649. *The Synthesis of 3-Oxototaryl Methyl Ether.*

By D. A. H. TAYLOR.

(±)-3-Oxototaryl methyl ether (IXb) has been synthesised from 2-naphthol by way of 5-isopropyl-6-methoxy-1-tetralone. This was converted by standard methods into 1,2,3,4,9,12-hexahydro-8-isopropyl-7-methoxy-1,1,12-trimethyl-2-oxophenanthrene (VIII), which on hydrogenation over palladised charcoal gave a mixture that on reoxidation and chromatography yielded (±)-3-oxototaryl methyl ether, identical in infrared spectrum with material of natural origin.

A DITERPENE isolated by Chow and Erdtmann [1] from the wood of *Tetraclinis articulata* has been shown to be 3-oxototarol (IXa). The present author was informed of this before publication, and enabled to carry out a synthesis.

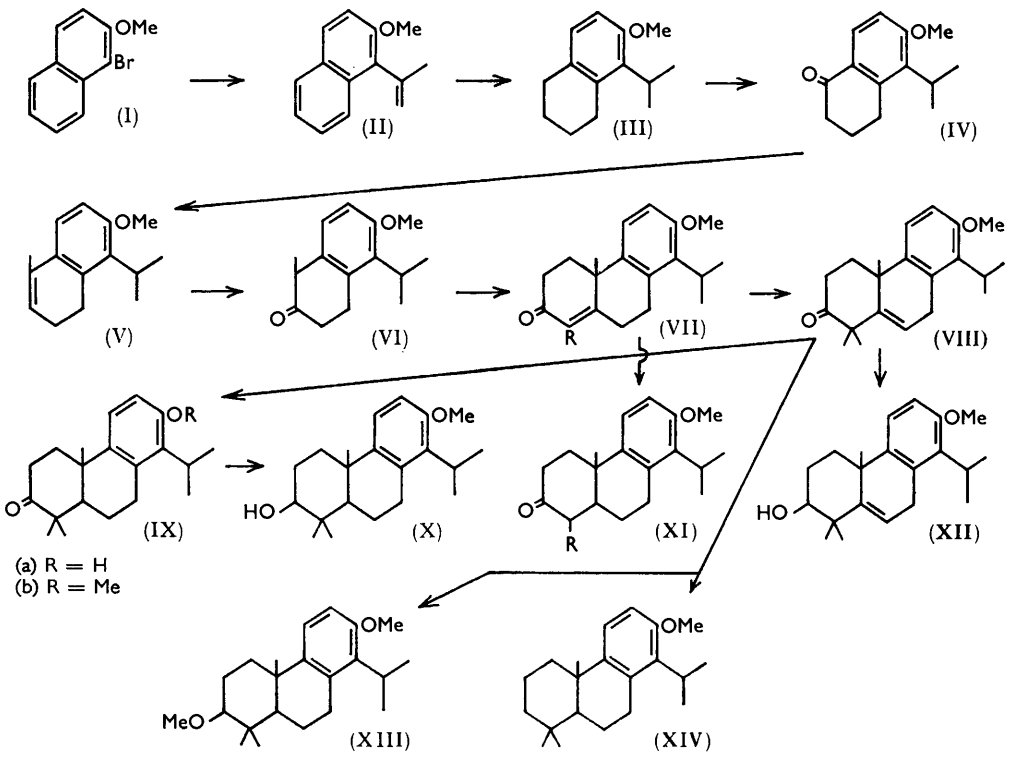
The scheme shown below, based on the recent general hexahydro-oxophenanthrene synthesis by Howell and Taylor,[2] was devised and has now been completed.

