

SYNTHETIC ROUTES TO BICYCLONONANONES

by

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INTRODUCTION

Recent advances in non-classical carbonium ion rearrangements of bicyclic systems encouraged interest in the simple and efficient syntheses of these compounds and their derivatives. Among these are the bicyclononanes, whose syntheses until now have been almost entirely neglected. We have approached this by attempting to synthesize the bicyclo[3.3.1]nonane ring system by a Dieckmann ring closure on an appropriate diester.

DISCUSSION

In an attempt to synthesize bicyclo[3.3.1]nonan-2-one, one of several possible routes was chosen. This is outlined in Fig. I (see page 3). For the synthesis of ethyl 6-carbethoxycyclohexanone-2- β -propionate (IV), cyclohexanone was used as the starting material. Condensation of cyclohexanone with diethyl oxalate and subsequent decarbonylation resulted in 2-carbethoxycyclohexanone (II), as described by Snyder, et al. (1).

The procedure for the alkylation of 2-carbethoxycyclohexanone has previously been described by Openshaw, et al. (2). The authors carried out the reaction in absolute ethyl alcohol, using sodium ethoxide as the base. However, it was found that this method gave yields of only 40 per cent, in spite of the authors' claim of 80 per cent yields. The low yields, perhaps, can be explained by considering the side reactions involved. Ethyl β -bromopropionate in a solution of sodium ethoxide and ethyl alcohol will undergo a Williamson ether synthesis and give the corresponding ethyl β -ethoxypropionate.



