179. *Constitution of Conessine. Part I.*

By Robert D. Haworth, James McKenna, and Nazar Singh.

The oil, $C_{21}H_{30}$, obtained by the action of heat on conessine dihydriodide gave, on selenium dehydrogenation, the hydrocarbons, $C_{19}H_{18}$, m. p. 78—79°, and $C_{19}H_{16}$, m. p. 194—195°. The former is essentially 3′-*ethyl*cyclo*pentenophenanthrene*, which has been synthesised for comparison purposes; certain inconsistencies between the synthetic product and the hydrocarbon obtained from conessine are ascribed to the presence of small amounts of inseparable impurities in the latter.

Späth and Hromatka (*Ber.*, 1930, **63**, 126) degraded conessine by Hofmann and Emde processes to a crystalline lævorotatory hydrocarbon, $C_{21}H_{30}$, m. p. 74°, which was reduced catalytically to a hexahydro-derivative, $C_{21}H_{36}$, m. p. 56—58°. A repetition of these experiments has shown that the final reduction yields two isomeric hydrocarbons, one of which is identical with the product obtained by Späth and Hromatka, and the second, m. p. 84°, $[\alpha]_D^{15°}$ 15°, with 5-*allo*pregnane.

Conessine is, therefore, a steroid alkaloid, containing one ethylenic linkage, a dimethylamino-group, a cyclic methylimino-group, and probably a 5-*allo*pregnane structure, but the present experimental data are insufficient for a complete solution of the problem.

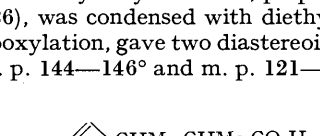
The alkaloid conessine, $C_{24}H_{40}N_2$, has been isolated from the bark (Haines, *Trans. Med. Soc. Bombay*, 1858, **4**, 28) and seeds (Stenhouse, *Pharm. J.*, 1864, **5**, 493) of Indian "kurchi", *Holarrhena antidysenterica*, from the African species, *Holarrhena febrifuga* (Siddiqui, Misra, and Sharma, *J. Sci. Ind. Res., India*, 1945, **3**, 555), *Holarrhena Wulfsbergii* (Henry and Brown, *Trans. Roy. Soc. Trop. Med. Hyg.*, 1923—1924, **17**, 381) and together with a subsidiary base, holarrhenine, $C_{24}H_{38}ON_2$, from *Holarrhena Congolensis* (Pyman, *J.*, 1919, **115**, 163). In addition to conessine a number of subsidiary bases have been isolated from extracts of "kurchi" bark and seeds. Ghosh and Ghosh (*J. Indian Chem. Soc.*, 1928, **5**, 477) and Ghosh and Bose (*Arch. Pharm.*, 1932, **270**, 100) isolated kurchine, $C_{23}H_{38}N_2$, and kurchicine, $C_{20}H_{36}ON_2$; Bertho, von Shuckmann, and Schonberger (*Ber.*, 1933, **66**, 786) obtained conessidine, $C_{21}H_{32}N_2$, conkurchine, $C_{21}H_{32}N_2$, and kurchenine, $C_{21}H_{32}O_2N_2$; Bertho (*Annalen*, 1944, **555**, 214) recorded the occurrence of conkurchenine, $C_{25}H_{36}N_2$: and Siddiqui and his collaborators (*J. Indian Chem. Soc.*, 1932, **9**, 553; 1934, **11**, 285; 787) separated conessimine, $C_{23}H_{38}N_2$, *iso*conessimine, $C_{23}H_{38}N_2$, conimine, $C_{22}H_{36}N_2$, conamine, $C_{22}H_{36}N_2$, conarrhimine, $C_{21}H_{34}N_2$, holarrhimine, $C_{21}H_{36}ON_2$, and holarrhine, $C_{20}H_{38}O_3N_2$.

The main alkaloid conessine is a ditertiary base containing a dimethylamino-group, a heterocyclic methylimino-group, and a double bond which is reduced with some difficulty. Many of the subsidiary oxygen-free alkaloids are *N*-demethylated conessines, and conessimine, *iso*conessimine, and conimine have been converted into conessine by methylation with formaldehyde and formic acid (Siddiqui, *J. Indian Chem. Soc.*, 1934, **11**, 283). Conkurchine gave conessine by partial reduction (2H) and *N*-methylation (Bertho, *loc. cit.*). Many of these bases have a pronounced tendency for molecular association and Bertho has suggested that kurchenine is a mixture of conessidine and conkurchine, and that kurchicine, conarrhimine, and *nor*conessine

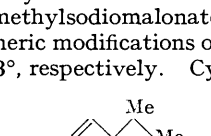
(Haworth, *J.*, 1932, 631) are probably impure holarrhimine, conkurchine, and kurchine, respectively. No relationships have yet been established between the oxygen-containing bases, some of which, *e.g.* holarrhenine and holarrhimine, contain hydroxyl groups, and obviously the C_{20}-bases, kurchicine and holarrhine, cannot be formulated as *N*-demethylated conessines.