1-Bromo-2-methoxynaphthalene (I) was converted into the Grignard reagent, best in tetrahydrofuran, and this with acetone gave a mixture of 1-isopropenyl-2-methoxynaphthalene (II) and 2-methoxynaphthalene. These could not be separated, but after hydrogenation over Adams catalyst fractionation readily gave crystalline 1-isopropyl-2-methoxynaphthalene. The hydrogenation was slow, and it was found better to continue the synthesis with the mixture. This was hydrogenated over Raney nickel at 120° to give 1,2,3,4-tetrahydro-5-isopropyl-6-methoxynaphthalene (III), which on oxidation with chromic acid in acetic acid below 20° gave 5-isopropyl-6-methoxy-1-tetralone (IV), obtained crystalline after fractionation. When this was treated with methylmagnesium bromide in ether the intermediate tertiary alcohol was dehydrated in the course of the reaction, and the product was 3,4-dihydro-5-isopropyl-6-methoxy-1-methylnaphthalene (V). Perbenzoic acid oxidised this to the 2-tetralone (VI), which with 4-chlorobutan-2-one afforded the hexahydrophenanthrene (VIIa). The corresponding 4-methyl derivative (VIIb) was obtained by the use of 1-chloropentan-3-one, but the yield was lower.

Each of these compounds (VII) was readily methylated with methyl iodide and potassium t-butoxide [3] to give the *gem*-dimethyl derivative (VIII). Hydrogenation over neutral Adams catalyst then reduced only the carbonyl group, giving the alcohol (XII), identical with a sample obtained by reduction with sodium borohydride and reoxidised to the ketone (VIII) by chromic acid in acetone.[4] Hydrogenation of the ketone (VIII) over palladised charcoal in dilute methanolic acetic acid gave a complex mixture, which

[1] Chow and Erdtmann, *Acta Chem. Scand.*, 1960, **14**, 1852.
[2] Howell and Taylor, *J.*, 1958, 1248.
[3] Woodward, Patchett, Barton, Ives, and Kelly, *J.*, 1957, 1131.
[4] Bowers, Halsall, Jones, and Lemin, *J.*, 1953, 2548.

after reoxidation with chromic acid in acetone was chromatographed. Elution with hexane–benzene gave three crystalline components, and partly crystalline intermediate fractions suggested the presence of at least two more. The first substance isolated was (±)-totaryl methyl ether (XIV), m. p. 95—98°, identical in infrared spectrum with a sample prepared by methylating natural totarol.[5] The production of totarol methyl



ether in this way is paralleled in the reduction of cholesterol,[6] which gives a small yield of cholestane. Presumably in both cases the reduction proceeds through a homoallylic bridged ion, similar to that postulated by Winstein's school[7] to explain the kinetics of the solvolysis of cholesteryl toluene-*p*-sulphonate. The second substance crystallised from methanol in plates, m. p. 136°, and gave analytical figures corresponding to a dimethyl ether (XIII). If this arises through the bridged ion, as seems probable, then it may also be the product of a homoallylic rearrangement, and have the methoxyl group in the 6-position. The third substance isolated crystalline was (±)-3-oxototaryl methyl ether, m. p. 102—103°, identical in infrared spectrum with a sample prepared by Dr. Chow from natural 3-oxototarol.

Experimental

1-Isopropyl-2-methoxynaphthalene.—1-Bromo-2-methoxynaphthalene (238 g.) in benzene (1 l.) was added to magnesium (40 g.) in ether (2 l.). The thick suspension was stirred and acetone (50 ml.) added dropwise, after which there was no further reaction. The mixture was treated with dilute hydrochloric acid, and the organic layer was separated and distilled. The product was collected as an oil at 136°/4 mm.; it contained no bromine. It was dissolved

[5] Short and Stromberg, *J.*, 1937, 516.
[6] Hershberg, Oliveto, Rubin, Stäudle, and Kuhlen, *J. Amer. Chem. Soc.*, 1951, **73**, 1144.
[7] Winstein and Adams, *J. Amer. Chem. Soc.*, 1948, **70**, 838; Simonetta and Winstein, *J. Amer. Chem. Soc.*, 1954, **76**, 18.

in methanol and hydrogenated over Adams catalyst; after filtration the solvent was evaporated and the residue fractionated. 2-Methoxynaphthalene, m. p. and mixed m. p. 72°, was collected at 130°/4 mm., followed by 1-*isopropyl*-2-*methoxynaphthalene* (65 g.) at 144°/4 mm. Crystallisation from methanol gave the analytical sample, m. p. 48—49° (Found: C, 83·3; H, 8·1. $C_{14}H_{16}O$ requires C, 84·0; H, 8·05%).

