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On the Structures of the Methylation Products of Sepedonin Derivatives with Diazomethane

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Synopsis

Methylation of anhydrosepedonin and deoxysepedonin with diazomethane afforded three different kinds of dimethyl ethers. The structures of these ethers were examined by their reaction with liquid ammonia, and long-range coupling between methoxyl protons and the adjacent ring proton by nmr spectra from which the structures of 3,4-dimethoxy, 2,6-dimethoxy, and 2,4-dimethoxy derivatives were clarified. The mass spectra of these dimethyl ethers showed the difference in the position of these methoxyls.

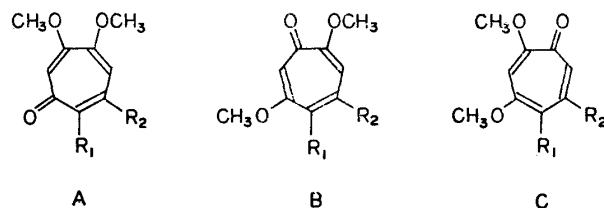
I. Introduction

It has been known for a long time that methylation of asymmetric tropolone by diazomethane gives two kinds of methyl ethers which have been separated and their structures determined.^(1,2,3) When a substituent is hydroxyl group, the situation becomes more complicated, because of tautomerism.⁽⁴⁾ In fact, experiments have shown that one kind of 5-hydroxytropolone dimethyl ether is formed (5). In this case, one of the expected compound, 4,5-dimethoxytropolone has not been known. In the case of 4-hydroxytropolone, there is a possibility for the formation of three kinds of dimethyl ethers, but only two have been obtained, the one being 2,4-dimethoxy and the other 2,6-dimethoxy compounds, and the presence of 3,4-dimethoxytropolone has not been proved.⁽⁶⁾

On the other hand, anhydrosepedonin (I), a derivative of 4-hydroxytropolone, has been isolated from *Sepedonium chrysospermum* by Divekar *et al.* They reported that application of diazomethane to I afforded two kinds of dimethyl ethers, one of which was labile and changed into a stable form.⁽⁷⁾

It is difficult to consider from chemical point of view that this change of the labile dimethyl ether is the mutual conversion of one of the forms of A, B and C.

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- (1) T. Nozoe, S. Seto, T. Ikemi and T. Arai, Proc. Japan Acad., **27** (1951), 102.
 - (2) T. Nozoe, S. Seto *et al.*, Proc. Japan Acad., **28** (1952) 192.
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 - (4) Y. Kitahara, Sci. Repts. Tohoku Univ., Ser. I, **39**, (1956) 265.
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 - (7) P.V. Divekar, H. Raistrick, Can. J. Chem., **43** (1965) 1835.



Therefore, structural determination of these dimethyl ethers was carried out under the assumption that these two kinds of dimethyl ethers and the stabilized dimethyl ether may be assigned to these A, B and C forms. For the structural determination of these dimethyl ethers, reaction with liquid ammonia was first carried out. In general, only 2-methoxytropone derivatives are known to react with liquid ammonia to form 2-aminotropone derivatives.⁽⁸⁾ In the second place, it is known that methoxyl group and the adjacent ring proton undergo a very small long-range coupling,⁽⁹⁾ and this phenomenon has been known to occur in tropolone derivatives.⁽¹⁰⁾ Therefore, this was also utilized for this structural determination. Since the fragmentation of the mass spectrum of 2-methoxytropone is known,⁽¹¹⁾ the comparison of the fragmentation pattern of these dimethyl ethers was also an important measure.

II. Results

Anhydrosepedonin (I) was obtained by the culture of *S. chrysospermum* according to the method of Divekar et al.⁽⁷⁾ Deoxysepedonin (II) was obtained by the catalytic reduction of I in ethanol over palladium-carbon. 4-Hydroxy-5-methyl-6-acetyl-tropolone (III) was obtained by treatment of I with hydrogen iodide in acetic acid.⁽¹²⁾

Application of diazomethane to I, II and III in methanol gave dimethyl ethers in quantitative ratios listed in Table I.

As will be clear from Table I, the yields of IC and IIC were extremely low. Catalytic reduction of IA, IB and IC in ethanol over palladium-carbon resulted in absorption of 1 mole of hydrogen and gave IIA, IIB and IIC, respectively.

In order to obtain the structural evidences of these ethers, the derivatives which have at least one methoxyl group at the known position in the tropolone ring are necessary. For this purpose, the procedure via the difluoroboron derivative^(13,14) was chosen, because these derivatives which have the chelate

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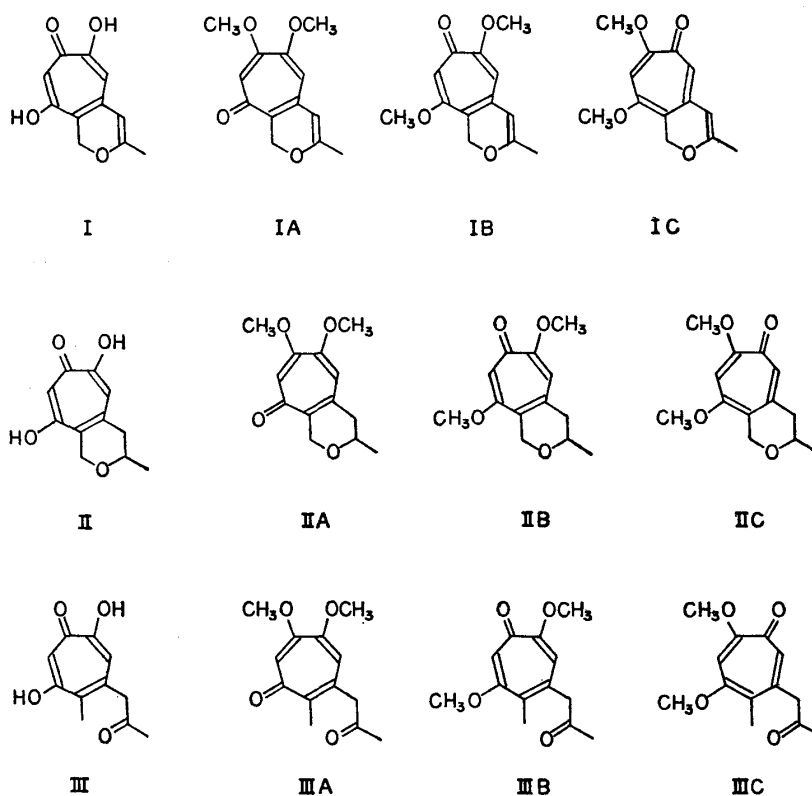


Table I. Formation Ratios of Dimethyl Ethers.

	A Form	B Form	C Form
I	45%	48%	7%
II	48%	48%	4%
III	57%	43%	*
IV	0%	91%	9%
V	0%	88%	12%

* Isolation of this compound was unsuccessful.

structure are known very stable and by the use of them, it is possible to effect selective methylation of the hydroxyl at 4-position alone. Monomethoxyl derivatives IV and V were prepared by the route shown in Chart I.

