[CONTRIBUTION FROM THE MASSACHUSETTS INSTITUTE OF TECHNOLOGY, DEPARTMENT OF CHEMISTRY]

The O-Alkylation of 2-Carbethoxycyclohexanone

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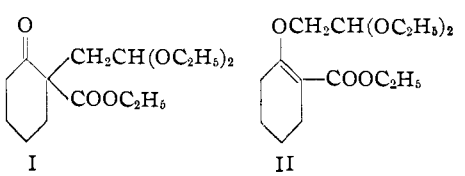
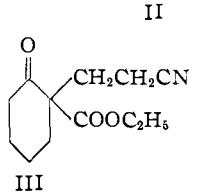
The O-alkylation of β-ketoesters is unusual under ordinary alkylating conditions. Formation of the sodium or potassium enolate from the metal in an inert solvent or from the metal alkoxide in an alcohol, followed by the addition of the alkyl halide, ordinarily gives C-alkylation. With very active alkyl halides, such as chloromethyl ethers,[2] O-alkylation is known to occur. The O-alkylated product can frequently be obtained by using other metal enolates, such as the silver,[3] copper,[4] or tellurium[5] enolates. Even with these metal enolates the yield of O-alkylated products depends on the structure of the β-ketoester.

In the present study involving the alkylation of 2-carbethoxycyclohexanone, two cases of O-alkylation were found using the sodium or potassium enolate in toluene with relatively inert alkyl halides. 2-Carbethoxycyclohexanone was alkylated with bromoacetaldehyde diethylacetal in 38.5% yield. The solution obtained from a mild acid hydrolysis gave an enol test (ferric chloride) along with the expected aldehyde test. From the reaction of the ether soluble fraction of the hydrolysis product with 2,4-dinitrophenylhydrazine, the 2,4-dinitrophenylhydrazone of 2-carbethoxycyclohexanone was obtained in good yields. Thus the compound appeared to be the O-alkylated product (II) instead of the expected C-alkylated product (I).





The alkylated product decolorized an aqueous potassium permanganate solution. The ultraviolet spectrum of the compound was quite different from that of a normal C-alkylation product (2-β-cyanoethyl-2-carbethoxycyclohexanone (III) (see Fig. 1)), but is consistent with an O-alkylated structure. By treatment of the aqueous phase from the acid hydrolysis with phenylhydrazine, the phenylosazone of glyoxal was obtained,

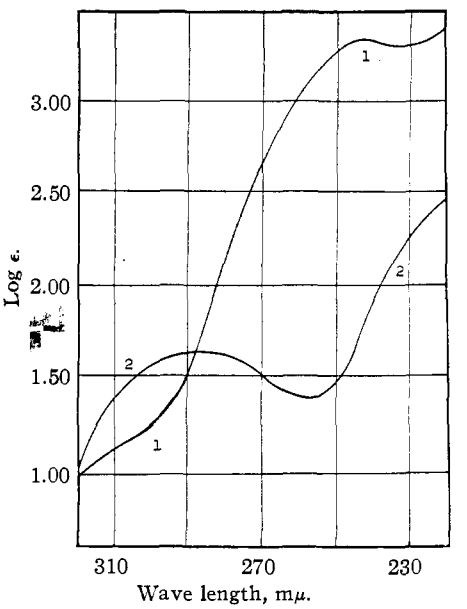
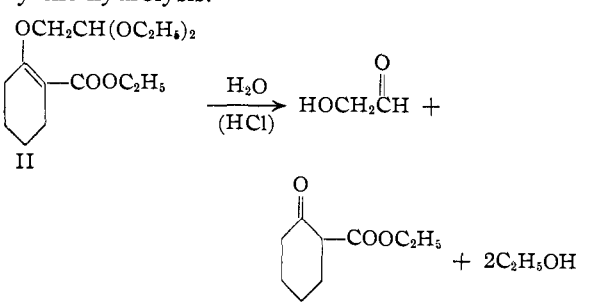


Fig. 1.—Absorption spectra: 1, ethyl 2-β,β-diethoxyethoxy-1-cyclohexenecarboxylate (II); 2, 2-β-cyanoethyl-2-carbethoxycyclohexanone (III). Spectra were taken in purified cyclohexane solution with a Beckmann quartz spectrophotometer.

apparently derived from glycolaldehyde formed by the hydrolysis.



A possible explanation for the O-alkylation would be the intermediate formation of ketene acetal, which might then add to the 2-carbethoxycyclohexanone. McElvain[6] has shown that ketene acetal will add to active methylene compounds; however, the product is an ortho ester and would be expected to yield acetic acid on hydrolysis. For example, compound IV is the product obtained from ketene acetal and dibenzoylmethane. Furthermore, ketene acetal does not appear to be an intermediate, since from the reaction of ketene acetal with 2-carbethoxycyclohexanone under conditions similar to the alkylation no

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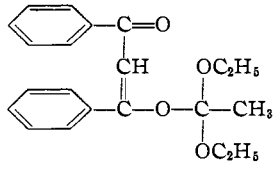
(2) Simonsen and Storey, *J. Chem. Soc.*, **95**, 2108 (1909).

