TABLE II

REDUCTION OF BENZILS BY TRIPHENYLMETHYLMAGNESIUM BROMIDE

Benzil	Benzil, g.	Yields of products: Benzoin G.	Benzoin %	Peroxide G.	Peroxide %
Benzil	5.2	4.2	80	11.5	88
Benzil	5.2	6.0[a]		10.5	80
4,4'-Dichlorobenzil	3.5	3.4	95	5.3	81
4,4'-Dichlorobenzil	3.5	4.0[b]		3.6	56
4,4'-Dimethylbenzil	3.0	2.3[c]		2.9	44

[a] Stilbene-diol dibenzoate.

[b] Dichloro-stilbene-diol dibenzoate [Gomberg and Van Natta, THIS JOURNAL, 51, 2238 (1929)] produced by treating the reaction mixture with 4 cc. of benzoyl chloride.

[c] Dimethyl-stilbene-diol dibenzoate. After recrystallization from alcohol it melted at 137–138° and was identical with the dibenzoate prepared from the benzil through the MgI reaction.

Summary

A number of aromatic ketones have been reduced to pinacols by means of the Grignard reagent, triphenylmethylmagnesium bromide. The reduction proceeds through the intermediate formation of radicals according to the following formulation: $RRC{=}O + (C_6H_5)_3CMgBr \longrightarrow RRC{-}OMgBr + (C_6H_5)_3C$. The ketyl radicals then associate to the pinacolate: $2RRC{-}OMgBr \rightleftarrows RRC(OMgBr)(OMgBr)CRR$.

Benzils are reduced by triphenylmethylmagnesium bromide to the bromomagnesium salt of stilbene-diols: $RCOCOR + 2(C_6H_5)_3CMgBr \longrightarrow RC(OMgBr){=}(OMgBr)CR + 2(C_6H_5)_3C$.

ANN ARBOR, MICHIGAN

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

SOME NEW LOCAL ANESTHETICS CONTAINING THE MORPHOLINE RING[1]

BY JOHN H. GARDNER[2] AND EDWARD O. HAENNI

RECEIVED MAY 11, 1931 PUBLISHED JULY 8, 1931

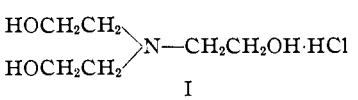
In view of the very pronounced local anesthetic activity of the aromatic esters of the dialkylamino alcohols, such as procaine and butyn, it has seemed of interest to study the preparation and physiological properties of an analogous series in which the dialkylamino group is replaced by a morpholine ring. It is not to be expected that the morpholine ring as such should have any particular effect but it is possible that the ether linkage in the ring might serve to increase the solubility of the morpholine derivatives in lipoids and so increase the anesthetic powers.

[1] Presented before the Organic Division of the American Chemical Society at Indianapolis, Indiana, April, 1931.

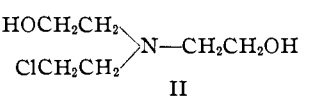
[2] This research has been assisted by a grant to the senior author from the Science Research Fund of Washington University.

The starting point in this investigation was the preparation of β-4-morpholine-ethanol from triethanolamine. This had been accomplished by Knorr,[3] who dehydrated triethanolamine by heating with sulfuric acid, but did not give a full description of the product. A repetition of Knorr's method led to unsatisfactory results. It was found much more satisfactory to start with triethanolamine hydrochloride. This was obtained from the commercial product by saturating an alcoholic solution with hydrogen chloride gas, the hydrochlorides of the mono- and diethanolamines being soluble in alcohol.[4]

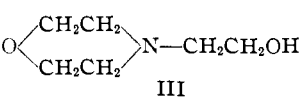
Boehmer and Hancock[5] dehydrated di-β-hydroxyethylaniline to 4-phenylmorpholine by heating under reduced pressure. Triethanolamine was not dehydrated under these conditions, but the hydrochloride (I) gave a product which, after heating with alcoholic potassium hydroxide, yielded the morpholine-ethanol. It seems probable that an intermediate chlorohydrin (II) is first formed and that this, on treatment with potassium hydroxide, is converted into morpholine-ethanol (III). This mechanism is supported by the fact that the crude dehydration product forms morpholine-ethanol only slowly on treatment with cold alkali. A similar mechanism was suggested by Knorr for the preparation of morpholine by heating diethanolamine with hydrochloric acid and subsequent treatment with alkali. He also isolated in an impure condition such an intermediate product obtained by heating di-β-hydroxyethylaniline with hydrochloric acid.[6]