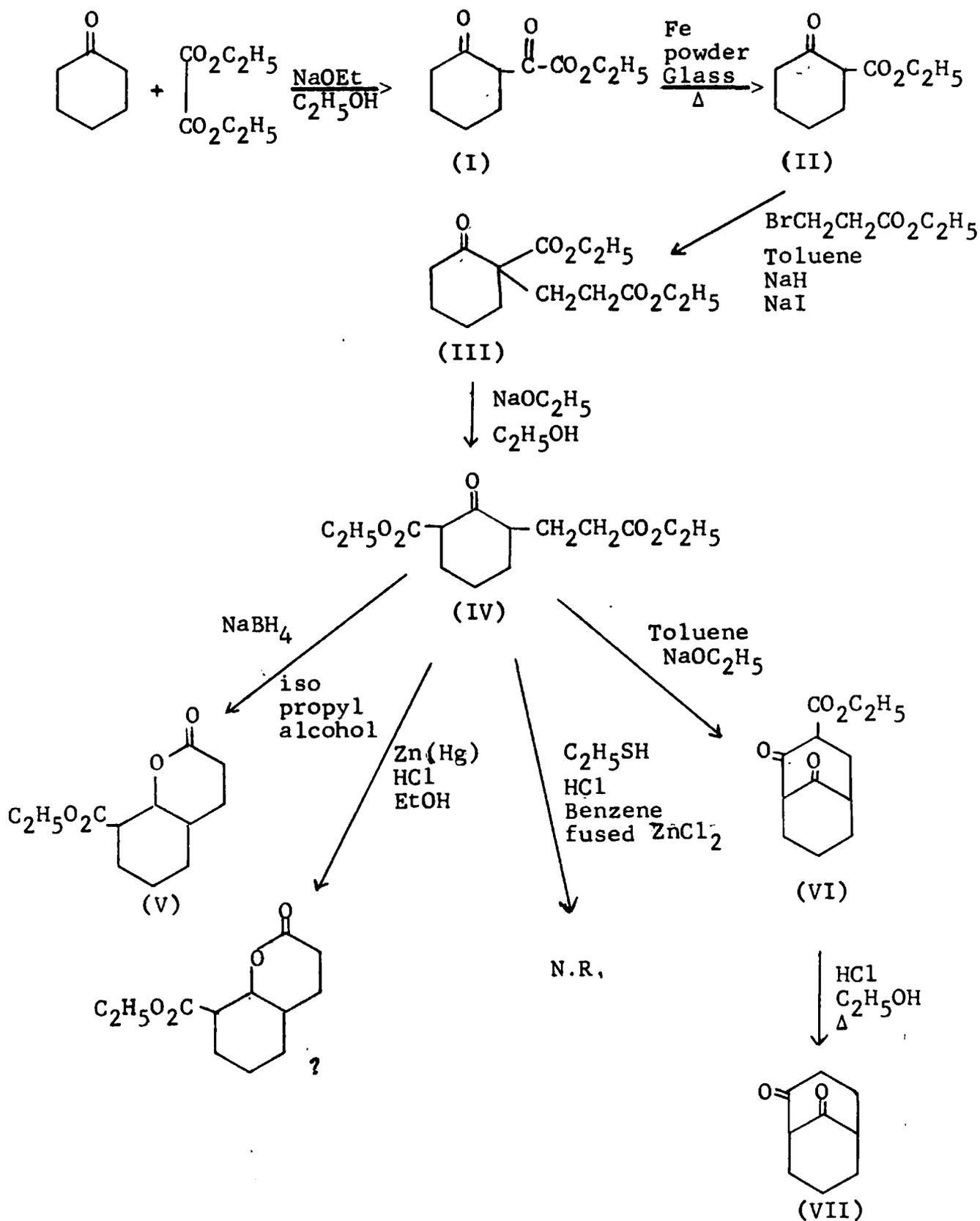
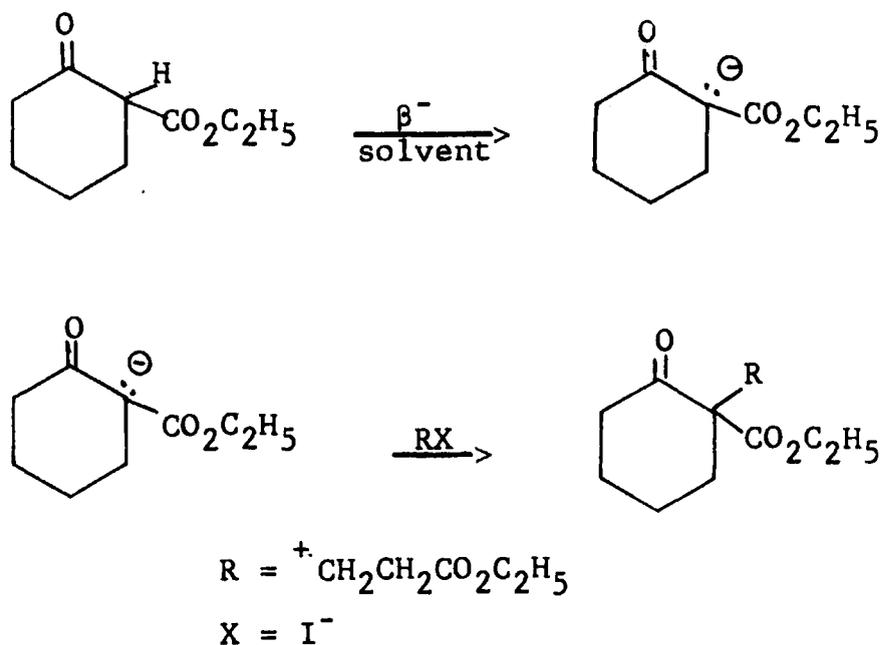


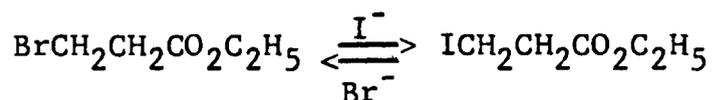
FIGURE I

This new product is not an alkylating agent, and in a polar solvent such as ethyl alcohol, relatively low yields would be expected. Consequently, it was suggested that a hydrocarbon may be a better solvent for this reaction, and, indeed, with toluene as solvent and sodium hydride as base, the yield of ethyl-2-carbethoxycyclohexanone-2- β -propionate was increased to 78 per cent.



