have described a number of high melting solids obtained by reaction of 2-alkylamino-2-methyl-1-propanols (III, R = *n*-

(3) Goldberg, Ringk and Spoerri, THIS JOURNAL, **61**, 3562 (1939).

(4) Kremer and Waldman, *ibid.*, **64**, 1089 (1942).

TABLE I (*Continued*)

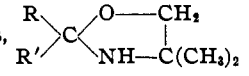
AMINOALCOHOLS

Refraction Found	Formula	Nitrogen, % Calcd.	Found	M. p., °C.	Picrates Formula	Nitrogen, % Calcd.	Found
RNHCH(CH_3)CH_2OH, I							
43.90	$C_8H_{19}ON$	9.65	9.47	128–130[k]	$C_{14}H_{22}O_8N_4$	14.97	15.02
53.11	$C_{10}H_{23}ON$	8.08	8.05	137–138[k]	$C_{16}H_{26}O_8N_4$	13.92	13.92
62.50	$C_{12}H_{27}ON$	6.96	6.91	126–128[k]	$C_{18}H_{30}O_8N_4$	13.02	12.95
62.49	$C_{12}H_{27}ON$	6.96	6.97	114–116[l]	$C_{18}H_{30}O_8N_4$	13.02	12.96
	$C_8H_{19}ON$	8.91	8.88	163–165[k]	$C_{15}H_{22}O_8N_4$	14.50	14.52
RNHCH(C_2H_5)CH_2OH, II							
	$C_7H_{17}ON$	10.68	10.71	103–105[k]	$C_{13}H_{20}O_8N_4$	15.55	15.50
48.43	$C_9H_{21}ON$	8.79	8.76	140–141[k]	$C_{15}H_{24}O_8N_4$	14.43	14.26
57.79	$C_{11}H_{25}ON$	7.48	7.43	132–133[k]	$C_{17}H_{28}O_8N_4$	13.46	13.42
66.75	$C_{13}H_{29}ON$	6.50	6.47	105–107[k]	$C_{19}H_{32}O_8N_4$	12.60	12.46
67.25	$C_{13}H_{29}ON$	6.50	6.43	138–139[k]	$C_{19}H_{32}O_8N_4$	12.60	12.58
	$C_{10}H_{21}ON$	8.18	8.07	142–143[k]	$C_{16}H_{24}O_8N_4$	13.99	14.11
RNHC(CH_3)$_2CH_2OH$, III							
43.78	$C_8H_{19}ON$	9.65	9.84	122–123[k]	$C_{14}H_{22}O_8N_4$	14.97	15.06
	$C_{11}H_{25}ON$	7.48	7.47	74.5–75.5[l]	$C_{17}H_{28}O_8N_4$	13.46	13.43
	$C_{10}H_{21}ON$	8.18	8.00	169–170[k]	$C_{16}H_{24}O_8N_4$	13.99	14.07
				135–136[k]	$C_{15}H_{24}O_8N_4$	14.42	14.44
RNHCH_2C(CH_3)$_2OH$, IV							
39.72	$C_7H_{17}ON$	10.68	10.57	165–167[h,k]	$C_{13}H_{20}O_8N_4$	15.55	15.58
48.69	$C_9H_{21}ON$	8.79	8.71	170–171.5[k]	$C_{15}H_{24}O_8N_4$	14.42	14.40
58.10	$C_{11}H_{25}ON$	7.48	7.33	115–116[k]	$C_{17}H_{28}O_8N_4$	13.46	13.39
62.73	$C_{12}H_{27}ON$	6.96	6.79	78–79[m]	$C_{18}H_{30}O_8N_4$	13.02	12.94
51.22	$C_{10}H_{21}ON$	8.18	8.00	195–196 (dec.)[k]	$C_{16}H_{24}O_8N_4$	13.99	14.05
48.96	$C_9H_{21}ON$	8.79	8.76[j]	145–147[h,k]	$C_{15}H_{24}O_8N_4$		

micro Kjeldahl method were 0.5% low. [k] Recrystallized from alcohol. [l] From alcohol and water. [m] From ether. [n] Ringk and Epstein (ref. 5) report b. p. 186–190°. [o] Ringk and Epstein (ref. 5) report b. p. 245–248, $n^{20}D$ 1.4410, d^{20}_{20} 0.8560.

TABLE II

2-SUBSTITUTED-4,4-DIMETHYL-OXAZOLIDINES,



Substituents in the 2-position	Condensation time, hrs.	Yield, %	Boiling point, °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction Calcd.	Found	Formula	Nitrogen, % Calcd.	Found
Methyl, ethyl[a]	67[d]	65	56–56.5	22	1.4260	0.8813	42.20	41.76	$C_8H_{17}ON$	9.78	9.66
Methyl, amyl	5[e]	50	102–103	19	1.4348	.8702	56.06	55.71	$C_{11}H_{23}ON$	7.56	7.49
Spirocyclohexane[b]	8[f]	73	95–97.5	20	1.4618	.9549	49.24	48.85	$C_{10}H_{19}ON$	8.28	8.38
Isobutyl, hydrogen	1.2	95	72–74	17	1.4322	.8781	46.82	46.60	$C_9H_{19}ON$[c]		

[a] Picrate, recrystallized from absolute alcohol, m. p. 165–167° (dec.). *Anal.* Calcd. for $C_{14}H_{20}O_8N_4$: N, 15.05. Found: N, 15.26. [b] Picrate, recrystallized from absolute alcohol, m. p. 178–180° (dec.). *Anal.* Calcd. for $C_{16}H_{22}O_8N_4$: N, 14.06. Found: N, 14.15. [c] *Anal.* Calcd.: C, 68.73; H, 12.18. Found: C, 68.97; H, 12.36. [d] The condensation required six hours when carried out in the presence of 0.1 equivalent of glacial acetic acid and the yield was 74%. No difficulty was encountered in fractionation from an amine acetate because of the low boiling point of this oxazolidine. [e] The condensation was catalyzed by 0.05 equivalent of glacial acetic acid. Traces of an amine acetate which distilled were removed by the addition of pentane, cooling, decanting and redistilling. [f] The condensation was complete in one hour when a trace of acetic acid was added, but it was impossible to separate the oxazolidine from the amine salt by distillation.

