

AN INSECTICIDAL ALKALOID, COCCULOLIDINE  
FROM COCCULUS TRILOBUS DC.

Kojiro Wada, Shingo Marumo, and Katsura Munakata  
Laboratory of Pesticides Chemistry  
Faculty of Agriculture, Nagoya University

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A new insecticidal alkaloid, cocculolidine, has been isolated from the fresh leaves of Cocculus trilobus DC. (Kamiebi in Japanese) through the solvent extraction and subsequent chromatography on alumina (the yield 0.007%). Cocculus trilobus DC., which is the host plant of Japanese fruit-piercing moths, Oraesia excavata Butler and Oraesia emarginata Fabricius (Akaeguriba and Himeeguriba in Japanese), was noticed not to be attacked by any other insects in the wild field.

Therefore, it was considered that the plant might contain insecticidal principles or feeding inhibitors for insects. The active principle thus isolated, cocculolidine exhibited the considerable toxicities for leaf-hopper (Nephotettix bipunctatus cincticeps Uhler) and Azuki-bean weevil (Callosobruchus chinensis L.).<sup>1)</sup>

This paper presents evidence which let us assign the structure (I) for cocculolidine.

Cocculolidine (I),  $C_{15}H_{19}O_3N$ , mp. 144-146°C, MW 281 (mass spectrum),  $(\alpha)_D^{25} + 273$  (1.0%,  $CHCl_3$ ), was structurally characteristic of a aliphatic lactone alkaloid, and quite different from the bisbenzylisoquinoline alkaloids, which had been isolated from the same plant by M.Tomita et al..<sup>2)</sup>

Functional groups in (I) were clarified as follows. The tertiary nitrogen atom was proved from the ready formation of the methiodide and absence of NH absorption in the infrared spectrum. The spectral data for (I),  $\lambda_{\text{max}}^{\text{MeOH}}$  215  $\mu$  ( $\epsilon=12,700$ );  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1760 and 1650  $\text{cm}^{-1}$ ; n.m.r.<sup>3)</sup> 4.68 (2H, s) ( $-\text{C}=\text{C}-\text{CH}_2-\text{O}-\text{C}=\text{O}$ ), 3.33 (3H, s) ( $\text{CH}_3\text{O}-$ ), 4.08 (1H, m) ( $\text{CH}_3\text{O}-\text{C}-\text{H}$ ) and 5.67 (1H, m) ( $\text{C}=\text{C}-\text{H}$ ), showed the presence of  $\Delta^{\alpha,\beta}$ - $\gamma$ -lactone (ring D), a methoxyl group and a trisubstituted double bond.

The base peak (m-58) in the mass spectrum of (I) suggested the presence of the ring A, which was cleaved by a retro-Diels-Alder decomposition to give m-58 fragment and  $\text{CH}_3\text{O}-\text{CH}=\text{CH}_2$ .


The half-height width (24 c.p.s.) of the signal of  $\text{CH}_3\text{O}-\text{C}-\text{H}$  in the n.m.r. spectrum of (I) suggested that the hydrogen was axial and four hydrogens presented on the two adjacent carbons.<sup>4)</sup>

Reduction of (I) with  $\text{NaBH}_4$  in MeOH gave dihydrococculolidine (II),  $\text{C}_{15}\text{H}_{21}\text{O}_3\text{N}$ , mp. 121-121.5°C. The spectral data of (II) showed end absorption in UV;  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1775  $\text{cm}^{-1}$ ; n.m.r.<sup>3)</sup> 3.92 (1H, d) and 4.18 (1H, q) ( $-\text{CH}-\text{CH}_2-\text{O}-\text{C}=\text{O}$ ), clearly indicating that  $\Delta^{\alpha,\beta}$ - $\gamma$ -lactone was reduced to the saturated one.

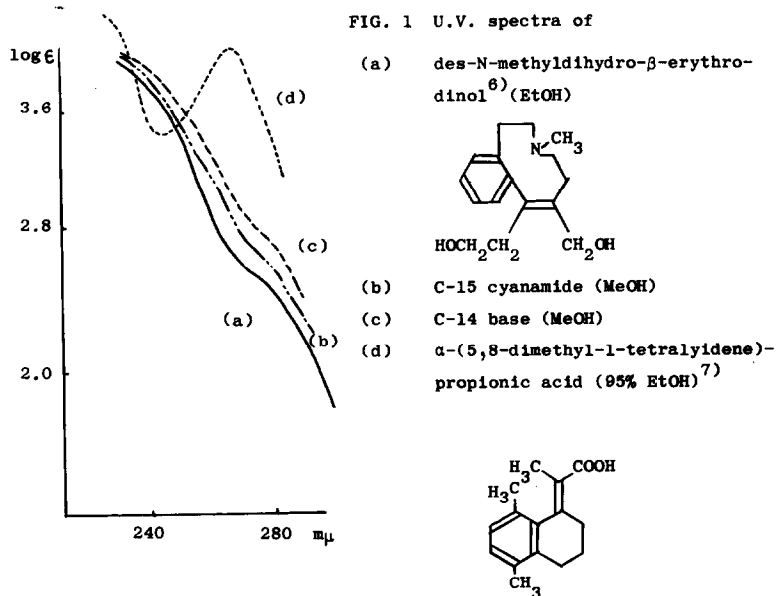
(II) was further hydrogenated with  $\text{PtO}_2$  in AcOH to tetrahydrococculolidine (III),  $\text{C}_{15}\text{H}_{23}\text{O}_3\text{N}$ , mp. 187-189°C, which showed no absorption in the ultraviolet spectrum. Thus, (I) was concluded to be a tetracyclic compound.

