

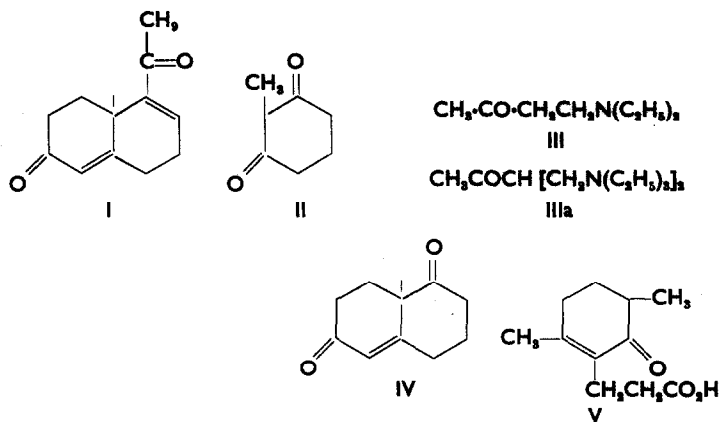
## INTERMEDIATE FOR STEROID SYNTHESSES

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**Abstract**—The synthesis of 1-acetyl-6-oxo-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalene, I, is described.

INTEREST in a practical synthesis of cortisone and other cortical hormones prompted this investigation, the first objective of which was the synthesis of 1-acetyl-6-oxo-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalene, I.



This compound could conceivably be used as an intermediate in many ways for building up the steroidal skeleton containing an 11-oxygenated function. Schemes employing this intermediate have been outlined.<sup>1</sup>

The starting material was 2-methyl-1,3-cyclohexanedione (II) which was made by cyclization of methyl 5-oxoheptanoate in 82 per cent yield. This keto ester was prepared in 75-80 per cent yield by the reaction of  $\gamma$ -carbomethoxybutyryl chloride with ethylcadmium. The dione II was also obtained by direct methylation<sup>2,3a,b,c</sup> of dihydroresorcinol, but the yield of pure II was never better than 42 per cent. The alkylation of II with methylvinyl ketone or 1-dimethylamino-3-butanone (III), to yield 1,6-dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (IV), in low yield has been reported.<sup>1a,4,5</sup> When II and III react in benzene in the presence of pyridine consistent yields of 60 per cent of IV may be obtained. The conventional method of alkylation of II with the methiodide of III in the presence of sodium methoxide resulted in the formation

<sup>1</sup> (a) C. A. Friedman and R. Robinson *Chem. and Ind.* 777, 1117 (1951).

(b) S. Swaminathan and M. S. Newman U.S. Pat. 2, 673, 872 (1954).

<sup>2</sup> Stetter and Dierichs *Ber. Dtsch. Chem. Ges.* 85, 61 (1952).

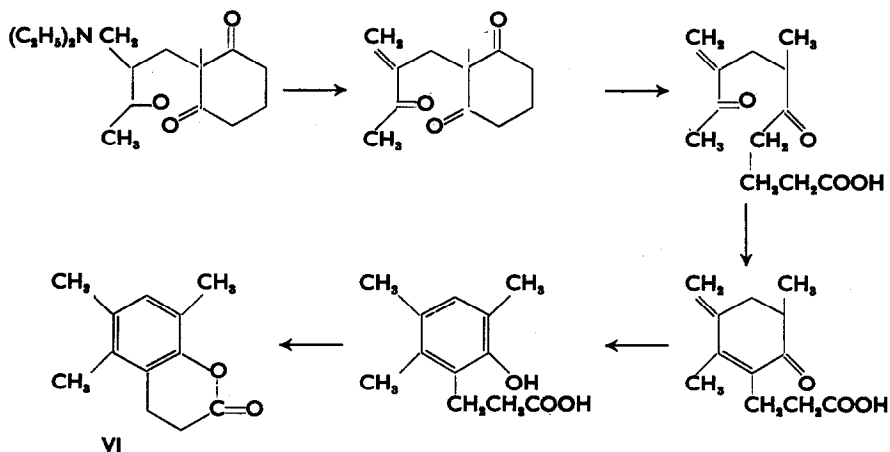
<sup>3</sup> (a) H. Smith *J. Chem. Soc.* 803, (1953), (b) E. G. Meek, J. H. Turnbull, W. Wilson *Ibid.* 811 (1953);

(c) H. Born, R. Pappo, and J. Szmuskovicz *Ibid.* 1779 (1953).

<sup>4</sup> P. Wieland and K. Miescher *Helv. Chim. Acta.* 33, 2215 (1950).

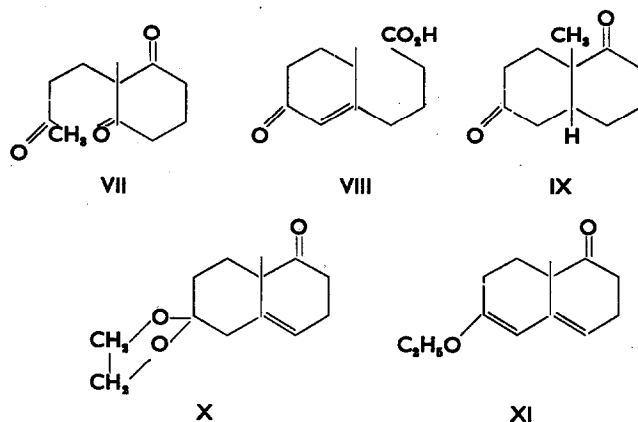
<sup>5</sup> H. L. Wendler, H. L. Slaters, and M. Tishler *J. Amer. Chem. Soc.* 73, 3816 (1951).

of three products: neutral IV obtained in low yield, and identified as the bis-2,4-dinitrophenylhydrazone, and two acidic products having the formulas  $C_{11}H_{16}O_3$  and  $C_{12}H_{14}O_2$ . The former has since been proved<sup>5</sup> to be  $\beta$ -(2,5-dimethyl-6-keto-1-cyclohexen-1-yl)propionic acid (V) and the latter could conceivably be VI arising from alkylation of II by the bis-Mannich base, IIIa, present as an impurity, followed by the sequence of reactions indicated below:



A similar case of formation of byproduct from a bis-Mannich base has been reported.<sup>6</sup>

The reaction of methyl vinyl ketone with II in the presence of Triton B furnished in 35 per cent yield the triketone<sup>7</sup> VII which could also be cyclized by means of a mixture of pyridine and diethylamine in benzene to give IV in 62 per cent yield. Compound IV when treated with dilute alkali underwent cleavage to  $\gamma$ -(6-methyl-3-oxo-1-cyclohexen-1-yl)-butyric acid, VIII.