alkyl or isopropyl) with *p*-nitrobenzoyl chloride in the presence of pyridine as the *p*-nitrobenzoates, *p*-$NO_2C_6H_4COOCH_2C(CH_3)_2NHR$. We have prepared the ester with this structure in which R is isoamyl by treating its hydrochloride (Table III) with sodium carbonate. The ester proved to be a very low melting solid, m. p. 25–26°, whereas Kremer and Waldman report m. p. 168–168.5°. The ester of m. p. 25–26° was reconverted to its hydrochloride, m. p. 174–175°, under mild conditions, proving that no rearrangement had occurred. This *p*-nitrobenzoate is very stable; no rearrangement to the corresponding amide occurred when a sample was heated at 42–45° for twenty-four days. On repeating Kremer and Waldman's preparation with 2-isoamylamino-2-methyl-1-propanol, the only pure compound which was isolated was the *p*-nitrobenzoic acid

TABLE III

AMINOESTER HYDROCHLORIDES

Alkyl group	*p*-Nitrobenzoate hydrochloride, formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Found
	p-Nitro- and *p*-Aminobenzoate Hydrochlorides of 2-Alkylamino-1-propanols,				
3-Pentyl	$C_{16}H_{23}O_4N_2Cl$	80	153–155[a]	10.72	10.68
4-Heptyl	$C_{17}H_{27}O_4N_2Cl$	70	125–127[b]	9.88	9.84
5-Nonyl	$C_{19}H_{31}O_4N_2Cl$	84	100–101[c]	9.16	9.25
4-(2,6-Dimethylheptyl)	$C_{19}H_{31}O_4N_2Cl$	44	185–186[a]	9.16	9.18
Cyclohexyl	$C_{16}H_{23}O_4N_2Cl$	72	207–208 (dec.)[d]	10.34	10.36
	p-Nitro- and *p*-Aminobenzoate Hydrochlorides of 2-Alkylamino-1-butanols,				
Isopropyl	$C_{14}H_{21}O_4N_2Cl$	73	174–176[a]	11.19	11.23
3-Pentyl	$C_{16}H_{25}O_4N_2Cl$	70	137.5–139[e]	10.28	10.34
4-Heptyl	$C_{18}H_{29}O_4N_2Cl$	77	169–170[d]	9.51	9.58
5-Nonyl	$C_{20}H_{33}O_4N_2Cl$	60	136–138[b]	8.84	8.86
4-(2,6-Dimethylheptyl)	$C_{20}H_{33}O_4N_2Cl$	70	154–156[a]	8.84	8.84
Cyclohexyl	$C_{17}H_{25}O_4N_2Cl$	84	168–170[a]	9.94	9.95
	p-Nitro- and *p*-Aminobenzoate Hydrochlorides of 2-Alkylamino-2-methyl-1-propanols,				
s-Butyl	$C_{15}H_{23}O_4N_2Cl$	60	173–174[a]	10.72	10.70
2-Heptyl	$C_{18}H_{29}O_4N_2Cl$	51	136–138[c]	9.51	9.56
Cyclohexyl	$C_{17}H_{25}O_4N_2Cl$	60	192–194[a]	9.94	9.95
Isoamyl	$C_{16}H_{25}O_4N_2Cl$	70	174–175[a]	10.28	10.27

[a] Recrystallized from absolute alcohol. [b] From acetone. [c] From acetone and ether. [d] From 95% alcohol. Obtained as dry salts by concentrating *in vacuo* the solutions obtained by reducing the *p*-nitrobenzoate hydrochlorides. [e] The salt melted at 156–159° when first isolated. It was transformed into the higher melting form by grinding with a few crystals obtained by crystallization from absolute alcohol. [f] A low melting isomorphous form was first isolated,

salt of the original aminoalcohol, m. p. 172–174°. Other derivatives of this aminoalcohol which were prepared in an effort to determine the identity of their product, m. p. 168–168.5°, were the ester-amide, p-$NO_2C_6H_4COOCH_2C(CH_3)_2N(C_5H_{11})CO$-$C_6H_4NO_2$, m. p. 119–120°, and the *p*-nitrobenzoic acid salt of the *p*-nitrobenzoate, p-$NO_2C_6H_4$-$COOCH_2C(CH_3)_2NHC_5H_{11}$·$p$-$NO_2C_6H_4COOH$, m. p. 157–158°. These include all of the probable reaction products except the N-*p*-nitrobenzoyl derivative of the aminoalcohol. No decision can be reached concerning the structure of Kremer and Waldman's products, except that the isoamyl derivative is *not* the *p*-nitrobenzoate ester. By analogy and because of their high melting points it is unlikely that the homologs which they report are *p*-nitrobenzoates.[5]

Experimental Part[6]

Materials.—Special research samples of 2-amino-1-propanol and 2-amino-1-butanol, obtained from the Commercial Solvents Corp., were dried by distilling with benzene and redistilled. 2-Amino-2-methyl-1-propanol (Commercial Solvents) and 1-amino-2-methyl-2-propanol (Shell Development Co.) were purified in the same manner. The ketones and aldehydes used were redistilled commercial products or samples prepared according to references previously cited.[2c]

Method of Hydrogenation.—The aminoalcohols described in Table I were prepared from the four aminoalcohols mentioned under *materials* by one or more of the following procedures. (a) By hydrogenation of a solution of 0.1 to 0.5 mole of the aminoalcohol and a ketone (equivalent quantity to 30% excess) in 30 to 75 cc. of absolute alcohol. Adams platinum oxide catalyst (0.5 g.) was reduced in alcohol, the solution to be hydrogenated was added, and the reduction carried out at 50 to 60° and one to two atmospheres pressure. (b) By hydrogenation of the anhydro compound prepared by condensing a ketone or an aldehyde with an aminoalcohol, under the conditions described in (a). (c) As in procedure (a), but at room temperature. (d) By hydrogenation of 0.1 to 0.2 mole of the anhydro compounds in cyclohexane solution in the presence of approximately 1 to 2 g. of Raney nickel catalyst at 140 to 160° and pressures of 100 to 150 atmospheres. (e) As in procedure (d) but in absolute alcohol solution.

