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

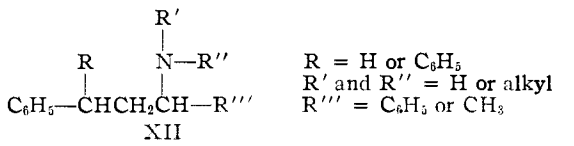
The Leuckart Reaction with β-Phenyl Ketones

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

The Leuckart reaction has been successfully applied to some ketones of high molecular weight, benzylacetophenone, 2,3-dimethoxybenzylacetophenone, 4,4-diphenyl-2-butanone and β,β-diphenylpropiophenone, to give the corresponding γ-phenylpropylamines, which were desired for pharmacodynamic and chemotherapeutic studies. In certain cases, the intermediate formamides could not be hydrolyzed with boiling hydrochloric acid or alkali to give the desired amine, but sulfuric acid proved to be effective. N-(1,3,3-Triphenyl-1-propyl)-formamide, the only crystalline amide isolated, was deaminated by boiling hydrochloric acid to give 1,3,3-triphenyl-1-propene, and the structure of the degradation product was confirmed by an alternate synthesis. Three of the amines were methylated by means of the Eschweiler–Clarke procedure.

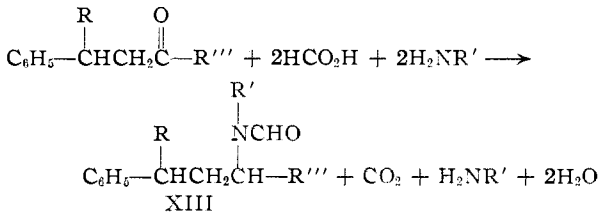
Discussion

Numerous drugs with important pharmacodynamic properties, such as the analgetics, spasmolytics, anticonvulsants, antihistaminics and adrenolytics, possess large space-occupying groups. In some cases it is agreed that these drugs act by blocking the effects of certain chemical mediators. For example, the adrenolytic agent Dibenamine is said to act by blocking the effects of epinephrine.[2] The number and size of the blocking groups, such as phenyl, as well as the distance between the "anchoring" functional groups,[3] are important. Our object is to learn the effect upon pharmacodynamic properties of changes in the position and number of phenyl groups in a series of di- and triphenylpropylamines. In planning the syntheses, we were particularly interested in having these compounds possess a γ-arylpropylamine skeleton, which would relate them remotely at least to morphine, and thus serve as an extension of prior studies.[4]



XII

Eight of the amines having general formula XII were prepared by means of the Leuckart reaction[5] using the appropriate ketone. The formamides XIII were then hydrolyzed to XII.[6]



XIII

Three other amines of the same general formula XII were prepared by a modification of the Leuckart reaction known as the Eschweiler–Clarke procedure.[7] This process, a methylation procedure for primary and secondary amines by means of formaldehyde and formic acid, was used for the preparation of IV from I (Table I), VIII from VII and XI from X. Attempts to prepare tertiary amine N,N-dimethyl-1,3,3-triphenyl-1-propylamine (XI) in a more direct manner, by using N,N-dimethylformamide in the Leuckart reaction according to a recent successful application,[8] resulted only in a recovery of the starting materials.

The intermediate formamides, except that of amine IX, were not readily crystallized, and so hydrolysis was effected without isolation of the amides from solution. It is perhaps noteworthy that after acid hydrolysis, when benzene was used for the removal of non-polar substances, the amine hydrochlorides were isolated from the benzene and not from the aqueous layer. However, once the salts had been isolated by evaporation of the benzene, they became easily soluble in water.

It was necessary to hydrolyze the formamide XV by means of 30% sulfuric acid. Earlier attempts to hydrolyze XV by means of hydrochloric acid failed to yield IX, but resulted in the formation of a non-ionic crystalline substance. The material was very soluble in a variety of organic solvents and could not be easily recrystallized. Heating of the solid resulted surprisingly in the removal of a relatively large volume of benzene. The gummy residue, after distillation under reduced pressure, became crystalline and was identified as 1,3,3-triphenyl-1-propene (XVII). XVII has been obtained by others[9] from the treatment of 3,3-dichloro-1-phenyl-1-propene with phenylmagnesium bromide, but no yield was given.

For a confirmation of the structure of XVII, 1,3,3-triphenyl-1-propanol (XVI) was prepared in 95% yield by an aluminum isopropoxide reduction[10] of β,β-diphenylpropiophenone (XIV).[11] XVI was then dehydrated to XVII in 85% yield by means of boiling 20% sulfuric acid.

4,4-Diphenyl-2-butanone, the intermediate required for the preparation of V, VI, VII and VIII, had previously been prepared, along with some diphenylpropionic acid, from ethyl α-acetyl-β,β-diphenylpropionate,[12] but no yield was given. It had also been obtained by the action of phenylmagnesium bromide on benzalacetone, but 1,3-diphenyl-1-buten-3-ol was formed as a by-product.[13] We have found that an adaptation of the method of

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

(2) Nickerson and Goodman, *J. Pharmacol.*, **89**, 168 (1947).

