Effectiveness compared to procaine hydrochloride in producing infiltration anesthesia was estimated by determining the duration of anesthesia following subcutaneous injection of solutions of the new compounds and procaine hydrochloride at different sites on the abdomen of the same guinea pig. Toxicities were determined by subcutaneous injection in white mice. The LD_{50} values found for the standards were: cocaine hydrochloride, 150 mg./kg.; procaine hydrochloride, 600 mg./kg.

Summary

The reaction of acid chlorides with the hydrochlorides of 2-alkylaminoethanols ($RNHCH_2CH_2OH \cdot HCl$), dissolved in a solvent such as chloroform or methylene chloride, has been found to be a satisfactory method for esterifying the aminoalcohols. The formation of amides through reaction with the secondary amino group is effectively blocked by converting the aminoalcohols to salts.

The local anesthetic activity of a number of benzoates, *p*-aminobenzoates and phenylurethans of 2-alkylaminoethanols has been examined.

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

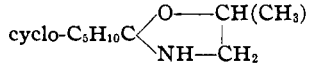
1-Alkylamino-2-propanols and their *p*-Nitro- and *p*-Aminobenzoates

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

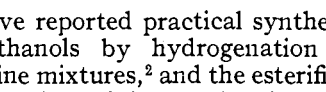
Recently we have reported practical syntheses of 2-alkylaminoethanols by hydrogenation of ketone-ethanolamine mixtures,[2] and the esterification of the hydrochlorides of these aminoalcohols.[3] Similar methods have proved to be equally satisfactory for preparing and esterifying 1-alkylamino-2-propanols, which are described in this paper.

The properties of seventeen 1-alkylamino-2-propanols and picrates derived from most of them are described in Table I. All but three of the aminoalcohols were prepared by hydrogenating ketone–isopropanolamine mixtures in alcohol solution with Adams platinum catalyst. 1-Isoamylamino-2-propanol was prepared similarly from isovaleraldehyde. The aminoalcohols derived from diisobutyl ketone and diisoamyl ketone were obtained by condensing isopropanolamine with these ketones and hydrogenating the anhydro compounds.

Anhydro compounds were prepared from the above ketones as well as cyclohexanone and isopropanolamine by refluxing benzene solutions of the reactants and removing the water formed with a continuous separator. Molecular refractions of the pure anhydro compounds indicate that the product from diisobutyl ketone is the Schiff base, $(i\text{-}C_4H_9)_2C{=}NCH_2CHOHCH_3$, while the cyclohexanone product is an oxazolidine



Anhydro compounds which were formed from these two ketones and ethanolamine were likewise open chain and cyclic, respectively. The molecular refraction of the product from diisoamyl ketone and isopropanolamine indicates that it is an oxazolidine,[4]



The fact that the anhydro compound from isopropanolamine and diisobutyl ketone is a Schiff base, while the diisoamyl ketone product is an oxazolidine, may be due to the factor of steric hindrance cited as a possible explanation of similar differences in the ethanolamine series. There would be less mechanical interference with the formation of a five-membered ring about the carbonyl group in diisoamyl ketone than in diisobutyl ketone, where the point of branching is one carbon atom nearer the carbonyl.

p-Nitrobenzoate hydrochlorides were prepared from the 1-alkylamino-2-propanols by reaction of *p*-nitrobenzoyl chloride with the aminoalcohol hydrochlorides in chloroform solution. As in the ethanolamine series, amide formation was blocked by employing the aminoalcohol salts rather than the free bases. Reaction periods of four to five days and temperatures of 50–60° gave relatively complete esterification of the secondary alcohol group present in the 1-alkylamino-2-propanols. The pure hydrochlorides were isolated in 36 to 75% yield (Table II). A similar procedure was used to convert 1-cyclohexylamino-2-propanol hydrochloride into its phenylurethan.

1-Alkylamino-2-propanols derived from unsymmetrical ketones contain two asymmetric carbon atoms and, therefore, yield mixtures of two diastereomeric *p*-nitrobenzoate hydrochlorides. It was possible to isolate the high melting diastereomer in a fairly pure state in two such

(1) Sharp and Dohme Research Associate.