The application of Indian "kurchi" bark for the treatment of amoebic dysentery and tubercular affections in the indigenous medical practice has stimulated numerous investigations of the constituents of both Indian and African *Holarrhena* species, and pure conessine has been shown to possess interesting pharmacological properties. It has no anti-amoebic action *in vitro*, but *in vivo*, after intensive dosing, it showed marked activity (Jones, *Ann. Trop. Med. and Parasitol.*, 1946, **40**, 134; *Brit. J. Pharmacol.*, 1947, **2**, 217), and Meissner and Hesse (*Arch. exp. Path. Pharm.*, 1930, **147**, 339) have shown that it inhibits the growth of tubercle bacilli *in vitro*. In view of these interesting pharmacological properties, a knowledge of the chemical constitution of the alkaloid is very desirable. The results of Spath and Hromatka (*Ber.*, 1930, **63**, 126), which are outlined later (p. 834), indicate the presence of a tetracarbocyclic, system, but subsequent researches (Siddiqui and co-workers, *Proc. Indian Acad. Sci.*, 1935, **2**, 426; 1936, **4**, 283; 1939, **10**, 417; *J. Sci. Ind. Res., India*, 1945, **3**, 559; 1946, **7**, 435, 40; Bertho, *Annalen*, 1947, **557**, 200; 1947, **558**, 62; *Ber.*, 1947, **80**, 316) have added little to our knowledge of the ring system. We have been engaged for some time in a series of researches on the nature of conessine and related bases, and the present communication is concerned with the elucidation of the molecular framework of the alkaloids; the more detailed structural features will, it is hoped, be considered in later publications. The bases employed in these researches were isolated from the seeds of *Holarrhena antidysenterica*, a generous supply of which was kindly placed at the disposal of one of us some twenty years ago by Sir John Simonsen, F.R.S. Conessine was purified as the hydrogen oxalate, and a welcome additional yield was obtained by adopting Siddiqui's valuable procedure (*J. Indian Chem. Soc.*, 1934, **11**, 283) of methylating with formaldehyde the crude *nor*-bases which were present in the mother liquors. Important evidence concerning the constitution of conessine has been obtained from an examination of the crude hydrocarbon, "conessene," $C_{21}H_{30}$, which Siddiqui and Sharma (*Proc. Indian Acad. Sci.*, 1937, **6**, 191) prepared by pyrolysis of conessine dihydriodide. This hydrocarbon was dehydrogenated with selenium at 320°, and the products, after tedious systematic chromatography and fractional crystallisation, were resolved into (*a*) an oil with a purple fluorescence, (*b*) a *hydrocarbon*, m. p. 78—79°, and (*c*) a *hydrocarbon*, m. p. 194—195°. The fluorescent oil was partially dehydrogenated, and gave additional yields of the solid hydrocarbons, m. p. 78—79° and m. p. 194—195°, on further dehydrogenation. Most of our attention was, however, focussed on the hydrocarbon, m. p. 78—79°, which gave crystalline complexes with nitro-compounds (see table). The *trinitrobenzene* compound was most convenient for purification and characterisation purposes because of its stability. The *picrate* gradually decomposed in solution to give a *semi-picrate*, the *trinitrotoluene* derivative and *styphnate* were difficult to purify, and the 2 : 7-dinitroanthraquinone derivative dissociated very readily. Analysis and molecular-weight determinations on the hydrocarbon suggested the formula, $C_{19}H_{18}$, which was supported by analysis of the derivatives, and molecular-weight determinations of the picrate and semi-picrate by titration with dilute sodium hydroxide. The hydrocarbon, which was not oxidised to a quinone by chromic acid, gave a violet fluorescence in ultra-violet light, and as the absorption spectrum resembled closely that of Diels's hydrocarbon, a dimethyl- or ethyl-1 : 2-*cyclo*pentenophenanthrene structure was suspected, although the properties did not correspond with those of the five dimethyl derivatives reported in the literature. 2′ : 3′-Dimethyl- and 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene were therefore synthesised for comparison purposes.

1-2-Phenanthrylethyl bromide, prepared by Bachmann and Struve's method (*J. Org. Chem.*, 1940, **5**, 426), was condensed with diethyl methylsodiomalonate; the product, after hydrolysis and decarboxylation, gave two diastereoisomeric modifications of β-2-*phenanthryl*-α-*methylbutyric acid* (I), m. p. 144—146° and m. p. 121—123°, respectively. Cyclisation of the acid chlorides of



(I.)



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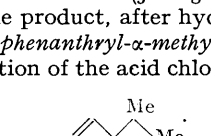


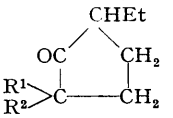
(III.)

either modification of (I) with aluminium chloride in nitrobenzene solution yielded 1′-*keto*-2′ : 3′-*dimethyl*-1 : 2-cyclo*pentenophenanthrene* (II). One modification of the ketone (II) was isolated

in a pure condition, m. p. 119—120°, and yielded on Clemmensen reduction *form* A, m. p. 119—120°, of 2′ : 3′-dimethyl-1 : 2-*cyclo*pentenophenanthrene (III). The second modification of the ketone (II) was not purified; an impure sample, m. p. 99—102°, reduced by Clemmensen's method, yielded a mixture of form *A* and *form* B, m. p. 143—144°, of 2′ : 3′-dimethyl-1 : 2-*cyclo*pentenophenanthrene (III).