(3) Pfeiffer, *Science*, **107**, 94 (1948).

(4) Burckhalter and Johnson, THIS JOURNAL, **73**, 4827 (1951).

(5) M. L. Moore, "Organic Reactions," Vol. V, John Wiley and Sons, Inc., New York, N. Y., 1949, p. 301.

(6) The general procedure of Ingersoll, *et al.*, THIS JOURNAL, **58**, 1808 (1936), was followed.

(7) Eschweiler, *Ber.*, **38**, 880 (1905); Clarke, Gillespie and Weisshaus, THIS JOURNAL, **55**, 4571 (1933).

(8) Bunnett and Marks, *ibid.*, **71**, 1587 (1949).

(9) Ziegler, Richter and Schnell, *Ann.*, **443**, 161 (1925).

(10) Wilds, "Organic Reactions," Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, p. 203.

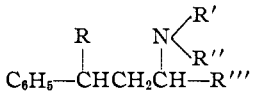
(11) Shildneck, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 236.

(12) Henderson and Parker, *J. Chem. Soc.*, **71**, 678 (1897).

(13) Kohler, *Am. Chem. J.*, **38**, 530 (1907).

TABLE I

DI- AND TRIPHENYLPROPYLAMINES

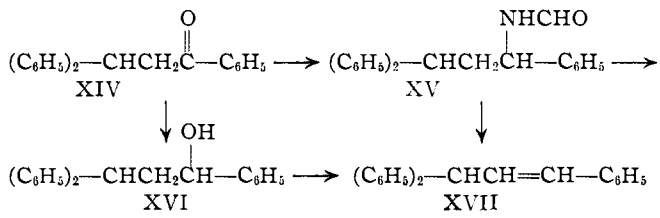


No.	R	R′	R″	R‴	Yield,[a] %	M.p., °C.	Formula	Chlorine, % Calcd.	Found
I[b]	H	H	H	C_6H_5	39[e]	195[p]	$C_{15}H_{17}N\cdot HCl$	14.32	14.45
II[c]	H	H	H	C_6H_5	58[f]	183	$C_{17}H_{21}NO_2\cdot HCl$	11.52	11.60
III[b]	H	H	C_4H_9	C_6H_5	10[f]	116	$C_{19}H_{25}N\cdot HCl$	11.67	11.79
IV[b]	H	CH_3	CH_3	C_6H_5	76[g,h]	191	$C_{17}H_{21}N\cdot HCl$	12.86	12.97
V	C_6H_5	H	H	CH_3	45[f]	175	$C_{16}H_{19}N\cdot HCl$	13.55	13.68
VI	C_6H_5	H	C_2H_5	CH_3	7[f,i]	147	$C_{18}H_{23}N\cdot HCl\cdot H_2O$	11.56	11.57
VII	C_6H_5	H	C_4H_9	CH_3	43[j]		$C_{20}H_{27}N$		
VIII	C_6H_5	CH_3	C_4H_9	CH_3	77[k]		$C_{21}H_{29}N$		
IX[d]	C_6H_5	H	H	C_6H_5	40[h,l]	170	$C_{21}H_{21}N\cdot HCl$	10.37	10.49
X[d]	C_6H_5	H	CH_3	C_6H_5	41[m]		$C_{22}H_{23}N$		
XI[d]	C_6H_5	CH_3	CH_3	C_6H_5	77[h,n]	119	$C_{23}H_{25}N\cdot HCl\cdot H_2O$	9.59	9.71

[a] Based on starting ketone, except as indicated in footnotes for IV, VIII, IX and XI. [b] Intermediate benzylacetophenone prepared by Adams, Kern and Shriner, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 101. [c] Same structure as I, except the γ-phenyl group is replaced by 2,3-dimethoxyphenyl. [d] For intermediate β,β-diphenylpropiophenone, see ref. 11. [e] From acetone–ethanol. [f] From acetone–ether. [g] Based on I from which it was prepared. [h] From acetone. [i] Crude amine boiled at 138–152° (3–5 mm.). [j] Obtained as yellow amine, b.p. 130–132° (1 mm.). *Anal.* Calcd.: C, 85.35; H, 9.67. Found: C, 85.74; H, 9.28. [k] Prepared from VII as a colorless liquid, b.p. 129–130° (0.5 mm.). *Anal.* Calcd.: C, 85.36; H, 9.89. Found: C, 85.64; H, 9.90. [l] Based on the formamide XV. Base distilled at 184–186° (4 mm.). [m] Obtained as a light yellow liquid, b.p. 170–175° (0.3–0.5 mm.). Analyzed as picrate (m.p. 151°, from ether-ethanol). *Anal.* Calcd.: C, 63.40; H, 4.94. Found: C, 63.20; H, 4.88. [n] Prepared from X. [p] Raiford and Davis, THIS JOURNAL, 50, 156 (1928), using a different process, reported 195.5°.

Friedel and Crafts,[11] using benzalacetone and benzene, gave an 87% yield of the desired ketone without the formation of any by-products.

