

0.56), respectively. The last mentioned free chalcone appeared only in a small quantity and gave a faint spot, while maritimetin was hardly detectable in a fresh extract. A spot (R_f 0.48), which became yellow with ammonia vapor and green with ferric chloride, corresponded to flavanonearein.

So as to make clear the distribution in the plant of these compounds, tube and ray flowers were carefully separated from the flower disks and, as described in the case with *Cosmos sulphureus*,¹¹ the former were dissected into stigma, style, ovary, anther, pollen, filament, upper and lower part of corolla and bract and the latter into corolla, bract and sterile ovary. One-hundredth to 1.0 g. each of these parts was extracted with 1–10 ml. of boiling ethanol for about 3 min., and the extraction was repeated two or three times. The combined ethanolic extracts were evaporated and the residue was dissolved in 0.01–1.0 ml. of 50% ethanol to give a solution of original volume, which was most adequate for the paper chromatographic detection. Spotting an equal volume of the plant extract and standard solution of control substance side by side, chromatograms were then run. A semi-quantitative determination was made by comparison of the size and depth of color of the spots, in visible or ultraviolet light, with those of known substances in known concentrations on filter paper. For the detection of anthocyanin, each part dissected was extracted with 5 times its

weight of 1% methanolic hydrochloric acid in the cold. Naked flower disk was also tested. The results are summarized in Table II. The concentration of chrysanthemin and of an unknown pigment in the table means merely a probable relative amount.

Chalconase Test.—Fresh rays were taken in a glass mortar with an equal volume of water, two-fifths of McIlvaine buffer solutions of various pH and 0.1 to 0.04 of 0.05 M potassium cyanide and macerated for 10 min. The homogenate was then mixed with an equal quantity of ethanol and heated on a boiling water-bath for a while followed by filtration. Five to ten drops of the filtrate was spotted on a filter paper. The chromatograms were run as above. The optimum pH for the conversion of chalcone to aurone was found to be 5.5 in the case of *C. tinctoria* and *C. maritima* or *Cosmos sulphureus* as well. An example for the chalconase-catalyzed reaction is shown in Fig. 1.

Acknowledgment.—The author wishes to express his hearty gratitude to Prof. S. Hattori for his kind advice given during this work and is very grateful to the Ministry of Education for a grant given Prof. S. Hattori, with which the cost of this study was defrayed. Thanks are also due to Prof. R. Florin, Director of the Bergianska Botanical Garden, Stockholm, Sweden, for the seeds of *C. maritima*.

TOKYO, JAPAN

(11) S. Hattori, M. Shimokoriyama and K. Oka, *Bull. soc. chim. Biol.*, **38**, 557 (1956).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE RICE INSTITUTE]

A Synthetic Approach to Polycyclic Hydroaromatic Systems Related to the 19-Norsteroids

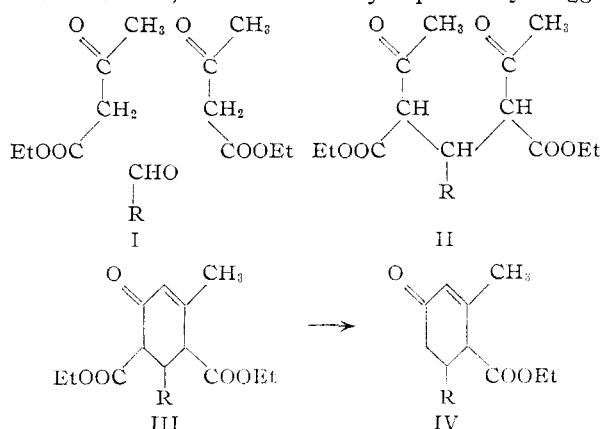
BY RUDOLF ANLIKER, A. S. LINDSEY, DONALD E. NETTLETON, JR., AND RICHARD B. TURNER

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Exploratory work directed toward the total synthesis of physiologically active 19-norsteroids possessing a carbonyl group at C.11 has led to the synthesis of a tricyclic diketone containing the elements of the A, B and C rings with carbonyl groups and a double bond in appropriate positions. Other experiments carried out in this connection suggest that modification of the present synthetic scheme to include incorporation of the D-ring should involve no insurmountable difficulties.

The formation of condensation products of type II in the reaction of aldehydes with two molecular equivalents of ethyl acetoacetate has been studied extensively by Knoevenagel,² Rabe,³ Horning,⁴ and others. The results of these investigations have established that the primary condensation products II can be readily cyclized to 5-alkyl-4,6-dicarbethoxy-3-methylcyclohexenones III, which are in turn convertible into monocarbethoxy derivatives IV by partial hydrolysis and decarboxylation under a variety of conditions. When formaldehyde is employed as the aldehyde component,⁵ the ultimate product is the well known Hagemann ester (IV, R = H),⁶ which has found wide application as an intermediate in various synthetic procedures. In particular, two projected

steroid syntheses involving the use of Hagemann's ester, as well as bicyclic and tricyclic analogs of this substance, have been briefly explored by Hogg⁷



and by Mukharji.⁸ In both approaches the ring possessing the vinylogous β -ketoester function provides the elements of ring C, although different applications of the functional groups were suggested by the two investigators.

(7) J. A. Hogg, *THIS JOURNAL*, **70**, 161 (1948).

(8) P. C. Mukharji, *J. Ind. Chem. Soc.*, **25**, 365, 373 (1948).

(1) This investigation was made possible by a generous grant from the National Science Foundation. Preliminary phases of the work were supported by funds provided by the Eli Lilly Co., Indianapolis.

(2) E. Knoevenagel, *Ann.*, **288**, 321 (1895); **303**, 223 (1898).

