149. *Hydroaromatic Steroid Hormones. Part VIII.* The Preparation of* 1,2,3,4,5,6,11,12-*Octahydro*-8-*methoxy*-1-*oxochrysene.*

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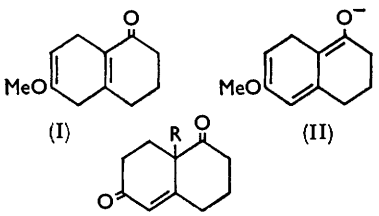
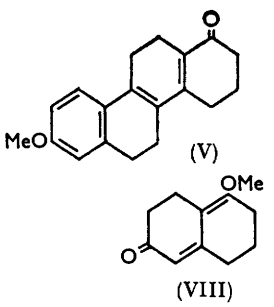
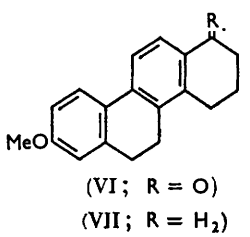
1,2,3,4,5,6,11,12-Octahydro-8-methoxy-1-oxochrysene (V) has been obtained in two ways, involving as an initial step alkylation of the mesomeric anions derived from 1,2,3,4,5,8-hexahydro-6-methoxy-1-oxonaphthalene (I), and 2,3,4,6,7,8-hexahydro-1-methoxy-6-oxonaphthalene (VIII), respectively, at position 5.

An easy synthesis of 1,2,3,4,5,6,11,12-octahydro-8-methoxy-1-oxochrysene (V) was desired, and we report attempts to obtain it in good yield. Although not very successful in this connection, the results illustrate the alkylation of two extended enolate anions. 1,2,3,4,5,8-Hexahydro-6-methoxy-1-oxonaphthalene (I) with potassium amide in ammonia yields a mesomeric anion (probably II) which colours the solution yellow-brown and is alkylated with methyl iodide at positions 5 and 8a, mainly at the latter position.[1] In the present work a similar result was obtained with ethyl iodide. In view of possible synthetic applications, the reaction of this mesomeric anion with 3-methoxyphenethyl bromide has been investigated, and derivatives resulting from alkylation at positions 5 and 8a have been isolated.







In order to facilitate separation, the initial products of alkylation were hydrolysed in dilute acid to remove the enol-ether grouping. The acidic diketone 1,2,3,4,6,7,8,8a-octahydro-1,6-dioxonaphthalene † (III), resulting either from incomplete alkylation, or from alkylation on oxygen and subsequent hydrolysis, was removed by extraction with water (28% from I). Dilute alkali removed any acidic alkylated derivatives [the alkaline extracts had a characteristic absorption band at 421 mμ, a bathochromic shift of 12 mμ relative to the intense absorption band of the alkali salt of (III)], and the alkali-insoluble residue after purification yielded 1,2,3,4,6,7,8,8a-octahydro-8a-3'-methoxyphenethyl-1,6-dioxonaphthalene (IV) (51% from I), characterised as its dioxime.

The alkali-extractable alkylation products afforded, on cyclodehydration in polyphosphoric acid at 60°, a mixture of two isomeric yellow tetracyclic ketones, separable by chromatography. The major constituent (9% from I) was shown to be 1,2,3,4,5,6,11,12-octahydro-8-methoxy-1-oxochrysene (V). Dehydrogenation on alumina at 100° afforded 1,2,3,4,5,6-hexahydro-8-methoxy-1-oxochrysene (VI), which on reduction and hydrogenolysis gave 1,2,3,4,5,6-hexahydro-8-methoxychrysene[2] (VII). Its identity was

* Part VII, Birch, Hughes, and Smith, *J.*, 1958, 967.

† Or the tautomeric 1,2,3,4,5,6,7,8-octahydro-compound; appreciable amounts of enolic form are present in solution.

[1] Birch, Quartey, and Smith, *J.*, 1952, 1768.

