N-(2-Chloroethyl)-N-methyl-pyrrolidinium Picrate by Incubation of (VI)——Hydrochloride of (VI) (10 g.), dissolved in water (100 cc.), was added with $NaHCO_3$ (5 g.) and the mixture was incubated at 37° for 10 min. The solution was added with picric acid. Picrate, m.p. 177~178°(from EtOH). It showed no depression on admixture with the synthesized specimen (No. 701). Yield of the purified picrate, 80%. *Anal.* Calcd. for $C_{13}H_{18}O_7N_4Cl$: C, 41.33; H, 4.80; N, 14.84; Cl, 9.38. Found : C, 41.60; H, 4.96; N, 15.03; Cl, 9.40.

Measurement of Cl^--Liberation and Thiosulfate Uptake——Titration was carried out at 37° by the procedure already reported.[3]

The author wishes to thank Prof. M. Ishidate and Dr. Y. Sakurai for their kind guidance throughout the course of this investigation. Thanks are also due to Prof. T. Yoshida and Dr. H. Satoh for their valuahle advices. This work was partially supported by the Grant-in-Aid for Scientific Research from the Ministry of Education, which is gratefully acknowledged.

Summary

Twenty-three derivatives of N-alkyl-N-2-chloroethyl-N-ω-chloroalkylamine were prepared. It was proved that these compounds are completely monofunctional biological alkylating agents from the estimation of reaction velocity *in vitro*, but neverthless they exhibit a strong antitumor effect on rats bearing Yoshida sarcoma. The fact is very interesting from the point of the mode of action of nitrogen mustards.

(Received February 17, 1961)

3) I. Aiko : This Bulletin, **9**, 350 (1961).

UDC 547.566.2.07

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

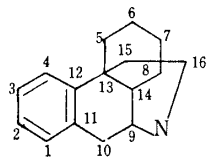
(*Tokyo Research Laboratory, Fujisawa Pharmaceutical Co., Ltd.**2)

In this paper is described a synthesis of the title compound (V) starting from safrole. As morphinane[1] (A) represents the fundamental skeleton of morphine and related alkaloids, crinane[2] (B) represents the skeleton of the Amaryllidaceae alkaloids derived from 5,10b-ethanophenanthridine, such as crinine,[2] powelline[3] and buphanidrine.[4] These alkaloids posses a strong Morphine-like analgesic action.[5]

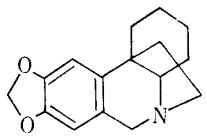
Even without methylenedioxy group, the skeleton (C) of which derivative, 9-methoxy-1*H*,6*H*-5,10b-propano-2,3,4,4a-tetrahydrophenanthridine,*3 was first synthesized by Sugimoto and Kugita[6] has not yet met in the natural alkaloid. However, the expression (C)

*1 Part XIV. T. Fujisawa : Yakugaku Zasshi, **79**, 783 (1959).
*2 Nukui, Koganei, Tokyo (岡田光三).
*3 Sugimoto named this compound 3-methyl-9-aza-morphinane.
1) R. Grewe, A. Mondon : Ber., **81**, 279 (1948).
2) W.C. Wildman : J. Am. Chem. Soc., **80**, 2567 (1958).
3) H.M. Fales, W.C. Wildman : *Ibid.*, **80**, 4395 (1958).
4) E.W. Warnhoff, W.C. Wildman : *Ibid.*, **82**, 1472 (1960).
5) N.B. Eddy *et al.* : Bull. World Health and Metabolic Diseases, **14**, 353 (1956). (C.A., **50**, 15944c (1956)).
6) N. Sugimoto, H. Kugita : This Bulletin, **3**, 11 (1955); *ibid.*, **5**, 378 (1957).

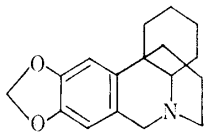
is related to crinane as well as to morphinane and may be called homocrinane (enlargement of five-membered ring) or 9-aza-methlenedioxy-des-N-morphinane (shift of nitrogen atom to 9-position). In accordance with this view, the title compound which has the skeleton (C) was synthesized for examination of the relationship between its structure and pharmacological action.



(A)

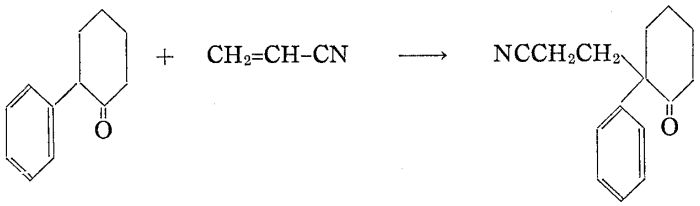


(B)

