[CONTRIBUTION FROM THE PHARMACEUTICAL RESEARCH INSTITUTE, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

ANALOGS OF SANTONIN. II. ATTEMPTED SYNTHESIS OF 3-KETO-8a-METHYL-3,5,6,7,8,8a-HEXAHYDRONAPHTHALENE[1]

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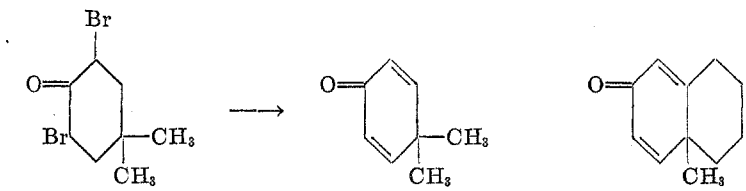
In a previous communication (1) from this laboratory, certain experimental observations were reported on the reaction of 2,6-dibromo-4,4-dimethylcyclohexanone (I) with quinoline or sodium acetate. The preparation of 4,4-dimethylcyclohexadienone (II) and other products was also described. In the present work, in an attempt to prepare the known 3-keto-8a-methyl-3,5,6,7,8,8a-hexahydronaphthalene (III) (2), bromination-dehydrobromination of 3-keto-8a-methyldecahydronaphthalene (IV) was investigated.



I II III

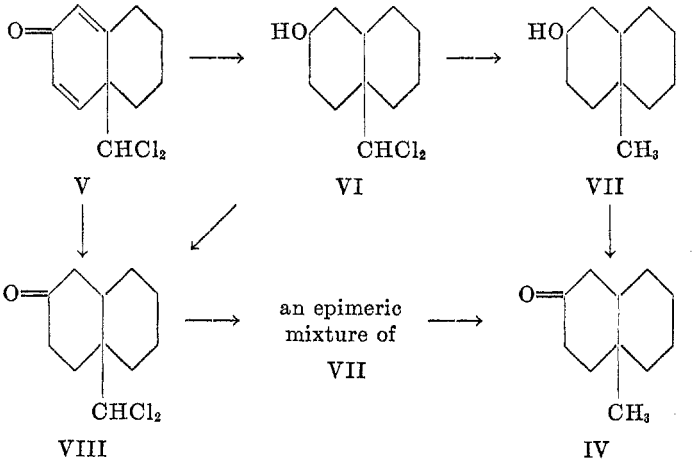
The preparation of the starting material (IV) has been reported by three different methods. First, this compound was prepared by du Feu, McQuillin, and Robinson (3) by the catalytic hydrogenation of 3-keto-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene (XII), which was obtained by the condensation of 2-methylcyclohexanone with 1-diethylaminobutan-3-one. Woodward (4) prepared this compound in three steps from 3-keto-8a-dichloromethyl-3,5,6,7,8,8a-hexahydronaphthalene (V → VI → VII → IV). The products obtained by these methods gave the same 2,4-dinitrophenylhydrazone, m.p. 151–152° (4). On the other hand, Woodward and Singh (2) reported that the compound (IV), prepared by the catalytic reduction of III, gave a 2,4-dinitrophenylhydrazone, m.p. 125.5–127°. It has not been established whether the different forms are stereoisomers or merely dimorphs.

Catalytic hydrogenation of V with palladium charcoal yielded 3-keto-8a-dichloromethyldecahydronaphthalene in quantitative yield. Only one pure stereoisomer of VIII was separated in 32% yield, but after the removal of this solid, there remained an oil from which only this same isomer was obtained after chromatography.

Reduction of the solid isomer with sodium and ether gave an epimeric mixture of the 3-hydroxy-8a-methyldecahydro compound (VII), from which, on repeated recrystallization, the only one isomer was isolated in the pure state. On chromic

[1] This work was supported in part by the Scientific Research Fund from the Ministry of Education of Japan.

acid oxidation, this mixture gave, in 75% yield, the ketone (IV) which formed, in a nearly quantitative yield, a 2,4-dinitrophenylhydrazone, m.p. 171–173°, different from the two already reported.



