of 1 N hydrochloric acid solution and the liberated carbon dioxide swept into the Ascarite tubes with nitrogen. The gain in weight of Ascarite tubes totalled 5.77 g. representing 0.131 mole (69.2%) of carbon dioxide. The reaction mixture was worked up by adding ether, washing the ether solution with water, drying over Drierite and distilling. After removal of the ether, the following fractions were obtained: (1) 88 g. of benzyl alcohol, b.p. 99–135° (20 mm.); (2) 10.08 g. (40.4%) of hydrocinnamonitrile, b.p. 135° (20 mm.) to 87° (0.2 mm.), n^{25}D 1.5207; (3) 1.34 g., b.p. 87° (0.2 mm.) to 158° (0.25 mm.); (4) 10.62 g. (25.4%) of dibenzylacetonitrile, b.p. 158–160°(0.25 mm.); (5) 18.21 g. (26.8%) benzyl dibenzylcyanoacetate, b.p. 160° (0.25 mm.) to 200° (0.15 mm.); a 2.0-g. residue remained from the distillation. Fractions (4) and (5) solidified and were identified by mixed melting points with authentic samples.

The above reaction was repeated except that five mole per cent. of sodium was used. The quantities of reactants were: 0.18 g. (0.008 g. atom) of sodium, 40.7 g. (0.154 mole) of VII, and 80.3 g. of benzyl alcohol. The total yield of carbon dioxide was 4.27 g. (63%), of which 0.28 g. was released on acidification. The other reaction products were: 8.20 g. (40.7%) of hydrocinnamonitrile, 7.86 g. (23.1%) of dibenzylacetonitrile and 16.32 g. (29.8%) of benzyl dibenzylcyanoacetate.

Reaction of Benzyl Dibenzylcyanoacetate (IX) with Sodium Benzyl Oxide.—This reaction was run in the same manner as described above for benzyl benzylcyanoacetate. The quantities of reactants were: 0.87 g. (0.04 g. atom) of sodium, 55.54 g. (0.157 mole) of IX, and 90.7 g. of benzyl alcohol. The mixture was kept at 165–167° for four hours, during which time no carbon dioxide was evolved. The reaction mixture set to a gel on cooling. It then was treated with 55 ml. of 1 N hydrochloric acid and the evolved carbon dioxide was swept into the Ascarite tubes by a stream of nitrogen. The weight gain of the Ascarite tubes was 1.41 g., indicating 0.032 mole (20.4%) of carbon dioxide had been liberated.

The reaction mixture was then taken up in ether, washed with water, dried over Drierite, and distilled to yield 8.80 g. (25.4%) of dibenzylacetonitrile, b.p. 126–128° (0.1 mm.), and 35.05 g. (62.8%) of unchanged benzyl dibenzylcyanoacetate (IX), b.p. 205–210° (0.2 mm.).

The reaction was repeated using 2.49 g. (0.108 g. atom) of sodium, 38.38 g. (0.108 mole) of IX, and 149 g. of benzyl alcohol. The yields of products were: 4.29 g. (90%) of carbon dioxide, 8.32 g. (39%) of dibenzyl ether, b.p. 94–96° (0.15 mm.), n^{25}D 1.5598; and 22.2 g. (93%) of dibenzylacetonitrile, b.p. 130° (0.10 mm.)–137° (0.08 mm.).

In another run, using 3.06 g. (0.122 mole) of sodium dissolved in 150 g. of benzyl alcohol and 47.3 g. (0.133 mole) of benzyl dibenzylcyanoacetate, the solid which formed was separated by the addition of ether, centrifuging and finally washing several times with ether. The resulting white powdery solid effervesced strongly when acidified with dilute nitric acid. The acidified mixture was extracted with ether; after drying and distillation this extract yielded 8.47 g. (59%) of benzyl alcohol.

MADISON, WISCONSIN RECEIVED MARCH 2, 1951

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

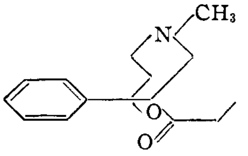
Esters of α-(2-Dialkylaminoethyl)-benzyl Alcohols

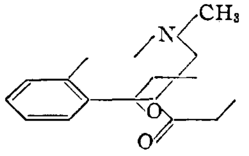
BY J. H. BURCKHALTER AND SAM H. JOHNSON, JR.[1]

