furic acid. (Only the formamide of IX was isolated and purified—see below.) Refluxing was maintained for six to eight hours. The solution was made basic with sodium hydroxide and extracted with ether. The extracts were dried over potassium carbonate. The hydrochloride of III was precipitated from solution by means of dry hydrogen chloride. VII could be isolated only as the free base, which was distilled. IX was first distilled and then the hydrochloride prepared.

An adaptation of the Eschweiler–Clarke procedure[18] was used for the methylations leading to IV, VIII and XI.

Compounds VI and X were obtained by hydrolysis of the un-isolated formamides over a period of ten hours with boiling 30% sodium hydroxide solution. The liquid amines were isolated by ether extraction in the regular manner.

**N-(1,3,3-Triphenyl-1-propyl)-formamide (XV).**—A general procedure for the Leuckart reaction was followed.[6] From the reaction of 15 g. (0.053 mole) of β,β-diphenylpropiophenone,[11] 10 g. (0.095 mole) of ammonium carbonate and 11 g. (0.2 mole) of 95% formic acid, the desired formamide precipitated. After recrystallization from alcohol, 12 g. (73% yield) was obtained, m.p. 175°.

*Anal.* Calcd. for $C_{22}H_{21}NO$: C, 83.77; H, 6.71. Found: C, 83.52; H, 6.85.

**1,3,3-Triphenyl-1-propanol (XVI).**—Through reduction of 28 g. (0.1 mole) of β,β-diphenylpropiophenone with aluminum isopropoxide,[10] 25 g. (95% yield) of 1,3,3-triphenyl-1-propanol was obtained, m.p. 72° (recrystallized from petroleum ether).

(18) Icke and Wisegarner, *Org. Syntheses*, **25**, 89 (1945).

*Anal.* Calcd. for $C_{21}H_{20}O$: C, 87.45; H, 6.99. Found: C, 87.47; H, 7.16.

**1,3,3-Triphenyl-1-propene (XVII) (a).**—In an attempt to prepare IX (Table I), 40 g. (0.127 mole) of the formamide (XV) was heated overnight at refluxing temperature with 20 ml. of concentrated hydrochloric acid. The cooled solution was extracted with benzene. The water layer failed to yield any amine when neutralized with alkali. The benzene layer was treated with activated charcoal and filtered. Upon cooling, the filtrate yielded a crystalline solid which was soluble in a variety of organic solvents. It did not contain ionic halogen. The material could not be recrystallized, but about 4 ml. of benzene was distilled from it leaving back a gummy residue. The gum was taken into acetone and then distilled under reduced pressure, b.p. 200° (2 mm.). Upon cooling the liquid solidified. After recrystallization from alcohol, 7 g. (20% yield) of pure white crystalline 1,3,3-triphenyl-1-propene was obtained, m.p. 98–99°.[8]

*Anal.* Calcd. for $C_{21}H_{18}$: C, 93.32; H, 6.68. Found: C, 93.17; H, 6.67.

(b).—A mixture of 25 g. (0.087 mole) of 1,3,3-triphenyl-1-propanol (XVI) and 100 ml. of 20% sulfuric acid was heated at refluxing temperature for two hours. The mixture was cooled and extracted with benzene. Upon removal of the benzene from the extract and cooling of the residue, solidification was induced. Recrystallization from alcohol yielded 20 g. (85%) of 1,3,3-triphenyl-1-propene which was identical by mixed melting point determination with a sample obtained by procedure (a).

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACEUTICAL CHEMISTRY, UNIVERSITY OF KANSAS SCHOOL OF PHARMACY]

# Open-chain Amino Ketones Related to Morphine

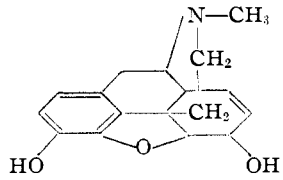
BY J. H. BURCKHALTER AND SAM H. JOHNSON, JR.[1]

