[Contribution from the Laboratory of Organic Chemistry of the University of Wisconsin]

Base-induced Reactions of Certain Benzyl Esters

By S. M. McElvain and Melvin M. Olson

The course of the reaction of benzyl cyanoacetate (I), benzyl benzylcyanoacetate (VII) and benzyl dibenzylcyanoacetate (IX) with sodium benzyl oxide in benzyl alcohol solution has been determined. The benzyl (ester) group of each of these esters is removed by anions present in the respective reaction mixtures to give benzylation products. With I and VII, the action of the base is catalytic and carbon dioxide far in excess of the amount of base present is evolved. With the ester IX, the reaction with sodium benzyl oxide is stoichiometric and yields dibenzylacetonitrile and sodium benzyl carbonate in high yields along with a lesser amount of dibenzyl ether. Benzyl cyanoacetate reacts with sodium acetate in acetic acid solution to yield carbon dioxide, benzyl acetate and acetonitrile.

In the course of some earlier work in this Laboratory the preparation of benzyl benzylcyanoacetate from the corresponding methyl ester was attempted through an alcohol exchange in the presence of a catalytic amount of sodium benzyl oxide.[1] Although the theoretical amount of methyl alcohol was formed, distillation of the reaction mixture was accompanied by extensive evolution of carbon dioxide and the formation of hydrocinnamonitrile, dibenzylacetonitrile and benzyl dibenzylcyanoacetate; the desired benzyl ester was obtained only in low yields. Removal of the sodium benzyl oxide before the distillation raised the yields of the esters and lowered the yields of the nitriles. The benzylating agent in these reactions was thought to be benzyl alcohol, although the function of the base remained unexplained.[2]

In an attempt to arrive at more definite conclusions as to the nature of these base-induced reactions, a study of the action of sodium benzyl oxide in benzyl alcohol solution on benzyl cyanoacetate (I), benzyl benzylcyanoacetate (VII), and benzyl dibenzylcyanoacetate (IX) was undertaken. The results of this work, which are now reported, show that each of these esters, although thermally stable in the absence of this base, undergoes characteristic benzylations and decarboxylations when the base is present. With I and VII the action of the base appears to be catalytic; with IX stoichiometric amounts of the base are required.

Benzyl cyanoacetate (I) showed the most complex reaction pattern. When it was heated to 170–180° in benzyl alcohol containing eighteen mole per cent. of sodium benzyl oxide, carbon dioxide (53%) was evolved while a mixture of acetonitrile (28.5%) and toluene[3] collected in a cold trap. Acidification of the reaction mixture caused some evolution of carbon dioxide (5.6%) and the separation of a large amount of an amorphous compound. Distillation of the remaining material yielded: 2.4% of hydrocinnamonitrile (XI), 3.5% of dibenzylacetonitrile (XIII), and 1.5% of benzyl dibenzylcyanoacetate (IX). The amorphous material, which forms a copper enolate, appears to be a polycondensation product (XV) of benzyl cyanoacetate.

The formation of the relatively large amount of the polymeric material (XV, in reaction (13)) made the resolution of this reaction mixture difficult and doubtless was responsible for the failure to find a closer correspondence between the amount of carbon dioxide (58.6%) evolved and the total amounts (34.4%) of the nitriles IV, XI and XIII isolated. In the hope that the use of a weaker base might not produce this polycondensation, the ester I was heated in glacial acetic acid with one equivalent of anhydrous sodium acetate. From this reaction carbon dioxide (77.5%), acetonitrile (57.5%) and benzyl acetate (88.5%) was obtained; only a trace of polymeric material was formed. The ester I was unaffected when heated alone in acetic acid solution.