Oxidation of (III) with  $\text{KMnO}_4$  in acetone- $\text{H}_2\text{O}$  produced oxo-tetrahydrococculolidine (IV),  $\text{C}_{15}\text{H}_{21}\text{O}_4\text{N}$ , mp. 122-126°C. The formation of  $\gamma$ -lactam newly in (IV) was indicated by the infrared spectrum,  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ ) 1775  $\text{cm}^{-1}$  ( $\gamma$ -lactone) and 1675  $\text{cm}^{-1}$  ( $\gamma$ -lactam), concluding that the nitrogen was contained in the 5-membered ring B.

The relationship between the ring A and the nitrogen was chemically elucidated by BrCN-degradation of (I).

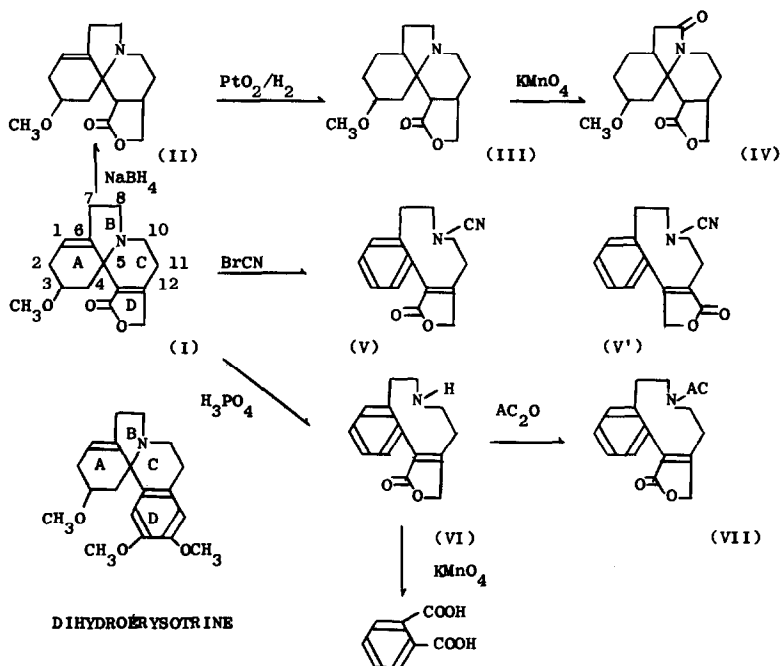
BrCN-degradation of (I) in  $\text{CHCl}_3$  gave C-15 cyanamide (V),  $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_2$ , mp. 169-171.5°C;  $\nu_{\text{max}}$  ( $\text{CHCl}_3$ )  $2205\text{ cm}^{-1}$  ( $-\text{C}\equiv\text{N}$ ),  $1765\text{ cm}^{-1}$  ( $\Delta^{\alpha,\beta}$ - $\gamma$ -lactone) and  $1670\text{ cm}^{-1}$  ( $\text{C}=\text{C}$ );  $\lambda_{\text{Sh.}}^{\text{MeOH}}$   $255\text{ m}\mu$  ( $\epsilon=1850$ ) and  $275\text{ m}\mu$  ( $\epsilon=540$ ); n.m.r. spectrum,<sup>3)</sup> 2.5-3.0 (4H, m) (two  $-\text{C}=\text{C}-\text{CH}_2-$ ), 3.0-3.7 (4H, m) ( $-\text{CH}_2-\text{N}(\text{CN})-\text{CH}_2-$ ),<sup>5)</sup> 4.95 (2H, s) () and 7.0-7.55 (4H, m) (four hydrogens on a benzene ring).


The aromatization of the ring A during this reaction suggested that the nitrogen was connected directly to the ring A at  $\text{C}_5$  and the cleavage of  $\text{C}_5-\text{N}$  bond was followed by dehydrobromination and loss of methanol successively, thus producing the benzene ring.



The ultraviolet spectrum of (V) which was compared with those of model compounds showed the broad general absorption typical of sterically hindered *o*-substituted styrene (see Fig. 1). It was strongly suggestive that the benzene ring should be conjugated to the carbon-carbon double bond of the  $\Delta^{\alpha,\beta}$ - $\gamma$ -lactone. Thus, C-15 cyanamide could be represented as (V). If C-15 cyanamide had the alternative structure (V'), it might show quite similar absorption curve with that of  $\alpha$ -(5.8-dimethyl-1-tetra-lydene)-propionic acid as shown in Fig. 1. Thus, the structure (V') was abandoned.