In view of the analgetic effect of two of the γ-phenylpropylamines described in the foregoing publication, it seemed worthwhile to synthesize other amines which would bear a closer structural relationship to morphine. A group of α-alkyl-α-(2-dialkylaminoalkyl)-phenylacetonitriles were prepared by sodamide alkylation of the appropriate nitriles with 2-dialkylaminoalkyl halides. One of these intermediates was treated with the ethyl Grignard reagent to give 6-dimethylamino-4-methyl-4-phenyl-3-hexanone, which may be considered to be an open-chain relative of morphine. It is also related to methadone, the principal difference being the replacement of a phenyl group of methadone by a methyl. Unsuccessful attempts were made to simulate more closely the structure of morphine by conversion of 6-dimethylamino-4-methyl-4-(2,3-dimethoxyphenyl)-3-hexanone to a compound possessing the phenolic hydroxyl and oxygen bridge. Neither of these amino ketones possessed analgetic effect. Speculations have been made concerning the inactivity.

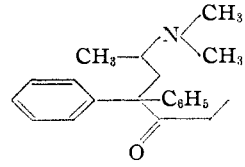
## Discussion

In further efforts to obtain γ-phenylpropylamines[2] similar to but simpler in structure than morphine (I) and which might possess desirable analgetic effect, we became interested in certain open-chain compounds having structures III and V.[3] At the same time, a structural relationship between III and methadone, a powerful analgetic with morphine-like action, was kept in mind. The structure of methadone (II) has been written so as to show this relationship, and it can be seen that IIIc differs from methadone only in the substitution of a methyl for a phenyl group. Further, V, by possessing a phenolic hydroxyl and oxygen bridge in the proper positions, is more closely related to morphine than is III. However, we have not yet succeeded in synthesizing compounds of structure V.

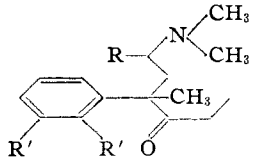
A group of intermediate α-alkyl-α-(2-dialkyl-



Morphine (I)

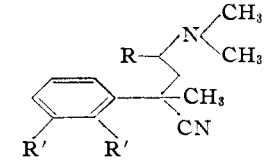


Methadone (II)

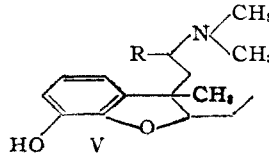


III R R′

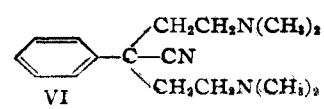
a, H H
b, H $OCH_3$
c, $CH_3$ H
d, $CH_3$ $OCH_3$



IV



V



VI

(1) Parke, Davis and Company Fellow, 1948–1950. Tennessee Eastman Corporation, Kingsport, Tennessee.

(2) For earlier studies, see Burckhalter and Johnson, THIS JOURNAL, **73**, 4827, 4830 (1951).

(3) For other studies of open-chain relatives of morphine, see, for example, Ziering and Lee, *J. Org. Chem.*, **12**, 911 (1947); Horning and Schock, THIS JOURNAL, **70**, 2941 (1948).

aminoalkyl)-phenylacetonitriles (Table I), four of which are represented by formula IV, were prepared from the appropriate phenylacetonitrile and 2-dialkylaminoalkyl halide by means of a sodamide condensation. In general the yields were lower than expected because of incomplete reaction, and both the alkyl halide and starting nitrile were recovered in amounts which accounted for the low yields. However, yields of 63 and 88%, respectively, of compounds 2 and 5 (Table I) were obtained by employing an alkyl bromide rather than a chloride. The small amounts of compounds 3 and 6 (IVc and IVd) can be explained on the basis of isomer formation. By analogy with studies on the synthesis and structure of methadone,[4] we have assumed that the position of the methyl group in the basic side chain of the products isolated is that shown by IVc and IVd.

When α-phenylpropionitrile containing unchanged phenylacetonitrile was used in the sodamide condensation with 2-dimethylaminoethyl chloride, not only was IVa formed, but also the new compound VI was isolated.

6-Dimethylamino-4-methyl-4-phenyl-3-hexanone (IIIa) was prepared in 76% yield from IVa and ethylmagnesium bromide. However, the analogous reaction with IVb resulted in only 35% of the desired 6-dimethylamino-4-methyl-4-(2,3-dimethoxyphenyl)-3-hexanone (IIIb). The low yield of IIIb may be explained by the formation of a stiff gummy Grignard complex which occluded recoverable unreacted starting material and prevented an efficient stirring of the mixture.