(3) P. Rabe, *ibid.*, **313**, 129 (1900); P. Rabe and F. Elze, *ibid.*, **323**, 83 (1902); P. Rabe and A. Billmann, *ibid.*, **332**, 22 (1904).

(4) E. C. Horning, M. O. Denekas and R. E. Field, *J. Org. Chem.*, **9**, 547 (1944); E. C. Horning and R. E. Field, *THIS JOURNAL*, **68**, 384 (1946).

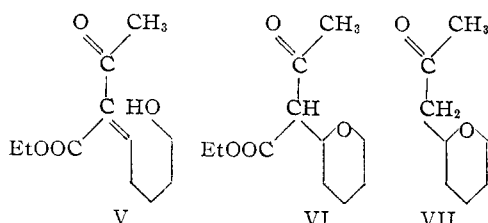
(5) E. Knoevenagel and A. Klages, *Ann.*, **281**, 94 (1894); E. Bergmann and A. Weizmann, *J. Org. Chem.*, **4**, 266 (1939); L. I. Smith and G. F. Rouault, *THIS JOURNAL*, **65**, 631 (1943).

(6) C. Th. L. Hagemann, *Ber.*, **26**, 876 (1893).

In view of current interest in modified steroids, especially in the physiologically active 19-nor analogs of the natural sex and adrenal hormones,⁹ we have undertaken an examination of the potentialities of the Knoevenagel procedure as a possible route to such substances. Particular consideration has been given to methods for the elaboration of derivatives possessing an 11-keto group, for which purpose the Knoevenagel approach is well suited. The present paper describes various synthetic operations involving the products derived from condensations of δ -hydroxyvaleraldehyde and of β -(2,5-dimethoxyphenyl)-propionaldehyde with ethyl acetoacetate.

δ -Hydroxyvaleraldehyde is readily obtainable as an equilibrium mixture of hydroxyaldehyde and lactol forms by hydration of dihydropyran.¹⁰ The mixture of ring-chain tautomers prepared in this way was employed directly in the condensation reactions noted below.

At the outset it was apparent that the presence of a hydroxyl group at carbon atom 5 of the aldehyde component might result in complications owing to the possibility of ring closure ($V \rightarrow VI$) at an intermediate stage in the Knoevenagel reaction. We were therefore prompted to investigate initially

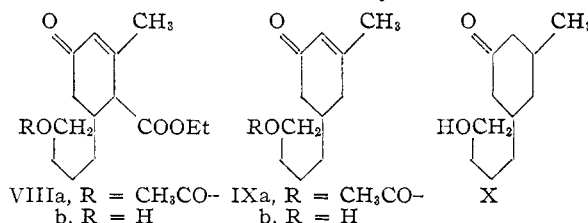


the reaction of δ -hydroxyvaleraldehyde with one molar equivalent of ethyl acetoacetate in benzene solution with piperidine as the catalyst. Under these conditions condensation proceeds rapidly with separation of the theoretical amount of water and formation of a product (79% yield) that was identified as ethyl tetrahydropyranylacetoacetate (VI) by carbon-hydrogen analyses and by infrared absorption measurements. The substance was further converted by hydrolysis and decarboxylation under the influence of barium hydroxide into tetrahydropyranylacetone (VII), from which a crystalline dinitrophenylhydrazone could be obtained. Compound VI fails to react with a second molecule of ethyl acetoacetate under piperidine catalysis, even at the boiling point of benzene, although reaction of this substance with ethyl acetoacetate and sodium ethoxide, followed by treatment with acetic acid-sulfuric acid furnishes a mixture of VIIIa and IXa in 30% yield.

In order to effect the condensation of δ -hydroxyvaleraldehyde with two molecules of ethyl acetoacetate under mild conditions, and at the same time to avoid insofar as possible diversion of material through formation of VI, the Knoevenagel reaction was carried out in an excess of ethyl aceto-

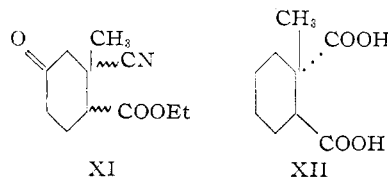
acetate without other solvent and with piperidine as the catalyst. The crude condensation product (II, $R = -(CH_2)_4OH$) thus obtained could not be purified by distillation owing to extensive decomposition and resinification, but a low boiling fraction containing the excess ethyl acetoacetate could be removed, which afforded 3% of ethyl tetrahydropyranylacetoacetate (VI) on redistillation. It was subsequently found that the Knoevenagel product can be crystallized from ether at low temperature, and a pure specimen, m.p. 88–89°, was finally obtained in this way. The losses of material on crystallization from ether, however, are considerable, and the crude condensation product was ordinarily employed in the next step without further purification.

Direct cyclization and decarboxylation of the Knoevenagel product in a mixture of acetic acid and sulfuric acid⁴ was accompanied by acetylation of the free hydroxyl group and yielded the substituted Hagemann ester VIIIa as a mobile oil, b.p. 132–133° (0.01 mm.), λ_{max} 232 μ , ϵ 14,150, contaminated by small amounts of the completely decarboxylated product IXa. Attempts to remove the latter impurity by fractional distillation were unsuccessful, and a satisfactory solution to this



problem was found in a two-step process involving cyclization with hydrochloric acid in benzene-ether solution, followed by partial hydrolysis and decarboxylation in aqueous ethylene glycol at 145°. The product VIIIb obtained in this way gave correct analyses for the formula $C_{14}H_{22}O_4$ and furnished a pure dinitrophenylhydrazone melting at 132–134°. Further transformations of VIIIb, described in the Experimental section, yielded 5-(δ -hydroxybutyl)-3-methylcyclohex-2-en-1-one (IXb) (dinitrophenylhydrazone, m.p. 76–77°) and 5-(δ -hydroxybutyl)-3-methylcyclohexan-1-one (X) (dinitrophenylhydrazone, m.p. 152–153°; *p*-nitrobenzoate, m.p. 82–83°).