5-*Isopropyl*-6-*methoxy*-1-*tetralone* (IV).—1-Bromo-2-methoxynaphthalene (700 g.) dissolved in tetrahydrofuran (2 l.) was added dropwise to magnesium (120 g.) in tetrahydrofuran (1 l.). Then the clear solution was stirred while acetone (250 ml.) was added. The complex was decomposed with aqueous hydrochloric acid, the organic layer separated and washed with water, the solvent evaporated, and the residue distilled in a vacuum. The product (580 g.) was obtained as an oil, b. p. 130—140°/4 mm. This was hydrogenated over Raney nickel catalyst at 120°/100 atm. (initial) until hydrogen uptake was complete. After filtration and redistillation, the crude product was dissolved in acetic acid (2 l.), and a solution of chromic acid (420 g.) in water (150 ml.) and acetic acid (1 l.) was added at such a rate that the temperature was held at ~ 15°. The mixture was allowed to warm to room temperature (30°) overnight and then diluted with water and ether. The organic layer was washed and evaporated, and the residue distilled (the tail fraction partly crystallised) and then fractionated. 5-*Isopropyl*-6-*methoxy*-1-*tetralone* was collected at 160—170°/2 mm. as an oil which mostly crystallised. Recrystallisation from pentane, followed by refractionation of the residues, gave the pure ketone (183 g., 28%) as pale yellow prisms, m. p. 74° (Found: C, 76·9; H, 8·2. $C_{14}H_{18}O_2$ requires C, 77·0; H, 8·3%).

3,4-*Dihydro*-5-*isopropyl*-6-*methoxy*-1-*methylnaphthalene* (V).—To a Grignard solution, prepared in ether from magnesium (24 g.) and an excess of methyl bromide, was added the above ketone (107 g.) in ether. After being worked up in the usual way, the product was distilled at 140°/2 mm., and then crystallised from methanol–ether. 3,4-*Dihydro*-5-*isopropyl*-6-*methoxy*-1-*methylnaphthalene* (89 g., 84%) formed colourless plates, m. p. 60—61° (Found: C, 83·15; H, 9·1. $C_{15}H_{20}O$ requires C, 83·3; H, 9·3%), $\lambda_{max.}$ (in MeOH) 268 mμ (log ε 3·9).

5-*Isopropyl*-6-*methoxy*-1-*methyl*-2-*tetralone* (VI).—The above dihydronaphthalene (63 g.), dissolved in chloroform (100 ml.), was oxidised with perbenzoic acid (39 g.) in chloroform (550 ml.) at <10°. After storage overnight in the refrigerator, the red solution was washed with sodium hydroxide solution and with water and evaporated. The residue was refluxed for 1·5 hr. with sulphuric acid (60 ml.), methanol (400 ml.), and water (320 ml.), and the product isolated with ether and distilled. 5-Isopropyl-6-methoxy-1-methyl-2-tetralone (55 g., 80%) was collected at 164°/2 mm. as a colourless oil. The *semicarbazone* formed crystals, m. p. 190°, from ethanol (Found: C, 66·5; H, 8·4. $C_{16}H_{23}N_3O_2$ requires C, 66·4; H, 8·0%).