Attempts to reduce IIIb catalytically to the alcohol, preparatory to demethylation and ring closure to V, resulted in failure. Also, efforts to demethylate IIIb to the catechol gave a product which rapidly decomposed to a dark tar. Ring closure experiments with related compounds are currently being attempted in our laboratory.

2,3-Dimethoxybenzyl alcohol, required for the synthesis of 2,3-dimethoxyphenylacetonitrile, was prepared in 95% yield by catalytic reduction of the benzaldehyde. This method was more convenient for our purposes than the crossed Cannizzaro reaction.[5]

During the application of a purification procedure for 2,3-dimethoxyphenylacetonitrile, which was later found to be unnecessary, small amounts of the corresponding amide and acid were isolated.

Because of the absence of any analgetic effect by amino ketones (IIIa and IIIb) in guinea pigs, the remaining nitriles of Table I were not converted to the corresponding ketones.

One might speculate as to why II is active and III inactive. As demonstrated by Stuart-type atom models, the phenyl group of II locks the aliphatic chains into a morphine-like spatial arrangement, thus establishing what might be a requisite rigidity. The methyl group of III which replaces the phenyl of II, apparently lacks the size to effect this steric hindrance.

**Acknowledgments.**—We wish to thank Parke, Davis and Company for financial aid, and Dr.

(4) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 2454 (1947).
(5) Horning, Horning and Platt, *ibid.*, **69**, 2929 (1947).

TABLE I

α-ALKYL-α-(2-DIALKYLAMINOALKYL)-PHENYLACETONITRILES

| | Name | Yield,[a] % | B.p., °C. | Mm. | M.p., °C. | Formula | Analyses, % Carbon Calcd. | Carbon Found | Hydrogen Calcd. | Hydrogen Found | Chlorine Calcd. | Chlorine Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Phenylacetonitriles | | | | | | | | | | | |
| 1 | α-Methyl-α-(2-dimethylaminoethyl)- (IVa) | 50 | 132 | 4 | 225[b] | $C_{13}H_{18}N_2 \cdot HCl$ | | | | | 14.85 | 14.94 |
| 2 | α-Methyl-α-(2-diethylaminoethyl)- | 63 | 145 | 4 | 105[c] | $C_{21}H_{35}N_3O_7$[d] | 54.90 | 55.35 | 5.49 | 5.57 | | |
| 3 | α-Methyl-α-(2-dimethylaminopropyl)- (IVc) | 48 | 144 | 4[e] | | $C_{14}H_{20}N_2$ | 77.72 | 77.66 | 9.32 | 8.89 | | |
| | 2,3-Dimethoxyphenylacetonitriles | | | | | | | | | | | |
| 4 | α-Methyl-α-(2-dimethylaminoethyl)- (IVb) | 55 | 148 | 0.8 | 138[f] | $C_{15}H_{22}N_2O_2 \cdot HCl$ | | | | | 11.87 | 11.94 |
| 5 | α-Methyl-α-(2-diethylaminoethyl)- | 88 | 186 | 4[g] | | $C_{17}H_{26}N_2O_2$ | 70.30 | 69.82 | 9.03 | 8.65 | | |
| 6 | α-Methyl-α-(2-dimethylaminopropyl)- (IVd) | 25 | 184 | 4[h] | | $C_{16}H_{24}N_2O_2$ | 69.52 | 69.51 | 8.75 | 8.39 | | |
| 7 | α-Ethyl-α-(2-dimethylaminoethyl)- | 59 | 153 | 0.8 | 163[f] | $C_{16}H_{24}N_2O_2 \cdot HCl$ | | | | | 11.33 | 11.28 |

[a] Represents yield of liquid base. Also considerable starting material was usually recovered. [b] From acetone–alcohol. [c] From alcohol. [d] Picrate. [e] Also molecularly distilled, $n^{20}D$ 1.5070. [f] From acetone. [g] Also molecularly distilled, $n^{20}D$ 1.5139. [h] Also molecularly distilled, $n^{20}D$ 1.5178.

C. V. Winder, of that Company, for pharmacological results.

## Experimental[6]

**α-Phenylpropionitrile** was prepared from phenylacetonitrile, methyl iodide and sodium hydroxide by the method of Victor Meyer.[7] Since phenylacetonitrile and the product have the same boiling range, the unchanged starting material was removed by treatment of the distilled mixture with benzaldehyde and sodium ethoxide. The desired product was then separated from the α-cyanostilbene by distillation.

