[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

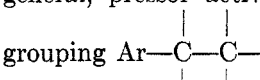
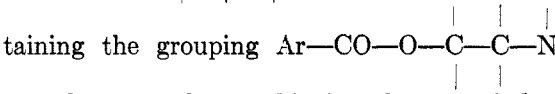
ANALOGS OF EPHEDRINE AND ADRENALINE CONTAINING THE MORPHOLINE NUCLEUS AND SOME OF THEIR ESTERS

NATHAN RUBIN AND ALLAN R. DAY

Received August 5, 1939

INTRODUCTION

Since the advent of cocaine as a local anesthetic, a large amount of literature has appeared on the synthesis of related compounds. The purpose of most of this work was to obtain active local anesthetics which would be less toxic than cocaine. These aims have been accomplished to some extent and there are now available a large number of compounds, mostly benzoates or *p*-aminobenzoates of N-substituted amino alcohols, which compare favorably with cocaine. In general, however, they lack the vasoconstricting power shown by cocaine and consequently must be used in conjunction with adrenaline. The latter, by decreasing the rate at which the anesthetic is carried away from the point of injection, permits the use of lower concentrations and also acts as a hemostatic agent.

Attempts have been made by several workers to combine structures essential for vasoconstriction and structures essential for anesthetic activity with the hope that the physiological effects might be cumulative. In general, pressor activity has been found in compounds possessing the grouping  and local anesthetic activity in compounds containing the grouping  . Most of the compounds prepared up to this time that contain both of the required groupings have not been entirely satisfactory. This work has been reviewed in two excellent papers by Hartung (1) and by Alles and Knoefel (2).

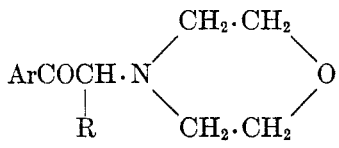
More recently, Coles and Loth (3) prepared some aromatic esters of N-β-hydroxyethyl- and N-γ-hydroxypropyl- *ac*-tetrahydro-β-naphthylamine. Although *ac*-tetrahydro-β-naphthylamine has been shown to have definite pressor action, the new derivatives were lacking in this property.

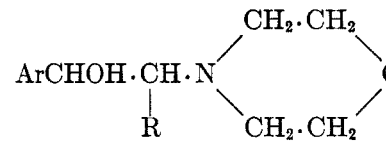
Osborne (4) reported that the synthesis of α-(3,4-dihydroxyphenyl)-β-(*p*-aminobenzoyl-β-diethylaminoethanol)-α-ethanone hydrochloride (epi-

caine) produced a drug which combines both local anesthetic and vasopressor action.

It does not seem possible to draw any definite conclusions from the above work, since the evidence for the various compounds does not agree very well. In some cases both anesthetic and pressor activity were reported and in other cases for closely related compounds pressor activity was lacking. The fact that none of these compounds appears to be in general use might indicate that the problem has by no means been solved.

Since certain morpholino compounds have been shown to possess local anesthetic action (5), it was planned to condense morpholine with structures known to exert vasopressor action, hoping to obtain compounds of medicinal value. Therefore morpholine was condensed with phenacyl bromide, α-bromopropiophenone, p-hydroxyphenacyl chloride, 3,4-dihydroxyphenacyl chloride and phenylethyl bromide, to yield amino ketones which in turn were catalytically reduced to the corresponding carbinols. Where R equals H, the side chain





R=H, CH_3 Ar=C_6H_5, p-HOC_6H_4, 3,4-$(HO)_2C_6H_3$

is structurally similar to adrenaline and where R equals CH_3, the side chain is similar to that found in ephedrine. The condensation product from phenylethyl bromide, of course contained no alcohol group in the side chain. Since aromatic esters of amino alcohols usually possess anesthetic activity, the benzoates of 1-phenyl-2-morpholinoethanol-1 and 1-phenyl-2-morpholinopropanol-1 were prepared as well as the cinnamate of the ethanol derivative.

Magee and Henze (6) have recently prepared a series of 5-alkylamino hydantoins. Certain hydantoins substituted in the five position have been shown to possess hypnotic activity. Since four new amino ketones were prepared in the course of the present work, it was thought that the corresponding hydantoins might be of some interest. Attempts to prepare these hydantoins by the Bucherer method (7) were successful only in the case of ω-morpholinoacetophenone from which 5-phenyl-5-morpholinomethyl hydantoin was obtained. These compounds are being tested and the pharmacological report will be made later.

EXPERIMENTAL

Analysis.—The semi-micro Kjeldahl method was used for the nitrogen determination. The distillate was absorbed in 15 cc. of 4% boric acid solution and titrated to a methyl-red endpoint according to the method of Meeker and Wagner (8).