Addition of excess boron trifluoride etherate to I and washing with water resulted in the liberation of difluoroboron group bonded to the 4-position and a complex formed at 2-position alone was obtained. Addition of diazomethane to this complex (IX) resulted in methylation of the 4-position and hydrolysis of its product (X) by heating in 6N sodium hydroxide gave the 4-methoxy compound (IV). 4-Methoxy compound (V) was also prepared via compounds (XI and XII) in the similar manner. Methylation of IV and V with diazomethane afforded IB and IIB respectively in the majority and formation of C form was extremely small. As a matter of course, IA and IIA were not formed at all. This result supports that IA and IIA have the assigned structures.

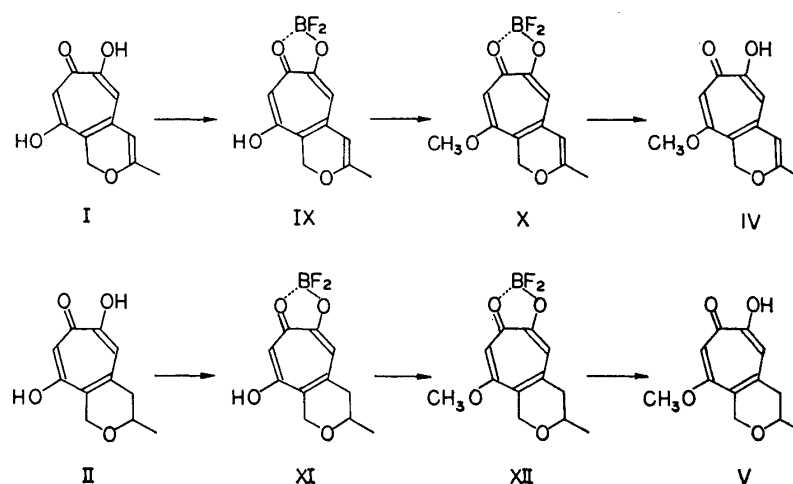


Chart I. Derivation of 4-Methoxyl Derivatives.

Furthermore, identification of the dimethyl ethers of I, II and III was carried out through the ir spectra. As shown in Fig. I, A, B and C forms show characteristic patterns in the region of $1600\text{--}1500\text{ cm}^{-1}$.

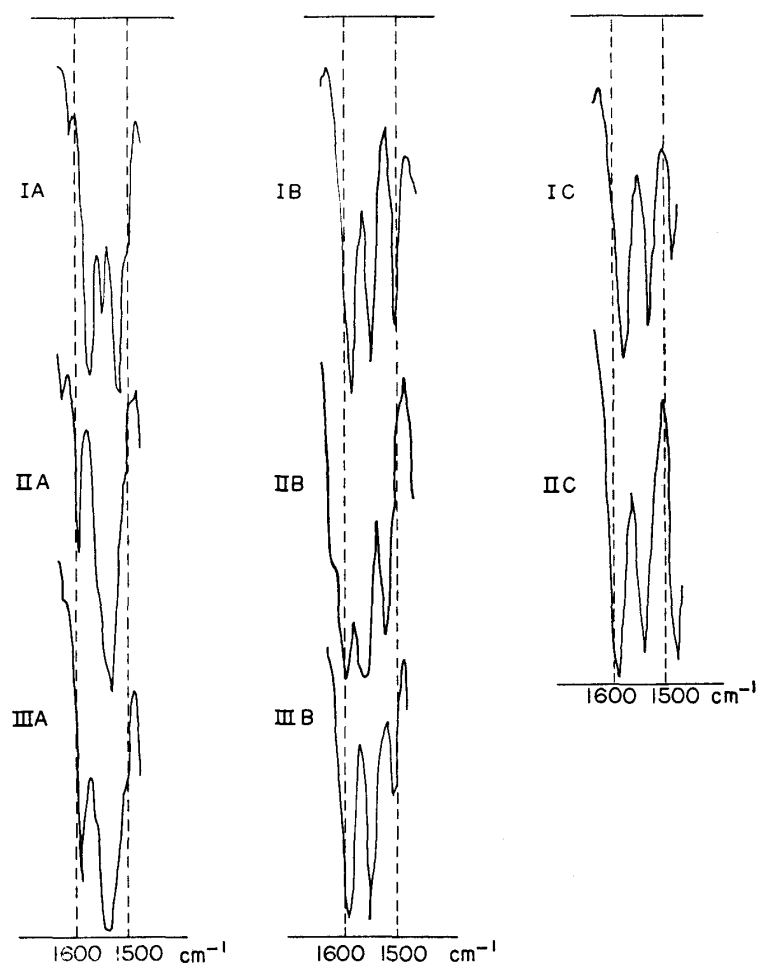


Fig. I. Characteristic Patterns of IR Spectra (KBr disk.)

Ultraviolet absorption spectra of the dimethyl ethers of I are fairly different from that of the dimethyl ethers of 4-hydroxytropone showing the influence of the presence of a double bond in a side chain, but the spectra of the dimethyl ethers of II and III are very similar to that of the dimethyl ether of 4-hydroxytropone. (Fig. II)

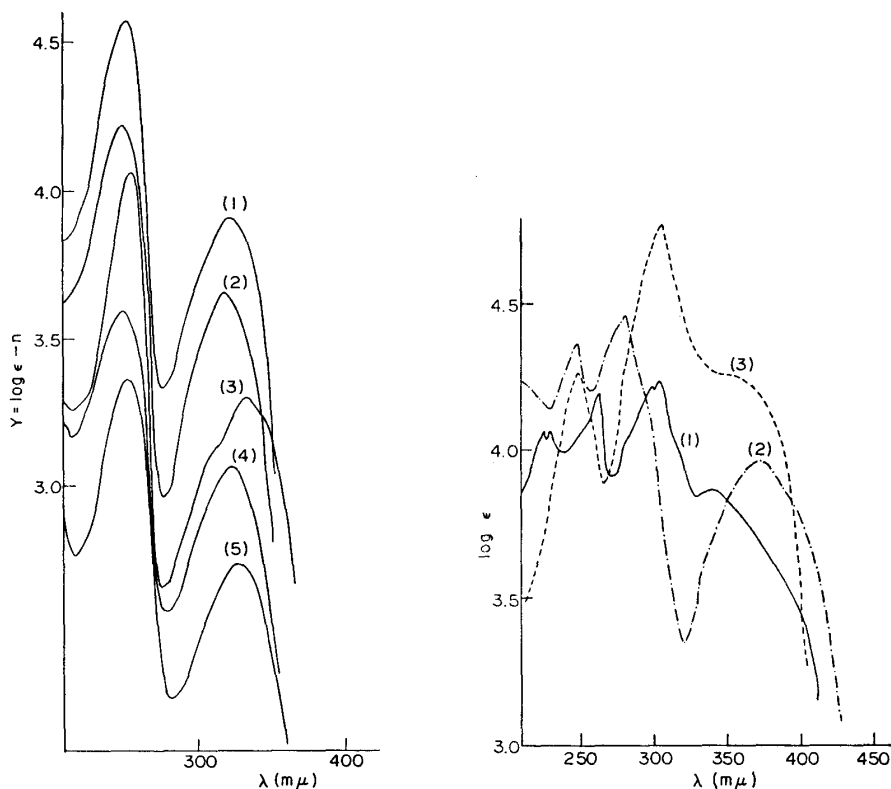


Fig. II. Ultraviolet Absorption Spectra (in MeOH)