2-Alkylamino-1-propanols (I) and 2-Alkylamino-1-butanols (II).—Hydrogenations by procedures (a) and (b) proceeded at erratic rates in both of these series, apparently because a catalyst poison was present in the original aminoalcohols. Several additions of platinum oxide catalyst were necessary to complete many of the hydrogenations, which frequently proceeded rapidly but stopped abruptly at intermediate stages of reduction. Procedure (d) gave better yields than (b) in two instances (see Table I).

Anhydro Compounds Derived from 2-Amino-1-propanol and 2-Amino-1-butanol: 2-[4-(2,6-Dimethylheptylidene)-amino]-1-propanol.—A solution of 22.5 g. (0.3 mole) of 2-amino-1-propanol and 56.8 g. (0.4 mole) of diisobutyl ketone in 100 cc. of benzene was refluxed under a constant water separator[7] for twenty-nine hours. The water layer (6.4 cc.) contained some 2-amino-1-propanol. Distillation of the benzene solution through a Widmer column gave 32 g. (53%) of an anhydro compound, b. p. 117–118° (15 mm.); $n^{25}D$ 1.4548; d^{25}_{25} 0.8828.

Anal. Calcd. for $C_{13}H_{25}ON$: N, 7.03. Found: N, 7.01.

(5) Since this paper was written Ringk and Epstein, THIS JOURNAL, **65**, 1223 (1943), have stated that the products obtained by Kremer and Waldman have the structure of amides rather than esters, *i. e.*, p-$NO_2C_6H_4CON(R)C(CH_3)_2CH_2OH$.

(6) All melting and boiling points are uncorrected. We are indebted to Mary Elizabeth Wright and Walter Kimel for gravimetric chlorine analyses; to John R. Taylor for nitrogen determinations (by semi-micro Kjeldahl method except where otherwise indicated); to Saul Gottlieb and the Arlington Laboratories for micro carbon-hydrogen and Dumas nitrogen analyses.

(7) Cope, Hofmann, Wyckoff and Hardenbergh, THIS JOURNAL, **63**, 3452 (1941).

TABLE III (*Continued*)

AMINOESTER HYDROCHLORIDES

p-Aminobenzoate hydrochloride, formula	Yield, %	M. p., °C.[e]	Chlorine, % Calcd.	Chlorine, % Found	Anesthetic activity Topical, × cocaine	Anesthetic activity Infiltration, × procaine	Toxicity, subcutaneous LD_{50}, mg./kg.
p-NO_2 (or *p*-NH_2) $C_6H_4COOCH_2CH(CH_3)NHR\cdot HCl$							
$C_{16}H_{25}O_2N_2Cl$	72	215–217 (dec.)	11.79	11.82	1	2	550
$C_{17}H_{29}O_2N_2Cl$	95	164–166[f]	10.78	10.81	2.5	2	350
$C_{19}H_{33}O_2N_2Cl$	74	166–168	9.93	9.90	2.5	2	250
$C_{18}H_{33}O_2N_2Cl$	96	178–180[g]	9.93	9.96	3	2	600
$C_{18}H_{25}O_2N_2Cl$	95	204–206	11.33	11.36	2	4	550
p-NO_2 (or *p*-NH_2) $C_6H_4COOCH_2CH(C_2H_5)NHR\cdot HCl$							
$C_{14}H_{23}O_2N_2Cl$	93	209–210	12.36	12.46	2		700
$C_{16}H_{27}O_2N_2Cl$	98	189–190	11.26	11.29	1	1	550
$C_{16}H_{31}O_2N_2Cl$	93	180–182	10.34	10.40	2.5	2.5	250
$C_{20}H_{35}O_2N_2Cl$	98	189–191	9.56	9.71	[i]		
$C_{20}H_{35}O_2N_2Cl$	93	192–194 (dec.)	9.56	9.69	10	3	700
$C_{17}H_{27}O_2N_2Cl$	97	216–217	10.85	10.90	2	2.5	500
p-NO_2 (or *p*-NH_2) $C_6H_4COOCH_2C(CH_3)_2NHR\cdot HCl$							
$C_{16}H_{25}O_2N_2Cl$[k]	80	204–205 (dec.)[h]	11.79	11.79	0.5		300
$C_{18}H_{31}O_2N_2Cl$	98	180–181 (dec.)	10.34	10.59	2.5		150
$C_{17}H_{27}O_2N_2Cl$	92	200–202 (dec.)[i]	10.85	10.87	2.5	4	225

m. p. 92–95°, which solidified and remelted at 178–180°. When ground with a small sample recrystallized from acetone the salt was transformed into the higher melting form. [h] Recrystallized from absolute alcohol and ether. [i] A low melting form of the salt was first isolated, m. p. 131°, which solidified and remelted at 175–185°. The higher melting form was produced by grinding with a small sample of the high melting salt obtained by crystallization from absolute alcohol. [j] Too insoluble for test. [k] Ringk and Epstein (ref. 5) report this compound as a monohydrate, m. p. 202–205°.

