small amount of hot ethanol. When cooled a yellow crystalline mass appeared. Repeated recrystallizations gave 1 g. of white needles melting at 76–77°. A mixed melting point with 2-benzyl-5-methoxycoumaran-3-one prepared by reduction of the benzal compound showed no depression.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.56; H, 5.53. Found: C, 75.50; H, 5.46.

2-Benzyl-6-methoxycoumaran-3-one.—The Friedel–Crafts reaction using resorcinol dimethyl ether and α-bromo-β-phenylpropionyl chloride proceeded exactly as that described for the hydroquinone dimethyl ether.

After the treatment with sodium acetate the mixture was poured into water and allowed to stand for four days. At the end of this time the oil had partially crystallized. The solid was removed by filtration and dissolved in hot ethanol. By very slow cooling the oil which came out first was allowed to settle and the solution decanted. Final cooling of the decanted solution in an ice–salt mixture caused a light yellow precipitate to form. This was recrystallized from ethanol again to gleaming white plates which melted at 92–93.5°. The yield of pure product was 1.1 g.

A mixed melting point with 2-benzyl-6-methoxycoumaran-3-one prepared by reduction of the corresponding benzal compound showed no depression.

Anal. Calcd. for $C_{16}H_{14}O_3$: C, 75.56; H, 5.53. Found: C, 75.39; H, 5.40.

Summary

The catalytic reduction of 2-benzal-5(and 6)-methoxycoumaran-3-one to 2-benzyl-5(and 6)-methoxycoumaran-3-one furnishes a better method for the synthesis of 2-substituted coumaran-3-ones than the Friedel–Crafts reaction in which hydroquinone dimethyl ether or resorcinol dimethyl ether is treated with α-bromo-β-phenylpropionyl chloride and aluminum chloride followed by ring closure of the resulting ω-chloro-2-hydroxy-5(and 4)-methoxyacetophenones.

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[CONTRIBUTION FROM THE ABBOTT LABORATORIES]

N-Aralkylmorpholines[1]

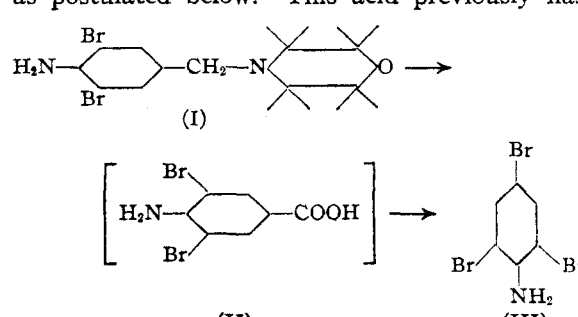
BY MARLIN T. LEFFLER AND E. H. VOLWILER

Introduction

It has been shown previously that the introduction of the morpholine ring into a series of known local anesthetics does not destroy nor greatly alter the anesthetic activity. Gardner and co-workers[2] and Leffler and Brill[3] have substituted the morpholine ring for the dialkylamino group of the procaine series and the first-mentioned authors later[4] have extended this work to the "Nupercaine" type. In all of these cases, however, the anesthesia found was not due fundamentally to the morpholine structure, since the simple dialkylamino analogs are, of course, also local anesthetics. On the other hand, in the work now being described, N-benzylmorpholines were found to be local anesthetics, while corresponding N-benzyl-diethylamines showed no anesthetic effect.

The N-aralkylmorpholines were prepared in good yields by condensing the desired aralkyl halide with either morpholine or 2,6-dimethylmorpholine. The aminoaralkylmorpholines were, in general, conveniently formed by an iron–water reduction of the intermediate nitro compounds.

An interesting cleavage reaction occurred when an attempt was made to brominate *p*-aminobenzylmorpholine. Bromine-laden air led into an aqueous solution of the base at room temperature gave a practically quantitative yield of 2,4,6-tribromoaniline. This, however, is not entirely unexpected, in view of the general weakness of the benzyl linkage and its ease of hydrolysis by acid reagents. Bromination first would be expected to give *p*-amino-*m*,*m*-dibromobenzylmorpholine (I) which by further bromination and subsequent hydrolysis could yield the intermediate (II), 4-amino-3,5-dibromobenzoic acid, as postulated below. This acid previously has



(1) Presented before the Medicinal Division of the American Chemical Society at Rochester, N. Y., September 10, 1937.

(2) Gardner and co-workers, THIS JOURNAL, **53**, 2763 (1931); *ibid.*, **55**, 2999 (1933).

(3) Leffler and Brill, *ibid.*, **55**, 365 (1933).

