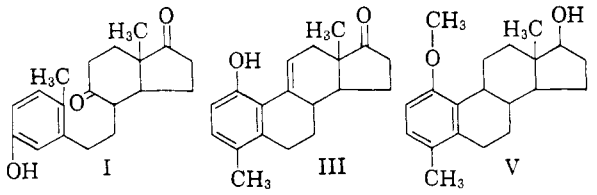
with acetic anhydride and pyridine yielded a monoacetate (II), m.p. 147–147.5°; $\lambda_{max}^{methanol}$ 266 mμ (ε 650), 273 mμ (ε 650); $[\alpha]D$ +82.5° ($CHCl_3$); λ_{max}^{KBr} 5.70 μ, 8.225 μ (ester), 5.77 μ (17C=O), 5.90 μ (C=O), 6.225 μ, 6.325 μ, 6.71 μ (aromatic ring), 11.10 μ, 11.97 μ; (found: C, 73.34; H, 7.61).



The structure of I as 9,10-seco-3-hydroxy-1,3,5(10)-androstatriene-9,17-dione was established by this series of reactions: a solution of II in methanol:concd. hydrochloric acid (2:1) on standing deposited crystals of 1-hydroxy-4-methyl-1,3,5(10),9(11)-estratetraen-17-one[4] (III), m.p. 194–197°; $\lambda_{max}^{methanol}$ 255.5 mμ (ε 13,200), 300 mμ (ε 3,830), shoulders 265 mμ, 310 mμ; $[\alpha]D$ +264° ($CHCl_3$); λ_{max}^{KBr} 3.07 μ (OH), 5.79 μ (17C=O), 6.18 μ, 6.29 μ, 6.84 μ; (found: C, 80.55; H, 7.73). Compound III was converted, using methyl iodide and potassium carbonate in acetone, to 1-methoxy-4-methyl-1,3,5(10),9(11)-estratetraen-17-one, m.p. 123–124°; (found: C, 80.91; H, 8.22); which, in turn, was reduced with sodium borohydride to 1-methoxy-4-methyl-1,3,5(10),9(11)-estratetraen-17-ol, (IV) m.p. 144–145°; (found: C, 80.38; H, 8.95). Removal of the double bond from IV by reduction with potassium in liquid ammonia[5] gave the desired 1-methoxy-4-methyl-1,3,5(10)-estratrien-17-ol (V), m.p. 116.5–117.5°; $[\alpha]D$ +185.3° ($CHCl_3$); (found: C, 80.14; H, 9.67); 17-acetate, m.p. 148.5–150°. Compound V (and its acetate) was identical in all respects (m.p., mixed m.p., and infrared spectra) with a sample of 1-methoxy-4-methyl-1,3,5(10)-estratrien-17-ol (and its acetate, respectively) prepared from 1-hydroxy-4-methyl-1,3,5(10)-estratrien-17-one[6] via methylation and reduction (and acetylation).[7]

The conversion of 4-androstene-3,17-dione to I appears to proceed through 1,4-androstadiene-3,17-dione via 9-hydroxylation and a reverse-aldol type reaction. Paper chromatographic studies indicated the formation and utilization of 1,4-androstadiene-3,17-dione during the course of the fermentation. 1,4-Androstadiene-3,17-dione was isolated from incomplete fermentations. Preliminary experiments indicate that 1,4-androstadiene-3,17-dione is not formed via 1α-hydroxy-4-androstene-3,17-dione.[1]

It should be noted that the formation of I parallels closely the course postulated for the formation of estrone[8] from 4-androstene-3,17-dione except that hydroxylation occurs at C_9 rather than C_{19}. In fact, fermentation of 19-hydroxy-4-androstene-3,17-dione with this *Pseudomonas* species produced estrone, m.p. 260–262°, identical in all respects (m.p., mixed m.p., and infrared spectrum) with an authentic sample. It is possible that the physiological degradation of steroids via compounds similar to I is a very general process.

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(4) The position of the double bond is not definitely established, but was assigned to $\Delta^{9(11)}$ on the basis of the fine structure in the ultraviolet spectrum: J. Heer and K. Miescher, *Helv. Chim. Acta*, **31**, 219 (1948).

(5) W. S. Johnson, A. D. Kemp, R. Pappo, J. Ackerman and W. F. Johns, THIS JOURNAL, **78**, 6312 (1956).

(6) A. S. Dreiding and A. Voltman, *ibid.*, **76**, 537 (1954).