TABLE IV

N-*p*-NITROBENZOYL DERIVATIVES AND *p*-NITRO- AND *p*-AMINOBENZOATE HYDROCHLORIDES OF 1-ALKYLAMINO-2-METHYL-2-PROPANOLS, *p*-$NO_2C_6H_4CON(R)CH_2C(CH_3)_2OH$ AND *p*-NO_2(OR *p*-NH_2)$C_6H_4COOC(CH_3)_2CH_2NHR\cdot HCl$

	Alkyl group	N-*p*-Nitrobenzoyl derivative, formula	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	*p*-Nitrobenzoate hydrochloride, formula	Yield, %
1	Isopropyl	$C_{14}H_{20}O_4N_2$[j]	81	105–106[a]	59.98	60.31	7.19	7.28	$C_{14}H_{21}O_4N_2Cl$	74
2	3-Pentyl	$C_{16}H_{24}O_4N_2$[i]	86	93.5–94.5[b]	62.31	62.63	7.84	7.92	$C_{16}H_{25}O_4N_2Cl$	69
3	2-Heptyl	$C_{18}H_{28}O_4N_2$	95	40.5–42.5[b]	64.26	64.14	8.39	8.51	$C_{18}H_{29}O_4N_2Cl$	93
4	2-Octyl	$C_{19}H_{30}O_4N_2$	90	47–49[b]	65.12	65.13	8.63	8.81	$C_{19}H_{31}O_4N_2Cl$	71
5	Cyclohexyl	$C_{17}H_{24}O_4N_2$	90	150.5–152.5[c]	63.73	64.08	7.55	7.54	$C_{17}H_{25}O_4N_2Cl$	75
6	Isoamyl	$C_{18}H_{24}O_4N_2$	88	114–115[c]	62.31	62.15	7.84	7.83	$C_{16}H_{25}O_4N_2Cl$	79

	M. p., °C.	Chlorine, % Calcd.	Chlorine, % Found	*p*-Aminobenzoate hydrochloride, formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Chlorine, % Found	Anesthetic activity Topical, × cocaine	Anesthetic activity Infiltration, × procaine	Toxicity, subcutaneous LD_{50}, mg./kg.
1	168–170[g]	11.19	11.15	$C_{14}H_{23}O_2N_2Cl$	85	175–176 (dec.)[f]	12.36	12.27		2	175
2	154.5–155.5[d]	10.28	10.21	$C_{16}H_{27}O_2N_2Cl$	97	176.5–177.5 (dec.)[k]	11.26	11.25	2.5	2	30
3	135–137 (dec.)[d]	9 51	9.55	$C_{18}H_{31}O_2N_2Cl$	74	164–165 (dec.)[d]	10.34	10.37	4	10	100
4	122–124[e]	9 16	9.15	$C_{19}H_{33}O_2N_2Cl$	80	131–133[d]	9.93	9.92	4	10	100
5	130–132 (dec.)[f]	9.94	9.89	$C_{17}H_{27}O_2N_2Cl$	85	187–188 (dec.)[g]	10.85	10.81	4	10	100
6	123–124[d]	10.28	10.27	$C_{16}H_{27}O_2N_2Cl$	64	129–130 (dec.)[h]	11.26	11.26	2	5	35

[a] Recrystallized from absolute alcohol. [b] From ether and pentane. [c] From benzene. [d] From acetone. [e] From methyl ethyl ketone and ether. [f] From methyl ethyl ketone. [g] From absolute alcohol and acetone. [h] From acetone and ether. [i] Semi-micro Kjeldahl analysis: Calcd.: N, 9.09. Found: N, 9.12. [j] Micro Dumas analysis: Calcd.: N, 9.99. Found: N, 9.72. [k] Obtained as the dry salt by concentrating *in vacuo* the solution from the reduction of the *p*-nitrobenzoate hydrochloride.

The molecular refraction of this compound (61.42) indicated that it was principally in the form of the Schiff base, $[(CH_3)_2CHCH_2]_2C{=}NCH(CH_3)CH_2OH$ (M_D calcd. 62.16; calcd. for the isomeric oxazolidine 60.68).[8]

2,2,4-Triethyl-oxazolidine.—A solution of 44.5 g. (0.5 mole) of 2-amino-1-butanol, 51.6 g. (0.6 mole) of diethyl ketone and 100 cc. of benzene was refluxed under a constant water separator for fourteen hours, during which time 9 cc. of water collected. Distillation through a

(8) See ref. 2a for the atomic refractions employed in this and subsequent calculations. The M_D found for this compound is farther from the value which would be expected for the oxazolidine structure than those figures indicate, for oxazolidines show an "optical depression" (see refs. 2a, c and values in this paper).

TABLE V

N-ACYL DERIVATIVES AND ESTER HYDROCHLORIDES OF 1-CYCLOHEXYLAMINO-2-METHYL-2-PROPANOL, $RCON(C_6H_{11})CH_2C(CH_3)_2OH$ AND $RCOOC(CH_3)_2CH_2NHC_6H_{11}\cdot HCl$

	Acid from which acyl group RCO is derived	Amide, formula	Yield, %	M. p., °C.	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found
1	Benzoic	$C_{17}H_{25}O_2N$	78	77.5–78[a]	74.14	74.47	9.15	9.28
2	Cinnamic	$C_{19}H_{27}O_2N$	76	Sirup				
3	Diphenylacetic	$C_{24}H_{31}O_2N$	84	154–155.5[b]	78.86	78.84	8.55	8.80
4	α-Phenylbutyric	$C_{20}H_{31}O_2N$	79	66.5–68[a]	75.66	75.80	9.84	9.70
5	Carbanilic	$C_{17}H_{28}O_2N_2$	83	131.5–132.5[c]	70.31	70.53	9.03	9.10

	Ester hydrochloride, formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Chlorine, % Found	Anesthetic activity Topical, × cocaine	Anesthetic activity Infiltration, × procaine	Toxicity, subcutaneous LD_{50}, mg./kg.
1	$C_{17}H_{26}O_2NCl$	84	162–163[d]	11.37	11.29	2	2	200
2	$C_{19}H_{28}O_2NCl$	64	161–163[d]	10.49	10.45	2.5	1	>500
3	$C_{24}H_{32}O_2NCl$	60	172–174[e]	8.82	8.70	5	2	>100
4								
5	$C_{17}H_{27}O_2N_2Cl$	41	196–197 (dec.)[f]	10.85	10.90	4.5	2	200

[a] Recrystallized from ether and pentane. [b] From alcohol. [c] From benzene. [d] From acetone. [e] From acetone and ether. [f] From alcohol and ether.

Widmer column yielded 73 g. (93%) of 2,2,4-triethyloxazolidine, b. p. 62–63° (8 mm.); $n^{25}D$ 1.4375; d^{25}_{25} 0.8950; MD calcd. 46.82, found 46.22.

Anal. Calcd. for $C_9H_{19}ON$: N, 8.91. Found: N, 8.80.