Left: (1) IIA $Y = \log \epsilon$ (2) IIB $Y = \log \epsilon - 0.3$ (3) IIC $Y = \log \epsilon - 0.6$

(4) IIIA $Y = \log \epsilon - 0.9$ (5) IIIB $Y = \log \epsilon - 1.2$

Right: (1) IA ——— (2) IB —.—.— (3) IC - - - - -

Reaction of Dimethyl Ethers of I and II with Liquid Ammonia. IA, IB, IC, IIA, IIB and IIC were each placed in a large excess of liquid ammonia and allowed to stand at room temperature. Purification of the product from IA through alumina chromatography afforded a compound (VI) corresponding to the analytical values for $C_{13}H_{17}NO_4$ and its uv spectrum was similar to those of the dimethyl ethers of II and III which have no double bond in the side chain, unlike that of 2-aminotropone.

From this fact and consideration on its nmr spectrum (Fig. III), it was deduced that this product has structure (VI).

The products (VIIB) and (VIIC) obtained from IB and IC respectively corresponded to the analytical values for $C_{12}H_{13}NO_3$ and their uv spectra showed 2-aminotropone type. From these facts their structures were assumed as shown below:

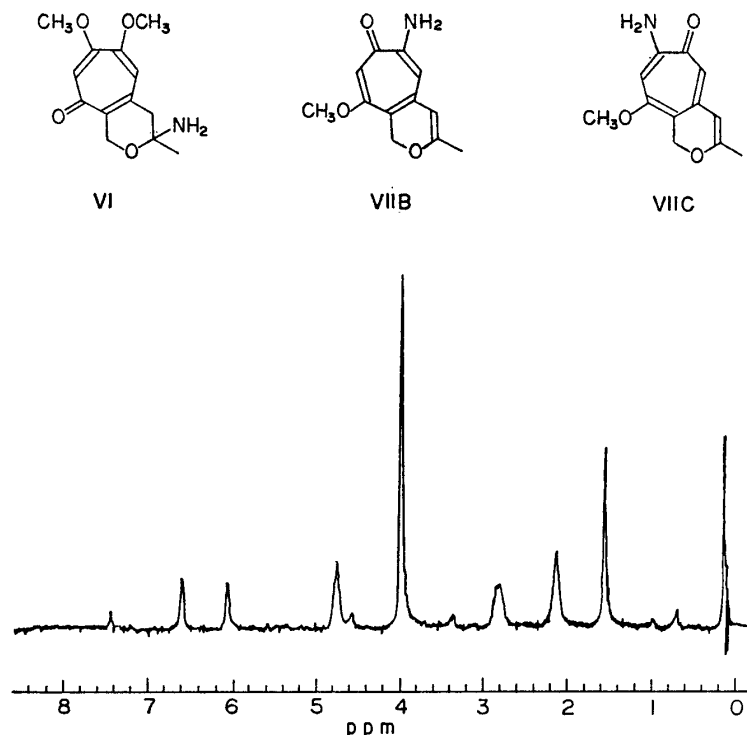
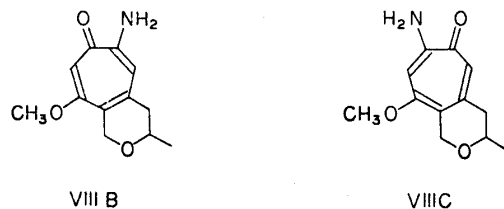


Fig. III. NMR Spectrum of VI

IIA failed to react with liquid ammonia and the starting material was recovered. IIB and IIC gave the compound (VIIIB) and (VIIC) corresponding to the analytical values of $C_{12}H_{15}NO_3$. From their uv spectra these compounds were assumed to be 2-aminotropone derivatives.



NMR Spectra of Dimethyl Ethers. Nmr spectra of IA, IB and IC, as shown in Fig. IV, V and VI, showed the methoxyl signals in the region of 3.70 to 4.00 ppm. The signals of spectrum of IA (Fig. IV) was assigned by decoupling technique as follows: Decoupling by irradiation of the signal at 5.27 ppm for methine proton on the double bond resulted in sharpening of the signal at 5.84 ppm, indicating that this signal can be assigned to the ring proton of C_5-H . Irradiation of the signal at 5.84 ppm resulted in sharpening of the methoxyl signal at 3.82 ppm, indicating that this signal can be assigned to the methoxyl of C_4-OCH_3 . The remaining signals at 6.48 and 3.78 ppm would respectively be assigned to the ring proton of C_2-H and the methoxyl of C_3-OCH_3 . Enlargement of the methoxyl signal region showed each signal separated into a doublet with a coupling

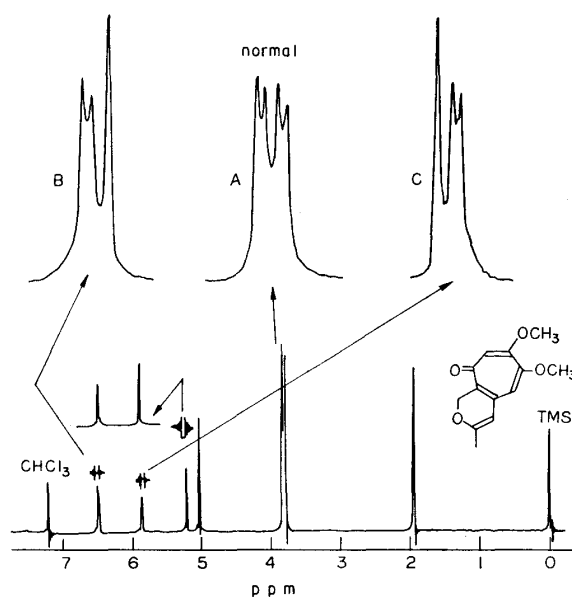


Fig. IV. NMR Spectra of IA

1.94 ($C_{10}-CH_3$), 3.78 (C_3-OCH_3), 3.82 (C_4-OCH_3), 5.05 ($C_{11}-H_2$), 5.27 (C_8-H), 5.84 (C_5-H) 6.48 ppm (C_2-H)

Signal A is the spreaded one of methoxyl region. The figure shows that signal A changes to signal B and C on irradiation at 6.48 and 5.84 ppm, respectively.