In consideration of a structural relationship to morphine, ten secondary and tertiary acetates and propionates of α-(2-dialkylaminoethyl)-benzyl alcohols have been prepared. The intermediate β-dialkylaminopropiophenones were obtained by means of the Mannich reaction. From these ketones, the secondary and tertiary benzyl alcohols were made, respectively, by catalytic reduction and by treatment with ethylmagnesium bromide. Acylation of the secondary alcohols using a trace of sulfuric acid gave the desired esters. However, the tertiary alcohols were dehydrated by this procedure. The structure of one of the products, 1-dimethylamino-3-phenyl-2-pentene, was established by ozonization. The desired tertiary esters were prepared by addition of the acyl chloride to the sodium salt of the alcohol. α-(2-Dimethylaminoethyl)-α-ethylbenzyl alcohol was unexpectedly acetylated and not dehydrated by means of a boiling mixture of acetic anhydride and acetic acid, thus suggesting a possibly superior method for obtaining other, related tertiary esters. The esters were tested as possible analgetic agents. Available pharmacological results failed to indicate any promising activity. Speculations have been made concerning this inactivity.

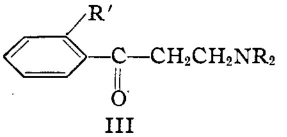
Discussion

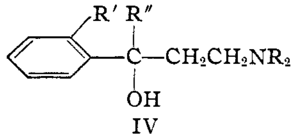
In view of the recent studies of those who have found analgetic activity of a high order in acylated piperidinol derivatives (*e.g.*, I),[2,3] we decided to prepare some related open chain esters (*e.g.*, II). Just as the structure I has been shown[2] to simulate the morphine skeleton, II can be shown to have a similar relationship.


I


II

Intermediate β-dialkylaminopropiophenones (III) were prepared by means of the Mannich reaction.[4] These Mannich ketone hydrochlorides were either reduced using Raney nickel or Adams catalyst to the secondary α-(2-dialkylaminoethyl)-benzyl alcohols (IV)[5] or were treated with ethylmagnesium bromide to give the corresponding tertiary alcohols (IV).[6]


III


IV

NR_2 = dimethylamino, piperidyl or morpholinyl; R′ = H or CH_3; R″ = H or CH_2CH_3

The six esters of secondary benzyl alcohols (Table I) were easily prepared with either acetic or propi-

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[1] Research Fellow, Parke, Davis and Company, 1949–1950. Tennessee Eastman Corp., Kingsport, Tenn.

[2] Ziering, Berger, Heineman and Lee, *J. Org. Chem.*, **12**, 894 (1947).

[3] Jensen, *et al.*, *C.A.*, **39**, 2506 (1945).

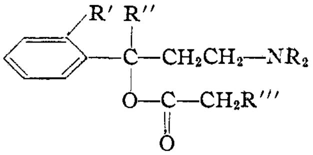
[4] Blicke, "Organic Reactions," Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1942, p. 303.

[5] If the temperature was elevated above 50°, we observed that a secondary reaction became important. Propiophenone in good yield resulted presumably through hydrogenolysis or through reduction of phenyl vinyl ketone formed by decomposition of the Mannich ketone hydrochloride. [See Burckhalter and Fuson, THIS JOURNAL, **70**, 4184 (1948).] But even at room temperature, Winstein, *et al.*, *J. Org. Chem.*, **11**, 215 (1946), reported a hydrogenolysis in the presence of Raney nickel of the analogous 1-naphthyl Mannich base to 1-propionaphthone.

[6] After one of the tertiary alcohols, α-(2-dimethylaminoethyl)-α-ethylbenzyl alcohol, had been prepared, its synthesis was reported by Denton, Neier and Lawson, THIS JOURNAL, **71**, 2053 (1949).

TABLE I

ESTERS OF α-(2-DIALKYLAMINOETHYL)-BENZYL ALCOHOLS



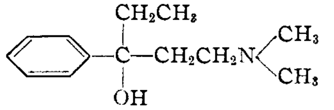
Recrystallizing solvents: compounds 1 and 6, isopropyl alcohol; 2 and 9, ether–ethyl alcohol; 3 and 5, ether–isopropyl alcohol; 4, ethyl alcohol; 7, acetone; 8 and 10, acetone–ether.