2,2-Dipropyl-4-ethyl-oxazolidine.—The condensation of 44.5 g. of 2-amino-1-butanol and 74 g. of dipropyl ketone under the conditions described above was complete in twenty-two hours (9.2 cc. of water collected). Distillation yielded 85 g. (92%) of the oxazolidine, b. p. 91–91.5° (8 mm.); $n^{25}D$ 1.4411; d^{25}_{25} 0.8824; MD calcd. 56.06, found 55.63.

Anal. Calcd. for $C_{11}H_{23}ON$: N, 7.56. Found: N, 7.42.

2-[4-(2,6-Dimethylheptylidene)-amino]-1-butanol.—A solution of 44.5 g. of 2-amino-1-butanol and 92 g. of diisobutyl ketone in 100 cc. of benzene was refluxed under a constant water separator for seventy-one hours, while 8.6 cc. of water collected. Distillation yielded 82 g. (77%) of an anhydro compound, b. p. 111.5–112° (7.5 mm.); $n^{25}D$ 1.4570; d^{25}_{25} 0.8807; MD calcd. for the Schiff base structure, 66.78; for the oxazolidine 65.30; MD found 66.17.

Anal. Calcd. for $C_{13}H_{27}ON$: N, 6.56. Found: N, 6.51.

2-Alkylamino-2-methyl-1-propanols (III).—Unsuccessful attempts were made to substitute *s*-butyl and cyclohexyl groups on the amino group of 2-amino-2-methyl-1-propanol by reducing mixtures of the aminoalcohol with methyl ethyl ketone and cyclohexanone according to procedures (a) and (c). Consequently, anhydro compounds were prepared by condensing 2-amino-2-methyl-1-propanol with methyl ethyl ketone, methyl amyl ketone, cyclohexanone and isovaleraldehyde. The condensations were carried out in the usual manner by refluxing 0.5 mole of the aminoalcohol with a 30% excess of the ketone (or a molecular equivalent of isovaleraldehyde) dissolved in 100 cc. of benzene under a constant water separator until no more water was formed. The oxazolidines produced by these condensations are described in Table II. As indicated in the footnotes, the condensations proceeded slowly with the three ketones unless they were catalyzed by small amounts of acetic acid. In two cases it proved inadvisable to add acetic acid, because compounds (probably acetates of the aminoalcohols or the oxazolidines) were formed, which distilled with the oxazolidines as immiscible liquids or solids which were difficult to separate completely from the products. Diisobutyl ketone failed to condense with 2-amino-2-methyl-1-propanol, even in the presence of acetic acid.

2-Alkylamino-2-methyl-1-propanols (III), prepared by hydrogenation of the oxazolidines, are described in the third section of Table I. Only the oxazolidine derived from isovaleraldehyde could be reduced with platinum (procedure b). The oxazolidines derived from the three ketones were hydrogenated at 140 to 160° in the presence of Raney nickel (procedure d or e). Mixtures of products formed by intermolecular dehydration of the monoalkylaminoalcohols were formed if the hydrogenations were carried out at higher temperatures. For example, hydrogenation of 2,4,4-trimethyl-2-ethyloxazolidine by procedure (e) but at 200° gave a mixture from which 2,2,5,5-tetramethyl-1,4-di-*s*-butylpiperazine was isolated; m. p. after crystallization from pentane 75–75.5°.

Anal. Calcd. for $C_{16}H_{34}N_2$: N, 11.01. Found: (micro Dumas method) N, 10.80.

1-Alkylamino-2-methyl-2-propanols (IV).—Aminoalcohols of this series, which are described in the fourth section of Table I, were prepared easily by rapid, exothermic hydrogenation of ketones and 1-amino-2-methyl-2-propanol by procedure (c). The compounds are less viscous and lower boiling than monoalkylaminoalcohols which are primary and secondary alcohols, indicating less extensive association of these *tertiary* alcohols.

Aminoalcohol picrates described in Table I were prepared by boiling alcohol solutions of the aminoalcohols with equivalent quantities of picric acid. They were recrystallized to constant melting point from the solvents indicated in the footnotes.

***p*-Nitro and *p*-Aminobenzoate Hydrochlorides of Aminoalcohols I, II and III.**—The aminoalcohols (0.05 to 0.1 mole) were converted to hydrochlorides in chloroform solution and esterified by reaction with *p*-nitrobenzoyl chloride according to a procedure described previously,[20] except that the reaction time varied from two to four days. The products were recrystallized from solvents listed in Table III. The *p*-nitrobenzoate hydrochlorides (5 to 15 g.) were dissolved or suspended in 200 to 500 cc. of distilled water and hydrogenated in the presence of 1 g. of palladinized charcoal at room temperature. The catalyst was removed by filtration in an atmosphere of carbon dioxide (maintained by adding dry ice to the solutions), and the filtrates were concentrated to dryness *in vacuo*. The *p*-aminobenzoate hydrochlorides (Table III) were obtained in this way as pure white crystalline salts. It was found to be unnecessary and inadvisable to recrystallize them. Recrystallization usually yielded slightly colored salts, and was resorted to only when the hydrochloride obtained on evaporation was a mixture of dimorphous forms.

The *p*-aminobenzoate hydrochloride of 2-cyclohexylamino-1-butanol (3.3 g.) was transformed into the corresponding glycolate (3.3 g.) by a procedure outlined previously[2b]; m. p. after recrystallization from alcohol and ether 156–157°.

Anal. Calcd. for $C_{19}H_{30}O_5N_2$: N, 7.65. Found: N, 7.64.

Pharmacological data. Topical anesthetic activity, 2×

cocaine; infiltration anesthetic activity, 3× procaine; LD_{50}, 400 mg./kg.

The *p*-aminobenzoate glycolate of 2-[4-(2,6-dimethylheptyl)-amino]-1-butanol was prepared without isolating the hydrochloride. The aqueous solution resulting from the hydrogenation of 4.0 g. of the corresponding *p*-nitrobenzoate hydrochloride was treated with sodium carbonate and extracted with benzene. The benzene solution was added to an equivalent quantity of glycolic acid in alcohol solution and distilled to dryness *in vacuo*. After recrystallization from acetone the glycolate (3.5 g.) melted at 140.5–141.5°.