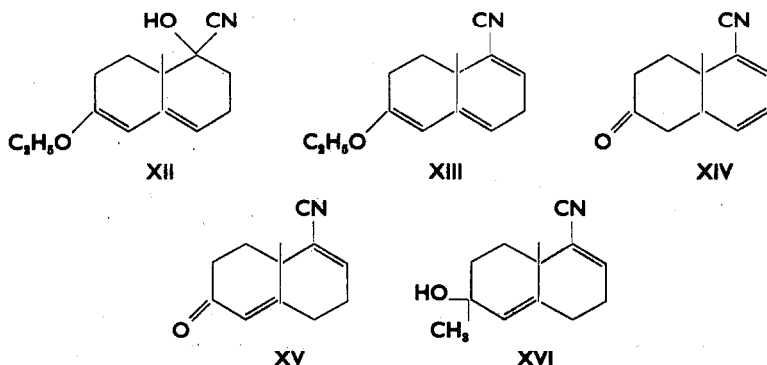
Hydrogenation of IV gave the saturated diketone *cis*-1,6-dioxo-8a-methyl-1,2,3,4,4a,5,6,7,8,8a,-decahydronaphthalene, IX. The *cis* configuration was indicated

<sup>6</sup> A. L. Wilds and C. H. Shunks *J. Amer. Chem. Soc.* **65**, 471 (1943).

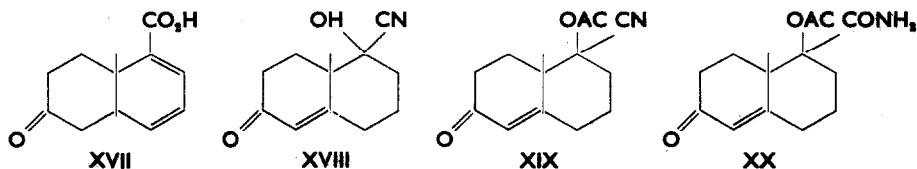
<sup>7</sup> Friedman and Robinson (*loc cit.*) have assigned this structure to the product with m.p. 47–48.5° encountered in the alkylation of II with the methiodide of III. We believe, however, this product to be the isomeric compound V whose structure has been established by Wendler *et al.* (ref. 5).

because an apparently identical compound has been prepared<sup>8</sup> through a Diels-Alder reaction between 2-methoxybutadiene and 2-methyl-2-cyclohexen-1-one followed by hydrolysis. Treatment of IV with ethylene glycol and p-toluenesulfonic acid gave a ketal formulated as X with the double bond in 4, 4a-position in accordance with recent work.<sup>9</sup> With ethyl orthoformate, IV gave the enol ether XI in excellent yield.

The synthesis of I was attempted in two different ways starting with XI. This enol ether when treated with hydrogen cyanide in the presence of triethylamine gave a mixture of the epimeric cyanohydrins, represented by XII, in 50-55 per cent yield. The latter was dehydrated with a mixture of pyridine and phosphorus oxychloride to give a 52 per cent yield of 1-cyano-6-ethoxy-8a-methyl-3,7,8,8a-tetrahydronaphthalene XIII. This unsaturated nitrile was then treated with methylmagnesium bromide; however, there was no evidence of formation of the desired ketone I, and from the



reaction mixture there was isolated after acidification a small amount of a tertiary alcohol, probably XVI, and a keto nitrile. This keto nitrile, which was obtained in better yield (62 per cent) by direct treatment of XIII with alcoholic hydrochloric acid, formed an orange 2,4-dinitro-phenylhydrazone and showed absorption at 289  $m\mu$  ( $\log_{10} \epsilon 2.1$ ). This evidence supports structure XIV rather than XV and other possible alternate structures. Alkaline hydrolysis of XIII or the keto nitrile gave the unsaturated acid XVII with absorption at 286  $m\mu$  ( $\log_{10} \epsilon 3.52$ ). This unsaturated acid, when treated with oxalyl chloride, lost a molecule of water to give a compound, probably a lactone, which, however, proved unreactive towards dimethyl cadmium. Further attempts in the same direction sought to utilize the fact that IV reacted directly and quantitatively with hydrogen cyanide to yield a mixture of the epimeric cyanohydrins, XVIII. This mixture resisted all attempts at dehydration by a variety of reagents, the



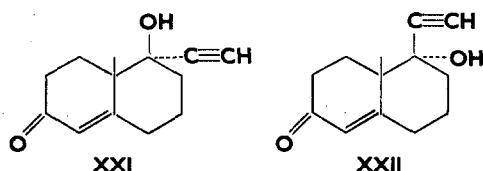
product isolated in most cases being the parent diketone, IV. With isopropenyl acetate, XVIII furnished a single acetoxy keto nitrile XIX in good yield. Prolonged

<sup>8</sup> I. N. Nazarov and O. Bergel'son *Zh. Obshch. Khim.* **20**, 648 (1950); *C.A.* **44**, 8913 (1950).

<sup>9</sup> G. I. Poos, C. E. Arth, R. E. Beyler and L. H. Sarett *J. Amer. Chem. Soc.* **75**, 422 (1953).

hydrolysis of XIX with acid led only to the amide XX; the acid apparently was not formed.

