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90. **Masanao Terashima**: Studies on the Stereochemistry of Emetine. III.[*1] Absolute Stereochemical Configuration of Emetine.

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In Parts I[1] and Ⅱ[*1] of this series, it was reported that mercuric acetate dehydrogenation of (−) 2′-acylemetines (Ib and Ic), having the same configuration as (−)-emetine (Ia), afforded 2′-acyl-5,11b-dehydroemetinium perchlorates (Ⅱb and Ⅱc). This dehydrogenation took longer for completion than a similar dehydrogenation of 9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (Ⅴ) to 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium iodide (Ⅵ).

These results suggested the possibility that the hydrogen atom at C-11b of (−)-emetine might not be axial but equatorial, as shown in (Ⅲ), in view of the general assumption that the hydrogen at C-11b of the compound (Ⅴ) is axial.

This paper describes further experiments for clarifying the stereochemistry of tricyclic system of emetine, which has led to the conclusion that natural (−)-emetine should be represented by formula (Ia)[*3] in terms of absolute configuration, excluding the possibility of formula (Ⅲ) for (−)-emetine.

If emetine were represented by formula (Ⅲ) with the equatorial C-H bond to C-ring at C-11b, it would be expected to change into a more stable structure of (Ia) or (Ⅳ) in acid-catalyzed epimerizations as are seen in pentacyclic indole alkaloids.[2] The formula (Ⅲ) for emetine was proposed by Brossi, *et al.*,[3a] but was later revised[3b] to (Ia) by the same authors; and (Ia) or (Ⅳ), the latter of which is equal to the former with the mirror image form of rings A, B, and C, was proposed by Battersby, *et al.*[4] and by van Tamelen, *et al.*[5] independently. Based upon this assumption, (−)-2′-benzoylemetine was heated with glacial acetic acid for eight hours but it was recovered unchanged in 45% yield after the usual treatment. Its identity with an authentic specimen of the initial compound was established by the melting point (180~181°), mixed melting point (181°), ultraviolet[1b] and infrared spectra,[1a] $[\alpha]_D^{16}$ −66.2° (pyridine), and Rf value (0.80 developed

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[*1] This paper constitutes a part of a series entitled "Studies on the Stereochemistry of Emetine" by Y. Ban. Part Ⅱ: This Bulletin, **8**, 194(1960). For preliminary communications of this work see Y. Ban, M. Terashima, O. Yonemitsu: Chem. & Ind. (London), **1959**, 568, 569.

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[*3] In this formula, the sign ▼ on N-5 shows that the lone-pair electrons of nitrogen lie above the plane of the page to avoid confusion between (Ia) and (Ⅲ) in respect to B/C-ring juncture, in accordance with a suggestion by Dr. T. Fujii, Faculty of Pharmaceutical Sciences, University of Tokyo, Tokyo. In a similar way, formulae (Ⅷ), (Ⅸ), and (Ⅹ) express the absolute configuration of (−)-canadine, (−)-tetrahydroprotoberberine, and (−)-norcoralydine, respectively.

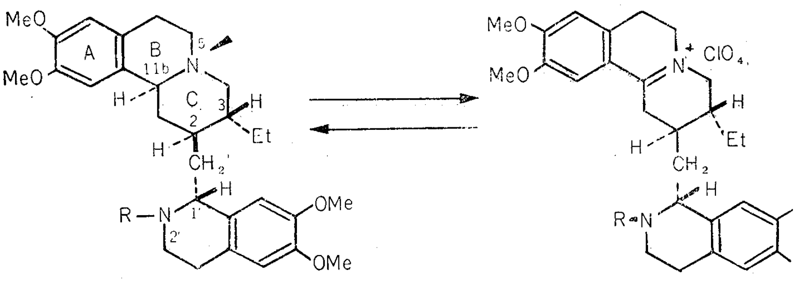
1) Part I. Y. Ban, O. Yonemitsu, M. Terashima: This Bulletin, **8**, 183(1960).

2) C. F. Hübner, M. E. Kühne, B. Korzum, E. Schlittler: Experientia, **12**, 249(1956).