In addition to the presence of a strong base for the removal of the α -hydrogen, a good leaving group on the alkyl ester was necessary to bring about the reaction smoothly and in good yields. To fulfill this requirement a small amount of iodide ion in the form of sodium iodide was added to the reaction mixture. The high polarizability

of this ion makes it both a stronger nucleophile than the bromide ion, which it replaces on the alkyl ester, ethyl β -bromopropionate,



and a better leaving group than the bromide ion, which is responsible for a lower transition energy in the alkylation step.

The rearrangement of ethyl 2-carbethoxycyclohexanone-2- β -propionate (III) was accomplished by refluxing the starting material in a solution of sodium ethoxide. The reaction mechanism, as shown in Fig. II (see page 6), furnishes the clue to the driving force of the reaction. Ordinarily, in an extended series of equilibrium reactions, the stability of one intermediate or one final product governs the course of the reaction. In this series the final product, ethyl 6-carbethoxycyclohexanone-2- β -propionate (IV) is stabilized by the formation of its sodium salt.

Attempts to reduce the keto group of ethyl 6-carb-ethoxycyclohexanone-2- β -propionate (IV) met with failure or gave unidentified products. In a reduction procedure involving sodium borohydride in isopropyl alcohol, two products appeared in approximately equal amounts. They were not separated, but the mixture gave a negative ferric

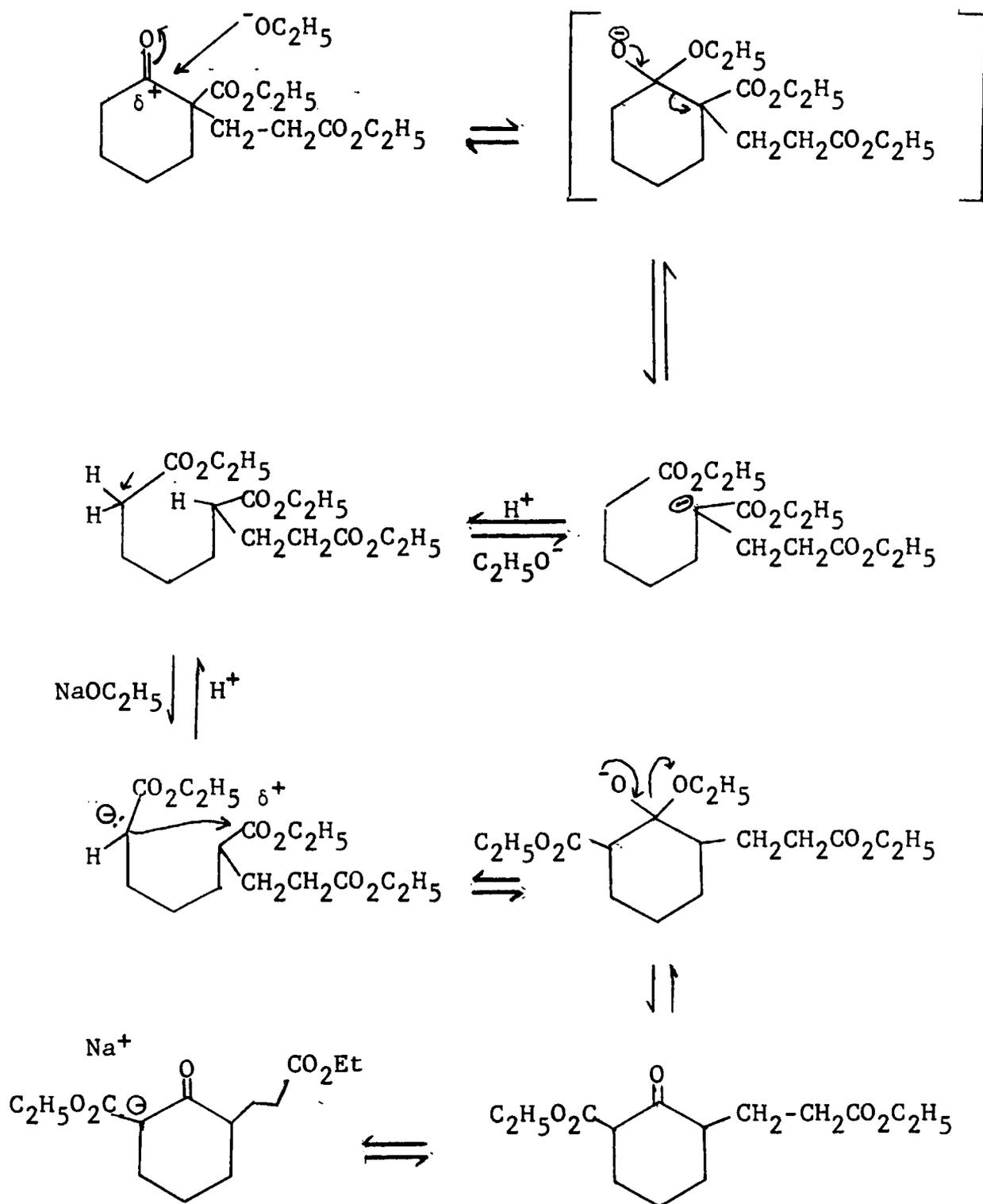
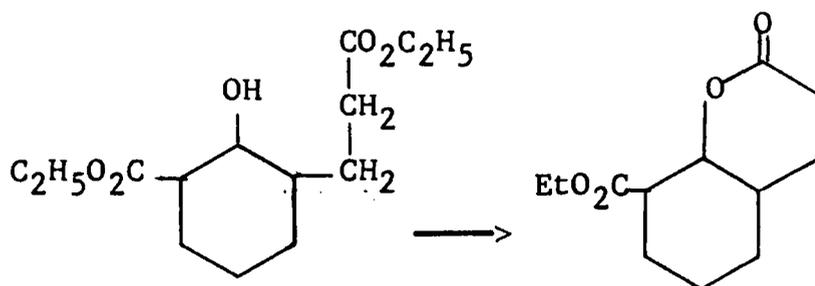


