[A CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Ketene Acetals. XX. The Preparation and Properties of Cyanoketene Acetals. Some Novel Benzylation Reactions

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In previous papers of this series benzylations of ketene diethylacetal[2] (I) and various alkyl- and phenylketene dimethylacetals[3] (VII) with benzyl bromide were reported. In each of these alkylations the reaction proceeded to the formation of disubstituted acetic esters (VI and IX), *i.e.*, the unsubstituted ketene acetal was dibenzylated, presumably through the intermediate ketene acetal IV ($R = C_6H_5CH_2$), while the monosubstituted ketene acetals (VII, X is *n*-propyl, *n*-heptyl or phenyl) yielded only monobenzylated products

$$\begin{tikzcd}
\underset{\text{I}}{CH_2{=}C(OC_2H_5)_2} \arrow[r, "RBr"] & \underset{\text{II}}{[RCH_2{-}CBr(OC_2H_5)_2]} \arrow[r] \arrow[dl, "-HBr"'] & \underset{\text{III}}{RCH_2COOC_2H_5 + C_2H_5Br} \\
\underset{\text{IV}}{RCH{=}C(OC_2H_5)_2} \arrow[r, "RBr"] & \underset{\text{V}}{[R_2CHCBr(OC_2H_5)_2]} \arrow[r] & \underset{\text{VI}}{R_2CHCOOC_2H_5 + C_2H_5Br}
\end{tikzcd}$$

$$\underset{\text{VII}}{XCH{=}C(OCH_3)_2} + RBr \longrightarrow \underset{\text{VIII}}{[XCHR{-}CBr(OCH_3)_2]} \longrightarrow \underset{\text{IX}}{XCHRCOOCH_3 + CH_3Br}$$

Inasmuch as there appeared to be no tendency for the intermediate VIII to lose hydrogen bromide as did II, even when X is phenyl, it seemed of interest to study the benzylation behavior of a ketene acetal containing the more negative cyano substituent.

Cyanoketene dimethylacetal (XI), as well as the homologous diethylacetal, was prepared by the pyrolysis of the corresponding orthoester (X). This pyrolysis is catalyzed by a trace of acid[4] as is the reverse reaction, the addition of alcohol to the ketene acetal

$$\underset{\text{X}}{CNCH_2C(OCH_3)_3} \overset{H^+}{\rightleftarrows} \underset{\text{XI}}{CNCH{=}C(OCH_3)_2} + CH_3OH$$

The reaction proceeds to the ketene acetal when X is heated and the alcohol removed by distillation; the orthoester is re-formed from its components at room temperature, but can be isolated only after the removal of all traces of the acid catalyst.[4]

Because of the tendency of ketene diethylacetals to lose ethylene on heating,[5] the reactions subsequently reported were carried out with cyanoketene *dimethyl*acetal (XI). This compound is a solid, m. p. 41–42°, which is surprisingly inert toward water; indeed, it may be recrystallized from this solvent. It dissolves in methanol with noticeable cooling. However, when a drop of hydrochloric acid is added to either an aqueous or methanolic solution of XI, the solution becomes warm and the ketene acetal is converted to methyl cyanoacetate or methyl orthocyanoacetate (X). Also, XI reacts with aniline, in a manner similar to ketene diethylacetal,[6] to yield methyl N-phenylcyanoiminoacetate, $CNCH_2C(OCH_3){=}NC_6H_5$.

A rapid reaction occurred when cyanoketene dimethylacetal (XI) was heated with one equivalent of benzyl bromide at 160–170°. Within thirty minutes, 97% of the halogen of the benzyl bromide was evolved as methyl bromide and distillation of the remaining reaction mixture yielded methyl cyanoacetate (XVI) (31%), methyl benzylcyanoacetate (XIII) (21%) and methyl dibenzylcyanoacetate (XV) (26%). It is apparent

$$\begin{tikzcd}
\underset{\text{XII}}{[C_6H_5CH_2CHCNCBr(OCH_3)_2]} \arrow[r] \arrow[d, "-HBr"'] & \underset{\text{XIII}}{C_6H_5CH_2CHCNCOOCH_3 + CH_3Br} \\
\underset{\text{XIV}}{C_6H_5CH_2C(CN){=}C(OCH_3)_2} \arrow[r, "C_6H_5CH_2Br"] & \underset{\text{XV}}{(C_6H_5CH_2)_2CCNCOOCH_3 + CH_3Br}
\end{tikzcd}$$

from these results that the cyano substituent causes the intermediate (XII), which corresponds to VIII and presumably is formed by the addition of benzyl bromide to XI, to undergo pyrolysis to the disubstituted ketene acetal (XIV) as well as to the monobenzylated ester (XIII). Further benzylation of XIV converts it to the trisubstituted acetic ester (XV). The methyl cyanoacetate (XVI) present in the reaction mixture results from the action of the hydrogen bromide lost by XII on cyanoketene acetal.[7]

$$CNCH{=}C(OCH_3)_2 + HBr \longrightarrow \underset{\text{XVI}}{CNCH_2COOCH_3} + CH_3Br$$

When cyanoketene acetal was heated with *two* equivalents of benzyl bromide at 170–180°, a steady evolution of methyl bromide continued

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[2] McElvain and Kundiger, THIS JOURNAL, **64**, 254 (1942).

[3] McElvain, Kent and Stevens, *ibid.*, **68**, 1922 (1946).

[4] McElvain and Schroeder, *ibid.*, **71**, 40 (1949).

[5] McElvain, *et al.*, *ibid.*, **64**, 2525 (1942); **68**, 1917 (1946).

[6] Barnes, Kundiger and McElvain, *ibid.*, **62**, 1281 (1940).

[7] Obviously, hydrogen bromide could convert XIV to XIII by a similar reaction, but the ratio of reaction products indicates that it is primarily the ketene acetal XI that combines with this acid.

after one equivalent of this halide had been collected. After five hours of heating the yield of methyl bromide amounted to 82% (of two equivalents); during this time carbon dioxide (30%) also was evolved. As the heating continued, the yield of the latter product increased until it reached (after twenty-six hours) 96% of the theoretical; in this time the yield of methyl bromide rose to 87%. Fractionation of the remaining reaction mixture yielded benzyl bromide (5%), hydrocinnamonitrile XVII (7%), dibenzylacetonitrile XVIII (43%), together with small amounts of toluene and stilbene. All attempts to isolate the expected tribenzylacetonitrile (XIX) from the products of this run were unsuccessful. From another run, which was interrupted after 65% of the theoretical amount of carbon dioxide had been evolved, a 22% yield of benzyl dibenzylcyanoacetate (XX) was obtained.[8] In this run tribenzylacetamide was obtained by treatment of certain of the higher boiling fractions with 50% sulfuric acid.