Preparation of catalyst.—The catalyst employed in most cases was 10% palladium on charcoal prepared according to the method of Hartung (9). The 20% palladium on charcoal catalyst was prepared similarly. In all cases the catalyst was shaken under an atmosphere of hydrogen until no more gas was absorbed, immediately before the introduction of the sample.

Preparation of phenacyl bromide.—To 30 g. (0.25 mole) of acetophenone dissolved in 35–40 cc. of glacial acetic acid, 40 g. (0.25 mole) of bromine was added all at once. The flask was then immediately attached to a reflux condenser suitably connected for the absorption of hydrogen bromide, shaken in order to make the mixture homogeneous and then allowed to stand. After a few minutes a vigorous reaction took place with the evolution of hydrogen bromide. The straw-colored liquid was poured into a mixture of ice and water and was permitted to stand approximately one hour. At the end of this time the solid was removed by filtration and the oil well pressed out. The solid was then immediately recrystallized from 95% alcohol. Yields of 25–30 g. (50–60%) of pure product melting at 49.5–50° were obtained. This method is similar to that employed by Schmidt (10) for the preparation of α-bromopropiophenone. The method of Rather and Reid (11) gave lower yields of a considerably darker product.

Preparation of α-bromopropiophenone.—This was prepared similarly to the phenacyl bromide according to the method of Schmidt (10). The reaction mixture after being poured into ice water was carefully separated and washed with sodium bicarbonate solution, then with water and finally dried over anhydrous sodium sulfate. This product, obtained in 90% yields, was used without purification in further reactions.

Preparation of p-*hydroxyphenacyl chloride.*—This was prepared according to Tutin, Caton and Hann (14), using ligroin, however, instead of carbon disulfide as the solvent. The use of ligroin greatly reduced the amount of gum formed. Thirty grams (0.277 mole) of anisole and 36 g. (0.318 mole) of chloroacetyl chloride were dissolved in 300 cc. of ligroin. To the rapidly stirred solution, 75 g. (0.56 mole) of anhydrous aluminum chloride was added over a period of three-quarters of an hour, the mixture permitted to stand one hour and then 45 g. (0.34 mole) more of aluminum chloride was added in about half an hour. The resulting mixture was heated for four hours on the water-bath. At the end of this time the solvent was removed by distillation and the complex was decomposed by ice, followed by 30 cc. of concentrated hydrochloric acid. The mixture was taken up in ether and extracted first with 5% ammonium carbonate solution and then with 10% sodium carbonate solution. Acidification of the sodium carbonate extract after treatment with charcoal yielded 17.0 g. of a yellow product. It may be recrystallized from methyl alcohol; m.p. 147.5°.

Preparation of 3,4-dihydroxyphenacyl chloride.—This was prepared essentially according to Mannich and Hahn (15). A mixture of 50 g. (0.454 mole) each of catechol, monochloroacetic acid (0.53 mole) and phosphorus oxychloride (0.325 mole) was placed in a large flask fitted with a reflux condenser and a tube to lead away hydrogen chloride. It was heated on a hot plate until gas was evolved and then immediately removed from the plate. The reaction proceeded spontaneously. By avoiding too long heating at this point a better yield was obtained. At the completion of the reaction, 500 cc. of boiling water was added to dissolve the mass, and the solution allowed to stand in an ice chest for two days. The product was then filtered and dried. Yields averaged from 40–47 g. (52–61%). Recrystallization from hot water, employing charcoal for decolorization, yielded a light colored product melting at 173°.

Preparation of 4-(-β-phenylethyl)-morpholine hydrochloride.—To 18.5 g. (0.1 mole) of phenylethyl bromide dissolved in 30 cc. of alcohol was added 17.4 g. (0.2 mole) of morpholine dissolved in 25 cc. of alcohol. The mixture was refluxed for two hours on a water-bath, and then cooled, whereupon a crystalline precipitate separated. The reaction mixture was diluted with one and one-half times its volume of ether, allowed to stand a short time and was then filtered. The crystalline residue, consisting of morpholine hydrobromide, was washed well with ether and the washings added to the filtrate. Dry hydrogen chloride was passed into the cooled filtrate and yielded 17.75 g. (78%) of crystalline hydrochloride. Recrystallization from hot alcohol gave a colorless product melting at 246° (corr.). This compound has been reported (16) as melting at 238°.

Anal. Calc'd for $C_{12}H_{18}ClNO$: N, 6.15; Cl, 15.57.
Found: N, 5.98; Cl, 15.64.