(7) We are indebted to Dr. Willard Hoehn of this laboratory for a sample of 1-methoxy-4-methyl-1,3,5(10)-estratrien-17-ol acetate, prepared from 1-hydroxy-4-methyl-1,3,5(10)-estratrien-17-one.

(8) A. S. Meyer, *Experientia*, **11**, 99 (1955), see also ref. 2.

THE REACTIVITY OF METHYLENE

Sir:

Differences have been noted between the reactivities of methylene produced from diazomethane and ketene toward various types of C–H bonds.[1,2,3] These have been ascribed to differences in excess energy of the methylene produced by the two methods.[2] Owing to the different conditions employed in the two methods there may be some objection to this comparison. Accordingly, the reactions of methylene from diazomethane under identical conditions to those used with ketene as a precursor have been investigated.

Mixtures of diazomethane with a large excess of the hydrocarbon being studied were photolysed using a medium pressure mercury arc and a Pyrex reaction vessel. Analyses were carried out gas chromatographically, and duplicate analyses indicated a high degree of reproducibility.

With propane the proportions of the main reaction products normal and isobutane did not vary with pressure in the range 200–1200 mm. and had a value of 2.62 ± 0.02:1. Similarly with *n*-butane the ratio of products, normal and isopentane, had a value of 1.25:1. With isobutane, iso- and neopentane were formed in the ratio 6.06:1. Hence methylene from diazomethane reacted 15 to 20% faster with secondary C–H bonds than with primary C–H bonds and approximately 50% faster with tertiary C–H bonds. These results compare favorably with those obtained in the liquid phase,[1] and indicate that the difference between the reactivities of methylene from the two precursors is real.

There are some discrepancies in the literature in relation to the reaction of methylene with the 2-butenes.[4,5] No evidence could be found for the formation of an associative complex between diazomethane and *cis*-2-butene. Both in liquid and gas phase (at pressures above 400 mm.) methylene reacted with both the *trans* and *cis* compounds similarly and gave *trans*-1,2-dimethylcyclopropane, *trans*-2-pentene and 2-methyl-2-butene in the former case and the corresponding *cis* compounds in the latter case, in agreement with the work of

(1) W. E. Doering, R. G. Butlery, R. G. Laughlin and N. Chaudhuri, THIS JOURNAL, **78**, 3224 (1956).

(2) H. M. Frey and G. B. Kistiakowsky, *ibid.*, **79**, 6373 (1957).

(3) J. H. Knox and A. F. Trotman-Dickenson, *Chemistry and Industry*, 1039 (1957).

(4) P. S. Skell and R. C. Woodworth, THIS JOURNAL, **78**, 4496 (1956).

(5) W. von E. Doering and P. LaFlamme, *ibid.*, **78**, 5447 (1956).

Skell and Woodworth.[4,6] More accurate analyses were possible when using *trans*-2-butene and in the liquid phase at −70° the amounts of the compounds mentioned were respectively 51.0, 39.7 and 9.2%. Very similar values were obtained in the gas phase at 25° and moderate pressures (>1200 mm.). At lower pressures the ratio *trans*-1,2-dimethylcyclopropane to *trans*-2-pentene decreased and the formation of some *cis*-2-pentene, 2-methylbutene-1 and *cis*-1,2-dimethylcyclopropane was observed. It appears probable that at the lower pressures some of the initially formed "hot" cyclo compound isomerizes before it is stabilized by collision. The pressure at which half the initially formed cyclo compound isomerizes indicates that its lifetime is considerably longer than that of cyclopropane formed from methylene and ethylene,[7] which is to be expected for the more complex molecule.

Other differences between the gas and liquid phase reactions were seen in the secondary products formed in the former case, which were suppressed by the "cage effect" in the latter case. These differences together with the effects of inert gases will be fully discussed in a later paper.

The author wishes to thank The Royal Society for a grant toward the purchase of apparatus in connection with this work.

(6) P. S. Skell, private communication.
(7) H. M. Frey, THIS JOURNAL, **79**, 1259 (1957).