(2) Cope and Hancock, THIS JOURNAL, **64**, 1503 (1942).

(3) Cope and Hancock, *ibid.*, **66**, 1448 (1944).

(4) The observed molecular refractions are in reasonable agreement with the structures indicated for the three anhydro compounds, but such data do not preclude the presence of smaller amounts of the isomeric structures. An oxazolidine and a Schiff base have been shown to form a mobile system in equilibrium by ring-chain tautomerism in one similar case (ref. 2).

TABLE I

1-ALKYLAMINO-2-PROPANOLS, $RNHCH_2CHOHCH_3$

Alkyl group/	Yield, %	Boiling point, °C.	Mm.	$n^{25}D$	d^{25}_{25}	Molecular refraction Calcd.	Found	Formula	Nitrogen, % Calcd.	Found	Picrate, m. p., °C.	Formula	Nitrogen, % Calcd.	Found
Isopropyl	97	75.5–76	22	1.4322	0.8721	35.04	34.97	$C_6H_{15}ON$	11.96	11.82	129–131	$C_{12}H_{18}O_8N_4$	16.18	15.95
s-Butyl	99	70–71	8	1.4376	.8734	39.66	39.56	$C_7H_{17}ON$	10.68	10.65				
3-Pentyl	88	96–96.5	19	1.4408	.8734	44.28	44.03	$C_8H_{19}ON$	9.65	9.65	130–131	$C_{14}H_{22}O_8N_4$	14.97	15.09
2-(4-Methylpentyl)	95	106–106.5	20	1.4392	.8610	48.90	48.82	$C_9H_{21}ON$	8.79	8.76				
2-Heptyl	97	123.5–124.5	20	1.4432	.8639	53.52	53.36	$C_{10}H_{23}ON$	8.08	7.83				
4-Heptyl	97	119–119.5	21	1.4429	.8640	53.52	53.32	$C_{10}H_{23}ON$	8.08	7.99	124–126	$C_{16}H_{26}O_8N_4$	13.92	13.96
2-Octyl	96	136–137	19	1.4452	.8617	58.14	58.05	$C_{11}H_{25}ON$	7.48	7.41				
5-Nonyl	81	135–137	16	1.4458	.8634	62.76	62.34	$C_{12}H_{27}ON$	6.96	6.93	115–116	$C_{18}H_{30}O_8N_4$	13.02	12.96
4-(2,6-Dimethylheptyl)[a]	93	130–131.5	21	1.4420	.8532	62.76	62.63	$C_{12}H_{27}ON$	6.96	6.98	136–138	$C_{18}H_{30}O_8N_4$	13.02	12.94
6-Hendecyl	88	160–161	17	1.4488	.8579	72.00	71.91	$C_{14}H_{31}ON$	6.11	6.12	95–97	$C_{20}H_{34}O_8N_4$	12.22	12.02
5-(2,8-Dimethylnonyl)[a]	85	154–155	20	1.4470	.8543	72.00	71.96	$C_{14}H_{31}ON$	6.11	5.99	127–128.5	$C_{20}H_{34}O_8N_4$	12.22	12.21
7-Tridecyl	80.5	133–134	1.5	1.4509	.8561	81.24	81.19	$C_{16}H_{35}ON$	5.44	5.29	83.5–85.5	$C_{22}H_{38}O_8N_4$	11.51	11.49
8-Pentadecyl	94	163–166	1	1.4530	.8571	90.48	90.30	$C_{18}H_{39}ON$	4.91	4.62	67–68.5	$C_{24}H_{42}O_8N_4$	10.88	10.88
10-Nonadecyl	68[b]							$C_{22}H_{47}ON$			71.5–72.5	$C_{28}H_{50}O_8N_4$	9.81	9.69
Cyclohexyl[c]	95	126–126.5[c]	20	1.4752				$C_9H_{19}ON$	8.91	8.96	139.5–140.5	$C_{15}H_{22}O_8N_4$	14.50	14.46
4-Methylcyclohexyl	93	133–133.5	21	1.4710	.9388	51.32	51.14	$C_{10}H_{21}ON$	8.18	8.31	123–125	$C_{16}H_{24}O_8N_4$	13.99	13.93
Isoamyl	90	105.5–106	19	1.4368	.8596	44.28	44.38	$C_8H_{19}ON$	9.65	9.40[d]	113–115	$C_{14}H_{22}O_8N_4$	14.97	14.90