Anal. Calcd. for $C_{22}H_{38}O_5N_2$: N, 6.82. Found: N, 6.74.

Pharmacological data. Topical anesthetic activity, 5× cocaine; infiltration anesthetic activity, 4× procaine. LD_{50}, 700 mg./kg.

N-*p*-Nitrobenzoyl Derivatives of 1-Alkylamino-2-methyl-2-propanols.—The following preparation illustrates the procedure used in preparing the five amides of this series which are described in Table IV: A solution of 27.8 g. (0.15 mole) of *p*-nitrobenzoyl chloride in 100 cc. of methylene chloride was added rapidly to a vigorously stirred suspension of 17.1 g. (0.1 mole) of 1-cyclohexylamino-2-methyl-2-propanol in 200 cc. of 5% aqueous sodium hydroxide. The mixture was heated in a water-bath so that the methylene chloride refluxed for one hour with vigorous mechanical stirring. The temperature of the reaction mixture was 40 to 45°. The layers were separated and the aqueous layer was extracted once with methylene chloride. The combined methylene chloride solutions were washed twice with water and concentrated to dryness *in vacuo*. The residue was recrystallized once from benzene, yielding 28.7 g. of the N-*p*-nitrobenzoyl derivative of 1-cyclohexylamino-2-methyl-2-propanol, m. p. 150.5–152°.

The amides described in Table IV are insoluble in water and dilute acids. Solutions of the amides in aqueous alcohol were acidified with hydrochloric acid and allowed to stand at room temperature for thirty minutes. On adding water the amides were precipitated unchanged. This behavior verifies the neutral character of the amides and shows that they are not rearranged to esters under these conditions.

***p*-Nitro- and *p*-Aminobenzoate Hydrochlorides of 1-Alkylamino-2-methyl-2-propanols.**—The *p*-nitrobenzoate hydrochlorides (Table IV) were prepared by boiling solutions of 0.02 to 0.05 mole of the corresponding *p*-nitrobenzamides in 50 to 250 cc. of absolute alcohol with a 35 to 75% molar excess of concentrated aqueous hydrochloric acid for five minutes. The solutions were cooled and distilled to dryness *in vacuo*. The residues were dried by adding benzene and reconcentrating *in vacuo*, and recrystallized from the solvents indicated in Table IV.

The *p*-aminobenzoate hydrochlorides, which are also described in Table IV, were prepared in the usual manner by hydrogenating solutions or suspensions of 4 to 7 g. of the corresponding *p*-nitrobenzoate hydrochlorides in 100 to 400 cc. of distilled water in the presence of 1 g. of palladinized charcoal. On concentration *in vacuo* the hydrochlorides were obtained as hydrates. Recrystallization yielded the anhydrous salts.

N-*p*-Nitrobenzoyl Derivative and *p*-Nitrobenzoate Hydrochloride of 2-Cyclohexylaminoethanol.—The general procedure used for synthesis of the amides listed in Table IV was used to prepare N-*p*-nitrobenzoyl-2-cyclohexylaminoethanol. The product obtained from 2-cyclohexylaminoethanol (14.3 g.) and *p*-nitrobenzoyl chloride (27.8 g.) was recrystallized from benzene. The pure amide was separated from impurities which were less soluble in benzene than the product in a yield of 6 g. (21%); m. p. 113.5–115.5°.

Anal. Calcd. for $C_{15}H_{20}O_4N_2$: C, 61.63; H, 6.89. Found: C, 61.74; H, 6.71.

N-*p*-Nitrobenzoyl-2-cyclohexylaminoethanol (2.9 g.) was dissolved in 20 cc. of absolute alcohol, 1.5 cc. of concd. hydrochloric acid was added, and the solution was boiled for five minutes. The *p*-nitrobenzoate hydrochloride was isolated by removing the alcohol *in vacuo*, distilling the residue with benzene to remove water and filtering the benzene suspension; yield 1.8 g. (53%), m. p. and mixed m. p. with a known sample[2b] 231–232°. The unchanged amide (1.1 g., 38%) was recovered from the benzene filtrate.

N-*p*-Nitrobenzoyl Derivative and *p*-Nitrobenzoate Hydrochloride of 1-Cyclohexylamino-2-propanol.—The amide was prepared by the procedure used for the amides listed in Table IV from 15.7 g. of 1-cyclohexylamino-2-propanol and 27.8 g. of *p*-nitrobenzoyl chloride and recrystallized from a mixture of ether and pentane; yield 11 g. (36%), m. p. 88.5–90.5°. Impure higher melting fractions were discarded.

Anal. Calcd. for $C_{16}H_{22}O_4N_2$: C, 62.73; H, 7.24. Found: C, 62.75; H, 7.43.

The above amide (3.1 g.) was dissolved in 20 cc. of absolute alcohol, 1 cc. of concd. hydrochloric acid was added and the mixture was boiled for five minutes. The solvent was removed *in vacuo*. The residue was dried with benzene and crystallized from absolute alcohol. The *p*-nitrobenzoate hydrochloride was obtained in yield of 2.1 g. (62%), m. p. and mixed m. p. with a known sample (ref. 2c) 208–210°.

Amides and Ester Hydrochlorides Derived from 1-Cyclohexylamino-2-methyl-2-propanol.—The amides described in Table V were prepared from 0.035 to 0.065 mole of 1-cyclohexylamino-2-methyl-2-propanol and a 50% excess of an acid chloride by the procedure described for preparation of the N-*p*-nitrobenzoyl derivative of this aminoalcohol (Table IV). The corresponding phenylurea (Table V) was prepared by adding 4.8 g. of phenyl isocyanate slowly to a solution of 6.8 g. of the aminoalcohol in methylene chloride and refluxing for one hour. The N-cinnamoyl derivative could not be obtained as a solid by crystallization from anhydrous solvents. Solvated crystals (m. p. about 70°) were obtained by crystallization from dilute alcohol, but they liquefied on drying *in vacuo*. The yield reported is based on this sirupy liquid product dried to constant weight. Each amide (Table V) was tested for neutrality and stability to rearrangement in the same manner as the N-*p*-nitrobenzoyl derivative, by dissolving it in dilute alcohol, acidifying the solution with hydrochloric acid, and allowing it to stand for thirty minutes. In each case the amide was precipitated unchanged by adding water.

