UDC 547.94.02 : 547.836.3

34. Yoshio Ban, Osamu Yonemitsu, and Masanao Terashima : Preliminary Studies on the Stereochemistry of Emetine. I. Mercuric Acetate Dehydrogenation of (−)-2′-Acylemetines.*1

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In regard to the stereochemistry of the ipecacuanha alkaloids, Battersby, *et al.*[1a] in 1957 proposed the formula (Ia) for natural (−)-emetine, in which the absolute configuration at C-1′ is (*R*), the conformations of both hydroisoquinolylmethyl group at C-2 and ethyl group at C-3 are equatorial (viz. they are in *trans* relation), and the absolute configuration at C-11b was arbitrarily set the same as that at C-1′ of emetine.

Apart from the foregoing works, van Tamelen, *et al.*[2a,b] and Brossi, *et al.* with Osbond[3a,b] reached the same conclusion about the relative configurations at C-2 and C-3 of emetine in a different way. As for the conformation of hydrogen at C-11b, Osbond, *et al.*[3a] reached the alternative conclusion, claiming that the hydrogen at this carbon atom was equatorial to the C-ring, which was contrary to the proposal of Battersby, *et al.*[1a,b] and van Tamelen, *et al.*[2a,b] Thus, Osbond and others proposed the formula (II) for (−)-emetine[3a] in 1958, but later revised it to (Ia) by themselves.[3b]

Independently from these workers, the present authors had been working to solve the same problem at C-11b and to clarify the stereochemistry of the tricyclic system of emetine. The present paper describes the mercuric acetate dehydrogenation of (−)-2′-acylemetines (Ib,c) which afforded 5,11b-dehydro-2′-acylemetines (IIIb,c), and preliminary experiments necessary for elucidation of the features of these dehydrogenations.

It is well known[4] that with quinolizidine, *cis* (V)-*trans* (IV) isomerism at the ring junction does not occur, in contrast to decalin, and this is due to mobility of the electron pair on the tertiary nitrogen atom at the bridge head. Thus, the two forms, (V) and (IV), of quinolizidine are not stereoisomers but are only conformational differences; the *trans*-conformation (IV) is generally selected as the most probable, because this may be more stable than the other.[4b] In spite of these stereochemical properties of quinolizidine itself, there are C-3-epimers in the pentacyclic indole derivatives, of which pseudo and epi-allo series correspond to *cis*-decalin form of quinolizidine, while

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*1 This work was presented as a paper at the Annual Meeting of the Pharmaceutical Society of Japan, April 8, 1958; Preliminary communication : Y. Ban, M. Terashima, O. Yonemitsu : Chem. & Ind. (London), **1959**, 568.

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1) *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. A. R. Battersby, G. C. Davidson, B. J. T. Harper : J. Chem. Soc., **1959**, 1744; A. R. Battersby, B. J. T. Harper : *Ibid.*, **1959**, 1748. *b*) A. R. Battersby : Chem. & Ind. (London), **1958**, 1324; A. R. Battersby, J. C. Turner : *Ibid.*, **1958**, 1324.

2) *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).

3) *a*) A. Brossi, A. Cohen, J. M. Osbond, Pl. A. Plattner, O. Schnider, J. C. Wickens : Chem. & Ind. (London), **1958**, 491 : M. Barash, J. M. Osbond : *Ibid.*, **1958**, 490. *b*) J. M. Osbond : *Ibid.*, **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 correction by these workers).

4) *a*) J. Ratuský, A. Reiser, F. Šorm : Collection Czechoslov. Chem. Communs., **20**, 798(1955). *b*) R. C. Cookson : Chem. & Ind. (London), **1953**, 337. *c*) N. J. Leonard : "The Alkaloid, Chemistry and Physiology," ed. R.H.F. Manske, H.L. Holmes, Part III, 134, 137(1953). Academic Press Inc., New York.

normal and allo series correspond to *trans*-decalin form of quinolizidine; some of them are even more stable in *cis*-forms than in *trans*-forms,[5] which seems to suggest that the mobility of a free electron pair of the nitrogen is markedly hindered by the fusion of D-E rings.

These facts suggested the possibility that the compound such as emetine, which has non-cyclized bulkier substituents at C-2 and C-3 in its benzoquinolizidine part, might appear in two epimers at C-11b, as seen in pentacyclic indoles, although there had never been any definite evidence about the presence of *cis*-decalin form of quinolizidine which is not fused with other alicyclic rings.*3 Thus, the attention was turned to the availability of mercuric acetate dehydrogenation as a tool to determine the precence of an axial or equatorial hydrogen adjacent to a tertiary nitrogen atom.