In 1948 Mukharji⁸ treated Hagemann's ester (IV, $R = H$) with potassium cyanide under the Lapworth conditions¹¹ and obtained a liquid nitrile-ester (XI), which on subsequent alcoholysis, Clemmensen reduction, and vigorous hydrolysis with concentrated hydrochloric acid gave *trans*-1-methylhexahydrophthalic acid (XII). The conclusion drawn by Mukharji that the nitrile-ester XI must likewise possess the *trans* structure is, in our



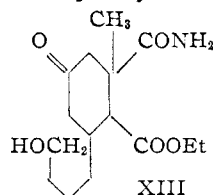
(9) A. Sandoval, L. Miramontes, G. Rosenkranz, C. Djerassi and F. Sondheimer, *THIS JOURNAL*, **75**, 4117 (1953); C. Djerassi, L. Miramontes and G. Rosenkranz, *ibid.*, **75**, 4440 (1953); A. L. Wilds and N. A. Nelson, *ibid.*, **75**, 5366 (1953); C. Djerassi, L. Miramontes, G. Rosenkranz and F. Sondheimer, *ibid.*, **76**, 4092 (1954).

(10) L. E. Schniepp and H. H. Geller, *ibid.*, **68**, 1646 (1946).

(11) A. Lapworth, *J. Chem. Soc.*, **89**, 945 (1906).

opinion, not entirely justified in view of the opportunities for epimerization that exist in the steps leading to XII. Although the stereochemistry of the cyanide addition reaction is a matter of some importance in connection with the present synthetic scheme, a discussion of this aspect of the problem must be deferred until more conclusive evidence is available.

In accordance with the general procedure outlined by Mukharji, compound VIIIb was treated with potassium cyanide in an aqueous ethanol solution containing 0.68 equivalent of acetic acid per equivalent of potassium cyanide. The product was isolated as a dark oil, which slowly deposited crystalline material on standing. Several recrystallizations of this substance afforded a pure sample of a neutral, nitrogen-containing compound, m.p. 142–143°, which showed no evidence of conjugated carbonyl absorption in the ultraviolet. The infrared spectrum was devoid of nitrile absorption, but possessed an amide band, and the product was subsequently identified as the ester-amide XIII. Hydrolysis of the nitrile func-

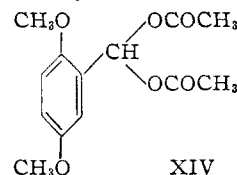


tion must therefore occur during the addition reaction which is carried out in weakly basic solution, or in the process of isolation.

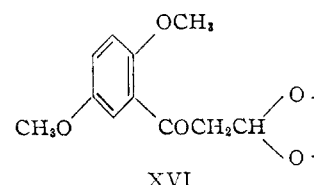
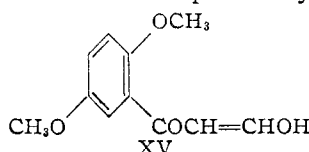
Since the carboxyl functions present in XIII provide groups that can be utilized for construction of the steroid D ring by well established procedures,¹² attention was next directed toward the more pressing problem of elaboration of the A/B ring system. Although methods for accomplishing this end starting with XIII can be visualized, experiments that have been carried out thus far have dealt with products derived from β -(2,5-dimethoxyphenyl)-propionaldehyde (XVIII) which constitutes a more promising starting point for this purpose than does the hydroxyvaleraldehyde.

Two procedures have been developed for preparation of the required β -(2,5-dimethoxyphenyl)-propionaldehyde. In the first method 2,5-dimethoxybenzaldehyde,¹³ obtained from hydroquinone dimethyl ether by the Gattermann cyanide synthesis, was converted into 2,5-dimethoxycinnamic acid¹⁴ by treatment with acetic anhydride and sodium acetate. In addition to the cinnamic acid, there was obtained a small amount of a neutral by-product, m.p. 112°, that was identified as the diacetate XIV.¹⁵ Catalytic hydrogenation of the unsaturated acid gave β -(2,5-dimethoxyphenyl)-propionic acid, m.p. 66–67°, which was converted into the corresponding acid chloride and thence into β -(2,5-dimethoxyphenyl)-propionaldehyde by Rosen-

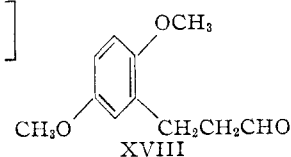
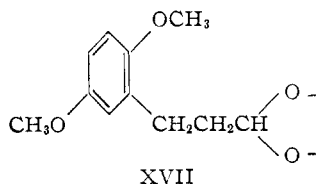
mund reduction. The over-all yield based on hydroquinone dimethyl ether was 26%.



A better yield of the propionaldehyde derivative was obtained by a second method of synthesis, in which commercially available 2,5-dimethoxyacetophenone served as the starting material. Condensation of this material with ethyl formate gave the hydroxymethylene ketone XV, which was converted directly without purification into the corresponding ethylene acetal (XVI), m.p. 47°, by treatment with ethylene glycol and *p*-toluenesulfonic acid. Removal of the carbonyl group of XVI was accomplished by a two-stage process in-



volving lithium aluminum hydride reduction followed by hydrogenolysis of the resulting benzyl alcohol over a palladium-charcoal catalyst. The free aldehyde group was finally liberated by shaking an ether-petroleum ether solution of the desoxo acetal (XVII) with 1 *N* aqueous hydrochloric acid. The over-all yield of β -(2,5-dimethoxyphenyl)-propionaldehyde (XVIII) obtained in this series of reactions was about 50%.