These reactions indicate that benzyl cyanoacetate undergoes a series of reactions, all of which are initiated by the attack and removal of the benzyl group by a base, followed by the decarboxylation of the resulting cyanoacetate anion. With sodium acetate (reactions (1) and (2)) the reaction is relatively simple and uncomplicated, but with the stronger base, sodium benzyl oxide, which may generate ester anions VI and VIII, additional reactions ((6)–(12)) are encountered.

$$\underset{\text{I}}{\mathrm{CHCH_2COOCH_2C_6H_5}} + \mathrm{CH_3COO{\ominus}} \longrightarrow \underset{\text{II}}{\mathrm{CH_3COOCH_2C_6H_5}} + \underset{\text{III}}{\mathrm{CNCH_2COO{\ominus}}} \tag{1}$$

$$\text{III} \xrightarrow{\mathrm{CH_3COOH}} \mathrm{CO_2} + \underset{\text{IV}}{\mathrm{CH_3CN}} \tag{2}$$

$$\text{I} + \underset{\text{V}}{\mathrm{C_6H_5CH_2O{\ominus}}} \longrightarrow \mathrm{(C_6H_5CH_2)_2O} + \text{III} \tag{3}$$

$$\text{III} + \mathrm{C_6H_5CH_2OH} \longrightarrow \mathrm{CO_2} + \text{IV} + \text{V} \tag{4}$$

$$\text{I} + \text{V} \longrightarrow \underset{\text{VI}}{\mathrm{CN{\ominus}CHCOOCH_2C_6H_5}} + \mathrm{C_6H_5CH_2OH} \tag{5}$$

$$\text{I} + \text{VI} \longrightarrow \underset{\text{VII}}{\mathrm{C_6H_5CH_2CH(CN)COOCH_2C_6H_5}} + \text{III} \longrightarrow \textit{via}\ (4) \tag{6}$$

$$\text{VII} + \text{V} \longrightarrow \underset{\text{VIII}}{\mathrm{C_6H_5CH_2C{\ominus}(CN)COOCH_2C_6H_5}} + \mathrm{C_6H_5CH_2OH} \tag{7}$$

$$\text{VIII} + \text{I} \longrightarrow \underset{\text{IX}}{\mathrm{(C_6H_5CH_2)_2C(CN)COOCH_2C_6H_5}} + \text{III} \longrightarrow \textit{via}\ (4) \tag{8}$$

$$\text{VII} + \text{VIII} \longrightarrow \text{IX} + \underset{\text{X}}{\mathrm{C_6H_5CH_2CH(CN)COO{\ominus}}} \longrightarrow \underset{\text{XI}}{\mathrm{C_6H_5CH_2CH_2CN}} + \mathrm{CO_2} \tag{9}$$

$$\text{VII} + \text{V} \longrightarrow \mathrm{(C_6H_5CH_2)_2O} + \text{X} \xrightarrow{\mathrm{C_6H_5CH_2OH}} \text{XI} + \text{V} + \mathrm{CO_2} \tag{10}$$

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[1] S. M. McElvain and J. P. Schroeder, This Journal, 71, 47 (1949).

[2] In the same work (ref. 1) it was found that benzyl bromide converted methyl α-cyano esters to benzyl esters, which in turn underwent further reaction with loss of carbon dioxide to yield the same benzylated nitriles and esters as were obtained in the alcohol exchange reactions. These benzyl bromide benzylations were postulated as free radical reactions. This interpretation has received some substantiation in the recently reported inhibition of such reactions by hydroquinone (H. R. Snyder, E. L. Eliel and R. E. Carnahan, This Journal, 72, 2958 (1950)).

[3] The toluene was found to originate from the reduction of benzyl alcohol by sodium during the preparation of sodium benzyl oxide.

$$\mathrm{IX} + \mathrm{V} \longrightarrow \underset{\mathrm{XII}}{(C_6H_5CH_2)_2C(CN)COO^{\ominus}} + (C_6H_5CH_2)_2O \quad (11)$$

$$\mathrm{XII} + C_6H_5CH_2OH \longrightarrow \underset{\mathrm{XIII}}{(C_6H_5CH_2)_2CHCN} + \underset{\mathrm{XIV}}{C_6H_5CH_2OCOO^{\ominus}} \quad (12)$$

$$n\text{-}CNCH_2COOCH_2C_6H_5 \xrightarrow{\mathrm{V}} \xrightarrow{H_3O^+} \underset{\mathrm{XV}}{CNCH_2CO[CH(CN)CO]_{n-2}CH(CN)COOCH_2C_6H_5} \quad (13)$$