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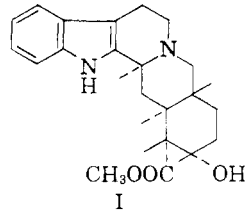
RECEIVED AUGUST 21, 1958

THE TOTAL SYNTHESIS OF YOHIMBINE

Sir:

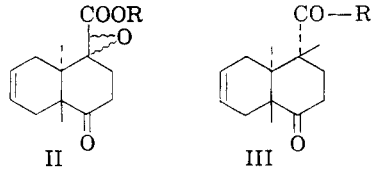
We wish to announce the total synthesis of the classical aphrodisiac alkaloid yohimbine (I), accomplished through a series of steps which repre-



I

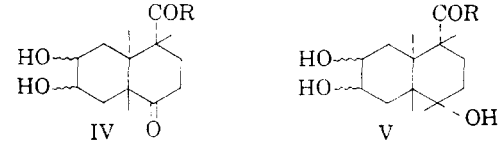
sents an entry into the D-E *trans* group of naturally occurring pentacyclic indole bases.[1]

cis-Δ^6-Octalin-1,4-dione, prepared by zinc–acetic acid reduction of the quinone–butadiene adduct,[2] was converted by the Darzens reaction, using ethyl chloroacetate and potassium *t*-butoxide, to the glycidic ester (II, R = C_2H_5), b.p. 135–155° (0.1 mm.). Saponification afforded a diastereoisomeric mixture of glycidic acids (II, R = H) (m.p.'s 138–140° and 210–211°) which, on heating, decarboxylated to give the unsaturated ketoaldehyde (III, R = H), b.p. 107–109° (0.01 mm.). Alkaline silver oxide converted the aldehyde to the acid (III, R = OH),[3] m.p. 145–146°.



II III

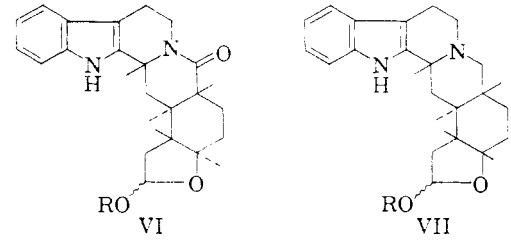
Treatment of the keto acid (III, R = OH) with oxalyl chloride yielded the corresponding acid chloride, which, without isolation, was used to acylate tryptamine, giving the amide (III, R = *β-ind*-CH_2CH_2NH), m.p. 161–162°. Hydroxylation with osmium tetroxide provided the keto diol (IV, R = *β-ind*-CH_2CH_2NH), m.p. 213–214°, which, on platinum-catalyzed hydrogenation,



IV V

yielded the triol (V, R = *β-ind*-CH_2CH_2NH),[3] m.p. 227–228°.

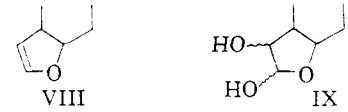
Glycol cleavage of the triol to the dialdehyde (not isolated), followed by cyclization to the hexacyclic lactol lactam (VI, R = H), m.p. 218–220° (dec.),[3] was achieved by periodate oxidation followed by brief heating with dilute phosphoric acid.



VI VII

Acid-catalyzed methanolysis to the lactol ether lactam (VI, R = CH_3), m.p. 268–270°, preceded lithium aluminum hydride reduction, which gave the lactol ether base (VII, R = CH_3), m.p. 133–137°.

The remainder of the synthesis was carried through without deliberate purification of intermediates. The acetic acid salt of the O-acetate (VII, R = CH_3CO), on brief heating at 280–290° (*in vacuo*), afforded a sublimate, the acetate salt of the enol ether (VIII). Osmium tetroxide



VIII IX

hydroxylation gave the expected diol (IX), which was cleaved, on treatment with metaperiodate, to the O-formate of *dl*-pseudoyohimbaldehyde produce. Chromic acid oxidation of the aldehyde, carried out in methanol–acetone in the presence of sulfuric acid, gave rise to *dl*-pseudoyohimbine m.p. 252–256°. Resolution of the synthetic base was accomplished by means of *l*-camphorsulfonic acid, which gave a salt (m.p. 274–278°) identical with the *l*-camphorsulfonate (m.p. 276–278°) of natural *d*-pseudoyohimbine (mixed m.p. undepressed and infrared spectra

(1) For synthesis of the D-E *cis* type, exemplified by reserpine, see R. B. Woodward, F. E. Bader, H. Bickel, A. J. Frey and R. W. Kierstead, THIS JOURNAL, **78**, 2023, 2657 (1956); *Tetrahedron*, **2**, 1 (1958).
(2) K. Alder and G. Stein, *Ann.*, **501**, 247 (1933).
(3) Direct evidence for the stereochemistry of this and related intermediates will be presented in a subsequent publication.