In order to compare this product with a sample prepared by the reported procedure, the method of Woodward (4) was repeated and the decahydro ketone (IV) was found to form a 2,4-dinitrophenylhydrazone, m.p. 171–173°, not m.p. 151–152° as reported. It is obvious that the difference in the melting point was merely due to dimorphism.[2] During these reactions, it was further found that the dichloromethyldecalol (VI) was oxidized to the ketone (VIII) and hydrogenated to the solid isomer of VII.

Treatment of the ketone (IV) with two moles of bromine in glacial acetic acid gave a crystalline 2,4-dibromo derivative (IX), in a satisfactory yield. On heating the dibromide with γ-collidine, a liquid product which did not contain bromine was obtained in poor yield. This product gave a semicarbazone whose analysis showed the parent compound to have the same formula $C_{11}H_{14}O$ as III, but it was not identical with III. It failed to undergo the dienone-phenol rearrangement, unlike III. Catalytic hydrogenation of its semicarbazone gave that of the parent ketone (IV). From these facts it can be reasonably assumed that this compound possesses the structure (X) of 3-keto-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene. Furthermore, an additional support for structure X was obtained by its ultraviolet absorption spectrum (Fig. 1).

The ketone (IV) was treated with one mole of bromine to yield smoothly the crystalline mono-bromo derivative (XI). Its dehydrobromination with γ-collidine gave, in 56% yield, a liquid product which was identified through the semicarbazone with that of the above reported (3) octahydroketone (XII). When XII was subjected to the action of N-bromosuccinimide, there resulted, in a nearly quantitative yield, an oily monobromo derivative (XIII), which could

[2] After the manuscript was submitted, Woodward, et al. [*J. Am. Chem. Soc.*, **74**, 4223 (1952)] reported that the 2,4-dinitrophenylhydrazone of *cis*-IV obtained from XII had the m.p. 174.5–175.5°.

not be purified. The location of the bromine atom at C_5 in this compound is most probable from the mode of its formation. Dehydrobromination of XIII with γ-collidine gave, in a moderate yield, an oily product whose semicarbazone