CHART 1



Further chemical evidence about the relationship between the ring A and the nitrogen in (I) was obtained by the acid catalyzed demethoxylation of (I). HCl salt of (I) was heated at 170° in 85% H<sub>3</sub>PO<sub>4</sub>, giving C-14 base (VI), C<sub>14</sub>H<sub>15</sub>O<sub>2</sub>N, mp. 97-99°C;  $\nu_{\max}$  (KBr) 3300 cm<sup>-1</sup>(-NH), 1730 cm<sup>-1</sup> ( $\Delta^{\alpha,\beta}$ - $\gamma$ -lactone) and 1660 cm<sup>-1</sup>(C=C);  $\lambda_{\text{Sh.}}^{\text{MeOH}}$  255 m $\mu$  ( $\epsilon$ =2570) and 275 m $\mu$  ( $\epsilon$ =1000). Acetylation of (VI) with acetic anhydride in benzene gave N-acetyl-C-14 base (VII), C<sub>16</sub>H<sub>17</sub>O<sub>3</sub>N, mp. 173-175°C,  $\nu_{\max}$  (CHCl<sub>3</sub>) 1750 cm<sup>-1</sup> ( $\Delta^{\alpha,\beta}$ - $\gamma$ -lactone) and 1630 cm<sup>-1</sup>(CH<sub>3</sub>CO-N-); n.m.r.<sup>3)</sup> 1.88 (3H, s) (-N-COCH<sub>3</sub>), 2.45-2.9 (4H, m) (two -C=C-CH<sub>2</sub>-) 3.20-3.80 (4H, m) (-CH<sub>2</sub>-N(COCH<sub>3</sub>)-CH<sub>2</sub>-), 4.83 (2H, s) () and 6.95-7.40 (4H, m) (four hydrogens on a benzene ring).

The aromatization of ring A accompanied by loss of methanol and appearing of secondary amine also showed the attached point of the nitrogen to the ring A to be at C<sub>5</sub>.

In view of the fact that (VI) had o-substituted styrene group, which was confirmed by the formation of phthalic acid on the KMnO<sub>4</sub>-oxidation of (VI), it was concluded that the lactone ring also originally connected to the ring A at C<sub>5</sub>, namely, (I) had a spiran structure at C<sub>5</sub>.

From a consideration of the n.m.r. spectra of (V) and (VII), which showed two types of signals, one corresponding to four allylic and benzylic protons and the other to four protons on the carbons adjacent to the nitrogen, and no signals in the region of normal methylene protons, it was reasonably concluded that the ring B was 5-membered and the ring C 6-membered, and not *vice versa*.

The similarity between (V) and BrCN-degradation product of dihydroerysotrine,<sup>8)</sup> also suggested that cocculolidine had same partial structure (A, B and C ring) with that of dihydroerysotrine (see chart 1).

On the basis of these data, cocculolidine was assigned to the structure (I).

Cocculolidine is the third lactone erythrina alkaloid and also the second erythrina alkaloid found in the plants of Menispermaceae.<sup>9)</sup>

#### Footnotes and References

- (1) We wish to thank the biological group of Tōa-Pesticides Co. in Tokyo for the insecticidal tests. The biological studies will be reported in near future.
- (2) "The Alkaloid Bearing Plants and Their Contained Alkaloids", Technical Bulletin No. 1234, U.S. Department of Agriculture. (1961)
- (3) N.m.r. spectra were measured in  $CDCl_3$  at 60 Mc., shifts are expressed as  $\delta$  values (p.p.m.) from tetramethylsilane as internal standard; We wish to thank Dr. S. Suzuki and Dr. K. Sasaki, The Institute of Physical and Chemical Research in Tokyo for measurement of n.m.r..
- (4) Samuel G. Levine, Nancy H. Eddy and E. Constance Farthing, Tetrahedron Letters No. 23, 1517 (1963)
- (5) Y. Inubushi, Y. Sasaki, Y. Tsuda, B. Yasui, T. Konita, J. Matsumoto, E. Katarao and J. Nakano Tetrahedron 20, 2007 (1964)
- (6) Joseph Weinstock and V. Boekelheide, J. Amer. Chem. Soc., 75, 2546 (1953)
- (7) R.A. Friedel and Milton Orchin, "Ultraviolet Spectra of Aromatic Compounds", John Wiley & Son. (1951)
- (8) V. Prelog, B.C. Mckusick, J.R. Merchant, S. Julia and M. Wilhelm, Helv. Chim. Acta., 39, 498 (1956)
- (9) A erythrina alkaloid, dihydroerysodine has been isolated from Cocculus laurifolius DC. (a Menispermaceae). M. Tomita and H. Yamaguchi, Pharm. Bull., 4, 225 (1965)