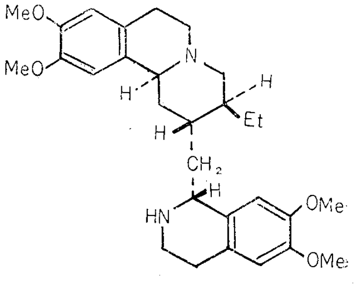
3) *a*) A. Brossi, A. Cohen, J. M. Osbond, Pl. A. Plattner, O. Schnider, J. C. Wickens: Chem. & Ind. (London), **1958**, 491. *b*) In 1959, Brossi, *et al.* withdrew their earlier formula (Ⅲ) and agreed with formula (Ia) or (Ⅳ) for emetine. cf. J. M. Osbond: Chem. & Ind. (London), **1959**, 257; A. Brossi, M. Baumann, L.H. Chopard-dit-Jean, J. Wursch, F. Schneider, O. Schnider: Helv. Chim. Acta, **42**, 772(1959). The present work had been completed before their correction.

4) *a*) A. R. Battersby, R. Binks, D. Davidson, G. C. Davidson, T. P. Edwards: Chem. & Ind. (London), **1957**, 982; A. R. Battersby, G. C. Davidson, B. J. T. Harper: *Ibid.*, **1957**, 983; A. R. Battersby, S. Cox: *Ibid.*, **1957**, 983. cf. also A. R. Battersby, G. C. Davidson, B. J. T. Harper: J. Chem. Soc., **1959**, 1744. *b*) A. R. Battersby: Chem. & Ind. (London), **1958**, 1324; A. R. Battersby, J. C. Turner: *Ibid.*, **1958**, 1324.

5) *a*) E. E. van Tamelen, P. E. Aldrich, J. B. Hester: J. Am. Chem. Soc., **79**, 4817(1957). *b*) E. E. van Tamelen, J. B. Hester: *Ibid.*, **81**, 507(1959).

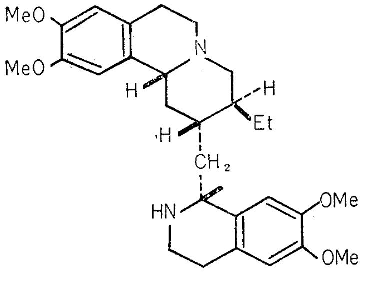


(Ia, b, c) (IIb, c)



(III)

a: R = H-
b: R = PhCO-
c: R = MeCO-



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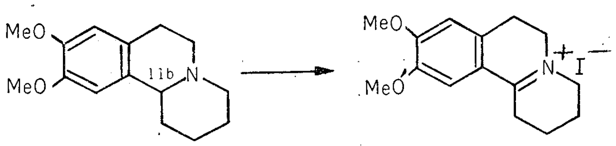
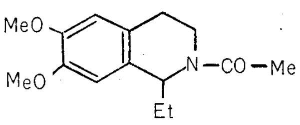


(V) (VI)



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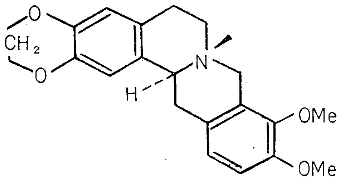

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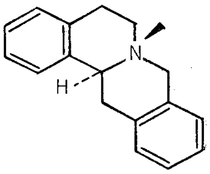
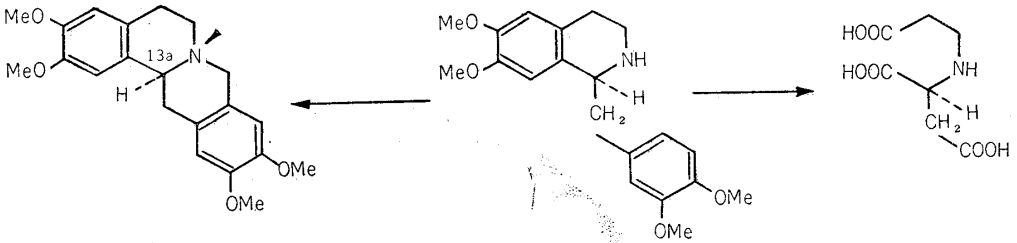


(IX)



(X) (XI) (XII)

TABLE I.

