terial with alkaline permanganate and loss of carbon dioxide an acid was obtained by Noyes and Skinner which was thought to be α,β,β-trimethylglutaric acid.

The possibility of this acid being α,β,γ-trimethylglutaric acid has been eliminated by the synthesis of this compound and direct comparison with a sample of the original acid. The α,β,γ- is a new acid and completes the trimethylglutaric acid series.

It has been shown also that the compound obtained by Noyes and Skinner is α,α,β-trimethylglutaric acid.

GRINNELL, IOWA

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

LOCAL ANESTHETICS DERIVED FROM β-PIPERIDYL CARBINOL

BY L. T. SANDBORN[1] WITH C. S. MARVEL

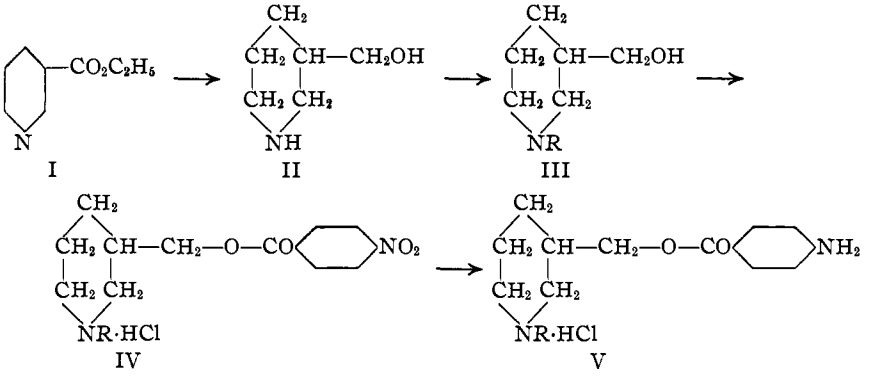
RECEIVED NOVEMBER 10, 1927 PUBLISHED FEBRUARY 4, 1928

Some of the molecular structures which produce local anesthetic action are very well known. Numerous compounds have been prepared in the attempt to find the best combination of high anesthetic value and low toxicity which is desirable for this type of drug. The earlier synthetic substitutes for cocaine were usually esters of cyclic amino alcohols; then with the discovery of novocaine the esters of open chain amino alcohols became more important. Recently McElvain[2] has shown that in a series with very closely related structures the closed ring derivatives are much more efficient in anesthetic action.

In connection with some other researches, a method for the preparation of β-piperidyl carbinol (II) was developed. The fact that it was a cyclic amino alcohol at once suggested its use for the synthesis of a compound which should have local anesthetic action. The very favorable properties which were shown by this substance led to a more complete study of the derivatives of β-piperidyl carbinol with a view to producing a drug that might have properties better than any of those now available. β-Piperidyl carbinol was obtained in about 43% yields by the reduction of ethyl nicotinate (I) with sodium and absolute alcohol. It was also obtained in 50% yields by a similar reduction of ethyl nipecotate, but the difficulties involved in the preparation of nipecotic ester make the former method more practical. It has the properties that would be expected of an amino alcohol of this type.

[1] This communication is an abstract of a thesis submitted by L. T. Sandborn in partial fulfilment of the requirements for the degree of Doctor of Philosophy in Chemistry at the University of Illinois.

[2] McElvain, THIS JOURNAL, **46**, 1721 (1924).



The common local anesthetics are *p*-aminobenzoates of tertiary amino alcohols. β-Piperidyl carbinol (a secondary amino alcohol) was therefore first alkylated on the nitrogen by treatment with an alkyl halide. The N-alkyl derivatives (III) obtained were the methyl, ethyl, *iso*propyl, *n*-butyl and allyl compounds. All of the alkyl derivatives boiled very close to the original carbinol and there was some difficulty on this account in obtaining them in a pure condition. The scheme finally adopted for their purification was to titrate the mixture of alkylated and unalkylated carbinol with standard acid and to obtain a mean molecular weight. From this value the amount of unalkylated carbinol was calculated. Then enough benzoyl chloride was added to react with the secondary amine to form the benzoyl amide. The alkylated carbinol was then extracted from this mixture with dilute acid, reprecipitated with alkali and extracted with benzene. An attempt was made to purify the carbinols by converting them to the hydrochlorides and crystallizing these derivatives. The salts were too hygroscopic for easy crystallization.