	R'	R''	R'''	NR₂	Formula	M.p., °C.	Yield,[a] %	Proced.	Chlorine, % Calcd.	Chlorine, % Found
1	H	H	H	$N(CH_3)_2$	$C_{13}H_{19}NO_2 \cdot HCl$	162	63	A	13.76	13.76
2	H	H	CH_3	$N(CH_3)_2$	$C_{14}H_{21}NO_2 \cdot HCl \cdot H_2O$	120	33[b]	A	12.23	12.30
3	H	H	H	NC_5H_{10}	$C_{16}H_{23}NO_2 \cdot HCl$	204	74	A	11.90	11.91
4	H	H	CH_3	NC_5H_{10}	$C_{17}H_{25}NO_2 \cdot HCl$	210	74	A	11.37	11.50
5	H	H	H	NC_4H_8O	$C_{15}H_{21}NO_3 \cdot HCl$	192	84	A	11.83	11.93
6	H	H	CH_3	NC_4H_8O	$C_{16}H_{23}NO_3 \cdot HCl$	189	83	A	11.31	11.41
7	H	C_2H_5	H	$N(CH_3)_2$	$C_{15}H_{23}NO_2 \cdot HCl$	188	44[c]	B	12.41	12.53
8	H	C_2H_5	CH_3	$N(CH_3)_2$	$C_{16}H_{25}NO_2 \cdot HCl$	150	64[d]	B	11.87	11.88
9	CH_3	C_2H_5	H	$N(CH_3)_2$	$C_{16}H_{25}NO_2 \cdot HCl$	206	52[e]	B	11.87	11.91
10	CH_3	C_2H_5	CH_3	$N(CH_3)_2$	$C_{17}H_{27}NO_2 \cdot HCl$	176	29[f]	B	11.37	11.45

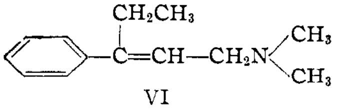
[a] Based on Mannich ketone hydrochloride. [b] Low yield resulted from hygroscopicity of sample. [c] 60% yield of free base; b.p. 126° (1 mm.). [d] 90% yield of free base; b.p. 124° (3 mm.). [e] 67% yield of free base; b.p. 110° (3 mm.). [f] 47% yield of free base; b.p. 140° (4 mm.).

onic anhydride and a trace of sulfuric acid, according to a method used previously.[2,7] With tertiary alcohols, the same procedure produced only olefinic compounds, and the action of the anhydride directly on the Grignard complex, which had been successful in the esterification of analogous compounds,[2] led to unsaturation. However, the four esters of tertiary alcohols (II and Table I) were prepared by addition of an acyl chloride to the sodium salt of the alcohol.[8] Also, surprisingly, treatment of the tertiary alcohol V in boiling acetic anhydride and acetic acid, a process designed to effect dehydration,[9] actually resulted in an 80% yield of the desired ester (see Table I, Compound 7).

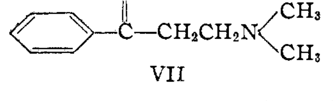
Attempted esterification of V by means of an acid anhydride and a trace of sulfuric acid resulted in dehydration, resulting in a 45% yield of a compound of structure VI or VII. The same unsaturated product was obtained in 28% yield from the attempted acylation of the Grignard complex, which could also be hydrolyzed to give V. Finally, the olefin was prepared in 80% yield by dehydration of V with 25% sulfuric acid. That VI is the exclusive or principal product of the dehydration of V has been demonstrated by ozonization of the unsaturated compound to give propiophenone, while no β-dimethylaminopropiophenone indicative of VII could be isolated.



V



VI



VII

Pharmacological Studies.—Data obtained by Dr. C. V. Winder, of Parke, Davis and Company, do not indicate any important analgetic activity of the ten esters in guinea pigs. Morpholinyl compounds 5 and 6 of the table possess a statistically significant effect intraperitoneally at 200 mg./kg. in water, but mild tremors, restlessness and weakness were noted. The esters of the tertiary alcohols, compounds 7, 8, 9 and 10, at the same dose level, led to convulsions and death.

Negative pharmacological results with type II compounds appear to indicate that the opening of the piperidine ring of I abolishes the rigidity of the molecule, which may be responsible for the analgetic effect of such compounds as I and morphine.

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

Experimental[10]

β-Dialkylaminopropiophenones (III).—The preparative procedure used is essentially that of Maxwell.[11] Three of the Mannich ketones had been previously described.[4]

β-Dimethylamino-o-methylpropiophenone Hydrochloride.—o-Methylacetophenone was prepared according to a procedure already described[12] in a yield of 73.5 g. (64%) from 100 g. of o-tolunitrile. Only a 39% yield of the same ketone was obtained by adding o-tolylmagnesium bromide to an ether solution of acetyl chloride, according to a general method of Gilman and Mayhue.[13]

By the procedure of Maxwell,[11] 43.5 g. of o-methylacetophenone, 30 g. of dimethylamine hydrochloride, 15 g. of paraformaldehyde and 20 ml. of alcohol gave 44 g. (58% yield) of white crystalline hydrochloride; m.p. 156°, from acetone.