Preparation of ω-morpholinoacetophenone hydrochloride.—To 9.95 g. (0.05 mole) of phenacyl bromide mixed with 30–40 cc. of alcohol and cooled to 0°, 8.7 g. (0.1 mole) of morpholine was slowly added with stirring, the addition being made at a rate such as to maintain the temperature below 15°. The mixture was then allowed to warm up to room temperature and allowed to stand for two hours, at the end of which time 150 cc. of ether was added. After standing overnight, it was filtered, and the crystalline morpholine hydrochloride was washed with ether, which was added to the filtrate. The amino ketone hydrochloride was precipitated by passage of dry hydrogen chloride over the ether. After collecting on a filter, washing with ether, and drying, 9.5–11 g. (79–91%) of crystalline material was obtained. Recrystallization from hot alcohol yielded a colorless product melting with decomposition at 222–223° (corr.). This compound has just been patented and reported as melting at 213–214° with decomposition (12).

Anal. Calc'd for $C_{12}H_{16}ClNO_2$: N, 5.80; Cl, 14.68.
Found: N, 5.76; Cl, 14.69.

This compound may also be prepared in 70–75% yield by refluxing one equivalent of amine with one equivalent of phenacyl bromide in alcohol solution in the presence of a slight excess of anhydrous potassium carbonate. The free base was obtained only as an impure oil.

Preparation of α-morpholinopropiophenone hydrochloride.—This was prepared similarly to the ω-morpholinoacetophenone hydrochloride in yields averaging 80–85%, employing either two equivalents of morpholine or one equivalent of morpholine with anhydrous potassium carbonate. Recrystallization from hot alcohol yielded a colorless product melting at 224° (corr.) with decomposition. This compound has just been patented and reported as melting with decomposition at 224° (12).

Anal. Calc'd for $C_{13}H_{18}ClNO_2$: N, 5.48; Cl, 13.98.
Found: N, 5.42; Cl, 13.78.

*Preparation of ω-morpholino-*p*-hydroxyacetophenone.*—To 6 g. (0.035 mole) of *p*-hydroxyphenacyl chloride in 10 cc. of alcohol, 6.12 g. (0.07 mole) of morpholine was slowly added, maintaining the temperature below 15°. Ten cubic centimeters of ether was added during the addition in order to keep the mixture from becoming solid. More ether was then added and the mixture allowed to stand overnight. It was then filtered and dried. The dried product was suspended in water to dissolve out the morpholine hydrochloride. The residue was filtered, washed well with water and dried, yielding 7.0 g. (90%) of product. Recrystallization from alcohol, using a small amount of charcoal, yielded colorless needles of melting point 201–201.7° (corr.).

Anal. Calc'd for $C_{12}H_{15}NO_3$: N, 6.33. Found: N, 6.13.

The hydrochloride was prepared by suspending the base in alcohol and passing hydrogen chloride into the solution. It melts with decomposition at 242–243° (corr.).

Anal. Calc'd for $C_{12}H_{16}ClNO_3$: N, 5.44; Cl, 13.76.
Found: N, 5.34; Cl, 13.79.

Preparation of ω-morpholino-3,4-dihydroxyacetophenone.—This was prepared similarly to the *p*-hydroxyacetophenone derivative from morpholine and 3,4-dihydroxyphenacyl chloride. The compound was obtained in 85–90% yields. The base was best recrystallized from 50% alcohol. The colorless product melted at 207° (corr.) with decomposition.

Anal. Calc'd for $C_{12}H_{15}NO_4$: N, 5.86. Found: N, 5.84.

The hydrochloride was obtained by passing hydrogen chloride over an alcoholic suspension of the base. The hydrochloride decomposes at 224–225° (corr.).

Anal. Calc'd for $C_{12}H_{16}ClNO_4$: N, 5.12; Cl, 12.95.
Found: N, 5.05; Cl, 12.97.

Preparation of 1-phenyl-2-morpholinoethanol-1 hydrochloride.—This compound was prepared by the catalytic reduction of the corresponding ketone in 95% alcohol solution, employing 10% palladium on charcoal as the catalyst (9). Ten grams of the amino ketone hydrochloride was added to 200 cc. of alcohol containing 4.5 g. of dry hydrogen chloride and 3.3 g. of catalyst. This was then shaken under an atmosphere of hydrogen in an apparatus similar to that of Schaefer (13) until the calculated volume of hydrogen had been absorbed. At the completion of the reduction the solution was filtered free of catalyst and evaporated to a small volume. After cooling, twice the volume of ether was added, and the mixture was allowed to stand in ice for complete precipitation. After filtration, washing with a small amount of ether and drying, 8.8 g. (87.5%) of product was obtained. Recrystallization from hot alcohol yielded a colorless product melting at 188–188.7° (corr.).