The method used by Harper, Kon, and Ruzicka (*J.*, 1934, 124) for the preparation of Diels's hydrocarbon was adapted to the synthesis of 3′-*ethyl*-1 : 2-cyclo*pentenophenanthrene*. *Ethyl* 1-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate*, prepared by ethylation of ethyl *cyclo*pentan-2-one-1-carboxylate, was converted into *diethyl α-ethyladipate* (IV) by treatment with a small amount of sodium ethoxide. A Dieckmann reaction with sodium ethoxide in benzene on the ester (IV) yielded *ethyl* 3-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = H$; $R^2 = CO_2Et$), which on ethylation gave *ethyl* 1 : 3-*diethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = Et$; $R^2 = CO_2Et$). Ketonic hydrolysis of the ester (V; $R^1 = Et$; $R^2 = CO_2Et$) was very slow; repeated treatment with concentrated hydrochloric acid and regeneration from the *semicarbazone*, m. p. 195—196°, was necessary for the preparation of 2 : 5-*diethyl*cyclo*pentanone* (V; $R^1 = Et$; $R^2 = H$). Condensation of this ketone (V; $R^1 = Et$; $R^2 = H$) with the Grignard reagent of 2-α-naphthylethyl bromide, and dehydration of the resultant carbinol with phosphoric oxide gave the tetrahydro*cyclo*pentenophenanthrene (VI) which was not purified. Selenium dehydrogenation of the crude hydrocarbon (VI) gave a mixture which was separated by chromatography and fractional crystallisation into (*a*) an oil with a purple fluorescence, (*b*) 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII), (*c*) 1 : 4-di-α-naphthylbutane, m. p. 174°, and (*d*) a small amount

$EtO_2C{\cdot}CHEt{\cdot}[CH_2]_3{\cdot}CO_2Et$
(IV.)



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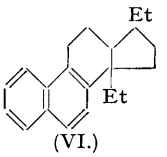


(VI.)

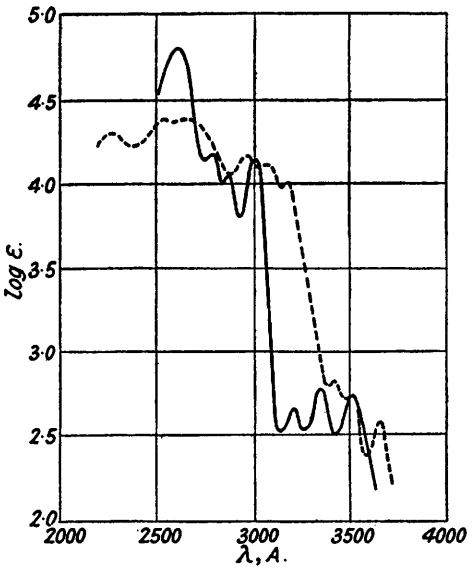
of a *hydrocarbon*, m. p. 194—195°. When the synthesis of 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII) was completed it was found that Riegel, Gold, and Kubico (*J. Amer. Chem. Soc.*, 1943, **65**, 1772) had prepared the hydrocarbon by a different method which did not involve selenium dehydrogenation, and we are deeply indebted to Dr. Riegel for specimens of his hydrocarbon, m. p. 84—85°, and the corresponding semi-picrate, m. p. 95—96°, which were identical with our preparations.

	Hydrocarbon "$C_{19}H_{18}$" from "conessine."	3′-Ethyl-1 : 2-*cyclo*-penteno-phenanthrene.	Mixed m. p.	3′-Ethyl-1 : 2-*cyclo*-penteno-phenanthrene + 5% of Diels's hydrocarbon.	2′ : 3′-Di-methyl-1 : 2-*cyclo*penteno-phenanthrene. Form A.	Form B.
Hydrocarbon.....	78— 79°	84— 85°	78— 79°	78— 79°	119—120°	143—144°
Trinitrobenzene derivative	119—120	120—121	119—121	119—120	143—144	155—156
Semi-picrate	95— 96	95— 96	95— 96	95— 96	119—121	125—127
Picrate	95— 96	—	—	95— 96	—	—
Trinitrotoluene derivative	90— 91	94— 95	92— 93	93— 94	88— 90	96— 98
Styphnate	121—123	122—123	122—123	122—123	—	—
2 : 7-Dinitroanthraquinone derivative	234—235	234—236	234—236	234—235	—	—

The hydrocarbon, "$C_{19}H_{18}$," obtained from "conessene" was carefully compared with synthetic 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII) (see table). Although the two hydrocarbons differed by about 6° in melting point, mixtures had intermediate melting points and no depression in melting point was observed when the corresponding derivatives were mixed. The synthetic hydrocarbons however did not give the normal picrate. Our general conclusion from these results was that the hydrocarbon "$C_{19}H_{18}$," is essentially 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene (VII), contaminated with small amounts of impurity, and it has been shown that a mixture of 3′-ethyl- and 3′-methyl-1 : 2-*cyclo*pentenophenanthrene containing about 5 per cent. of the latter, had m. p. 78—79°, was inseparable by chromatography or crystallisation, and gave a series of derivatives, including the normal picrate, m. p. 96°, indistinguishable from those given by the hydrocarbon, "$C_{19}H_{18}$." Furthermore, the behaviours of "conessene" and of the tetrahydro*cyclo*pentenophenanthrene (VI) during selenium dehydrogenation were

remarkably similar, and the hydrocarbons, m. p. 195—196°, produced in both cases were identical and gave identical *trinitrobenzene* derivatives, m. p. 138—139°. Owing to the small amounts available, it has not been possible to identify the hydrocarbon; the analytical results indicate the formula "$C_{19}H_{16}$," and the shift of the absorption spectra curve (see Fig.) as a whole to the higher wave-length may suggest the formation of an additional ring by loss of two hydrogen atoms from the hydrocarbon "$C_{19}H_{18}$" (see Ruzicka, Thomann, Brandenberger, Furter, and Goldberg, *Helv. Chim. Acta*, 1934, **17**, 200).