FIGURE II

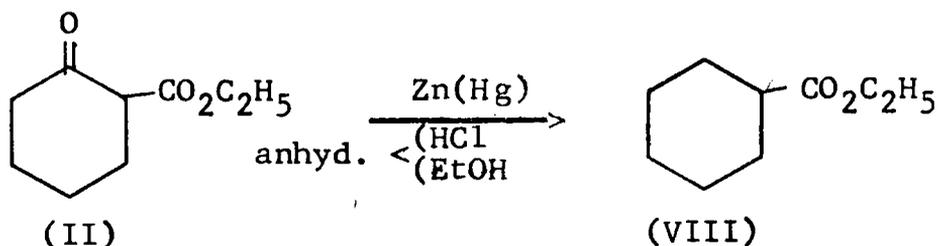
chloride test. An I.R. spectrum showed no peak in the region of 3300 cm^{-1} , which indicated that the expected alcohol was not formed. On the basis of the I.R. spectrum, however, it was postulated that one of the products could be 8-carbethoxyoctahydrocoumarin (V). The carbonyl peak for a lactone, 1740 cm^{-1} was present. This seems reasonable in view of the fact, that if the keto group had been reduced to the alcohol, a lactone could have formed during the workup procedure.



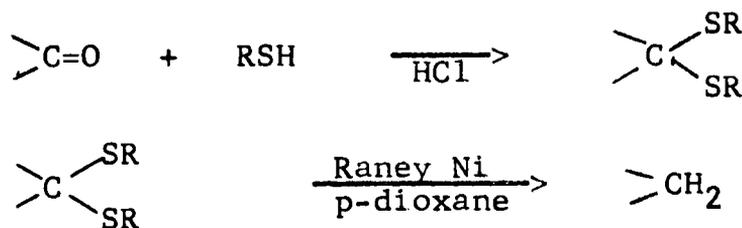
The lower boiling component of the mixture appears to be identical with a single liquid component obtained from a Clemmensen reduction on the same keto ester. This was determined by vapor phase chromatographic retention times. Again, the product gave a negative ferric chloride test, but did not show any absorption in the 3300 cm^{-1} infrared region. A sample of this compound was analyzed for carbon and hydrogen. The values which were obtained correspond very closely to the empirical formula, $\text{C}_{12}\text{H}_{22}\text{O}_4$.