When the reaction was interrupted before any appreciable evolution of carbon dioxide had occurred (one and one-half hours), 1.24 equivalent (62%) of methyl bromide was collected and benzyl bromide (28%), XVI (20%), XIII (11%), XV (3%), benzyl cyanoacetate (8%), XXI (19%) and XX (10%) were separated from the reaction mixture.

$C_6H_5CH_2CH_2CN$ XVII $(C_6H_5CH_2)_2CHCN$ XVIII $(C_6H_5CH_2)_3CCN$ XIX

$(C_6H_5CH_2)_2CCNCOOCH_2C_6H_5$ XX

$C_6H_5CH_2CHCNCOOCH_2C_6H_5$ XXI

From these results it appeared that the second equivalent of benzyl bromide had reacted further with one or all of methyl esters (XIII, XV and XVI) produced in the initial reaction of the halide with cyanoketene dimethylacetal, converting them to methyl bromide and the corresponding benzyl esters, the latter of which then lost carbon dioxide to yield the nitriles, XVII, XVIII and XIX. The order in which the methyl bromide and carbon dioxide were formed in the reaction together with the isolation of XX from both of the interrupted runs not only seemed to justify this conclusion, but to point to a study of the reaction of benzyl bromide with the individual methyl esters.

A mixture of methyl cyanoacetate (XVI) and benzyl bromide remained apparently unchanged at 170–180° for two hours before any methyl bromide appeared, and after twenty-four hours only a 17% yield of this bromide was collected. After forty-eight hours of heating, an 81% yield of methyl bromide and a 64% yield of carbon dioxide were obtained. However, distillation of the remaining material gave only a small amount of benzyl bromide; the main reaction product was an undistillable tar.

Methyl dibenzylcyanoacetate (XV) gave no evidence of reaction when heated with benzyl bromide; after twenty-two hours, both reactants were recovered unchanged. Methyl benzylcyanoacetate (XIII) had an induction period of one and one-half hours before it reacted with benzyl bromide, but after twenty hours at 170–180°. methyl bromide and carbon dioxide were obtained in 60 and 64% yields, respectively. The other products isolated from this reaction were XVII (19%), XXI (41%) and XX (3%).

The relatively high yield of XXI from XIII indicated that the former ester was probably the key intermediate in the decarboxylation reaction. This supposition was strengthened by the results obtained in an attempt to prepare XXI by an alcohol exchange between an excess of benzyl alcohol and methyl benzylcyanoacetate (XIII). When these reactants were heated together in the presence of a small amount of sodium benzyloxide, the theoretical quantity of methanol distilled out. However, distillation of the remaining reaction mixture was accompanied by loss of carbon dioxide, and XVII (23%), XVIII (39%), XIX (7%) and XX (5%) were the products isolated.[9] When this reaction was repeated and the alkaline catalyst removed after the distillation of the methanol and excess benzyl alcohol, the reaction products were XVIII (14%), the desired ester XXI (13%) and XX (26%).

The presence of XX among the products of this alcohol-exchange reaction indicates that benzyl alcohol functioned as a benzylating agent as did benzyl bromide in certain of the previously described reactions. It appears also that it was the benzyl ester XXI rather than the original methyl ester XIII that was further benzylated, because the yield of XX was much lower in the reaction in which considerable decarboxylation of XXI to XVII—and possibly also to XVIII—had occurred.

From the results described above it is evident that cyanoketene dimethyl acetal reacts with one equivalent of benzyl bromide, probably by an ionic mechanism, to produce the methyl esters XIII, XV and XVI. In the presence of two equivalents of the bromide, however, the reaction apparently takes a different course: the conversion of the primary intermediate XII to XV is suppressed (very little of XV was found among the reaction products although it was shown to be stable to the reaction conditions), and the formation of XIII is favored. This latter ester is then converted by

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[8] From one of the earlier runs dibenzyl ether and N-benzylhydrocinnamamide, $C_6H_5CH_2CH_2CONHCH_2C_6H_5$, also were isolated in small amounts. These products, however, were found to be due to the presence of benzyl alcohol in the benzyl bromide, as they did not appear when an alcohol-free bromide was used.

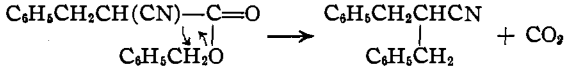
[9] A similar alcohol exchange between benzyl alcohol and ethyl cyanoacetate gave 25% of benzyl cyanoacetate and 5.5% of XXI. During the distillation of these esters, a considerable amount of benzyl alcohol was formed, which, together with the large amount of tar that remained, indicated that benzyl cyanoacetate was suffering intermolecular loss of benzyl alcohol. This reaction is being investigated further

the excess benzyl bromide to methyl bromide and the benzyl ester XXI, which then undergoes further benzylation and/or decarboxylation, probably *via* a series of free radical interchanges

$$\mathrm{XXI} \longrightarrow C_6H_5CH_2CHCNCOO\cdot + \cdot CH_2C_6H_5$$
$$C_6H_5CH_2\cdot + \mathrm{XXI} \longrightarrow \mathrm{XX} + H\cdot$$
$$C_6H_5CH_2CHCNCOO\cdot \longrightarrow C_6H_5CH_2\underset{\cdot}{C}HCN + CO_2$$
$$C_6H_5CH_2\underset{\cdot}{C}HCN + H\cdot\ (\text{or } H{-}C{\equiv}) \longrightarrow \mathrm{XVII}$$
$$C_6H_5CH_2CHCN + C_6H_5CH_2\cdot \longrightarrow \mathrm{XVIII}$$
$$\mathrm{XX} \longrightarrow (C_6H_5CH_2)_2CCNCOO\cdot + \cdot CH_2C_6H_5$$
$$(C_6H_5CH_2)_2CCNCOO\cdot \longrightarrow (C_6H_5CH_2)_2\underset{\cdot}{C}CN + CO_2$$
$$(C_6H_5CH_2)_2\underset{\cdot}{C}CN + H\cdot\ (\text{or } HC{\equiv}) \longrightarrow \mathrm{XVIII}$$
$$(C_6H_5CH_2)_2\underset{\cdot}{C}CN + C_6H_5CH_2\cdot \longrightarrow \mathrm{XIX}$$

The presence of toluene and stilbene among the products of this reaction lend further support to the free radical interpretation of this reaction.

It is possible that the nitriles XVII, XVIII and XIX may be formed also by an ionic mechanism involving a concurrent intramolecular rearrangement and loss of carbon dioxide from a benzyl ester, *e.g.*, XXI → XVIII



$$\begin{matrix} C_6H_5CH_2CH(CN){-}C{=}O \\ C_6H_5CH_2O \end{matrix} \longrightarrow \begin{matrix} C_6H_5CH_2CHCN \\ C_6H_5CH_2 \end{matrix} + CO_2$$

However, further work will be required to establish either of these reaction mechanisms.