Compound	$[M]_D$	Compound	$[M]_D$	$\Delta[M]_D$	Solvent
(Ib)	− 387.1°	(IIb)	+475.5°	− 862.6°	Pyridine
(Ic)	− 401.4°	(IIc)	+625.5°	−1026.9°	〃
(X)	− 983.4°[9]				$CHCl_3$
(IX)	−1072°[10]				Pyridine
(VIII)	−1265°[10]				〃

by BuOH-AcOH-H_2O-EtOH=50:1:40:2), which are described in the Experimental Part.

Paper chromatography was carried out with the mother liquor of recrystallization and showed two bands, at Rf 0.80 (pale blue fluorescence) and 0.69 (yellowish green fluorescence) under the ultraviolet light. The former was in complete agreement with the spot of (−)-2′-benzoylemetine. The latter was extracted with ethanol and exhibited no absorptions at around 230 and 280 mμ in its ultraviolet spectrum, showing that no veratryl group is present in the molecule. This was not investigated further.

Moreover, (−)-2′-benzoylemetine, when heated with 10% acetic acid at 80~100° for five hours, was recovered unchanged in 89% yield and paper chromatography of the mother liquor of recrystallization gave a single band, whose Rf value (0.78) was almost consistent with that (0.80) of the initial compound. These results showed that (−)-2′-benzoylemetine was stable to such acid-catalyzed epimerization conditions, which were adjusted to that of mercuric acetate dehydrogenation of this compound, but not severe enough for the general complete conversion of *cis*- to *trans*-quinolizidine.[2] However, as (−)-emetine and its benzoyl derivative are both sensitive to boiling mineral acids yielding viscous resins, these conditions could not be adopted.

Next, the compound (Ⅱb) was hydrogenated over Adams catalyst in methanol to furnish (−)-2′-benzoylemetine (Ib) as the sole detectable product in 78.8% yield, which is particularly indicative of an axial hydrogen at C-11b, because a hydrogen atom will enter C-11b position from the reverse side of the equatorial substituent at C-2, by analogy with catalytic hydrogenation in the closely related indole alkaloid series.

The compound (Ⅱb) was reduced with zinc and 50% acetic acid to afford (Ib) and no epimer was detectable in spite of a careful search for it. Since *cis*-quinolizidine type of pseudoyohimbine and reserpine are obtained under similar conditions from the cor-

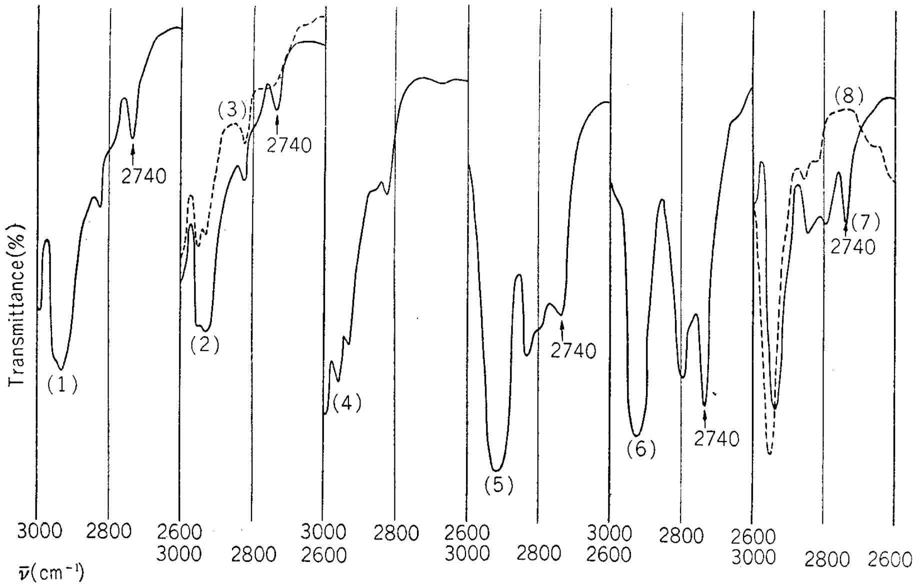


Fig. 1. Infrared Spectra in the Range of 2600~3000 cm^{-1} (in $CHCl_3$)