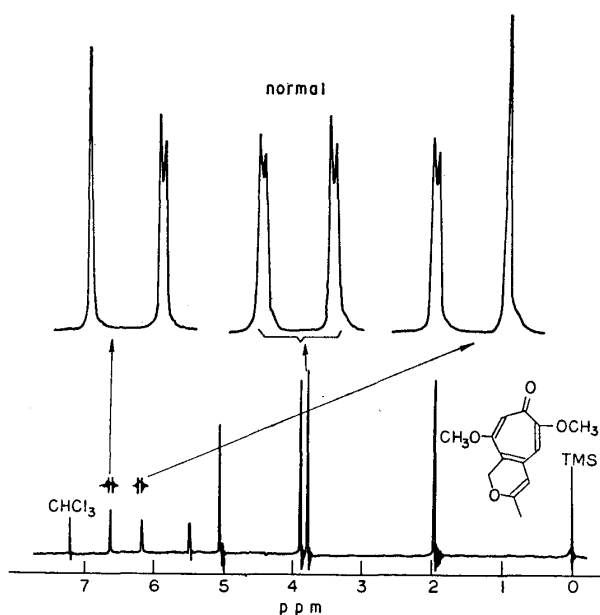


Fig. V. NMR spectra of IB

1.06 ($C_{10}-CH_3$), 3.79 ($C_{10}-CH_3$), 3.79 (C_1-OCH_3), 3.88 (C_4-OCH_3), 5.03 ($C_{11}-H_2$), 5.49 (C_8-H), 6.16 (C_5-H), 6.62 (C_2-H).

constant of 0.5–0.6 Hz. Irradiation of the ring protons at 5.84 and 6.48 ppm showed that one coupling of each methoxyl signal disappears, indicating that one each of ring protons is present adjacent to each of the methoxyl. In addition, from its reaction with liquid ammonia and from the result of the methylation of

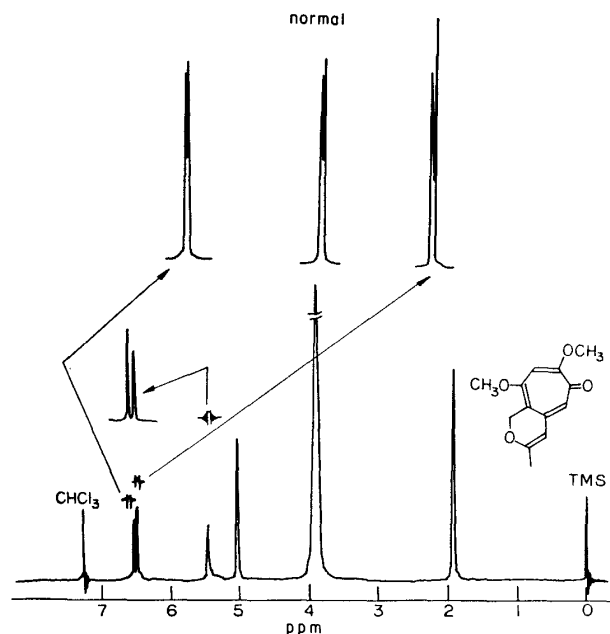


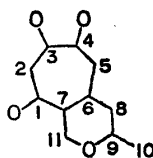
Fig. VI. NMR Spectra of IC (100 Mc)

1.95 ($C_{10}-CH_3$), 3.90 (C_1- or C_3-OCH_3), 3.92 (C_1- or C_3-OCH_3), 5.03 ($C_{11}-H_2$), 5.43 (C_8-H), 6.51 (C_2-H), 6.62 (C_5-H).

IV, it must be considered that IA is a 3,4-dimethoxytropone derivative.

The nmr spectra of IC are shown in Fig. VI.

Each of these signals was assigned as in the case of IA. In this case, irradiation of the ring proton of C_5-H at 6.62 ppm had no effect at all on the methoxyl signals at 3.90 and 3.92 ppm and any effect was observed only when the ring proton of C_2-H at 6.51 ppm was irradiated. Consequently, a compound which shows such a phenomenon must have a structure shown in Fig. VI,



Numbering for NMR Spectra

and this structure is therefore assigned to IC. At last, IB must be assigned to the formula shown in Fig. V, and the nmr spectra of IB support this structure. Decoupling of the ring proton of C_2-H at 6.62 ppm resulted in sharpening of the methoxyl signal of C_1-OCH_3 at 3.88 ppm, while decoupling of the ring proton of C_5-H at 6.16 ppm resulted in sharpening of the methoxyl signal of C_4-OCH_3 at 3.79 ppm, indicating the presence of one each of ring protons in the adjacent to each of the methoxyls.

The nmr spectra of IIA, IIB, IIC, IIIA and IIIB, as shown in Fig. VII, VIII, IX, X and XI, showed the same behavior as IA, IB and IC, respectively.

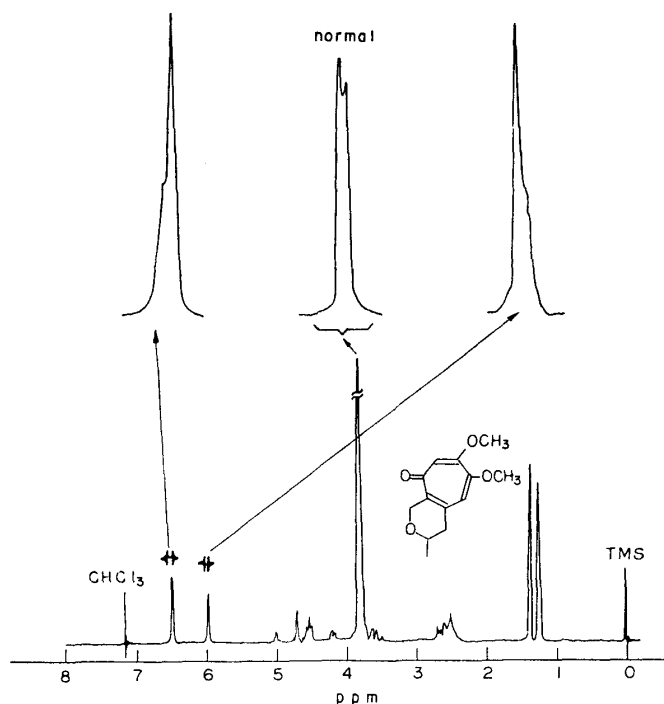


Fig. VII. NMR Spectra of IIA

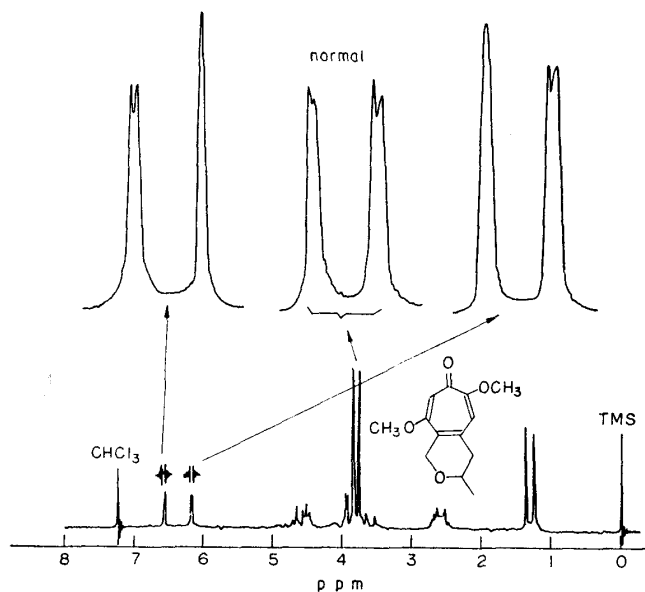


Fig. VIII. NMR Spectra of IIB

Mass Spectra of IA, IB, IC, IIA, IIB and IIC. Fragmentation of 2-methoxytropone has been reported to be as shown in Chart II. The most important decomposition is the loss of the methoxyl group to yield the m/e 105 species (A), and the elimination of carbon monoxide from the molecular ion, so characteristic of tropone and tropolone, occurs only to a minor extent.