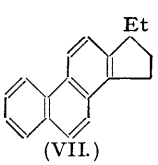
The natural and synthetic hydrocarbons, "$C_{19}H_{18}$," show no differences in ultra-violet absorption spectra, but as Diels's hydrocarbon and the two forms of 2′ : 3′-dimethyl-1 : 2-*cyclo*pentenophenanthrene also gave identical curves (Fig.), the method is of little diagnostic value. There is, however, a serious and inexplicable discrepancy in the *X*-ray powder photographs of



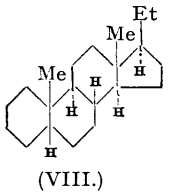
——— "$C_{19}H_{18}$", 3′-*ethyl*cyclo*pentenophenanthrene and* "cis" *and* "trans"-2′ : 3′-*dimethyl*cyclo*pentenophenanthrene.*
– – – – – "$C_{19}H_{16}$".

"$C_{19}H_{18}$" and 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene which were kindly measured by Mr. D. K. Hill of the University Glass Technology Department, who reports that "the photographs show no exact resemblance apart from one line (d = 3·49 A.)."

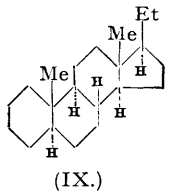
In spite of this inconsistency we remained convinced that "conessene" contained the 3′-ethyl-1 : 2-*cyclo*pentenophenanthrene framework, and that the alkaloid conessine was a steroid base which should be convertible into pregnane (VIII), $C_{21}H_{36}$, or one of its stereoisomeric forms, of which four are recorded in the chemical literature. During their investigation on conessine, Spath and Hromatka (*loc. cit.*) converted the dimethiodide, by the action of silver oxide, into *apo*conessine, $C_{23}H_{35}N$ (see also Kanga, Azyar, and Simonsen, *J.*, 1926, 2123), the



(VII.)



(VIII.)



(IX.)

metho-salts of which did not undergo further Hofmann degradation. *apo*Conessine methochloride was, however, reduced by sodium amalgam to a strongly lævorotatory hydrocarbon, $C_{21}H_{30}$, m. p. 74—76°, which was reduced catalytically to a weakly dextrorotatory hexahydro-derivative, $C_{21}H_{36}$, m. p. 56—58°, $[\alpha]_D^{15°}$ 14·5° in benzene. This hexahydro-derivative, $C_{21}H_{36}$, does not correspond with pregnane or any of the known isomeric forms, but a repetition

of the work of Spath and Hromatka reveals the important fact that reduction of the lævorotatory hydrocarbon, $C_{21}H_{30}$, m. p. 74—76°, with a palladium–charcoal catalyst in acetic acid solution, yields about equal amounts of two stereoisomeric hexahydro-derivatives. One of these, m. p. 56—58°, $[\alpha]_D^{10°}$ 17° in chloroform, is obviously the form obtained by Spath and Hromatka, and the second isomer, which the previous workers failed to observe, had m. p. 84°, $[\alpha]_D^{15°}$ 15° in chloroform, and corresponded in properties with either 5-*allo*pregnane (IX) or pregnane (VIII). Samples of 5-*allo*pregnane and pregnane were therefore prepared from progesterone by conversion into 5-*allo*pregnane-3 : 20-dione and pregnane-3 : 20-dione by a modification of the method of Butenandt and Fleischer (*Ber.*, 1935, **68**, 2096), and the diones were reduced to the corresponding hydrocarbons by Clemmensen's method. 5-*allo*Pregnane and pregnane melted at 83—84° and 80—81°, respectively; no depression in m. p. was observed with mixtures of 5-*allo*pregnane and the hexahydro-derivative, m. p. 84°, but a large depression was obtained with pregnane. We are again indebted to Mr. D. K. Hill for the *X*-ray powder photographs which establish the identity of the hexahydro-derivative, m. p. 84°, and 5-*allo*pregnane.

Reduction of the hydrocarbon $C_{21}H_{30}$ has given a mixture of *allo*pregnane and an isomer, not identical with pregnane. A Δ^5-pregnene structure is considered unlikely for the alkaloid, as this should lead to a mixture of pregnane and 5-*allo*pregnane, or alternatively to a larger number of isomers.

These experiments have, therefore, accounted for all the carbon atoms of the conessine molecule, and the remaining problem of assembling a dimethylamino-group, a methylimino-group, and a double bond into the 5-*allo*pregnane (IX) framework will be discussed in later communications.

Experimental.

Isolation of Conessine.—Seeds (12 lbs.) of *Holarrhena antidysenterica* were crushed, passed through a 10-mesh sieve, mixed thoroughly with lime (2 lbs.), and extracted for 48 hours with alcohol (11 l.) in a tinned-copper Soxhlet apparatus. The extract was concentrated to a thick syrup, dissolved in chloroform, and bases removed in dilute hydrochloric acid. The acid extract was made alkaline with ammonia, and the bases (71 g.), isolated with ether, were mixed with a hot solution of oxalic acid (70 g.) in alcohol (250 c.c.). On cooling, conessine hydrogen oxalate (51 g.), m. p. 260° (decomp.), separated in colourless prisms. The filtrate was concentrated, diluted with water, and made alkaline with ammonia, and the recovered bases (30 g.), isolated with ether, were *N*-methylated by heating under reflux for 2 hours with 90% formic acid (15 c.c.), 36% formaldehyde (20 c.c.), and water (40 c.c.). Concentrated hydrochloric acid (20 c.c.) was added, and the solution concentrated to one half of its volume, diluted with water, and neutral impurities removed in chloroform. The acid liquors were made alkaline, and the recovered bases converted into hydrogen oxalate (18 g.), m. p. 260—262°, as described above.