[a] Prepared by hydrogenation of the anhydro compound prepared from the ketone and isopropanolamine and described in the Experimental Part. [b] Isolated as the hydrochloride salt, m. p. 109–110.5°. *Anal.* Calcd. for $C_{22}H_{48}ONCl$: Cl, 9.38. Found: Cl, 9.33. [c] Solidified during distillation, m. p. 44–47°. Index of refraction determined on the supercooled liquid. [d] Micro Dumas analysis by the Arlington laboratories. Kjeldahl analyses were low. [e] M. p. of the hydrochloride (recrystallized from acetone and ether), 161–163°. *Anal.* Calcd. for $C_9H_{20}ONCl$: Cl, 18.30. Found: Cl, 18.29. [f] The alkyl groups are derived from the following ketones and aldehydes (reading from top to bottom of the table): acetone; methyl ethyl ketone; diethyl ketone; methyl isobutyl ketone; methyl amyl ketone; dipropyl ketone; methyl hexyl ketone; dibutyl ketone; diisobutyl ketone; diamyl ketone; diisoamyl ketone; dihexyl ketone; diheptyl ketone; dinonyl ketone; cyclohexanone; 4-methylcyclohexanone; isovaleraldehyde.

TABLE II

1-ALKYLAMINO-2-PROPANOL *p*-NITRO- AND *p*-AMINOBENZOATE HYDROCHLORIDES, $p\text{-}NO_2$ (OR $p\text{-}NH_2$)$C_6H_4COOCH(CH_3)CH_2NHR\cdot HCl$

Alkyl group	*p*-Nitrobenzoate hydrochloride formula	Yield %	M. p., °C.	Chlorine, % Calcd.	Found	*p*-Aminobenzoate hydrochloride formula	Yield, %	M. p., °C.	Chlorine, % Calcd.	Found	Anesthetic activity: Topical, × cocaine	Infiltration, × procaine	Toxicity, subcutaneous LD_{50}, mg./kg.
Isopropyl	$C_{13}H_{19}O_4N_2Cl$	50	200–201[a]	11.71	11.72	$C_{13}H_{21}O_2N_2Cl$	93	168–169[b]	13.00	13.00	0		750
s-Butyl	$C_{14}H_{21}O_4N_2Cl$	31	176–178[a,m]	11.19	11.10	$C_{14}H_{23}O_2N_2Cl$	44	165–168[c]	12.36	12.29	0		400
3-Pentyl	$C_{15}H_{23}O_4N_2Cl$	73	171–172[a]	10.72	10.66	$C_{15}H_{25}O_2N_2Cl$	80	94–95 (dec.)[c]	11.79	11.75	0.5		250
2-(4-Methylpentyl)	$C_{16}H_{25}O_4N_2Cl$	6	177–179[c,m]	10.28	10.24	$C_{16}H_{27}O_2N_2Cl$	90	201–203[k]	11.26	11.25	1		150
4-Heptyl	$C_{17}H_{27}O_4N_2Cl$	60	153–155[b]	9.88	9.88	$C_{17}H_{29}O_2N_2Cl$	90	148–150[b]	10.78	10.76	1	2	150
5-Nonyl	$C_{19}H_{31}O_4N_2Cl$	36	118–120[c,g]	9.16	9.18	$C_{19}H_{33}O_2N_2Cl$	92	133–134[h]	9.93	9.85	2.5	2	225
4-(2,6-Dimethylheptyl)	$C_{18}H_{31}O_4N_2Cl$	75	181–183[a]	9.16	9.14	$C_{19}H_{33}O_2N_2Cl$	89	183–184[c,i]	9.93	9.94	2.5	2	250
6-Hendecyl	$C_{21}H_{35}O_4N_2Cl$	72	128–130[d]	8.54	8.58	$C_{21}H_{37}O_2N_2Cl$	80	107–109[j]	9.21	9.13	1	1	>300
5-(2,8-Dimethylnonyl)	$C_{21}H_{35}O_4N_2Cl$	57	151.5–152.5[d]	8.54	8.50	$C_{21}H_{37}O_2N_2Cl$	91	89–91[k]	9.21	9.18	2	3	>400
7-Tridecyl	$C_{23}H_{39}O_4N_2Cl$	59	143–144[e]	8.00	8.07								
8-Pentadecyl	$C_{25}H_{43}O_4N_2Cl$	53	105–106.5[e]	7.53	7.54	$C_{25}H_{45}O_2N_2Cl$	98	131–133[j]	8.04	7.94			
10-Nonadecyl	$C_{29}H_{51}O_4N_2Cl$	53	105–106.5[e]	6.73	6.82								
Cyclohexyl	$C_{16}H_{23}O_4N_2Cl$	75	208–209[f]	10.34	10.39	$C_{16}H_{25}O_2N_2Cl$	98	186–187.5[k,l]	11.33	11.25	1	4	250
4-Methylcyclohexyl	$C_{17}H_{25}O_4N_2Cl$	70	171–173[b]	9.94	9.92	$C_{17}H_{27}O_2N_2Cl$	71	161–163[b]	10.85	10.88	1	3	175
Isoamyl	$C_{15}H_{23}O_4N_2Cl$	52	133–136[b]	10.72	10.79	$C_{15}H_{25}O_2N_2Cl$	90	150–151[e]	11.79	11.79	1.5	2.5	125