(1) (−)-2′-Benzoylemetine
(2) (−)-2′-Acetylemetine
(3) 2′-Acetylemetine perchlorate
(4) 1-Ethyl-2-acetyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline
(5) *dl*-Canadine
(6) 5,6,13,13a-Tetrahydro-8*H*-dibenzo[*a,g*]quinolizine
(7) 9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine
(8) 9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine hydrochloride

responding 3,4-dehydro compounds,[6] these results seem to suggest that even if C-11b epimer of (−)-emetine of *cis*-quinolizidine type were present, it would be extremely unstable.

In addition to these results, the infrared spectra of (−)-2′-acylemetines (Ib and Ic) in chloroform exhibit absorption band at 2740 cm^{-1} as shown by (1) and (2) in Fig. 1 and the band is not so intense as the characteristic ones which are observed in the range of 2700~2800 cm^{-1} in the infrared spectra of *trans*-quinolizidines, pointed out by Wenkert[7] and Bohlmann.[8] These groups of bands were suggested by Bohlmann[8] to be due to the interaction between the lone-pair electrons of nitrogen and at least two axial C-H bonds which are present at neighboring positions of the nitrogen atom and *trans* to the lone pair of nitrogen. Thus, the N-oxide and lactam, in which the electron pair is either absent or fixed by mesomeric effect, have no absorption in this region. As shown by (3) in Fig. 1, the perchlorate of 2′-acetylemetine, its electron pair of nitrogen being coordinated to a proton, similarly has no absorption at 2740 cm^{-1}, which strongly suggests that the band at 2740 cm^{-1} in the infrared spectra of (−)-2′-acylemetines should be ascribed to the *trans*-quinolizidine ring in its molecule for the above-described reasons and inasmuch as N-acyl-tetrahydroisoquinoline part of 2′-acylemetine is expected to have no effect upon this region as shown in the spectrum ((4) in Fig. 1) of 1-ethyl-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VII).

For further confirmation, the infrared spectra of *dl*-canadine (*dl*-VIII), 5,6,13,13a-tetrahydro-8*H*-dibenzo[*a,g*]quinolizine (*dl*-IX) and 9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (V) in this region are noted and shown by (5), (6), and (7) in Fig. 1. These compounds are generally assumed as derivatives of *trans*-quinolizidine and exhibit the typical band at 2740 cm^{-1}, but the hydrochloride of (V) lacks any absorption in this region as shown by (8) in Fig. 1, supporting the above interpretation of the infrared spectra of (−)-2′-acylemetines. All these data show that tricyclic system of (−)-emetine is of *trans*-quinolizidine type and accordingly (−)-emetine should be represented by formula (Ia) or alternatively by (IV).

Molecular optical rotations of these compounds are shown in Table I in comparison with those of (−)-tetrahydroprotoberberine derivatives.

Corrodi and Hardegger[9] established the absolute configuration of (−)-norcoralydine (X) by chemically correlating this compound to (−)-tetrahydropapaverine (XI), which was oxidized to afford N-(2-carboxyethyl)-L-aspartic acid (XII) of known absolute steric structure[9b] and they supported Leithe's view that all of the (−)-tetrahydroberberine alkaloids with only one asymmetric carbon possess almost equal $[M]_D$ values of average of ca. −1000°, and have the same configurations as (−)-norcoralydine.[10]

The large negative contribution of the axial hydrogen at C-11b in (−)-2′-acylemetines to the rotation is shown by the difference in rotation between the compounds (Ib, c) and (IIb, c), values of which are reasonably equivalent to $[M]_D$ values of (−)-norcoralydine and its homologs. This result suggests that (−)-emetine should have the same configuration at C-11b as that at C-13a of (−)-norcoralydine and this assignment is compatible with analogy in the determination of absolute configuration at C-3 of yohimbine and

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[6] F. L. Weisenborn, P. A. Diassi: J. Am. Chem. Soc., **78**, 2022(1956); M. W. Klohs, F. Keller, R. E. Williams, G. W. Kusserow: *Ibid.*, **79**, 3763(1957).