I



II



III

From β-4-morpholine-ethanol, the hydrochlorides of the benzoate and *p*-aminobenzoate were prepared. Morpholine-ethanol, on treatment with benzoyl chloride and sodium hydroxide, yielded the benzoate from which β-4-morpholine-ethyl benzoate hydrochloride was obtained by precipitation with hydrogen chloride gas in benzene solution. β-4-Morpholine-ethyl *p*-nitrobenzoate hydrochloride was prepared by the interaction of morpholine-ethanol and *p*-nitrobenzoyl chloride in benzene solution. On reduction with hydrogen using Adams' platinum–platinum oxide catalyst, this yielded β-4-morpholine-ethyl *p*-aminobenzoate hydrochloride.

For the preparation of γ-4-morpholinepropanol, trimethylene chloro-

[3] Knorr, *Ann.*, **301**, 9 (1898).

[4] Wurtz, *ibid.*, **121**, 227 (1862); Knorr, *Ber.*, **30**, 919 (1897).

[5] Boehmer and Hancock, cited by Adkins and Simington, THIS JOURNAL, **47**, 1688 (1925).

[6] Knorr, *Ber.*, **22**, 2084 (1889).

hydrin was condensed with potassium phthalimide and the product hydrolyzed to γ-aminopropanol. The general procedure is that described by Putochin[7] with the substitution of trimethylene chlorohydrin for the trimethylene bromide which he used, avoiding complications due to the formation of the diphthalimido compound. γ-Hydroxypropyl phthalimide has been previously prepared by Gabriel.[8]

γ-Aminopropanol was converted into γ-4-morpholinepropanol by condensation with β,β′-dichloroethyl ether in the presence of anhydrous potassium carbonate. Some other morpholine derivatives have been prepared in a similar manner by Cretcher and his associates,[9] using an excess of the amine in place of the potassium carbonate, but the method has never been described for the preparation of morpholine alcohols. A similar procedure was used in a preliminary experiment for the preparation of morpholine-ethanol from ethanolamine.

γ-4-Morpholinepropanol was converted into the benzoate and *p*-aminobenzoate hydrochlorides in the same manner as the corresponding compounds were prepared from morpholine-ethanol.

Experimental

Triethanolamine Hydrochloride.—Four hundred grams of commercial triethanolamine[10] was dissolved in an equal volume of alcohol, the solution cooled in an ice-bath, and dry hydrogen chloride passed in until precipitation was complete. The precipitate was filtered off, washed with cold alcohol and recrystallized from 70% alcohol; yield, 338 g. of colorless rhombohedral crystals, m. p. 176.5–177°.[11] Knorr gives 177°.[4b]

β-4-Morpholine-ethanol.—Five hundred sixty-one grams of triethanolamine hydrochloride in a 3-liter flask provided with a reflux condenser was heated in an oil-bath at 200–205° under a pressure of 40 mm. for fourteen hours, keeping the water in the condenser jacket at 50–60° to facilitate the removal of water. The resulting brown mass was repeatedly extracted with hot alcohol until only a slight residue of tarry matter remained. The alcoholic extract was cooled and filtered from 65 g. of triethanolamine hydrochloride which crystallized out. The filtrate, about 1500 cc., was boiled under reflux with 175 g. of potassium hydroxide, the resulting solution being strongly alkaline. The morpholine-ethanol solution was filtered from the precipitated potassium chloride and the alcohol removed by distillation. The residue was distilled under 25 mm. pressure, yielding 158 g. (46%) of crude morpholine-ethanol, b. p. 116–123°. Upon redistillation, β-4-morpholine-ethanol was obtained as a colorless oil with a piperidine-like odor, b. p. 118–120° under 24 mm.; d_{25}^{25} 1.0712; d_4^{25} 1.0681; n_D^{25} 1.4770; M_D calcd.: 34.71. Found: 35.46. *Anal.* Subs., 0.3776, 0.4023: 31.14, 31.26 cc. of 0.1116 *N* HCl; 5.49, 3.95 cc. of 0.1235 *N* NaOH. Calcd. for $C_6H_{13}O_2N$: N, 10.68. Found: N, 10.37, 10.44. Neutral equivalent. Subs., 0.1990, 0.2733: 16.94, 19.69 cc. of 0.1070

[7] Putochin, *Ber.*, **59**, 628 (1926).