[a] Recrystallized from absolute alcohol. [b] From alcohol and ether. [c] From acetone. [d] From acetone and ether. [e] From acetone, ether and pentane. [f] From 95% alcohol. [g] Solidifies and remelts at 139–140°. [h] From benzene. A low melting isomorphous form was isolated by crystallization from acetone, m. p. 105–107°. [i] When crystallized from alcohol and ether an isomorphous form was obtained which melted at 100–105°, solidified and remelted at 181–183°. The more stable variety can be obtained by grinding with a small amount of the high melting form. [j] From water. [k] Isolated as the dry salt by concentrating in vacuum the solution obtained by reducing the *p*-nitrobenzoate hydrochloride. [l] When crystallized from alcohol and ether an isomorphous form was obtained which melted at 135–140°, solidified and remelted at 183–185°. The low melting form can be transformed into the high melting by grinding the dry salt with a small amount of the high melting form. [m] M. p. of the high melting diastereomer.

cases (Table II); in two other cases the mixed diastereomers failed to crystallize.

Table II also contains the properties of the *p*-aminobenzoate hydrochlorides which were prepared by catalytic hydrogenation of the *p*-nitrobenzoate hydrochlorides as in the previous work. Three of the hydrochlorides were converted into the glycolates to obtain additional salts for pharmacological testing. The hydrochloride and glycolate of one high molecular weight compound in this series, 1-(8-pentadecylamino)-2-propanol *p*-aminobenzoate, proved to be very insoluble in water and thus poorly suited to tests for physiological activity. The corresponding 1-(7-tridecylamino)- and 1-(10-nonadecylamino)-2-propanol *p*-nitrobenzoate hydrochlorides consequently were not hydrogenated to the *p*-aminobenzoates, which would also be expected to give water-insoluble salts.

Experimental Part[5]

Preparation of 1-Alkylamino-2-propanols.—Monoisopropanolamine (Carbide and Carbon Chemicals Corp.) was distilled with benzene to remove water and fractionated in vacuum; b. p. 73–74° (19 mm.), $n^{25}D$ 1.4460. Di-*n*-butyl, diamyl, diisoamyl, dihexyl and diheptyl ketones were prepared by the Claisen condensation according to Briese and McElvain,[6] except that sodium methoxide (Mathieson Alkali Works) was used as the condensing agent. Yields were 50 to 67%. The remaining ketones and isovaleraldehyde were redistilled commercial products.