From the reaction of XI with potassium acetylide in tertiary amyl alcohol, a mixture of the epimeric ethynyl alcohols XXI and XXII was obtained in 35–40 per cent yield in a ratio of 5:1 respectively. Structure XXI was assigned to the higher melting, less



soluble isomer. The ultra-violet and infra-red absorption data leave no doubt as regards the structures of the ethynyl alcohols, previously reported as liquids, obtained by reacting IV with sodium acetylide in liquid ammonia. A byproduct isolated in the preparation of the above ethynyl alcohols was the acid VIII indicating that XI underwent cleavage to some extent during the reaction.

The action of formic acid on XXI resulted largely in epimerization to XXII. The desired ketone, I, isolated as the dioxime, was formed only in poor yield. The conversion of XXI to I in good yield was tried with a number of reagents but without success. The difficulty we encountered in effecting this conversion, coupled with the fact that we obtained both the epimeric ethynyl alcohols as fairly high melting solids, prompted us to re-examine the nature of the liquid obtained<sup>1(a)</sup> by reacting sodium acetylide with IV and described as the ethynyl alcohol. On repeating this reaction we obtained a 50–55 per cent yield of a liquid product (b.p. 125–130° at 0.1 mm) along with varying amounts of XXI which, however, did not exceed 5 per cent in any experiment. The same liquid, analyzed for  $C_{13}H_{16}O_2$ , afforded a crystalline dioxime in 52 per cent yield based on the weight of the liquid used, in contrast to the solid ethynyl alcohols XXI and XXII from which no crystalline oxime could be prepared. There was no depression of melting point on admixture of this product with the dioxime of the product obtained after treatment of XXI with formic acid. Evidently, the liquid product referred to is a mixture of products containing at least 45 per cent of the desired ketone 1, probably formed by isomerization of the intermediate ethynyl alcohols during acidification of the reaction mixture. The dioxime when decomposed with pyruvic acid gave I in 85 per cent yield.

We wish to thank the Upjohn Company, Kalamazoo, Michigan, for their generous support of this research.

#### EXPERIMENTAL\*

##### 1-Diethylamino-3-butanone

*Method A.* 1-Diethylamino-3-butanone was prepared according to the method of Wilds and Shunk<sup>6</sup> from acetone, formaldehyde, and diethylamine hydrochloride. Since the yields of the material were quite erratic, procedure (B) was followed.

*Method B.* To a stirred cooled (ice bath) mixture of 160.9 g of diethylamino (2.2 moles) and 4.5 ml of glacial acetic acid were added dropwise 140.3 g (2.00 moles) of methyl

\* All of the compounds described gave correct analytical values but since many have been described<sup>4,5</sup> since this work was completed we have omitted duplications. Analyses are given where differences in m.p. appear.

vinyl ketone. Stirring was continued for 2 hr while the temperature of the solution was allowed to rise to 27°. After extraction with 50 per cent potassium hydroxide solution and washing with water the dried solution was fractionally distilled through a 10 in. Vigreux column. Following a forerun of volatile material with an amine-like odor, there were obtained 195.4 g (68 per cent) of colorless liquid, b.p. 69–73°/16 mm.

#### 2-Methyl-1,3-cyclohexanedione. II

*Method A.* To a solution of 90 g of sodium in 1 l. of absolute methanol was added slowly 430 g of dihydroresorcinol<sup>10</sup> (3.84 moles). Gentle reflux was maintained as 650 g of methyl iodide was added over a period of 2 hr. After standing at 25° overnight, 130 g of long white needles of II, m.p. 208–210°, were obtained. Concentration of the remaining solution afforded an additional 73 g of material of the same melting point. The combined fractions, 203 g (42 per cent) were used directly in the next step.

#### Methyl 5-oxoheptanoate<sup>11</sup>

*Method B.* To a cooled solution of ethylmagnesium bromide, prepared from 109 g of ethyl bromide and 24.5 g of magnesium in 500 cm<sup>3</sup> of anhydrous ether, were added 98 g of anhydrous cadmium chloride during 20 min. After the addition was over, the mixture was stirred for an additional period of 45 min at room temperature. Ether was distilled rapidly from the stirred mixture until distillation slowed down and a nearly dry, dark semisolid remained. To this were added 500 ml of thiophene-free benzene and the benzene suspension was well stirred. A solution of 82.5 g of *ν*-carbo-methoxybutyryl chloride in 125 ml of benzene was added dropwise. After completion of the addition, the mixture was refluxed with stirring for 30 min and then decomposed with ice and 15 per cent sulfuric acid. After washing with bicarbonate and saturated salt solutions the solvents were stripped. Distillation afforded 61 g (77 per cent) of ester, b.p. 96–97° at 8 mm  $n_D^{20}$  1.4325.

The cyclization of 76.5 g of this ester<sup>12</sup> gave 48 g (79 per cent) of II, m.p. 207–210°.

#### 1,6-Dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene (IV)

A mixture of 25.2 g of II, 17 ml of pyridine, 34 g of 1-diethylamino-3-butanone and 250 ml of benzene was refluxed for 18 hr. After cooling, the solution was washed successively with 240 ml of 7.5 per cent hydrochloric acid, two 200 ml portions of water and saturated sodium chloride solution. After removal of solvent, the residual liquid (30 g) was distilled *in vacuo*. The fraction (20 g) with b.p. 109–115° at 0.05 mm solidified when cooled in ice and was crystallized from ether to give 13 g of IV, m.p. 47–48°. An additional 2.5 g of IV was obtained by diluting the ether filtrate with petroleum ether and cooling.