**2,3-Dimethoxybenzyl Alcohol.**—At room temperature, 425 g. (2.56 mole) of freshly distilled 2,3-dimethoxybenzaldehyde[8] dissolved in 500 ml. of ethyl alcohol was reduced in a low pressure Parr hydrogenator using 10 g. of Raney nickel catalyst. After a theoretical uptake of hydrogen, the catalyst and solvent were removed in the customary way. It was found that further purification of the resulting 2,3-dimethoxybenzyl alcohol was unnecessary for the next step. However, when distilled, a 95% yield was obtained, b.p. 144–146° (8 mm.). Readily crystallized, the product melted at 48–49°.[5]

**2,3-Dimethoxyphenylacetonitrile.**—An adaptation of a standard procedure was used.[9] From 406 g. of 2,3-dimethoxybenzyl chloride and 113 g. of sodium cyanide, 375 g. (96% yield) of the nitrile was obtained, b.p. 106–108° (0.4 mm.).[10]

**α-(2,3-Dimethoxyphenyl)-propionitrile.**—A mixture of 20 g. (0.5 mole) of sodamide and 250 ml. of dry benzene was stirred at reflux temperature, and 89 g. (0.5 mole) of 2,3-dimethoxyphenylacetonitrile was slowly added. Stirring and refluxing was maintained for an hour after the addition was complete. To the cooled and stirred mixture, 75 g. (0.5 mole) of methyl iodide was slowly added. Reflux temperature was maintained for three hours after the addition was complete. The mixture was cooled, and the theoretical quantity of sodium iodide was collected on a funnel. The benzene layer was washed with water and dried over potassium carbonate. The benzene was removed, and the residue was distilled under reduced pressure giving 72 g. (75% yield) of a colorless oil, b.p. 106–108° (0.4 mm.), $n^{20}D$ 1.5173.

*Anal.* Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85. Found: C, 68.84; H, 6.58.

Before the foregoing analytical results were at hand, 35 g. of α-(2,3-dimethoxyphenyl)-propionitrile was treated with an alcoholic solution of sodium ethoxide and benzaldehyde by a variation of the Meyer procedure to remove any unchanged starting nitrile. Water was added to the reaction mixture, and most of the alcohol was removed by evaporation. From a benzene extract of the residue, 20 g. of the initial 35 g. of nitrile was recovered by distillation and 8 g. of a higher boiling fraction, b.p. 180–185° (4 mm.), was obtained. Upon cooling, it partially solidified. Recrystallization from Skelly solvent (65–80°) gave 4 g. of white crystalline material, m.p. 78–79°, which undoubtedly was **α-(2,3-dimethoxyphenyl)-propionamide.**

*Anal.* Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23. Found: C, 63.34; H, 7.30.

Acidification of the water layer with hydrochloric acid precipitated 4 g. of an acid which was **α-(2,3-dimethoxyphenyl)-propionic acid**, m.p. 120°, from alcohol.

*Anal.* Calcd. for $C_{11}H_{14}O_4$: C, 62.84; H, 6.71. Found: C, 63.14; H, 6.68.

**α-(2,3-Dimethoxyphenyl)-butyronitrile.**—Following the foregoing procedure, 133 g. (0.75 mole) of 2,3-dimethoxyphenylacetonitrile, 87 g. (0.8 mole) of ethyl bromide and 30 g. (0.75 mole) of sodamide gave, besides 10 g. of unchanged starting material, 108 g. (71%)[11] of a colorless liquid boiling at 116–119° (0.8 mm.); $n^{20}D$ 1.5190.

*Anal.* Calcd. for $C_{12}H_{15}NO_2$: C, 70.22; H, 7.37. Found: C, 70.41; H, 7.26.

**α-(Alkyl-α-(2-dialkylaminoalkyl)-phenylacetonitriles (Table I).**—A mixture of 200 ml. of dry benzene and 0.2 mole of sodamide was kept at refluxing temperature and stirred while 0.2 mole of the α-alkylphenylacetonitrile was slowly added. After the addition was completed, refluxing and stirring were continued for an hour. The mixture was then cooled and stirred, and to it was added a dry benzene solution of at least an equivalent amount of 2-dialkylaminoalkyl halide.[12] After the addition was complete, refluxing and stirring were continued for an hour. The cooled mixture was treated with water, and the benzene layer was separated and dried over potassium carbonate. The benzene was removed and the residue distilled under reduced pressure.