In preparing 1-alkylamino-2-propanols from diethyl and dipropyl ketones and the methyl ketones and cyclic ketones listed in Table I, isopropanolamine (0.5 mole), the ketone (0.65 mole) and 100 cc. of absolute alcohol were added to the platinum catalyst prepared by reducing 0.5 g. of platinum oxide in 50 cc. of alcohol. Shaking with hydrogen at one to two atmospheres pressure and room temperature resulted in rapid, exothermic reductions which were complete in four to fifteen hours. The excess ketone was partly or completely reduced to the corresponding alcohol in most cases. The higher symmetrical ketones (containing nine to nineteen carbon atoms) were available in smaller amount and were used in smaller (0 to 10%) excess. In these cases reductions of 0.06 to 0.2 mole quantities were complete in 9–20 hours at 50 to 60°. A mixture of diisobutyl ketone and isopropanolamine failed to hydrogenate under these conditions. 1-Isoamylamino-2-propanol was prepared from isovaleraldehyde and isopropanolamine under the conditions employed with aldehydes in the ethanolamine series.[2] The products (Table I) were purified by distillation as in the previous work.

Picrates of the 1-alkylamino-2-propanols were prepared by the method used in the ethanolamine series. As would be expected, the aminoalcohols derived from unsymmetrical ketones gave mixtures of diastereomeric picrates, which melted over a range of several degrees and consequently are omitted from Table I.

Anhydro Compounds from Ketones and Isopropanolamine. 5'-Methylspiro-[cyclohexane 1,2'-oxazolidine].—A mixture of 37.5 g. of isopropanolamine, 52 g. of cyclohexanone and 50 cc. of dry benzene was refluxed under a constant water separator for two hours, during which time a water layer of 9.7 cc. collected. The benzene was removed in vacuum and the residue distilled through a Widmer column; yield 67 g. (86%); b. p. 95–96° (19 mm.); $n^{25}D$ 1.4697; d^{25}_{25} 0.9793; M_D calcd. 44.62, found 44.33.

Anal. Calcd. for $C_9H_{17}ON$: N, 9.02. Found: N, 8.81.

This oxazolidine is perfectly stable when dry, but is rapidly hydrolyzed by water. An attempt to prepare its picrate in the usual manner gave isopropanolamine picrate, m. p. and mixed m. p. 138–139°.

1-[4-(2,6-Dimethylheptylidene)-amino]-2-propanol.—Isopropanolamine (37.5 g.) diisobutyl ketone (92 g.) and 50 cc. of benzene were refluxed under a constant water separator for eight hours. The water layer which collected (15 cc.) contained some isopropanolamine and a small amount of the ketone. Distillation gave 66 g. (66%) of the Schiff base, b. p. 124–125° (20 mm.); $n^{25}D$ 1.4487; d^{25}_{25} 0.8676; M_D calcd. 62.16, found 61.77.

Anal. Calcd. for $C_{12}H_{25}ON$: N, 7.03. Found: N, 6.95.

Hydrogenation of 50 g. of the above anhydro compound with 0.5 g. of platinum catalyst in absolute alcohol solution at 50–60° during ten hours gave 46 g. of 1-[4-(2,6-dimethylheptyl)-amino]-2-propanol (Table I).

2,2-Diisoamyl-5-methyloxazolidine.—Isopropanolamine (15 g.), diisoamyl ketone (34 g.) and 100 cc. of benzene were refluxed for six hours under a constant water separator. Distillation gave 34.5 g. (76%) of the oxazolidine, b. p. 140–141.5° (19 mm.); $n^{25}D$ 1.4449; d^{25}_{25} 0.8691; M_D calcd. 69.92, found 69.83.

Anal. Calcd. for $C_{14}H_{29}ON$: N, 6.16. Found: N, 6.02.

Hydrogenation of 32.5 g. of this anhydro compound for eight hours at 50–60° gave 29 g. of the corresponding aminoalcohol (Table I).

***p*-Nitrobenzoate Hydrochlorides from 1-Alkylamino-2-propanols.**—The 1-alkylamino-2-propanols (0.1 mole) in 30 g. of chloroform were saturated with dry hydrogen chloride gas with cooling. A solution of 18.6 g. (0.1 mole) of *p*-nitrobenzoyl chloride in 30 g. of chloroform was added and the solution was heated at 50 to 60° under a reflux condenser for 110 to 120 hours. The chloroform was removed in vacuum and the residual sirups were crystallized by agitation with dry ether. The solid salts were allowed to stand under dry ether for several hours, filtered, washed with ether and dried. The properties and yields of the recrystallized hydrochlorides are recorded in Table II.