In a subsequent run employing 151.2 g (1.2 moles) of II the reaction product remaining after removal of benzene was solidified by seeding with the product obtained above. The material was then triturated with ether and filtered to give 85 g of IV. The filtrate after concentration gave 100 g of liquid which when distilled *in vacuo* gave 55 g of a fraction, b.p. 109–115° at 0.05 mm and 30 g of a higher fraction, b.p. 115–140° at 0.05 mm. The former yielded 32 g of crystalline IV. The filtrate from this

<sup>10</sup> R. B. Thompson *Org. Syntheses* 27, 21 (1947).

<sup>11</sup> B. W. Clutterback and H. S. Raper *Biochem. J.* 19, 393 (1925).

<sup>12</sup> E. E. Blaise and M. Maire *Bull. Soc. Chim.* (4) 3, 421 (1908).

crystallization was concentrated and the residual liquid (23 g) as well as the higher boiling fraction obtained above were treated with hydroxylamine hydrochloride to give the dioxime of IV. After decomposition with pyruvic acid the dioxime yielded an additional 15–20 g of crystalline IV. The total yield of IV was 61–64 per cent.

The analytical sample of IV,<sup>5</sup> m.p. 47.5–48.5°  $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$  243 m $\mu$ ,  $\log_{10} \epsilon$  4.18 was obtained after two recrystallizations from ether. The i.r. spectrum showed two carbonyl absorptions at 5.82 and 5.98 $\mu$  in chloroform.

The bis 2,4-dinitrophenylhydrazones<sup>5</sup> of IV melted at 247.5–248.5° (dec.) after crystallization from ethanol-pyridine. A mono-2,4-DNPH was also obtained and crystallized from ethanol-pyridine, m.p. 185.5–186.5°. *Anal.* Calcd. for  $\text{C}_{17}\text{H}_{18}\text{N}_4\text{O}_5$ : C, 57.0; H, 5.1; N, 15.6 Found: C, 56.7; H, 5.2; N, 16.0.

The dioxime of IV was crystallized from methanol and melted at 199–200°. *Anal.* Calcd. for  $\text{C}_{11}\text{H}_{16}\text{N}_2\text{O}_2$ : C, 63.4, H, 7.7; N, 13.5. Found: C, 63.5; H, 7.6; N, 13.8.

#### *Regeneration of IV from its dioxime*

A mixture of 1 g of the dioxime, 5 ml of acetic acid, 10 ml of water and 2.3 g of pyruvic acid was refluxed for 2 hr and diluted with 20 ml of water. After neutralization with 10 g of sodium bicarbonate, the solution was extracted with ether. The ether extract after washing with saturated sodium chloride solution and drying over anhydrous sodium sulfate was concentrated to give 0.7 g (82 per cent) of crystalline IV.

#### *Cis-1,6-Dioxo-8a-methyl-1,2,3,4,4a,5,6,7,8,8a-decahydronaphthalene (IX)*

A solution of 0.5 g of IV in 25 ml of absolute alcohol was hydrogenated at 40 lb/in<sup>2</sup> in the presence of 0.2 g of 1 per cent palladized calcium carbonate for 30 min at 27°. After removal of the catalyst, and concentration of the filtrate to 5 ml, 440 mg (88 per cent) of small white crystals, m.p. 63–64°, was obtained. The analytical sample, obtained by recrystallization from ether-petroleum ether, b.p. 35–40° (Skellysolve F) melted at 64.5–65.5°,  $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$  288 m $\mu$ ,  $\log_{10} \epsilon$  1.59.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{16}\text{O}_2$ : C, 73.3; H, 9.0. Found: C, 73.3; H, 8.8. The disemicarbazone<sup>6</sup> melted at 219–222°.

#### *2-Methyl-2-(3'-oxobutyl)-1,3-cyclohexanedione, VII*

A mixture of 7.6 g (0.06 mole) of II, 6 ml of 85 per cent methyl vinyl ketone,\* 35 ml of methanol, and 0.8 ml. of 40 per cent Triton B (quaternary ammonium hydroxide base) was refluxed for 7 hr. The methanol was removed by distillation and the residual liquid was poured into 50 ml of water acidified with 1.6 ml of 1.5 N hydrochloric acid, and extracted with ether. The extract was washed with 5 per cent sodium bicarbonate solution, followed by saturated sodium chloride solution. After drying and removal of solvent, the residue was distilled *in vacuo* to give 4.1 g (35 per cent) of VII, b.p. 114–116° at 0.1 mm. Treatment with hydroxylamine hydrochloride in pyridine-methanol gave a trioxime, m.p. 181–182°, after two crystallizations from methanol.

*Anal.* Calcd. for  $\text{C}_{11}\text{H}_{18}\text{N}_3\text{O}_3$ : C, 54.8; H, 7.9; N, 17.4. Found: C, 55.2, H, 8.1; N, 17.3.

Cyclization of 1.96 g of VII in the presence of diethylamine and pyridine afforded IV, m.p. and mixed m.p. 46–48°, in 62 per cent yield.

\* We are indebted to the Du Pont Company for generous gifts of methyl vinyl ketone.

*1-Oxo-6-ethoxy-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene*, XI

A mixture of 43.2 g of IV, 41 g of triethyl orthoformate, 240 ml of dry benzene, and 10 ml of 5 per cent anhydrous ethanolic hydrochloric acid was refluxed for 2 hr. The dark mixture was cooled, neutralized with 5 per cent alcoholic sodium hydroxide solution, and taken up in 200 ml of ether. The ether-benzene solution was successively washed with 100 ml of water, 300 ml of 5 per cent sodium hydroxide solution, 100 ml of water, and saturated sodium chloride solution, and then dried over sodium sulfate. Distillation afforded 40 g (80 per cent) of a lemon yellow liquid, b.p. 101–104° at 0.1 mm. The analytical sample, b.p. 103° at 0.1 mm,  $n_D^{24}$  1.5257,  $\lambda_{\max}^{C_6H_5OH}$  243 m $\mu$ ,  $\log_{10} \epsilon$  4.17, absorption at 5.82 and 6.1  $\mu$  (Sandwich cell), was obtained by redistillation.