Experimental

Cyanoketene Dimethylacetal (XI).—In a 50-cc. flask equipped with a six-inch Vigreux column 14.7 g. of methyl orthocyanoacetate[4] was heated in a metal-bath maintained at 220–225°, whereupon 2.7 g. of methanol, b. p. 63–66°, distilled rapidly. The pyrolysis was stopped when the rate of methanol distillation dropped and the residue in the flask became dark. Distillation of this residue under reduced pressure gave an additional 0.25 g. of methanol in the cold trap, bringing the yield to 2.95 g. (90%), 2.65 g. of forerun, b. p. 90–127° (11 mm.), and 7.85 g. of cyanoketene dimethylacetal, b. p. 127–128° (11 mm.), m. p. 41.5–42°, $n^{50}\text{D}$ 1.4630, d^{50}_4 1.055.

Anal. Calcd. for $C_5H_7NO_2$: N, 12.4; CH_3O, 54.9. Found: N, 12.6; CH_3O, 54.1.

The residue from the distillation amounted to 1.1 g. of a red tar, which was brittle at room temperature and was completely soluble in concentrated hydrochloric acid.

From the forerun 1.65 g. (17%) of methyl cyanoacetate and an additional 1 g. of XI was obtained on fractionation. The presence of approximately this amount of XI in the lower boiling fraction was indicated by its refractive index.[10] The total yield of XI was 8.85 g. (77%).

The above pyrolysis requires careful attention. Insufficient heating produced low yields of methanol and ketene acetal while an excessively long pyrolysis period resulted in increased tar formation and, consequently, low yields of the desired product. For example, in a run in which a yield of only 78% of methanol was obtained, the amount of tar formed was negligible but, correspondingly, the yield of ketene acetal was 68%. On the other hand, a run in which a quantitative yield of methanol was obtained produced considerably more tar and only 36% of ketene acetal.

Cyanoketene dimethylacetal crystallizes in beautiful rectangular prisms. It is insoluble in cold water and dilute alkali but is soluble in the ordinary organic solvents and in concentrated sulfuric acid. It readily decolorizes a solution of bromine in carbon tetrachloride. It shows a remarkable inertness toward water as compared to other ketene acetals. For example, a few crystals were shaken with 5 ml. of distilled water for several minutes without apparent change. On warming to about 70°, however, the compound melted and finally dissolved. When the solution was cooled to room temperature an oil separated which quickly crystallized and was filtered off. This proved to be the unchanged ketene acetal, m. p. 41–42°, mixed m. p. 42–42.5°.

The compound dissolved in dilute hydrochloric acid with evolution of heat. Extraction of the solution with ether and evaporation of the extract, after drying over Drierite, left a residue of methyl cyanoacetate, b. p. 210°, $n^{20}\text{D}$ 1.4192, which was readily converted by concentrated aqueous ammonia to cyanoacetamide, m. p. 117–119°.

Solution of 4.0 g. of cyanoketene dimethylacetal in 30 ml. of absolute methanol was accompanied by cooling to 17°. When a thermometer moistened with concentrated hydrochloric acid was inserted in the solution the temperature rose immediately to 29°. After several minutes sodium bicarbonate was added and, after stirring, the supernatant liquid was decanted and distilled at reduced pressure. The yield of methyl orthocyanoacetate,[4] b. p. 90–93° (8 mm.), $n^{20}\text{D}$ 1.4232, was 4.2 g. (81%).

A solution of 5.2 g. (0.046 mole) of cyanoketene dimethylacetal and 4.3 g. (0.046 mole) of aniline was heated for fifteen hours on the steam-bath under a reflux condenser. Distillation under reduced pressure gave: 0.7 g. (48%) of methanol (cold-trap) and 5.9 g. of liquid which boiled over a wide range. The principal fraction was 3.6 g. (45%) of **methyl N-phenylcyanoiminoacetate**, b. p. 132–136° (4 mm.), $n^{25}\text{D}$ 1.5380, d^{25}_4 1.097.

Anal. Calcd. for $C_{10}H_{10}N_2O$: N, 16.1; CH_3O, 17.8. Found: N, 15.7; CH_3O, 17.7.

Cyanoketene Diethylacetal.—To 4.00 g. of ethyl orthocyanoacetate[4] was added one drop of 85% phosphoric acid and the mixture distilled. After 0.8 g. of forerun, b. p. 125–145° (20 mm.); $n^{20}\text{D}$ 1.4378, 2.0 g. (66%) of cyanoketene diethylacetal, b. p. 145–146° (20 mm.); m. p. 37–38°, $n^{20}\text{D}$ 1.4621 (supercooled liquid), $n^{40}\text{D}$ 1.4536, was collected.

Anal. Calcd. for $C_7H_{11}NO_2$: N, 9.9; C_2H_5O, 63.8. Found: N. 9.8; C_2H_5O, 63.7.

A yield of 1.05 g. (quantitative) of ethanol was found in the cold-trap after the distillation.

A thermometer moistened with concentrated hydrochloric acid was inserted into a solution of 1.60 g. of this ketene acetal in 3.0 ml. of absolute ethanol. On stirring, the temperature rose from 26 to 39°. Fifty mg. of anhydrous potassium carbonate was added and the mixture distilled, yielding 1.46 g. (69%) of ethyl orthocyanoacetate,[4] b. p. 111–118° (19 mm.), $n^{20}\text{D}$ 1.4218.

The Reaction of Cyanoketene Dimethylacetal with One Equivalent of Benzyl Bromide.—A mixture of 68.4 g. (0.4 mole) of benzyl bromide and 45.2 g. (0.4 mole) of cyanoketene dimethylacetal was placed in a Claisen flask fitted with a condenser and receiving flask. To the receiving flask was connected a trap protected from atmospheric moisture and immersed in a mixture of Dry Ice and acetone.

The mixture was slowly heated until the bath temperature reached 174°. At this point there was such a vigorous evolution of gas that the bath was cooled to 160°. When ebullition had practically ceased (thirty minutes) the bath was lowered. A total of 39.5 g. of liquid had condensed in the trap of which 37.0 g. (97%) proved to be methyl bromide, b. p. 4°; the remainder was benzyl bromide, which had been swept over by the rapidly evolved methyl bromide.

The residual red oil in the flask was distilled and the following fractions collected: (a) 12.1 g. (31%) of methyl cyanoacetate, b. p. 59–65° (0.5 mm.); (b) 0.2 g., b. p.

