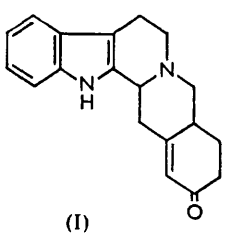
613. (±)-allo*Yohimbone and* (±)-3-epiallo*Yohimbone.*

By P. G. Philpott and A. M. Parsons.

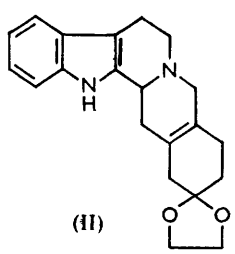
*allo*Yohimbone and 3-*epiallo*yohimbone have been obtained from the ketal (II), which was prepared from the unsaturated ketone (I), an intermediate in the total synthesis of yohimbone.

Swan [1] obtained (±)-yohimbone by hydrogenation of 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13a : 14-decahydro-2-oxobenz[*g*]indolo[2 : 3-*a*]quinolizine (I) over Adams catalyst in acid solution.

In yohimbone the fusion of rings D and E is *trans*. It was hoped that by suitable change of experimental conditions a *cis*-ring junction could be obtained. du Feu, McQuillin,



(I)



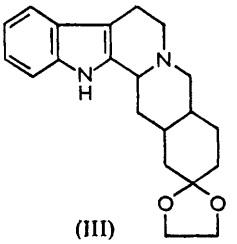
(II)

and Robinson [2] obtained *cis*-β-decalone by hydrogenation of 2 : 3 : 4 : 5 : 6 : 7 : 8 : 10-octahydro-2-oxonaphthalene over palladised strontium carbonate, but in spite of the relatively close analogy only (±)-yohimbone was obtained when the compound (I) was reduced under these mild conditions.

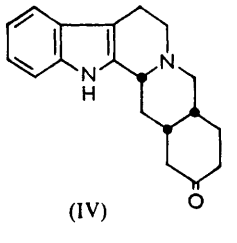
Cornforth *et al.*[3] have shown that preparation of the ethylene ketal of 5 : 6 : 7 : 9 : 10 : 13-hexahydro-1-methoxy-13-methyl-7-oxophenanthrene (involving migration of the double bond) followed by reduction invariably gave a *cis*-ring junction. The ethylene ketal of ketone (I) was therefore prepared and its hydrogenation investigated. It was suspected that the double bond had migrated to the bridgehead because it proved rather difficult

[1] Swan, *J.*, 1950, 1534.
[2] du Feu, McQuillin, and Robinson, *J.*, 1937, 53.
[3] Cornforth, Kauder, Pike, and Robinson, *J.*, 1955, 3348.

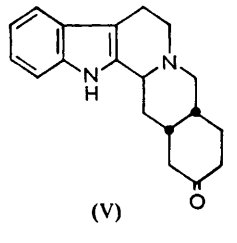
to reduce. However, by use of palladised charcoal in dioxan at elevated temperature and pressure the saturated ketal (III) was obtained smoothly and in good yield.



(III)



(IV)



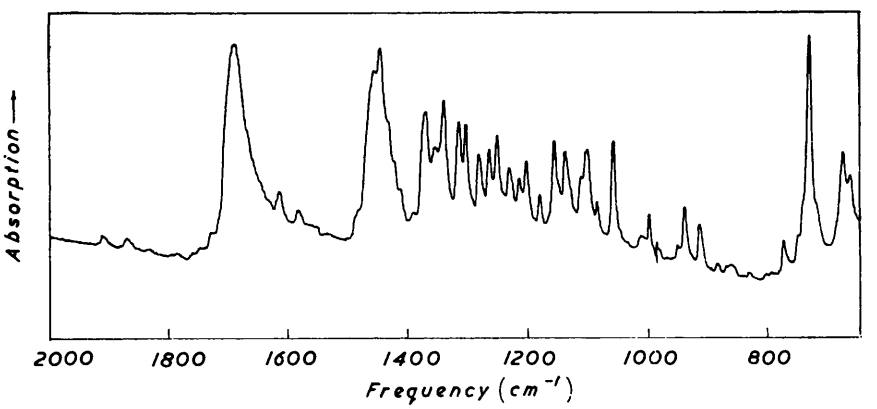
(V)

In support of formula (II), comparison of infrared spectra with that of the reduced ketal (III) revealed little change in the region 1700—1600 cm.$^{-1}$ where an absorption band due to a trisubstituted double bond would normally occur. This result is surprising, for in an analogous decahydrophenanthrene derivative ketal formation is reported not to give a double bond of the tetrasubstituted type in a main product.[4]

Hydrolysis of the ketal (III) gave a ketone (IV) isomeric, but not identical, with (±)-yohimbone. The infrared spectrum agreed in all essential bands with that given for (−)-*allo*yohimbone by Le Hir, Janot, and Goutarel [5] and had some important differences from that of (±)-yohimbone.