It has been shown by many workers[6,7] that tertiary amines can be dehydrogenated to immonium salts with mercuric acetate in dilute acetic acid. In their dehydrogenation studies on yohimbine and other pentacyclic indole derivatives, Weisenborn, *et al.*[7e] reported that normal and allo series undergo dehydrogenation, whereas pseudo and epi-allo series do not, and concluded that only compounds containing an axial hydrogen at C-3 react with mercuric acetate according to the reaction mechanism proposed by Leonard.[6]

A general procedure used in the present work for the dehydrogenations is similar to that of Leonard, *et al.*,[6] which is as follows : A solution of secondary or tertiary amine and more than two molar equivalents of mercuric acetate in acetic acid was heated on a water bath for several hours, when mercurous acetate precipitated as white scales. After removal of the mercurous acetate by filtration and precipitation of the excess mercuric ion with hydrogen sulfide, there was obtained the corresponding dehydro compound. In this procedure, the measures of the relative rate of precipitation of mercurous acetate as dehydrogenation proceeds seem to be certainly effective for stereochemical assignment when the epimers at that carbon atom are subjected to these dehydrogenations at the same time for comparison,*3 but when only one epimer is available, the result is not always conclusive so long as there is a possibility of epimerisation at that atom.[6a,7f,g]

In applying mercuric acetate dehydrogenation for emetine, Openshaw[7a,b] obtained rubremetine (VI) and tetradehydroemetine in good yield, to the latter of which was assumed formula (VII) based on the remakably close correspondence of its absorption spectrum with that of a synthetic 1,3-bis(3,4-dihydro-6,7-dimethoxy-1-isoquinolyl)-2-methylpropyl hydrogenoxalate.[14]

Consequently, if the secondary nitrogen atom at C-2′ of emetine is acylated and protected from oxidation, the mercuric acetate dehydrogenation of (−)-2′-acylemetine (Ib,c)

*3 Recently, E. Ochiai and Masayuki Ishikawa reported the studies on dihydrocorynanthean and 3-epidihydrocorynanthean, to the latter of which was assigned *cis*-decalin form of quinolizidine based on the results of mercuric acetate dehydrogenations. cf. This Bulletin, **7**, 386(1959); also see H. W. Bersch : Angew. Chem., **71**, 136(1959).

5) R. E. Woodson, Jr., H. W. Youngken, E. Schlittler, J. A. Schneider : "Rauwolfia (Botany, Pharmacognosy, Chemistry and Pharmacology)," 86(1956). Little, Brown & Co., Boston.

6) *a*) For leading references see N. J. Leonard, D. F. Morrow : J. Am. Chem. Soc., **80**, 371(1958) and earlidr papers by N.J. Leonard and co-workers. *b*) N. J. Leonard, A. S. Hay, R.W. Fulmer, V. W. Gash : *Ibid.*, **77**, 439(1955).

7) *a*) A. R. Battersby, H. T. Openshaw : J. Chem. Soc., **1949**, 67. *b*) H. T. Openshaw, H. C. S. Wood: *Ibid.*, **1952**, 391. *c*) S. Sugasawa, Y. Ban : Proc. Japan Acad., **31**, 31(1955); Y. Ban : This Bulletin, **3**, 53(1955). *d*) N. J. Leonard, P. D. Thomas, V. W. Gash : J. Am. Chem. Soc., **77**, 1552 (1955). *e*) F. L. Weisenborn, P. A. Diassi : *Ibid.*, **78**, 2022(1956). *f*) E. Wenkert, D. K. Roychaudhuri : J. Org. Chem., **21**, 1315(1956). *g*) E. Farkas, E.R. Lavagnino, R. T. Rapala : *Ibid.*, **22**, 1261(1957). *h*) J. Gadamer : Arch. Pharm., **253**, 274(1915).

would be expected to afford 5,11b-dehydro-2′-acylemetine (IIIb,c) as the sole product. It has already been shown by Battersby, *et al.*[1a] that (−)-2′-acylemetine has the same configurations as (−)-emetine, since no inversion takes place during Schotten-Baumann reaction. Therefore, configurations of (−)-emetine (Ia) can be discussed in terms of (−)-2′-acylemetines (Ib and/or Ic).

