The author wishes to express his gratitude to Prof. Emeritus S. Sugasawa for his guidance and also to Dr. Toshiro Fujisawa, the Director of this Institute, and to Dr. M. Ohara, the Director of the Osaka Research Laboratory, for their active interest in this work. Thanks are also due to Mr. Ohta and Miss Komuro for analytical data, and to Misses Kobayashi and Ninomiya, and Mr. Kondo for infrared data.

Summary

3-Methyl-8,9-methylenedioxy-1*H*,6*H*-5,10b-propano-2,3,4,4a-tetrahydrophenanthridine, i.e. homocrinane or 9-aza-methylenedioxy-des-N-morphinane, was synthesized from 2-(3,4-methylenedioxyphenyl)-5-methylcyclohexanone which is derived from safrole.

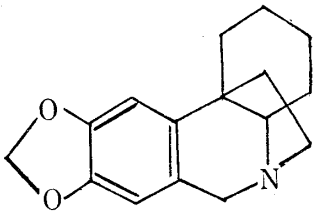
(Received March 23, 1961)

UDC 547.566.2.07

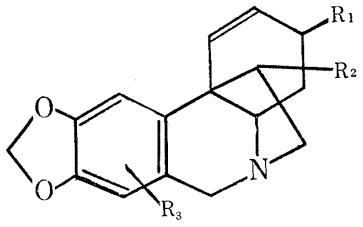
65. Kozo Okada : Studies on the Utilization of Safrole as Medicinal Raw Material. XVI.*1 A Synthesis of 3-Methyl-8,9-methylenedioxy-1*H*,6*H*-5,10b-ethano-2,3,4,4a-tetrahydrophenanthridine.

(*Tokyo Research Laboratory, Fujisawa Pharmaceutical Co., Ltd.**2)

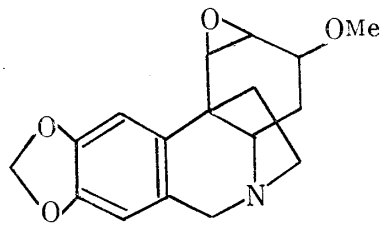
In the preceding paper,*1 synthesis of a compound which may be called methyl-homocrinane (V in that paper) was described, rendering feasible also the synthesis of a derivative of crinane (A), which forms skeleton of the Amaryllidaceae alkaloids, crinine[1] (B; R_1=OH, R_2,R_3=H), haemultine[2] (B; R_1,R_3=H, R_2=OH), haemanthidine[3] (B; R_1=OMe, R_2=OH, R_3=H), haemanthamine[4] (B; R_1,R_2=OMe, R_3=H), buphanidrine[1] (B; R_1,R_3=OMe, R_2=H), undulatine[5] (C), starting from safrole.



(A)



(B)



(C)

As the key intermediate for the projected synthesis 1-(3,4-methylenedioxyphenyl)-2-oxo-4-methylcyclohexaneacetonitrile (II) was required, which may be prepared by cyanomethylation at 2-position of 2-(3,4-methylenedioxyphenyl)-5-methylcyclohexanone (I), which is readily obtainable from safrole by the known method.[6]

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*1 Part XV. This Bulletin, **10**, 398 (1962).
*2 Nukui, Koganei, Tokyo (岡田光三).

1) W.C. Wildman : J. Am. Chem. Soc., **80**, 2567 (1958).
2) H.G. Boit, W. Döbke : Chem. Ber., **91**, 1965 (1958).
3) S. Uyeo, H.M. Fales, R.J. Highet, W.C. Wildman : J. Am. Chem. Soc., **80**, 2590 (1958).
4) H.M. Fales : Chem & Ind. (London), **1958**, 561 : Ibid, **82**, 197; 1472 (1960).
5) E.W. Warnhoff, W.C. Wildman : Ibid. **82**, 1472 (1960).
6) Tomokichiro Fujisawa : Yakugaku Zasshi, **79**, 783 (1959).

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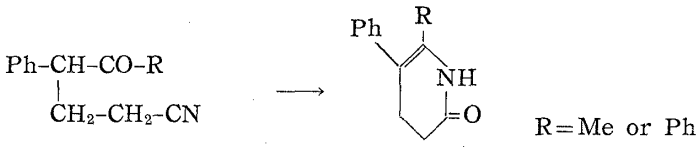
The cyanomethylation of 2-phenylcyclohexanone[7] to give 1-phenyl-2-oxo-cyclohexaneacetonitrile was achieved by treating the former with chloroacetonitrile in the presence of sodium amide. In a similar manner, 2-(4-methoxyphenyl)cyclohexanone[8] could also be cyanomethylated at 2-position, but with difculty. When applied to the ketone (I), however, this method failed to furnish the desired product (II), recovering the starting ketone. Sodium hydride, pulverized sodium, potassium *tert*-butoxide, and sodium amide in liquid ammonia used as the condensing agent uniformly failed to give the ketone (II), either recovering the starting ketone or yielding unspecified material. The desired ketone was first obtained when the condensation of (I) with chloroacetonitrile was carried out by means of lithium amide in liquid ammonia. The difficulty of this condensation is probably due to the presence of the methylenedioxy group, as can be understood from the two above-mentioned examples.