[8] Gabriel and Lauer, *ibid.*, **23**, 88 (1890); Gabriel, *ibid.*, **38**, 633 (1905).

[9] Cretcher and Pittenger, THIS JOURNAL, **47**, 164 (1925); Cretcher, Koch and Pittenger, *ibid.*, **47**, 1174 (1925).

[10] We are indebted to the Carbide and Carbon Chemicals Corporation for the triethanolamine used in this investigation.

[11] All melting points in this paper are corrected.

N HCl; 3.09, 0.18 cc. of 0.0956 *N* NaOH. Calcd. for $C_6H_{13}O_2N$: neut. equiv., 131.1. Found: 131.2, 130.8.

β-4-Morpholine-ethyl Benzoate Hydrochloride.—To a mixture of 8 g. of benzoyl chloride and 7.2 g. of morpholine-ethanol, there was added a 10% solution of sodium hydroxide until the mixture was alkaline. A vigorous reaction occurred and a heavy brown oil separated. The mixture was warmed until the odor of benzoyl chloride was no longer noticeable. The oil was dissolved in benzene and the solution dried over anhydrous sodium sulfate. The benzene solution was saturated with dry hydrogen chloride with the formation of a voluminous white precipitate which was filtered off, washed several times with benzene and dried in the air; yield, 10.7 g. (72%); m. p. 204.6–205.8°.

Anal. Subs., 0.5930, 0.5406: 24.58, 24.81 cc. of 0.1070 *N* HCl; 4.77, 7.31 cc. of 0.0956 *N* NaOH. Subs., 0.5253, 0.5994: 24.67, 25.09 cc. of 0.1026 *N* $AgNO_3$; 5.00, 3.09 cc. of 0.1159 *N* KSCN. Calcd. for $C_{13}H_{18}O_3NCl$: N, 5.15; Cl, 13.05. Found: N, 5.13, 5.06; Cl, 13.17, 13.11. Neutral equivalent. Subs., 0.6792, 0.6526: 26.38, 25.26 cc. of 0.0956 *N* NaOH. Calcd. for $C_{13}H_{18}O_3NCl$: neut. equiv., 271.6. Found: 269.3, 270.2.

β-4-Morpholine-ethyl *p*-Nitrobenzoate Hydrochloride.—To a solution of 32 g. of *p*-nitrobenzoyl chloride in 250 cc. of benzene there was slowly added a solution of 22 g. of morpholine-ethanol in 50 cc. of the same solvent. The mixture was warmed on the steam-bath for an hour, forming a yellow pasty mass. The solid product was filtered off and washed with benzene. After recrystallization from alcohol, the yield was 26 g. (49%) of short yellow needles, m. p. 214.6–215.4°.

Anal. Subs., 0.5560, 0.6024: 39.91, 39.84 cc. of 0.1070 *N* HCl; 8.68, 5.19 cc. of 0.0956 *N* NaOH. Subs., 0.6010, 0.6195: 30.30, 30.39 cc. of 0.1026 *N* $AgNO_3$; 10.42, 9.94 cc. of 0.1159 *N* KSCN. Calcd. for $C_{13}H_{17}O_5N_2Cl$: N, 8.85; Cl, 11.20. Found: N, 8.66, 8.75; Cl, 11.21, 11.25. Neutral equivalent. Subs., 0.5122, 0.5256: 16.87, 17.30 cc. of 0.0956 *N* NaOH. Calcd. for $C_{13}H_{17}O_5N_2Cl$: neut. equiv., 316.6. Found: 317.5, 317.7.

