147. *Synthesis of Cholanthrene.*

By J. W. Cook, G. A. D. Haslewood, and (Mrs.) A. M. Robinson.

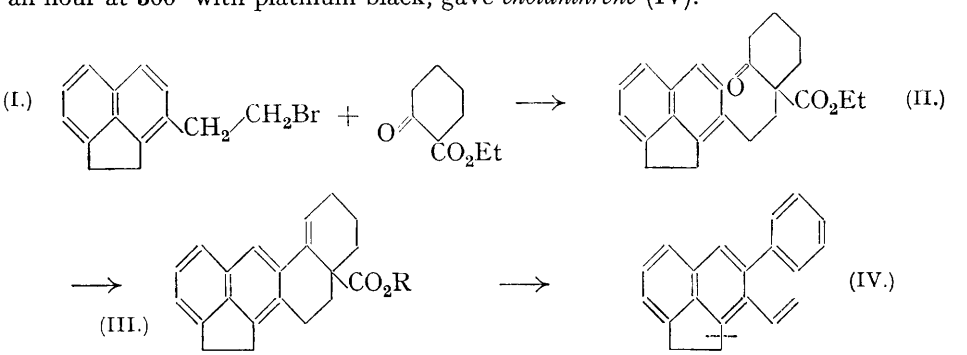
The most potent carcinogenic compound so far encountered is methylcholanthrene, a transformation product of the bile acid, deoxycholic acid (Cook and Haslewood, J., **1934**, 428; Barry, Cook, Haslewood, Hewett, Hieger, and Kennaway, *Proc. Roy. Soc.*, **1935**, *B*, **117**, 318). This suggested the desirability of examining for carcinogenic action other compounds containing the cholanthrene * ring system, and possible synthetic routes to this ring system have been under investigation in this Institute for the past year. We now describe a synthesis of the parent hydrocarbon, *cholanthrene*, by a method which establishes its structure. The same hydrocarbon has been obtained also by two other independent methods which will be described by two of us in a subsequent communication. The synthesis of methylcholanthrene, identical with that obtained from deoxycholic acid, has been announced recently by Fieser and Seligman (*J. Amer. Chem. Soc.*, 1935, **57**, 228).

The starting point in our cholanthrene synthesis was the 1-iodoacenaphthene † of Morgan and Harrison (*J. Soc. Chem. Ind.*, 1930, **49**, 413T). The Grignard compound of this iodoacenaphthene reacted with ethylene oxide to give β-1-*acenaphthylethyl alcohol*,

* For definition, see Wieland and Dane, *Z. physiol. Chem.*, 1933, **219**, 241.

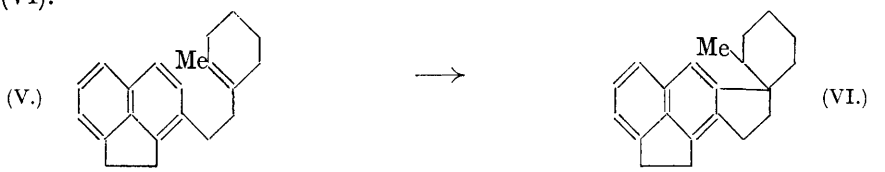
† We adhere to the convention commonly used in this Journal for the numbering of the acenaphthene ring. This differs from that used by Morgan and Harrison, who describe the compound in question as 2-iodoacenaphthene.

but the yield was extremely poor on account of the reluctance of the halogen compound to react with magnesium. No better result was obtained with 1-bromoacenaphthene. This difficulty was overcome, and the alcohol obtained in 55% yield, by making use of the recent device of Grignard (*Compt. rend.*, 1934, **198**, 625, 2217), who found that halogen compounds which are normally non-reactive towards magnesium readily give magnesio-derivatives in the presence of a molecule of ethyl bromide. β-1-*Acenaphthylethyl bromide* (I) condensed smoothly with the potassio-compound of ethyl *cyclo*hexanone-2-carboxylate, yielding *ethyl* 2-(β-1′-*acenaphthylethyl*)cyclo*hexanone*-2-*carboxylate* (II), which was cyclised to *ethyl hexahydrocholanthrenecarboxylate* (III; R = Et) by boiling 55% sulphuric acid. An analogous synthesis of the chrysene ring system has been recorded by Ruzicka, Ehmann, Goldberg, and Hösli (*Helv. Chim. Acta*, 1933, **16**, 833). The ester (III; R = Et) was very difficult to hydrolyse, which accords with its structure; the corresponding *acid* (III; R = H) was obtained by heating with sodium ethoxide. This acid, when heated for an hour at 300° with platinum-black, gave *cholanthrene* (IV).