Anal. Calc'd for $C_{12}H_{18}ClNO_2$: N, 5.75; Cl, 14.56.
Found: N, 5.65; Cl, 14.58.

Preparation of 1-phenyl-2-morpholinoethanol-1.—This compound was prepared from the hydrochloride by the addition of dilute ammonia or dilute sodium hydroxide to an aqueous solution of the hydrochloride. It was recrystallized from dilute alcohol; m.p. 80.9–81.3° (corr.).

Anal. Calc'd for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.68.

Preparation of 1-phenyl-2-morpholinopropanol-1 hydrochloride.—This compound was prepared similarly to the ethanol derivative by catalytic reduction, in 80–85% yields. After the reduction, due to the lesser solubility of the propanol derivative, it was necessary to filter the solution hot. Recrystallization from alcohol yielded a colorless product melting at 235° (corr.).

Anal. Calc'd for $C_{13}H_{20}ClNO_2$: N, 5.44; Cl, 13.87.
Found: N, 5.45; Cl, 13.80.

Preparation of 1-phenyl-2-morpholinopropanol-1.—This was prepared from the hydrochloride by the addition of dilute ammonium hydroxide or dilute sodium hydroxide. A pure product, m.p. 73–73.5° (corr.) was obtained by recrystallization from dilute alcohol.

Anal. Calc'd for $C_{13}H_{19}NO_2$: N, 6.33. Found: N, 6.25.

Preparation of 1-(p-hydroxyphenyl)-2-morpholinoethanol-1 hydrochloride.—This was prepared by catalytic reduction of the corresponding ketone hydrochloride in water solution employing 20% palladium on charcoal as the catalyst. After filtering off the catalyst, the aqueous solution was evaporated almost to dryness, cooled, and acetone added. The compound was obtained in 78% yield. Recrystallization of

the compound from alcohol yielded a colorless product melting with decomposition at 178° (corr.).

Anal. Calc'd for $C_{12}H_{18}ClNO_3$: N, 5.39; Cl, 13.65.
Found: N, 5.36; Cl, 13.67.

Preparation of 1-(3,4-dihydroxyphenyl)-2-morpholinoethanol-1 hydrochloride.—This was prepared similarly to the *p*-hydroxy derivative employing 10% palladium on charcoal. After the removal of the catalyst by filtration the solution was evaporated to dryness. Crude yields of 81–98% were obtained. Recrystallization from alcohol and ether and employing charcoal yielded a colorless product decomposing at 250° (corr.).

Anal. Calc'd for $C_{12}H_{18}ClNO_4$: N, 5.08; Cl, 12.86.
Found: N, 4.96; Cl, 12.98.

Preparation of the benzoate of 1-phenyl-2-morpholinoethanol-1 hydrochloride.—Heating the amino alcohol hydrochloride with excess benzoyl chloride on a steam-bath for three hours failed to cause complete esterification. Benzoylation attempted in benzene solution, heating until no more hydrogen chloride was evolved, yielded the apparently unchanged amino alcohol hydrochloride. The ester was best prepared by heating 4.0 g. (0.0164 mole) of the amino alcohol hydrochloride with 15 cc. (0.13 mole) of benzoyl chloride for three hours at 120–130° in an oil-bath. At the end of this time, the solution was cooled, ether was added, and the mixture allowed to stand overnight. The crystalline product was then filtered, washed repeatedly with ether and dried. Recrystallization from hot alcohol and ether yielded 60–65% of a colorless product melting at 173.5–175° (corr.).

Anal. Calc'd for $C_{19}H_{22}ClNO_3$: N, 4.03; Cl, 10.09.
Found: N, 3.97; Cl, 10.20.

Preparation of the cinnamate of 1-phenyl-2-morpholinoethanol-1 hydrochloride.—To 3.35 g. (0.02 mole) of cinnamoyl chloride dissolved in 35 cc. of dry xylene was added 3.11 g. (0.015 mole) of 1-phenyl-2-morpholinoethanol-1 dissolved in 50 cc. of dry xylene. This mixture was heated in an oil-bath maintained at 150° for two hours. At the end of this time, the reaction mixture was cooled, filtered, and the product washed with ether. The yield was 4.96 g. (88%). Recrystallization from alcohol yielded a colorless product melting at 220–221° (corr.).

Anal. Calc'd for $C_{21}H_{24}ClNO_3$: N, 3.75; Cl, 9.49.
Found: N, 3.69; Cl, 9.49.