[2] Johnson, David, Dehm, Highet, Warnhoff, Wood, and Jones, *J. Amer. Chem. Soc.*, 1958, **80**, 661.

confirmed by dehydrogenation with sulphur to 2-methoxychrysene.[3] The other tetracyclic ketone, isomeric with (V) (1% from I), underwent a parallel series of reactions, yielding finally an isomer of 2-methoxychrysene. Comparison showed that this is not 3-methoxybenz[*a*]anthracene,[4] and its ultraviolet absorption spectrum more resembles those of the methoxychrysenes.[5] From its constants, however, this isomer cannot be a chrysene derivative, since all the monomethoxychrysenes are known, and none corresponds.[5]

Since the group introduced by alkylation enters the mesomeric anion (II) predominantly at position 8a, *i.e.*, α to the carbonyl group, it was considered that the mesomeric anion derived similarly from 2,3,4,6,7,8-hexahydro-1-methoxy-6-oxonaphthalene [6] (VIII), by the action of potassium amide in ammonia, might be alkylated predominantly at position 5, that is also α to the carbonyl group. With potassium amide in ammonia, the ketone (VIII) gave a yellow solution, which when treated with 3-methoxyphenethyl bromide and subsequently subjected to the hydrolysis, separation, and cyclisation procedure outlined previously, afforded the diketone (III) (49% from VIII). the diketone (IV) (11% from VIII), the ketone (V) (17% from VIII), and the same unelucidated isomer of the ketone (V) (2% from VIII). Though the main product was the unalkylated diketone (III), the principal *C*-alkylation product was the one predicted, *i.e.*, that resulting from alkylation α to the carbonyl group.

Experimental

Alkylations were carried out in anhydrous redistilled liquid ammonia at its b. p., with a guard tube containing potassium hydroxide.

Ethylation of 1,2,3,4,5,8-*Hexahydro*-6-*methoxy*-1-*oxonaphthalene* (I).—This compound (6·0 g.) in ether (30 c.c.) was added to a solution of potassium amide (from 1·5 g. of potassium) in ammonia (100 c.c.). Ethyl iodide (17 g.) in tetrahydrofuran (20 c.c.) was run in, removing the yellow-brown colour. The product, isolated with ether as a viscous oil, was distilled (b. p. 105—107°/0·3 mm.). Hydrolysis with 0·25N-sulphuric acid (20 c.c.) at 100° for 30 min. under nitrogen, followed by isolation with ether, yielded an oil (6·2 g.). Separation into acidic and neutral fractions by partition between aqueous sodium hydroxide and ether afforded an acidic (1·55 g.) and a neutral fraction (4·65 g.) the latter consisting of 8a-*ethyl*-1,2,3,4,7,8-*hexahydro*-1,6-*dioxonaphthalene*, m. p. 69—70° (from ether–pentane) (3·5 g.), $\lambda_{max.}$ 245 mμ (ε 11,400) (Found: C, 75·3; H, 8·05. $C_{12}H_{16}O_2$ requires C, 75·0; H, 8·4%). The 2,4-*dinitrophenylhydrazone*, recrystallised from ethyl acetate–light petroleum, had m. p. 136—138° (Found: C, 58·3; H, 5·65. $C_{18}H_{20}N_4O_5$ requires C, 58·1; H, 5·4%). The *disemicarbazone* (from ethanol) had m. p. >340° (Found: C, 55·1; H, 7·05. $C_{14}H_{22}N_6O_2$ requires C, 54·9; H, 7·2%).

Alkylation of 1,2,3,4,5,8-*Hexahydro*-6-*methoxy*-1-*oxonaphthalene* (I) *with* 3-*Methoxyphenethyl Bromide*.—1,2,3,4,5,8-Hexahydro-6-methoxy-1-oxonaphthalene (4·5 g.) in tetrahydrofuran (10 c.c.) was added to a solution of potassium amide (from potassium, 1·05 g.) in ammonia (300 c.c.). After 5 minutes' stirring, 3-methoxyphenethyl bromide (5·06 g.) in tetrahydrofuran (10 c.c.) was run in, the colour changing from yellow-brown to green. The mixture was stirred for 2 hr., then diluted with saturated ammonium sulphate solution and extracted with ether. The extract was concentrated to remove ammonia and ether, and the residual solution in tetrahydrofuran, diluted with N-sulphuric acid (7 c.c.) and tetrahydrofuran (50 c.c.), was refluxed under nitrogen for 1 hr. On cooling, it was treated with N-sodium hydroxide (50 c.c.) and extracted with ether. The extract was dried ($MgSO_4$) and on evaporation yielded the neutral fraction as an oil (5·04 g.).