*Anal.* Calcd. for  $C_{18}H_{18}O_2$ : C, 75.7; H, 8.8. Found: C, 75.2; H, 9.1.

The oxime was prepared through treatment with an aqueous-alcoholic solution of sodium hydroxide and hydroxylamine hydrochloride. After two crystallizations from methanol, it melted at 132.5–134°.

*Anal.* Calcd. for  $C_{18}H_{19}NO_2$ : C, 70.6; H, 8.7; N, 6.3. Found: C, 70.9; H, 8.4; N, 6.2.

*The reaction of 2-methyl-1,3-cyclohexanedione with 1-diethylamino-3-butanone methiodide in the presence of sodium methoxide*

To a solution of 5.4 g of sodium methoxide in 25 ml of anhydrous methanol was added a solution of 12.6 g of II in 50 ml of dry methanol. The mixture was stirred and treated with 50 ml of a methanolic solution of 40.9 g of 1-diethylamino-3-butanone methiodide. After stirring at 27° for 4 hr, the mixture was refluxed for 2 hr. It was then concentrated by distillation to 45 ml, diluted with 300 ml of water, and extracted with ether. The aqueous layer containing acidic material and the ether layer containing neutral material were worked up separately.

The ethereal solution was washed successively with dilute hydrochloric acid and saturated sodium chloride, and dried over sodium sulfate. After removal of the ether, distillation afforded 2g of a yellow liquid, b.p. 110–115° at 0.29 mm, which gave a 2,4-dinitrophenylhydrazone, m.p. 249–251°, undepressed by admixture with the bis-2,4-DNPH derivative of IV.

The alkaline aqueous layer remaining after extraction from ether was acidified with dilute hydrochloric acid and the acidified solution was extracted with ether. Distillation yielded 11.5 g of a yellow liquid, b.p. 160–170° at 2 mm. The partially solid distillate was dissolved in the minimum amount of ethanol; on addition of a few drops of water and chilling, 0.99 g of material, m.p. 99–102°, were obtained. After two crystallizations from ethanol, the product melted at 103°, and had  $\lambda_{\max}^{C_6H_5OH}$  273 m $\mu$ ,  $\log_{10} \epsilon$  3.01,  $\lambda_{\max}^{C_6H_5OH}$  282 m $\mu$ ,  $\log_{10} \epsilon$  3.0. I.r. absorption showed a maximum at 5.68  $\mu$  (chloroform). This product is probably 3,4-dihydro-5,6,8-trimethylcoumarin, VI.

*Anal.* Calcd. for  $C_{12}H_{14}O_2$ : C, 75.8; H, 7.4. Found: C, 75.7; H, 7.2.

The alcoholic filtrate obtained from the product above was freed of solvent and dissolved in ether. After the usual working up 7 g of a liquid b.p. 130–132° at 0.7 mm, were obtained which solidified completely. A portion<sup>5</sup> of V recrystallized three times from ether-Skellysolve F melted at 47–48°, and had  $\lambda_{\max}^{C_6H_5OH}$  242 m $\mu$ ,  $\log_{10} \epsilon$  4.25. I.r. absorption maxima at 5.75 and 5.96  $\mu$  (tetrahydrofuran).

*Anal.* Calcd. for  $C_{11}H_{16}O_3$ : C, 67.3; H, 8.2. Found: C, 67.6; H, 8.1; N.E. Calcd. 196.2; Found: 198.2.

The semicarbazone<sup>5</sup> melted at 195–196° after two crystallizations from absolute ethanol.

*Anal.* Calcd. for  $C_{12}H_{19}N_3O_3$ : C, 56.9; H, 7.6; N, 16.6. Found: C, 56.9; H, 7.8; N, 17.0.

The 2,4-dinitrophenylhydrazone<sup>5</sup> melted at 103–104° after two crystallizations from ethanol.

*Anal.* Calcd. for  $C_{19}H_{24}N_4O_6$ : C, 56.4; H, 6.0; N, 13.9. Found: C, 56.2; H, 6.1; N, 13.9.

*γ*-(6-Methyl-3-keto-1-cyclohexen-1-yl)-butyric acid (VIII)

A mixture of 0.5 g of IV and 5 ml of 10% potassium hydroxide was allowed to stand for 20 min at 27°, heated on a steam bath for 5 min, cooled and diluted with 5 ml of water, and acidified. The cloudy suspension was extracted with ether, and the solution worked up as usual. There was obtained in 75 per cent yield the acid, VIII,<sup>5</sup> m.p. 77.5–78.0°,  $\lambda_{\text{max}}^{C_{17}H_{25}OH}$  238 m $\mu$ ,  $\log_{10} \epsilon$  4.17, i.r. absorption at 5.82 and 5.98  $\mu$  (chloroform).

1,6-Dioxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene-6-ethylene ketal, X

A mixture of 8.9 g of IV, 3.4 g of ethylene glycol, 110 ml of benzene and 0.25 g of *p*-toluenesulfonic acid was refluxed for 5 hr, after which 75 ml of benzene was removed by distillation. The concentrated reaction mixture was refluxed for 4 hr, cooled, and taken up in ether. On distillation at 0.01 mm in a magnetically stirred Hickman still with bath temperature at 100–115° there was obtained 6.1 g (55 per cent) of X as a lemon-yellow liquid having i.r. absorption maxima at 5.85, 6.0, and 6.16  $\mu$  (Sandwich cell).

*Anal.* Calcd. for  $C_{13}H_{18}O_3$ : C, 70.2, H, 8.2. Found: C, 70.2, H, 7.9.