The *p*-nitrobenzoate hydrochlorides prepared from the 1-alkylamino-2-propanols containing two asymmetric carbon atoms were obtained as mixtures of diastereomers. The products from 1-(2-heptylamino)-2-propanol and 1-(2-octylamino)-2-propanol failed to crystallize and were discarded. The *p*-nitrobenzoate hydrochlorides obtained from 1-*s*-butyl-2-propanol and 1-[2-(4-methylpentyl)-amino]-2-propanol eventually crystallized, and from the mixed diastereomers obtained in 50 and 39% yield in these two cases the less soluble, higher melting diastereomers were separated in 31 and 6% yield by recrystallization (see Table II).

***p*-Aminobenzoate Hydrochlorides of 1-Alkylamino-2-propanols.**—Suspensions or solutions of 5 to 13 g. of the finely powdered *p*-nitrobenzoate hydrochlorides in 200 to 500 cc. of distilled water were hydrogenated in the presence of palladinized charcoal (see ref. 3). The products are described in Table II.

Three of the hydrochlorides were transformed into glycolic acid salts by the procedure previously described.

1-Cyclohexylamino-2-propanol *p*-aminobenzoate glycolate crystallized from dilute alcohol as a monohydrate, m. p. 96–98°.

Anal. Calcd. for $C_{18}H_{28}O_5N_2 \cdot H_2O$: N, 7.56. Found: N, 7.60.

Pharmacological data: Topical anesthetic activity, 2.5 × cocaine; infiltration anesthetic activity, 2.5 × procaine; LD_{50}, 250 mg./kg.

1-[4-(2,6-Dimethylheptyl)-amino]-2-propanol *p*-aminobenzoate glycolate crystallized from acetone and ether as an anhydrous salt, m. p. 115–117°.

Anal. Calcd. for $C_{21}H_{36}O_5N_2$: N, 7.06. Found: N, 7.07.

(5) Melting and boiling points are uncorrected. We are indebted to Miss Mary Elizabeth Wright for gravimetric chlorine analyses and to J. P. Lutz and John R. Taylor for semi-micro Kjeldahl analyses.

(6) Briese and McElvain, THIS JOURNAL, **55**, 1697 (1933).

Pharmacological data: Topical anesthetic activity, 5 × cocaine; infiltration anesthetic activity, 5 × procaine, LD_{50}, 475 mg./kg.

The corresponding free base, 1-[4-(2,6-dimethylheptyl)-amino]-2-propanol *p*-aminobenzoate was prepared and recrystallized from pentane; m. p. 49.5–50.5°.

Anal. Calcd. for $C_{19}H_{32}O_2N$: N, 8.74. Found: N, 8.81.

1-(8-Pentadecylamino)-2-propanol *p*-aminobenzoate glycolate was recrystallized from a mixture of acetone, ether and pentane as an anhydrous salt, m. p. 101–103°.

Anal. Calcd. for $C_{27}H_{48}O_5N_2$: N, 5.83. Found: N, 5.79.

An attempt to prepare 1-[4-(2,6-dimethylheptyl)-amino]-2-propanol *p*-aminobenzoate borate was unsuccessful. The free base (described above) and boric acid were isolated from the attempted preparation, and evidently the base is not sufficiently basic to form a stable salt with boric acid. The free base could not be dissolved in a dilute water solution containing four or eight equivalents of boric acid.

1-Cyclohexylamino-2-propanol Phenylurethan Hydrochloride.—1-Cyclohexylamino-2-propanol (7.9 g.) was converted to the hydrochloride and heated with an equivalent quantity of phenyl isocyanate in chloroform solution for ninety hours at 50 to 55°. The product was isolated in the manner employed in the aminoethanol series[3]; yield 11.5 g. (73%), m. p. 192–193°.

Anal. Calcd. for $C_{16}H_{25}O_2N_2Cl$: Cl, 11.33. Found: Cl, 11.34.

