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53. Shigehiko Sugasawa*1 and Hiroshi Yoshikawa*2 : Synthesis in the Erythrinane Group of Compounds. I. A Synthesis of *dl*–15,16–Dimethoxyerythrinane.

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Prelog[1] with his co-workers studied the chemical structures of aromatic erythrina alkaloids and put forward the structure (I), called erythrinane, as their fundamental skeleton. The first synthetical support for this view was provided by Belleau,[2] who succeeded in synthesizing *dl*–15,16–dimethoxyerythrinane (X), which had been derived from the natural alkaloid. Further syntheses related to this compound were reported also by Mondon[3] and Prelog, *et al.*[4] Thus, erythrina alkaloids have a unique skeleton (I), which has never been met in natural products.

An interest was focussed upon the synthesis of 15,16–dimethoxyerthrinane (X) or its dehydro derivative (XI) via different route capable of extending to the synthesis of various derivatives of (X) for pharmacological evaluation.

In 1955, Gardent[5] reported a synthesis of 6,7–diethoxy–1,2,3,4–tetrahydroisoquinoline–1–spirocyclohexane (III) by treating a mixture of 3,4–diethoxyphenethylamine and cyclohexanone with phosphoric acid. When this method was applied to a mixture of 3,4–dimethoxyphenethylamine and cyclohexane–1,2–dione there was produced 6,7–dimethoxy–1,2,3,4–tetrahydroisoquinoline–1–spiro–1′–cyclohexan–2′–one (II), which on reduction gave 6,7–dimethoxy–1,2,3,4–tetrahydroisoquinoline–1–spirocyclohexane (III), identical with an authentic sample prepared according to the procedure of Gardent.

The amino ketone (II) gave a crystalline N–acetyl derivative (IV), which could be cyclized by means of sodium hydride in boiling ethanol to yield a tetracyclic compound (V), in which the presence of hydroxyl group was proved by its infrared spectrum. The dehydration product (VI) of (V) was also obtained in one step when the above cyclization reaction was carried out for a longer period of time. The product thus obtained remained oily and the location of its double bond could not be established. If it were located in conjugation with the C=O group, the compound should crystallize as will be shown later by (VIII), and thus the structure (VI) was tentatively put forward for this compound, implying also that this compound may exist as a mixture of double–bond isomers. The presence of a double bond was supported, since this on catalytic reduction gave 8–oxo–15,16–dimethoxyerythrinane (IX) also obtainable from (VIII) by the same procedure.

The alternative method gave a better result for the preparation of (IX). Thus (II) was acylated with ethoxycarbonylacetyl chloride to yield a crystalline amide (IV′), which on being treated as above gave the cyclized product (VII) in a good yield. The decarboxylation of the latter proceeded smoothly in a boiling xylene solution to furnish a solid product, to which the structure (VIII) was assigned from its spectral features. When reduced catalytically this absorbed one molar equivalent of hydrogen to give the saturated lactam (IX), which was also obtained from the oily (VI) as was mentioned above.

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2) B. Belleau : J. Am. Chem. Soc., **75**, 5765(1953); Chem. & Ind. (London), **1956**, 410; Can. J. Chem., **35**, 651(1957).