The N-alkyl-β-piperidyl carbinols were converted to the *p*-nitrobenzoyl ester hydrochlorides (IV) by the action of *p*-nitrobenzoyl chloride. The nitro ester hydrochlorides were reduced to the corresponding amino ester hydrochlorides (V) with hydrogen in the presence of a platinum-oxide platinum black catalyst.[3] This process could not be used on the allyl derivative and reduction with iron and hydrochloric acid was tried. The reduced product was not isolated in a crystalline condition either as a free base or as a salt.

Pharmacological Tests[4]

A 1% solution of the monohydrochloride of each amino ester was used. The toxicity was determined by intravenous injection in rabbits and the

[3] Adams and Shriner, THIS JOURNAL, **45**, 2171 (1923).

[4] The pharmacological tests were performed by H. J. Cannon at the Abbott Laboratories. The authors desire to take this opportunity of expressing their thanks to the Abbott Laboratories for their kind assistance in this investigation.

onset time and duration of anesthesia by application to the cornea of a rabbit's eye.

TABLE I

PHARMACOLOGICAL PROPERTIES

Alkyl carbinol	Average onset time in min.	Average duration of anesthesia in minutes	Minimum lethal dose in mg. per kg. of body weight
Methyl	2	25	15
Ethyl	1.5	45–50	16
*Iso*propyl	3.5–3.75	30–35	16
n-Butyl	1.75	25–30	15

These pharmacological properties compare very favorably with those of the local anesthetics now in common use.

Experimental Part

β-Piperidyl Carbinol.—In a 5-liter two-necked, round-bottomed flask fitted with a large bore condenser and a mechanical stirrer, was placed 800 cc. of absolute alcohol (dried with sodium or magnesium methylate) and 45.3 g. (0.3 mole) of ethyl nicotinate. The solution was stirred and heated to boiling over a flame. The flame was then removed and 92 g. (4 atoms) of sodium was added through the condenser as rapidly as possible.

In our experiments several rather characteristic color changes were noticed during the reduction. A green color appeared when the first portion of sodium was added. This color then quickly disappeared and the mixture turned yellow. At this point moderate foaming occurred. As the reaction continued, there was a gradual change in color from yellow to reddish brown and then back to light yellow. With this last change the sodium, which was usually in fairly large pieces up to this stage, melted and was broken up into fine globules which were suspended in the alcohol. A vigorous reaction set in, foaming occurred and it was often necessary to cool the flask with wet towels to prevent loss of material through the condenser. On the other hand, if this vigorous reaction did not set in by the time all of the sodium had been added, the flask was heated until it did occur. Occasionally it was necessary to add a 100-cc. portion of absolute alcohol to keep the sodium ethylate in solution.

The reaction mixture was heated for about a half hour after the sodium had dissolved and was then cooled to room temperature. About 250 cc. of water was added to decompose the sodium ethylate and the alcohol was removed by distillation under reduced pressure. When the solution became quite concentrated another 50 cc. of water was added and distillation continued until all of the alcohol was removed. The strong sodium hydroxide solution containing the β-piperidyl carbinol was extracted with five 500-cc. portions of ether. The ether was distilled off and the residual amino alcohol was distilled under reduced pressure. The yield was 14–15 g. (40–43% of the theoretical amount) of a product which is a thick, viscous oil; b. p. 106–107° (3.5 mm.); d_4^{20} = 1.0263; n_D^{20} = 1.4964; M_D, calcd., 32.74; observed, 32.69.