The conessine hydrogen oxalate (69 g.), decomposed with sodium hydroxide, yielded the base which was distilled at 0·1 mm. (oil-bath temp. 220°) and crystallised from acetone in plates (30 g.), m. p. 125—126°.

" Conessene ".—Dry conessine dihydriodide [(25 g.) prepared from a dilute hydrochloric acid solution of conessine (15 g.) and a concentrated solution of potassium iodide (15 g.)] was covered with glass wool and heated in a distillation flask (500 c.c.) in a slow stream of hydrogen. When decomposition was complete, the oily contents of the flask and receiver were taken up in chloroform, diluted with an equal volume of ether, decanted from gum, washed with dilute hydrochloric acid, and dried, and the solvent removed, and the residue distilled at 0·1 mm. " Conessene " (6·5 g.), b. p. 165—170°/0·1 mm., had $[\alpha]_D^{13°}$ 32° in 1% alcoholic solution (Siddiqui and Sharma, *loc. cit.*, give $[\alpha]_D^{31°}$ 35°).

Selenium Dehydrogenation of " Conessene ".—" Conessene " (23 g.) and selenium (48 g.) were heated at 320—325° for 48 hours, and the product isolated first with chloroform and then with ether. Removal of the ether gave a pale yellow oil (23 g.) with a violet fluorescence, which was dissolved in light petroleum (b. p. 60—80°) (100 c.c.), and adsorbed on a column of alumina (25 cm. × 2 cm.). Successive elutions were made with (1) light petroleum (10 portions of 25 c.c.; b. p. 60—80°), (2) light petroleum containing 5% benzene (4 portions of 25 c.c.), (3) light petroleum containing 10 per cent. benzene (2 portions of 25 c.c.), (4) light petroleum and 20% benzene (1 portion of 25 c.c.), and the adsorption and elutions were repeated systematically until the product was separated into (*a*) an oil (10 g.), (*b*) a solid (10 g.), m. p. 52—100°, and (*c*) a solid (0·9 g.), m. p. 110—180°.

After a prolonged fractional crystallisation from alcohol, the solid, m. p. 52—100°, gave the hydrocarbon " $C_{19}H_{18}$ " (2·5 g.), m. p. 76—77°, raised to 78—79° by decomposing the trinitrobenzene complex (see below) by allowing its solution in light petroleum containing 5% of benzene to percolate through a column of alumina, when the trinitrobenzene was retained. The purified *hydrocarbon* crystallised from alcohol in colourless leaflets, m. p. 78—79° [Found : C, 92·7, 92·7, 92·9; H, 7·3; *M* (Rast), 235, 240; *M* (cryoscopic in benzene), 242; *M* (cryoscopic in *cyclo*hexane), 243. $C_{19}H_{18}$ requires C, 92·7; H, 7·3%; *M*, 246]. The hydrocarbon, which was optically inactive, could not be purified further by chromatographic adsorption, by distribution between light petroleum and methanol, or by recrystallisation. On long standing in the air, or when boiled in alcohol, the hydrocarbon suffered slight decomposition, and the pale yellow higher-melting impurities were easily removable by adsorption on alumina. Catalytic reduction proceeded very slowly in alcoholic solution in the presence of platinic oxide, and yielded a *tetrahydro*-derivative, b. p. 140—145°/0·05 mm. (Found : C, 91·2; H, 8·6. $C_{19}H_{22}$ requires C, 91·2; H, 8·8%), which was reconverted to the hydrocarbon, " $C_{19}H_{18}$," by dehydrogenation

with selenium. The *trinitrobenzene* derivative separated from methanol in long, flat, brownish-orange needles, m. p. 119—120° (Found: C, 65·4, 65·5, 65·4; H, 4·5, 4·6, 4·5; N, 9·2. $C_{25}H_{25}O_6N_3$ requires C, 65·4; H, 4·6; N, 9·2%). The normal *picrate*, prepared from the hydrocarbon (0·1 g.) and picric acid (0·15 g.) in methanol (2 c.c.), separated in long orange-yellow needles, m. p. 95—96° (Found: N, 8·6; *M*, 489. $C_{25}H_{21}O_7N_3$ requires N, 8·8%; *M*, 475), slowly changed in solution to the *semipicrate*, dark-red microscopic crystals, m. p. 96° [Found: C, 73·2; H, 5·3; N, 6·1; *M* (titration), 722. $C_{44}H_{39}O_7N_3$ requires C, 73·0; H, 5·4; N, 5·8%; *M*, 721] from alcohol–ether. This was also prepared directly from the hydrocarbon and less than the equivalent amount of picric acid. The *trinitrotoluene* derivative separated from methanol in pale yellow needles, m. p. 90—91° (Found: C, 65·5; H, 5·1; N, 8·7, $C_{26}H_{23}O_6N_3$ requires C, 66·0; H, 5·0; N, 8·9%); the *styphnate* crystallised from methanol in small needles, m. p. 121—123° (Found: N, 8·4. $C_{25}H_{21}O_8N_3$ requires N, 8·1%); and the 2 : 7-dinitroanthraquinone derivative crystallised from benzene–alcohol in red needles, m. p. 234—236°.

The fraction (*c*), m. p. 110—180°, from the dehydrogenation with selenium, was fractionally crystallised from alcohol. The *hydrocarbon* "$C_{19}H_{16}$" separated as colourless needles (30 mg.), m. p. 195—196° [Found: C, 92·9; H, 6·6; *M* (Rast), 249. $C_{19}H_{16}$ requires C, 93·4; H, 6·6%; *M*, 244]. The *trinitrobenzene* derivative crystallised from ethanol in orange-red needles, m. p. 138—139° (Found: C, 64·9; H, 3·9. $C_{25}H_{19}O_6N_3$ requires C, 65·6; H, 4·2%).