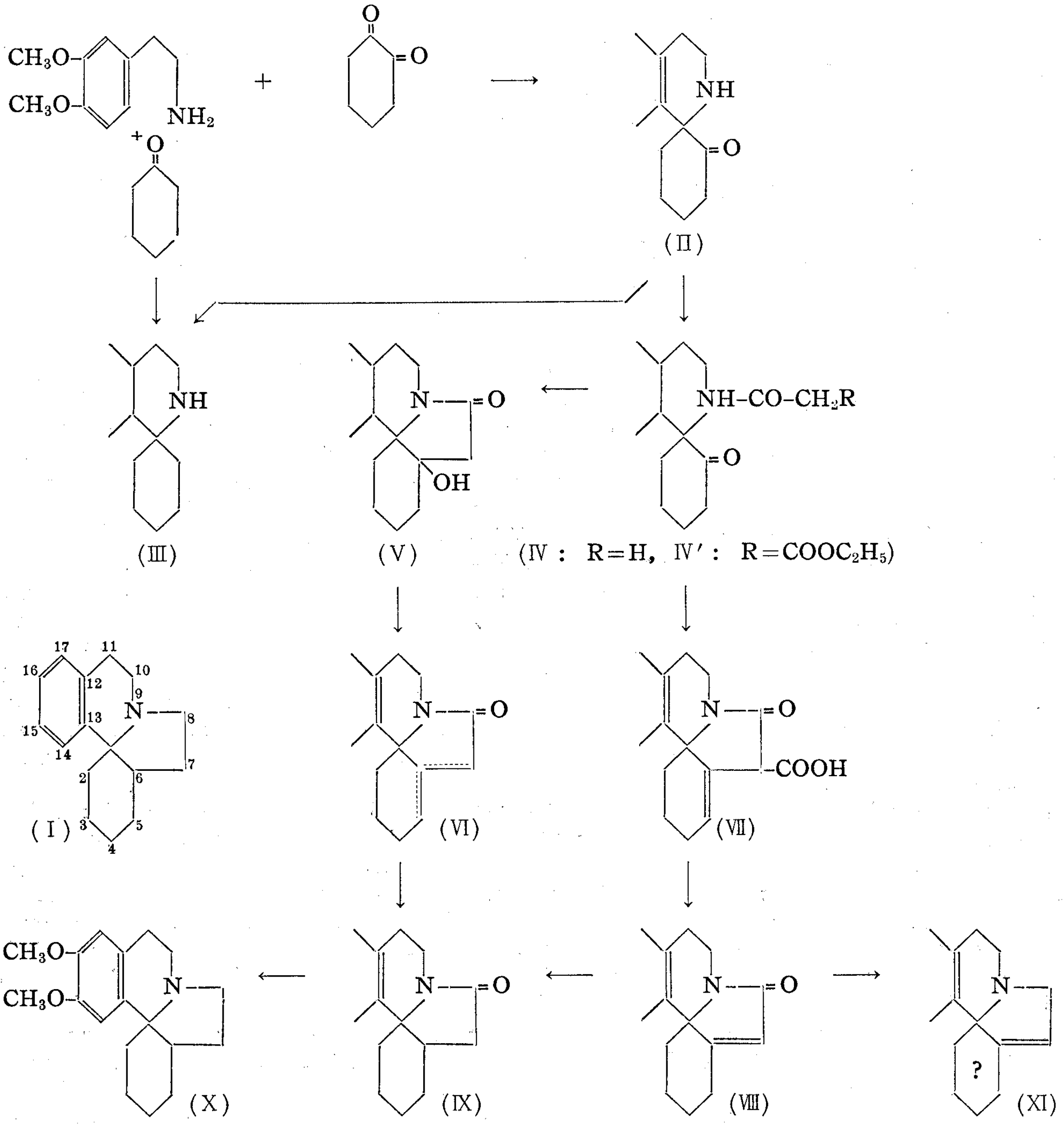
3) *a*) A. Mondon : Z. angew. Chem., **68**, 578(1956). *b*) *Ibid.*, **70**, 406(1958). *c*) Chem. Ber., **92**, 1467, 1472(1959).

4) V. Prelog, A. Langemann, O. Rodig, M. Ternbach : Helv. Chim. Acta, **42**, 1301(1959).

5) J. Gardent : Ann. Chim., **10**, 420(1955).

Lithium aluminum hydride reduction converted (IX) into an oily base, 15,16-dimethoxyerythrinane (X), in a good yield, which was characterized by its crystalline picrate. The latter was identified with a specimen prepared from an authentic base (X), kindly supplied by Professor B. Belleau, through mixed melting point test and infrared spectral data.

When (VIII) was reduced in a like manner the unsaturated base (XI), a compound of interest as an intermediate for further synthetical works, was probably produced, but unfortunately this was a very unstable compound*[3] and could not be characterized.



The present method established a new route to the erythrinane (X), which may be applicable also to the synthesis of its derivatives. The poor yield at the first stage (preparation of (II)), however, blocks the way and the present effort is directed to the betterment of this yield.

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*[3] This compound was found very sensitive both to acid and air in acid solution. See also footnote 3b.