Structure (IV) was confirmed by using the observation that under certain conditions [6] mercuric acetate reacts with compounds of this type containing an axial hydrogen atom at $C_{(3)}$. Our ketone reacted with mercuric acetate, as did yohimbine, whilst reserpine did not react. *allo*Yohimbone is the only stereoisomer of yohimbone which would be expected to give this reaction.

Infrared spectrum of 3-epialloyohimbone *in Nujol mull.*



From the *allo*yohimbone mother-liquors a third racemate was obtained which was suspected of being 3-*epiallo*yohimbone (V). Treatment of *allo*yohimbone with pivalic acid [7] gave a mixture containing about 20% of this ketone and its structure was confirmed when it was found not to react with mercuric acetate under the above conditions.

A stereoisomer of yohimbone obtained by Bader *et al.*[8] from a naturally occurring stereoisomer of yohimbine, has been assumed by Karrer and his colleagues [9] to be

[4] Birch and Smith, *J.*, 1956, 4909.
[5] Le Hir, Janot, and Goutarel, *Bull. Soc. chim. France*, 1953, 1027.
[6] Weisenborn and Diassi, *J. Amer. Chem. Soc.*, 1956, **78**, 2022.
[7] Cf. Woodward, Bader, Bickel, Frey, and Kierstead, *ibid.*, p. 2023.
[8] Bader, Dickel, Lucas, and Schlittler, *Experientia*, 1954, **10**, 298.
[9] Vamvacas, Philipsborn, Schlittler, Schmid, and Karrer, *Helv. Chim. Acta*, 1957, **40**, 1793.

(+)-*epialloyohimbone*, but insufficient infrared data were given for a comparison with our racemate (see Figure) to be made.

3-*epialloYohimbone* did not show significant hypotensive activity when tested in a rat anæsthetised with pentobarbitone.

Experimental

Hydrogenation of 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13a : 14-*Decahydro*-2-*oxobenz*[g]*indolo*[2 : 3-a]-*quinolizine* (I).[1]—Compound (I) (304 mg., 1 mmol.) in ethanol (100 c.c.) was hydrogenated at atmospheric temperature and pressure in the presence of 2% palladised strontium carbonate (100 mg.). One mmol. of hydrogen was quickly absorbed and the solution was filtered and evaporated to small bulk. Crystallisation of the precipitated product from methanol gave colourless needles of (±)-yohimbone, m. p. 265—269° (decomp.), indistinguishable from the product obtained by carrying out the reduction under the conditions used by Swan.[1]

2-*Ethylenedioxy*-1 : 2 : 3 : 4 : 5 : 7 : 8 : 13 : 13b : 14-*decahydrobenz*[g]*indolo*[2 : 3-a]*quinolizine* (II).—A mixture of 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13a : 14-decahydro-2-oxobenz[*g*]indolo-[2 : 3-*a*]quinolizine (I) [1] (1·26 g.), toluene-*p*-sulphonic acid (1·8 g.), and ethylene glycol (20 c.c.) was heated at 100°/14 mm. under a stream of dry nitrogen for 3 hr. The solution was poured rapidly into stirred 2N-sodium carbonate (100 c.c.), and the precipitated crude ketal collected, washed with water, and dried *in vacuo*. The *product* was purified by chromatography on alumina, eluted with 1 : 1 benzene–ethyl acetate, and crystallised from ethyl acetate, to give rhombohedra (1·26 g., 87%), m. p. 238—240° (decomp.) (Found: C, 74·7; H, 7·4; N, 8·3. $C_{21}H_{24}O_2N_2$ requires C, 75·0; H, 7·1; N, 8·3%).