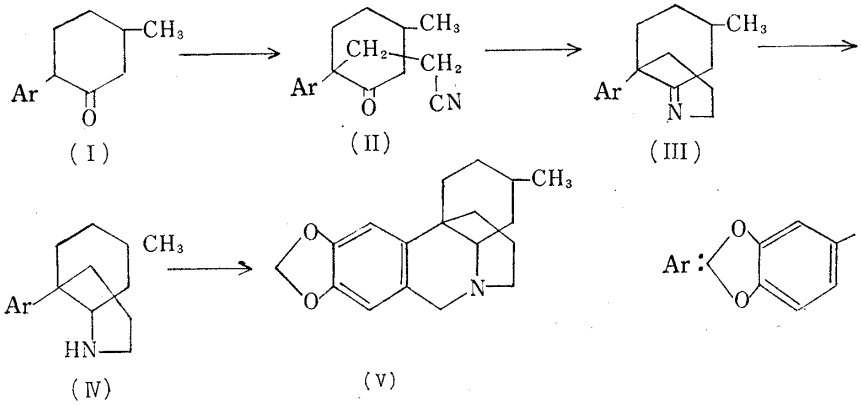


(C)

3,4-Methylenedioxybenzyl methyl ketone,[7] readily obtainable from safrole, was converted to 2-(3,4-methylenedioxyphenyl)-5-methyl-cyclohexanone[8] (I) by the known method. The latter then was condensed with acrylonitrile by the agency of Triton B to furnish 1-(3,4-methylenedioxyphenyl)-2-oxo-3-methylcyclohexanepropionitrile (II) in a good yield. The position of cyanoethyl group to give (II) is supported from a similar experiment in which 1-phenyl-2-oxo-cyclohexanepropionitrile[9] was proved to be the sole product of the Michael condensation of 2-phenylcyclohexanone with acrylonitrile.



The compound (II) thus prepared was now reduced with hydrogen over Raney nickel catalyst at 120° under a initial hydrogen pressure of 80 atm. The product was an oil, in which the presence of -C=N- bond was revealed from its infrared absorption spectrum (1652 cm^{-1}). Thus, the structure (III) is proposed for the reduction product.*4 Though



*4 Sugimoto and Kugita succeeded in obtaining the saturated cyclized base in one step using nickel catatyst.

7) Toshiro Fujisawa, Y. Deguchi : Yakugaku Zasshi, **74**, 975, 977, 1110 (1954).
8) Tomokichiro Fujisawa : *Ibid.*, **79**, 783 (1959).
9) W.E. Bachmann, L.B. Wick : J. Am. Chem. Soc., **72** 3388 (1950).

indifferent towards catalytic reduction over nickel catalyst, this oil could readily be hydrogenated over Adams platinum catalyst to give the saturated base, 4a-(3,4-methylenedioxyphenyl)-7-methyldecahydroquinoline (IV). The secondary nature of nitrogen in this compound was supported by the positive Liebermann test (purple) and *N*-benzoyl derivative also formed well defined crystals. Some infrared absorption data are described in the experimental section.

This base (IV) underwent a smooth Pictet-Spengler type cyclization with formaldehyde to yield the title compound (V).

Experimental*5

1-(3,4-Methylenedioxyphenyl)-2-oxo-4-methylcyclohexanepropionitrile (II)——To a benzene (35 ml.) solution of (I) (8.0 g.) added with Triton B (0.1 ml.), and cooled in cold water, a benzene (5 ml.) solution of acrylonitrile (2.03 g.) was added with stirring. The water bath was removed 25 min. later, the mixture was allowed to stand for 3 hr. at 30°, and then gradually warmed and kept at 50° with stirring. When cooled, the reaction mixture was diluted with H_2O and neutralized with dil. HCl. The aqueous layer was extracted thoroughly with benzene and the combined benzene solution was washed with water, dried, and the solvent was removed. The residue was distilled *in vacuo* recovering (I) as forerunner of $b.p_{0.05}$ 130~143°(360 mg.), which solidified on standing to melt at 80~85°, followed by the main fraction of $b.p_{0.05}$ 188~196°; yield, 7.3g. or 75%.
Dinitrophenylhydrazone : Orange needles from AcOEt m.p. 206.5~207°(decomp.). *Anal.* Calcd. for $C_{23}H_{23}O_6N_5$: C, 59.35; H, 4.98; N, 15.05. Found C, 59.53; H, 4.89; N, 15.24.

4a-(3,4-Methylenedioxyphenyl)-7-methyl-2,3,4,4a,5,6,7,8-octahydroquinoline (III)——An EtOH solution of the foregoing compound (7.3 g. in 60 ml. EtOH) was treated with H_2 activated over Raney Ni W-7 (1 g.) at 120° and under the initial H_2 pressure of 82 atm. until no more H_2 was absorbed (ca. 2 hr.). When cooled, EtOH was evaporated and the residue was mixed with H_2O, acidified with dil. HCl, and extracted with Et_2O to remove non-basic impurity. The aqueous layer was basified with NaOH and the liberated base was taken up in Et_2O, which was washed, dried, and the solvent was evaporated. The residue distilled at 157~161°/0.06 mm. Hg. Yield, 4.7 g. or 65%.
Picrate : Yellow needles (from EtOH), m.p. 165~165.5°(decomp.). *Anal.* Calcd. for $C_{23}H_{24}O_9N_4$: C, 55.20; H, 4.83; N, 11.20. Found : C, 55.53; H, 5.06; N, 11.35.