When benzyl benzylcyanoacetate (VII) was heated in benzyl alcohol containing twenty mole per cent. of sodium benzyl oxide, carbon dioxide was evolved at temperatures above 160°. Cooling and acidification of the reaction mixture produced additional carbon dioxide in an amount approximately equivalent to the base originally present in the benzyl alcohol. The total yield of carbon dioxide was 69%. Distillation of the reaction products yielded 40.4% of hydrocinnamonitrile (XI), 25.4% of dibenzylacetonitrile (XIII) and 26.8% of benzyl dibenzylcyanoacetate (IX). When this reaction was repeated using only five mole per cent. of sodium benzyl oxide the yields of carbon dioxide, XI, XIII and IX were 63, 40.7, 23.1 and 29.8%, respectively. Thus the catalytic effect of the base is apparent. No polymeric material similar to that represented by XV was formed in the reaction of VII. This fact indicates the validity of the postulated reaction (13) to account for the formation this material in the reaction of I, as the ester VII with a single α-hydrogen would not yield a polycondensation product, such as XV, that could form a metal enolate.

It should be noted that there is a close correspondence between the yields of carbon dioxide (69 and 63%) and the combined yields (65.8 and 63.8%) of the decarboxylation products, XI and XIII, in the two reactions of VII with different amounts of sodium benzyl oxide reported above. It should also be pointed out that the presence of such relatively large amounts of acetonitrile (IV) among the products of the reaction of the ester I and of hydrocinnamonitrile (XI) from the reaction of VII indicate that the benzylation reactions are predominantly *inter*molecular rather than *intra*molecular, as originally suggested,[1] since these simpler nitriles could not be formed in the latter type of reaction.

The reaction of benzyl dibenzylcyanoacetate (IX) followed a significantly different reaction course with sodium benzyl oxide (reactions (11) and (12)) than those taken by I and VII. With IX the reaction was not catalytic and no carbon dioxide was evolved from the basic solution, but acidification of the reaction mixture produced this gas in amounts equivalent to the base present in the reaction mixture. From the reaction of IX with one equivalent of sodium benzyl oxide in benzyl alcohol were obtained: carbon dioxide (91%, after acidification), dibenzyl acetonitrile (92.5%), dibenzyl ether (39%), and a higher boiling oil, which doubtless resulted from the polymerization of the dibenzyl ether.[4] The carbon dioxide was held in the form of sodium benzyl carbonate, the separation of which caused the reaction mixture to gel as the reaction proceeded. When twenty-five mole per cent. of the base was used with IX, an equivalent amount of the ester reacted in the manner just described; the remainder of IX was recovered. It thus appears that the anion (XII), which is formed by the nucleophilic attack of the benzyloxy anion (V) on the benzyl (ester) group of IX (reaction (11)), does not spontaneously decarboxylate as the anions III and X appear to do, but instead undergoes alcoholysis (reaction (12)) to yield the nitrile (XIII) and the benzyl carbonate anion (XIV).

The absence of any detectable amounts of dibenzyl ether among the reaction products of I and VII indicates that the postulated reactions (3) and (10), which involve an attack of the benzyloxy anion (V) on the ester benzyl group of these esters, are relatively insignificant. Instead, the base V produces the anions VI and VIII (reactions (5) and (7)); VI may then polycondense to anions of XV which along with VI may be benzylated by I to produce IV and regenerate V; an attack of the anion VIII on the ester VII produces IX, XI and XIII, the combined yields of which represent 93% of the amount of VII put into the reaction. The inability of the trisubstituted acetic ester IX to form an ester anion doubtless accounts for its relatively simple behavior. In this reaction the only base present is V and as consequence the reactions of IX are confined to (11) and (12).

Experimental

Benzyl Cyanoacetate (I).—In a 5-l. round-bottomed flask, 500 g. (5.3 moles) of chloroacetic acid was dissolved in 700 ml. of water. The solution was warmed to 50° and neutralized with anhydrous sodium carbonate. To this solution was added a solution of 294 g. (5.8 moles) of sodium cyanide in 750 ml. of water, which was previously warmed to 55°. The temperature of the reaction mixture was kept below 95° by external cooling. After the heat of reaction subsided, the solution was heated to boiling for five minutes and then cooled. Cyanoacetic acid was liberated from the filtered solution by the addition of 600 ml. (5.8 moles) of concentrated hydrochloric acid and extracted from the aqueous solution with ether.