(±)-allo*Yohimbone* (IV).—The above ketal (4·0 g.) was hydrogenated in dry dioxan (200 c.c.) in the presence of 5% palladised charcoal (4·0 g.) at 80°/70 atm. for 17 hr. The solution was filtered and evaporated and a sample of the crude product was purified by chromatography in benzene followed by crystallisation from ethyl acetate–light petroleum (b. p. 60—80°), to give 2-*ethylenedioxy*-1 : 2 : 3 : 4 : 4a : 5 : 7 : 8 : 13 : 13b : 14 : 14a-*dodecahydrobenz*[g]*indolo*-[2 : 3-a]*quinolizine* (III), colourless rhombohedra, m. p. 198—200° (Found: N, 8·4. $C_{21}H_{26}O_2N_2$ requires N, 8·3%). The rest of the unpurified product was hydrolysed by stirring it with 2N-hydrochloric acid (200 c.c.) at room temperature for 3 hr. The resulting suspension was basified and extracted with chloroform. The residue from the dried extracts was purified by chromatography in hot ethyl acetate on alumina. Elution with the same solvent gave a product which was isolated and crystallised from ethyl acetate as rhombic plates of (±)-allo-*yohimbone* (IV) (2·88 g., 82%), m. p. 261—267° (decomp.), mixed m. p. with (±)-yohimbone [m. p. 265—269° (decomp.)], 230—255° (decomp.) (Found: C, 77·0; H, 7·5; N, 9·4. $C_{19}H_{22}ON_2$ requires C, 77·5; H, 7·5; N, 9·5%), $\lambda_{max.}$ 283 mμ (log ε 3·91) in EtOH. The infrared spectrum agrees in all essential bands with that of (−)-*allo*yohimbone.[5]

No other conditions used for the hydrogenation of the unsaturated ketal (II) were found to be satisfactory although partial reduction was effected by using Raney nickel in ethanol at 70° and 80 atm. The use of freshly prepared Raney nickel W7 gave a little dihydro-compound (III), but the major product was a perhydro-ketal isolated as the *dipicrate* which crystallised from ethanol in small yellow rhombohedra, exploding violently at 277° (Found: C, 48·9; H, 4·7; N, 13·9. $C_{21}H_{34}O_2N_2,2C_6H_3O_7N_3$ requires C, 49·2; H, 5·0; N, 13·9%).

The mother-liquors from several preparations of (±)-*allo*yohimbone (IV) were combined and yielded a small quantity of a product, m. p. 282—284° (decomp.), proved to be identical with (±)-3-*epialloyohimbone* (V) (see below).

(±)-3-epiallo*Yohimbone* (V).—A solution of (±)-*allo*yohimbone (1·0 g.) in dry xylene (100 c.c.) was heated under reflux with pivalic acid (0·8 g.) under nitrogen for 3 days. Colourless leaflets separated on chilling and these were collected and dried (0·77 g.; m. p. 265° after softening at 235°). Conversion into the free base gave almost pure (±)-*allo*yohimbone (0·60 g.). The xylene mother-liquors were evaporated to dryness under reduced pressure and the residue partitioned between 2N-sodium carbonate and chloroform. The chloroform extracts were dried, evaporated to small bulk, and chilled, and the solid was collected. Recrystallisation from ethyl acetate–light petroleum (b. p. 60—80°) gave (±)-3-*epialloyohimbone* (0·12 g., 12%) as elongated rhombohedra (or needles), m. p. 284—287° (decomp.), mixed m. p. with (±)-*allo*-yohimbone 243—250° (Found: C, 77·7; H, 7·3; N, 9·9. $C_{19}H_{22}ON_2$ requires C, 77·6; H, 7·5; N, 9·5%).

Mercuric Acetate Reactions with Yohimbine, Reserpine, (±)-allo*Yohimbone and* (±)-3-epiallo*Yohimbone.*—A few mg. each of yohimbine, reserpine, (±)-*allo*yohimbone and (±)-3-*epialloyohimbone* were added separately to equal volumes (2 c.c.) of a solution of mercuric acetate in glacial acetic acid. The solutions were kept at 60° for 2 hr., by which time there was a precipitate of mercurous acetate in the tubes containing the yohimbine and (±)-*allo*-yohimbone but not with reserpine or (±)-3-*epialloyohimbone*, as expected.

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