Anal. Calcd. for $C_{12}H_{17}NO \cdot HCl$: Cl, 15.57. Found: Cl, 15.60.

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[7] Burckhalter, *et al.*, THIS JOURNAL, **68**, 1896 (1946).

[8] Lee, *et al.*,[2] without isolating the tertiary alcohol, added an acid anhydride directly to the reaction mixture containing the lithium salt which had formed in the preceding step.

[9] Riegel, Moffett and McIntosh, *Org. Syntheses*. **24**, 41 (1944).

[10] C and H analyses by Mr. Charles Beazley, Skokie, Illinois.

[11] Maxwell, *Org. Syntheses*, **23**, 30 (1943).

[12] Borsche and Wagner-Roemmich, *Ann.*, **546**, 273 (1941).

[13] Gilman and Mayhue, *Rec. trav. chim.*, **51**, 47 (1932).

Secondary α-(2-Dialkylaminoethyl)-benzyl Alcohols.—All the basic secondary alcohols were prepared by reducing 50 g. of the Mannich ketone hydrochloride in water solution with either Raney nickel or Adams catalyst at room temperature and under three to four atmospheres of hydrogen. The used catalyst was removed by filtration and the water removed on the steam-bath under reduced pressure. The liquid residue was solidified by trituration with acetone and then recrystallized from alcohol or isopropyl alcohol.

α-(β,4-Morpholinylethyl)-benzyl alcohol hydrochloride[14] could not be crystallized from the reduction mixture. The residue was rendered basic with ammonia, the free base extracted with ether, the extracts dried over potassium carbonate and then filtered. The ether was removed and the residue distilled at 165–170° (1–2 mm.), yielding 29 g. (67%) of oil which soon solidified. After recrystallization from a mixture of ethyl acetate and Skellysolve B, the product melted at 62°.

Anal. Calcd. for $C_{13}H_{16}NO_2$: N, 6.33. Found: N, 6.10.

The hydrochloride, prepared by passing dry hydrogen chloride into an ether solution of the base, was recrystallized from a mixture of acetone and ethyl acetate, m.p. 120°.

Anal. Calcd. for $C_{13}H_{16}NO_2 \cdot HCl$: Cl, 14.08. Found: Cl, 14.04.

α-(2-Dimethylaminoethyl)-α-ethyl-*o*-methylbenzyl Alcohol.—The preparative procedure is a variation of one recently reported.[6] The free base of 42 g. (0.183 mole) of β-dimethylaminopropiophenone hydrochloride was liberated from a water solution of the salt by the addition of excess ammonium hydroxide. The base was extracted with ether, the ether solution dried over potassium carbonate and the filtered solution added to a cooled solution of 0.4 mole of ethylmagnesium bromide. Then, 250 ml. of dry benzene was added and the temperature of the mixture slowly raised until the ether had been removed by distillation. The benzene solution was heated at reflux temperature for six hours, cooled and then treated with ammonium chloride solution. The benzene layer was washed with water, dried over potassium carbonate, filtered and heated under reduced pressure to remove the solvent. Distillation of the residue gave 27 g. (67% yield) of the colorless amine boiling at 100° (0.5 mm.).

Anal. Calcd. for $C_{14}H_{23}NO$: C, 75.97; H, 10.47. Found: C, 76.46; H, 9.73.

The hydrochloride, prepared in the customary manner and recrystallized from acetone, melted at 130°.

Anal. Calcd. for $C_{14}H_{23}NO \cdot HCl$: Cl, 13.75. Found: Cl, 13.80.

α-(2-Dimethylaminoethyl)-α-ethylbenzyl Alcohol (V).—This product, prepared in 63% yield by the foregoing procedure, boiled at 122° (5 mm.) and upon solidifying melted at 46°.

Anal. Calcd. for $C_{13}H_{21}NO$: C, 75.32; H, 10.21. Found: C, 75.28; H, 10.32.

By a variation of this procedure, the product had been isolated by Denton, Neier and Lawson[6] as the hydrochloride in 26% yield. For our purposes the free base was preferred; however, the hydrochloride, m.p. 125–126°, was prepared from the base in high yields.

Procedure A. Esters of Secondary Alcohols.—To 30 ml. of acetic or propionic anhydride, 15 g. of amino alcohol hydrochloride was added. The mixture was heated until the salt dissolved. To the hot solution two drops of sulfuric acid was added. The addition of acetone or ether precipitated the hydrochloride.