*Preparation of 1-hydroxy-1-cyano-6-ethoxy-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene, XII*

*A. By reaction with potassium cyanide and glacial acetic acid.* To a cooled stirred suspension of 99 g of potassium cyanide in 160 ml of ethanol was added 90 ml of glacial acetic acid followed with a solution of 24.7 g of XI in 100 ml of ethanol. After 3 hr at 0° the reaction mixture was diluted with 480 ml of water and the yellow solid which separated (17 g) was collected and dried. On further dilution with 600 ml of water, there was obtained 3.2 g of the same material; crystallization from ether afforded 13 g (48 per cent) of cyanohydrin, m.p. 145–155°, undoubtedly a mixture of stereoisomers of XII. After three crystallizations from ether, the m.p. rose to 155–158°;  $\lambda_{\text{max}}^{C_{14}H_{19}OH}$  242 m $\mu$ ,  $\log_{10} \epsilon$  4.3, i.r. absorption maxima at 3.0, 4.59, 6.03, and 6.13  $\mu$  (mineral oil, Nujol).

*Anal.* Calcd. for  $C_{14}H_{19}NO_2$ : C, 72.1; H, 8.2; N, 6.0. Found: C, 71.7; H, 8.0; N, 6.2.

*B. By reaction with liquid hydrogen cyanide.* To 100 ml of cooled and stirred liquid hydrogen cyanide was added five drops of aqueous potassium cyanide and 100 g of XI dropwise. After the addition was complete, the mixture was allowed to stand for 45 min, and the excess hydrogen cyanide was removed by distillation. Crude material (60 g) was collected. On crystallization from ether 55 g (48 per cent) of XII, m.p. 150–156° was obtained.



1-Cyano-6-ethoxy-8a-methyl-3,7,8,8a-tetrahydronaphthalene, XIII

To an ice cold solution of 42 g of XII in 175 ml of pyridine were added dropwise 34 ml of phosphorus oxychloride. The resulting solution was allowed to stand at 27° for 20 hr and then heated on a steam bath for two hours. After cooling, the reaction mixture was poured on ice, acidified with concentrated hydrochloric acid and immediately extracted with ether. On distillation of the ether-soluble material there was obtained 24 g of liquid, b.p. 125–130° at 0.2 mm. In order to insure that the product was free from material arising from hydrolysis of the enol ether the distillate was heated on a steam bath with a mixture of 24 ml of ethyl orthoformate, 250 ml of benzene and 4 ml of 12 per cent alcoholic hydrochloric acid for 2.5 hr. There was obtained 20 g (52 per cent) of XIII b.p. 105–109° at 0.2 mm.,  $\lambda_{\text{max}}^{\text{C}_6\text{H}_5\text{OH}}$  232 m $\mu$ ,  $\log_{10} \epsilon$  4.08, i.r. absorption at 4.6  $\mu$  (Sandwich cell).

Anal. Calcd.  $\text{C}_{14}\text{H}_{17}\text{NO}$ : N, 6.5 Found: N, 6.3.

Attempted preparation of 1-acetyl-6-oxo-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalene (I) from XIII

A solution of 5.7 g of XIII in 50 ml of ether was treated with excess methylmagnesium bromide in ether. After 7 hr at reflux with stirring, the mixture was decomposed with 85 ml of 6 N hydrochloric acid. The ethereal layer was concentrated and the residual liquid (4 g) distilled to yield 1.8 g of distillate, b.p. 95–110° at 0.08 mm. I.r. analysis of this material indicated the presence of —OH, —CN and —CO-groups. Crystallization afforded 0.5 g of material, m.p. 69–70°, undepressed by XIV (see below), obtained by hydrolysis of XIII. The liquid remaining in the mother liquor after removal of the crystalline XIV was dissolved in ether and chromatographed over deactivated alumina. The ethereal eluate deposited crystals after concentration and cooling. When crystallized from a mixture of ether and petroleum ether 18 mg of 1-cyano-6-hydroxy-6,8a-dimethyl-3,4,6,7,8,8a-hexahydronaphthalene, XVI, m.p. 92–93° were obtained. The compound had no maxima between 225 and 300 m $\mu$ . I.r. maxima were at 2.83, 4.56 and 6.08  $\mu$  (chloroform).

Anal. Calcd. for  $\text{C}_{13}\text{H}_{17}\text{NO}$ : C, 76.7 H, 8.4; N, 6.9. Found: C, 76.9; H, 8.4; N, 6.7.

1-Cyano-6-oxo-8a-methyl-4a,5,6,7,8,8a-hexahydronaphthalene XIV

A mixture of 10.5 g of XIII, 50 ml of ethanol, 25 ml of water, and 5 ml of concentrated hydrochloric acid was refluxed for 45 min. After concentration of the mixture *in vacuo*, the residue was diluted with 100 ml of water and extracted with ether. After the usual working up of the ethereal solution, the residue was distilled at 0.1 mm in a Hickman still, giving 5.67 g (62 per cent) of product, with the bath temperature at 92–96°. The distillate solidified, and after two crystallizations from ether-Skellysolve F, yielded XIV, m.p. 69–70°,  $\lambda_{\text{max}}^{\text{C}_6\text{H}_5\text{OH}}$  289 m,  $\log_{10} \epsilon$  2.1. I.r. absorption maxima at 4.75, 5.84, and 6.04  $\mu$  (chloroform).

Anal. Calcd. for  $\text{C}_{12}\text{H}_{13}\text{NO}$ ; C, 77.0; H, 7.0; N, 7.5. Found: C, 76.9; H, 6.8 N, 7.7.

The orange 2,4-dinitrophenylhydrazone of XIV melted at 161.5–162.5° after crystallization from ethyl acetate-ethanol.

Anal. Calcd. for  $\text{C}_{18}\text{H}_{17}\text{N}_5\text{O}_4$ : C, 58.8; H, 4.7; N, 19.1. Found: C, 58.2; H, 4.7; N, 18.6.