After drying the ether extract and distillation of the ether, the remaining crystalline cyanoacetic acid was treated with 573 g. (5.3 moles) of benzyl alcohol and this mixture was heated at 60–70° under a pressure of about 25 mm. with stirring. When no more water distilled from the reaction mixture, it was washed with water and the organic layer dried over Drierite. Distillation gave 408 g. (44.1%) benzyl cyanoacetate, $n^{25}\mathrm{D}$ 1.5173, b.p. 100–105° (0.2 mm.).

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.6; H, 5.2; N, 8.0. Found: C, 68.6; H, 5.3; N, 8.0.

On standing, the ester solidified into large transparent crystals, m.p. 28–29°.

Benzyl Benzylcyanoacetate (VII) and Benzyl Dibenzylcyanoacetate (IX).—In a 2-l., three-neck flask equipped with a dropping funnel, a mercury-seal stirrer, and a reflux condenser protected by a calcium chloride tube, was placed 18 g. (0.75 mole) of sodium hydride and the system filled with nitrogen. The flask then was half filled with absolute ether and 131.3 g. (0.75 mole) of benzyl cyanoacetate was added slowly through the dropping funnel. When evolution of hydrogen had ceased the ether suspension of the sodium enolate was cooled in an ice-bath and 128.3 g. (0.75 mole) of benzyl bromide added. The mixture was allowed to stand in an ice-bath overnight and at room temperature for three days. It was then worked up by adding water, extracting with ether, washing the ether layer successively with 5% hydrochloric acid and water, drying over anhydrous sodium sulfate and distilling. The following fractions were collected: (1) 9.4 g., b.p. 48–118° (0.6 mm.); (2) 37.6 g. (28.5 %) of benzyl cyanoacetate b.p. 118° (0.6 mm.), $n^{25}\mathrm{D}$ 1.5187; (3) 2.2 g., b.p. 118° (0.6 mm.) to 158° (0,18 mm.),

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[4] *Cf.* A. Lachman, THIS JOURNAL, 45, 2358 (1923).

n^{25}_{D} 1.5276; (4) 50.5 g. (25.4%) of benzyl benzylcyanoacetate (VII) b.p. 158° (0.18 mm.) to 175° (0.35 mm.); and (5) 76 g. (28.6%) of benzyl dibenzylcyanoacetate (IX), b.p. 175° (0.35 mm.) to 202° (0.2 mm.); m.p. 89–91°. After recrystallization from ethanol, fraction (5) melted at 92°.

The above preparation was repeated with the same quantities of materials but with a reverse order of addition, 58.5 g. (29.5%) of VII and 47 g. (17.6%) of IX were obtained.

Reaction of Benzyl Cyanoacetate (I) with Sodium Benzyloxide.—A 500-ml. round-bottomed flask was equipped with a stirrer for operation under diminished pressure, a dropping funnel, and a condenser set for distillation and carrying a receiver attached to two Dry Ice–acetone cold traps and a bank of Ascarite tubes protected from the atmosphere by a soda-lime tube. In the flask was placed 3.64 g. of sodium and the entire apparatus filled with nitrogen. Then 114 g. of anhydrous benzyl alcohol was added to the sodium. After the sodium had dissolved, 152.4 g. (0.871 mole) of benzyl cyanoacetate was added and the mixture was stirred and heated to 170–180° for six hours. The system was then flushed with nitrogen to carry over all the evolved carbon dioxide into the Ascarite tubes. The gain in weight of these tubes indicated 20.26 g. (0.460 mole) of carbon dioxide had been evolved. The cold traps and receiver had collected 14.34 g. of liquid. A portion of the combined condensate was extracted with water until saturation of the aqueous extract with sodium bicarbonate no longer caused the separation of a layer. The acetonitrile thus obtained from the aqueous extract, after drying over Drierite, boiled at 78–80°, n^{25}_{D} 1.3443. The water insoluble layer was toluene; m.p. of 2,4-dinitro derivative 70–71°. Analysis (Kjeldahl) of the remainder of the combined condensate showed 24.8% nitrogen, indicating that it originally contained 10.15 g. (28.5%) of acetonitrile and 4.19 g. of toluene.