The N-benzoyl derivative (0.02 mole) and N-cinnamoyl derivative (0.017 mole) were rearranged to the corresponding ester hydrochlorides (Table V) in alcohol solution by boiling with a 50% excess of concd. hydrochloric acid, according to the procedure used for the *p*-nitrobenzoate hydrochlorides. When this procedure was followed with the diphenylacetyl derivative, a large proportion of the amide was recovered unchanged. The diphenylacetate hydrochloride was prepared by refluxing a solution of 3.7 g. of the corresponding amide in 25 cc. of absolute alcohol containing 0.9 cc. of concd. hydrochloric acid for one hour. Part of the amide (0.9 g., 24%) crystallized from the solution on cooling, while the ester hydrochloride (2.4 g., 60%) was obtained from the filtrate by recrystallization from acetone. The phenyl urea (Table V) underwent hydrolysis under conditions used for rearranging the other amides. Its rearrangement to the phenylurethan hydrochloride was accomplished by dissolving 4.4 g. in 75 cc. of chloroform, saturating the solution with dry hydrogen chloride, and heating the solution in a bath at 55° for seventy hours. The residue remaining after removal of the solvent was recrystallized from alcohol and ether; yield 2 g. (41%) (Table V).

The phenylurethan of 1-cyclohexylamino-2-methyl-2-propanol was prepared by treating a solution of 0.1 g. of the phenylurethan hydrochloride in water with a slight excess of sodium carbonate, filtering the crystals which formed and recrystallizing from pentane; yield 80 mg., m. p. 107–107.5°.

Anal. Calcd. for $C_{17}H_{26}O_2N_2$: C, 70.31; H 9.03. Found: C, 70.37; H, 9.18.

The α-phenylbutyrate hydrochloride, prepared by rearrangement of the amide in alcohol or chloroform solution, was not analytically pure and consequently is not reported.

p-Nitrobenzoate of 2-Isoamylamino-2-methyl-1-propanol.—The *p*-nitrobenzoate hydrochloride of 2-isoamylamino-2-methyl-1-propanol (Table III) (1 g.) in 100 cc. of water was treated with 100 cc. of 10% sodium carbonate. The oil was extracted with benzene and dried by removing the benzene *in vacuo*. The residue crystallized on standing in the icebox and was recrystallized from pentane; m. p. 25–26°.

Anal. Calcd. for $C_{16}H_{24}O_4N_2$: C, 62.31; H, 7.84. Found: C, 62.33; H, 7.88.

The ester was reconverted to its hydrochloride, m. p. 174–175°, with hydrochloric acid in alcohol solution. The ester is hydrolyzed rapidly by sodium hydroxide in aqueous alcohol solution, and does not rearrange readily to an amide. The ester obtained from 2.6 g. of the *p*-nitrobenzoate hydrochloride was dried carefully by distilling benzene *in vacuo* and heated at 42–45° for twenty-four days *in vacuo* over phosphorus pentoxide. The product was identified as the unchanged ester by dissolving it in pentane and saturating the solution with dry hydrogen chloride. The original *p*-nitrobenzoate hydrochloride (2.0 g., 80%) was obtained.

p-Nitrobenzoic Acid Salt of the *p*-Nitrobenzoate of 2-Isoamylamino-2-methyl-1-propanol.—*p*-Nitrobenzoic acid (0.41 g.) was added to a solution of the *p*-nitrobenzoate (0.77 g.) in 100 cc. of benzene. The mixture was boiled until solution was complete. The salt was recrystallized from benzene; yield 1.1 g., m. p. 157–158°.

Anal. Calcd. for $C_{23}H_{29}O_8N_3$: C, 58.10; H, 6.14. Found: C, 58.31; H, 6.31.

The above compound was proved to be a salt by cleavage into its components under mild conditions. The salt (140 mg.) was dissolved in 15 cc. of methylene chloride and shaken with a water solution of 27.7 mg. of sodium bicarbonate. The aqueous extract was acidified, evaporated to a volume of 5 cc., cooled and filtered. *p*-Nitrobenzoic acid (44.3 mg., 88%) was obtained. The hydrochloride of the *p*-nitrobenzoate of 2-isoamylamino-2-methyl-1-propanol was obtained from the methylene chloride solution by adding hydrochloric acid.

p-Nitrobenzoate of N-*p*-Nitrobenzoyl-2-isoamylamino-2-methyl-1-propanol.—The *p*-nitrobenzoate was prepared from 1.72 g. of the hydrochloride as described above and dried by distilling benzene from it *in vacuo*. The residue was refluxed for forty-eight hours with 1 g. of *p*-nitrobenzoyl chloride in 50 cc. of benzene. The product was separated into an ether insoluble fraction, from which 0.5 g. of the *p*-nitrobenzoate hydrochloride was recovered, and an ether soluble fraction, which yielded 0.25 g. (22%) of the ester-amide after recrystallization from alcohol; m. p. 119–120°.

Anal. Calcd. for $C_{23}H_{27}O_7N_3$: C, 60.38; H, 5.95. Found: C, 60.68; H, 5.85.

The ester-amide was also prepared by refluxing a dry benzene solution of 3.0 g. of 2-isoamylamino-2-methyl-1-propanol and 7.4 g. of *p*-nitrobenzoyl chloride for four days. From this mixture 3.4 g. (37%) of the ester-amide and 1.0 g. (14%) of the *p*-nitrobenzoate hydrochloride were isolated. When the procedure used for preparing the amides described in Table IV was followed with 2-isoamylamino-2-methyl-1-propanol, the ester-amide was obtained in 40% yield.

p-Nitrobenzoic Acid Salt of 2-Isoamylamino-2-methyl-1-propanol.—*p*-Nitrobenzoic acid (0.17 g.) and the aminoalcohol (0.16 g.) were dissolved in hot benzene. The salt which crystallized on cooling was recrystallized from benzene; m. p. 172–174°.