However, any structures which can be assigned are unreasonable in the light of what is now known about the chemical and physical properties of the compound. A comparison of this compound with an authentic sample of ethyl carbethoxycyclohexane-3- β -propionate, indicated that the expected reduction did not proceed to the hydrocarbon as expected. The only likely possibility is that (IV) was reduced to an intermediate which cyclized to the lactone, as in the case of the sodium borohydride reduction. The empirical formula for 8-carbethoxyoctahydrocoumarin (V) is $C_{12}H_{18}O_4$, which, unfortunately, is not in accord with the present analytical data.

To ascertain whether a β -keto ester could be reduced by the Clemmensen method, it was necessary to make an attempt on a compound on which most, if not all, steric factors were eliminated and side reactions, particularly those which could occur after the completion of the reduction step, were not expected to take place. Therefore, 2-carbethoxycyclohexanone (II) was chosen as a model compound, and the same conditions as those applied to (IV) were again applied. It was found that reduction took place smoothly to give carbethoxycyclohexane (VIII) in 25 per cent yield. No attempts were made to improve the method on the reduction of this compound.



A procedure for the reduction of ketones to hydrocarbons developed by Mozingo (3) involves the formation of a thioketal and the subsequent desulfurization with Raney nickel to give the methylene unit. The application of this method is simple, and thioketals appear to form with relative ease under mild conditions.



This same procedure was applied to ethyl 6-carbethoxycyclohexanone-2- β -propionate (IV), but we were unable to form the thioketal. The only explanation for this which seems reasonable, is that the keto group is sterically hindered.

The Dieckmann ring closure on the β -keto ester (IV) was successful to give 3-carbethoxy bicyclo[3.3.1]nonan-2,9-dione (VI) if the procedure as described by Pinkney (4) was followed. The lowest boiling fraction consisted of two components which were temporarily identified as two epimers

of the cyclized compound. Other than a meticulous separation of this fraction from the rest of the reaction mixture, no further purification or analyses were made. An infrared spectrum indicated that there are several different carbonyl absorption peaks, at 1760 cm^{-1} , 1735 cm^{-1} , 1710 cm^{-1} and 1685 cm^{-1} . In a second fraction, an intermediate compound was observed, whose boiling point was lower than that for the starting material and higher than that which was identified as the ring-closed compound. However, this component remains unidentified.

The removal of the carbethoxy group on (VI) was effected by refluxing the compound in a 1:1 solution of concentrated hydrochloric acid and absolute ethyl alcohol. The final ketone was then isolated after neutralization of the acidic solution. The compound, after it had been sublimed had a melting point of $55\text{-}56^\circ\text{ C.}$, and an I.R. spectrum indicated that there was only one carbonyl peak, which was somewhat low-- 1700 cm^{-1} .

EXPERIMENTAL

Ethyl 2-Ketocyclohexylglyoxalate (I).--The procedure of H. R. Snyder, et al. (5), was followed. A 2-l., three-necked flask equipped with a stirrer, a dropping funnel, and a reflux condenser carrying a calcium chloride tube, was set up and charged with 1000 cc of anhydrous ethyl alcohol. To this ethyl alcohol, 46 g. (2 g. atoms) of freshly cut sodium was added cautiously, so that the reaction between the sodium and the ethyl alcohol proceeded under gentle reflux. After all of the sodium had reacted, the reaction flask was immersed in an ice bath and allowed to cool. Meanwhile, a solution of 196 g. (2 moles) of cyclohexanone and 292 g. (2 moles) of ethyl oxalate which had previously been chilled to 10° C. was added to the dropping funnel. After the sodium ethoxide solution in the reaction flask had cooled to 10° C., the stirrer was started, and the contents in the dropping funnel were added dropwise over a period of 20-25 minutes. The orange solution was stirred for an additional hour under the reduced temperature conditions, and finally the ice bath was removed, and stirring at room temperature was continued for eight hours.