(4) Gardner and Hammel, *ibid.*, **58**, 1360 (1936).

been shown[5] to give 2,4,6-tribromoaniline (III) in the presence of bromine.

Although the aqueous bromination of *p*-aminobenzylmorpholine, described above, failed to yield the desired product, bromination in glacial acetic acid solution gave *p*-amino-*m*,*m*-dibromobenzylmorpholine in 55% yield.

This research is being extended into an investigation of the aralkylpiperazine analogs and their physiological properties.

Physiological Activity

We are indebted to Dr. Richard Kohn of the Pharmacologic Department, Abbott Laboratories, for investigating the anesthetic activity of these compounds. It was found that several members in the N-benzylmorpholine series possessed an anesthetic activity comparable to that of procaine with a considerably lower toxicity. In fact, benzylmorpholine, the simplest member of the series, was one-half as toxic[6] as procaine and, in 2% solution, approached the latter in activity.

The introduction of a halogen atom into the benzene ring was most effective in enhancing the activity without increasing the toxicity. In this connection *p*-bromobenzylmorpholine was one of the most interesting members studied, being only one-fourth as toxic[6] as and practically equivalent to procaine in activity.[7] This compound as the hydrochloride and tartrate gave *p*H values, in 2% solution, of 4.8 and 5.3, respectively; it was not sufficiently basic to form a borate. The hydrochloride in 2% solution, sterilized under nitrogen according to the accepted procedure, suffered no hydrolysis as evidenced by no loss in efficiency of the solution, no change in *p*H, and also by complete recovery of the free base by alkalinization. As the hydrochloride, *p*-bromobenzylmorpholine gave only slight or no necrosis, but did produce a brief but definite stinging sensation on injection. The corresponding *o*-bromo and *p*-chloro analogs were less efficient. The anesthetic efficiency was shown to be closely connected with the benzylmorpholine structure, since lengthening of the chain between the benzene and morpholine rings greatly lowered the activity. In fact, substituted γ-phenylpropylmorpholine exerted no anesthetic effect. The introduction of an amino group into the benzene ring, surprisingly enough, did not enhance the efficiency and in several cases increased the toxicity.

With the exception of the alkoxybenzylmorpholines, none of the compounds studied exerted topical anesthesia. As was predicted, the introduction of the butoxy group raised the toxicity to within the range of procaine; the topical effectiveness was much less than that of γ-dibutylaminopropyl - *p* - aminobenzoate - N - sulfate ("Butyn").

Experimental Part

3-Bromo-4-butoxytoluene.—A mixture of 187 g. (1 mole) of *o*-bromo-*p*-cresol,[8] 150 g. (1.1 moles) of *n*-butyl bromide, 138 g. (1 mole) of potassium carbonate in 350 cc. of acetone and 25 cc. of methanol was refluxed with stirring for twenty hours. At the end of this time the reaction mixture was cooled, filtered, and the filtrate concentrated *in vacuo*. The residue was then washed with 10% potassium hydroxide solution until free from the unreacted cresol. The insoluble layer, after taking up in ether and drying over anhydrous sodium sulfate, gave 180 g. (74%) of 3-bromo-4-butoxytoluene boiling at 107–109° (4 mm.); $n^{25}D$ 1.5295.

Anal. Calcd. for $C_{11}H_{15}BrO$: Br, 32.87. Found: Br, 32.97.

Preparation of Aralkyl Halides

***o*- and *p*-Nitrobenzyl Chloride.**—These two halides were prepared by the method of Alway.[9]

***p*-Nitrophenethyl Bromide.**—The procedure of Slotta and Altner[10] was followed.

γ-*p*-Nitrophenylpropyl Bromide.—Nitration of γ-phenylpropyl bromide by a procedure identical to that described for the chloride by v. Braun and Deutsch[11] gave an 82% yield of γ-*p*-nitrophenylpropyl bromide boiling at 152–156° (2 mm.); $n^{23}D$ 1.5760.

Anal. Calcd. for $C_9H_{10}BrNO_2$: N, 5.74. Found: N, 5.72.

α-Chloromethylnaphthalene.—The method of Anderson and Short[12] gave a 25% yield of α-chloromethylnaphthalene with boiling point at 120–125° (3 mm.).

4-Butoxy-3-nitrobenzyl Chloride.—The method used was a modification of that employed for the methoxy analog.[13] A solution of 78.4 g. (1 mole) of *o*-butoxynitrobenzene,[14] 9 g. (0.75 mole) of paraformaldehyde, and 1 g. of anhydrous zinc chloride in 300 cc. of petroleum ether (b. p. 85–100°) was treated for five hours under stirring with a vigorous stream of dry hydrogen chloride. The temperature of the reaction mixture was then held at 85° for ten hours while the hydrogen chloride treatment was

(5) Beilstein and Geitner, *Ann.*, **139**, 1 (1866); Sudborough and Lakhumalani, *J. Chem. Soc.*, **111**, 41 (1917).