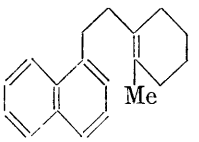
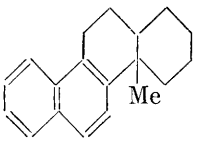
Additional evidence of the structure of the hydrocarbon so obtained was afforded by its oxidation by chromic acid to an acid which gave the Liebermann anthraquinol reaction. This acid, formed by fission of the five-membered ring at the point indicated by the dotted line, was decarboxylated to 5-methyl-1 : 2-benzanthraquinone, a degradation exactly comparable with the transformation of methylcholanthrene into 5 : 6-dimethyl-1 : 2-benzanthraquinone (Cook and Haslewood, *loc. cit.*).

Cyclisation of 2-*methyl*-(β-1′-*acenaphthylethyl*)-Δ^1-cyclo*hexene* (V), obtained from β-1-acenaphthylethylmagnesium chloride and 2-methyl*cyclo*hexanone, by aluminium chloride led to an inseparable mixture of hydrocarbons, one of which appeared to be unaffected by treatment with selenium at 320°, a behaviour consistent with its formulation as the spiran (VI).



Hence this reaction was unsuitable for the synthesis of cholanthrene. In view of the favourable influence of a similarly disposed methyl group in promoting cyclisation of arylethyl*cyclo*pentenes to condensed-ring compounds, with avoidance of spiran formation (Cohen, Cook, Hewett, and Girard, J., 1934, 653; Cook, Hewett, Mayneord, and Roe, *ibid.*, p. 1727), the failure to obtain a satisfactory yield of octahydrocholanthrene by cyclisation of (V) was somewhat surprising. Consideration of stereochemical and other factors showed it to be unlikely that such an influence of a methyl group would depend upon the size of the ring to which this group is attached, but in order to examine this possibility the cyclisation of 2-*methyl*-(β-1′-*naphthylethyl*)-Δ^1-cyclo*hexene* (VII) has been studied. Previous experiments had shown that the analogous hydrocarbon without the methyl group is converted by aluminium chloride into a mixture of saturated isomerides, the

principal constituent of which is **7 : 8**-dihydrophenalyl-7-*spirocyclo*hexane, readily isolated by means of its sparingly soluble picrate (Cook and Hewett, J., 1934, 365). As was expected by analogy with the *cyclo*pentene derivatives already studied, this spiran formation was suppressed in the case of the methyl compound (VII) now reported, for the only cyclisation product which could be isolated was methyloctahydrochrysene (VIII).

(VII.)  →  (VIII.)

From this it is evident that the cyclisation of (V) is anomalous, but in the absence of further data we are unable to offer any explanation of the anomaly.

Methyloctahydrochrysene (VIII) was dehydrogenated to chrysene by selenium at 300°, but was unaffected by platinum-black. Failure of the latter catalyst to dehydrogenate hydroaromatic compounds containing quaternary carbon atoms was first observed by Zelinsky (*Ber.*, 1923, **56**, 1716). An example of a hydroaromatic compound which is dehydrogenated by platinum, but not by selenium, at 300°, will be given in a future communication (Cook and Hewett).

Experimental.

* and † denote microanalyses by Dr. A. Schoeller and Dr. G. Weiler respectively.

β-1-*Acenaphthylethyl Alcohol*.—The nitration of acenaphthene with diacetylorthonitric acid, the separation of the 1-nitro-compound and its reduction by aluminium amalgam, and the conversion of the amine into 1-iodoacenaphthene were carried out exactly as described by Morgan and Harrison (*loc. cit.*). Purification of the iodo-compound was best effected by vacuum distillation (b. p. 158°/0·3 mm.), followed by recrystallisation from alcohol.