Pharmacological data: Topical anesthetic activity, 1 × cocaine; infiltration anesthetic activity, 2 × procaine; LD_{50}, 200 mg./kg.

The 1-alkylamino-2-propanol *p*-aminobenzoate hydrochlorides in Table I and the additional salts described above were soluble in water at room temperature to the extent of 2% or more except for the hydrochlorides in which the alkyl group was 5-(2,8-dimethylnonyl) (1%); 6-hendecyl (0.55%) (all ±0.1%); 8-pentadecyl (and its glycolate) (less than 0.05%).

Pharmacological.—The pharmacological data included in Table II were obtained at the Merck Institute for Therapeutic Research, and will be published elsewhere in detail by Albert O. Seeler and Samuel Kuna. The method of testing is outlined in ref. 3.

Summary

A number of 1-alkylamino-2-propanols have been prepared by the hydrogenation of ketone-isopropanolamine mixtures in the presence of Adams platinum catalyst. The synthesis is convenient, and gives excellent yields.

The hydrochlorides of the 1-alkylamino-2-propanols have been esterified by reaction with *p*-nitrobenzoyl chloride in chloroform solution. The *p*-nitrobenzoate hydrochlorides were converted by catalytic hydrogenation into *p*-aminobenzoate hydrochlorides, and the local anesthetic activity of these esters has been studied.

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

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE JOHNS HOPKINS UNIVERSITY]

Some 3,4-Disubstituted Pyridines[1]

BY JAMES L. WEBB[2] AND ALSOPH H. CORWIN

The researches of Rabe during the past twenty-five years have strongly suggested possible methods for the synthesis of the quinine alkaloids. Among possible intermediates are several 3,4-disubstituted pyridines. Some of the most important methods for the synthesis of these compounds[3] are due to Rabe,[4] McElvain and Goese,[5] Stevens, Beutel and Chamberlin[3] and Koelsch.[6] In consideration of its availability, 4-methylpyridine (γ-picoline) was utilized as the starting product for the preparations reported in this paper.

After all the work described here had been completed the paper by McElvain and Goese[5] appeared in which they describe the sulfonation of the 2-, 3-, and 4-methylpyridines and of pyridine itself using mercuric sulfate as catalyst. Their yields of 4-methylpyridine-3-sulfonic acid varied between 0–35%. Using basic mercuric sulfate catalyst our average yield of the very crude sodium 4-methylpyridine-3-sulfonate was 57%.

The conditions necessary for the cyanide fusion of pyridine sulfonic acid salts are, at best, drastic since the reaction mixture contains the very basic cyanide ion and the temperature necessary for reaction is approximately 300–400°. We have found that the yield is inversely proportional to the time required for the fusion. Procedures which overcome some of the disadvantages inherent in this reaction are described in the Experimental Section. McElvain and Goese report a yield of 12% of the 3-cyano-4-methylpyridine. Our yield varied from 25–33% based on the crude sodium 4-methylpyridine-3-sulfonate.

While 2-, 3- and 4-cyanopyridine are hydrolyzed readily and in good yields by alkali to the corresponding pyridine carboxylic acids, the sterically hindered 3-cyano-2,4-dimethylpyridine on heating in a sealed tube in alkaline medium is converted only to the amide.[7] However, McElvain and Goese[5] successfully hydrolyzed 3-cyano-4-methylpyridine to 4-methylpyridine-3-carboxylic acid in 80% yield. Upon attempting to hydrolyze

(1) This paper is from the doctoral dissertation of James L. Webb, The Johns Hopkins University, 1943.

(2) Du Pont Fellow in Chemistry, 1942-43; American Can Company Fellow, 1943.

(3) Stevens, Beutel and Chamberlin, THIS JOURNAL, **64**, 1093 (1942).

(4) Rabe, *et al.*, *Ber.*, **64**, 2487 (1931).

(5) McElvain and Goese, THIS JOURNAL, **65**, 2233 (1943), and earlier papers.

(6) Koelsch, *ibid.*, **65**, 2458, 2459, 2460 (1943).

(7) Meyer, *J. prakt. Chem.*, [2] **78**, 519 (1908).