Procedure B. Esters of Tertiary Alcohols.—To 200 ml. of dry dioxane, the theoretical amount of metallic sodium was added and the mixture stirred and heated at reflux temperature until sodium sand resulted. About 0.2 mole of the tertiary alcohol was slowly added and refluxed until the sodium had reacted. The solution was cooled and a 10% excess of acid chloride slowly added. After refluxing for two hours, the mixture was cooled, water was added and the mixture was made basic to litmus. The solution was extracted four times with 75-ml. portions of ether, and the combined extracts were dried over potassium carbonate. The solvent was removed on the steam-bath, the residue was distilled under reduced pressure and the product converted in the usual manner to the hydrochloride.

α-(2-Diethylaminoethyl)-α-ethylbenzyl Acetate (Alternate Procedure for Compound 7).—A solution of 45 g. of α-(2-dimethylaminoethyl)-α-ethylbenzyl alcohol (V), 30 ml. of acetic anhydride and 50 ml. of glacial acetic acid was refluxed for three hours. The excess solvent was removed under reduced pressure and the residue distilled to yield 42 g. (80%) of a colorless liquid, b.p. 125–126° (0.7 mm.). Conversion of 24 g. to the hydrochloride gave 20 g., m.p. 188–189°.

1-Dimethylamino-3-phenyl-2-pentene (VI).—(a) In the manner of a related procedure,[2] the free base from 60 g. (0.28 mole) of β-dimethylaminopropiophenone hydrochloride was treated with 0.56 mole of ethylmagnesium bromide, and to the complex was added 65 g. (0.5 mole) of propionic anhydride. The reaction was very exothermic, and the color of the mixture changed from gray to yellow. An effective stirrer was required to disintegrate the solid material. At the end of three hours heating at reflux temperature, the mixture was treated with saturated ammonium chloride solution and extracted with benzene. The solvent was removed from the dried extracts, and the residue upon distillation gave 18 g. (28% yield) of a clear liquid, b.p. 92° (2 mm.). Its hydrochloride melted at 160° after recrystallization from acetone.

Anal. Calcd. for $C_{13}H_{19}N \cdot HCl$: Cl, 15.71. Found: Cl, 15.82.

(b) When procedure A, the esterification method for secondary alcohols, was applied to α-(2-dimethylaminoethyl)-α-ethylbenzyl alcohol (V), a tertiary alcohol, an ester was not obtained. Instead a pure sample of the pentene (VI) hydrochloride was prepared in 45% yield.

(c) A mixture of 36 g. (0.18 mole) of α-(2-dimethylaminoethyl)-α-ethylbenzyl alcohol (V) and 100 ml. of 25% sulfuric acid solution was refluxed for two hours. The solution was cooled and made basic with alkali. The precipitated oily layer was separated and then combined with ether extracts of the water layer. The combined extracts were washed with water and dried over magnesium sulfate. The ether was removed on a steam-bath and the residual oil distilled giving 28 g. (80%) of a water white liquid; b.p. 76° (0.5 mm.). A small amount converted to the hydrochloride proved to be identical with that of VI.

Ozonization of 1-Dimethylamino-3-phenyl-2-pentene.—A solution of 29 g. of the pentene was dissolved in carbon tetrachloride and treated with ozone. The solution absorbed ozone beyond the calculated time, and a viscous oil considered to be the ozonide began to form. The oil was refluxed with water for an hour; the mixture was cooled and then extracted with ether. After the ether extract was washed with three 50-ml. portions of 10% hydrochloric acid, it was dried over potassium carbonate. Removal of the ether from the filtered solution left a residue which yielded 6 g. of propiophenone; b.p. 66–69° (0.5 mm.). The identity of this ketone was confirmed by preparation of its 2,4-dinitrophenylhydrazone; m.p. 188°.[15]

The acid layer was made basic with ammonium hydroxide and extracted with ether. An oily hydrochloride was precipitated from the dried ether solution by hydrogen chloride. It could not be crystallized even when seeded with the hydrochloride of β-dimethylaminopropiophenone.

LAWRENCE, KANSAS RECEIVED MARCH 26, 1951

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[14] The other basic secondary alcohols have been reported by Mannich and Lammering, *Ber.*, **55**, 3510 (1922).

[15] Shriner and Fuson, "Identification of Organic Compounds," 3rd ed., John Wiley and Sons, Inc., New York, N. Y., 1948, p. 263.