(3) Lander, *ibid.*, **77**, 740 (1900).

(4) Nef, *Ann.*, **276**, 202 (1893).

(5) Morgan and Drew, *J. Chem. Soc.*, **119**, 614 (1921).

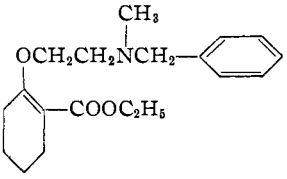
(6) Barnes, Kundiger and McElvain, THIS JOURNAL, **62**, 1281 (1940).



IV

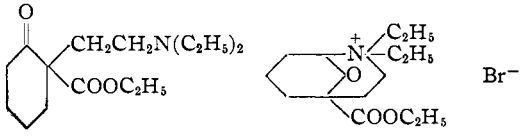
product corresponding to compound II was obtained; only a small amount of starting ester was recovered along with undistillable polymer.

The other O-alkylated product obtained was compound V, obtained by alkylating 2-carbeth-



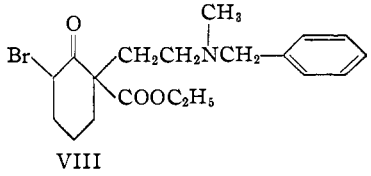
V

oxycyclohexanone with methylbenzyl-β-chloroethylamine. Barltrop[7] had found that diethyl-β-chloroethylamine alkylated 2-carbethoxycyclohexanone normally to give compound VI, which could be brominated and cyclized to give com-



VI VII

pound VII. When the benzylmethyl compound V was brominated, an acid insoluble product was formed which proved to be 6-bromo-2-carbethoxycyclohexanone instead of the expected amine, VIII.



VIII

It was shown that 2-bromo-2-carbethoxycyclohexanone is rearranged readily to the 6-bromo compound, so the isolation of this latter compound is compatible with structure V, the O-alkylated product.

The alkylation procedure differed from that of Barltrop only in the use of the potassium enolate. The procedure was repeated with the sodium enolate and identical results were obtained. After mild acid hydrolysis of compound V, 2-carbethoxycyclohexanone was isolated as the 2,4-dinitrophenylhydrazone. From a similar hydrolysis of Barltrop's amine (VI), no 2-carbethoxycyclohexanone could be isolated.

(7) Barltrop, *J. Chem. Soc.*, 899 (1947).

Experimental[8]

Ethyl 2-β,β-Diethoxyethoxy-1-cyclohexenecarboxylate (II).—To a suspension of 3.9 g. (0.1 mole) of potassium sand in 100 ml. of xylene in a 250-ml. three-necked flask equipped with a stirrer, reflux condenser, dropping funnel and protected from moisture, 17 g. (0.1 mole) of 2-carbethoxycyclohexanone was added dropwise with stirring. After the addition was complete the mixture was refluxed until a clear solution was obtained (about twenty minutes). To the cooled solution was added slowly 21 g. (0.107 mole) of bromoacetaldehyde diethylacetal, and the mixture was refluxed for twenty-four hours. The solution was cooled to room temperature and washed with three portions of water. After filtration of the dried (sodium sulfate) xylene solution, the solvent was removed under reduced pressure, and the residue was fractionated under reduced pressure through an 8-inch Vigreux column. A yield of 11.0 g. (38.5%) of liquid boiling at 115–130° (0.30–0.35 mm.) was obtained. Refractionation gave an analytical sample boiling at 115–116° (0.25 mm.); $n^{25}D$ 1.4572; d^{25}_4 1.0321.

Anal. Calcd. for $C_{15}H_{26}O_5$: C, 62.90; H, 9.15; M_D 75.04. Found: C, 63.14; H, 8.96; M_D 75.60.

Hydrolysis of Ethyl 2-β,β-Diethoxyethoxy-1-cyclohexenecarboxylate (II).—A solution of 1.0 g. of ethyl 2-β,β-diethoxyethoxy-1-cyclohexenecarboxylate in a mixture of 10 ml. of water, 10 ml. of acetic acid and 2 drops of concentrated hydrochloric acid was allowed to stand overnight. The mixture was diluted with an equal volume of water and extracted with ether. To the water solution was added a dilute acetic acid solution containing 1 ml. of phenylhydrazine and the solution was heated two hours at 50–60°. The crystals formed were collected by filtration and dried; the yield was 0.7 g. (50%), and after two recrystallizations the melting point was constant at 166–168°. The melting point of a mixture with an authentic sample of the phenylosazone of glyoxal (m. p. 169–170°)[9] showed no depression.