**Bis-α,α-(2-dimethylaminoethyl)-phenylacetonitrile (VI).**—When the purification step using benzaldehyde was omitted in the preparation of α-phenylpropionitrile, there was present a considerable amount of unchanged phenylacetonitrile. Employing 0.2 mole of the impure nitrile, 0.25 mole of sodamide and 0.3 mole of 2-dimethylaminoethyl chloride in the foregoing procedure, 14 g. of IVa was obtained, b.p. 130–134° (4 mm.), and also 9 g. of a yellow viscous liquid, b.p. 181–183° (4 mm.). The latter, assumed to be VI, was converted in the customary manner to its dihydrochloride and recrystallized from acetone or alcohol, m.p. 285°.

*Anal.* Calcd. for $C_{18}H_{25}N_3 \cdot 2HCl$: Cl, 21.34. Found: Cl, 21.40.

**6-Dimethylamino-4-methyl-4-phenyl-3-hexanone (IIIa) Hydrochloride.**—To a cooled solution of 0.2 mole of ethylmagnesium bromide in 75 ml. of anhydrous ether was added a solution of 29 g. (0.14 mole) of α-methyl-α-(2-dimethylaminoethyl)-phenylacetonitrile (Table I) in 150 ml. of dry xylene. The solution was heated at reflux temperature for four hours, during which time the ether was removed and the solution changed in color from black to dark green. The boiling mixture was poured into 30 ml. of 30% hydrochloric acid. The heat of reaction removed most of the xylene and left a straw-colored acidic solution which was heated on the steam-bath for two hours. After the solution was cooled, 150 ml. of benzene was added. Upon shaking the mixture, three layers formed. As in the preparation of methadone,[13] the middle layer was separated and made basic with sodium hydroxide to precipitate an oil. This mixture was extracted with ether, the ether extracts were dried over potassium carbonate, the solvent was removed and the residue was distilled under reduced pressure to give 25 g. (76%) of a light yellow oil, b.p. 155–157° (2 mm.). Converted in the usual way to the hydrochloride, 24 g. of the salt was obtained, m.p. 168°. Recrystallization from acetone–ether gave 20 g., m.p. 169–170°.

*Anal.* Calcd. for $C_{15}H_{23}NO \cdot HCl$: Cl, 13.14. Found: Cl, 13.20.

**6-Dimethylamino-4-methyl-4-(2,3-dimethoxyphenyl)-3-hexanone (IIIb) Hydrochloride.**—By the foregoing procedure, 0.6 mole of ethylmagnesium bromide and 84 g. (0.32 mole) of α-methyl-α-(2-dimethylaminoethyl)-2,3-dimethoxyphenylacetonitrile gave 40 g. of unchanged nitrile and 37 g. (35%) of a light yellow oil, b.p. 156–158° (0.6 mm.). The hydrochloride was prepared in the usual manner and recrystallized from acetone, m.p. 204–205°.

*Anal.* Calcd. for $C_{17}H_{27}NO_3 \cdot HCl$: Cl, 10.75. Found: Cl, 10.76.

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(6) C and H analyses by Mr. C. W. Beazley, Skokie, Illinois.

(7) Meyer, *Ann.*, **250**, 123 (1888).

(8) Supplied by Monsanto Chemical Co., St. Louis, Mo.

(9) Adams and Thal, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 107.

(10) Horning, Horning and Platt found 181–185° (33 mm.); Bergel, *et al.*, *J. Chem. Soc.*, 261 (1944), found 158–160° (12 mm.).

(11) Using ethyl iodide in a modification of this procedure, Horning and Shock, THIS JOURNAL, **70**, 2941 (1948), got an 84% yield.

(12) The benzene solution of 2-dialkylaminoalkyl halide was prepared as described by Burckhalter, Stephens and Hall, *J. Am. Pharm. Assoc.*, **39**, 271 (1950).

(13) Reported by Office of Publication Board, Department of Commerce, Washington, D. C., P.B. 981, 94–96 (1945).