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[10] In order to make the latter calculation it was necessary to estimate $n^{20}\text{D}$ of the ketene acetal, which is a solid at 20° and could not be supercooled to that temperature. The value $n^{20}\text{D}$ 1.4774, was obtained by plotting the refractive indices at 20° of known mixtures of dioxane and the ketene acetal against composition and extrapolating the resulting straight line to 100% ketene acetal.

65–112° (0.5 mm.); (c) 12.0 g., b. p. 112–129° (0.5 mm.); (d) 8.8 g., b. p. 129–180° (0.5 mm.); (e) 11.8 g., b. p. 180–200° (0.9 mm.); (f) 14.4 g., b. p. 200° (0.9 mm.) –205° (2 mm.). The residual tar weighed 10.4 g.

Redistillation of fractions (c) and (d) gave 14.0 g. of **methyl benzylcyanoacetate** (XIII), b. p. 115–123° (0.5 mm.). Careful refractionation yielded a middle cut of the pure ester, b. p. 114–115° (0.1 mm.), $n^{25}D$ 1.5119, d^{25}_4 1.105.

Anal. Calcd. for $C_{11}H_{11}NO_2$: CH_3O, 16.4; N, 7.4. Found: CH_3O, 15.8; N, 7.2.

The ester was hydrolyzed to benzylcyanoacetic acid, m. p. 101–102°, by the method used[11] for the ethyl ester.

Two smaller, higher-boiling fractions were also collected following the methyl benzylcyanoacetate. The last one and the residue in the distilling flask solidified on cooling. Fraction (e) also solidified on standing to a crystalline mass, m. p. 64–67°. This was combined with the solid products just mentioned and the mixture recrystallized from alcohol to give 11.0 g. of methyl dibenzylcyanoacetate (XV), m. p. 78–79° (reported[12] 78–79°), methoxyl content 11.4% (calcd. 11.1%), nitrogen content 5.2% (calcd. 5.0%). This ester was hydrolyzed in 20% aqueous potassium hydroxide to dibenzylcyanoacetic acid, m. p. 188–189° dec. (reported, 188–189°,[13] 194–195°[12]), neut. equiv., 269 (calcd. 265), nitrogen content 5.4% (calcd. 5.3%). Since one melting point reported in the literature disagreed with the value obtained, the ester was characterized further by hydrolysis in 50% sulfuric acid (by volume) to give ammonia and dibenzylacetic acid, m. p. 87–88°, neut. equiv. 230 (calcd. 240).

The remaining material, *i.e.*, fraction (f), the mother liquor from the recrystallization of (e) and the high boiling liquid obtained in the purification of methyl benzylcyanoacetate, was subjected to a systematic purification scheme involving fractionation followed by recrystallization of those portions boiling in the range 170–200° (0.5 mm.). The process was then repeated on the mother liquors. In this manner an additional 10.0 g. of methyl dibenzylcyanoacetate boiling in the range indicated was obtained. Also an additional 2.0 g. of crude methyl benzylcyanoacetate, b. p. 110–123° (0.2 mm.), $n^{25}D$ 1.5257, was obtained, bringing the total yield of that compound to 16.0 g. (21%).

The material remaining from the above isolations was distilled and two fractions collected: (g) b. p. 192–225° (0.2 mm.) and (h) b. p. 219–250° (0.2 mm.). Fraction (h) solidified and, after recrystallization from ethanol, yielded 0.3 g. of benzyl dibenzylcyanoacetate (see below), m. p. 91–91.5°. The mother liquor from these recrystallizations were combined with (g) and evaporated to a constant weight of 3.7 g. Saponification of this material left 0.7 g. unsaponified. From the alkaline solution 2.1 g. of crude dibenzylcyanoacetic acid was obtained, which calculated as the methyl ester brought the total yield of the latter product to 29.3 g. (26%).

The Reaction of Cyanoketene Dimethylacetal with Two Equivalents of Benzyl Bromide.—A mixture of 41.5 g. (0.37 mole) of cyanoketene dimethylacetal and 126.0 g. (0.74 mole) of benzyl bromide was placed in a Claisen flask provided with a condenser and receiving flask. To the latter was connected an absorption train consisting of a wash bottle containing 50% aqueous potassium hydroxide followed by a calcium chloride tube and, finally, a cold trap protected from atmospheric moisture and immersed in a mixture of Dry Ice and alcohol.

The mixture was heated slowly by means of an oil-bath and when the temperature of the bath reached 170° a vigorous evolution of gas began. This subsided after forty-five minutes but mild ebullition continued quite steadily for eight hours. The reaction was allowed to continue for fifteen hours at 170–180°. At this time gas evolution had practically ceased and 47.0 g. (67%) of methyl bromide had collected in the cold-trap. The aqueous alkali had gained in weight by 10.5 g. (65% yield as carbon dioxide). Acidification of a portion of the solution liberated a gas which gave a heavy precipitate when bubbled through lime-water; another portion of this alkaline solution showed no significant content of bromide ion.

The clear, red residue was distilled and the following fractions were collected: (a) 12.3 g., b. p. 50–160° (1 mm.), (b) 25.2 g., b. p. 160–198° (1 mm.), (c) 19.8 g., b. p. 198–252° (1 mm.), (d) 12.9 g., b. p. 252–265° (1 mm.) and (e) 4.6 g. collected at full-oil-pump vacuum but accompanied by so much decomposition that the pressure was too high to measure on a McLeod gage. The tarry residue weighed 10.0 g.

Fraction (a) was refractionated to give (1) 6.1 g. (5%) of benzyl bromide, b. p. 39–45° (0.5 mm.), $n^{25}D$ 1.5639; (2) an intermediate fraction of 0.7 g., b. p. 45–75° (0.5 mm.); (3) 2.8 g. (6%) of hydrocinnamonitrile, b. p. 75–78° (0.4 mm.), $n^{25}D$ 1.5228; and (4) an afterrun of 0.4 g., b. p. 78–85° (0.5 mm.). The residue (2.0 g.) solidified on cooling.

Fractionation of (c) and (d) yielded 6.1 g. of liquid which boiled almost entirely at 160–190° (0.2 mm.) and solidified on cooling. This was combined with (b) which also had solidified and with the solid residue from the distillation of (a), and the resulting mixture was recrystallized from ethanol to give 18.6 g. of dibenzylacetonitrile (XVIII), m. p. 91–91.5° (reported,[14] 89–91°). The major product of the redistillation of (c) and (d) was 24.0 g. of light amber oil which was collected in four fractions boiling at 190–245° (0.2 mm.). All four crystallized on standing and recrystallization of each from ethanol gave **benzyl dibenzylcyanoacetate** (XX), m. p. 91–92°, saponification equiv. 340 (calcd. 355).