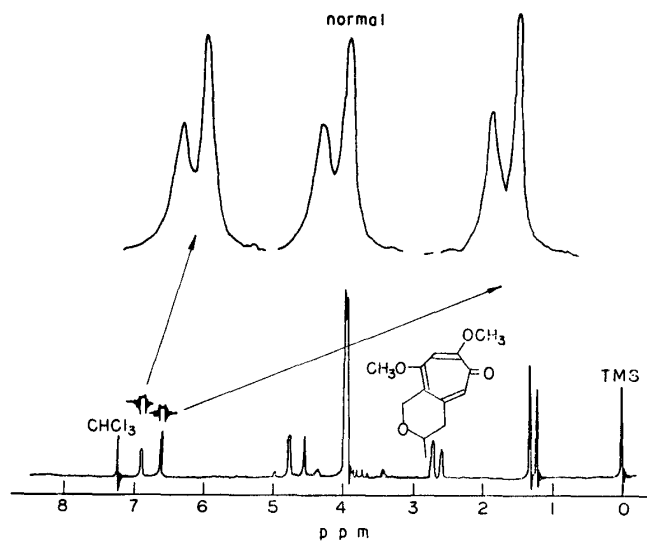


Fig. IX. NMR Spectra of IIC (100 Mc)

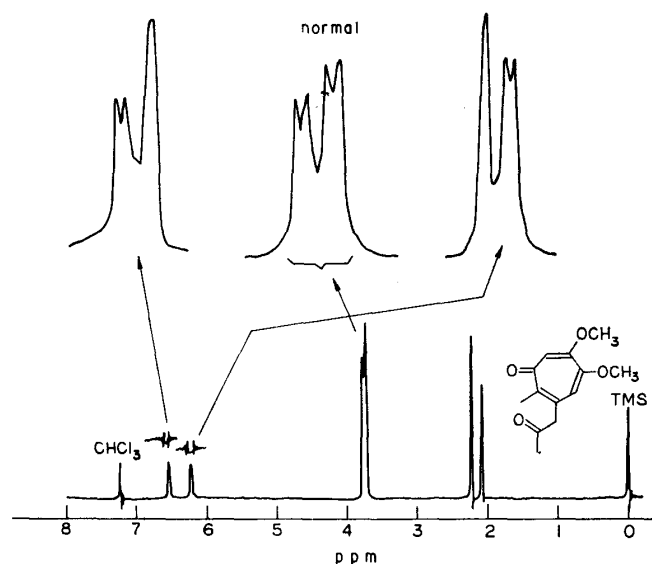


Fig. X. NMR Spectra of IIIA

In case of 3-methoxytropone⁽¹⁵⁾, fragmentation of parent ion m/e 136, gave only a major ion m/e 108 attributed to the process (C), and minor ions m/e 121, 107, 106 and 105. The decomposition of 3-methoxytropone is different from that of 2-methoxytropone on the point of the strength of each peak. A fragment peak (m/e 121) corresponding to the loss of a methyl radical is stronger than those of fragment ions m/e 107, 105 and 106.

The spectral features of three isomeric dimethyl ethers of anhydrosepedonin are entirely the same, but there is apparently a difference in the strength of their fragmental peaks. The percentage of each peak at $\Sigma 50$ of IA, IB, IC, IIA, IIB and IIC is listed in Table II.

(15) The authors' unpublished result.