β-4-Morpholine-ethyl *p*-Aminobenzoate Hydrochloride.—A solution of 5 g. of the nitrobenzoic ester hydrochloride in 200 cc. of boiling alcohol was shaken for twenty minutes with hydrogen under two to three atmospheres' pressure in the presence of 0.20 g. of Adams' platinum–platinum oxide catalyst.[12] The theoretical amount of hydrogen was absorbed in about seven minutes. The solution was filtered from the catalyst and evaporated under reduced pressure to 40 cc. Upon cooling light yellow crystals deposited. A further quantity was obtained on concentrating the solution to 10 cc. and cooling; yield, 3.3 g. (73%), m. p. 225.8–226.2°.

Anal. Subs., 0.4016, 0.3724: 31.12, 31.19 cc. of 0.1116 *N* HCl; 6.17, 7.85 cc. of 0.1235 *N* NaOH. Subs., 0.4604, 0.4885: 30.28, 30.31 cc. of 0.0986 *N* $AgNO_3$; 14.43, 13.44 cc. of 0.0977 *N* NH_4SCN. Calcd. for $C_{13}H_{19}O_3N_2Cl$: N, 9.77; Cl, 12.37. Found: N, 9.45, 9.44; Cl 12.14, 12.17. Neutral equivalent. Subs., 0.4604, 0.4885: 12.74, 13.49 cc. of 0.1235 *N* NaOH. Calcd. for $C_{13}H_{19}O_3N_2Cl$: neut. equiv., 286.6. Found: 292.6, 293.2.

γ-Aminopropanol.—A mixture of 50 g. of trimethylene chlorohydrin and 88 g. of potassium phthalimide in a three-necked 500-cc. flask provided with a reflux condenser and an efficient mechanical stirrer was heated, with stirring, in an oil-bath to 155°. At this temperature a vigorous reaction took place and the bath was removed until the reaction subsided. The bath was again placed under the flask and the mixture was heated

[12] Adams, Voorhees and Shriner, "Organic Syntheses," John Wiley and Sons, Inc., New York, **1928,** Vol. VIII, p. 92.

to 180–190° for two and one-half hours. The resulting pasty mass was extracted several times with hot water. The extract was filtered and cooled. The heavy brown oil which precipitated was separated. After standing for two days it solidified to a yellowish sticky mass. A portion dried on a porous plate softened at 68° and melted at 74°. Gabriel[8b] gives m. p. 75° for γ-hydroxypropyl phthalimide.

The crude product was boiled for a half hour under reflux with a solution of 100 g. of potassium hydroxide in 450 cc. of water. The resulting solution was distilled using a short Hempel tube until 200 cc. of distillate had been collected. This fraction was practically free of γ-aminopropanol and was discarded. The Hempel tube was then removed and the remaining liquid distilled without a column. In order to drive over the last of the aminopropanol, two portions of 50 cc. of water were added to the residue and distilled. The combined distillates were freed from water by redistillation using the Hempel tube and the residue was finally purified by distillation from a Claisen flask; yield 15 g. (42%), b. p. 185–190°. Putochin gives 185–186°.[7]

γ-4-Morpholinepropanol.—A mixture of 22.5 g. of γ-aminopropanol, 45 g. of β,β′-dichlorodiethyl ether and 45 g. of powdered anhydrous potassium carbonate in a two-necked 200-cc. flask provided with a reflux condenser and an efficient mechanical stirrer was heated with vigorous stirring in an oil-bath. When the temperature reached 120° a vigorous reaction set in with a rapid evolution of carbon dioxide. The oil-bath was removed until the reaction moderated. After about half an hour, the bath was replaced and the mixture was heated for two and one-half hours at 170°. After cooling, the mixture was extracted four times with 50-cc. portions of hot benzene, the combined extracts dehydrated over anhydrous potassium carbonate and the benzene distilled off. The residue was distilled under 24-mm. pressure, the γ-4-morpholinepropanol being collected at 134–136°. The yield was slightly increased by redistilling the lower and higher fractions; yield, 29 g. (67%); d_{25}^{25} 1.0452; d_4^{25} 1.0422; n_D^{25} 1.4752; M_D calcd.: 39.33. Found: 39.21.