In the preliminary experiments which were carried out with this expectation, mercuric acetate dehydrogenations of 1-alkyl-1,2,3,4-tetrahydroisoquinolines (VIIIa,b,c) afforded 1-alkyl-3,4-dihydroisoquinolines (IXa,b,c) in rather a good yield,*4 in which it took longer time to complete reaction than with the corresponding tertiary isoquinolines (cf. Fig. 1),

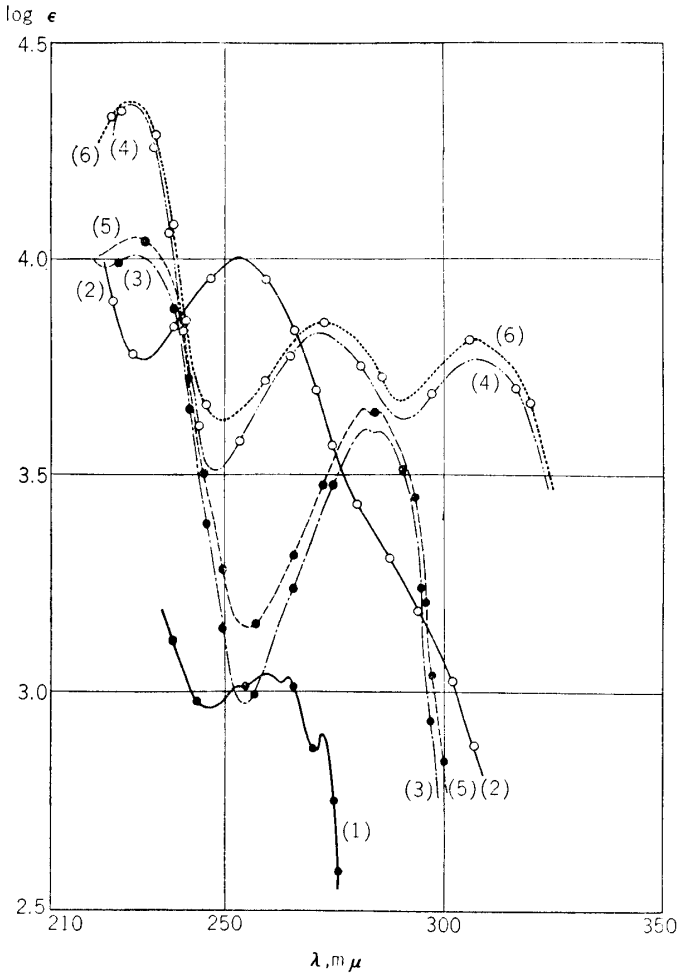


Fig. 1.
Ultraviolet Absorption Spectra

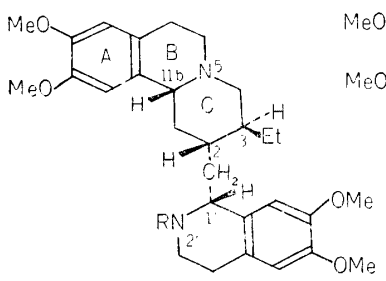
(1) 1-Benzyl-1,2,3,4-tetrahydroisoquinoline (VIIIa)
(2) 1-Benzyl-3,4-dihydroisoquinoline (IXa)
(3) 1-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIb)
(4) 1-Ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IXb)
(5) 1-Propyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIc)
(6) 1-Propyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IXc)

but 1-alkyl-2-acyl-1,2,3,4-tetrahydroisoquinolines resisted the same dehydrogenation of continuous heating for several hours and were recovered unchanged.*5 On the other hand, 9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XI), which had been synthesized according to the method of Sugasawa,[8] was readily dehydrogenated to 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium salt (XII) in a good yield, and mercurous acetate began to precipitate in several minutes after start of heating. This

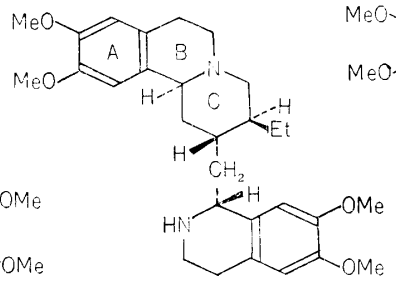
*4 It was already reported that 1-methyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline was dehydrogenated in a similar way to afford 1-methyl-3-(3,4-dimethoxyphenyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. cf. A. R. Battersby, R. Binks : J. Chem. Soc., **1958**, 4333.

