Studies on the Syntheses of Heterocyclic Compounds. Part CCCXV (1) Erythrinan and Related Compounds. II (2). An Alternative Synthesis of *cis*-16-Hydroxy-15-methoxyerythrinan-8-one and Its Mass Spectrum

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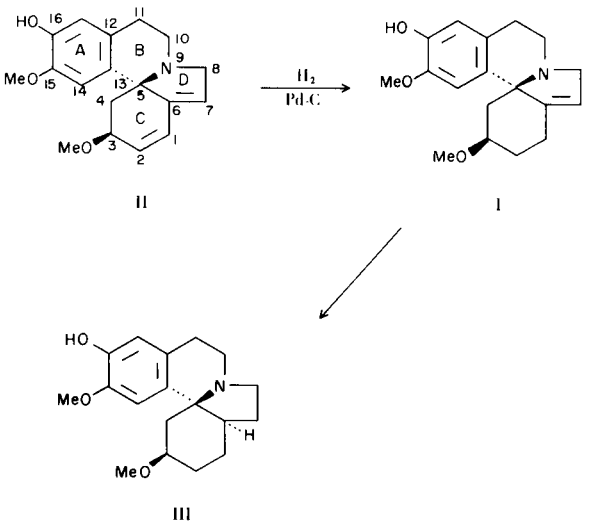
Phenolic cyclization of 2-ethoxycarbonylmethylidenecyclohexanone (IV) with 3-hydroxy-4-methoxyphenethylamine (V) were performed in the process of finding a synthetic approach to dihydroerysolidine (I). Thus, 16-hydroxy-15-methoxyerythrinan-6-ene-8-one (VI) and 16-hydroxy-15-methoxyerythrinan-7-ene-8-one (VII) were synthesized, both of which were hydrogenated in the presence of Adams platinum to give the same product (XI). Furthermore, on the basis of the mass spectra of XI and XII, these compounds were assumed to be stereoisomeric at the C_5- and C_6-positions.

Dihydroerysolidine (I) was isolated from *Cocculus laurifolius* as colorless needles, m.p. 208-209°, by Tomita and Yamaguchi (4). Its structure was confirmed by comparison with the partial hydrogenation product from natural erysolidine (II) (4,5,6) and also by comparison of its reduction product with tetrahydroerysolidine (III) derived from erysolidine (II).

SCHEME 1



The purpose of the present investigation was to study the phenolic cyclization (7,8) of 2-ethoxycarbonylmethylidenecyclohexanone (IV) with 3-hydroxy-4-methoxyphenethylamine (V), leading to a synthetic approach to I. Thus, 16-hydroxy-15-methoxyerythrinan-6-ene-8-one (VI) and 16-hydroxy-15-methoxyerythrinan-7-ene-8-one (VII) were synthesized.

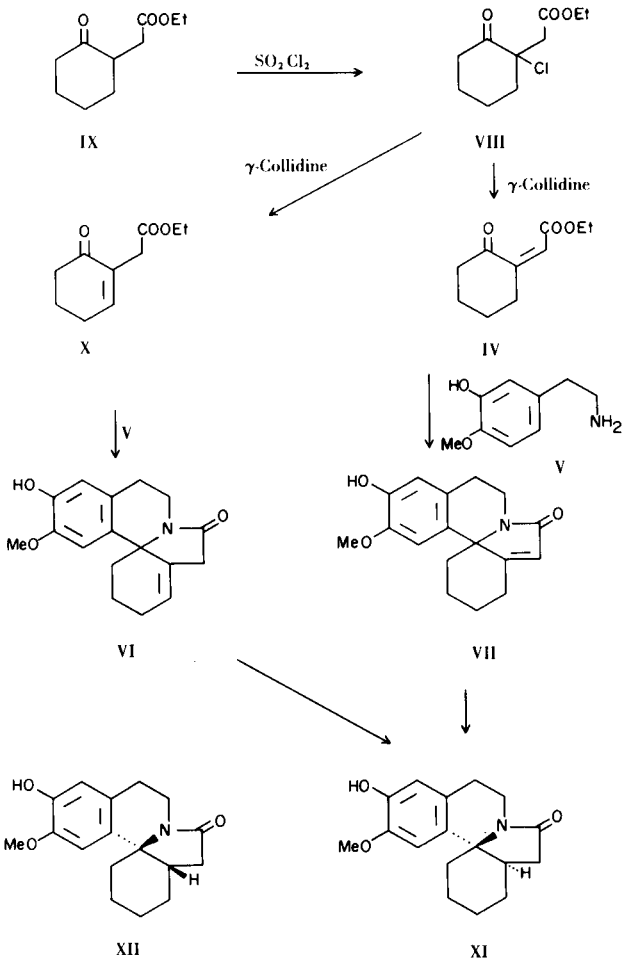
Dehydrochlorination of the chloride (VIII) (9), which had been obtained by chlorination of 2-ethoxycarbonylmethylcyclohexanone (IX) with sulfuryl chloride, was carried out by refluxing in γ-collidine affording a mixture of unsaturated compounds, b.p.$_2$ 100-110°. The mixture was separated by chromatography on silicic acid to give 2-ethoxycarbonylmethylcyclohex-2-enone (X), b.p.$_5$ 120-122° and 2-ethoxycarbonylmethylidenecyclohexanone (IV), b.p.$_2$ 106-108°. The ir spectrum (in chloroform) of the former compound (X) showed carbonyl bands at 1722 and 1670 cm^{-1}, and the nmr spectrum (in deuteriochloroform) showed methyl protons centered at 1.26 ppm as a triplet, two methylene protons at 4.10 ppm and 3.80 ppm and an olefinic proton as a triplet at 6.88 ppm. This data revealed that this compound had the structure of X. On the other hand, the latter compound (IV) showed carbonyl bands at 1706 and 1685 cm^{-1} in its ir spectrum (in chloroform), and methyl protons as a triplet centered at 1.28 ppm, methylene protons as a quartet at 4.12 ppm and an olefinic proton at 6.37 ppm in its nmr spectrum.