Synthesis of 3′-*Ethyl*-1 : 2-cyclo*pentenophenanthrene*.—*Ethyl* 1-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate*. Diethyl adipate was prepared in 95% yield, as described in *Org. Synth.*, Coll. Vol. II, p. 264, and converted in 85% yield into ethyl *cyclo*pentan-2-one-1-carboxylate by the method of Linstead and Meade (*J.*, 1934, 940). Granulated sodium (23·5 g.) and ethyl *cyclo*pentan-2-one-1-carboxylate (174 g.) were refluxed in benzene (400 c.c.) for 3 hours; ethyl iodide (200 g.) was added to the sodio-derivative, which separated as a thick cake, and the mixture heated under reflux for 10 hours. A further addition of sodium (2 g.) and ethyl iodide (20 g.) was made, and the heating continued for another 7 hours. The benzene layer was washed successively with water and dilute sodium hydroxide, dried, and distilled. *Ethyl* 1-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (144 g.), b. p. 120—122°/16 mm. (Found: C, 65·1; H, 8·5. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%), was obtained, which gave a negative ferric test.

Diethyl α-ethyladipate (IV). The above ester (92 g.) was heated with a solution of sodium (2·3 g.) in absolute alcohol (250 c.c.) for 12 hours, and after dilution with water (1500 c.c.) the product was extracted with ether, dried, and distilled. *Diethyl α-ethyladipate* (IV) (92 g.), b. p. 139—140°/12 mm. (Found: C, 62·6; H, 9·4. $C_{12}H_{22}O_4$ requires C, 62·6; H, 9·6%), was obtained.

Ethyl 3-*ethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = H$; $R^2 = CO_2Et$). Diethyl α-ethyladipate (92 g.) was heated on the water-bath for 18 hours with pulverised sodium (13·8 g.), benzene (400 c.c.), and alcohol (1 c.c.). After decomposition with ice-cold 10% acetic acid (400 c.c.) the benzene layer was separated, dried, and distilled. *Ethyl* 3-*ethyl*cyclo*pentanone*-1-*carboxylate* (45 g.), b. p. 127—130°/18 mm. (Found: C, 65·2; H, 8·6. $C_{10}H_{16}O_3$ requires C, 65·2; H, 8·7%), was obtained, and gave a strong blue colour with ferric chloride.

Ethyl 1 : 3-*diethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (V; $R^1 = Et$; $R^2 = CO_2Et$). The above ester (63 g.) was heated with sodium (8 g.) in benzene (400 c.c.) for 1 hour, and ethyl iodide (60 g.) was then added to the cake of sodio-compound. After 3 hours at room temperature, the mixture was heated under reflux overnight, and decomposed by the addition of water. The benzene layer was washed with dilute sodium hydroxide solution, dried, and distilled. *Ethyl* 1 : 3-*diethyl*cyclo*pentan*-2-*one*-1-*carboxylate* (55 g.), b. p. 128—130°/13 mm. (Found: C, 67·7; H, 9·5. $C_{12}H_{20}O_3$ requires C, 67·9; H, 9·4%), was obtained.

2 : 5-*Diethyl*cyclo*pentanone* (V; $R^1 = Et$; $R^2 = H$). The above ester (32 g.) was heated under reflux for 12 hours with concentrated hydrochloric acid (65 c.c.). The mixture was diluted with water and extracted with ether, the extract washed with dilute sodium hydroxide and dried, the solvent removed, and the residual oil distilled. The fraction, b. p. 175—195°, was collected, and heated in methyl-alcoholic solution (150 c.c.) for 1½ hours with semicarbazide hydrochloride (32 g.) and sodium acetate (30 g.). The *semicarbazone*, precipitated by water and crystallised twice from methyl alcohol, was obtained as colourless prisms (12 g.), m. p. 195—196° (Found: C, 60·9; H, 9·6; N, 21·3. $C_{10}H_{19}ON_3$ requires C, 60·8; H, 9·4; N, 21·3%).

The unchanged keto-ester (V; $R^1 = Et$; $R^2 = CO_2Et$) was recovered from the mother liquors and the hydrolysis repeated.

2 : 5-*Diethyl*cyclo*pentanone*, recovered from the semicarbazone (11 g.) by heating with 15% hydrochloric acid (300 c.c.) for 1 hour, was isolated with ether and distilled; an oil (7 g.), b. p. 182°, was obtained (Found: C, 77·1; H, 11·3. $C_9H_{16}O$ requires C, 77·1; H, 11·4%).

3′-*Ethyl*-1 : 2-cyclo*pentenophenanthrene* (VII). The Grignard reagent prepared from 2-α-naphthylethyl bromide (15 g.), and magnesium (1·4 g.) in ether (90 c.c.) was added to a solution of 2 : 5-diethyl*cyclo*pentanone (7 g.) in benzene (50 c.c.). After being boiled for 1 hour, the mixture was left for 12 hours, and the ether removed on the water-bath and benzene (50 c.c.) added. The benzene solution was heated under reflux for 5 hours, the benzene was then removed, and the red, oily residue decomposed by the addition of 10% acetic acid (100 c.c.). The product, isolated with ether, was distilled, and the fraction (8·5 g.), b. p. 160—200°/0·2 mm., was collected and heated at 15 mm. pressure with phosphoric oxide (15 g.) at 140—150° for 1 hour. The mixture was cooled and decomposed with ice, and the dehydrated product isolated with ether, and distilled. The oil (7·0 g.), b. p. 180—190°/0·2 mm., was heated with selenium (15 g.) at 320—330° for 24 hours, and the product was extracted with chloroform, the solvent removed, and the residue taken up in light petroleum (b. p. 40—60°), and distilled over sodium. The fraction (6·0 g.) distilling at 160—200°/0·4 mm. was dissolved in light petroleum (b. p. 40—60°) (100 c.c.), adsorbed upon a column of alumina (30 × 2 cm.), and eluted first with 10 successive quantities (each 25 c.c.) of light petroleum (b. p. 40—60°), then with 3 similar washings containing 10% of benzene, and finally with 7 washings with benzene. Of the 20 fractions collected, the first 3 yielded an oil with a characteristic purple fluorescence.