Condensation of XVIII with two molar equivalents of ethyl acetoacetate proceeded smoothly in the presence of small amounts of piperidine, and furnished 69% of a product (XIX) melting at 114–115°. In this connection it was observed that the use of ether as a solvent for the condensation reaction has a retarding effect on the rate of formation of XIX, although reaction of β -(2,5-dimethoxyphenyl)-propionaldehyde with the first molecule of ethyl acetoacetate is apparently fast, judged by the rapid separation of water from the reaction mixture.

Treatment of XIX with acetic acid-sulfuric acid yielded an oily product containing substantial

(12) Cf. W. E. Bachmann, W. Cole and A. L. Wilds, *THIS JOURNAL*, **62**, 824 (1940); J. C. Sheehan, R. A. Coderre and P. A. Cruickshank, *ibid.*, **75**, 6231 (1953).

(13) A. Neuberg, *Biochem. J.*, **43**, 599 (1948).

(14) H. Kauffmann and K. Burr, *Ber.*, **40**, 2352 (1907).

(15) We are indebted to Drs. D. Buckley and M. S. Gibson for this information.

efforts in this direction may be rewarding. Additional work along these lines is now in progress.

Experimental²¹

Preparation of Ethyl Tetrahydropyranylacetoacetate (VI).—A benzene solution of 40 g. of δ -hydroxyvaleraldehyde, prepared as a mixture of hydroxyaldehyde and lactol forms by the method of Schniepp and Geller¹⁰ (b.p. 53–57°, 3 mm., n_D^{20} 1.4493), and 52 g. of ethyl acetoacetate was treated with 4 ml. of anhydrous piperidine. A vigorous reaction ensued, and the water which separated from the reaction mixture was removed continuously by azeotropic distillation. After 1.5 hours, 6.8 ml. (1 molar equivalent) of water had been collected. The solution was then cooled, diluted with ether, and washed successively with dilute hydrochloric acid, saturated sodium carbonate solution and water. After drying over anhydrous sodium sulfate the solvents were removed, and the product was distilled under reduced pressure. The main fraction consisted of 66 g. (79%) of a colorless liquid boiling at 92–94° (0.5 mm.), n_D^{20} 1.4502, d_4^{27} 1.0555.

Anal. Calcd. for $C_{11}H_{18}O_4$: C, 61.66; H, 8.47. Found: C, 61.71; H, 8.65.

Preparation of Tetrahydropyranylaceton (VII).—A mixture of 30 g. of ethyl tetrahydropyranylacetoacetate and 15.3 g. of barium hydroxide in 140 ml. of water and 60 ml. of ethanol was refluxed with stirring for 6 hours. The reaction mixture was then filtered, and the bulk of the alcohol was removed under reduced pressure. The product VII was finally extracted into ether and was isolated by fractional distillation. In this way 9.9 g. of material, b.p. 106–108° (41 mm.), n_D^{20} 1.4450, d_4^{27} 0.9732, was obtained.

Anal. Calcd. for $C_8H_{14}O_2$: C, 67.57; H, 9.93. Found: C, 67.21; H, 9.97.

The dinitrophenylhydrazones prepared as a derivative was purified by recrystallization from dilute methanol, m.p. 97–98°.

Anal. Calcd. for $C_{14}H_{18}N_4O_5$: C, 52.17; H, 5.63; N, 17.38. Found: C, 51.87; H, 5.70; N, 17.26.

Reaction of δ -Hydroxyvaleraldehyde with Excess Ethyl Acetoacetate.—A mixture of 100 g. of δ -hydroxyvaleraldehyde and 380 g. of ethyl acetoacetate was cooled to 0° and treated with a solution of 8 ml. of anhydrous piperidine in 10 ml. of absolute ethanol. Three additional 4-ml. portions of piperidine were added at 24-hour intervals, and at the end of 5 days at 0° the reaction mixture was diluted with ether and washed with dilute aqueous acetic acid, saturated sodium bicarbonate solution and finally with water. Distillation of the dried solution under reduced pressure gave 187 g. of volatile material, which on redistillation furnished ethyl acetoacetate, b.p. 90–91° (40 mm.), n_D^{20} 1.4130, and 5.4 g. of ethyl tetrahydropyranylacetoacetate, b.p. 148–152° (40 mm.), n_D^{20} 1.4430. The major portion of the condensation product (230 g.) could not be distilled without decomposition, and the crude material was accordingly cyclized directly by the procedure described below. Crystallization of a small sample of the crude product from ether at low temperature gave fine needles, which after repeated recrystallization from ether melted at 88–89°.

Anal. Calcd. for $C_{17}H_{26}O_7$: C, 59.28; H, 8.19. Found: C, 59.04; H, 8.23.

Cyclization and decarboxylation of the crude Knoevenagel product was accomplished by the following methods. (A) A solution of 25.9 g. of the crude diester in 40 ml. of acetic acid was treated with 2.5 ml. of concentrated sulfuric acid and refluxed for a period of 1 hour. The reaction mixture was then poured onto ice, and the product was extracted into ether. The ethereal solution was washed with water and sodium bicarbonate solution and was dried over anhydrous sodium sulfate. Removal of the solvent gave a dark oil that on distillation under diminished pressure afforded 12.4 g. of a pale yellow liquid VIIIa, b.p. 122–125° (0.005 mm.), n_D^{20} 1.4806, d_4^{27} 1.0741, λ_{max} 232 m μ , ϵ 10,600. The material showed broad absorption in the carbonyl region of the infrared, and no band corresponding to hydroxyl absorption was present. Carbon-hydrogen analysis gave results that were somewhat high, and the

product was evidently contaminated with IXa, which, however, could not be removed by repeated fractional distillation.