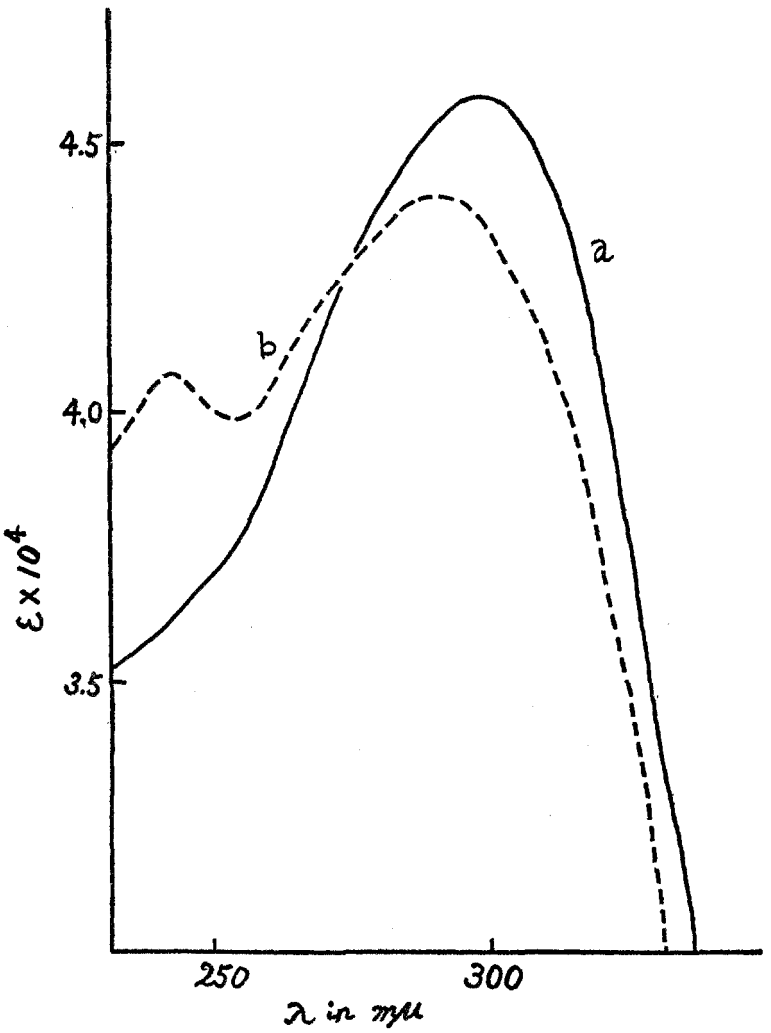
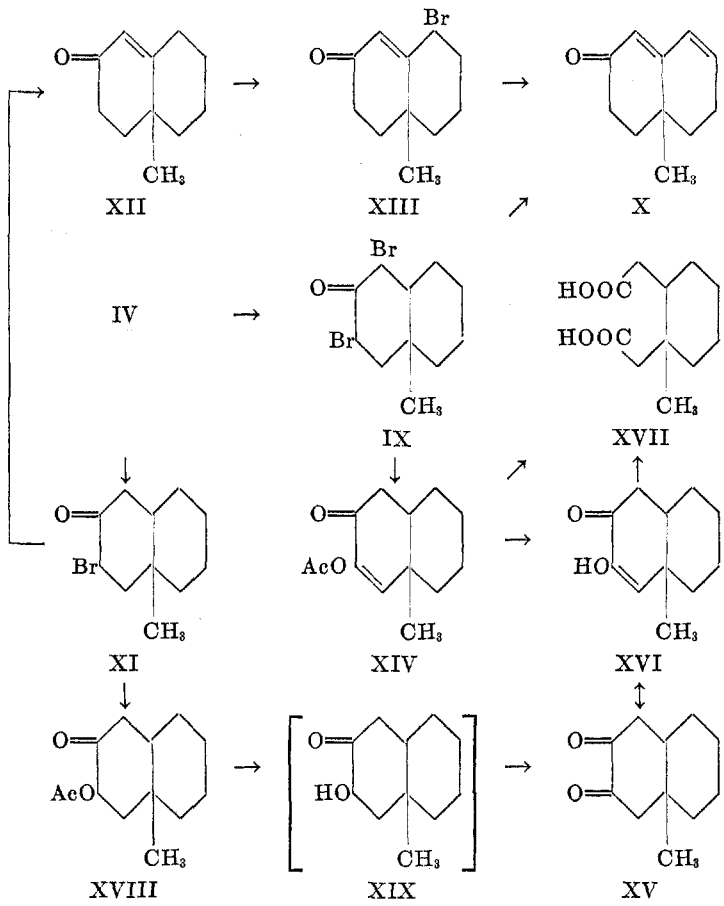


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA IN ALCOHOL SOLUTION OF (a) 3-keto-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene (X) (semicarbazone) and (b) 3-keto-8a-methyl-3,5,6,7,8,8a-hexahydronaphthalene (III) (semicarbazone). (Beckman Model DC spectrophotometer).

was identical with the semicarbazone of X as prepared from the dibromide (IX). The present series of reactions is considered to prove the structure of X.

Dehydrobromination of the dibromo compound (IX) with sodium acetate proceeded in full analogy to that of I (1). There was obtained, together with a

neutral oil, 22% yield of an α-diketone (XV or enol form XVI), which gave a dark violet coloration with ferric chloride, and formed a glyoxime. The neutral oil was readily hydrolyzed with methanolic alkali to the same α-diketone (XV), indicating that it consisted chiefly of the expected acetate (XIV). In this hydrolysis an acid was obtained in addition to XV, the yield of which was raised to 63% by addition of a small amount of Perhydrol in the reaction. This acid



was identical with the 1-methylcyclohexan-1,2-diacetic acid[3] prepared from IV (5). On the basis of this evidence, it can be concluded that the acetate and ketone have the structure XIV and XV, respectively. Moreover, it follows that the bromines in IX are located at C_2 and C_4.

The monobromide (XI) was converted by the action of sodium acetate, in

[3] The possibility of the identification of the diacid with XVIII was pointed out by a referee of the *Journal of Organic Chemistry*, and the present paper has been rewritten in part to take this into account. The authors take this opportunity to express their appreciation for the kind and helpful suggestions made by Dr. André Dreiding, and the other referees of this paper.