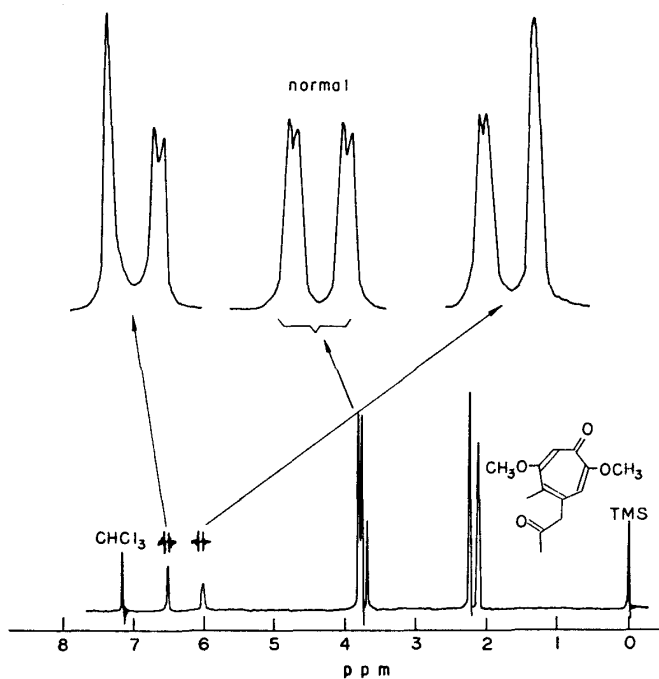


Fig. XI. NMR Spectra of III B

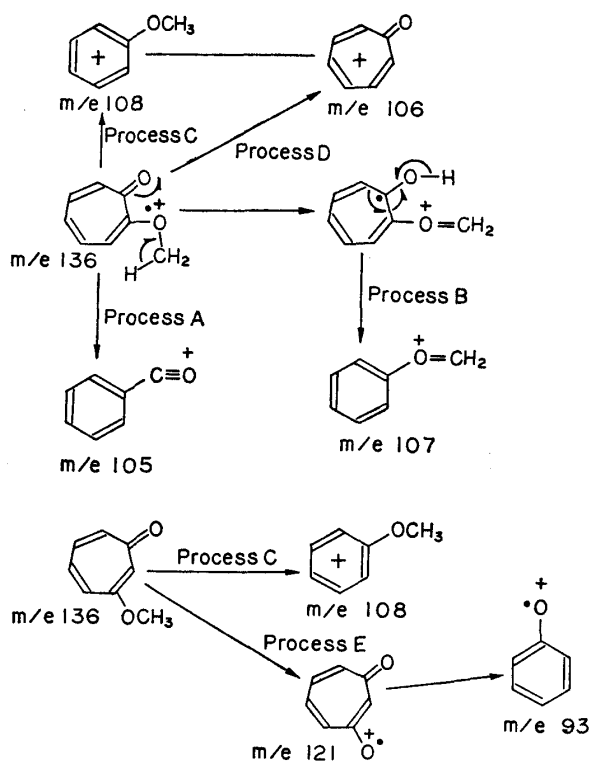


Chart II. Fragmentation of 2- and 3-Methoxytropones

Table II. Fragmentation of Dimethyl Ethers of Sepedonin Derivatives

m/e	IA	IB	IC	IIA	IIB	IIC
235/237	1.43	1.22	0.76	2.24	1.93	1.69
334/236	9.79	7.68	3.80	14.14	11.59	11.16
220/222	0.86	0.76	0.10	0.70	0.24	0.34
219/221	6.29	5.26	0.78	4.62	0.30	1.18
218/220					0.24	0.17
217/219					0.72	
206/208	2.15	5.80	8.19	1.26	1.20	1.01
205/207	3.00	14.12	11.79	1.96	6.28	5.75
204/206	0.29	0.53	0.26	0.42	0.97	1.18
203/205	1.00	1.45	0.52	0.70	2.90	3.55
202/204					0.24	0.17
201/203					0.48	0.34
192/194				1.54	0.48	0.34
191/193	13.85	2.90	5.18	11.06	1.45	1.69
190/192				1.96	0.97	1.86

The parent ion, m/e 234, gave ions m/e 219, 207, 206, 205, 203 and 191. The ion m/e 206 is attributed to the process (C) in case of 2-methoxytropone, and ions m/e 205, 204, 203 also to the process (B), (D) and (A), respectively. The ion corresponding to the loss of a methyl radical is also observed in case of 3-methoxytropone. Especially, the most important decomposition corresponding to the loss of methyl radical to yield the ion m/e 219 is shown in IA. Fragment ion m/e 219 was also observed in case of IB, but was minor in case of IC. These behaviors are reasonable, taking these structures into consideration. In case of IB and IC, the most important decomposition is the loss of formyl group to yield the m/e 205 species in contrast to 2-methoxytropone. In case of IA, the ion m/e 205 is also observed and this is thought to show that deformylation have taken place, with the participation of neighboring methylene.

Fragmentation of IIA, IIB and IIC also showed the characteristic pattern according to the structure, as shown in Table II.

III. Discussion

The structures of the dimethyl ethers of I, II, and III, the derivatives of 4-hydroxytropolone, were determined as described above. Up to the present, the methylation products of 4-hydroxytropolone had been considered to be the B and C forms, but the methylation products of II and III, which have no conjugated system in the side chain, are major of A and B forms, that of C form being minor. This fact suggests that there is a possibility of the methyl group at 4-position being interfered due to steric hindrance of the 5-methyl or methylene group. The methylation products of IV and V, the 4-methoxy compounds of I and II, are also in B form in the majority so that this steric hindrance must be denied. In other words, conjugation of 4-hydroxytropolone controls to some extent the formation ratio of these dimethyl ethers.

According to the theory of Ingold and others,¹⁶⁾ reaction with diazomethane is exothermic, and under such reaction condition, the formation ratio is affected by equilibrium rather than kinetic stability. It is matter of course that the formation will change by varying kinetic condition such as prolongation of reaction time or the use of dimethyl sulfate on sodium salt of 4-hydroxytropolone. Equilibrium of 4-hydroxytropolone will be represented as shown in Chart IV.

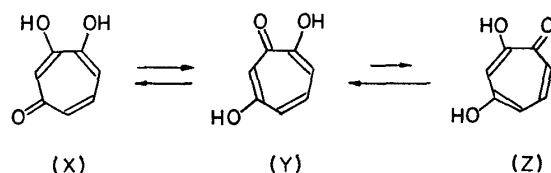


Chart IV. Equilibrium of 4-Hydroxytropolone

However, result of methylation reaction suggests that there is very little contribution of Z form. In other words, in the tautomerism of 4-hydroxytropolone, contribution of X and Y forms, i.e., β -diketone, is more predominant than that of Z form. In the methylation of 4-hydroxytropolone, the hydroxyl group in 1-position with the strongest acidity is first methylated, and the methylation of 2- and 4-positions follows in approximately 1:1 ratio.

IV. Experimental

All melting points are uncorrected. The ultraviolet spectra measured in methanolic solutions with a Cary Model 14 recording spectrometer. The infrared spectra were measured by KBr disk method with a Hitachi Model EPI-G2 spectrophotometer. The nmr spectra were recorded with Hitachi R-20 (60 Mc) and JOEL JUM-4H-100 (100 Mc) instruments with tetramethylsilane as an internal standard. The mass spectra were measured with a Hitachi Model RMU-6D mass spectrometer.

Anhydrosepedonin (I). Sepedonin, anhydrosepedonin, the metabolites of *Sepedonium chrysospermum*, were isolated from the cultures according to the method of Divekar et al.

Deoxysepedonin (II). Anhydrosepedonin (I) (433 mg) in 50 ml of ethanol and 5 ml of acetic acid was hydrogenated under the hydrogen atmosphere with 50 mg of palladium carbon as catalyst at room temperature. After absorption of an equivalent mole of hydrogen the solvent was evaporated under a reduced pressure and the residue was recrystallized from methanol to afford II, mp 234–235°C. Yield, 425 mg.

Found: C, 63.69; H, 6.01. Calcd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81%. UV: λ_{max} m μ (log ϵ); 254 (4.56), 325 (3.80).

(16) C.K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell University Press, New York (1953), p 565.

4-Hydroxy-5-methyl-6-acetylpropolone (III). A mixture of sependonin and anhydrosepedonin (700 mg), iodine (800 mg) and red phosphorus (800 mg) in 15 ml of acetic acid and 2 ml of water was refluxed for 7 hours. The resulting solution was concentrated to dryness and a residue was adjusted to pH 3 with 2N sodium hydroxide and small amount of sodium thiosulfate was added to the acidic solution. This solution was continuously extracted with ether for 48 hours. The white precipitate which was obtained from the ether layer was recrystallized from a mixture of methanol and benzene to give III, as colorless needles, mp 208–209°C. Yield, 643 mg.

Found: C, 66.87; H, 6.01. Calcd for $C_{11}H_{12}O_4 \cdot 1/3 C_6H_6$: C, 66.65; H, 6.02%. UV: λ_{max} m μ (log ϵ); 254 (4.52), 330 (3.81), 350 (3.71). IR: ν ; 3225, 1713, 1614, 1590, 903, 718 cm^{-1} .