Anal. Calcd. for $C_{24}H_{21}NO_2$: C, 81.1; H, 5.9; N, 3.95. Found: C, 81.4; H, 6.1; N, 3.96.

Saponification of this ester in 10% aqueous sodium hydroxide produced benzyl alcohol, b. p. 204°; m. p. of 3,5-dinitrobenzoate, 113.5–114°, and dibenzylcyanoacetic acid,[13] m. p. 189–191°, neut. equiv. 272 (calcd. 265).

A 3.0-g. sample of the ester was hydrolyzed in refluxing 50% (by volume) sulfuric acid, and after making the solution basic it was distilled until the ammonia was removed. Extraction of the remaining alkaline residue with ether gave 1.3 g. of a neutral, semi-crystalline product. Acidification of the aqueous layer gave 1.6 g. of oil, from which dibenzylacetic acid, m. p. 87–88°, neut. equiv. 243, was isolated by distillation at reduced pressure and subsequent recrystallization from petroleum ether. The neutral product was likewise distilled. The light yellow distillate crystallized on cooling and repeated recrystallization from 60–68° petroleum ether gave silky crystals, m. p. 132.5–134°. This compound had the correct analysis for tribenzylacetamide.

Anal. Calcd. for $C_{23}H_{23}NO$: C, 83.8; H, 7.0; N, 4.25. Found: C, 83.8; H, 7.1; N, 4.68.

This product probably resulted from the hydration of the cyano group of benzyl dibenzylcyanoacetate (XX), followed by loss of carbon dioxide from the resulting amide. It seems unlikely that it was formed directly from tribenzylacetonitrile (XIX), as this compound (see below) was found to be extremely stable to hydration with sulfuric acid.

The deep red residue from the distillation of (c) and (d) was added to (e) and the mixture subjected to vacuum sublimation. A small quantity of solid and 1.2 g. of clear, red oil were obtained. The residue was a dark red tar from which nothing could be isolated. The oil, from its carbon and hydrogen content, appeared to be impure benzyl dibenzylcyanoacetate. The crystalline sublimate after recrystallization from ethanol yielded 0.4 g. of stilbene, m. p. 123–124°; dibromide,[15] m. p. 237–237.5°.

The mother liquor from the recrystallization of dibenzylacetonitrile was distilled and collected in three fractions: (f) b. p. 59–150° (0.4 mm.); (g) b. p. 150–181° (0.4 mm.); and (h) b. p. 181–225° (0.4 mm.). Refractiona-

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[11] Hessler, *Am. Chem. J.*, **22**, 176 (1899).

[12] Hessler, This Journal, **38**, 915 (1916).

[13] Cassirer, *Ber.*, **25**, 3027 (1892).

[14] Schneidewind, *ibid.*, **21**, 1328 (1888).

[15] Wislicenus and Seeler, *ibid.*, **28**, 2694 (1895).

tion of (f) gave 0.3 g. of dibenzyl ether, b. p. 111–116° (0.1 mm.), n^{25}_{D} 1.5580, which gave a characteristic heavy precipitate of yellow-green resin with concentrated sulfuric acid. Recrystallization of (g) from ethanol gave 1.3 g. of dibenzylacetonitrile while similar treatment of (h) yielded 0.6 g. of benzyl dibenzylcyanoacetate. The mother liquor from the latter was distilled; the portion boiling at 171–220° (0.5 mm.) solidified and was recrystallized from 60–68° petroleum ether. The yield of N-benzylhydrocinnamamide,[16] m. p. 81–83°, mixed m. p. 81–84°, was 1.2 g. (1%). The yields of both this product and dibenzyl ether were due to benzyl alcohol and were negligible when benzyl bromide,[17] n^{25}_{D} 1.5730, was used.

The remaining mother liquors were subjected to a systematic scheme of purification involving alternate fractionations and recrystallizations. In this manner an additional 2.1 g. of dibenzylacetonitrile, 0.6 g. of benzyl dibenzylcyanoacetate and 8.0 g. of oil, b. p. 187–238° (0.2 mm.), which had a nitrogen content of 5.6%, were obtained. Treatment of this latter fraction with hot 10% aqueous sodium hydroxide for five hours gave 0.6 g. of benzyl alcohol and 2.0 g. of dibenzylcyanoacetic acid; 5.1 g. remained unsaponified (hydrolysis of the same quantity of benzyl dibenzylcyanoacetate under identical conditions left only 5% unsaponified). The unsaponified material was subjected to refluxing 50% (by volume) sulfuric acid. This treatment produced 0.6 g. of a neutral solid, m. p. 122–128°, mixed m. p. with tribenzylacetamide 127–131°. The other products were ammonia and 1.8 g. of ether-soluble, acidic oil which, on sublimation, gave 0.1 g. of hydrocinnamic acid, m. p. 45–47°, neutral equiv. 154 (calcd. 150). The high-boiling residue had a neutral equivalent of 236 and, therefore, appeared to be crude dibenzylacetic acid (neut. equiv. 240).

These results indicated that the 8 g. of oil, which was subjected to saponification, was a mixture of approximately 3 g. of benzyl dibenzylcyanoacetate, 4 g. of dibenzylacetonitrile and 1 g. of tribenzylacetonitrile. Such a mixture would contain 5.2% nitrogen and leave the 5 g. of the alkali-inert nitriles unchanged after saponification of the ester.

The yields of *pure* dibenzylacetonitrile and benzyl dibenzyl cyanoacetate finally obtained were 21.9 g. (27%) and 13.0 g. (10%), respectively. However, since this experiment was designed to give information as to the course of the reaction, the more significant yields are those of the crude materials which make possible a relatively complete material balance. The failure to find but traces of other products in these crudes emphasizes their quantitative significance. The yield of crude dibenzylacetonitrile boiling almost entirely at 160° (0.2 mm.) to 190° (1 mm.) and which solidified on standing was 33.3 g. (41%) and of benzyl dibenzylcyanoacetate, b. p. 190–245° (0.2 mm.), was 29.9 g. less 1.2 g. of N-benzylhydrocinnamamide which was isolated from this fraction, or 28.7 g. (22%). In another run the yield of dibenzylacetonitrile was 43.5%.

Quantitative Determination of the Carbon Dioxide and Methyl Bromide Evolved in the Reaction of Cyanoketene Acetal and Benzyl Bromide.—A mixture of 11.3 g. (0.10 mole) of the ketene acetal and 34.2 g. (0.20 mole) of benzyl bromide was heated in a bath maintained at 170–180° and the amounts of methyl bromide (cold-trap) and carbon dioxide (absorption bulbs containing 50% aqueous potassium hydroxide solution) determined periodically. The results are summarized in Table I.