**6-Oxo-8a-methyl-4a,5,6,7,8,8a-hexahydro-1-naphthoic acid, XVII**

A mixture of 6g of XIII, 40ml of ethylene glycol, 5g of sodium hydroxide, and 10ml of water was refluxed for 8 hr. After cooling, the mixture was poured into water and extracted with ether to remove unreacted nitrile; the aqueous layer was acidified with dilute sulfuric acid and heated on a steam bath for 10 min. The solution was filtered while hot, and on cooling, 0.5 g of crystals was deposited. Ether extraction of the filtrate afforded 1.05 g of material. The combined fractions were crystallized from ethanol to give 1.1 g (19 per cent) of the acid XVII, m.p. 158–159°,  $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$  286 m $\mu$ ,  $\log_{10} \epsilon$  3.52. I.r. absorption maximum at 5.88  $\mu$  (Nujol).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_3$ : C, 69.9; H, 6.8. Found: C, 70.0, 70.1; H, 7.2, 7.0.

The same acid was obtained in comparable yields by hydrolysis of XIV under similar conditions.

**Lactonization (?) of XVII and reaction with methylcadmium**

A mixture of 1 g of 6-oxo-8a-methyl-4a,5,6,7,8,8a-hexahydro-1-naphthoic acid XVII, 3 ml of oxalyl chloride and 20 ml of benzene was kept at 27° for 3 hr. Excess benzene and oxalyl chloride were removed *in vacuo*, and the residual solid was dissolved in 12 ml of benzene. To this solution was added an ethereal solution of methylcadmium (0.0135 mole). The reaction mixture was refluxed for 2 hr and then treated with dilute sulfuric acid. Ether extraction and concentration afforded 0.6 g (64 per cent) of crystalline product, which after two crystallizations from ether melted at 119.0–120.5°. The material was judged to be a lactone, from the i.r. absorption maximum at 5.55  $\mu$ . When the acid XVII was heated and sublimed *in vacuo*, the same compound was formed.

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{12}\text{O}_3$ : C, 76.6; H, 6.4. Found: C, 76.6, 76.8; H, 6.4, 6.3.

**1-Cyano-1-hydroxy-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene, XVIII**

To an ice-cold solution of 40 g of IV in 70 ml of liquid hydrogen cyanide was added five drops of aqueous potassium cyanide solution. After the mixture had stood at 27° for 30 min the excess hydrogen cyanide was removed by distillation. The residue which solidified on cooling was collected, washed with water, and dried. The yield of crude cyanohydrin was quantitative. After crystallization from ether-methanol or from chloroform five times, XVIII was obtained as a mixture of stereoisomers, m.p. 115–120°,  $\lambda_{\text{max}}^{\text{C}_2\text{H}_5\text{OH}}$  244 m $\mu$ ,  $\log_{10} \epsilon$  4.13, i.r. absorption maxima at 3.0, 6.01, and 6.15  $\mu$  (Nujol).

*Anal.* Calcd. for  $\text{C}_{12}\text{H}_{15}\text{NO}_2$ : C, 70.2; H, 7.4; N, 6.8. Found: C, 70.4, 70.2; H, 7.4, 7.1; N, 6.9, 7.0.

**1-Acetoxy-1-cyano-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene, XIX**

A mixture of 5 g of XVIII, 4 ml of isopropenyl acetate, and 10 mg of *p*-toluenesulfonic acid was heated on a steam bath for 30 min. The mixture was clear initially, but solid material appeared as the reaction progressed, and the mass was solid when the heating period was over. After crystallization from alcohol, 5.1 g (85 per cent) of product, m.p. 203–207° was obtained; recrystallization from alcohol yielded the analytical sample, m.p. 208–210°; i.r. absorption maxima at 5.68, 5.96, and 6.12  $\mu$  (Nujol).

*Anal.* Calcd. for  $\text{C}_{14}\text{H}_{17}\text{NO}_3$ : C, 68.0; H, 6.9; N, 5.7. Found: C, 68.1; H, 7.0; N, 5.7.

1-Acetoxy-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydro-1-naphthoic amide, XX

A mixture of 2.5 g of XIX and 15 ml of concentrated hydrochloric acid was refluxed for 12 hr. Excess acid was removed *in vacuo*, and the residue was extracted with boiling acetone. The acetone solution afforded 0.8 g of material m.p. 228–231°, the acetone-insoluble residue was treated with sodium carbonate solution and the alkali-insoluble portion was crystallized from ethanol to give an additional 0.41 g of material m.p. 234–237°. The combined crops (46 per cent) were crystallized twice from ethanol to give crude XX, m.p. 240–242°, i.r. maxima at 3.08, 5.83 and 5.93  $\mu$  (Nujol).

*Anal.* Calcd. for  $C_{14}H_{19}NO_4$ ; C, 63.4; H, 7.2; N, 5.3. Found: C, 62.9; H, 7.9; N, 5.9.

1-Ethynyl-1-hydroxy-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene, XXI and XXII

Purified and dried acetylene was bubbled through a stirred mixture of anhydrous ether (100 ml) and a solution of 4 g of potassium in 70 ml t-amyl alcohol cooled in ice. After 2 hr, a solution of 20.6 g of freshly distilled XI in 100 ml of anhydrous ether was added over a period of 1 hr. The dark red reaction mixture was allowed to stand overnight in the ice-bath with continued passage of acetylene and stirring. After treatment of the mixture with 200 ml of 6 per cent hydrochloric acid, the ether layer was separated and combined with an additional ethereal extract of the aqueous layer. The combined extracts were washed twice with 150 ml portions of 5 per cent potassium carbonate solution, followed by water and sodium chloride solution. After drying, the solution was concentrated to a volume of 40 ml when crystals were deposited. After chilling, collecting, and washing the material with cold ether, 8.2 g (40 per cent) of light tan crystals, m.p. 140–170°, was obtained. Two crystallizations of this material from alcohol gave 6.6 g of large white prisms, m.p. 170–172°; this represented a yield of 32 per cent of the alcohol XXI. The analytical sample, m.p. 171.5–172.5°,  $\lambda_{\max}^{C_{13}H_{16}OH}$  240  $m\mu$ , 316  $m\mu$ ,  $\log_{10} \epsilon$  4.14, 1.76, was obtained through two more crystallizations from alcohol. I.r. absorption maxima at 2.99, 3.08, 4.79, and 6.07  $\mu$  (Nujol).