The reaction mixture, which had completely solidified by this time, was decomposed by the careful addition of an

ice-cold solution of 56 cc of concentrated sulfuric acid in 435 g. of cracked ice. The reaction mixture was kept cold (about 10° C.), and as soon as feasible during the addition of the acid, stirring was continued. Then the contents of the reaction flask were poured into enough cold water to bring the total volume to 4-l. The product separated as a heavy oil, which was removed. The aqueous layer was then extracted with four 500-ml portions of benzene, and these extracts were combined with the crude ethyl 2-ketocyclohexylglyoxalate. The resulting solution was washed twice with 200 ml portions of water.

The benzene solution was then transferred in reasonable portions to a 1-l., round-bottomed flask, and the solvents were removed by distillation. The traces of water also were removed in an azeotropic system. After no more benzene came over, the flask was heated in an oil bath at 90° C., and the system was evacuated to 10-15 mm of pressure. Small quantities of benzene, unreacted ester, and ketone were distilled off, and after their complete removal, the product began to distill. This was detected by a positive ferric chloride test. The oil bath temperature was gradually raised, and when the temperature of the distillate reached 105°/10-12 mm, it was collected as the final product. The boiling temperature range of the distillate was 105-165°/10-15 mm, while the major portion came over at

145°/20 mm. The yield of product was 242 g. (approximately 60 per cent of the theoretical amount).

2-Carbethoxycyclohexanone (II).--Without further purification, the ethyl 2-ketocyclohexylglyoxalate, whose preparation is described above, was transferred to a 500-ml, round-bottomed flask containing 1 g. of powdered soft glass, and a trace of powdered iron. Decarbonylation, with the evolution of carbon monoxide was effected as the liquid was distilled under reduced pressure. The oil bath temperature, was carefully maintained at 165-175° C. and the pressure at 40 mm. The product distilled at 125-135°/40 mm. The yield of 2-carbethoxycyclohexanone was 186 g. (55 per cent of the theoretical amount based on cyclohexanone).

Ethyl 2-Carbethoxycyclohexanone-2- β -propionate (III).--The procedure of H. T. Openshaw, et al. (6), was followed with certain modifications. A 3-l., three-necked flask equipped with a stirrer, a dropping funnel, and a reflux condenser fitted with a calcium chloride tube was set up and charged with 2000 ml of dry toluene. To this toluene was added 40 g. of sodium hydride (53.5 per cent dispersion of sodium hydride in mineral oil was used). The reaction flask and its contents were immersed in an ice bath, and when the temperature of the stirred suspension had reached 10° C., 131 g. (0.77 mole) of 2-carbethoxycyclohexanone was added dropwise from the dropping funnel over a

period of one hour, into the stirred suspension. After the complete addition of the β -keto ester (II), 2 g. of sodium iodide was added to the reaction mixture, and 146 g. (5 per cent excess of 0.77 mole) of ethyl β -bromopropionate was introduced into the stirred reaction mixture from the dropping funnel over a period of 30 minutes. The ice bath was then removed, and the reaction mixture was stirred at room temperature for a period of eight hours, and finally under reflux for an additional 1-1/2 hours.

Without cooling, the contents of the reaction flask were poured into 3000 ml of ice water, stirred well, and the toluene layer separated. The aqueous solution was extracted four times with 100 ml portions of ether, and these extracts were combined with the toluene layer. The solution was transferred to a 1-l., round-bottomed flask, and the solvents were removed by distillation, the toluene carrying with it traces of water. After no more toluene came over, the residual liquid was transferred to a 500-ml flask and distilled under reduced pressure. A small quantity of unreacted keto ester was first removed, and finally the product, identified by a negative ferric chloride test, came over at 128°/0.4 mm. The yield of ethyl 2-carbethoxy-cyclohexanone-2- β -propionate was 160 g. (77 per cent of the theoretical amount, based on 2-carbethoxycyclohexanone).