Anal. Subs., 0.1853: H_2O, 0.1908; CO_2, 0.4254. Calcd. for $C_7H_{15}ON$: H, 11.45; C, 62.61. Found: H, 11.52; C, 62.61.

In a similar way 47.1 g. of ethyl nipecotate in 450 cc. of absolute ethyl alcohol was reduced with 46 g. of sodium to give 17–19 g. (49–55% of the theoretical amount) of β-piperidyl carbinol.

General Procedure for the Preparation of N-Alkyl-β-piperidyl Carbinols.—In a 500-cc. three-necked, round-bottomed flask, fitted with a reflux condenser, a mechanical stirrer and a separatory funnel, was placed 23 g. (0.2 mole) of β-piperidyl carbinol dissolved in 100 cc. of benzene, and 0.1 mole of alkyl bromide or iodide dissolved in about 75 cc. of benzene was added through the separatory funnel. With methyl iodide, ethyl iodide and allyl bromide the reaction went rapidly and heat was liberated. The reaction mixture was then stirred at room temperature for about eight hours to complete the reaction. When *iso*propyl bromide or *n*-butyl bromide was used the reaction was much less vigorous and the reaction mixture was stirred and heated on the steam cone for about five hours. During the mixing of the halide and the amine, a gummy material consisting of a mixture of the hydrochlorides of β-piperidyl carbinol and the N-alkyl-β-piperidyl carbinol separated from the solution.

When the reaction was complete, the mixture was made strongly alkaline by the addition of 30% sodium hydroxide solution. The benzene layer was separated and the aqueous layer was extracted with two 100-cc. portions of benzene. The benzene was distilled and the residue distilled under reduced pressure. A sample of the distillate was titrated with standard acid to determine the mean molecular weight of the mixture of alkylated and unalkylated carbinol. Then sufficient benzoyl chloride was added to the benzene solution of this mixture to react with the unalkylated material to form an amide. After standing for a few hours to allow complete reaction to occur, the N-alkyl-β-piperidyl carbinol was extracted from the benzene with dilute hydrochloric acid solution. The N-alkyl carbinol was then liberated as the free base by the addition of sodium hydroxide solution and was extracted with two 100-cc. portions of benzene. The benzene was distilled off and the residue then distilled under reduced pressure. The average yield of the alkylated carbinol was about 60% of the theoretical amount. The physical properties and analyses of the N-alkyl-β-piperidyl carbinols are given in Table II.

TABLE II

PROPERTIES AND ANALYSES OF N-ALKYL-β-PIPERIDYL CARBINOLS

Alkyl group	B. p., °C.	d_4^{20}	n_D^{20}	M_D, calcd.	M_D, obs.	Subs. g.	Cc. of 0.1116 *N* HCl	% N, calcd.	Found
Methyl	110–112 (7 mm.)	1.0125	1.4988	37.8	37.39	0.1743	12.1	10.85	10.84
Ethyl	110–111 (6.5 mm.)	0.9904	1.4911	42.42	41.86	.2929	18.55	9.79	10.05
*Iso*propyl	93–94 (3.5 mm.)	.9881	1.4916	47.04	46.03	.2198	12.23	8.91	8.97
n-Butyl	100–102 (4 mm.)	.9484	1.4838	51.66	51.42	.1039	5.4	8.18	8.14
Allyl	110–111 (7 mm.)	.9873	1.4982	46.57	46.00	.1990	11.6	9.04	9.11

Preparation of the N-Alkyl-β-piperidyl *p*-Nitrobenzoate Hydrochlorides.—To 0.1 mole of N-alkyl-β-piperidyl carbinol dissolved in 100 cc. of benzene in a 500-cc. two-necked flask, fitted with a reflux condenser and a mechanical stirrer, was added 0.15 mole of *p*-nitrobenzoyl chloride. The mixture was heated on the steam cone and stirred for three hours, during which time a gummy mass separated. About 200 cc. of water containing a little hydrochloric acid was added and the benzene layer was separated. The water layer was extracted with two 100-cc. portions of ether and then made alkaline by the addition of cold sodium hydroxide solution. The oily *p*-nitrobenzoic acid ester which separated was collected in ether and the ether solution acidified with alcoholic hydrogen chloride. The nitro ester hydrochlorides usually separated as gummy solids

and were purified by crystallization from absolute alcohol. The yields were about 50% of the theoretical amount. The properties of the compounds are indicated in Table III.