The next 6 fractions were crystallised from methyl alcohol and yielded 3′-*ethyl*-1 : 2-cyclo*penteno*-*phenanthrene* (1·3 g.) as flat needles (not leaflets), m. p. 84—85° (Found: C, 92·7; H, 7·3. $C_{19}H_{18}$

requires C, 92·7; H, 7·3%), after chromatography of the trinitrobenzene complex, m. p. 120—121°. The semipicrate, m. p. 95—96°, styphnate, m. p. 120—122°, trinitrotoluene derivative, m. p. 94—95°, gave correct analytical figures and were identical with the derivatives described on p. 833 (see table). The 2 : 7-dinitroanthraquinone derivative, m. p. 234—236°, was also prepared.

The next 7 fractions gave 1 : 4-di-α-naphthylbutane (0·2 g.), as needles, m. p. 100—102°, from alcohol (Found : C, 92·6; H, 7·3. Calc. for $C_{24}H_{22}$: C, 92·8; H, 7·2), which gave a yellow dipicrate, m. p. 174° (Harper, Kon, and Ruzicka, *J.*, 1934, 127, gave m. p. 174°).

The last four fractions, crystallised from methanol, gave the hydrocarbon, "$C_{19}H_{16}$," m. p. 194—195° (Found : C, 92·9; H, 6·5) (trinitrobenzene derivative, m. p. 138—139°) identical with the hydrocarbon described on p. 836.

Synthesis of 2′ : 3′-*Dimethyl*-1 : 2-cyclo*pentenophenanthrene*.—β-2-*Phenanthryl*-α-*methylbutyric acids* (I). To a solution of diethyl methylsodiomalonate prepared from sodium (0·48 g.), diethyl methylmalonate (4·2 c.c.), and alcohol (20 c.c.) was added 1-2-phenanthrylethyl bromide (4·0 g.) in benzene (30 c.c.). After 12 hours at room temperature, the mixture was refluxed for 2 hours, the alcohol removed, and benzene and dilute hydrochloric acid added. The benzene was removed, and the residue heated at 100° for 1 hour with excess of 45% potassium hydroxide solution. After dilution and acidification the dicarboxylic acid was isolated with ether, and heated at 180° for ½ hour. Crystallisation from chloroform–light petroleum gave the mixture of β-2-*phenanthryl*-α-*methylbutyric acids* (I) (2·0 g.), m. p. 110—130°, which was separated by fractional crystallisation from *cyclo*hexane into *form* A, needles, m. p. 144—146° (Found : C, 82·2; H, 6·8. $C_{19}H_{18}O_2$ requires C, 82·0; H, 6·5%), and *form* B, small needles, m. p. 121—123° (Found : C, 82·1; H, 6·8%).

1′-*Keto*-2′ : 3′-*dimethyl*-1 : 2-cyclo*pentenophenanthrene* (II). The acid chloride, prepared from the mixture (6 g.), m. p. 110—130°, of the acid (I) and thionyl chloride (6 c.c.) in ether (60 c.c.) containing pyridine (2 drops), was dissolved in nitrobenzene (25 c.c.), and added dropwise to a solution of aluminium chloride (4·5 g.) in nitrobenzene (50 c.c.). After stirring for 12 hours at room temperature and for 2 hours at 80°, the mixture was decomposed with ice and hydrochloric acid, and the nitrobenzene removed. The product, isolated with benzene and decolourised with charcoal, was separated by repeated crystallisation from methyl alcohol and methyl alcohol–acetone (2 : 1) into *form* A of the ketone (II) which separated as prisms (0·9 g.), m. p. 119—120° (Found : C, 87·7; H, 6·2. $C_{19}H_{16}O$ required C, 87·7; H, 6·2%), and a mixture *B*, crystallising in plates (2·7 g.), m. p. 99—101° (Found : C, 87·6; H, 6·3%), and which yielded a mixture of hydrocarbons on reduction.

2′ : 3′-*Dimethyl*-1 : 2-cyclo*pentenophenanthrene* (III). *Form* A. Form *A* of ketone (II) (0·9 g.) was reduced by Clemmensen's method using amalgamated zinc (10 g.), toluene (5 c.c.), glacial acetic acid (20 c.c.), and concentrated hydrochloric acid (12 c.c.); a mixture of glacial acetic acid (12 c.c.) and concentrated hydrochloric acid (8 c.c.) was gradually added during the reduction. The product, isolated with ether, crystallised from methanol in platelets (0·75 g.), m. p. 119—120° (Found : C, 92·7; H, 7·3. $C_{19}H_{18}$ requires C, 92·7; H, 7·3%). The *trinitrobenzene* derivative crystallised from methanol in yellow needles, m. p. 143—144° (Found : C, 65·4; H, 4·4; N, 9·3. $C_{25}H_{21}O_6N_3$ requires C, 65·4; H, 4·6; N, 9·2%). The *picrate* crystallised from methanol in golden-red needles, m. p. 119—121° (Found : C, 62·7; H, 4·1; N, 8·4. $C_{25}H_{21}O_7N_3$ requires C, 63·2; H, 4·4; N, 8·8%).