Ethyl 6-Carbethoxycyclohexanone-2- β -propionate

(IV).--The procedure of H. T. Openshaw, et al. (7), was followed. Carefully prepared absolute ethyl alcohol (200 ml) was added to a 500-ml, round-bottomed flask, equipped with a reflux condenser, whose opening was fitted with a calcium chloride tube. To the ethyl alcohol was added 7.81 g. (0.344 g. atoms) of freshly cut sodium. This was done cautiously so that the reaction between the sodium and the ethyl alcohol proceeded under gentle reflux. After the complete reaction of the sodium, 93 g. (0.344 mole) of ethyl 2-carbethoxycyclohexanone-2- β -propionate was added in one portion. The reaction mixture was refluxed for a period of eight hours.

The solution was poured into 1000 ml of ice water, stirred well, and extracted three times with a total volume of 750 cc of ether. The combined ether extract were dried over anhydrous magnesium sulfate. After six or eight hours, the solution was filtered into a 500-ml, round-bottomed flask, and the ether was removed by distillation. The final residual liquid was distilled under reduced pressure. The product was collected at 164-168°/2.1 mm. The boiling point of ethyl 6-carbethoxycyclohexanone-2- β -propionate is recorded in the literature as 189-190°/11 mm. The yield was 63 g. (71 per cent of the theoretical amount).

8-Carbethoxyoctahydrocoumarin (V).--A 500-ml, three-necked flask equipped with a stirrer, a reflux condenser, and a dropping funnel was set up and charged with 16 g. of sodium borohydride in 100 ml isopropyl alcohol. The reaction flask was set in an ice bath, and when the temperature of the contents had reached 10° C., 55.5 g. (0.205 mole) of ethyl 6-carbethoxycyclohexanone-2- β -propionate was added from the dropping funnel into the stirred suspension over a period of 30 minutes. Stirring was continued at room temperature for an additional two-hour period. The reaction mixture was poured over 900 g. of ice, and then 60 ml of concentrated hydrochloric acid was cautiously added with stirring. The product was extracted four times with 150 ml portions of ether. A little toluene (50 ml) was added to the extract, and then all the solvents were removed by distillation. The final residual liquid was distilled under reduced pressure. A clear, colorless liquid distilled at 158°/0.3 mm. It gave a negative ferric chloride test, and the yield was 32.5 g.
 $n_D^{31} = 1.4390.$

Clemmensen Reduction on Ethyl 6-Carbethoxycyclohexanone-2- β -propionate.--A 1-l., three-necked flask equipped with a stirrer, a gas inlet tube, and a reflux condenser fitted with a calcium chloride tube, was set up, and charged with 300 cc of absolute ethyl alcohol, 20 g. of zinc amalgam, and 27 g. (0.1 mole) of ethyl 6-carbethoxycyclohexanone-2- β -

propionate. The mixture was stirred, and at the same time dry hydrogen chloride gas, generated by the action of concentrated sulfuric acid on ammonium chloride, was introduced through the gas inlet tube, which extended well below the surface of the liquid in the reaction flask. Heat was generated as the reaction proceeded, and refluxing began after a short time. Periodic tests were made on the ethanolic solution with ferric chloride, and when the test became negative (after approximately 36 hours), the introduction of hydrogen chloride was discontinued, and the mixture was poured into 1000 ml of water, cooled in an ice bath, and extracted with ether. The ether extracts were combined and dried over magnesium sulfate. After drying in this manner, the solvent was removed by distillation. The residual liquid was distilled under vacuum. A clear, colorless liquid was obtained which gave a negative ferric chloride test, and the I.R. spectrum of the compound was similar to that of the product obtained from the sodium borohydride reduction of (IV).

Anal. Calcd. for $C_{12}H_{18}O_4$: C, 63.72%; H, 7.95%.

Found: C, 62.13%; H, 9.33%.