79% yield, into the liquid acetate (XVIII), which was relatively stable to warm sulfuric acid, but readily reacted with cold methanolic alkali to give the ketone (XV) and the acid (XVII) in 18% and 30% yields, respectively. Apparently, both products were formed by air-oxidation of the expected intermediate, α-ketol (XIX), which was undetected. Although the position of the bromine in XI was not proved by the results described in this work, its location at C_2 appeared more probable than at C_4 in view of the formation of X and XIV from the dibromide (IX). It is interesting to note that the marked difference in behavior of collidine and sodium acetate toward the bromo derivatives of IV is striking.

After the present work was completed, an interesting paper of Gunstone and Heggie (6) appeared describing the results of bromination-dehydrobromination of 3-ketomono- and -dimethylhydronaphthalene. It was reported that C_4-methyl homolog of XII was catalytically hydrogenated to the *cis*-decahydro ketone. In analogy with this result, one isomer of IV and its transformation products obtained in the present research can be assigned C_{4a}/C_{8a}-*cis* configuration. These authors also reported that on bromination-dehydrobromination, the stereoisomeric mixture of IV yielded the 3,5,6,7,8,8a-hexahydro ketone (III). Although this result seems to be in a sharp contrast to the present work, it would appear that the product obtained by the British workers is a mixture of two hexahydro ketones (III and X), from which only III has been detected.

This work is in progress.

EXPERIMENTAL[4, 5]

3-Keto-8a-dichloromethyl-3,5,6,7,8,8a-hexahydronaphthalene (V). This was prepared from 2-tetralol according to the method of Woodward (4). The yield was 6.4%. Reported yield 15%.

3-Keto-8a-dichloromethyldecahydronaphthalene (VIII). A suspension of 15.0 g. of V in 160 ml. of methanol was hydrogenated in the presence of palladium-on-charcoal (prepared from 15 ml. of 1% palladium chloride solution and 3.0 g. of charcoal) at ordinary temperature and pressure. The crystals gradually went into solution, and 3,260 ml. (2,910 ml. equals 2 moles) of hydrogen was absorbed very smoothly. After filtering from the catalyst, the solvent was removed under a reduced pressure, and the residue was poured into water and extracted with ether. The ether solution was washed with 5% aqueous sodium hydroxide, then with water, and dried over sodium sulfate. Evaporation of the ether gave 15.0 g. (100%) of a yellowish oil, which partly crystallized to a waxy solid on standing in a refrigerator overnight. After removing most of the oil (9.5 g.) by suction, the solid (5.4 g.) was once recrystallized from methanol by adding a little water until appearance of turbidity, to give 3.8 g. (25%) of colorless prisms, m.p. 69.5–71°. A sample was further recrystallized from the same solvent, m.p. 71–72°.

Anal. Calc'd for $C_{11}H_{16}Cl_2O$: C, 56.17; H, 6.81.
Found: C, 56.11; H, 7.20.

This formed, in 97% yield, a semicarbazone which was recrystallized from methanol containing a little water to give white crystalline powder, m.p. 204–205° (decomp.).

Anal. Calc'd for $C_{12}H_{19}Cl_2N_3O$: N, 14.38. Found: N, 14.72.

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[4] All temperatures are not corrected.

[5] Microanalyses were carried out in the Pharmaceutical Institute, University of Tokyo, and in the Analytical Laboratory, Daiichi Pharmaceutical Co. Ltd., Tokyo.

The above oil (1 g.) dissolved in petroleum ether was chromatographed on 52 ml. of alumina, and eluted first with benzene-petroleum ether, and then with benzene. The benzene fraction, on evaporation, afforded 0.45 g. of the isomer of VIII, m.p. 53–60° which, after two crystallizations, showed m.p. 70–71.5°. The material from the benzene-petroleum ether fraction was a viscous oil, forming a *semicarbazone* of broad m.p. 122–135°. No other pure material could be isolated from this mixture.

8a-Methyl-3-hydroxydecahydronaphthalene (VII). To a stirred solution of 3.8 g. of the pure solid (VIII) in 100 ml. of ether saturated with water was added 8.0 g. of sodium in small portions. Water was cautiously added until all the sodium was completely dissolved. This required about 24 hours. The yellowish ether solution was separated, washed with water, and dried over sodium sulfate. The ether was removed and the residue was distilled to give 1.8 g. (66%) of a colorless, viscous oil, b.p. 101–102° at 4 mm. It solidified on standing to crystals, m.p. 56–58°. A sample was repeatedly recrystallized from alcohol by adding water until the appearance of turbidity, giving colorless needles, m.p. 69–70°. This gave no depression of m.p. when mixed with VII from VI. The distillate was used for the next step without further purification.