Phenolic cyclization of X with V in ethanol in a current of nitrogen was carried out as usual to give an orange syrup, which was purified by chromatography on silicic acid. The ir spectrum (in chloroform) of this compound showed the carbonyl band at 1672 cm^{-1} and the hydroxyl group at 3500 cm^{-1}. Furthermore, the nmr spectrum (in deuteriochloroform) showed the protons of

the methoxyl group at 3.82 ppm, and the olefinic proton at 6.72 ppm as a multiplet. These facts support the structure of VI.

The same reaction of IV with V afforded another erythrinanone (VII), which showed the carbonyl band at 1668 cm^{-1} and the hydroxyl group at 3500 cm^{-1} in its ir spectrum. The nmr spectrum (in deuteriochloroform) of VII also showed the protons attributable to the methoxyl group at 3.82 ppm and the olefinic proton as a broad singlet at 6.60 ppm.

SCHEME 2

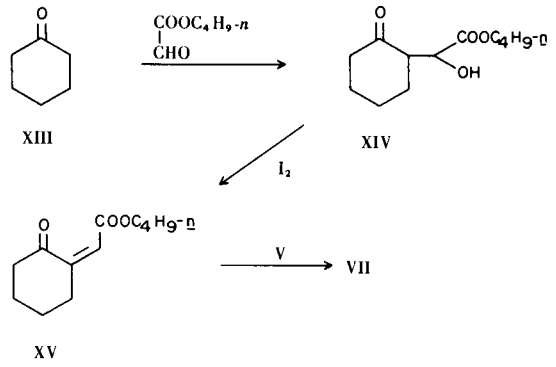


Catalytic hydrogenations of both VI and VII were carried out in the presence of platinum to give stereoselectively, the *cis*-16-hydroxy-15-methoxyerythrinan-8-one (XI), which had already been synthesized in our laboratory (2). This fact is in accord with the formation of only the *cis*-iosmer in the case of catalytic hydrogenation of erysotrine (10,11,12,13,14). Thus an alternative synthesis of the compound (XI) had been accomplished by phenolic cyclization.

Since the compound (IV) was obtained as the minor product in the case of dehydrochlorination of VIII and the total yield of the dihydroerysolidine-type compound having a double bond at the *endo*-position of the D ring was so low, the following precedure was adopted.

Knoevenagel reaction of cyclohexanone (XIII) with butyl glyoxalate (15) in the presence of pyridine afforded the hydroxyketone (XIV), which was dehydrated with iodine to give 2-butoxycarbonylmethylidenecyclohexanone (XV).

SCHEME 3



The phenolic cyclization of V with XV by refluxing in butanol afforded a dark reddish oil, which, after washing with hexane, was chromatographed on silicic acid to give a syrup. The chemical and physical data of this compound were identical with those of the sample (VII) which was obtained by phenolic cyclization of V with VI as above.