Attempted Formation of the Ethyl Thioketal of Ethyl 6-Carboethoxycyclohexanone-2- β -propionate (IV).--A

1-1., three-necked flask was set up and fitted with a stirrer, a reflux condenser carrying a calcium chloride tube, and a

gas inlet tube. Dry benzene (400 ml), 54 g. (0.2 mole) of ethyl 6-carbethoxycyclohexanone-2- β -propionate, 80 g. of fused zinc chloride and 36.4 g. (0.6 mole) of ethyl mercaptan, were added to the flask. The stirrer was started, and dry hydrogen chloride gas was bubbled into the mixture. The mixture became yellow and gradually turned to a deep red color, after several hours. The periods of time during which the reactants were allowed to remain in contact, as described, ranged from one to twenty hours, in several different attempts at forming the thioetal.

At the end of the reaction period in each case, the reaction mixture was decanted into a 1-l. Erlenmeyer flask. The zinc chloride was kept behind in the reaction flask, and washed several times with 70 ml of anhydrous ether. A total volume of 70 ml of a sodium hydroxide solution, made by dissolving 35 ml of 25 per cent sodium hydroxide solution in 35 ml of water, was then added to the reaction mixture. The organic layer was separated from the aqueous layer, and stored over anhydrous magnesium sulfate for a period of eight hours. It was then filtered, and the ether was removed by distillation. The residual liquid was distilled under vacuum. A "mixed" vapor phase chromatogram identified the product as the starting material.

3-Carbethoxy Bicyclo[3.3.1]nonan-2,9-dione (VI).--

A 3-l., three-necked flask was set up, and equipped with a

high speed stirrer, a reflux condenser carrying a calcium chloride tube, and a dropping funnel. Dry toluene (1300 ml), 2.3 g. (0.1 g atoms) of sodium, and 1 cc of absolute ethyl alcohol were added to the reaction flask. Ethyl 6-carbethoxy-cyclohexanone-2- β -propionate [27.0 g. (0.1 mole)] in 200 ml of dry toluene was added to the dropping funnel. The toluene was brought to a reflux, and then the contents of the dropping funnel were added dropwise into the vigorously stirred solution over a period of fifteen hours. Refluxing and stirring were continued for an additional two hours. Then the toluene was distilled off, until the remaining volume was approximately 300 ml.

The mixture was poured into a solution containing 200 ml of 5 per cent acetic acid and 100 ml of water. The solution was stirred well, and the organic phase was removed. The aqueous layer was extracted once with 200 ml of ether, and then again with 100 ml of ether. The extracts were combined with the organic phase, and the solvents were removed by distillation. The residual liquid was distilled under reduced pressure and finally refractionated through a spinning band column under vacuum. The fraction boiling at 126-143°/1.8 mm was used without further purification in the synthesis of bicyclo[3.3.1]nonan-2,9-dione, whose procedure is described.

Bicyclo[3.3.1]nonan-2,9-dione (VII).--Approximately 5 g. of 3-carbethoxy bicyclo[3.3.1]nonan-2,9-dione (VI) was added to a 100 ml Erlenmeyer flask, which was equipped with a small condenser. To this flask was also added 25 ml of 100 per cent ethyl alcohol, and 25 ml of concentrated hydrochloric acid. The solution was refluxed on a hot plate for 12 hours. The reaction mixture was then neutralized with 25 per cent sodium hydroxide solution. Ether (two 100-ml portions) was used to extract the product, and these combined extracts were set aside and the ether was allowed to evaporate over a period of three days. A white precipitate appeared, which was sublimed under reduced pressure. The compound had a soft consistency and a coumarin-like odor. The compound melted at 55-56° and formed a 2,4-dinitrophenylhydrazone derivative.

BIBLIOGRAPHY

1. Snyder, H. R., Brooks, L. A., and Shapiro, S. H., Organic Syntheses, Vol. II, p. 531.
2. Openshaw, H. T. and Robinson, R., J. Chem. Soc., 1937, p. 941.
3. Mozingo, Ralph, J. Am. Chem. Soc., 65, 1013 (1943).
4. P. S. Pinkney, Organic Syntheses, Vol. II, p. 116, 1959.
5. Snyder, H. R., op. cit., p. 531.
6. Openshaw, H. T., op. cit., p. 941.
7. Ibid.