Ethyl bromide (10·8 c.c.), diluted with anhydrous ether (100 c.c.), was gradually added to a mixture of 1-iodoacenaphthene (40 g.), magnesium turnings (7 g.), and anhydrous ether (100 c.c.). After all had been added and the reaction had subsided, the whole was boiled for 1½ hours. The ice-cold solution was then slowly treated with ethylene oxide (25 g.) in ethereal solution, then kept at 0° for ½ hour, and finally at room temperature over-night. Toluene (50 c.c.) was added, the ether removed on the water-bath, and the residue heated at 100° for an hour. The product was treated with dilute hydrochloric acid, extracted with ether, dried, and distilled in a vacuum. β-1-*Acenaphthylethyl alcohol* (14·9 g., b. p. 179—180°/0·3 mm.) formed a pale yellow liquid which readily crystallised, and was purified for analysis through its **3 : 5**-*dinitrobenzoate*, which crystallised from benzene–alcohol in microscopic yellow needles, m. p. 233—234·5° (Found : C, 64·2; H, 4·5. $C_{21}H_{16}O_6N_2$ requires C, 64·3; H, 4·1%). The alcohol obtained by hydrolysis of this ester crystallised from ligroin in colourless plates, m. p. 94—95° (Found : C, 85·0; H, 7·4. $C_{14}H_{14}O$ requires C, 84·8; H, 7·1%).

β-1-*Acenaphthylethyl chloride* (28·2 g.) was obtained from the alcohol (33·7 g.) by means of thionyl chloride and dimethylaniline (compare Cook and Hewett, J., 1933, 1107). This chloride (b. p. 145—150°/0·1 mm.) crystallised from alcohol in almost colourless rhombs, m. p. 54—55° (Found : Cl, 16·5. $C_{14}H_{13}Cl$ requires Cl, 16·4%).

β-1-*Acenaphthylethyl bromide* (I) was obtained by addition of phosphorus tribromide (10 g.) to a solution of the alcohol (20 g.) in carbon tetrachloride (28 c.c.) at 60°. After being kept at this temperature for ¼ hour, the solution was twice shaken with dilute aqueous sodium carbonate, and the filtered carbon tetrachloride solution distilled. The bromide, b. p. 165°/0·4 mm., crystallised from alcohol in rectangular plates (13 g.), m. p. 66° († Found : C, 64·2; H, 5·1. $C_{14}H_{13}Br$ requires C, 64·4; H, 5·0%).

Ethyl 2-(β-1′-*Acenaphthylethyl*)cyclo*hexanone*-2-*carboxylate* (II).—Powdered potassium (3·3 g.) was dissolved in a mixture of ethyl *cyclo*hexanone-2-carboxylate (14·2 g.) and pure anhydrous benzene (50 c.c.), and the solution heated on the water-bath for 6 days with β-1-acenaphthylethyl bromide (11 g.). The whole was treated with ice and extracted with ether. The *keto-ester* (II) was isolated by distillation (10·6 g.; b. p. 210—220°/0·4 mm.), forming a colourless gum which slowly crystallised. After recrystallisation from alcohol it formed colourless stout needles (7 g.), m. p. 76—77° († Found : C, 79·2; H, 7·3. $C_{23}H_{26}O_3$ requires C, 78·8; H, 7·5%). Hydrolysis of this ester with methyl-alcoholic potash gave α-(β′-1-*acenaphthylethyl*)*pimelic acid*, which was crystallised from benzene and then alcohol, forming colourless

rectangular plates, m. p. 165° († Found : C, 74·3; H, 7·1. $C_{21}H_{24}O_4$ requires C, 74·0; H, 7·1%).

Ethyl Hexahydrocholanthrenecarboxylate (III).—An attempt to effect cyclisation of the keto-ester (II) by boiling sulphuric acid (equal volumes of concentrated acid and water), a procedure successfully used in other cases (Ruzicka, *loc. cit.*; Cohen, Cook, and Hewett, this vol., p. 445), led only to amorphous black polymerisation products. When the concentration of sulphuric acid was 50% by weight, the keto-ester was recovered unchanged. However, a small increase in this concentration sufficed for cyclisation : A suspension of the keto-ester (II) (1·9 g.) in water (18·4 c.c.) and concentrated sulphuric acid (12 c.c.) was boiled for 30 hours. The product was isolated by ether extraction and distilled in a high vacuum from a bath at 200°. The pale yellow distillate was recrystallised several times from alcohol. *Ethyl hexahydrocholanthrenecarboxylate* (III; R = Et) (0·5 g.) formed long colourless needles, m. p. 150° (* Found : C, 82·8; H, 7·2; *M*, Rast method, 356, 365. $C_{23}H_{24}O_2$ requires C, 83·1; H, 7·3%; *M*, 332). Solutions of this ester had an intense violet fluorescence. For hydrolysis to *hexahydrocholanthrenecarboxylic acid* (III; R = H) the ester (0·45 g.) was heated at 180° for 18 hours with sodium ethoxide (2 g. of sodium in 30 c.c. of alcohol). A specimen of the precipitated acid crystallised from acetic acid in stout yellowish prisms, m. p. 241—242° with gas evolution (* Found : C, 82·0; H, 6·6. $C_{21}H_{30}O_2$ requires C, 82·85; H, 6·6%). The low value for carbon was probably due to absorption of oxygen during recrystallisation, during which the colourless solution became markedly yellow.