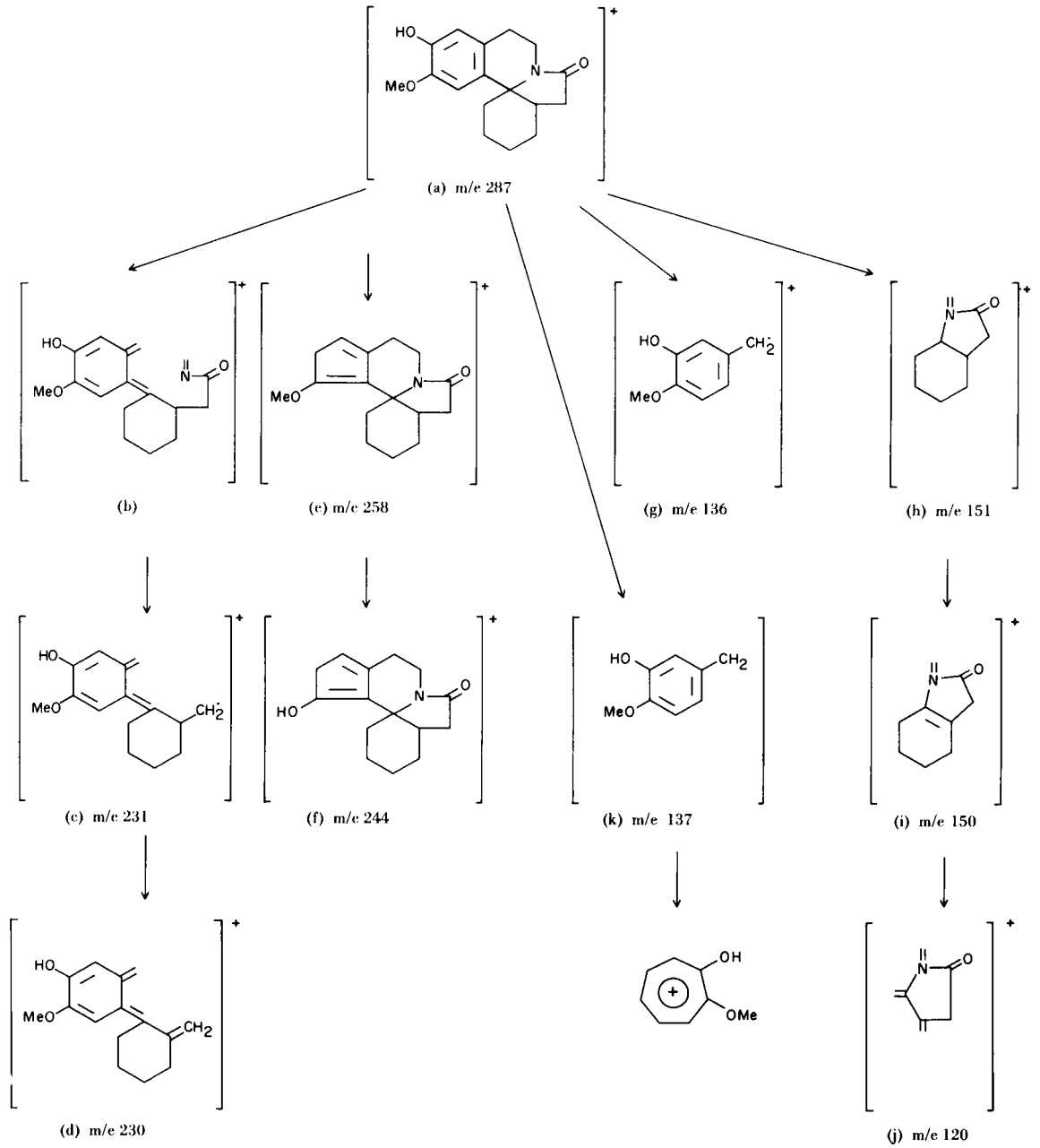
The following mass spectra also support the structures of XI and XII, which are thought to be diastereomeric at the C_5- and C_6-positions.

The molecular ion (a) which appeared at m/e 287, afforded the ion (b) by retro Diels-Alder cleavage, and it is characteristic that the ion peak (M^+ - 1) observed in almost all the 1-substituted isoquinoline derivatives is not shown.

These facts reveal that phenolic cyclization affords the isoquinoline nucleus and that it has a spiro-ring at the C_5-position. Furthermore, both mass spectra of XI and XII showed the same fragmentation patterns, but the relative intensities were different from each other. This fact supports the assumption that these compounds are stereoisomers.