As an intermediate in the synthesis of II, 2,3-dimethoxybenzalacetophenone was prepared in 98% yield from 2,3-dimethoxybenzaldehyde and acetophenone through an application of the method of Kohler and Chadwell.[14] Reduction to 2,3-dimethoxybenzylacetophenone was readily accomplished by analogy with the findings of Adams, Kern and Shriner,[15] who prepared benzylacetophenone.



Dr. C. V. Winder, of Parke, Davis and Company, has studied the analgetic activity of the amines in guinea pigs. α-(Benzhydrylmethyl)-benzylamine (IX) exhibited activity approaching that of morphine, while 4,4-diphenyl-2-butylamine (V) was less effective. However, all members of the series were rather toxic.

Acknowledgment.—The authors wish to thank Parke, Davis and Company for financial support.

Experimental[16]

4,4-Diphenyl-2-butanone.—In applying the general procedure of Shildneck,[11] 85 g. (0.58 mole) of benzalacetone, 158 g. (1.16 mole) of anhydrous aluminum chloride and 1700 ml. of dry benzene were employed. After the completion of the isolation steps, the product failed to crystallize. It was distilled under reduced pressure; 96 g. (87% yield) of 4,4-diphenyl-2-butanone boiled at 164.5–168° (4–5 mm.). The distillate solidified upon cooling, m.p. 46°.[17]

2,3-Dimethoxybenzalacetophenone.—Following the method of Kohler and Chadwell, who prepared benzalacetophenone,[14] 83 g. (0.5 mole) of 2,3-dimethoxybenzaldehyde gave 130 g. (98% yield) of yellow viscous oil which boiled at 208–210° (1.5 mm.), $n^{20}D$ 1.6396.

Anal. Calcd. for $C_{15}H_{16}O_3$: C, 76.09; H, 6.07. Found: C, 75.84; H, 6.08.

The 2,4-dinitrophenylhydrazone was prepared, m.p. 222–223°, from a chloroform and alcohol mixture.

Anal. Calcd. for $C_{21}H_{20}N_4O_6$: C, 61.61; H, 4.50. Found: C, 61.41; H, 4.55.

2,3-Dimethoxybenzylacetophenone.—Following the directions used in the preparation of benzylacetophenone,[15] 56 g. (0.2 mole) of 2,3-dimethoxybenzalacetophenone was reduced with 0.4 g. of platinum oxide to give 46 g. (82% yield) of clear liquid product; b.p. 186–189° (1.5 mm.). Upon standing for a week, the liquid crystallized. Recrystallized from a mixture of ethyl acetate and petroleum ether, it melted at 43°.

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.63; H, 6.67.

The 2,4-dinitrophenylhydrazone melted at 204–205° after recrystallization from chloroform–alcohol.

Anal. Calcd. for $C_{23}H_{22}N_4O_6$: C, 61.32; H, 4.92. Found: C, 61.47; H, 4.90.

Di- and Triphenylpropylamines (Table I).—The general procedure is that of Ingersoll, *et al.*[6] Compounds I, II and V (Table I), were prepared by hydrolysis of the un-isolated formamides by means of concentrated hydrochloric acid. Upon extraction of the mixtures with benzene for the removal of non-polar substances, the amine hydrochlorides were unexpectedly found in solution in the benzene layer and not in the water layer. However, once the salts had been isolated by removal of the benzene, they were readily soluble in water and could be recrystallized from a suitable solvent.

Compounds III, VII and IX were obtained by hydrolysis of the corresponding un-isolated formamides with 30% sul-

(14) Kohler and Chadwell, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1941, p. 78.

(15) Adams, Kern and Shriner, *ibid.*, p. 101.

(16) C and H analyses by Mr. Charles Beazley, Skokie, Illinois.

(17) Henderson and Parker, using a different procedure, reported 47.5°.

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).

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

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

Open-chain Amino Ketones Related to Morphine

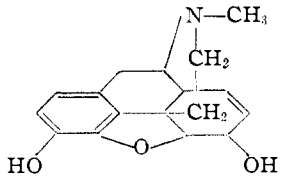
BY J. H. BURCKHALTER AND SAM H. JOHNSON, JR.[1]

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.

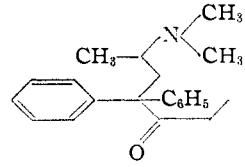
Discussion

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.

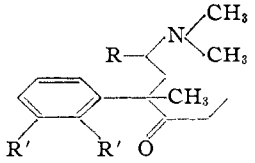
A group of intermediate α-alkyl-α-(2-dialkyl-

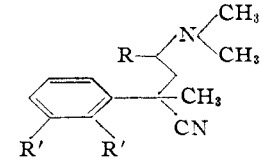


Morphine (I)



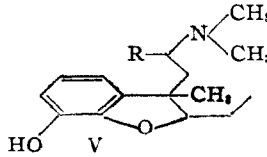
Methadone (II)



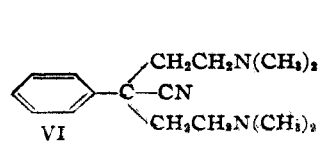


III R R′ IV

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



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).