The products obtained from the residue were: (a) 0.9 g. (2.5%) of unchanged benzyl bromide, (b) 0.9 g. (7%) of hydrocinnamonitrile, (c) 9.5 g. (43%) of dibenzylacetonitrile, (d) 5.6 g. of viscous oil, b. p. 220–240° (1 mm.), (e) 0.3 g. of stilbene and (f) 4.1 g. of tarry residue. The condensate in the cold trap was 0.5 g. of toluene, b. p. 100–110°, 2,4-dinitro derivative, m. p. 70–70.5°.

TABLE I

YIELDS OF METHYL BROMIDE AND CARBON DIOXIDE FROM CYANOKETENE ACETAL (0.10 MOLE) AND BENZYL BROMIDE (0.20 MOLE)

Time, hr.	CH_3Br, mole	CO_2, mole
1	0.091	0.004
3	.146	.016
5	.164	.030
16	.174	.085
23	.175	.093
26	.176	.096
37	.176	.103[a]

[a] A semi-quantitative determination of the carbonate present in the absorption tube was made by acidification of an aliquot of the solution and passing the liberated gas into a barium hydroxide solution. A 90% yield of barium carbonate was obtained. A titration of another aliquot of this solution, after acidification with nitric acid, against silver nitrate showed sufficient bromide ion to account for the discrepancy between the amount of carbon dioxide obtained in the absorption bulbs and that obtained as barium carbonate.

Because of the high yield of carbon dioxide it was thought that (d) was tribenzylacetonitrile, and the fact that saponification of this fraction gave only small quantities of benzyl alcohol also indicated this possibility. However, all attempts to isolate this nitrile from the unsaponified material were unsuccessful.

Interrupted Reaction of Cyanoketene Dimethylacetal with Two Equivalents of Benzyl Bromide.—A mixture of 31.5 g. (0.28 mole) of cyanoketene dimethylacetal and 96.0 g. (0.56 mole) of benzyl bromide was placed in a Claisen flask connected to the absorption train described above and heated at 170–175° for one and one-half hours. During this time 33.0 g. (62%) of methyl bromide was evolved, but the carbon dioxide-trap did not show any gain in weight. The residue was fractionated into: (a) 31.9 g., b. p. 83–84° (15 mm.); (b) 0.6 g., b. p. 46–108° (0.3 mm.); (c) 9.7 g., b. p. 108–122° (0.3 mm.); (d) 0.7 g., b. p. 122–154° (0.3 mm.); (e) 7.8 g. of a thick oil, b. p. 154–163° (0.3 mm.); (f) 24.6 g. of very viscous amber-colored oil, b. p. 177° (0.6 mm.) to 240° (2.5 mm.). Some decomposition during the distillation of (f) was apparent from the pressure rise and fuming which occurred. The tarry residue amounted to 8.5 g.

The refractive index and nitrogen and methoxyl content showed (a) to consist of 26.5 g. of benzyl bromide and 5.4 g. (19.5%) of methyl cyanoacetate (XVI). Fraction (c) contained 10.0% methoxyl and 7.3% nitrogen and gave a positive test for the benzoxy group with concentrated sulfuric acid. When 3.6 g. of (c) was shaken with 25 ml. of 10% aqueous sodium hydroxide the mixture warmed slightly and the oil dissolved. Extraction with ether gave 1.0 g. of benzyl alcohol; acidification of the aqueous residue gave a liquid acid, which was extracted with ether. After drying and evaporation of the solvent, the acid solidified; recrystallization from benzene gave pure benzylcyanoacetic acid, m. p. 101–102°. The aqueous solution, from which this product had been extracted, was evaporated under 20–30 mm. in a bath at 60–70° to a semi-crystalline residue. This was extracted with ether and the extract evaporated to dryness and allowed to stand over concentrated sulfuric acid in a desiccator overnight. The product was 0.3 g. of hygroscopic crystals which, after drying between filter papers, proved to be cyanoacetic acid, m. p. 60–66°. These results show that (c) was a mixture of methyl benzylcyanoacetate and benzyl cyanoacetate in the proportions 3:2 (based on the methoxyl content of (c)). The nitrogen value is in satisfactory agreement with

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(16) Mohr, *J. prakt. Chem.*, [2] **71**, 235 (1905).

(17) Benzyl bromide was prepared by allowing a solution of benzyl alcohol in sufficient 48% hydrobromic acid to contain approximately 2.3 equivalents of hydrogen bromide to stand at room temperature. After two days 83–87% yields of benzyl bromide, n^{25}_{D} 1.5700, were obtained. This product, however, contained sufficient benzyl alcohol to give the products noted. The benzyl bromide, n^{25}_{D} 1.5730, was obtained from an alcohol–acid reaction mixture that had stood for two weeks.

this composition (calcd. N, 7.6; found N, 7.2), but the refractive index of such a mixture is 1.530 instead of the observed 1.515. This indicates the presence in the mixture of still another component of lower refractive index than that of either of these esters. Assuming the methoxyl value to be due solely to methyl benzylcyanoacetate, fraction (c) contained 5.9 g. (11%) of that ester. As to the benzyl cyanoacetate, the data indicate only that the maximum yield of that ester was 3.8 g. (8%).

On standing, fraction (e) partially crystallized. Recrystallization from alcohol gave 2.5 g. of methyl dibenzylcyanoacetate (XV), m. p. 76–79°. Further recrystallization raised the melting point to 79–80°, and a mixed melting point with an authentic sample showed no depression. Fraction (f) also partially crystallized on standing. It was treated with ethanol and the insoluble crystals (4.8 g.) of benzyl dibenzylcyanoacetate (XX), m. p. 90–91°, filtered off.

The alcoholic mother liquors from the recrystallizations of (e) and (f) were combined and distilled. After 1.8 g. of forerun, b. p. 67–165° (1 mm.), there was obtained 14.2 g. (19%) of benzyl benzylcyanoacetate (XXI), b. p. 165–195° (1 mm.), $n^{25}\text{D}$ 1.5550, which boiled almost entirely at 182–188° (1 mm.). Following this, 2.1 g. of an intermediate fraction, b. p. 195–205° (1 mm.), and 5.4 g. of benzyl dibenzylcyanoacetate, b. p. 210–240° (1.5 mm.), were collected. The latter ester was obtained as a red oil which was taken up in ethanol, seeded and the mixture allowed to stand overnight in the refrigerator; 2.0 g. of relatively pure ester, m. p. 89–90°, separated. Recrystallization from ethanol raised the melting point to 91–92°. The total yield of crude benzyl dibenzylcyanoacetate was 10.2 g. (10%).