Anal. Calcd. for $C_{16}H_{26}O_5N_2$: C, 58.87; H, 8.03. Found: C, 59.09; H, 7.84.

Reaction of 2-Isoamylamino-2-methyl-1-propanol with *p*-Nitrobenzoyl Chloride in Pyridine.—The only pure compound isolated from these reactants by the procedure described by Kremer and Waldman[4] was a small amount (7%) of the *p*-nitrobenzoic acid salt of the aminoalcohol, described in the preceding section.

N-*p*-Nitrobenzoyl Derivative of 1-Isoamylamino-2-methyl-2-propanol.—The properties of this amide and its preparation in 88% yield are described in Table IV. The reaction of 1-isoamylamino-2-methyl-2-propanol and *p*-nitrobenzoyl chloride under the conditions described by Goldberg, Ringk and Spoerri[3] yielded the same amide in smaller amount (40%). The corresponding *p*-nitrobenzoate hydrochloride (also described in Table IV) was prepared by rearrangement of the amide. The ester rearranges to the amide very rapidly when solutions of its hydrochloride are made alkaline. The *p*-nitrobenzoate hydrochloride (3 g.) in 100 cc. of water was made alkaline with an excess of sodium carbonate and the mixture was extracted with ether. Evaporation of the ether yielded 2.3 g. (89%) of the N-*p*-nitrobenzoyl derivative.

p-Nitrobenzoate Sulfate and Acid Sulfate of 1-Isoamylamino-2-methyl-2-propanol.—A solution of 4.6 g. (0.015 mole) of N-*p*-nitrobenzoyl-1-isoamylamino-2-methyl-2-propanol in 50 cc. of isopropyl alcohol was heated to boiling. Sulfuric acid (0.5 cc., 0.008 mole) in 5 cc. of water was added and the solution was boiled for five minutes. The solvent was removed *in vacuo* and the residue washed with dry ether (0.5 g., 11%, of the original amide was recovered from this ether solution). The salt was ground with water and filtered; recrystallization from a mixture of absolute alcohol and acetone yielded 1.1 g. (28%) of the *p*-nitrobenzoate neutral sulfate, m. p. 144–146°.

Anal. Calcd. for $C_{32}H_{46}O_8N_4 \cdot H_2SO_4$: C, 53.76; H, 7.05. Found: C, 53.97; H, 7.31.

The aqueous filtrate from this salt was concentrated *in vacuo* and the residue recrystallized from a mixture of acetone and ether. This procedure yielded the pure acid sulfate; 1.7 g. (28%), m. p. 109–110°.

Anal. Calcd. for $C_{16}H_{24}O_4N_2 \cdot H_2SO_4$: C, 47.28; H, 6.45. Found: C, 47.34; H, 6.59.

Half-neutralization of an aqueous solution of this acid sulfate with standard alkali converted it into the neutral sulfate.

p-Aminobenzoate Sulfate of 1-Isoamylamino-2-methyl-1-propanol.—A solution of 0.6 g. of the *p*-nitrobenzoate sulfate of 1-isoamylamino-2-methyl-1-propanol in 100 cc. of water was hydrogenated at room temperature in the presence of 1 g. of palladinized charcoal. The solution was filtered from the catalyst, concentrated under diminished pressure and the residue recrystallized from a mixture of absolute alcohol and acetone, yielding 0.37 g. (71%) of the *p*-aminobenzoate sulfate, m. p. 150–152°.

Anal. Calcd. for $C_{32}H_{52}O_4N_4 \cdot H_2SO_4$: C, 58.69; H, 8.31. Found: C, 58.84; H, 8.59.

Reaction of *p*-Nitrobenzoyl Chloride and 1-Isoamylamino-2-methyl-2-propanol Hydrochloride.—A solution of 15.9 g. of 1-isoamylamino-2-methyl-2-propanol in 60 g. of chloroform was saturated with hydrogen chloride, 18.6 g. of *p*-nitrobenzoyl chloride was added, and the mixture was allowed to stand at 30° for ninety hours. From this reaction mixture 15 g. (76%) of the hydrochloride of the original aminoalcohol was recovered. No other pure product was isolated.

An exactly similar reaction mixture was refluxed for forty-eight hours. The solvent was removed *in vacuo* and the residue stirred with dry ether and filtered. The ether insoluble material after washing with ether and recrystallization from alcohol yielded 8 g. (17%) of the *p*-nitrobenzoate of N-*p*-nitrobenzoyl-1-isoamylamino-2-methyl-2-propanol, m. p. 127–128°.

Anal. Calcd. for $C_{23}H_{27}O_7N_3$: C, 60.38; H, 5.95; N, 9.18; mol. wt., 457. Found: C, 60.48; H, 6.17; N, 9.10; mol. wt. (b. p. method, chloroform), 433.

Addition of ether to the alcohol filtrate from the crystallization of the ester-amide described above precipitated a solid which was recrystallized from alcohol and yielded 8.0 g. (41%) of 1-isoamylamino-2-methyl-2-propanol hydrochloride m. p. 211–213°. This salt was identical (m. p.

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

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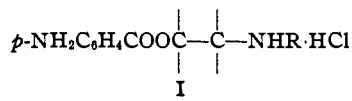
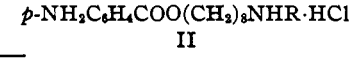
A number of *p*-aminobenzoates of aminoalcohols containing secondary amino groups recently have been found to have pronounced local anesthetic activity.[2] These esters correspond to the general formula I, in which R has been varied widely, while the substituents on the ethanol fragment have been hydrogen,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

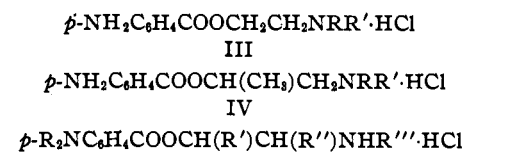


I

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).