3-Keto-8a-methyldecahydronaphthalene (IV) was prepared by the chromic acid oxidation of VII, essentially by the procedure of Woodward (4). The product was a colorless oil (75%), b.p. 94–94.5° at 3 mm. Reported b.p. 95–96° at 3 mm. (4). It formed, in an almost quantitative yield, a *2,4-dinitrophenylhydrazone*, m.p. 163–166°, which was recrystallized from methanol giving pale yellow needles, m.p. 171–173°.

Anal. Calc'd for $C_{17}H_{22}N_4O_4$: C, 58.96; H, 6.36; N, 16.18.

Found: C, 59.19; H, 6.68; N, 16.08.

It also formed a *semicarbazone*, m.p. 203–204°.

8a-Dichloromethyl-3-hydroxydecahydronaphthalene (VI) was prepared essentially by the procedure reported (4). A suspension of 5.0 g. of V in methanol was hydrogenated in the presence of 0.05 g. of platinic oxide at room temperature and atmospheric pressure. When about 880 ml. of hydrogen was absorbed the reaction became subdued, and a second portion of 0.05 g. of the catalyst was added after which the hydrogenation proceeded to completion. The total time required was 4 hours. The product was a light brown oil, which almost completely solidified on standing in a refrigerator. After washing with a small amount of petroleum ether, it was recrystallized from petroleum ether and then from methanol by adding water until the appearance of turbidity. There was obtained 2.7 g. (52%) of VI as white needles, m.p. 92–94°. Reported m.p. 92.5–93° (4). It formed almost quantitatively a *p*-nitrobenzoate which was recrystallized from alcohol giving white needles, m.p. 109–110°.

Anal. Calc'd for $C_{18}H_{21}Cl_2NO_3$: N, 3.64. Found: N, 3.54.

This compound was oxidized with chromic acid in the usual manner to give an 80% yield of the ketone, m.p. 71–72°, which gave no depression in m.p. when mixed with VIII obtained directly from V.

The combined petroleum ether solutions, on evaporation, gave 1.3 g. of an oil which did not solidify.

8a-Methyl-3-hydroxydecahydronaphthalene (VII) *from VI*. The pure material (VI) was hydrogenated with palladium-on-barium sulfate exactly by the procedure reported (4). The product (VII), which has been reported as not solidifying, was obtained almost quantitatively as crystals, m.p. 67–69°. A sample was recrystallized from alcohol, by adding water until the appearance of turbidity, to give silky white needles, m.p. 69–70°.

Anal. Calc'd for $C_{11}H_{20}O$: C, 78.57; H, 11.90.

Found: C, 78.38; H, 12.16.

It formed in a nearly quantitative yield a *p-nitrobenzoate* which was recrystallized from alcohol containing a little water giving platelets, m.p. 65–67°.

Anal. Calc'd for $C_{18}H_{23}NO_4$: N, 4.46. Found: N, 5.04.

Compound VII was oxidized with chromic acid to IV, which gave a *2,4-dinitrophenylhydrazone*, m.p. 171–173°. Reported m.p. 151–152° (4).

2,4-Dibromo-3-keto-8a-methyldecahydronaphthalene (IX). To a cooled and stirred solu-

tion of 0.5 g. of the ketone (IV) in 5 ml. of glacial acetic acid there was added a solution of 1.0 g. of bromine in 4 ml. of the same solvent. After first few drops of the bromine solution which were added had been decolorized, the residual bromine was added dropwise during about 10 minutes. Stirring was continued for 3 hours. The slightly colored solution thus obtained was poured into water. The viscous oil which separated completely solidified on standing in a refrigerator. Thus there was obtained 0.9 g. (90%) of pale yellow crystals, which were recrystallized from petroleum ether giving colorless needles, m.p. 121.5–123°.

Anal. Calc'd for $C_{11}H_{16}Br_2O$: C, 40.74; H, 4.98.

Found: C, 40.72; H, 5.06.