TABLE III

PROPERTIES AND ANALYSES OF THE N-ALKYL-β-PIPERIDYL CARBINOL *p*-NITROBENZOATE HYDROCHLORIDES

Alkyl group	M. p., °C. (corr.)	Subs., g.	Cc. of 0.09744 *N* $AgNO_3$	Empirical formula	Cl, calcd.	Cl, found
Methyl	187–190	0.1598	5.13	$C_{14}H_{19}N_2O_4Cl$	11.27	11.09
Ethyl	194–195	.1537	4.83	$C_{15}H_{21}N_2O_4Cl$	10.79	10.86
*Iso*propyl	196–200	.1566	4.62	$C_{16}H_{23}N_2O_4Cl$	10.34	10.19
n-Butyl	197–198	.1537	4.36	$C_{17}H_{25}N_2O_4Cl$	9.94	9.80
Allyl	186–187.5	.1491	4.5	$C_{16}H_{21}N_2O_4Cl$	10.41	10.43

Preparation of the N-Alkyl-β-piperidyl Carbinol *p*-Aminobenzoate Hydrochlorides.—To a solution of 0.05 moles of the nitro ester hydrochloride in 200 cc. of absolute alcohol was added 0.25 g. of platinum oxide catalyst[3] and then this mixture was treated with hydrogen at about two atmospheres' pressure. The pressure gage indicated that the theoretical amount of hydrogen was absorbed in ten minutes but the reducing conditions were maintained for about forty-five minutes. The mixture was filtered to remove the catalyst and the alcoholic solution was concentrated under reduced pressure to about 75 cc. About 300 cc. of dry ether was added and the solution was cooled in an ice-salt bath. A gummy solid separated which was obtained crystalline by recrystallization from alcohol-ether mixtures. These crystals were usually slightly yellow. The color could not be removed by treating the alcoholic solution with decolorizing carbon (Norit) but by treating a second time with hydrogen in the presence of the platinum catalyst, white or only slightly yellowish products were obtained. In every case a considerable amount of gummy material which could not be crystallized was obtained. The average yield of crystalline material was about 45% of the theoretical amount. The physical properties and analyses of the products are listed in Table IV.

TABLE IV

PROPERTIES AND ANALYSES OF THE N-ALKYL-β-PIPERIDYL CARBINOL *p*-AMINOBENZOATE HYDROCHLORIDES

Alkyl group	M. p., °C. (corr.)	Subs., g.	Cc. of 0.0999 *N* $AgNO_3$	Empirical formula	Cl, calcd.	Cl, found
Methyl	174–177	0.1807	6.31	$C_{14}H_{21}O_2N_2Cl$	12.46	12.38
Ethyl	188–190	.1804	6.07	$C_{15}H_{23}O_2N_2Cl$	11.87	11.93
*Iso*propyl	235.5–237.5	.1890	6.00	$C_{16}H_{25}O_2N_2Cl$	11.33	11.24
n-Butyl	205–207	.1911	5.83	$C_{17}H_{27}O_2N_2Cl$	10.85	10.82

Summary

1. Methods for the preparation of β-piperidyl carbinol and its N-alkyl derivatives have been devised.

2. The *p*-aminobenzoate hydrochlorides of these alkyl carbinols have been prepared.

3. Pharmacological tests show that these aminobenzoyl ester hydrochlorides have relatively low toxicity and strong local anesthetic action.

URBANA, ILLINOIS