Treatment of the material with ethanolic hydrogen chloride resulted in removal of the acetoxy group and formation of a hydroxyl containing substance VIIIb, which was finally obtained in pure form by careful fractionation, b.p. 135–136° (0.001 mm.), n_D^{20} 1.4948, d_4^{27} 1.0760, λ_{max} 233 m μ , ϵ 12,500.

Anal. Calcd. for $C_{14}H_{22}O_4$: C, 66.11; H, 8.72. Found: C, 66.07; H, 8.66.

The dinitrophenylhydrazones melted at 132–134°.

Anal. Calcd. for $C_{20}H_{26}O_7N_4$: C, 55.29; H, 6.03; N, 12.90. Found: C, 55.22; H, 5.91; N, 12.90.

(B) A more satisfactory preparation of VIIIb involved the following procedure. The crude Knoevenagel product (163 g.) was dissolved in 100 ml. of benzene and 250 ml. of ether, and 5 ml. of concentrated hydrochloric acid was added. After standing overnight at room temperature, the solvents were removed under reduced pressure, benzene being added from time to time until all of the hydrochloric acid had been removed. The residual material (III, R = $-(CH_2)_4OH$) was then taken up in 480 ml. of ethylene glycol and 20 ml. of water and was heated for 6 hours at 145°. The resulting solution was cooled, diluted with an equal volume of water, and extracted repeatedly with benzene. Distillation of the benzene soluble product afforded 47 g. of VIIIb identical in all respects with material obtained by procedure A.

Preparation of 5-(δ -Hydroxybutyl)-3-methylcyclohex-2-en-1-one (IXb).—A solution of 25 g. of keto ester VIIIb in 70 ml. of water and 50 ml. of ethanol containing 12 g. of sodium hydroxide was heated to reflux temperature for 0.5 hour. A mixture of 25 ml. of concentrated sulfuric acid and 50 ml. of water was then added, and refluxing was continued for an additional 15 minutes. The product was finally isolated by ether extraction, and on distillation furnished 12.5 g. of material boiling at 140–142° (0.6 mm.), n_D^{20} 1.5008, d_4^{27} 1.0210, λ_{max} 234 m μ , ϵ 11,800.

Anal. Calcd. for $C_{11}H_{18}O_2$: C, 72.49; H, 9.96. Found: C, 72.52; H, 9.72.

The compound yielded a dinitrophenylhydrazones as red needles, m.p. 76–77°.

Anal. Calcd. for $C_{17}H_{22}O_5N_4$: C, 56.34; H, 6.12; N, 15.46. Found: C, 56.39; H, 6.44; N, 15.57.

Preparation of 5-(δ -Hydroxybutyl)-3-methylcyclohexanone (X).—A solution of 3.3 g. of the unsaturated ketone IXb in 35 ml. of ethyl alcohol was stirred in a hydrogen atmosphere in the presence of 300 mg. of a 10% palladium-charcoal catalyst. When the absorption of hydrogen ceased, the catalyst was removed by filtration, and the product was distilled under reduced pressure. Redistillation furnished the analytical sample, b.p. 103° (0.001 mm.), n_D^{20} 1.4755, d_4^{27} 0.9942.

Anal. Calcd. for $C_{11}H_{20}O_2$: C, 71.69; H, 10.94. Found: C, 71.73; H, 10.83.

The product yielded a dinitrophenylhydrazones melting at 153–154°.

Anal. Calcd. for $C_{17}H_{24}O_5N_4$: C, 56.03; H, 6.64; N, 15.38. Found: C, 56.34; H, 6.72; N, 15.41.

The *p*-nitrobenzoate was also prepared, and after several recrystallizations from ether-petroleum ether a pure sample, m.p. 82–83°, was obtained.

Anal. Calcd. for $C_{18}H_{26}O_5N$: C, 64.85; H, 6.95; N, 4.20. Found: C, 64.82; H, 7.06; N, 3.93.

Reaction of VIIIb with Hydrogen Cyanide.—To a solution of 19.5 g. of the keto ester VIIIb in 50 ml. of ethanol, there was added 10 g. of potassium cyanide dissolved in a small amount of water. The mixture was cooled to 0°, and 6.0 ml. of acetic acid was introduced by slow addition through a tube extending below the surface of the solution. After standing at 5° for 2 days, an additional 1.8 ml. of acetic acid was added, and the reaction mixture was heated on the steam-bath for 20 minutes. At the end of this time, the solution was cooled, diluted with water and extracted with ether and with ethyl acetate. Removal of the solvents (hood!) gave a dark oil, which furnished 5.0 g. of a crude product, m.p. 110–115°, on crystallization from ethyl acetate containing a small amount of methanol. After several re-

(21) All melting points are corrected. Microanalyses were carried out by S. M. Nagy, M.I.T.

crystallizations from the same solvent mixture, a pure sample melting at 142–143° was obtained. The infrared spectrum of the material XIII showed maxima at 3380 cm^{-1} (OH), 3225 cm^{-1} (NH), 1712 cm^{-1} (C=O) and 1675 cm^{-1} (—CONH₂).

Anal. Calcd. for C₁₅H₂₅O₅N: C, 60.18; H, 8.42; N, 4.68. Found: C, 60.15; H, 8.58; N, 4.89.

Preparation of 2,5-Dimethoxycinnamic Acid.—A mixture of 241 g. of 2,5-dimethoxybenzaldehyde (m.p. 50–51°; dinitrophenylhydrazone, m.p. 204–206°),¹³ 142 g. of freshly fused and powdered sodium acetate, and 380 g. of acetic anhydride was heated under reflux for 8 hours according to the procedure of Kauffmann and Burr.¹⁴ The mixture was then cooled and diluted with water, whereupon the product separated as a crystalline mass. The material was isolated by filtration and purified by extraction from an ethereal solution with 2 *N* sodium carbonate. The acidic product obtained in this way crystallized as long needles melting at 147–148°, literature value, 143°. The yield was 64%.