3-Keto-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene (X). A solution of 3.5 g. of the crude dibromide (IX), m.p. 85–95°, in 15 ml. of γ-collidine was refluxed for 75 minutes. After cooling, the dark red solution was diluted with ether, and the collidine hydrobromide (4.4 g., quantitative for 2 moles) which separated was filtered off. The ether solution was washed with dilute hydrochloric acid, then with dilute sodium hydroxide, and finally with water, and dried over sodium sulfate. Evaporation of the solvent gave 1.3 g. of an aromatic black oil, which was fractionally distilled. The main fraction (0.4 g.), b.p. 60–117° at 1 mm., was redistilled to give 0.2 g. (12%) of a pale yellow oil, b.p. 100° at 1 mm. This oil formed, in 86% yield, a *semicarbazone* which was recrystallized from dilute methanol giving colorless, small prisms, m.p. 213–214°. These prisms gave an obvious depression of the m.p. when mixed with the semicarbazone, m.p. 202°, of III prepared by the method of Woodward and Singh (2).

Anal. Calc'd for $C_{12}H_{17}N_3O$: C, 65.75; H, 7.76; N, 19.18.

Found: C, 65.66; H, 7.99; N, 19.38.

Catalytic hydrogenation of the semicarbazone with palladium-charcoal in methanol gave the *semicarbazone of IV*, m.p. 195–198° (mixture m.p.), in 77% yield.

On treatment of X with acetic anhydride and sulfuric acid, no rearrangement product could be isolated.

2(?)-Bromo-3-keto-8a-methyldecahydronaphthalene (XI) was prepared from IV with one mole of bromine by a procedure similar to that described above for the dibromide (IX). The crude product (92%) was twice recrystallized from petroleum ether giving colorless needles, m.p. 99–100°.

Anal. Calc'd for $C_{11}H_{17}BrO$: C, 53.87; H, 6.94.

Found: C, 53.53; H, 6.94.

3-Keto-8a-methyl-1,2,3,5,6,7,8,8a-octahydronaphthalene (XII). A solution of 1.38 g. of the above bromide in 5 ml. of γ-collidine was refluxed for 15 minutes and worked up as described above for X. There was obtained 0.6 g. of a red-brown oil which was fractionally destilled giving 0.52 g. of a colorless oil, b.p. 117° at 8 mm. or 104° at 5 mm. Reported (3) b.p. 139° at 15 mm.

It formed, in a quantitative yield, a *semicarbazone* which was recrystallized from alcohol giving white needles, m.p. 201–202°. This gave no depression of m.p. when mixed with the semicarbazone of XII, prepared by the method of du Feu, McQuillin, and Robinson (3).

3-Keto-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene (X) *from XII, via XIII.* N-Bromosuccinimide (0.27 g.) and 0.1 g. of benzoyl peroxide was added to 0.25 g. of XII dissolved in 8 ml. of carbon tetrachloride. The mixture was gently refluxed on a water-bath for 1.5 hours. After cooling, the solution was filtered from succinimide, and the solvent was removed under a reduced pressure. There was obtained 0.35 g. (95%) of a brown oil (XIII), which did not solidify and was used for the next step without purification.

The monobromide was dehydrobrominated with γ-collidine, essentially as described above for XII. The product, a reddish-brown oil (0.15 g.), was fractionally distilled. A fraction (0.08 g. 38%), boiling at 140–170° at 2 mm. (bath temperature), gave, in 91% yield, a *semicarbazone* which was recrystallized from alcohol giving colorless prisms, m.p. 206°. An admixture with the semicarbazone of X from IX was m.p. 209°.

Reaction of the dibromo compound (IX) *with sodium acetate.* A solution of 0.95 g. of the dibromide and 1.5 g. of anhydrous sodium acetate in 5 ml. of glacial acetic acid was refluxed for two hours. After cooling, the reddish brown solution was poured into water and extracted with ether. The ether solution was shaken with dilute sodium carbonate, then with dilute sodium hydroxide (*b*), and dried over sodium sulfate (*a*).

(*a*) *Neutral product.* The ether solution (*a*), on evaporation, gave 0.37 g. of reddish brown oil, which was distilled to yield 0.31 g. (49%) of pale yellow oil, boiling up to 145° at 5 mm. This showed no ketonic character and contained mainly 3-keto-2-acetoxy-8a-methyl-3,4,4a,5,6,7,8,8a-octahydronaphthalene (XIV).