2′ : 3′-*Dimethyl*-1 : 2-cyclo*pentenophenanthrene*. *Form* B. The mixture *B* of ketone (II) (1·7 g.), m. p. 99—102°, reduced similarly, yielded a mixture which, on fractional crystallisation from methanol, gave form *A*, described above, and *form* B of (III). The latter was obtained as plates (1 g.), m. p. 143—144° (Found : C, 92·7; H, 7·2%). The *trinitrobenzene* derivative crystallised from methanol in yellow needles, m. p. 155—156° (Found : C, 65·2; H, 4·6; N, 9·4%). The *picrate*, golden-red prisms from methanol, had m. p. 125—127° (Found : C, 52·7; H, 3·4; N, 11·5%).

Hydrogenation of the Unsaturated Hydrocarbon $C_{21}H_{30}$.—The unsaturated hydrocarbon (0·20 g.) [prepared as described by Spath and Hromatka (*loc. cit.*)] in glacial acetic acid (20 c.c.) was shaken in a hydrogen atomsphere with 8% palladium–charcoal (0·20 g.). The hydrogenation, which was very rapid at first, was complete in a few hours (total uptake at 12° and 753 mm., 55 c.c.; calculated for 6H, 50 c.c.). Shaking was continued overnight, and the mixture then warmed and filtered, and the catalyst washed with hot glacial acetic acid (10 c.c.). On being kept, the combined filtrate and washings slowly deposited white flakes (80 mg.; m. p. 75—80°), which after several recrystallisations from methanol gave the *hydrocarbon*, $C_{21}H_{36}$, as rectangular prisms, m. p. 83—84°, saturated to bromine and to a cold acetone solution of potassium permanganate (Found : C, 87·0; H, 12·3. $C_{21}H_{36}$ requires C, 87·4; H, 12·6%). $[\alpha]_D^{20°}$ + 15° (in chloroform : *c*, 0·3). Mixtures with the unsaturated hydrocarbon, m. p. 74—76°, and with pregnane, m. p. 80—81°, melted at 55—60° and 50—55° respectively, but no depression in m. p. was observed in admixture with 5-*allo*pregnane, m. p. 83—84°.

The acetic acid mother-liquors were evaporated to dryness under reduced pressure, and the residue dissolved in absolute ether (15 c.c.) and filtered through a column of activated alumina (8 × 1 cm.). The filtrate was evaporated, and the residue recrystallised from methanol, giving rectangular plates (70 mg.), m. p. 56—58°, unchanged on further recrystallisation (Found : C, 87·2; H, 12·1%); $[\alpha]_D^{20°}$ + 17° (in chloroform : *c*, 0·25). Spath and Hromatka (*loc. cit.*) give m. p. 56—58° and $[\alpha]_D^{15°}$ + 14·5° (in benzene : *c*, 7·5).

5-allo*Pregnane*-3 : 20-*dione* and *Pregnane*-3 : 20-*dione from Progesterone*.—Progesterone (0·238 g.) dissolved in glacial acetic acid (20 c.c.) was shaken with Adams's catalyst (0·025 g.) in a hydrogen atmosphere. Hydrogenation was complete in 20 minutes (uptake at 19° and 740 mm., 66 c.c.; calculated for 6H and catalyst, 62 c.c.). After being shaken for one hour the catalyst was removed, the filtrate evaporated under reduced pressure, and the residue heated under reflux for five minutes with methanol (20 c.c.) containing potassium hydroxide (0·5 g.), and the solution neutralised with carbon dioxide, and evaporated. The residue was treated with ether and water, the ether removed, and the resulting mixture of pregnane- and 5-*allo*pregnane-diols was oxidised by treatment with a solution of chromic anhydride (0·240 g.) in glacial acetic acid (20 c.c.). After being left overnight, the solvent was removed under reduced pressure at 30°, and the residue taken up in ether, washed first with dilute sulphuric acid and then with sodium carbonate solution, and evaporated. The residue, crystallised thrice from acetone–

ether (1 : 1), gave pure 5-*allo*pregnanedione (50 mg.), m. p. 201—203° (literature, 199°; 200·5°). After the separation of a further crop of 5-*allo*pregnanedione the mother liquors were evaporated, the residue distilled at 0·0001 mm., and the first portion of the distillate, on crystallisation from dilute methanol, gave pregnanedione (11 mg.), m. p. 115—117° (literature, 119°; 123°).

5-allo*Pregnane and Pregnane.*—A solution of 5-*allo*pregnanedione (50 mg.) in glacial acetic acid (5 c.c.) was heated under reflux for 2½ hours with concentrated hydrochloric acid (5 c.c.) and amalgamated zinc (2 g.). The hydrocarbon, isolated with light petroleum, was dissolved in dry light petroleum (b. p. 40—60°, 2 c.c.), the solution poured on to an alumina column (18 × 1 cm.), and eluted with the same solvent. The first fraction (2 c.c.) from the column gave a semi-solid residue, and the second fraction (2 c.c.) on evaporation yielded a residue which solidified immediately, and, after two recrystallisations from acetone, gave 5-*allo*pregnane as colourless rectangular prisms, m. p. 83—84°.

Pregnane, m. p. 80—81° (from methanol), was prepared by a similar method from pregnanedione.

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