(6) Toxicity: intraperitoneally in rats; intravenously in rabbits.

(7) Duration: intradermal wheal, guinea pigs.

(8) Zincke and Wiederhold, *Ann.*, **320**, 199 (1902).

(9) Alway, THIS JOURNAL, **24**, 1060 (1902).

(10) Slotta and Altner, *Ber.*, **64**, 1510 (1931).

(11) Von Braun and Deutsch, *ibid.*, **45**, 2504 (1912).

(12) Anderson and Short, *J. Chem. Soc.*, 485 (1933).

(13) Schorygin and Shoblinskaja, *Chem. J. Ser. A. J. allg. Chem.*, [68], **6**, 1578 (1936); ref. *Chem. Zentr.*, **108, I**, 1678 (1937).

(14) Li and Adams, THIS JOURNAL, **57**, 1565 (1935).

TABLE I

N-NITROARALKYLMORPHOLINES

No.	Morpholine	Yield, %	B. p. °C.	Mm.	Formula	N Analyses, % Calcd.	Found
1	*o*-Nitrobenzyl-	88	160–163	4	$C_{11}H_{14}N_2O_3$	12.61	12.44
2	*p*-Nitrobenzyl-[a]	90	M. p., 79–80		$C_{11}H_{14}N_2O_3$	12.61	12.68
3	*p*-Nitrobenzyl-2,6-dimethyl-[a]	77	163–165 M. p., 66–67	3	$C_{13}H_{18}N_2O_3$	11.19	10.94
4	*p*-Butoxy-*m*-nitrobenzyl-[b]	86	162–164	3	$C_{15}H_{22}N_2O_4$	9.50	9.58
5	*p*-Nitrophenethyl-	56	260	740	$C_{12}H_{16}N_2O_3$	11.85	11.58
6	γ-*p*-Nitrophenylpropyl-[c]	80	175–8	2	$C_{13}H_{18}N_2O_3$	11.19	11.00

[a] Recrystallized from alcohol. [b] $n^{24}D$ 1.5355. [c] $n^{24}D$ 1.5461.

continued. As soon as the reaction was complete, the cooled mixture was washed rapidly with cold water and the petroleum ether layer dried over anhydrous sodium sulfate. After the solvent had been removed *in vacuo*, the 4-butoxy-3-nitrobenzyl chloride distilled at 162–165° (4 mm.); $n^{24}D$ 1.5432; yield 35 g. (36%).

Anal. Calcd. for $C_{11}H_{14}ClNO_3$: N, 5.74. Found: N, 5.83.

***o*-Butoxybenzyl Chloride.**—Anhydrous hydrogen chloride was passed for four hours into 18.0 g. of *o*-butoxybenzyl alcohol[15] maintained at 5–10°. Isolated from the reaction mixture in the usual manner, the *o*-butoxybenzyl chloride distilled at 102–103° (4 mm.); $n^{24}D$ 1.5188; yield 15.0 g. (65%).

Anal. Calcd. for $C_{11}H_{15}ClO$: Cl, 17.86. Found: Cl, 17.91.

3-Bromo-4-butoxybenzyl Chloride.—Dry chlorine gas was passed into 77.7 g. (0.3 mole) of 3-bromo-4-butoxytoluene maintained at 170°, until the increase in weight amounted to 10.7 g. The reaction carried out in the light of an incandescent lamp required about five hours for completion. When the correct amount of chlorine had been absorbed, the reaction mixture was cooled, diluted with 200 cc. of benzene, washed with cold water, and the benzene layer dried over anhydrous sodium sulfate. The residue, after vacuum removal of the solvent, gave 45 g. (51%) of 3-bromo-4-butoxybenzyl chloride boiling at 135–140° (3 mm.); $n^{23}D$ 1.5508.

Anal. Calcd. for $C_{11}H_{14}BrClO$: BrCl, 41.59. Found: BrCl, 41.93.

Preparation of N-Aralkylmorpholines

Condensation of Morpholines with Aralkyl Halides. General Procedure.—In 150 cc. of dry benzene was dissolved 1 mole of the desired aralkyl halide and 2.1 moles of morpholine (or 2,6-dimethylmorpholine). The reaction mixture was then heated in an oil-bath at 85° for approximately six hours. At the end of this time, the amine salt[16] was separated from the reaction mixture by filtration and the filtrate washed twice with cold water. The benzene layer, after drying over anhydrous sodium sulfate and subsequently vacuum evaporating, gave the crude product which was purified by distillation or crystallization (Tables I and III).