2,3,4,9,10,12-*Hexahydro*-8-*isopropyl*-7-*methoxy*-12-*methyl*-2-*oxophenanthrene* (VIIa).—Sodium hydride (10 g. of a 50% suspension in oil) was stirred with cyclohexane (200 ml.) under nitrogen, and the above ketone (50 g.) in cyclohexane (100 ml.) added slowly. After 10 minutes' stirring 4-chlorobutan-2-one (20 g.) was added dropwise. After the vigorous reaction was over, another portion of sodium hydride (10 g. of 50%) was added cautiously, and the whole stirred and refluxed for 15 min. Methanol (20 ml.) was then added, and, after 5 min., dilute hydrochloric acid. The organic layer was dried and run through a column of alumina (900 g.). After being washed with light petroleum to remove the oil introduced with the sodium hydride, the column was eluted with ether. Evaporation of the ether left a residue which from hexane gave 2,3,4,9,10,12-*hexahydro*-8-*isopropyl*-7-*methoxy*-12-*methyl*-2-*oxophenanthrene* (22 g., 36%) as off-white prisms, m. p. 105—106° (Found: C, 80·2; H, 8·0. $C_{19}H_{24}O_2$ requires C, 80·2; H. 8·5%), $\lambda_{max.}$ (in MeOH) 235 mμ (log ε 4·5), $\nu_{max.}$ (in Nujol) 1667 cm.$^{-1}$.

2,3,4,9,10,12-*Hexahydro*-8-*isopropyl*-7-*methoxy*-1,12-*dimethyl*-2-*oxophenanthrene* (VIIb).—A similar preparation with the 2-tetralone (27 g.) and 1-chloropentan-3-one (12·5 g.) gave 2,3,4,9,10,12-*hexahydro*-8-*isopropyl*-7-*methoxy*-1,12-*dimethyl*-2-*oxophenanthrene* (9·8 g.), crystallising from methanol in colourless prisms, double m. p. 85—86°/108—109° (Found: C, 81·0; H, 8·9. $C_{20}H_{26}O_2$ requires C, 80·5; H, 8·8%), $\lambda_{max.}$ (in MeOH) 232 (log ε 4·04), 245 mμ (log ε 4·07), $\nu_{max.}$ (in Nujol) 1667 cm.$^{-1}$.

1,2,3,4,9,10,11,12-*Octahydro*-8-*isopropyl*-7-*methoxy*-12-*methyl*-2-*oxophenanthrene* (XIa).—The hexahydro-compound (VIIa) (6·5 g.) in ether (100 ml.) was added to a solution of sodium (2 g.) in liquid ammonia (200 ml.). After 5 min. ammonium chloride was added, then ether and water. The ether layer was washed and evaporated; the residue crystallised from methanol to give 1,2,3,4,9,10,11,12-*octahydro*-8-*isopropyl*-7-*methoxy*-12-*methyl*-2-*oxophenanthrene* (4·3 g.)

as colourless plates, m. p. 112—113° (Found: C, 79·5; H, 9·1. $C_{19}H_{26}O_2$ requires C, 79·7; H, 9·1%), $\nu_{max.}$ (in Nujol) 1705 cm.$^{-1}$.

1,2,3,4,9,10,11,12-*Octahydro*-8-*isopropyl*-7-*methoxy*-1,12-*dimethyl*-2-*oxophenanthrene* (XIb).—Reduction of the hexahydro-compound (VIIb) (8·3 g.) as above gave the *octahydro-ketone* (XIb) (5·5 g.), prisms (from methanol), m. p. 116° (Found: C, 80·2; H, 9·2. $C_{20}H_{28}O_2$ requires C, 80·0; H, 9·4%), $\nu_{max.}$ (in Nujol) 1705 cm.$^{-1}$.