The Dimethyl Ethers (IA, IB and IC) of Anhydrosepedonin. To a suspension of anhydrosepedonin (I) (710 mg) in a small amount of methanol, an ethereal solution of diazomethane was added until a portion of the solution was no longer colored with ferric chloride, and then the resulting solution was allowed to stand at room temperature overnight. A brownish yellow oil obtained by evaporation of the solvent was dried well and chromatographed on alumina by elution with ether. The first fraction gave IA as yellow needles after recrystallization from ether. The second fraction, which was obtained by elution with 10% ethyl acetate-ether, gave IB as yellow needles after recrystallization from ether. The third fraction, which was obtained by elution with 50% ethyl acetate-ether, gave yellow oil which was a mixture of IB and oily substance. The fourth fraction, which was obtained by elution with ethyl acetate, gave IC as yellow needles after recrystallization from a mixture of ether and ethyl acetate.

IA, mp 157–158°C, yield 139 mg. Found: C, 66.69; H, 6.17. UV: λ_{max} m μ (log ϵ); 225 (4.06), 231 (4.06), 261 (4.20), 300 (4.23), 308 (4.34), 341 (3.87).

IB, mp 147–148°C, yield 147 mg. Found: C, 66.78; H, 5.72. UV: λ_{max} m μ (log ϵ); 250 (4.27), 281 (4.47), 372 (3.96).

IC, mp 145–146°C, yield 21 mg. Found: C, 66.43; H, 6.28. Calcd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02%. UV: λ_{max} m μ (log ϵ); 249 (4.36), 308 (4.59), 350 (4.27).

The Dimethyl Ethers (II A, IIB and IIC) of Deoxysepedonin. To a suspension of deoxysepedonin (II) (136 mg) in a small amount of methanol, an ethereal solution of diazomethane was added until a portion of the solution was no longer colored with ferric chloride, and then the resulting solution was allowed to stand at room temperature overnight. A brownish yellow oil obtained by evaporation of solvent was dried well and chromatographed on alumina by elution with ether. The first fraction, which was obtained by elution with 10% ethyl acetate-ether, gave IIA as a colorless powder after recrystallization from a mixture of ethyl acetate and ether. The second fraction, which was obtained by elution with 5% methanol-ethyl acetate, gave IIB as a colorless powder after recrystallization from ethyl acetate.

IIA, mp 178.8–179.9°C, yield 72 mg. Found: C, 65.82; H, 6.45. UV: λ_{max} $m\mu$ ($\log \epsilon$); 253 (4.56), 324 (3.91).

IIB, mp 164.5–165.8°C, yield 71 mg. Found: C, 66.03; H, 6.57. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%. UV: λ_{max} $m\mu$ ($\log \epsilon$); 250 (4.51), 319 (3.95).

IIC, mp 198.5°C, yield 4 mg. Found: C, 65.99; H, 6.86. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%. UV: λ_{max} ($\log \epsilon$): 250 (4.52), 319 (3.95).

The Dimethyl Ethers (IIIA and IIIB) of 4-Hydroxy-5-methyl-6-acetonyltropolone.

To a suspension of 4-hydroxy-5-methyl-6-acetonyltropolone (III) (70 mg) in small amount of methanol, an ethereal solution of diazomethane was added until a portion of the solution was no longer colored with ferric chloride, and then the resulting solution was allowed to stand at room temperature overnight. A brownish yellow oil obtained by evaporation of the solvent was dried well and chromatographed on alumina by elution with ether. The first fraction gave IIIA as colorless needles after recrystallization from a mixture of ether and ethyl acetate. The second fraction, which was obtained by elution with ethyl acetate, gave IIIB as colorless needles after recrystallization from minimal ethyl acetate. IIIA, mp 144.5–145.5°C, yield 27 mg. Found: C, 66.14; H, 6.35. UV: λ_{max} $m\mu$ ($\log \epsilon$); 252 (4.49), 326 (3.97).

IIIB, mp 108–109°C, yield 20 mg. Found: C, 65.82; H, 6.35. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%. UV: λ_{max} $m\mu$ ($\log \epsilon$); 254 (4.57), 329 (3.93).

Catalytic Reduction of IA, IB and IC. A solution of the dimethyl ether (IB) (40 mg) in ethanol (20 ml), added with palladium-carbon (20 mg), was shaken in a hydrogen stream at room temperature. When the absorption of hydrogen had ceased, the catalyst was filtered off, the ethanol was evaporated from the filtrate under a reduced pressure, and the residue was recrystallized from a mixture of ether and ethyl acetate to give 25 mg of IIB.

The catalytic reduction of IA and IC was carried out in the same manner as above, and the products agreed with IIA and IIC, respectively.

Difluoroboron Compound (IX) of Anhydrosepedonin. To a suspension of anhydrosepedonin (I) (500 mg) in chloroform (50 ml) was added 1 ml of borontrifluoride etherate. The reaction mixture was allowed to stand overnight at 4°C, and evaporated under a reduced pressure. The residue was triturated with small amount of water, collected by filtration and washed with water. Then difluoroboron compound (IX) was obtained as a yellow powder, mp 217–219°C, yield 600 mg. UV: λ_{max} $m\mu$ ($\log \epsilon$); 224 (4.03), 247 (4.23), 258 (4.26 ref), 264 (4.29), 302 (4.46), 355 (3.81), 380 (3.81).

Methylation of IX. To a solution of 500 mg of the anhydrosepedonin derivative (IX) in 15 ml of methanol was added an ethereal solution of diazomethane until evolution of nitrogen had ceased. After standing overnight, the reaction mixture was evaporated under a reduced pressure and the residue was collected by filtration and washed with water. O-Methyl difluoroboron derivative (X) was obtained as a yellow powder, mp 227–229°C, yield 500 mg. UV: λ_{max} $m\mu$ ($\log \epsilon$); 248 (4.35),

260 (4.55), 320 (3.87).

Hydrolysis of O-Methyl Derivative (X). A solution of 300 mg of X in a mixture of 5 ml of ethanol and 10 ml of 6N sodium hydroxide was heated on a water bath for 6 hours and then acidified with 6N hydrochloric acid. After standing overnight in an ice box, crystals which separated out, were collected and washed with a small amount of water. Then the crystals were recrystallized from methanol to give IV (200 mg), mp 148–149°C.

Found: C, 65.23; H, 6.17. Calcd for $C_{12}H_{12}O_4$: C, 65.44; H, 5.49%. UV: λ_{max} $m\mu$ (log ϵ); 247 (4.25), 284 (4.47), 376 (3.83).

Methylation of IV. To a solution of 70 mg of IV in 5 ml of methanol was added an ethereal solution of diazomethane until the mixture had not shown any coloration with ferric chloride. After standing overnight at room temperature, the mixture was evaporated under a reduced pressure, the residue was placed on the top of an alumina column and eluted at first with ethyl acetate and then with a mixture of ethyl acetate and methanol. The first fraction, which was obtained by elution with ethyl acetate gave IB as a yellow powder. The second fraction which was obtained by elution with ethyl acetate and 2% methanol gave IC as a yellow powder. Yield: IB, 53 mg; IC, 5 mg.