Acidification of the reaction mixture with 13 ml. of concentrated hydrochloric acid caused the release of more carbon dioxide, which was swept into the Ascarite tubes by a stream of nitrogen. The gain in weight shown by the Ascarite tubes was 1.03 g. The precipitated sodium chloride was removed from the reaction mixture by centrifugation and washed with ether. The ether washings were combined with the benzyl alcohol solution and distilled. After the ether and a small amount of water had been removed, 120.6 g. of benzyl alcohol was collected. The residue was exhaustively extracted with anhydrous ether to leave 18.76 g. of an orange-yellow powder.

The ether extracts were combined and distilled. After the ether had been removed, the following fractions were collected: (a) 7.18 g., b.p. 62° (1.5 mm.) to 87° (2 mm.), n^{25}_{D} 1.5358; (b) 2.57 g., b.p. 87–102° (2 mm.), n^{25}_{D} 1.5268; (c) 10.45 g., b.p. 105–163° (1.5 mm.), n^{25}_{D} 1.5448; (d) 8.15 g. (solid), b.p. 163° (1.5 mm.) to 180° (1.3 mm.); (e) 2.28 (solid), b.p. 180° (1.3 mm.) to 190° (2.0 mm.); (f) 41.94 g. tarry residue, remained. During this distillation an Ascarite tube in the system gained 1.18 g. to make the total yield of carbon dioxide 22.47 g. (58.6%). Fractions (a) and (b) were combined and redistilled to yield (1) 5.61 g. of benzyl alcohol, b.p. 91–91.5° (11 mm.), n^{25}_{D} 1.5373; (2) 0.22 g., b.p. 91.5–93° (11 mm.), n^{25}_{D} 1.5372; (3) 0.22 g., b.p. 93–119° (11 mm.), n^{25}_{D} 1.5317; (4) 0.56 g., 119–121.5° (11 mm.), n^{25}_{D} 1.5220, 9.31% N, (5) 1.66 g. of liquid, b.p. 121.5–122° (11 mm.), n^{25}_{D} 1.5210, 10.3% N (calcd. for hydrocinnamonitrile, 10.7%).

Fractions (a) and (b) were thus shown to be mixtures of benzyl alcohol and hydrocinnamonitrile. Calculations based upon refractive index and nitrogen content showed fractions (a) to be 1.03 g. of hydrocinnamonitrile and 6.15 g. of benzyl alcohol for a total of 2.73 g. (2.4%) of hydrocinnamonitrile.

Fractions (c), (d) and (e) were allowed to crystallize in the refrigerator. The solids were removed from all three fractions by filtration and recrystallized from 95% ethanol. In this manner 6.66 g. (3.5%) of dibenzylacetonitrile, m.p. 91–92°, was obtained.

Fraction (f) was extracted by stirring for several days with absolute ether. A red, insoluble powder remained which was separated by centrifugation and washed several times with anhydrous ether. After drying overnight in a vacuum desiccator, the powder weighed 7.82 g. and contained 10% nitrogen. These ether extracts and washings were combined; removal of the ether left 32.59 g. of a residue containing 7.80% nitrogen. Attempted fractional distillation of an aliquot of this material was unsuccessful due to decomposition. A 6.1-g. aliquot was then steam distilled using steam superheated to 250° and introduced into the mixture through an orifice small enough to allow a reduced pressure of 15 mm. in the distilling flask. The outlet of the flask was attached to a long air-cooled condenser leading to a receiver surrounded by an ice-bath and attached to an aspirator. The steam was superheated by a system similar to that described by Morton.[5] The solid whch appeared in the condenser was crystallized from 95% ethanol. In this way 0.85 g. of benzyl dibenzylcyanoacetate and 0.38 g. of a very light flaky solid, m.p. 106–107.5°, and which was not investigated further, were obtained. The amount of benzyl dibenzylcyanoacetate thus shown to be present in the 32.59 g. of residue was 4.59 g. (1.46%).