The orange-yellow aqueous alkaline extract was cooled in ice and immediately acidified with N-sulphuric acid (60 c.c.), then saturated with ammonium sulphate and extracted with ether. The extract was washed three times with saturated ammonium sulphate solution, dried (Na_2SO_4), and evaporated, yielding the acidic fraction as a pale yellow glass (2·83 g.). This was taken up in ether (100 c.c.) and extracted with water (5 × 50 c.c.). The aqueous extracts,

[3] Cook and Schoental, *J.*, 1945, 288; Johnson, Banerjee, Schneider, Gutsche, Shelberg, and Chinn, *J. Amer. Chem. Soc.*, 1952, **74**, 2845.
[4] Smith, unpublished work.
[5] Holiday and Jope, *Spectrochim. Acta*, 1950, **4**, 158.
[6] Nazarov and Zavyalov, *Izvest. Akad. Nauk S.S.R., Otdel khim. Nauk*, 1957, 207.

saturated with ammonium sulphate and re-extracted with ether, yielded 1,2,3,4,6,7,8,8a-octahydro-1,6-dioxonaphthalene (1·17 g.), m. p. 44—46° (ether at 0°) (Found: C, 73·0; H, 7·4. Calc. for $C_{10}H_{12}O_2$: C, 73·1; H, 7·4%), $\lambda_{max.}$ (in ethanol) 237 (ε 9400), 340 mμ (ε 4800) (enolic tautomer) [cf. $\lambda_{max.}$ of 2,3,4,6,7,8-hexahydro-1-methoxy-6-oxonaphthalene (VIII) at 343 mμ (ε 18,000)], $\lambda_{max.}$ (in aqueous NaOH) 409 mμ (ε 37,000), $\nu_{max.}$ (melt) 1663, 1718 cm.$^{-1}$ (C=O).

The residual ether extract, when dried (Na_2SO_4) and evaporated, yielded mixed acidic alkylation products as a pale yellow glass (1·58 g.), $\lambda_{max.}$ (in ethanol) 241 (ε 12,100), 344 mμ (ε 4400) (enolic tautomer), $\lambda_{max.}$ (in aqueous NaOH) 421 mμ (ε 27,700). This product was stirred with a solution of phosphoric oxide (5 g.) in syrupy phosphoric acid (5 c.c.) under nitrogen at 60° for 1 hr., then poured on ice, extracted with chloroform, washed with dilute sodium hydroxide solution, dried ($MgSO_4$), and recovered as a yellow glass (1·40 g.). This was separated into two components by chromatography on Florex in pentane–ether mixtures: 1,2,3,4,5,6,11,12-*octahydro*-8-*methoxy*-1-*oxochrysene* (V) (0·90 g.) was eluted first, forming yellow prisms (from ether), m. p. 116—118°, $\lambda_{max.}$ (in ethanol) 243, 289, 386 mμ (ε 11,200, 2500, 24,000), $\nu_{max.}$ (in CS_2) 1650 cm.$^{-1}$ (C=O) (Found: C, 81·3; H, 7·2. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·2%). The second component, a *ketone*, $C_{19}H_{20}O_3$ (0·14 g.), crystallised as yellow needles (from ethyl acetate), m. p. 170—172°, $\lambda_{max.}$ (in ethanol) 243, 393 mμ (ε 9100, 27,000), $\nu_{max.}$ (in CS_2) 1650 cm.$^{-1}$ (C=O) (Found: C, 81·0; H, 6·8. $C_{19}H_{20}O_2$ requires C, 81·4; H, 7·2%).