The oil (0.1 g.) was added to 1.7 ml. of a 6% methanolic potassium hydroxide solution and allowed to stand overnight at room temperature. The reddish solution was poured into water and extracted with ether. Evaporation of the ether solution resulted in the recovery of 0.04 g. of the original acetate. The alkaline solution, after acidification, was extracted with ether, and the ether solution was shaken with dilute sodium carbonate, dried over sodium sulfate, and evaporated. The residual oil (XV or XVI), amounting to 0.02 g. (25%), gave a dark violet coloration with ferric chloride, and formed a *glyoxime* (red nickel salt), which was recrystallized from alcohol giving light pink, microscopic platelets, m.p. 230–232° (decomp.).

Anal. Calc'd for $C_{11}H_{18}N_2O_2$: N, 13.38. Found: N, 13.63.

The above sodium carbonate solution was acidified and extracted with ether. The dried ether solution, on evaporation, afforded 0.01 g. (10%) of the acid (XVII), which was recrystallized from ethyl acetate giving white, microscopic platelets, m.p. 191.5–192.5°. These gave no depression of m.p. when mixed with 1-methyl-cyclohexan-1,2-diacetic acid m.p. 192° (reported 190°), prepared from IV by the procedure of Linstead, Millidge, and Walpole (5).

Anal. Calc'd for $C_{11}H_{18}O_4$: C, 61.68; H, 8.41.
Found: C, 61.31; H, 8.21.

To a solution of 0.2 g. of the oil (XIV) in 5 ml. of 6% methanolic potassium hydroxide was added 1 ml. of 30% Perhydrol (H_2O_2). The whole was allowed to stand in a refrigerator for 48 hours. There was obtained 0.13 g. (63%) of the acid (XVII). The acetate (XIV) was also hydrolyzed by warming with 10% sulfuric acid to the diketone (XV) in 38% yield.

(*b*) *Acid product.* The alkaline solution (*b*) was acidified and extracted with ether. The dried ether solution, on evaporation, gave 0.15 g. of a reddish oil, which was distilled to yield 0.11 g. (21%) of XV as a colorless, viscous oil, boiling until 114° at 5 mm. This formed, in 90% yield, a *glyoxime*, m.p. 230–232° (mixture m.p.).

Reaction of the monobromo compound (XI) *with sodium acetate.* A solution of 0.67 g. of XI and 0.6 g. of anhydrous sodium acetate in glacial acetic acid was refluxed for 1 hour and worked up as described above for XIV.

(*a*) *Neutral product.* The ether solution, after removal of alkali-soluble material, was evaporated and the residue (0.52 g.) was distilled to give 0.48 g. (78%) of 3-keto-8a-methyl-2-acetoxydecahydronaphthalene (XVIII) as a colorless oil, boiling until 138° at 5 mm. This formed, in 90% yield, a semicarbazone which was recrystallized from alcohol to give colorless needles, m.p. 177–178° (decomp.).

Anal. Calc'd for $C_{14}H_{23}N_3O_3$: C, 59.78; H, 8.18.
Found: C, 59.43; H, 8.07.[3]

(*b*) *Acid product.* A yellowish oil, obtained from the alkaline solution, gave a dark violet coloration with ferric chloride, and formed a *glyoxime*, m.p. 230–232°, identical with that of XV (mixture m.p.).

Reaction of the acetoxyketone (XVIII) *with methanolic alkali.* To 1 ml. of a 6% methanolic potassium hydroxide solution there was added 0.07 g. of XVIII; the mixture was allowed to stand in a refrigerator for 36 hours, and worked up as described above for XV. There were obtained 0.01 g. (15%) of the diketone (XV), forming a glyoxime, m.p. 230–232° (mixture m.p.), and 0.02 g. (35%) of the acid (XVII), m.p. 191.5–192.5° (mixture m.p.).

SUMMARY

1. The preparation of *cis*-3-keto-8a-methyldecahydronaphthalene (IV) has been described.

2. The dehydrobromination of the di- and mono-bromo derivatives of IV has been investigated.

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