From the mother liquors from crystallizations of the ethynyl alcohol, XXI, there were obtained 1.3 g of white crystals of the isomeric alcohol, XXII, m.p. 145–147°,  $\lambda_{\max}^{C_{13}H_{16}OH}$  240  $m\mu$ ,  $\log_{10} \epsilon$  4.16. i.r. absorption maxima at 2.99, 3.08, 4.79, and 6.07  $\mu$  (Nujol).

*Anal.* Calcd. for  $C_{13}H_{16}O_2$ ; C, 76.4; H, 7.9. Found: (172° isomer) C, 76.4; 76.3; H, 7.8, 7.8. (147° isomer) C, 76.1, 76.3, H, 7.6, 7.7.

The reddish purple 2,4-dinitrophenylhydrazine of XXI melted at 221.5–222.5° after two crystallizations from ethyl acetate-alcohol. The deep red 2,4-DNPH of XXII melted at 195–198° after crystallization from alcohol.

*Anal.* Calcd. for  $C_{19}H_{20}N_4O_5$ ; C, 59.4; H, 5.3; N, 14.6. Found: (DNPH of XXI) C, 59.7; H, 5.4 (DNPH of XXII) C, 59.3; H, 5.4; N, 14.6.

Working up of the original potassium carbonate extract, by acidifying and extracting with ether, afforded 5.6 g of a product which after crystallization from ether-Skellysolve F melted alone and mixed with authentic VIII at 77–78°.

*The reaction of 1-ethynyl-1- $\beta$ -hydroxy-6-oxo-8a-methyl-1,2,3,4,6,7,8,8a-octahydronaphthalene, XXI, with formic acid.*

A solution of 4.5 g of XXI in 20 ml of 92 per cent formic acid was refluxed for 1 hr. The excess formic acid was then removed by distillation *in vacuo* and the dark brown

residue was taken up in 150 ml of ether. The ethereal solution was washed successively with 100 ml. of 2 per cent potassium carbonate solution and saturated sodium chloride solution. After drying over sodium sulfate, the ether solution was treated with charcoal (Norite) and concentrated to yield 1.4 g of crystals which after crystallizations from ether containing some ethanol melted at 145–146° alone and mixed with authentic XXII.

The ether filtrate left after separation of XXII was freed of solvent and the residual tarry liquid treated with hydroxylamine hydrochloride in pyridine and methanol. A small amount of the dioxime of I, m.p. 200–202°, was obtained.

In a subsequent similar run with 2.8 g of XXI, the crude liquid left after separation of XXII was chromatographed over deactivated alumina. Elution with ether afforded a small amount of liquid which solidified on cooling. After crystallization from a mixture of ether and petroleum ether, the product (5 mg) melted at 92–93° and was presumably I.

*Anal.* Calcd. for  $C_{13}H_{16}O_2$ : C, 76.4; H, 7.9. Found: C, 76.7; H, 8.0.

The amount available of this material was quite small and no further work was done to characterize it.

#### *The reaction of sodium acetylide with IV*

Dry acetylene was bubbled into approximately 200 ml of liquid ammonia in a 500 ml three necked flask equipped with a gas inlet tube and a mechanical stirrer, while 2.3 g of sodium was added over a period of 20 min. The flow of acetylene was then reduced and a solution of 17.8 g of IV in 100 ml of dry ether was added over a period of 1 hr. After this addition was completed, the reaction mixture was allowed to stand for 20 hr. The mixture was then decomposed with 100 ml of ice-cold water and acidified with dilute hydrochloric acid. After washing with alkali and drying, the ether was removed and the residue distilled to yield 9–10 g of a viscous yellow distillate, b.p. 125–130° at 0.1 mm. A portion was redistilled and analyzed.

*Anal.* Calcd. for  $C_{13}H_{16}O_2$ : C, 76.4; H, 7.9. Found: C, 76.6, 76.4; H, 7.9, 7.9.

The distillate obtained above (9 g) when triturated with ether and cooled, deposited 0.5 to 0.7 g of XXI, m.p. and mixed m.p. with authentic XXI, 171–172°. The filtrate was freed of ether and heated for 15 min with a mixture of 7.5 g of hydroxylamine hydrochloride, 25 ml of absolute ethanol and 20 ml of pyridine. The dioxime (4.7 g) of I crystallized after diluting the reaction mixture with water and cooling. After a crystallization from ethanol, it melted at 200–202° alone and mixed with the dioxime of the product of reaction of formic acid with XXI.

*Anal.* Calcd. for  $C_{13}H_{18}N_2O_2$ : C, 66.6; H, 7.7; N, 12.0. Found: C, 66.9, 66.9; H, 7.9, 7.7; N, 11.6, 11.8.

#### *1-Acetyl-6-oxo-8a-methyl-3,4,6,7,8,8a-hexahydronaphthalene, I*

A mixture of 2 g of the dioxime obtained above, 5 ml of pyruvic acid, 10 ml of acetic acid and 20 ml of water was refluxed for 1 hr. The reaction mixture was diluted with 100 ml of water, neutralized with sodium carbonate and extracted twice with ether. The combined ether extracts were washed with saturated sodium chloride solution and dried over sodium sulfate. On distillation there was obtained 1.5 g of I, b.p. 85–88° at 0.002 mm.,  $\lambda_{\max}^{C_2H_5OH}$  246 m $\mu$ ,  $\log_{10} \epsilon$  3.91. i.r. absorption peaks at 5.85, 6.0, and 6.17  $\mu$ .

*Anal.* Calcd. for  $C_{13}H_{16}O_2$ : C, 76.4; H, 7.9. Found: C, 76.6, 76.4; H, 7.9, 7.9.