Experimental

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-1′-cyclohexan-2′-one (II)—A mixture of 3,4-dimethoxyphenethylamine (40 g.), 1,2-cyclohexanedione (25.4 g.), and H_3PO_4(110 cc., 85%) was heated on a steam bath for 20 hr. with stirring. When cool, the reaction mixture was poured onto crushed ice (400 g.), stirred with charcoal, and filtered. The filtrate, after being shaken with ether, was basified with Na_2CO_3 and thoroughly extracted with benzene. The combined benzene solution was mixed with H_2O (200 cc.) and saturated with CO_2 with vigorous shaking. The supernatant benzene layer was washed with H_2O, dried, and filtered through an alumina column. On evaporation of the solvent there remained a viscous, yellow syrup (21 g.), which was characterized as a picrate of yellow pillars, m,p. 174~175°(from EtOH). Judging from the amount of the picrate precipitated the yield of (II) is probably less than 10%. *Anal.* Calcd. for $C_{22}H_{24}O_{10}N_4$: C, 52.4; H, 4.8; N, 11.1. Found : C, 52.6; H, 4.6; N, 11.7. IR of (II) : $\nu_{C=O}$ 1660, ν_{N-H} 3260 cm^{-1}(Nujol).

6,7-Dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spirocyclohexane (III)—The foregoing base (alumina-purified product, 0.3 g.) dissolved in ethylene glycol (2 cc.) was mixed with hydrazine hydrate (0.25 cc.) and KOH (0.3 g.), and the whole was heated in an oil bath at 155~160° for 1.5 hr. and then at 220° for an additional 1 hr. When cool, the reaction mixture was poured into cold H_2O, extracted with ether, and the ethereal solution was extracted with dil. HCl. The acid layer, after being shaken with ether, was basified with Na_2CO_3, salted out with NaCl, and the base that liberated was collected in ether. The ethereal solution was worked up as usual to leave an oily base (0.1 g.), whose picrate formed greenish yellow pillars (from EtOH), m.p. 176°, which was not depressed when admixed with an authentic sample of m.p. 177° prepared according to the method of Gardent. *Anal.* Calcd. for $C_{22}H_{26}O_9N_4$: C, 53.9; H, 5.3; N, 11.4. Found : C, 53.75; H, 5.3; N, 11.3.

2-Acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-1′-cyclohexan-2′-one (IV)—A solution of the crude base[*4] (II) (21 g.) in pyridine (38 g.) was acetylated by warming with Ac_2O (41 g.) on a steam bath for 6 hr. Pyridine and an excess of Ac_2O were then removed *in vacuo* and the residue was dissolved in benzene, which was washed, dried, and filtered through an Al_2O_3 column. Benzene was evaporated from the filtrate and the residue was purified from benzene to form colorless pillars, m.p. 146~147°; yield, 6.8 g. *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.1; H, 7.3; N, 4.4. Found: C, 68.1; H, 7.0; N, 4.6. IR cm^{-1} : $\nu_{C=O}$ (amide), 1637, $\nu_{C=O}$ (ketone) 1701 (Nujol).

6-Hydroxy-8-oxo-15,16-dimethoxyerythrinane (V)—The afore-mentioned compound (IV)(0.5 g.) was added to a solution of NaH (0.1 g.) and anhyd. EtOH (10 cc.), and the whole was refluxed on a steam bath for 4.5 hr. EtOH was then removed, the residue was mixed with ice water, and extracted with benzene. The benzene solution was washed, dried, and evaporated, and the residue was purified from a mixture of benzene and ether to form colorless prisms (60 mg.), m.p. 143~144°. *Anal.* Calcd. for $C_{18}H_{23}O_4N$: C, 68.1; H, 7.3; N, 4.4. Found : C, 68.2; H, 7.0; N, 4.4. IR cm^{-1} : $\nu_{C=O}$ 1661, ν_{O-H} 3311 (Nujol). A distinct depression of m.p. was observed when (IV) and (V) were admixed. When the starting mixture was refluxed for 14 hr. and worked up as above, a clear syrup (VI) (1.9 g. from 3 g. of (IV)) was obtained, which could not be induced to crystallize.

2-Ethoxycarbonylacetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-spiro-1′-cyclohexan-2′-one (VI′)—The crude base (II) (3.2 g.) in ether (300 cc., free from EtOH) was acylated by adding an ethereal solution of ethoxycarbonylacetyl chloride (17.5 g.) in the presence of powdered Na_2CO_3 (12.3 g.) with stirring. The mixture was stirred for 3 hr. at room temperature. The precipitate was collected and washed with benzene, which was combined with the original ethereal solution and the solvents were evaporated to leave a syrupy residue, which formed colorless prisms of m.p. 128°, when purified from EtOH; yield, 9.1 g. *Anal.* Calcd. for $C_{21}H_{27}O_6N$: C, 64.8; H, 7.0; N, 3.6. Found : C, 64.6; H, 7.3; N, 3.9. IR cm^{-1} : $\nu_{C=O}$ (amide) 1637, $\nu_{C=O}$ (ketone) 1709, $\nu_{C=O}$ (ester) 1733 (Nujol).