The Reaction of Methyl Cyanoacetates with Benzyl Bromide. (a) **Methyl Cyanoacetate.**—A mixture of 10.5 g. (0.11 mole) of this ester and 36.8 g. (0.22 mole) of benzyl bromide was heated in an apparatus similar to the one used for the reaction of cyanoketene dimethylacetal and two moles of benzyl bromide. The heating-bath was held at 170–180° throughout the experiment. During the first two and one-half hours there was no reaction but at the end of that time a very slow evolution of gas commenced. The rate of evolution increased very gradually, finally reached a maximum after thirty hours and then slowly subsided until, after forty-seven hours, no more gas was being given off. The system was swept out for fifteen minutes with nitrogen before the products were examined. The yield of methyl bromide, b. p. 4–5°, condensed in the cold trap was 8.2 g. (81%) (after twenty-four hours the yield was 17%). The aqueous potassium hydroxide had gained 3.0 g., which represented a yield of 64% of carbon dioxide. The residue in the flask was distilled at reduced pressure but underwent decomposition (heavy fuming). The distillate consisted of 6.3 g. of benzyl bromide, b. p. 52–70° (1 mm.), and 5.8 g. of liquid, b. p. 70° (1 mm.), 195° (2 mm.), which was not investigated. The principal product was 16 g. of a black, tarry residue.

(b) **Methyl Dibenzylcyanoacetate.**—A mixture of 11.0 g. (0.04 mole) of this ester and 13.5 g. (0.08 mole) of benzyl bromide was heated at 170–180° for twenty-two hours without any apparent reaction. During this time the flask and contents lost no weight and on distillation there were obtained 11.5 g. of benzyl bromide, b. p. 92–97° (22 mm.), 10.4 g. of the original ester, b. p. 185–205° (0.1 mm.), and 1.6 g. of tar residue.

(c) **Methyl Benzylcyanoacetate.**—A mixture of 10.0 g. (0.053 mole) of this ester and 18.2 g. (0.106 mole) of benzyl bromide was heated at 170–180°. No apparent reaction occurred until one and one-half hours had elapsed when a slow evolution of gas commenced. The rate of evolution increased slowly over a period of several hours but had decreased after eleven hours and after twenty hours had ceased altogether. The yields of methyl bromide and carbon dioxide were 60 and 64%, respectively.

The residue was fractionated and the following fractions collected: (a) 9.3 g. of unreacted benzyl bromide, b. p. 92–102° (23 mm.); (b) 1.3 g. (19%) of hydrocinnamonitrile, b. p. 86–98° (0.1 mm.), $n^{25}\text{D}$ 1.5242; (c) 5.8 g. (41%) of benzyl benzylcyanoacetate, b. p. 160–190° (0.1 mm.), $n^{25}\text{D}$ 1.5530; (d) 2.9 g. of a viscous oil, b. p. 200–230° (1 mm.); and (e) 1.0 g. of tar as residue.

Fraction (d) was dissolved in ethanol and seeded with a crystal of benzyl dibenzylcyanoacetate (XX). On standing in a refrigerator for several days, 0.6 g. (3%) of crystalline XX separated from the solution.

The Reaction of Cyanoacetic Esters with Benzyl Alcohol. (a) **Ethyl Cyanoacetate.**—To a solution of 0.3 g. of metallic sodium in 100 ml. of anhydrous benzyl alcohol was added 20.0 g. (0.18 mole) of ethyl cyanoacetate. The clear solution was heated in an oil-bath and when the bath temperature reached 110° a gelatinous precipitate began to separate. At a bath temperature of 170° a rapid evolution of ethanol began and continued for about ten minutes. Heating at 170–175° (bath temperature) was continued for an additional five minutes, after which time distillation of alcohol had practically ceased. Redistillation of the distillate gave 7.6 g. (92%) of ethanol and 0.2 g. of benzyl alcohol.

The excess benzyl alcohol was distilled from the residue at a pressure of 2 mm. and the residual red oil extracted with two 100-ml. portions of anhydrous ether. Finally, the ether-insoluble semi-solid which remained was taken up in cold water containing sodium chloride to prevent emulsification. This mixture was extracted repeatedly with ether and the ether solution combined with the previous ether extracts. This combined extract was washed repeatedly with the dilute aqueous sodium chloride solution, dried over Drierite, after which the ether was evaporated and the residue distilled. The first fraction collected boiled at 65–152° (1.5 mm.). Further distillation was accompanied by marked decomposition which was apparent from the copious fumes and a rise in pressure. A second fraction was collected during this decomposition at a vapor temperature of 152–200°. The undistillable residue weighed 5.9 g.

Redistillation of the first fraction gave 1.4 g. of forerun, b. p. 60–127° (1 mm.), and 6.7 g. of **benzyl cyanoacetate**, b. p. 127–137° (1 mm.). The latter portion of this fraction was selected for analysis and proved to be the pure ester, b. p. 131–137° (1 mm.); $n^{25}\text{D}$ 1.5188; $d^{25}{}_4$ 1.139.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.6; H, 5.2; N, 8.0. Found: C, 68.6; H, 5.4; N, 7.6.

The second fraction was fractionated to yield: 1.7 g. of benzyl alcohol, b. p. 64–65° (1.5 mm.); 0.5 g. of an intermediate fraction, b. p. 65–131° (1.5 mm.); 1.1 g. of benzyl cyanoacetate, b. p. 131–141° (1.5 mm.); and 2.6 g. (5.5%) of benzyl benzylcyanoacetate, b. p. 175–195° (1.5 mm.). The total yield of benzyl cyanoacetate was 7.8 g. (25%). The combined residues from the second distillations weighed only 0.3 g.

Attempts to avoid the formation of large amounts of tar in this reaction by the use of no catalyst or an acid catalyst were unsuccessful. In the former instance, no reaction occurred up to 190°. Catalysts such as sulfuric acid, oxalic acid and sulfosalicylic acid caused only sluggish reaction, the yields of alcohol at the end of two hours heating at 180–200° being of the order of only 50%.

(b) **Methyl Benzylcyanoacetate.**—To a solution of 0.3 g. of metallic sodium in 100 ml. of benzyl alcohol was added 22.2 g. (0.118 mole) of methyl benzylcyanoacetate. The mixture was heated at 180–195° for twenty minutes; 4.0 ml. of methanol was collected. The excess benzyl alcohol was distilled at reduced pressure (1.5 mm.) and during this operation an additional 0.5 ml. of methanol collected in the cold trap (total yield, 94%). To the residue was added 150 ml. of anhydrous ether and the precipitated sodium salt removed by filtration. The filtrate was washed with cold water until the washings were no longer alkaline to phenolphthalein and then dried over Drierite. Fractionation of the ether solution yielded: (a) 2.8 g. of forerun, b. p. 55–93° (1 mm.); (b) 3.7 g. (14%) of dibenzylacetonitrile, b. p. 150–175° (1 mm.); (c) 3.9 g. (12.5%) of benzyl benzylcyanoacetate, b. p. 175–188° (1 mm.); and (d) 10.8 g. (26%) of benzyl dibenzylcyanoacetate, b. p. 220–230° (1 mm.).