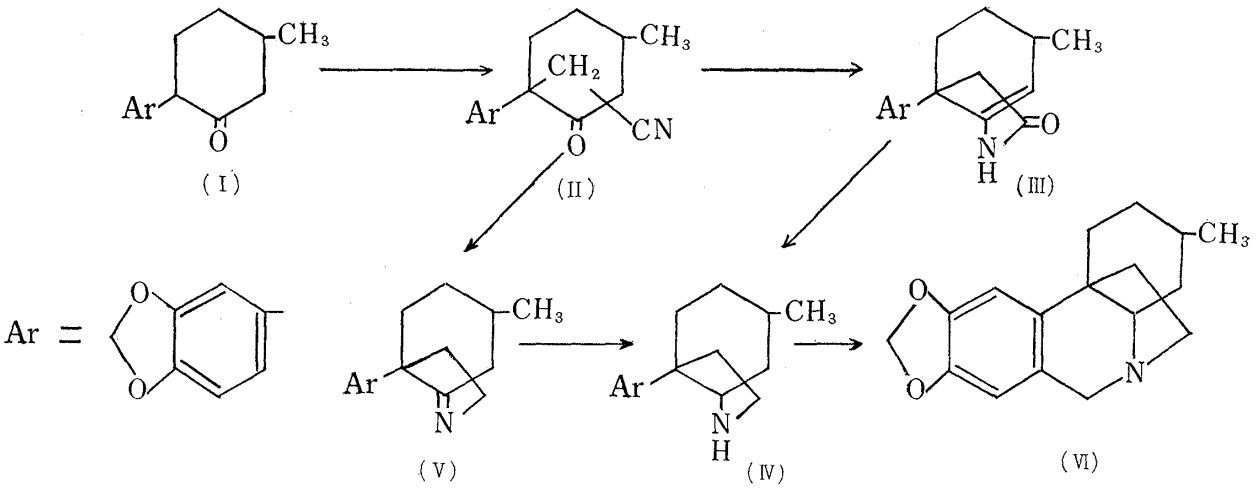
The conversion of (II) into the final product (VI) was effected in two ways.

According to Campbell, *et al.*[9] 4-phenyl-5-oxo-hexanenitrile, when refluxed in *tert*-butanol in the presence of conc. methanolic potassium hydroxide solution, underwent a partial hydrolysis and intramolecular cyclization to give 5-phenyl-6-methyl-3, 4-dihydro-2(1*H*)-pyridone. This reaction was later applied by Sugasawa and Ushioda[10] to 4-benzoyl-4-phenylbutyronitrile to yield 5,6-diphenyl-3,4-dihydro-2(1*H*)-pyridone.



Under similar conditions, the compound (II) suffered the same type of chemical change yielding a five-membered cyclization product (III) in a fair yield. The absorption band at 1700 cm^{-1} (characteristic to the five-membered amide) present in its infrared spectrum lends support to this view. On being reduced over Adams platinum catalyst, followed by reduction with lithium aluminum hydride, this compound (III) furnished the perhydroindole derivative (IV).

Reduction of (II) over Raney nickel catalyst was next studied. In contrast to the corresponding 2-cyanoethyl derivative, which was reduced and cyclized smoothly when hydrogenated in ethanolic solution over Raney nickel under pressure as shown in the



7) V. Boekelheid, W.M. Shilling : J. Am. Chem. Soc., **72**, 712 (1950).
8) L.H. Schwartzman, G.F. Wood : J. Org. Chem., **17**, 492 (1952).
9) A.D. Campbell, I.D.R. Stevens : J. Chem. Soc., **1956**, 959.
10) S. Sugasawa, S. Ushioda : Tetrahedron, **5**, 48 (1959).

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preceeding paper,*1 the present ketone (II) gave a satifactory result only when the reduction was carried out in ethanol saturated with ammonia. The hydroindole derivative (V) thus prepared was further hydrogenated over Adams platinum catalyst absorbing an additional one molar equivalent of hydrogen to yield the hydroindole derivative (IV), which gave a positive Liebermann test (blue) of the secondary amine and was proved to be identical with the one prepared *via* the alternative route.