The orange-yellow amorphous, ether-insoluble powder, which was obtained after removal of the benzyl alcohol from the original reaction mixture, was insoluble in water, petroleum ether, benzene and chloroform. It was quite soluble in benzyl alcohol but only slightly soluble in methanol or ethanol; it could not be recrystallized from any of these solvents. It gave a small amount of an oil when sublimed at 265° and 0.2 mm. and left a carbonaceous residue. The amorphous powder was partially soluble in 5% aqueous sodium hydroxide solution but insoluble in saturated bicarbonate solution. The material which dissolved in 5% sodium hydroxide was precipitated by acidification. The general properties of the precipitate were the same as those of the original amorphous powder. An attempted acid cleavage using concentrated sulfuric acid failed to yield any volatile material during six hours of heating to 180–200°. Attempted cleavage with 45% aqueous sodium hydroxide as well as with 10% ethanolic sodium ethoxide gave no identifiable products.

It was found that addition of methanolic cupric acetate to a solution of the amorphous powder in the same solvent gave a greenish-brown precipitate. Accordingly 2.5 g. of the powder was treated with boiling methanol and filtered. A saturated methanolic solution of copper acetate was added dropwise until no more precipitate occurred. The precipitate weighed 0.74 g. after drying in a vacuum desiccator overnight. This precipitate was then washed several times with absolute methyl alcohol and dried at 100° and 0.5 mm. pressure for six hours. This material gave the following analytical data: C, 58.18; H, 3.95; N, 10.6; Cu, 10.4; calcd. for XV (n = 2): C, 57.19; H, 3.32; N, 10.3; Cu, 11.6.

Reaction of Benzyl Cyanoacetate (I) with Sodium Acetate in Acetic Acid.—The apparatus used in this reaction was the same as that described below for the reaction of benzyl benzylcyanoacetate with sodium benzyloxide. A mixture of 34.85 g. (0.20 mole) of benzyl cyanoacetate, 16.4 g. (0.20 mole) of anhydrous sodium acetate, 12 g. (0.20 mole) of glacial acetic acid was heated at 150–165° for six hours during which time carbon dioxide was evolved and 4.71 g. (57.5%) of acetonitrile, b.p. 75–83°, distilled from the reaction. At the end of the heating period the system was swept with nitrogen until no further heating of the Ascarite tubes was noted. The total gain in weight of these tubes was 6.81 g., indicating a 77.5% yield of carbon dioxide. The reaction mixture was treated with 5% hydrochloric acid in an amount equivalent to the sodium acetate used and extracted with ether. After drying over Drierite and removal of the ether, distillation of the residue yielded 26.57 g. (88.5%) of benzyl acetate, b.p. 103° (20 mm.) to 62° (0.6 mm.), n^{25}_{D} 1.4994.

Reaction of Benzyl Benzylcyanoacetate (VII) with Sodium Benzyl Oxide.—A 500-ml. round-bottomed flask was fitted with a stirrer through a rubber sleeve, a dropping funnel, and a condenser set for downward distillation; the condenser was connected to a receiver attached through a Dry Ice–acetone cold trap to a series of five Ascarite tubes. After the entire system had been swept with nitrogen, 0.87 g. (0.038 g. atom) of sodium was placed in the flask and to it was added 90.2 g. of benzyl alcohol. After the sodium had dissolved 50.3 g. (0.19 mole) of benzyl benzylcyanoacetate was added. The mixture was heated with stirring; at 160° gas evolution began and the Ascarite tubes became warm. The reaction mixture was kept at 160–168° for four hours, and during the last hour the system was flushed with nitrogen. The reaction mixture then was acidified with 45 ml.

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[5] A. A. Morton, "Laboratory Technique in Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1938, pp. 144.

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]

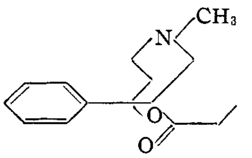
Esters of α-(2-Dialkylaminoethyl)-benzyl Alcohols

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.



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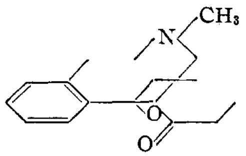
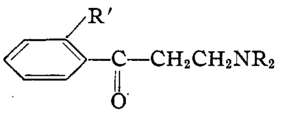
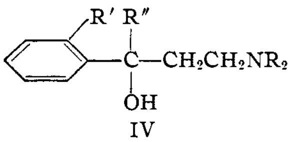


II

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).