Anal. Subs., 0.3618, 0.3922: 30.18, 29.81 cc. of 0.1116 *N* HCl; 8.18, 5.52 cc. of 0.1235 *N* NaOH. Calcd. for $C_7H_{15}O_2N$: N, 9.65. Found: 9.55, 9.45. Neutral equivalent. Subs., 0.5309, 0.5178: 32.21, 31.48 cc. of 0.1116 *N* HCl. Calcd. for $C_7H_{15}O_2N$: neut. equiv., 145.1. Found: 147.7, 147.4.

γ-4-Morpholinepropyl Benzoate Hydrochloride.—The procedure was the same as that used in the preparation of β-4-morpholine-ethyl benzoate hydrochloride: yield from 8 g. of γ-4-morpholinepropanol and 9 g. of benzoyl chloride, 8 g. (51%), m. p. 190.1–190.5°.

Anal. Subs., 0.5220, 0.4937: 29.98, 30.10 cc. of 0.1116 *N* HCl; 12.53, 13.39 cc. of 0.1235 *N* NaOH. Subs., 0.4229, 0.5186: 30.06, 30.48 cc. of 0.0986 *N* $AgNO_3$; 12.63, 12.37 cc. of 0.0977 *N* NH_4SCN. Calcd. for $C_{14}H_{20}O_3NCl$: N, 4.90; Cl, 12.42. Found: N, 4.83, 4.84; Cl, 12.29, 12.28. Neutral equivalent. Subs., 0.5207, 0.5314: 14.80, 15.10 cc. of 0.1235 *N* NaOH. Calcd. for $C_{14}H_{20}O_3NCl$: neut. equiv., 285.6. Found: 284.9, 285.0.

γ-4-Morpholinepropyl *p*-Nitrobenzoate Hydrochloride.—The procedure was the same as that used in the preparation of the lower homolog except that a mechanical stirrer was used and the time of heating was increased to two hours; yield from 10 g. of γ-4-morpholinepropanol and 17 g. of *p*-nitrobenzoyl chloride, 20 g. (89%), after recrystallization from alcohol, m. p. 232.8–233.2°.

Anal. Subs., 0.6190, 0.5307: 38.01, 30.15 cc. of 0.1116 *N* HCl; 5.45, 2.13 cc. of 0.1235 *N* NaOH. Subs., 0.5046, 0.5006: 30.11, 30.03 cc. of 0.0986 *N* $AgNO_3$; 14.98, 15.03 cc. of 0.0977 *N* NH_4SCN. Calcd. for $C_{14}H_{19}O_5N_2Cl$: N, 8.47; Cl, 10.72. Found: N, 8.08, 8.18; Cl, 10.58, 10.58. Neutral equivalent. Subs., 0.5006, 0.5355: 12.25,

13.08 cc. of 0.1235 *N* NaOH. Calcd. for $C_{14}H_{19}O_4N_2Cl$: neut. equiv., 330.6. Found: 330.9, 331.2.

γ-4-Morpholinepropyl *p*-Aminobenzoate Hydrochloride.—The reduction was carried out in the same manner as was described for the lower homolog. From 7.5 g. of the *p*-nitrobenzoate hydrochloride there was obtained 4.8 g. (70%) of γ-4-morpholinepropyl *p*-aminobenzoate hydrochloride, m. p. 193.3–193.7°.

Anal. Subs., 0.3303, 0.3342: 29.92, 30.43 cc. of 0.1116 *N* HCl; 10.04, 9.88 cc. of 0.1235 *N* NaOH. Subs., 0.3727, 0.5436: 25.21, 30.30 cc. of 0.0986 *N* $AgNO_3$; 12.91, 12.38 cc. of 0.0977 *N* NH_4SCN. Calcd. for $C_{14}H_{21}O_3N_2Cl$: N, 9.31; Cl, 11.79. Found: N, 8.90, 9.12; Cl, 11.66, 11.60. Neutral equivalent. Subs., 0.4977, 0.5436: 13.05, 14.25 cc. of 0.1235 *N* NaOH. Calcd. for $C_{14}H_{21}O_3N_2Cl$: neut. equiv., 300.6. Found: 308.8, 308.9.