8-Oxo-15,16-dimethoxyerythrin-5-ene-7-carboxylic Acid (VII)—The foregoing compound (9.1 g.) was dissolved in a solution of NaH (0.9 g.) and anhyd. EtOH (126 cc.), and the whole was refluxed on a steam bath for 8 hr. EtOH was evaporated and the residue was dissolved in cold H_2O, shaken with benzene, and the aqueous layer was acidified with 10% HCl. The solid substance that separated was taken up in benzene, which was washed, dried, and the solvent was evaporated. The solid residue was purified from EtOH to form orange-yellow pillars, m.p. 167°(decomp.); yield, 5.3 g. or 66%. *Anal.* Calcd. for $C_{19}H_{21}O_5N$: C, 66.5; H, 6.2; N, 4.1. Found : C, 66.7; H, 6.4; N, 4.15. IR cm^{-1} : $\nu_{C=O}$ (amide) 1650, $\nu_{C=O}$ 1736 (Nujol). UV λ_{max}^{EtOH} 282 mμ (log ε 3.65).

8-Oxo-15,16-dimethoxyerythrin-6-ene (VIII)—A solution of the foregoing acid (5.3 g.) in xylene (50 cc.) was refluxed in an oil bath for 15 hr. until the evolution of CO_2 had ceased. When cool, the reaction solution was washed with 5% NaOH and H_2O, dried, and the solvent was removed.

[*4] The crude base was used throughout this experiment, since its purification was attended with difficulty and a great loss of material.

The residual syrup formed colorless pillars of m.p. 138~139° when purified from EtOH; yield, 3.0 g. or 65%. *Anal.* Calcd. for $C_{18}H_{21}O_3N$: C, 72.2; H, 7.1; N, 4.7. Found : C, 72.4; H, 7.2; N, 4.7. IR cm^{-1} : $\nu_{C=O}$ 1681 (s), 1704 (m) (Nujol). UV λ_{max}^{EtOH} mμ (log ε) : 233 (4.01), 283.5 (3.64).

8-Oxo-15,16-dimethoxyerythrinane (IX)—A solution of the afore-mentioned compound (VIII) (1.3 g.) in EtOH (65 cc.), acidified with AcOH was reduced catalytically over Adams' Pt catalyst, ca. 1 molar equivalent of H_2 being absorbed. The resultant syrup was dissolved in benzene, washed with $NaHCO_3$ solution and H_2O, dried, and the solvent was removed. The residue solidified on being treated with petr. ether, m.p. 114~118° (1.2 g. or 91.7%), and was purified from EtOH to form colorless pillars, m.p. 117~118°. *Anal.* Calcd. for $C_{18}H_{23}O_3N$: C, 71.7; H, 7.7; N, 4.65. Found : C, 71.55; H, 8.0; N, 4.65. IR : $\nu_{C=O}$ 1681 cm^{-1} (Nujol). UV : λ_{max}^{EtOH} 284 mμ (log ε 3.61).

15,16-Dimethoxyerythrinane (X)—The above-mentioned compound (IX, 0.7 g.) in pure ether (120 cc.) was added dropwise into a solution of $LiAlH_4$ (0.4 g.) in pure ether (140 cc.) during 30 min. with ice cooling (reaction solution at 6~8°). The mixture was refluxed for an additional 1 hr. and worked up as usual to yield a colorless syrup; yield, 0.65 g. or 97.4%. This was characterized as the picrate of yellow prisms (from EtOH), m.p. 177~179°. *Anal.* Calcd. for $C_{24}H_{28}O_9N_4$: C, 55.8; H, 5.5; N, 10.85. Found : C, 55.7; H, 5.5; N, 11.2.

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Summary

A new synthesis of 15,16-dimethoxyerythrinane was described. 3,4-Dimethoxyphenethylamine was condensed with cyclohexane-1,2-dione in the presence of phoshoric acid to yield the basic spiroketone (II), which was converted into N-ethoxycarbonylacetyl derivative (IV′) by the conventional method. The latter was cyclyzed by means of sodium hydride in boiling ethanol to give the dehydrated tatracyclic compound (VII) in a good yield. The decarboxylation product (VIII) of (VII) was reduced catalytically to furnish (IX), which on being reduced with lithium aluminum hydride gave rise to 15,16-dimethoxyerythrinane (X).

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