The total neutral fraction was taken up in ether and fractionally precipitated with pentane. The main fraction was chromatographed on Florisil in ether–pentane, yielding 1,2,3,4,6,7,8,8a-octahydro-8a-3′-methoxyphenethyl-1,6-dioxonaphthalene as a colourless glass (2·38 g.), yielding a *dioxime* which crystallised in two modifications from ethyl acetate: a metastable form, m. p. 157—159°, and on subsequent handling a stable form, m. p. 180—182° (Found: C, 69·4; H, 7·4; N, 8·6. $C_{19}H_{24}N_2O_3$ requires C, 69·5; H, 7·4; N, 8·6%).

Alkylation of 2,3,4,6,7,8-*Hexahydro*-1-*methoxy*-6-*oxonaphthalene* (VIII) *with* 3-*Methoxyphenethyl Bromide*.—2,3,4,6,7,8-Hexahydro-1-methoxy-6-oxonaphthalene (0·68 g.) (m. p. 62—64° as prepared by Nazarov and Zavyalov [6]) in tetrahydrofuran (5 c.c.) was added to a solution of potassium amide (from potassium, 0·15 g.) in ammonia (200 c.c.). An immediate yellow colour was produced. After 5 minutes' stirring, 3-methoxyphenethyl bromide (0·82 g.) in tetrahydrofuran (5 c.c.) was added. The mixture was stirred for 2 hr., then worked up as in the previous experiment, yielding after acidic hydrolysis and separation: (*a*) a neutral fraction (0·33 g.), separated by distillation into volatile material (0·18 g.; b. p. 95—127°/15 mm.) and a residue, mainly 1,2,3,4,6,7,8,8a-octahydro-8a-3′-methoxyphenethyl-1,6-dioxonaphthalene (0·13 g.); (*b*) 1,2,3,4,6,7,8,8a-octahydro-1,6-dioxonaphthalene (0·31 g.), m. p. 39—42° (from ether); (*c*) mixed acidic alkylation products (0·45 g.). Fraction (*c*) on cyclisation and separation as in the previous experiment yielded 1,2,3,4,5,6,7,8-octahydro-8-methoxy-1-oxochrysene (V) (0·28 g.), yellow prisms (from ether), m. p. 116—118°, and the yellow ketone $C_{19}H_{20}O_2$ (0·02 g.), needles (from ethyl acetate), m. p. 170—172°. Both these products were shown by mixed m. p. determinations and comparisons of infrared spectra to be identical with the products of the previous alkylation.

1,2,3,4,5,6-*Hexahydro*-8-*methoxy*-1-*oxochrysene* (VI).—1,2,3,4,5,6,11,12-Octahydro-8-methoxy-1-oxochrysene (0·24 g.) in ether (40 c.c.) was adsorbed on alumina (sufficient to give a dry powder) and baked at 95—100°. After 6 hr. the yellow colour had vanished; the product was eluted with chloroform and methanol, evaporated, and chromatographed in benzene on alumina, benzene–ether yielding 1,2,3,4,5,6-*hexahydro*-8-*methoxy*-1-*oxochrysene*, colourless crystals (from ether) (0·032 g.), m. p. 129—130°, $\lambda_{max.}$ 234, 329 mμ (ε 19,500, 27,900), $\nu_{max.}$ (in CS_2) 1680 cm.$^{-1}$ (C=O) (Found: C, 81·6; H, 6·6. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%).

The alternative possible dehydrogenation product, 1,2,3,4,11,12-hexahydro-8-methoxy-1-oxochrysene has been fully characterised,[7] and its m. p. (189°) and ultraviolet spectrum [$\lambda_{max.}$ 224, 277, 286, 351 mμ (ε 31,000, 28,600, 32,900, 18,000)] are distinct from those of the above compound.