A small amount of neutral product, m.p. 112°, was isolated from the ether solution remaining after carbonate extraction, which proved to be the diacetate of 2,5-dimethoxybenzaldehyde hydrate (XIV).

Anal. Calcd. for C₁₃H₁₆O₆: C, 58.20; H, 6.01. Found: C, 58.23; H, 5.89.

Preparation of β -(2,5-Dimethoxyphenyl)-propionic Acid.—2,5-Dimethoxycinnamic acid (180 g.) was dissolved in 95% ethanol and shaken with hydrogen at atmospheric pressure in the presence of 6 g. of 10% palladium-charcoal catalyst. The theoretical amount of hydrogen was absorbed in 2.5 hours. At the end of this time, the catalyst was removed by filtration, and the filtrate was clarified by passage through Celite. Removal of the solvent, and crystallization of the product from dilute methanol gave 159 g. (87%) of β -(2,5-dimethoxyphenyl)-propionic acid melting at 64–66.5°. The analytical sample, m.p. 66–67°, was obtained after several recrystallizations from the same solvent.

Anal. Calcd. for C₁₁H₁₄O₄: C, 62.84; H, 6.71. Found: C, 63.07; H, 6.61.

Preparation of β -(2,5-Dimethoxyphenyl)-propionaldehyde (XVIII) from β -(2,5-Dimethoxyphenyl)-propionic Acid.— β -(2,5-Dimethoxyphenyl)-propionic acid (40 g.) was carefully dried under vacuum and was heated to a temperature just above the melting point with 25 g. of freshly distilled thionyl chloride, added in portions. After addition of the thionyl chloride was complete (about 30 minutes), the mixture was heated on the steam-bath for 20 minutes, and the excess thionyl chloride was finally removed under vacuum. Distillation of the residual material afforded 35.3 g. (82%) of the acid chloride, b.p. 125–128° (0.01 mm.), which was reduced directly by the Rosenmund procedure.

A solution of 34.0 g. of acid chloride in 200 ml. of anhydrous xylene together with 4 g. of 5% palladium-barium sulfate catalyst was placed in a 500-ml. 3-neck flask equipped with a mercury-sealed stirrer, a gas inlet tube extending below the surface of the solution, and a reflux condenser connected through a drying tube to a trap containing 1 *N* sodium hydroxide. A quinoline-sulfur poison²² (80 mg.) in 10 ml. of xylene was then added, and the mixture was heated to reflux temperature while a slow stream of hydrogen was passed through the solution with vigorous stirring. When the evolution of hydrogen chloride ceased (as determined by titration of the sodium hydroxide solution), the catalyst was filtered out, and the filtrate was shaken for a period of two days with 300 ml. of a concentrated aqueous solution of sodium bisulfite. The bisulfite addition compound separated as a voluminous precipitate, which was filtered and thoroughly washed with ether. This material was then treated with an excess of 2 *N* sodium carbonate, and the resulting aldehyde was extracted with ether and finally distilled; yield 19.6 g. (68%), b.p. 105–107° (0.001 mm.), n_D^{25} 1.5272, d_4^{25} 1.1046.

Anal. Calcd. for C₁₁H₁₄O₃: C, 68.02; H, 7.27. Found: C, 68.22; H, 7.20.

A yellow dinitrophenylhydrazone, m.p. 133–134°, was prepared as a derivative.

Anal. Calcd. for C₁₇H₁₈O₅N₄: C, 54.54; H, 4.85; N, 14.97. Found: C, 54.75; H, 4.91; N, 14.66.

Preparation of β -Ethylenedioxy-2,5-dimethoxypropionone (XVI).—Ethyl formate (330 g.) was added slowly with stirring to a suspension of alcohol-free sodium methoxide (prepared from 60 g. of sodium) in 1 l. of anhydrous benzene. The air in the reaction vessel was displaced by a stream of dry nitrogen, and a solution of 156 g. of 2,5-dimethoxyacetophenone (Aldrich Chemical Co., Milwaukee, Wisc.) in 300 ml. of anhydrous benzene was added over a period of one to two hours with external cooling. Stirring was continued and the mixture was allowed to warm up to room temperature. Ice was then added, and the aqueous phase containing the sodium salt of the hydroxymethylene derivative was washed with ether and immediately acidified with cold 2 *N* sulfuric acid. The acidified solution was extracted several times with ether, and the ether layers were finally combined and dried over anhydrous magnesium sulfate. Removal of the solvent left 174 g. of a yellow oil, λ_{max} 287 μ , ϵ 13,600, which crystallized on cooling (m.p. about 30°). The material could not be satisfactorily recrystallized, however, and was employed in the next step without further purification.

The crude hydroxymethylene ketone XV was dissolved in 1.5 l. of anhydrous benzene containing 52 g. of ethylene glycol and 0.5 g. of *p*-toluenesulfonic acid. The resulting solution was then refluxed (nitrogen atmosphere) under a water separator for 18 hours. At the end of this time the dark solution was cooled and washed twice with 15% potassium carbonate solution and several times with water. After drying over anhydrous magnesium sulfate, the solvent was removed under reduced pressure, and the product was rapidly distilled *in vacuo* in two batches; total yield 167 g., b.p. 184–185° (0.4 mm.). The oily product crystallized on standing, and after recrystallization from ether-petroleum ether afforded 142 g. (77% based on 2,5-dimethoxyacetophenone) of white needles, m.p. 45.5–46.5°, λ_{max} 250, 335 μ , ϵ 5,800, 3,400. The analytical sample melted sharply at 47°.