Cholanthrene (IV).—A mixture of the crude hexahydrocholanthrenecarboxylic acid (0·37 g.) and platinum-black (0·2 g.) was heated at 295—305° for 1¼ hours. The product was extracted with benzene, and the concentrated extract treated with alcohol. The crystalline product (0·2 g.) was sublimed at 170—190°/0·05 mm., and the sublimate recrystallised from benzene–alcohol. *Cholanthrene* (IV) formed pale yellow leaflets, m. p. 170—171° (* Found : C, 94·5, 94·3; H, 5·5, 5·6; *M*, Rast method, 255, 262. $C_{20}H_{14}$ requires C, 94·45; H, 5·55%; *M*, 254). The *picrate* crystallised from benzene in purplish-black needles, m. p. 167—168° (* Found : C, 64·5; H, 3·6. $C_{20}H_{14},C_6H_3O_7N_3$ requires C, 64·6; H, 3·55%). The m. p. of the hydrocarbon was unaltered by purification through the picrate.

Oxidation of cholanthrene (40 mg.) with sodium dichromate in acetic acid, and decarboxylation of the crude acid with boiling quinoline containing copper powder, was carried out as in the case of methylcholanthrene (Cook and Haslewood, *loc. cit.*). The resulting quinone, after vacuum sublimation and recrystallisation from acetic acid, had m. p. 166—168°, not depressed by 5-methyl-1 : 2-benzanthraquinone (m. p. 174°; Cook, J., 1933, 1596). There was insufficient for complete purification.

2-*Methyl*-(β-1′-*acenaphthylethyl*)-Δ^1-cyclo*hexene* (V).—To an ice-cold Grignard solution prepared from β-1-acenaphthylethyl chloride (21·3 g.), anhydrous ether (150 c.c.), and magnesium turnings (2·5 g.) activated with iodine, was added 2-methyl*cyclo*hexanone (12·3 g.). After 16 hours at room temperature the product was treated with ice and dilute hydrochloric acid, and the ethereal solution washed and distilled. The fraction, b. p. 120—125°/0·4 mm., consisted of 1-*ethylacenaphthene*, which was purified through its *picrate*, bright red needles (from alcohol–*cyclo*hexane), m. p. 102—102·5° (Found : C, 58·2; H, 5·0. $C_{14}H_{14},C_6H_3O_7N_3$ requires C, 58·4; H, 4·2%). The hydrocarbon isolated from this picrate was distilled in a vacuum over sodium and then recrystallised from methyl alcohol, forming colourless needles, m. p. 30° (Found : C, 92·1; H, 7·8. $C_{14}H_{14}$ requires C, 92·2; H, 7·8%).

The higher-boiling fraction from the products of the Grignard reaction (11 g., b. p. 210°/0·7 mm.) formed a viscous liquid, which was heated for an hour at 155—165° with potassium hydrogen sulphate (16·5 g.), and then redistilled over sodium. Treatment with alcoholic picric acid gave the *picrate* of 2-*methyl*-(β-1′-*acenaphthylethyl*)-Δ^1-cyclo*hexene*, golden-red needles, m. p. 107—108° (Found : C, 64·2; H, 5·8. $C_{21}H_{24},C_6H_3O_7N_3$ requires C, 64·1; H, 5·4%). The *hydrocarbon* (V), regenerated from this picrate and distilled over sodium, formed a pale yellow, viscous liquid, b. p. 182—185°/0·2—0·3 mm. (Found : C, 91·2; H, 8·5. $C_{21}H_{24}$ requires C, 91·2; H, 8·8%).

Cyclisation of 2-*Methyl*-(β-1′-*acenaphthylethyl*)-Δ^1-cyclo*hexene*.—Anhydrous aluminium chloride (10·3 g.) was added to an ice-cold solution of the foregoing hydrocarbon (10·7 g.) in carbon disulphide (100 c.c.). After keeping at 0° for 21 hours, the dark green liquid was decanted from the aluminium chloride sludge and worked up in the usual way. The product, b. p. 200°/0·4 mm., was a yellow oil which crystallised on cooling. By repeated crystallisation from benzene, the m. p. of the bright red picrate obtained from the product was raised to 157—158°, and this gave, after removal of the picric acid, followed by four recrystallisations

from light petroleum, colourless needles, m. p. 178—182° (*Found : C, 90·9; H, 8·7%). We believe this to be mainly the spiran (VI), although evidence of this is lacking.