The intermediate ion (b) which was obtained from the retro Diels-Alder type cleavage of the M^+ ion at m/e 287 was converted into the ion (c) at m/e 231. Deprotonation of the ion (c) gave the ion (d) at m/e 230. Further expulsion of HCO from the M^+ ion (a) afforded the ion

SCHEME 4



(e) at m/e 258, which was converted into the ion (f) at m/e 244 by the expulsion of a CH_2 group.

Furthermore, the ion (g) (m/e 136) and ion (h) (m/e 151) were also formed from the molecular ion (a) through β-cleavage at the nitrogen atom. Loss of one proton from the ion (h) gave the ion (i) at m/e 150. Further retro Diels-Alder cleavage of the ion (i) afforded the ion (j) at m/e 120. On the other hand, direct β-cleavage of M^+ ion followed by rearrangement of hydrogen afforded the above ion (i) and the (k) (m/e 137).

Although the base peak appears at m/e 150, it is scaled out. Therefore, the abundance of the ion peak at m/e 151 is estimated as 100%, and the relative intensities are shown in Table I.

TABLE I

The Mass Spectra of The Erythrinanone Derivatives. (XI) and (XII).

m/e	XI	XII
287	75	58.9
258	2.7	0.52
244	72.2	8.42
231	11.8	2.1
230	11.8	2.1
151	100	100
150	>100	>100
137	88.9	74.8
136	19	10.5
120	12.5	7.36

EXPERIMENTAL (16)

Dehydrochlorination of Ethyl 2-Chlorocyclohexanon-2-acetate (VIII).

A mixture of 25 g. of VIII and 16.5 g. of γ-collidine was heated at 180-190° in an oil-bath for 45 minutes and γ-colliding hydrochloride was thus precipitated as colorless crystals. After the reaction mixture had been cooled, the crystals were collected by filtration and the filtrate was extracted with 100 ml. of ether. The extract was washed with water and then 50 ml. of 10% hydrochloric acid, dried over sodium sulfate, and evaporated to give a pale reddish liquid, which was distilled to give 16 g. of a colorless oil, b.p.$_2$ 100-110°. Thin layer chromatography on silica gel using chloroform-benzene (5:2) as an eluant showed two spots, R_f 0.64 and R_f 0.2.

Chromatography of 9.43 g. of the above mixture on 80 g. of silicic acid using chloroform was performed. Evaporation of the first eluate (160 ml.) afforded 1.5 g. of the substance showing R_f 0.64, which was then distilled to give 1 g. of IV as a colorless oil, b.p.$_2$ 106-108° (17). Infrared ν max (chloroform) cm^{-1}, 1706 (C=O), 1685 (C=O); nmr (ppm) (deuteriochloroform), 1.28 (3H, triplet, J = 6 cps, CH_3), 4.12 (2H, quartet, J = 6 cps, $-CH_2$), 6.37 (olefinic proton).

After removal of 320 ml. of the fraction which showed two spots, evaporation of the successive eluant afforded 3 g. of X as a colorless oil, b.p.$_5$ 120-122° (17). Infrared ν max (chloroform) cm^{-1}, 1722, 1670 (C=O); nmr (ppm) (deuteriochloroform), 1.26 (3H, triplet, CH_3), 4.10 (2H, quartet, $-OCH_2-$), 3.80 (2H, broad singlet, $CO-CH_2-$), 6.88 (olefinic proton).

16-Hydroxy-15-methoxerytyrinan-7-ene-8-one (VII).

A solution of 0.7 g. of IV and 0.7 g. of V in ethanol was refluxed on a water-bath for 12 hours. After the reaction, removal of the solvent by distillation in a current of nitrogen afforded a reddish syrup, which was washed several times with hexane. Chromatography of the above residue on 15 g. of silicic acid using the mixture (chloroform:methanol, 10:1) as an eluant gave 0.3 g. of an orange syrup, which could not be crystallized. Infrared ν max (chloroform) cm^{-1}, 3500 (OH), 1668 (C=O); nmr (ppm) (deuteriochloroform): 3.82 (3H, singlet, OCH_3), 4.37 (1H, OH), 6.60 (1H, broad singlet, olefinic proton).

16-Hydroxy-15-methoxyerythrinan-6-ene-8-one (VI).

A solution of 0.5 g. of X and 0.5 g. of V in ethanol was refluxed on a water-bath for 12 hours. Following the reaction, evaporation of the solvent in a current of nitrogen gave a dark reddish syrup, which was washed with hexane and then extracted with chloroform. After filtration, evaporation of the extract in a current of nitrogen afforded 0.8 g. of a reddish syrup, which was chromatographed on 10 g. of silicic acid. Evaporation of the chloroform eluate afforded 0.11 g. of a syrup, which could not be crystallized. Infrared ν max (chloroform) cm^{-1}, 3500 (OH), 1672 (C=O); nmr (ppm) (deuteriochloroform): 3.82 (3H, singlet, OCH_3), 4.09 (1H, singlet, OH), 6.72 (1H, multiplet, olefinic proton).