Anal. Calcd. for C₁₃H₁₆O₅: C, 61.89; H, 6.39. Found: C, 62.22; H, 6.61.

Preparation of β -(2,5-Dimethoxyphenyl)-propionaldehyde Ethylene Acetal (XVII).—Lithium aluminum hydride (25.0 g.) was stirred under reflux with 1 l. of anhydrous ether for 1 hour. A solution of 98.5 g. of XVI, obtained as described in the preceding experiment, in 250 ml. of dry ether was then added dropwise with stirring. After gentle refluxing overnight, the reaction mixture was hydrolyzed by the cautious addition of the minimum amount of water,²³ and the granular precipitate that formed was removed by filtration. The filtrate was then dried over anhydrous magnesium sulfate, and after evaporation of the solvent, 95 g. of a viscous oil was obtained that could not be induced to crystallize.

The crude alcohol obtained at this stage was dissolved in 200 ml. of glacial acetic acid and was stirred in an atmosphere of hydrogen with 15 g. of 10% palladium-charcoal catalyst. After about 20 hours the uptake of hydrogen ceased, and the catalyst was removed by filtration. The filtrate, after clarification by passage through Celite, was poured into water containing excess potassium carbonate, and the product was isolated by ether extraction. Distillation gave 81 g. (87%) of a colorless oil, b.p. 159° (0.04 mm.), λ_{max} 227, 279 μ , ϵ 8,400, 3,800.

Anal. Calcd. for C₁₃H₁₈O₄: C, 65.53; H, 7.61. Found: C, 65.58; H, 7.49.

Preparation of β -(2,5-Dimethoxyphenyl)-propionaldehyde (XVIII) from XVII.—To a solution of 30 g. of XVII in 1 l. of ether-petroleum ether (1:3) there was added 500 ml. of 1 *N* hydrochloric acid. The mixture was vigorously agitated under nitrogen by means of a "vibromischer"²⁴ for a period of 4 hours. The organic layer was then separated and washed with dilute sodium carbonate solution, and the product XVIII was finally isolated *via* the bisulfite addition compound as described in the previous preparation; yield 11.5 g. (67%).

Condensation of β -(2,5-Dimethoxyphenyl)-propionaldehyde (XVIII) with Ethyl Acetoacetate.—A mixture of 10.3 g. of β -(2,5-dimethoxyphenyl)-propionaldehyde (XVIII) and 13.8 g. of ethyl acetoacetate was cooled to 0° and treated

(22) E. Mosettig and R. Mozingo, Chapter 7 in "Organic Reactions," Vol. IV, John Wiley and Sons, New York, N. Y., 1948, p. 368.

(23) Since the reduction product is unusually soluble in water, the use of excessive amounts of water is to be avoided.

(24) A. G. für Chemie-Apparatebau, Zürich.

with a solution of 1 ml. of piperidine in 2 ml. of absolute ethanol. After standing at 0° for 3 days, considerable quantities of crystalline material had separated. The reaction mixture was then diluted with ether, and, after a period of several hours at 0°, the product (12.4 g., m.p. 114–115°) was collected by filtration. The filtrate was dried over anhydrous magnesium sulfate, and, after standing for 3 more days at 0°, an additional 3.0 g. was obtained; total yield, 15.4 g. (69%).

Several recrystallizations from dilute ethanol furnished the analytical sample, m.p. 116–117°.

Anal. Calcd. for $C_{23}H_{22}O_8$: C, 63.28; H, 7.39. Found: C, 63.10; H, 7.23.

Reaction of XIX with Acetic Acid-Sulfuric Acid.—The Knoevenagel condensation product XIX obtained in the preceding experiment (19.0 g.) was dissolved in 30 ml. of acetic acid containing 2 ml. of concentrated sulfuric acid, and the resulting solution was refluxed for 1 hour, during which time the vigorous evolution of carbon dioxide was observed. The reaction product was isolated by standard procedures, and on distillation under reduced pressure 7.8 g. of a pale yellow oil, b.p. 186–190° (0.001 mm.) n_D^{20} 1.5389, was obtained. The material gave unsatisfactory analyses, and could not be purified further by fractional distillation.

A sample of the material was treated with dinitrophenylhydrazine, and the resulting oily product was chromatographed on alumina. Two pure dinitrophenylhydrazones were obtained in this way. One of these substances (m.p. 127–128°) was identified as the dinitrophenylhydrazone of XXI (see below), whereas the second product (m.p. 137–138°) proved to be the dinitrophenylhydrazone of XX.

Anal. Calcd. for $C_{28}H_{30}O_9N_4$: C, 59.31; H, 5.74; N, 10.64. Found: C, 59.37; H, 6.06; N, 10.48.

Preparation of 5- β -(2,5-Dimethoxyphenyl)-ethyl-3-methylcyclohex-2-en-1-one (XXI).—A solution of 45 g. of XIX in 270 ml. of benzene and 225 ml. of ether was treated under nitrogen with 4.5 ml. of concentrated hydrochloric acid. After standing at room temperature for 2 days, the mixture was washed successively with water, saturated sodium bicarbonate solution, water, saturated sodium chloride, filtered through anhydrous magnesium sulfate and evaporated to dryness. The residual oil (43.8 g.) was then taken up in a mixture of 90 ml. of ethanol and 135 ml. of water containing 28.3 g. of sodium hydroxide and allowed to stand at room temperature under nitrogen for 2 days. At the end of this time the solution was heated under reflux for 1 hour, cooled and treated cautiously with a solution of 36 ml. of concentrated sulfuric acid in 135 ml. of water. When the evolution of carbon dioxide had subsided, the mixture was carefully heated to reflux temperature, and refluxing was continued for 0.5 hour. Distillation of the neutral product XXI under diminished pressure afforded 20.8 g. (74%) of a viscous oil boiling at 172–174° (0.06 mm.).