(15) Hart and Hirschfelder, THIS JOURNAL, **43**, 1688 (1921).

(16) Morpholine hydrochloride or hydrobromide crystallized out as the reaction progressed; the corresponding salts of 2,6-dimethylmorpholine, however, did not crystallize.

Preparation of N-Aminoaralkylmorpholines

Iron–Water Reduction.—N-Nitroaralkylmorpholines (Table I) were reduced readily by iron turnings in practically neutral solution using the regular procedure. It was found, however, that in the case of liquid nitro derivatives, the use of 70% alcohol instead of water at the beginning of the reduction greatly aided the initiation of the reaction. The resulting N-aminoaralkylmorpholines, or their hydrochlorides, were recrystallized from the proper solvent (see footnotes, Table II).

N-*p*-Amino-*m*,*m*-dibromobenzylmorpholine.—A solution of 16.0 g. (0.1 mole) of bromine in 35 cc. of glacial acetic acid was added dropwise with stirring to a solution of 9.6 g. (0.05 mole) of N-*p*-aminobenzylmorpholine (No. 2, Table II) in 150 cc. of glacial acetic acid. The temperature of the reaction mixture was maintained at 15–20° during the addition of bromine. As soon as all of the bromine had been added, the solid material which had precipitated was separated by filtration, dissolved in water, the resulting solution filtered, and the cold filtrate made alkaline with dilute sodium hydroxide. The oil which separated soon solidified and on recrystallization from dilute alcohol gave 9.5 g. (54%) of light tan prisms of N-*p*-amino-*m*,*m*-dibromobenzylmorpholine (No. 9, Table II) melting at 62–63°.

Anal. Calcd. for $C_{11}H_{14}Br_2N_2O$: N, 8.00. Found: N, 7.86.

Action of Aqueous Bromine on N-*p*-Aminobenzylmorpholine.—Bromine-laden air was drawn through a solution of 1.0 g. of N-*p*-aminobenzylmorpholine in 100 cc. of water until the solution assumed a distinctly yellow-red tint. The solid material which precipitated was separated by filtration and on recrystallization from dilute alcohol gave 1.2 g. of needles melting at 119–120°. This material was acid insoluble; the analysis corresponded to that of tribromoaniline and a 50% mixture with an authentic specimen of 2,4,6-tribromoaniline melted at 119–120°.

Anal. Calcd. for $C_6H_4Br_3N$: N, 4.24. Found: N, 4.30.

N-*p*-Bromo-*m*-aminobenzylmorpholine.—To a solution of 10 g. of N-*p*-bromobenzylmorpholine (No. 3, Table III) in 25 cc. of concentrated sulfuric acid (sp. gr. 1.84), maintained at 40°, was added with stirring 4.35 g. (6.5 cc.) of fuming nitric acid (sp. gr. 1.49). The stirring was continued at this temperature for two hours and the reaction mixture then allowed to stand overnight. When poured into 250 g. of ice-water and made alkaline with sodium hydroxide solution, an oil separated which failed to crystal-

TABLE II

N-AMINOARALKYLMORPHOLINES

No.	Morpholine	Yield, %	M. p., °C.	M. p., °C. of monohydrochloride[a]	Formula (base or hydrochloride)	N analyses, % Calcd.	Found
1	*o*-Aminobenzyl-	61	(B. p.) 150–152 (4 mm.)	.....	$C_{11}H_{16}N_2O$	14.58	14.43
2	*p*-Aminobenzyl-[b]	76	100.5–101.5	188–190	$C_{11}H_{16}N_2O$	14.58	14.80
3	*p*-Aminobenzyl-2,6-dimethyl-[c]	71	(B. p.) 160–162 (2 mm.)	214[d]	$C_{13}H_{21}ClN_2O$	Cl 13.80	13.62
4	*m*-Amino-*p*-butoxybenzyl-	75	.....	199.5–200.5	$C_{15}H_{24}N_2O_2$	9.32	9.47
5	*p*-Aminophenethyl-[e]	77	80.5–81.5	.....	$C_{12}H_{18}N_2O$	13.59	13.53
6	γ-*p*-Aminophenylpropyl-[f]	82	(B. p.) 156–160 (2 mm.)	195–196	$C_{13}H_{21}ClN_2O$	Cl 13.83	13.84
7	*p*-(*n*)-Butylaminobenzyl-	51	.....	180–182	$C_{15}H_{25}ClN_2O$	9.84	9.96
8	*m*-Amino-*p*-bromobenzyl-[b]	75	102–103	.....	$C_{11}H_{15}BrN_2O$	10.33	10.52
9	*p*-Amino-*m*,*m*-dibromobenzyl-[b]	55	62–63	260	$C_{11}H_{14}Br_2N_2O$	8.00	7.86

[a] Recrystallized from a mixture of absolute alcohol and ethyl acetate. [b] Recrystallized from dilute alcohol. [c] $n^{21}D$ 1.5522. [d] Melting point on the Maquenne block. [e] Recrystallized from benzene. [f] $n^{24}D$ 1.5578.