[7] E. Wenkert, D. Roychaudhuri: *Ibid.*, **78**, 6417(1956).

[8] F. Bohlmann: Ber., **91**, 2157(1958).

[9] *a*) H. Corrodi, E. Hardegger: Helv. Chim. Acta, **39**, 889(1956). *b*) H. Corrodi, E. Hardegger: *Ibid.*, **38**, 2038(1955).

[10] W. Leithe: Ber., **63**, 2343(1930); **67**, 1261(1934); cf. K. W. Bentley, H. M. E. Cardwell: J. Chem. Soc., **1955**, 3252.

other indole alkaloids.[11]

Therefore, the hydrogen at C–11b should be α, and this suggests formula (Ia) (2S:3S:5R:11bS:1'R)[*4] as the absolute configuration of natural (−)-emetine, in accordance with Bose's suggestion about the configuration of hydrogen at C–2.[12]

Experimental

Reduction of 2'-Benzoyl-5,11b-dehydroemetinium Perchlorate Monohydrate to (−)**-2'-Benzoylemetine**—i) Catalytic hydrogenation: A solution of 0.550 g. of (IIb)·H_2O in 40 cc. of dehyd. MeOH was subjected to hydrogenation over Adams catalyst at room temperature under atmospheric pressure of hydrogen. One molar equivalent of H_2 (18.2 cc.) was absorbed in 1 hr. and the ultraviolet absorption spectrum of a sample of the reaction mixture showed complete identity with that of (−)-2'-benzoylemetine. After removal of the catalyst and solvent, colorless amorphous solid was obtained to which was added 40 cc. of 10% Na_2CO_3 solution and extracted with 100 cc. of benzene-EtOAc(1:1). The supernatant layer was separated and worked up in the usual way. After drying over K_2CO_3 and removal of solvent, a brownish yellow syrup was obtained and it was recrystallized from 2 cc. of anhyd. EtOH to afford 0.361 g. (78.8%) of white needles, m.p. 181°, which was shown to be identical with (−)-2'-benzoylemetine by mixed m.p. 181.5°, Rf value, and $[\alpha]_D$ (Tables II and III, (C–I)). Paper chromatography was carried out with the mother liquor of recrystallization and its result is shown in Table II (M–I).

TABLE II. Result of Paper Chromatography

Run	Rf value (BuOH:AcOH:H_2O:EtOH=50:1:40:2)	Color of fluorescence under UV
(−)-2'-Benzoylemetine	0.80	pale blue
C-I	0.80	〃
M-I	0.80	〃
C-II	0.81	〃
M-II	0.77	〃
M-II'	0.81 (0.66)[a]	〃 (yellowish green)
C-III	0.80	〃
M-III	0.80 (0.69)[a]	〃 (yellowish green)
C-IV	0.80	〃
M-IV	0.78	〃

a) On taking the ultraviolet spectrum in ethanol solution, no absorption was recognized in the range of 230～340 mμ.

TABLE III. $[\alpha]_D$ Values (in pyridine)[a]

Run	$[\alpha]_D$
(−)-2'-Benzoylemetine	− 66.2° (c=1.51)
(−)-2'-Acetylemetine	− 76.8° (c=1.00)[b]
C-I	− 67.1° (c=1.46)
C-II	− 62.9° (c=0.175)
C-IV	− 67.4° (c=1.84)
(+)-2'-Benzoyl-5,11b-dehydroemetinium perchlorate	+ 69.6° (c=0.92)
(+)-2'-Acetyl-5,11b-dehydroemetinium perchlorate	+ 100.8° (c=1.00)[b]

a) At 16°, unless otherwise stated. *b*) At 21°.

ii) Reduction with Zn and 50% AcOH: To a solution of 0.200 g. of (IIb)·H_2O in 20 cc. of 50% AcOH, 1 g. of activated Zn powder was added and the mixture was heated at 100° for 5 hr. till the ultraviolet spectrum of a sample of the reaction mixture showed identity with that of (−)-2'-benzoyl-

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[*4] After this work had been completed, the authors learned of the reference to "The Stereochemistry of the Ipecac Alkaloid Emetime" by E.E. van Tamelen and J.B. Hester (J. Am. Chem. Soc., **81**, 507(1959)) and of "The Absolute Stereochemistry of Emetine" by A.R. Battersby and S. Garratt(Proc. Chem. Soc., **1959**, 86) in which the same conclusion was reached in different ways.