Anal. Calcd. for $C_{17}H_{22}O_3$: C, 74.42; H, 8.08. Found: C, 74.22; H, 7.82.

The dinitrophenylhydrazone melted at 127–128° and did not depress the melting point of the dinitrophenylhydrazone m.p. 127–128°, isolated in the preceding experiment.

Anal. Calcd. for $C_{23}H_{26}O_6N_4$: C, 60.78; H, 5.77; N, 12.33. Found: C, 60.71; H, 5.93; N, 12.37.

Birch Reduction of XXI.—Liquid ammonia (1 l.) dried by distillation from sodium was collected in a 2-l. 3-neck flask equipped with a mechanical stirrer, dropping funnel and outlet tube protected from the atmosphere by a soda lime drying tower. The reaction vessel was maintained at a temperature of about –40° and a solution of 16.9 g. of 5- β -(2,5-dimethoxyphenyl)-ethyl-3-methylcyclohex-2-en-1-one (XXI) in 80 ml. of absolute ethanol was introduced. Sodium (30.0 g.) was then added in small pieces with stirring over a period of 2 hours. At the end of 12 hours alcohol was added until the blue color disappeared, and the ammonia was then allowed to evaporate. The product was taken up in ether, washed with water, and the ether was removed *in vacuo*. Hydrolysis of the residual oil was carried out by warming the material for 0.5 hour with 1 *N* hydrochloric acid

in 20% aqueous ethanol, in which solvent the hydroxy-diketone XXII is quite soluble. After hydrolysis was complete, the remaining insoluble material was removed by extraction with small amounts of petroleum ether, and the clear aqueous alcoholic phase was saturated with ammonium sulfate, and thoroughly extracted with ether. The ether extracts were combined, dried over anhydrous sodium sulfate, concentrated to small volume, and allowed to stand overnight at 0°. At the end of this time 2.0 g. (15%) of the hydroxydiketone XXII, m.p. 92–94°, had separated. A further 2.0 g. of this material could be obtained from the filtrate by repeated chromatography on alumina. Several recrystallizations from benzene-petroleum ether gave the analytical sample, m.p. 103–104°.

Anal. Calcd. for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.21; H, 9.78.

The compound furnished a bis-dinitrophenylhydrazone melting at 210° dec.

Anal. Calcd. for $C_{27}H_{32}O_9N_8$: C, 52.93; H, 5.27; N, 18.28. Found: C, 52.97; H, 5.57; N, 18.21.

Preparation of 5- β -(2,5-Diketocyclohexyl)-ethyl-3-methylcyclohexanone (XXIII).—A solution of 2.44 g. of the hydroxydiketone XXII in 15 ml. of glacial acetic acid and 5 ml. of alcohol-free chloroform was cooled to 0° and treated with a solution of 1.3 g. of chromium trioxide in 3 ml. of acetic acid and 2 ml. of water. After standing overnight at 0° the reaction mixture was diluted with water, and the product was isolated by extraction with methylene chloride. Crystallization from methylene chloride-ether gave 1.5 g. of triketone XXIII melting at 122–123°. The analytical sample, m.p. 123–124°, was obtained after several recrystallizations from benzene-petroleum ether.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 72.23; H, 9.09.

Preparation of 2-Methyl- $\Delta^8(9a)$ -dodecahydrophenanthrene-4,7-dione (XXV).—The triketone XXIII (503 mg.) was dissolved in 50 ml. of acetic acid. Concentrated hydrochloric acid was added, and the mixture was heated to 100° under nitrogen for 16 hours. The dark solution was then poured into water containing an excess of potassium carbonate, and the product was extracted with ether. Removal of the solvent gave 443 mg. of a red oil that crystallized on standing. The material was taken up in benzene, and after passage through a short column of alumina, 384 mg. of light yellow crystals was obtained. Recrystallization from hexane afforded the analytical sample as white prismatic needles melting sharply at 119°, λ_{max} 239 μ , ϵ 15,700, ν_{max} 1700, 1659, 1617 cm^{-1} .

Anal. Calcd. for $C_{15}H_{20}O_2$: C, 77.55; H, 8.68. Found: C, 77.82; H, 8.52.

Birch Reduction of 2,5-Dimethoxytoluene (XXVII).—Liquid ammonia (1.3 l.) was dried with sodium and distilled into a 2-l. 3-neck flask equipped with a mechanical stirrer and maintained at a temperature of about –40°. A solution of 21.3 g. of 2,5-dimethoxytoluene in 75 ml. of absolute ethanol was introduced, and 30 g. of sodium was added in small pieces with stirring over a period of several hours. After 12 hours the ammonia was allowed to evaporate, ether being added from time to time in order to precipitate the sodium ethoxide formed during the reduction. The ethereal solution was decanted from the solid material, and was thoroughly washed with water, dried and distilled. The product (15.9 g., b.p. 208° at 760 mm.) was suspended in aqueous methanol to which several drops of concentrated hydrochloric acid were added. The flask was then shaken until all of the material dissolved (about 15 minutes), and the solution was diluted with water, washed with a small amount of ether and saturated with ammonium sulfate. Repeated extraction with ether furnished 10.3 g. of crystalline 2-methylcyclohexane-1,4-dione, which, after recrystallization from ether-petroleum ether melted at 48° (literature value, 50°).¹⁸ The compound furnished a bis-semicarbazone, m.p. 240° dec. (literature value, 240°).¹⁸

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