TABLE III

OTHER N-ARYLKYLMORPHOLINES

No.	Morpholine	Yield, %	B. p., °C.	M. p., °C. HCl[a]	Formula (base or hydrochloride)	N analyses, % Calcd.	Found
1	Benzyl-2,6-dimethyl-	65	102–104 (3 mm.)	184–185	$C_{13}H_{20}ClNO$	Cl 14.68	14.68
2	*o*-Bromobenzyl-	66	.....	216–217	$C_{11}H_{15}BrClNO$	4.79	4.73
3	*p*-Bromobenzyl-	70	138–142 (4 mm.) M. p. 83–84[b]	280[c]	$C_{11}H_{14}BrNO$	5.47	5.50
4	*p*-Chlorobenzyl-	81	M. p., 68–69	258[c]	$C_{11}H_{15}Cl_2NO$	5.65	5.46
5	*p*-Chlorobenzyl-2,6-dimethyl-	62	.....	189–190	$C_{13}H_{19}Cl_2NO$	5.07	4.96
6	*p*-Butoxy-*m*-bromobenzyl-	58	185–188 (3 mm.)	183.5–184.5	$C_{15}H_{23}BrClNO_2$	3.84	3.76
7	*o*-Butoxybenzyl-	70	.....	159.5–160.5	$C_{15}H_{24}ClNO_2$	4.90	5.06
8	α-Phenylethyl-	25	.....	211–212	$C_{12}H_{18}ClNO$	6.16	5.98
9	β-Phenylethyl-	65	107–108 (3 mm.)	238[c]	$C_{12}H_{18}ClNO$	6.16	6.13
10	γ-Phenylpropyl-	64	113–115 (2 mm.)	138–139	$C_{13}H_{20}ClNO$	Cl 14.68	14.69
11	Cinnamyl-	86	132–134 (3 mm.)	216[c]	$C_{13}H_{17}NO$	6.90	6.96
12	Cinnamyl-2,6-dimethyl-	81	140–142 (3 mm.)	.....	$C_{15}H_{21}NO$	6.06	6.08
13	α-Naphthylmethyl-	52	.....	234–235	$C_{15}H_{18}ClNO$	5.32	5.46

[a] Recrystallized from mixture of absolute alcohol and ethyl acetate. [b] Recrystallized from alcohol. [c] Melting point on Maquenne block.

lize and was extracted with benzene. The benzene layer, after drying over anhydrous sodium sulfate, was concentrated *in vacuo*. The residue did not crystallize, but on reduction described above, gave 8 g. (75% based on the bromobenzylmorpholine used) of N-*m*-amino-*p*-bromobenzylmorpholine[17] (No. 8, Table II).

N-*p*-(*n*)-Butylaminobenzylmorphloine.—A mixture of 19.2 g. (0.1 mole) of N-*p*-aminobenzylmorpholine (No. 2, Table II) and 13.0 g. (0.095 mole) of *n*-butyl bromide was warmed at 50° for two hours and finally at 90° for three hours. At the end of this time the base was liberated from the reaction mixture with strong alkali and extracted with ether. The ether layer after drying over solid potassium hydroxide was concentrated and the residue redissolved in a 1:1 mixture of ethyl acetate and pentane. Titration of this solution with absolute alcoholic hydrogen chloride until just acid to litmus gave the monohydrochloride of N-*p*-*n*-butylaminobenzylmorpholine (No. 7, Table II) which was recrystallized from the solvent listed in Table II, footnote (*a*).

(17) It is assumed that the amino group is in the meta position due to the strong ortho-para directing influence of the bromine atom.

All analyses reported in this paper were run according to standard micro methods and were carried out by Mr. E. F. Shelberg of the Microanalytical Department, Abbott Laboratories.

Summary

Various N-aralkylmorpholines have been synthesized. The N-benzylmorpholines are local anesthetics. N-*p*-Bromobenzylmorpholine is one-fourth as toxic and has practically the same anesthetic effectiveness as procaine.

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