Difluoroboron Compound (XI) of Deoxysepedonin. To a suspension of deoxysepedonin (II) (250 mg) in 25 ml of chloroform was added 0.5 ml of borontrifluoride etherate and the reaction mixture was allowed to stand overnight at 4°C. Evaporation under a reduced pressure gave a residual solid which was triturated with water, collected by filtration and washed with water. XI was obtained as colorless crystals, mp 235–236°C, yield 300 mg.

UV: λ_{max} $m\mu$ (log ϵ); 253 (4.53), 330 (3.91).

Methylation of XI. To a solution of 300 mg of XI in 10 ml of methanol was added an ethereal solution of diazomethane. After standing overnight at 4°C, the crystals separated out, was collected by filtration and washed with ether to give XII as pale yellow scales, mp 204–206°C, yield 250 mg.

UV: λ_{max} $m\mu$ (log ϵ): 254 (4.59), 307 (3.86), 334 (4.00).

Hydrolysis of XII. A solution of 500 mg of XII in a mixture of ethanol and 10 ml of 6N sodium hydroxide was heated on a water bath for 6 hours and then acidified with 6N hydrochloric acid to pH 1. After standing overnight in an ice box, crystals separated out, were collected by filtration, washed with water and recrystallized from a mixture of benzene and pet. ether to afford 300 mg of V, as pale yellow crystals, mp 157–158°C, yield 356 mg.

Found: C, 65.08; H, 6.62. Calcd for $C_{12}H_{14}O_4$: C, 64.85; H, 6.35%. UV: λ_{max} $m\mu$ (log ϵ); 253 (4.59), 260 (4.55 ref), 320 (3.87).

Methylation of V. To a solution of 200 mg of V in 5 ml of methanol was added an ethereal solution of diazomethane until the mixture had not shown any coloration with ferric chloride. After standing overnight at room temperature, the mixture was evaporated under a reduced pressure, the residue was placed on the

top of an alumina column and eluted at first with ether and then with a mixture of ethyl acetate and ether. The first fraction which was obtained by elution with ether gave IIB as a colorless powder. The second fraction which was obtained by elution with ethyl acetate gave IIC as a yellow powder.

Yield: IIB 152 mg; IIC 21 mg.

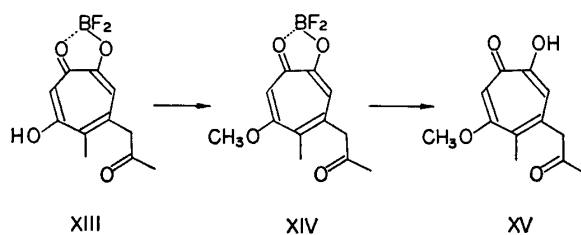
Diffuoroboron Compound (XIII) of III. To a solution of 50 mg of III in 5 ml of chloroform was added 0.1 ml of borontrifluoride etherate and the mixture was allowed to stand overnight at 4°C. After evaporation under a reduced pressure, the residue was triturated with water, collected by filtration and washed with water to give 50 mg of XIII as a colorless powder, mp 232–234°C, yield 48 mg.

UV: λ_{max} m μ (log ϵ); 254 (4.52), 331 (3.94).

Methylation of XIII. To a solution of 50 mg of XIII in small amount of methanol was added an ethereal solution of diazomethane and the mixture was allowed to stand overnight at room temperature. Evaporation of the mixture gave residual crystals which was recrystallized from methanol to give 40 mg of XIV, mp 250–252°C, yield 42 mg. UV: λ_{max} m μ (log ϵ); 253 (4.61), 318 (3.85 ref), 340 (3.97).

Hydrolysis of XIV. To a suspension of 30 mg of XIV in 1 ml of methanol was added 1 ml of 6N sodium hydroxide. The mixture was heated on a water bath. It was colored orange, and then turned to pale yellow. The needles separated out were collected, washed with water, suspended in water and adjusted to pH 1 with 1N hydrochloric acid. Colorless crystals (XV) were obtained, recrystallized from a mixture of methanol and ethyl acetate.

XV: mp 153–154°C, yield 21 mg. Found: C, 65.01; H, 6.95. Calcd for C₁₂H₁₄O₄: C, 64.85; H, 6.35%. UV: λ_{max} m μ (log ϵ); 246 (4.60), 328 (4.01).



Ammonolysis of IB. Dimethyl ether (IB) (50 mg) was suspended in 50 ml of liquid ammonia in a sealed tube and stood at room temperature for fortnight. The yellow oil which was obtained by evaporation of liquid ammonia, was chromatographed on alumina by elution with ether. Recrystallization from a mixture of ether and ethyl acetate gave VIIB as yellow needles, mp 164–165°C, yield 31 mg. Found: N, 5.84. Calcd for C₁₂H₁₃NO₃: N, 6.39%. UV: λ_{max} m μ (log ϵ); 252 (4.28), 270 (4.13), 286 (4.18 ref), 306 (4.36), 312 (4.35), 380 (3.77), 405 (3.69).

Ammonolysis of IC. Dimethyl ether (IC) (9 mg) was suspended in 20 ml of liquid ammonia in a sealed tube and stood for fortnight. The yellow oil, which was obtained by evaporation of liquid ammonia, was chromatographed on alumina

by elution with ether. Recrystallization from ether gave yellow crystals, mp 176–178°C. UV: λ_{max} m μ (log ϵ); 255 (3.99), 308 (4.50), 393 (3.65), 408 (3.76).

Ammonolysis of IA. Dimethyl ether (IA) (50 mg) was suspended in 50 ml of liquid ammonia in a sealed tube and stood for fortnight. Colorless needles which was obtained by evaporation of liquid ammonia, was recrystallized from ethyl acetate to give VI, mp 182–183°C, yield 25 mg. Found: C, 62.36; H, 6.40; N, 5.44. Calcd for C₁₃H₁₇NO₄: C, 62.14; H, 6.82; N, 5.57%. UV: λ_{max} m μ (log ϵ); 251 (4.52), 319 (4.02).

Ammonolysis of IIA. Dimethyl ether (IIA) (42 mg) in 30 ml of liquid ammonia was allowed to stand for 4 days in a sealed tube at room temperature. On evaporation of ammonia, the starting material was recovered without any change.

Ammonolysis of IIB. Dimethyl ether (IIB) (42 mg) in 30 ml of liquid ammonia was allowed to stand for 4 days in a sealed tube. Evaporation of ammonia gave yellow crystals VIIIB (30 mg), mp 127–129°C. Found: N, 6.30, Calcd for C₁₂H₁₅NO₃: N, 6.33%. UV: λ_{max} m μ (log ϵ); 254 (4.55), 280 (4.05), 337 (4.03), 376 (3.94).

Ammonolysis of IIC. Dimethyl ether (IIC) (22 mg) in 30 ml of liquid ammonia was allowed to stand for 2 days in a sealed tube. Evaporation of ammonia gave yellow crystals VIIIC (12 mg), mp 222–224°C. Found: N, 5.83%. UV: λ_{max} m μ (log ϵ); 255 (4.49), 279 (4.12 ref), 340 (4.00), 381 (4.08).

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