Preparation of the benzoate of 1-phenyl-2-morpholinopropanol-1 hydrochloride.—The ester was obtained in 85% crude yield by heating the amino alcohol hydrochloride with excess benzoyl chloride for five hours to 120–125°, similar to the ethanol derivative. Recrystallization from hot alcohol and ether yielded a colorless product melting at 210–211° (corr.).

Anal. Calc'd for $C_{20}H_{24}ClNO_3$: N, 3.87; Cl, 9.80. Found: N, 4.04; Cl, 10.23.

Preparation of 5-phenyl-5-morpholinomethyl hydantoin.—This hydantoin was prepared according to the method of Bucherer and Steiner (7). Five grams (0.02 mole) of ω-morpholinoacetophenone hydrochloride was dissolved in 40 cc. of 50% alcohol. To this was added 2 g. (0.03 mole) of potassium cyanide and 8 g. (0.083 mole) of powdered ammonium carbonate. This mixture was shaken well and heated on the water-bath for eight and one-half hours, maintaining the bath between 55–65°. Needles started to separate at the end of two hours. The mixture was allowed to cool, diluted with water, and filtered. The crude yield was 5.3 g. (93%). Recrystallization from hot alcohol yielded colorless needles melting at 204–204.5° (corr.).

Anal. Calc'd for $C_{14}H_{17}N_3O_3$: N, 15.26. Found: N, 15.17.

The hydrochloride of this base was prepared by suspending the base in alcohol and passing in dry hydrogen chloride. Recrystallization from alcohol yielded a product melting at 206° (corr.) with decomposition.

Anal. Calc'd for $C_{14}H_{18}ClN_3O_3$: N, 13.48; Cl, 11.37.
Found: N, 13.40; Cl, 11.26.

Attempts to prepare the hydantoins of α-morpholinopropiophenone, ω-morpholino-*p*-hydroxyacetophenone and ω-morpholino-3,4-dihydroxyacetophenone using the method of Bucherer (7) failed.

SUMMARY

1. The following amino ketones, ω-morpholinoacetophenone, α-morpholinopropiophenone, ω-morpholino-*p*-hydroxyacetophenone and ω-morpholino-3,4-dihydroxyacetophenone, have been prepared.

2. The corresponding carbinols have been prepared by catalytic reduction employing palladium on charcoal as the catalyst.

3. The benzoates of 1-phenyl-2-morpholinoethanol-1 and 1-phenyl-2-morpholinopropanol-1, as well as the cinnamate of the ethanol derivative, have been prepared.

4. The compound 5-phenyl-5-morpholinomethyl hydantoin has been prepared by the method of Bucherer. Attempts to prepare hydantoins of the other amino ketones failed.

PHILADELPHIA, PA.

REFERENCES

(1) HARTUNG, *Chem. Rev.*, **9**, 389 (1931).
(2) ALLES AND KNOEFEL, *Arch. Internat. de Pharmacodynamie et d. therap.*, **47**, 96 (1934).
(3) COLES AND LOTH, *J. Am. Chem. Soc.*, **58**, 1989 (1936).
(4) OSBORNE, *Science*, **85**, 105 (1937).
(5) GARDNER AND HAENNI, *J. Am. Chem. Soc.*, **53**, 2763 (1931); GARDNER, CLARKE AND SEMB, *ibid.*, **55**, 2999 (1933); GARDNER AND HAMMEL, *ibid.*, **58**, 1360 (1936); LEFFLER AND BRILL, *ibid.*, **55**, 365 (1935); SMITH AND POLLARD, *ibid.*, **59**, 131 (1937).
(6) MAGEE AND HENZE, *ibid.*, **60**, 2148 (1938).
(7) BUCHERER AND STEINER, *J. prakt. chem.*, **140**, 291 (1934).
(8) MEEKER AND WAGNER, *Ind. Eng. Chem. Anal. Ed.*, **5**, 396 (1933).
(9) HARTUNG, *J. Am. Chem. Soc.*, **50**, 3370 (1928).
(10) SCHMIDT, *Ber.*, **22**, 3251 (1889).
(11) RATHER AND REID, *J. Am. Chem. Soc.*, **41**, 77 (1919).
(12) German Patent 667,356, November, 1938.
(13) SCHAEFER, *Ind. Eng. Chem. Anal. Ed.*, **2**, 115 (1930).
(14) TUTIN, CATON AND HANN, *J. Chem. Soc.*, **95**, 2113 (1909).
(15) MANNICH AND HAHN, *Ber.*, **44**, 1548 (1911).
(16) LEFFLER AND VOLWILER, *J. Am. Chem. Soc.*, **60**, 896 (1938).