When treated with formaldehyde solution in the presence of hydrochloric acid the latter underwent a smooth Pictet-Spengler type cyclization[11] to yield the compound (VI) mentioned in the title.

Experimental

1-(3,4-Methylenedioxyphenyl)-2-oxo-4-methylcyclohexanacetonitrile (II)——To metallic Li (90 mg.) dissolved in liquid NH_3 (ca. 300 ml., containing a small amount of $Fe(NO_3)_3$), a solution of 2-(3,4-methylenedioxyphenyl)-5-methylcyclohexanone (I) (2.8 g.) in dehyd. tetrahydrofurane (20 ml.) was added with chilling in a dry ice-acetone bath and stirring. After 1 hr.'s stirring a solution of freshly distilled chloroacetonitrile (1.25 g.) in dehyd. tetrahydrofurane (5 ml.) was added dropwise and stirring was continued for additional 5 hr. with chilling. The reaction mixture was then allowed to stand at room temperature overnigt, during which time NH_3 evaporated. H_2O was added to the residue and the mixture was thoroughly extracted with benzene, which was washed with saturated NaCl solution, dried, and the solvent was removed, leaving 3.3 g. of syrupy substance.

This was again dissolved in benzene and filtered through a column of alumina (30 g.), which was eluted with benzene. A syrupy substance (0.83 g.) was obtained from the first 50-ml. fraction, 620 mg. of a solid (m.p. 95~112°) from the second, and 270 mg. of a syrup fraction Nos. 3~10 (each fraction 50 ml.). These syrupy substances were dissolved in benzene and the combined solution (total 1.10 g. in 8 ml. benzene) was poured into an alumina (20 g.) column. The column was eluted first with 500 ml. of hexane, from which nothing obtained and then with a mixture of hexane and benzene (2:1). After 230 mg. of syrupy substance was obtained from the first 100-ml. fraction, 0.54 g. of a solid (m.p. 94~110°) was recovered from the next four fractions (each fraction 100 ml.). Together with the solid previously obtained, this was purified from EtOH to colorless rhombs, m.p. 115~118°; yield, 0.82 g. For analysis this was once again purified from diisopropyl ether to yield a specimen of m.p. 118°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found : C, 71.08; H, 6.25; N, 4.95.

3a-(3,4-Methylenedioxyphenyl)-6-methyl-2,3,3a,4,5,6-hexahydroindol-2-one (III)——A solution of the foregoing compound (1.1 g.) in tert-BuOH (2 ml.) was mixed with KOH-MeOH solution (0.3 ml., 30%) and the whole was refluxed on a steam bath for 15 hr. The solvent was evaporated and the residue was diluted with H_2O to separate a solid, which was collected and purified from diisopropyl ether to colorless rhombs, (0.21 g.) m.p. 168°. *Anal.* Calcd. for $C_{16}H_{17}O_3N$: C, 70.83; H, 6.32; N, 5.16. Found : C, 70.70; H, 6.41; N, 4.95. IR ν^{Nujol} cm^{-1} : 3200, 3080, 1695.

3a-(3,4-methylenedioxyphenyl)-6-methyl-2,3,3a,4,5,6,7,7a-octahydroindole (IV)——i) From II : The compound (II) (0.82 g.) was dissolved in EtOH (60 ml.) saturated with NH_3 and reduced over Raney Ni (1 g.) at 120~125° with initial H_2 pressure 80 aftm. After 2 hr., EtOH was evaporated and the residue was acidified with dil. HCl, and then shaken with benzene. The aqueous layer was basified with NaOH solution and the base that liberated was extracted with Et_2O. The extract was washed, dried, and Et_2O was evaporated. The residue, after destillation ($b.p_{0.7}$ 175°), was dissolved in EtOH and reducedover Adams Pt catalyst. On working up the reduction mixture as usual there was obtained a fraction of $b.p_{0.5}$ 170°(0.54 g.), which gave a blue Liebermann test.

Picrate : Yellow needles (from AcOH), m.p. 186~188°(decomp.). *Anal.* Calcd. for $C_{22}H_{24}O_9N_4$: C, 54.09; H, 4.95; N, 11.47. Found : C, 54.06; H, 4.73; N, 11.76.

ii) From III : The compound (III) (0.2 g.) dissolved in EtOH was reduced with H_2 activated over Adams Pt catalyst. The residue from the reduction mixture was dissolved in dehyd. tetrahydrofurane (15 ml.) and reduced by adding $LiAlH_4$ (40 mg.) dissolved in tetrahydrofurane (20 ml.) with stirring. The whole was warmed to 45~50° and stirring was continued for further 5 hr. To the reduction mixture, a small amount of H_2O and NaOH were added and filtered. The residue on the filter was repeatedly washed with benzene. From the combined filtrate and washing, the solvent was evaporated. The residue was mixed with H_2O, acidified with HCl, and shaken with benzene. The aqueous layer was basified with NaOH solution, extracted with Et_2O and worked up as usual to leave a

11) By means of heating with formaline and formic acid, 3a-(3,4-methylenedioxyphenyl)-perhydroindole cyclized very easily. (W.C. Wildman : J. Org. Chem., **25**, 287 (1960)).