11) W. Klyne: Chem. & Ind. (London), **1953**, 1032; R.E. Woodson, H.W. Youngken, E. Schlittler, J.A. Schneider: "Rauwolfia: Botany, Pharmacognosy, Chemistry and Pharmacology," 92, (1957). Little, Brown & Company, Canada.

12) A.K. Bose: Chem. & Ind. (London), **1958**, 1690.

emetine. The excess of Zn powder was filtered off, washed with water, and the filtrate was diluted with 5 volumes of water. Excess of 10% NaOH was added under ice-cooling, separating a white solid which was extracted with ca. 100 cc. of benzene, the benzene extract was worked up in the usual way, and evaporated to afford 0.18 g. of a pale yellow solid. This was recrystallized from anhyd. EtOH to 0.052 g. of white prismatic needles, m.p. 180~181°, undepressed on admixture with a sample of (−)-2′-benzoylemetine (Tables II and III (C-II)). Yield, 31%.

The mother liquor of recrystallization was evaporated *in vacuo* to leave 0.100 g. of a brownish yellow, viscous syrup, which was chromatographed over alumina. Elution with Et_2O yielded 0.090 g. of pale yellow caramel (M-II) and from the EtOH eluate, there was obtained 0.005 g. of brownish yellow caramel (M-II′). These crude products were developed on filter paper and the results are shown in Table II.

Treatment of (−)-2′-Benzoylemetine with Acetic Acid for Testing C-11b Epimerization—i) With glacial acetic acid: A solution of 0.10 g. of (−)-2′-benzoylemetine in 10 cc. of glacial AcOH was refluxed in an oil bath for 8 hr. during which time the reaction mixture remained yellow and transparent. After AcOH was removed *in vacuo*, the residual brownish yellow syrup was dissolved in water, made alkaline with 10% Na_2CO_3, and extracted with benzene. The benzene solution was worked up in the usual way to afford a brownish yellow syrup, which was chromatographed over alumina. Elution with Et_2O yielded a pale yellow syrup, to which was added a small amount of dehyd. EtOH and the whole was allowed to stand at room temperature. The separated white needles (C-III) were collected by filtration and melted at 180~181°, undepressed on admixture with a sample of the original compound. Yield, 0.045 g. or 45%. The mother liquor of recrystallization was developed on filter paper and the results are shown in Table II (M-III).

ii) With 10% AcOH: A solution of 0.10 g. of (−)-2′-benzoylemetine in 8 cc. of 10% AcOH was heated in a water bath kept at 80~100° for 5 hr., during which time color of the reaction mixture remained pale yellow. The whole was made alkaline with 10% Na_2CO_3 under ice-cooling, separating white amorphous solid, and the mixture was allowed to stand in an ice-box overnight. The solid was collected by filtration, dried *in vacuo* at room temperature, and recrystallized from dehyd. EtOH to white needles (C-IV), m.p. 180°, undepressed on admixture with a sample of the initial compound. Yield, 0.089 g. or 89%.

Paper chromatography was carried out with the mother liquor of recrystallization. See Table II (M-IV).

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Summary

The results of acid catalyzed epimerization of (−)-2′-benzoylemetine, which possesses the same configuration as the original alkaloid, and of reduction of 2′-benzoyl-5,11b-dehydroemetinium salt, and the presence of *trans*-quinolizidine bands in infrared spectra of (−)-2′-acylemetines suggested that (−)-emetine should be represented by (Ia) or (IV), alternatively. The large negative contribution of C-11b hydrogen of (−)-2′-acylemetine to the $[M]_D$ value gave evidence for (Ia) as the absolute configuration of (−)-emetine.

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