Catalytic Hydrogenation of 16-Hydroxy-15-methoxyerythrinan-6-ene-8-one (VI) and 16-Hydroxy-15-methoxyerythrinan-7-ene-8-one (VII).

To a suspension of platinum-catalyst prepared in the usual manner from 25 mg. of platinum oxide in 10 ml. of methanol, was added a solution of 100 mg. of VI in 10 ml. of methanol, and the mixture was hydrogenated at room temperature and atmospheric pressure for 2 days, during which time the calculated amount of hydrogen was absorbed. After removal of the catalyst by filtration the resultant solution was distilled *in vacuo* in a current of nitrogen to give a pale orange syrup, which was washed with hexane. Recrystallization from ethanol-ether afforded 20 mg. of colorless needles, m.p. 120-124°. This compound was identical with an authentic *cis*-16-hydroxy-15-methoxyerythrinan-8-one (XI) (2) based on nmr spectrum, R_f values, and a mixed melting point test.

Using the same procedure as above, catalytic hydrogenation of 150 mg. of VII using 50 mg. of platinum oxide afforded 100 mg. of a compound which was identical to the compound (XI) obtained above.

The Reaction of Cyclohexanone (XIII) with Butyl Glyoxalate.

A mixture of 7.5 g. of butyl glyoxalate, 9.4 g. of cyclohexanone, 20 ml. of pyridine, and 2 ml. of piperidine was heated on a water-bath for 4 hours and then refluxed in an oil-bath for 30 minutes. After cooling, the reaction mixture was extracted with 50 ml. of ether. The extract was washed with 10% hydrochloric acid and water, dried over sodium sulfate, and evaporated to give a syrup, which was distilled *in vacuo* to give 2 g. of the compound (XIV) as a colorless oil, b.p.$_7$ 148-150°. Infrared ν max (chloroform) cm^{-1}, 3500 (OH), 1725 (C=O), 1701 (C=O); nmr (ppm) (deuteriochloroform): 4.13 (2H, triplet, J = 6 cps, $-OCH_2CH_2-$), 4.60 (1H, doublet, J = 3 cps, $-CH(OH)-COOCH_2-$), 3.21 (1H, singlet, -OH, disaopeared on substitution with deuterium oxide).

2-Butoxycarbonylmethylidenecyclohexanone (XV).

A mixture of 2 g. of XIV, 0.5 mg. of iodine, and 20 ml. of dry benzene was refluxed on a water-bath for 4 hours. After the reaction mixture had been cooled, it was washed with saturated sodium thiosulfate solution and then water, dried over sodium sulfate and evaporated to give a syrup, which was distilled *in vacuo* to give 1 g. of the compound (XV) as a colorless oil, b.p.$_{3-4}$ 100-105°. Infrared ν max (chloroform) cm^{-1} 1753 (C=O); nmr (ppm) (deuteriochloroform): 4.01 (2H, triplet, J = 6 cps, $-COOCH_2CH_2-$), 5.76 (1H, doublet, J = 2 cps, olefinic proton).

Anal. Calcd. for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63. Found: C, 68.70; H, 8.52.

The Reaction of V with XV.

A mixture of 0.3 g. of V, 0.3 g. of XV, and 10 ml. of *n*-butanol was heated on a water-bath for 24 hours and the solvent

was removed by distillation in a current of nitrogen to give 0.7 g. of a dark reddish syrup, which after washing with hexane, was chromatographed on 6 g. of silicic acid. Evaporation of the chloroform eluant afforded 100 mg. of VII as a pale orange syrup, which was identical with the above authentic sample (VII) based on spectral data.

Acknowledgments.

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(16) All melting points are uncorrected. Infrared and nmr spectra were measured on type EPI-3 Hitachi recording spectrophotometer and H-60 Hitachi spectrophotometer, respectively. The mass spectra were measured with a Hitachi spectrometer RMU-6D equipped with a direct inlet system: accel. voltage, 1700 v; chamber voltage, 70 v; total emission, 80 μA; target current, 60 μA; evaporation temp., 170°; ion-chamber temp., 250°.

(17) Since these compounds could not be crystallized, the oil obtained was used in the succeeding reaction.

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