The hydrocarbon mixture (4 g.), m. p. 123—129°, from which this product had been separated was heated with selenium (4·6 g.) at 320—330° for 32 hours. After distillation and recrystallisation, the product had m. p. 120—125°. By crystallisation of the picrate from benzene, followed by removal of picric acid, the m. p. was brought to 165—173°, and was not depressed by the above product, m. p. 178—182°. Thus it appeared that the original cyclised material contained a constituent which resisted the dehydrogenating action of selenium. Whether cholanthrene was also present in the mixture after dehydrogenation we are unable to say, as no pure compound could be isolated from the amount of material available.

2-*Methyl*-1-(β-1′-*naphthylethyl*)cyclo*hexanol*.—2-Methylcyclohexanone (31 g.) was added gradually to an ice-cold Grignard solution prepared from β-1-naphthylethyl chloride (48 g.), magnesium turnings (6 g.), and anhydrous ether (125 c.c.). Ice and ammonium chloride were added after 2 hours at room temperature, and the product was worked up in the usual way. The crude carbinol (36 g.) formed a thick syrup, b. p. 185—195°/0·5 mm., which could not be obtained crystalline. It was characterised by its 3 : 5-*dinitrobenzoate*, which crystallised from ligroin in pale yellow, hexagonal prisms, m. p. 136° († Found : C, 67·7; H, 5·8. $C_{26}H_{26}O_6N_2$ requires C, 67·5; H, 5·7%). During the purification of this compound there was also isolated a colourless crystalline neutral substance of lower carbon and hydrogen content († Found : C, 45·55; H, 2·8%), which was sparingly soluble in benzene but readily soluble in alcohol.

2-*Methyl*-(β-1′-*naphthylethyl*)-Δ^1-cyclo*hexene* (VII).—This was obtained by dehydration of the foregoing carbinol (10 g.) with potassium hydrogen sulphate (10 g.) at 160—170° (1 hour). The distilled product (7 g.) was purified through its picrate, which readily dissociated and could not be obtained analytically pure. The regenerated *hydrocarbon* (VII), distilled over sodium, formed a colourless viscous liquid, b. p. 135°/0·1 mm., $d_4^{8°}$ 1·0158, $n_D^{8°}$ 1·5992, $[R_L]_D$ 83·1 (calc., 83·22) (Found : C, 90·9; H, 8·9. $C_{19}H_{22}$ requires C, 91·1; H, 8·9%).

Methyloctahydrochrysene (VIII).—Cyclisation of the unsaturated hydrocarbon (VII) (11 g.) with anhydrous aluminium chloride (13 g.) in carbon disulphide (100 c.c.) at 0° was complete in 7 hours. The distilled product (6·6 g.) was treated with alcoholic picric acid. After several recrystallisations from alcohol the *picrate* of *methyloctahydrochrysene* formed deep orange needles, m. p. 105—106° (* Found : C, 62·7; H, 4·7. $C_{19}H_{22},C_6H_3O_7N_3$ requires C, 62·6; H, 5·2%). No other crystalline product could be isolated from the liquors, although concentration gave a heavy oil, apparently a hydrocarbon which formed no picrate. It may be remarked that only one of the two stereoisomeric *as*.-octahydrochrysenes forms a picrate (Cook and Hewett, J., 1934, 373). *Methyloctahydrochrysene* (VIII), distilled over sodium, formed a thick colourless syrup, b. p. 145°/0·1 mm. (Found : C, 90·8; H, 9·0. $C_{19}H_{22}$ requires C, 91·1; H, 8·9%).

Dehydrogenation of methyloctahydrochrysene. (i) The pure hydrocarbon (0·5 g.) was heated with excess of selenium at 295—305° for 20 hours. The resulting chrysene, obtained in good yield, was identified by mixed m. p. with an authentic sample, and by conversion into its 2 : 7-dinitroanthraquinone complex. (ii) Methyloctahydrochrysene (1 g.) was heated with platinum-black (0·5 g.) at 300° for 8 hours. No crystals separated on cooling. After distillation the substance gave the picrate of the original methyloctahydrochrysene.

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