The ethereal solution was concentrated and the residual oil was taken up in 5 ml. of 95% alcohol. A 2,4-dinitrophenylhydrazone was prepared by the method of Shriner and Fuson,[10] yield 0.8 g. (67%). The melting point after two recrystallizations from alcohol was 154.5–155° and the melting point of a mixture with an authentic sample of the 2,4-dinitrophenylhydrazone of 2-carbethoxycyclohexanone (m. p. 156°)[11] showed no depression.

2-β-Cyanoethyl-2-carbethoxycyclohexanone (III).—A mixture of 102 g. (0.6 mole) of 2-carbethoxycyclohexanone 31.8 g. (0.6 mole) of acrylonitrile and 3 ml. of 40% benzyltrimethylammonium hydroxide solution in 100 ml. of dioxane solution was cooled in ice-water until the exothermic reaction ceased (about ten minutes). The solution was allowed to stand at room temperature for three hours, then acidified with concentrated hydrochloric acid to congo red paper and diluted with an equal volume of water. The crude product was separated and the aqueous phase extracted with three 50-ml. portions of ether. The combined organic portions were washed with sodium bicarbonate solution followed by water. The ether was removed from the dried (sodium sulfate) and filtered ethereal solution and the residue fractionated through an 8-inch Vigreux column under reduced pressure. The yield was 113 g. (85%), b. p. 141–144° (0.4 mm.). Refractionation through a packed column gave an analytical sample; b. p. 125° (0.25 mm.); $n^{25}D$ 1.4700; d^{25}_4 1.0927.

Anal. Calcd. for $C_{12}H_{17}O_3N$: C, 64.63; H, 7.69; N, 6.28; M_D 56.85. Found: C, 64.61; H, 7.72; N, 6.30; M_D, 57.37.

A 2,4-dinitrophenylhydrazone was prepared. After

(8) All melting points are corrected. We are indebted to Mr. S. M. Nagy and his associates for the microanalyses.

(9) Fischer, *Ber.*, **17**, 575 (1884).

(10) Shriner and Fuson, "Identification of Organic Compounds," third ed., John Wiley and Sons, New York, N. Y., 1948, p. 171.

(11) Ruhkopf, *Ber.*, **72**, 1890 (1939).

several recrystallizations from alcohol the melting point was constant at 151–151.5°.

Anal. Calcd. for $C_{18}H_{21}O_6N_5$: C, 53.60; H, 5.25; N, 17.36. Found: C, 53.70; H, 5.49; N, 17.43.

Methylbenzyl-β-chloroethylamine Hydrochloride.—A solution of 28 g. of methylbenzylethanolamine[12] in 75 ml. of chloroform was saturated with dry hydrogen chloride. To the ice-cold mixture was added 15 ml. of thionyl chloride with stirring. The solution was allowed to stand for thirty minutes, then refluxed for two hours. The chloroform was removed under reduced pressure and the residue allowed to crystallize. The crystals were taken up in 95% alcohol and the alcohol removed under reduced pressure to dispel the last traces of thionyl chloride. The product was dissolved in 150 ml. of 95% alcohol and ether added to initiate crystallization. The crystals were separated from the chilled solution by filtration, washed with ether and dried. The yield was 30 g. (80%), m. p. 140–141° (recorded m. p. 142–143°).[13]

Ethyl 2-(β-Methylbenzylaminoethoxy)-1-cyclohexenecarboxylate (V).—To a suspension of 3.9 g. (0.1 mole) of potassium sand in 100 ml. of toluene in a 250-ml. three-necked flask equipped with a stirrer, reflux condenser, dropping funnel and protected from moisture was added 17 g. (0.1 mole) of 2-carbethoxycyclohexanone dropwise with stirring. After the addition was complete the mixture was refluxed until a clear solution was obtained (about twenty minutes). The solution was cooled to room temperature and a toluene solution of methylbenzyl-β-chloroethylamine added. (The toluene solution of the amine was prepared by dissolving 29 g. of hydrochloride in 30 ml. of water, adding 100 ml. of saturated potassium carbonate solution, and extracting with three 25-ml. portions of toluene. The toluene solution of amine was dried over anhydrous potassium carbonate.) The solution was refluxed seven hours, cooled to room temperature and extracted with three 35-ml. portions of 3 *N* hydrochloric acid. The aqueous solution was cooled in ice, made strongly basic with concentrated sodium hydroxide solution and extracted with three 50-ml. portions of ether. The ethereal solution was dried over anhydrous sodium sulfate, filtered and the ether removed under reduced pressure. The residue was distilled through an 8-inch Vigreux column and, after a forerun of methylbenzyl-β-choroethylamine, gave 15.3 g. (48.4%) of product, b. p. 175–180° (1.5 mm.). Refractionation gave an analytical sample boiling at 174–175° (0.4 mm.); $n^{25}D$ 1.5191; d^{25}_4 1.5043.