1,2,3,4,9,12-*Hexahydro*-8-*isopropyl*-7-*methoxy*-1,1,12-*trimethyl*-2-*oxophenanthrene* (VIII).—Potassium (1 g.) was dissolved in t-butyl alcohol (70 ml.), and 2,3,4,9,10,12-hexahydro-8-isopropyl-7-methoxy-12-methyl-2-oxophenanthrene (VIIa) (3 g.) was added. After a few minutes methyl iodide (5 ml.) was added and the solution refluxed for 30 min. After evaporation in a vacuum the residue was taken up in water and ether, and the ether layer evaporated. Crystallisation from methanol gave the 1,1,12-*trimethyl derivative* (1·9 g., 60%) as colourless prisms, m. p. 112° (Found: C, 80·7; H, 9·2. $C_{21}H_{28}O_2$ requires C, 80·7; H, 9·0%), $\nu_{max.}$ (in Nujol) 1705 cm.$^{-1}$.

1,2,3,4,9,12-*Hexahydro*-2-*hydroxy*-8-*isopropyl*-7-*methoxy*-1,1,12-*trimethylphenanthrene* (XII).—The ketone (VIII) (700 mg.) in methanol (10 ml.) was treated with sodium borohydride (52 mg.) in a little water. After 1 hr. more borohydride (25 mg.) was added, and after a further hour the solution was diluted with aqueous sulphuric acid. The precipitate was collected and crystallised from hexane to give 1,2,3,4,9,12-*hexahydro*-2-*hydroxy*-8-*isopropyl*-7-*methoxy*-1,1,12-*trimethylphenanthrene* (630 mg.) as needles, m. p. 119—120° (Found: C, 80·3; H, 9·8. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%).

(±)-3-*Oxototaryl Methyl Ether* (IX).—The unsaturated trimethyl ketone (VIII) (1·0 g.) was hydrogenated in methanol (50 ml.) and acetic acid (1 ml.) over palladised charcoal (500 mg.). Hydrogen uptake was rapid, and ceased after the absorption of 140 ml. The solution was then filtered from catalyst and evaporated, the residue was dissolved in ether, filtered from a little insoluble material, washed until neutral, and recovered. The residue was dissolved in acetone (25 ml.) and oxidised with 8N-chromic acid (about 1 ml.) until an orange colour persisted. The solution was then diluted with water and ether, the organic layer evaporated, and the product chromatographed on alumina (30 g. of type H). Elution with hexane and then with hexane–benzene gave the following three substances in order of elution from the column: (a) (±)-*totaryl methyl ether* (XIV) (25·6 mg.), plates, m. p. 95—98°, from ether–methanol (Found: 83·7; H, 11·0. $C_{21}H_{32}O$ requires: C, 83·9; H, 10·7%). The infrared spectrum was identical with that of a specimen of natural totaryl methyl ether; (b) (±)-3(?)-*methoxytotaryl methyl ether* (XIII) (162 mg.), plates (from methanol), m. p. 136° (Found: C, 79·95; H, 10·5. $C_{22}H_{34}O_2$ requires: C, 79·95; H, 10·4%); (c) (±)-3-*oxotaryl methyl ether* (IX) (173 mg.), prisms, m. p. 102—103° (from methanol) (Found: C, 80·3; H, 10·0. $C_{21}H_{30}O_2$ requires C, 80·2; H, 9·6%). The infrared spectrum of fraction (c) was identical with that of natural 3-oxototaryl methyl ether. The oily mother-liquors from the chromatography were combined and reduced with sodium borohydride. Chromatography of the product gave (±)-*totaradiol methyl ether* (X) (140 mg.), needles, m. p. 160° (from methanol) (Found: C, 79·3; H, 10·3. $C_{21}H_{32}O_2$ requires C, 79·7; H, 10·2%). This was identical with a sample produced by the reduction of pure (±)-3-oxototaryl methyl ether, and 3-oxototaryl methyl ether was recovered after oxidation with chromic acid in acetone.

The author is grateful to Dr. Yuan-Lang Chow for information, for specimens of natural products, and for comparing the infrared spectra of natural and synthetic oxototaryl methyl ether. Microanalyses are by Patrick Mowete of this department.

DEPARTMENT OF CHEMISTRY, UNIVERSITY COLLEGE,
IBADAN, NIGERIA.

[*Received, February 16th,* 1961.]