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viscous syrup (50 mg.), which was characterized as a picrate of yellow needles (from EtOH), m.p. 185~186° (decomp.). This was identical with the one obtained as above.

3-Methyl-8,9-methylenedioxy-1*H*,6*H*-5,10b-ethano-2,3,4,4a-tetrahydrophenanthridine (VI)——The hydrochloride (200 mg.) of the foregoing base was dissolved in H_2O (1 ml.), to which $NaHCO_3$ (0.2 g.) and HCHO solution (0.2 ml.) were added. The mixture was heated on a steam bath for 30 min., when an oil separated. This oil was isolated from the mixture by decantation, washed thoroughly with H_2O to remove HCHO and then heated with conc. HCl (0.2 ml., 38%) on a steam bath for 1 hr. When cooled, the product was diluted with H_2O, shaken with Et_2O, and the aqueous layer was basified with NaOH to separate the base, which was extracted with Et_2O and worked up as usual. The residue was a syrup and distilled at 170~180° (bath temp.) at 1 mm. Hg. Yield, 130 mg.
Picrate : Yellow needles (from AcOH), m.p. 188° (decomp.). *Anal.* Calcd. for $C_{23}H_{24}O_9N_4$: C, 55.20; H, 4.83; N, 11.20. Found : C, 55.04; H, 4.83; N, 11.49.

Greatful acknowledgement is offered to Prof. Emeritus, S. Sugasawa for his guidance. Thanks are also due to Dr. T. Fujisawa, the Director of this laboratory, and to Dr. M. Ohara, the Director of Osaka Research Laboratory, for their active interest in this work.

Summary

3-Methyl-8,9-methylenedioxy-1*H*,6*H*-5,10b-ethano-2,3,4,4a-tetrahydrophenanthridine, which has the skeleton of crinane, was synthesized from the ketone, 2-(3,4-methylenedioxyphenyl)-5-methylcyclohexanone, which was derived from safrole.

(Received March 23, 1961)

UDC 547.92 : 547.918

66. Hiroshi Ōsaka : On Steroidal Sapogenins. V.*1 Synthesis of 11-Oxygenated Spirostanes. (3).

(*Research Laboratory, Shionogi & Co., Ltd.**2)

Several kinds of 2,3-dihydroxyspirostan-11-one were synthesized in order to examine their behavior in Huang-Minlon reduction and reported in the previous papers.[1],*1 In the present series of work, several kinds of 2-hydroxyspirostan-11-one were prepared.

There are few reports on the preparation of steroids oxygenated at 2-position of the A-ring. One of them is the report by Pataki and others[2] who obtained 2β-hydroxy (axial) derivative by reduction of 2β,3β-epoxy-25D,5α-spirostane with lithium aluminium hydride and the other is that of Sheehan and others[3] who obtained 2-oxo derivative in one step by treatment of 2β-hydroxy-3β-tosyloxycholestane with collidine. On the other hand, synthesis of monohydroxy-steroids by reduction of monotosylate of vicinal diol with lithium aluminium hydride is known.[4] Attempt was therefore made to utilize this latter reaction to effect liberation of hydroxyl group at C-3 position of several kinds of 2,3-dihydroxy-11-oxo-sapogenins obtained earlier.[1],*1

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*1 Part IV : Yakugaku Zasshi, **81**, 1662 (1961).
*2 Sagisu, Fukushima-ku, Osaka (大坂 弘).
1) Part III. K. Takeda, H. Ōsaka, N. Maezono : Yakugaku Zasshi, **81**, 1657 (1961).
2) J. Pataki, G. Rosenkranz, C. Djerassi : J. Am. Chem. Soc., **73**, 5375 (1951).
3) J. C. Sheehan, W. F. Erman : *Ibid.*, **79**, 6050 (1957).
4) (a) P. Karrer, H. Asmis, K. N. Sarren, R. Schwyzer : Helv. Chim. Acta, **34**, 1022 (1951). (b) C. W. Shoppee, D. N. Jones, G. H. R. Summers : J. Chem. Soc., **1957**, 3100.

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