Recrystallization of (b) and (d) from ethanol gave pure dibenzylacetonitrile, m. p. 91–92°, and benzyl dibenzylcyanoacetate, m. p. 91–92°, respectively. A center cut from (c) was pure **benzyl benzylcyanoacetate** (XXI), b. p. 180–183° (1 mm.), n^{25}_D 1.5533, d^{25}_4 1.124.

Anal. Calcd. for $C_{17}H_{15}NO_2$: C, 77.0; H, 5.7; N, 5.3. Found: C, 77.5; H, 5.7; N, 5.3.

From a similar run of 0.13 mole of methyl benzylcyanoacetate, in which the alkaline catalyst was not removed, a partial decarboxylation occurred during the distillation as indicated by an increase in the pressure and a gain in weight of an Ascarite tube in the system. The products of this run were: (a) 3.9 g. (23%) of hydrocinnamonitrile, b. p. 78–92° (1 mm.); (b) 8.0 g. of dibenzylacetonitrile, b. p. 158–170° (1 mm.); and (c) 8.0 g. of an oil, b. p. 180–220° (1 mm.), which crystallized on cooling. Recrystallization of (b) from ethanol gave pure dibenzylacetonitrile, m. p. 91–92°. Extraction of (c) with ether left 2.9 g. (7%) of **tribenzylacetonitrile** (XIX), m. p. 210–217°, which after recrystallization from a chloroform–alcohol mixture gave white needles, m. p. 222–223.5°.

Anal. Calcd. for $C_{23}H_{21}N$: C, 88.7; H, 6.8; N, 4.5. Found: C, 88.1; H, 7.0; N, 4.5.

Tribenzylacetonitrile is insoluble in cold, concentrated sulfuric acid, but dissolves when the acid is warmed to 95–100° to give a pale yellow solution, which yields no precipitate on dilution with water. The nitrile (XIX) is recovered unchanged after heating with 75% (by volume) sulfuric acid at 100–125° for five minutes or with refluxing 50% sulfuric acid for fourteen hours; under the former set of conditions dibenzylacetonitrile (XVIII) is converted in good yield to dibenzylacetamide, which, after recrystallization from ethanol–water, melts at 127–129°.

The ether extract from which XIX was separated was distilled and gave an additional 3.2 g. of dibenzylacetonitrile (total yield, 39%) and 2.5 g. (5%) of benzyl dibenzylcyanoacetate, b. p. 200–220° (0.7 mm.), which crystallized on standing and which after recrystallization from ethanol melted at 91–92°.

Summary

Cyanoketene dimethyl- and diethylacetals have been prepared by the pyrolysis of the corresponding orthoesters and certain of their properties and reactions reported.

With one equivalent of benzyl bromide the dimethylacetal gives methyl dibenzylcyanoacetate as one of the reaction products, showing that the negative cyano substituent makes possible the replacement of the single methylene hydrogen of the acetal.

In the presence of a second equivalent of benzyl bromide the reaction continues with the methyl esters produced by the first equivalent to yield benzyl esters of mono- and dibenzylcyanoacetates, which lose carbon dioxide to yield mono-, di- and tribenzylacetonitriles.

These novel benzylation reactions are also shown to occur with these methyl esters and benzyl alcohol.

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[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Ketimines and Acylketimines Related to Amidone[1]

BY L. C. CHENEY, R. R. SMITH AND S. B. BINKLEY

Because of the great importance of morphine and related opium alkaloids in medicine and the associated problem of liability to drug addiction, it is not surprising that information pertaining to the discovery of the potent analgesic drug, amidone (I)[2a,b] has already stimulated rather extensive chemical and clinical investigation.[3–18]

Inasmuch as it has been reported[19] that nuclear substitution of the two phenyl groups in amidone does not enhance analgesic potency or lead to more desirable activity, attention has been focused in this Laboratory on other structural modifications, including the synthesis of certain carbinols, esters,[20] ketimines and acylated ketimines related to amidone. Several examples of the latter class have been described by other investigators[7,12,17] since the completion of this work.

Although ketimines are commonly dealt with as unstable intermediates in the synthesis of ketones by means of the Grignard reagent[21] and the Hoesch and Hoesch–Houben syntheses, few, if any, imines or acylimines of physiologically active ketones appear to have been studied pharmacologically. Our interest was initially aroused in this class of compounds when the remarkably stable isoamidone imine (II)[12,17] was unexpectedly isolated while carrying out the synthesis of amidone in essential accordance

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(1) Presented before the Medicinal Division of the American Chemical Society, Chicago, Illinois, April 19–23, 1948.

(2) (a) Kleiderer, Rice, Conquest and Williams, Report No. P. B. 981, Office of Publication Board, Department of Commerce, Washington, D. C., p. 96; (b) B. I. O. S. Final Report, No. 116, Item No. 24, pp. 51, 56, 65.

(3) Scott and Chen, *J. Pharmacol.*, **87**, 63 (1946).

(4) Scott, Robins and Chen, *Science*, **104**, 587 (1946).

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(6) Thorp, Walton and Ofner, *Nature*, **159**, 679 (1947).

(7) Easton, Gardner and Stevens, THIS JOURNAL, **69**, 976, 2941 (1947).

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(9) Elliott, *Fed. Proc.*, **6**, 327 (1947).

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(12) Schultz, Robb and Sprague, THIS JOURNAL, **69**, 188, 2454 (1947).

(13) Brode and Hill, *ibid.*, **69**, 724 (1947).

(14) Scott, Kohlstaedt and Chen, *Anesthesia & Analgesia*, **26**, 12 (1947).

(15) Hewer and Keele, *Lancet*, **2**, 28 (1947).

(16) Eddy, *J. Am. Pharm. Assoc.*, **8**, 537 (1947).

(17) Easton, Gardner, Evanick and Stevens, THIS JOURNAL, **70**, 76 (1948).

(18) Schultz and Sprague, *ibid.*, **70**, 48 (1948).

(19) Reference 1, p. 93.

(20) Speeter, Byrd and Cheney, *ibid.*, **71**, 57 (1949).

(21) Runge, "Organometallverbindungen," Wissenschaftliche Verlagsgesellschaft m. b. H., Stuttgart, 1944, pp. 500, 587.