4a-(3,4-Methylenedioxyphenyl)-7-methyl decahydroquinoline (IV)——The foregoing base (0.34 g.) in EtOH was reduced with H_2 activated over Adams Pt. H_2 uptake stopped after 1 molar equivalent volume was absorbed. The product was worked upas us usal to furnish an oil, $b.p_{0.3}$ 188~196°;*6 yield, 0.3 g. Picrate : Yellow needles (from AcOH), m.p. 203~204°(decomp.). *Anal.* Calcd. for $C_{23}H_{26}O_9N_4$: C, 54.97; H, 5.22; N, 11.15. Found : C, 54.79; H, 5.41; N, 11.12.
Hydrochloride : Colorless scaly crystals (from EtOH), m.p. 250~252°(decomp.). *Anal.* Calcd. for $C_{17}H_{24}O_2NCl$: C, 66.05; H, 7.83; N, 4.53. Found : C, 66.03; H, 7.84; N, 4.40. IR ν_{Nujol} cm^{-1} : 2710, 2640, 2530, 2420, 1570, 875, 805.
Benzoyl derivative : Prepared by refluxing the benzene solution of (IV) with $(BzO)_2O$; yield, quantitative. Colorless rhombs (from EtOH), m.p. 184~185.5°. *Anal.* Calcd. for $C_{24}H_{27}O_3N$: C, 76.36; H, 7.21; N, 3.71. Found : C, 76.44; H, 7.43; N, 3.57.

3-Methyl-8,9-methylenedioxy-1*H*,6*H*-5,10b-propano-2,3,4,4a-tetrahydrophenanthridine (V)——The hydrochloride (0.6 g.) of the above base was dissolved in a mixture of H_2O (2 ml.) and EtOH (2 ml.) and $NaHCO_3$ (0.4 g.) and aqueous HCHO solution (0.3 ml., 37%) were added to the solution separating an oil. After the whole was heated on a steam bath for 50 min., H_2O was added and the mixture was allowed to cool. H_2O was discarded by decantation, the residue was repeatedly washed with H_2O, and dissolved in conc. HCl (2.5 ml.). The resultant solution was heated on a steam bath for 1 hr., cooled, and shaken with benzene to remove impurity. The aqueous layer was made NaOH-alkaline and repeatedly extracted with Et_2O. The extract was washed, dried, and the Et_2O was evaporated. The residue was distilled *in vacuo* and a fraction came over at the temperature above 180°/0.05 mm. Hg was collected as the product. It was characterized as a crystalline picrate and a methiodide.
Picrate : Yellow needles (from AcOH), m.p. 250~252°(decomp.). *Anal.* Calcd. for $C_{24}H_{26}O_9N_4$: C, 56.03; H, 5.09; N, 10.89. Found : C, 55.89; H, 5.17; N, 10.92.
Methiodide : Colorless rhombic crystals (from EtOH), m.p. 236~238°(decomp.). *Anal.* Calcd. for $C_{19}H_{26}O_2NI$: C, 53.38; H, 6.14; N, 3.28. Found : C, 53.45; H, 6.21; N, 3.07.
Infrared spectrum of hydrochloride ν_{Nujol} cm^{-1} : 2460 (broard), 833.

*5 All melting points are uncorrected.
*6 Temperature of bath.

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.

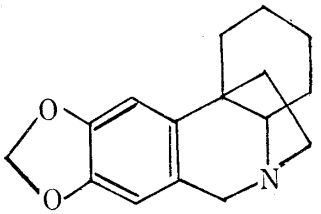
(Received March 23, 1961)

UDC 547.566.2.07

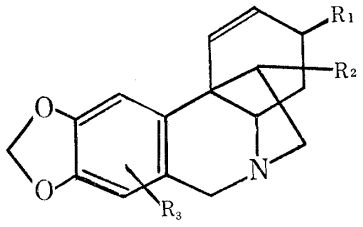
65. Kozo Okada : Studies on the Utilization of Safrole as Medicinal Raw Material. XVI.*1 A Synthesis of 3-Methyl-8,9-methylenedioxy-1*H*,6*H*-5,10b-ethano-2,3,4,4a-tetrahydrophenanthridine.

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

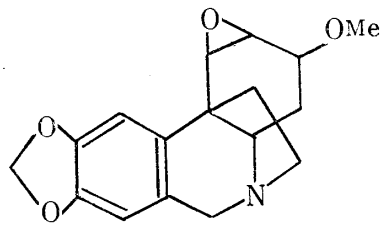
In the preceding paper,*1 synthesis of a compound which may be called methyl-homocrinane (V in that paper) was described, rendering feasible also the synthesis of a derivative of crinane (A), which forms skeleton of the Amaryllidaceae alkaloids, crinine[1] (B; R_1=OH, R_2,R_3=H), haemultine[2] (B; R_1,R_3=H,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