1,2,3,4,5,6-*Hexahydro*-8-*methoxychrysene* (VII).—1,2,3,4,5,6-Hexahydro-8-methoxy-1-oxochrysene (0·021 g.) in ethanol (10 c.c.) was treated with potassium borohydride at room temperature for 24 hr., then diluted with water, extracted with ethyl acetate, washed, and obtained crystalline (qualitative measurement showed $\lambda_{max.}$ at 280 mμ; no band at 329 mμ, indicating complete reduction). The total product was hydrogenated in methanol on palladium–charcoal, absorbing 7 c.c. of hydrogen during 1 hr. The product was isolated in benzene, freed from

[7] Birch and Smith, *J.*, 1951, 1882.

catalyst by filtration through alumina, and recrystallised from methanol, giving 1,2,3,4,5,6-hexahydro-8-methoxychrysene (0·019 g.), colourless needles, m. p. 119—120°, $\lambda_{max.}$ 280 mμ (ε 22,800) (Found: C, 85·75; H, 7·45. Calc. for $C_{19}H_{20}O$: C, 86·3; H, 7·6%).

2-*Methoxychrysene.*—1,2,3,4,5,6-Hexahydro-4-methoxychrysene (0·010 g.) and sulphur (0·005 g.) was heated at 220° for 1 hr., then cooled and extracted with boiling benzene (20 c.c.). The extract was shaken with mercury for 16 hr., then filtered through alumina and evaporated, leaving 2-methoxychrysene, colourless plates (from benzene) (0·0035 g.), m. p. 255—257° (lit.,[3] 250—251°), $\lambda_{max.}$ (in hexane) 263·5, 272·5, 296, 308, 319, 347, 364·5 mμ (ε 87,000, 162,000, 23,100, 17,400, 12,400, 1130, 750) (cf. ref. 5) (Found: C, 85·0; H, 5·4. Calc. for $C_{19}H_{14}O$: C, 88·4; H, 5·4%).

Investigation of the Yellow Ketone, $C_{19}H_{20}O_2$, m. p. 170—172°.—This substance (0·4 g.) was partially dehydrogenated, in the same way as the isomeric chrysene derivative, yielding a colourless *ketone*, $C_{19}H_{18}O_2$, that, recrystallised from ethyl acetate, had m. p. 209—210° (0·080 g.), $\lambda_{max.}$ 328 mμ (ε 30,000), $\nu_{max.}$ (in Nujol) 1670 cm.$^{-1}$ (C=O) (Found: C, 81·9; H, 7·35. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%). This substance (0·075 g.) was hydrogenated in benzene–tetrahydrofuran in presence of palladium–charcoal. Uptake of hydrogen was arrested after 17·8 c.c., and the products were freed from catalyst by filtration through alumina and evaporation (0·074 g.). Recrystallisation from ethyl acetate gave colourless crystals, melting over a wide range of temperature (0·046 g.). These were taken up in benzene and filtered through active alumina, then recrystallised from ethyl acetate, giving a *substance* $C_{19}H_{20}O$ (0·028 g.), m. p. 137—139°, $\lambda_{max.}$ 276 mμ (ε 24,000) (Found: C, 85·9; H, 7·2. $C_{19}H_{20}O$ requires C, 86 3; H, 7·6%).

This substance (0·022 g.) and sulphur (0·011 g.) were heated at 220° for 1 hr., then cooled and extracted with boiling benzene (20 c.c.). The extract was shaken with mercury for 16 hr., then filtered through alumina and evaporated, leaving an orange-brown crystalline residue. This was recrystallised from ethyl acetate–methanol, giving a *substance* $C_{19}H_{14}O$ (0·009 g.), colourless plates, m. p. 178—180°, $\lambda_{max.}$ (in hexane) 218, 252, 260, 270, 305, 318, 337, 355 mμ (ε 38,000, 23,700, 53,200, 85,500, 25,700, 27,900, 2160, 523) (Found: C, 86·2; H, 5·7. $C_{19}H_{14}O$ requires C, 88·4; H, 5·4%). The mother-liquors deposited red needles (0·001 g.), m. p. 110—114°, having a broad absorption band ($\lambda_{max.}$ 430 mμ) typical of polycyclic quinones.

Some preliminary experiments were carried out by Dr. R. J. Harrison in the Chemistry Department, University of Sydney. We are grateful to the Polish Ministry of Education for a Fellowship (M. K.).

DEPARTMENT OF CHEMISTRY, UNIVERSITY OF MANCHESTER. [*Received, July 24th,* 1961.]