Pharmacological Report.—Some preliminary pharmacological tests on these compounds were made by Dr. H. S. Gasser of the Washington University School of Medicine. While the data available will not justify any quantitative summary, some qualitative conclusions can be drawn. Studying the effect in nerve block, all compounds showed at most slight action when made up to one per cent. in Ringer's solution. When adjusted to P_H 7.4, however, all were effective. In each case it was found that the *p*-aminobenzoate was more effective than the corresponding benzoate, and each of the propanol derivatives more effective than the corresponding ethanol derivative. γ-4-Morpholinepropyl *p*-aminobenzoate hydrochloride was more effective than cocaine.

On the rabbit's cornea, none of the compounds was effective when applied in one per cent. solution, but when adjusted to P_H 8, the propanol derivatives produced almost immediate anesthesia. In 0.2% solution at P_H 8, γ-4-morpholinepropyl *p*-aminobenzoate hydrochloride produced anesthesia in almost as short a time as cocaine, but in 0.05% solution, P_H 8, while cocaine produced anesthesia in two minutes, the new compound was without effect.

The toxicity of only two of the new compounds has been tested. β-4-Morpholine-ethyl benzoate hydrochloride gave a minimum lethal dose in rabbits of approximately 120 mg. per kg. body weight, and γ-4-morpholinepropyl *p*-aminobenzoate hydrochloride, 60 mg., as compared to 15 mg. for cocaine.

Relative Acidities.—Since it is well known that the effectiveness of a local anesthetic varies with the hydrogen-ion concentration of the solution in which it is applied,[13] determinations were made of the hydrogen-ion concentrations of 0.5% solutions of each of these compounds. Since precipitates were formed on adding alkali to solutions of the *p*-aminobenzoate hydrochlorides, the P_H values at precipitation were determined in these cases. For comparison, similar determinations were made on solutions of procaine and diethylaminoethyl benzoate hydrochloride.

[13] Trevan and Boock, *Brit. J. Exp. Path.*, **8**, 307 (1927).

The latter compound was prepared for us by Mr. L. A. Burrows of this Laboratory. The results are shown in Table I.

TABLE I

RELATIVE ACIDITIES

Morpholine-( )-hydrochloride	*P*H	0.5% solution *P*H at precipitation
Ethyl benzoate	4.0	8.0 no precipitation
Ethyl *p*-aminobenzoate	4.2	6.7
Propyl benzoate	4.3	8.0 no precipitation
Propyl *p*-aminobenzoate	4.4	6.9
Procaine	5.2	8.0 no precipitation
Diethylaminoethyl benzoate hydrochloride	4.8	7.9

Summary

1. A series of local anesthetics of the alkamine ester type in which the dialkylamino group has been replaced by a morpholine ring has been prepared and described.

2. Some preliminary pharmacological tests on these compounds have been made.

3. These compounds have been found to possess considerable local anesthetic activity and low toxicity.

This investigation is to be continued.

ST. LOUIS, MISSOURI

[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ORGANIC CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY, NO. 72]

CONDENSATIONS BY SODIUM INSTEAD OF BY THE GRIGNARD REACTION. II.[1] REACTION WITH BENZONITRILE. PREPARATION OF DIPHENYLKETAZINE

BY AVERY A. MORTON AND JOSEPH R. STEVENS

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When benzonitrile is added to a mixture of chlorobenzene and sodium in ether the solution becomes intensely red. We ascribe the occurrence of this color to the presence of sodium diphenyl methylene imine, which is formed according to equation (1) below. This appears reasonable since the reactions of the solution with water, oxygen and iodine lead to the formation of benzophenone, benzophenone oxime and diphenylketazine, respectively (equation 2), in all of which the red color is destroyed.

$$C_6H_5CN + C_6H_5X + 2Na \longrightarrow (C_6H_5)_2C{=}NNa + NaX \quad (1)$$

$$2(C_6H_5)_2C{=}NNa + \begin{cases} 4H_2O \longrightarrow 2(C_6H_5)_2C{=}O + 2NH_3 + 2NaOH \\ O_2 \longrightarrow 2(C_6H_5)_2C{=}NONa \\ I_2 \longrightarrow [(C_6H_5)_2C{=}N]_2 + 2NaI \end{cases} \quad (2)$$

The action of iodine on the corresponding magnesium compound, diphenyl methylene imino magnesium bromide, obtained by the addition

[1] First paper of this series, THIS JOURNAL, 53, 2244 (1931).