Anal. Calcd. for $C_{19}H_{27}O_3N$: C, 71.89; H, 8.58; N, 4.41; M_D, 90.97. Found: C, 71.75; H, 8.50; N, 4.69; M_D, 91.19.

Bromination of 2-(β-Methylbenzylaminoethoxy)-1-cyclohexenecarboxylate (V).—To a stirred solution of 6.34 g. (0.02 mole) of ethyl 2-(β-methylbenzylaminoethoxy)-1-cyclohexenecarboxylate in 30 ml. of water plus 2 ml. of 40% hydrobromic acid, 3.2 g. (0.02 mole) of bromine was added dropwise. The solution was stirred for fifteen minutes after addition was complete. The oil which separated was removed by extraction with three portions of chloroform. The dried (sodium sulfate) solution was saturated with dry hydrogen bromide and allowed to stand overnight. The chloroform was removed under reduced pressure and the residue evaporatively distilled. The yield was 3.0 g. (60%) at 90–95° (0.02 mm.); $n^{25}D$ 1.5267. (The refractive index of a sample of 6-bromo-2-carbethoxycyclohexanone prepared as outlined below was $n^{25}D$ 1.5260.) The product was identified by reaction with methylethanolamine and formation of the picrate as described below. The melting point of the picrate was 147–148° and the melting point of a mixture with an authentic sample of the picrate of 6-(methyl-β-hydroxyethylamino)-2-carbethoxycyclohexanone (m. p. 148–148.5°) was not depressed.

6-Bromo-2-carbethoxycyclohexanone.—To an ice-cold solution of 17 g. (0.1 mole) of 2-carbethoxycyclohexanone in 50 ml. of chloroform 16 g. (0.1 mole) of bromine was added with stirring. After the addition was complete the solution was saturated with dry hydrogen bromide, stoppered and allowed to stand in a refrigerator overnight. The solution then was heated under reflux three hours and the chloroform and hydrogen bromide removed under reduced pressure. The residue was distilled, yield 20.4 g. (85%); b. p. 93–95° (0.4 mm.). Refractionation afforded an analytical sample, b. p. 93–93.5° (0.4 mm.); $n^{25}D$ 1.5260; d^{25}_4 1.4412.

Anal. Calcd. for $C_9H_{13}O_3Br$: C, 43.39; H, 5.25; Br, 32.08; M_D (keto form), 51.00. Found: C, 43.38; H, 5.29; Br, 31.93; M_D, 53.42.

6-(Methyl-β-hydroxyethylamino)-2-carbethoxycyclohexanone.—A mixture of 12.5 g. (0.05 mole) of 6-bromo-2-carbethoxycyclohexanone (II), 7.5 g. (0.1 mole) of methylethanolamine and 40 ml. of benzene was heated under reflux overnight. The cooled solution was extracted with three 25-ml. portions of 2 *N* hydrochloric acid. The combined hydrochloric acid solution was made basic by adding 75 ml. of 40% potassium carbonate solution and the mixture was extracted with benzene. The benzene was removed under reduced pressure and the residue evaporatively distilled, yield 10.5 g. (92%) at 98–100° (0.005 mm.); $n^{25}D$ 1.4849. The product was analyzed as the picrate, prepared in alcohol and recrystallized from the same solvent, m. p. 148–148.5°.

Anal. Calcd. for $C_{15}H_{24}O_{11}N_4$: C, 45.76; H, 5.12; N, 11.86. Found: C, 45.71; H, 5.23; N, 11.83.

Hydrolysis of Ethyl 2-(β-Methylbenzylaminoethoxy)-1-cyclohexenecarboxylate (V).—A solution of 1 g. of amine in 5 ml. of 2 *N* hydrochloric acid was boiled gently until turbid (about five minutes). The cooled mixture was extracted with three portions of ether. The ether was removed on a steam-bath and the residue dissolved in 5 ml. of 95% alcohol. The 2,4-dinitrophenylhydrazone was formed by the method of Shriner and Fuson[9]; yield, 0.55 g. (60%). After two recrystallizations from alcohol the melting point was constant at 155–156° and the melting point of a mixture with an authentic sample of the 2,4-dinitrophenylhydrazone of 2-carbethoxycyclohexanone (m. p. 156°)[11] showed no depression.

Summary

Two alkylating agents, bromoacetaldehyde diethylacetal and methylbenzyl-β-chloroethylamine, were found to O-alkylate 2-carbethoxycyclohexanone. The structures of the products were established by hydrolysis.

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(12) Mannich and Kryshal, *Arch. Pharm.*, **250**, 542 (1913).

(13) German Patent 550,672 (*Chem. Zentr.*, **103**, 615 (1932)).