*5 Leonard, *et al.* have already reported that 4-oxoquinolizidine is not dehydrogenated with mercuric acetate.[7h]

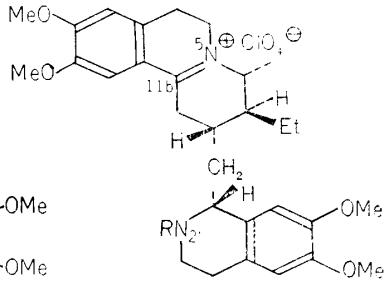
8) S. Sugasawa, K. Mizukami : This Bulletin, **6**, 359(1958).



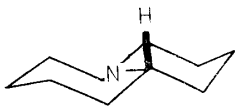
(I a) R=H
(I b) R=C_6H_5CO
(I c) R=Ac



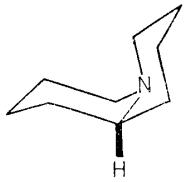
(II)



(III b) R=C_6H_5CO
(III c) R=Ac



(IV)



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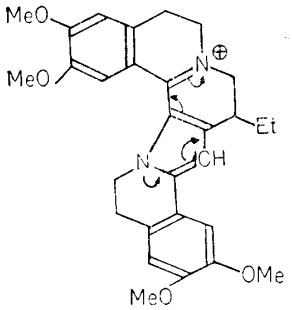

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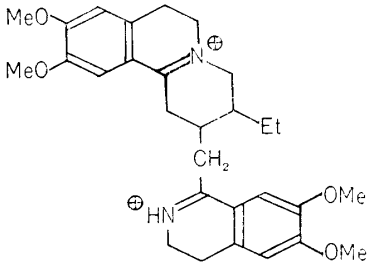
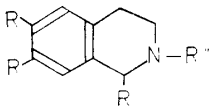
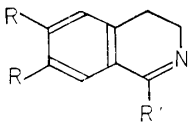
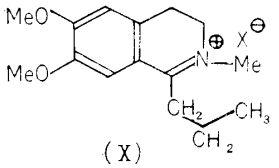


(VII)



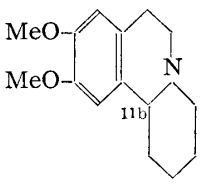




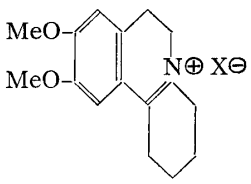
(X)

(VIIIa) R=H R′=$C_6H_5CH_2$ R″=H
(VIIIb) R=OMe R′=Et R″=H
(VIIIc) R=OMe R′=n-C_3H_7 R″=H
(VIIId) R=OMe R′=n-C_3H_7 R″=Me
(VIIIe) R=OMe R′=Et R″=C_6H_5CO
(VIIIf) R=OMe R′=Et R″=Ac

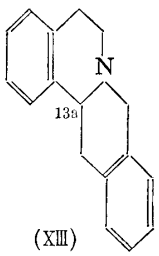
(IXa) R=H R′=$C_6H_5CH_2$
(IXb) R=OMe R′=Et
(IXc) R=OMe R′=n-C_3H_7



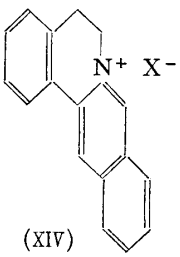
(XI)



(XII)



(XIII)



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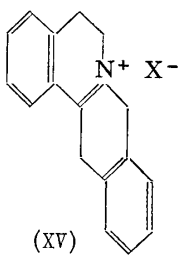

(XV)

behavior of the compound (XI) toward dehydrogenation is well understood by general assumption of the axial hydrogen at C-11b,[4] which agrees with Brossi's view about hydrogen in the same position of 2-oxo-3-ethyl-9,10-dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine.[9]

All these dehydrogenation products were identified with an authentic sample both by mixed melting point determination and by infrared and ultraviolet spectral comparison.

In view of these results, (−)-2′-benzoylemetine was dehydrogenated in a similar way to give a product, to whose quaternary perchlorate (white needles, m.p. 163~165°) was assigned the formula (IIIb) monohydrate, as had been expected, since the summation of ultraviolet absorption spectra of 1-ethyl-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIe) and 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium iodide (XII) gave a spectrum remarkably similar to that of this quaternary perchlorate as shown in Fig. 2. This was also supported by analytical data, infrared absorption spectrum,[10]

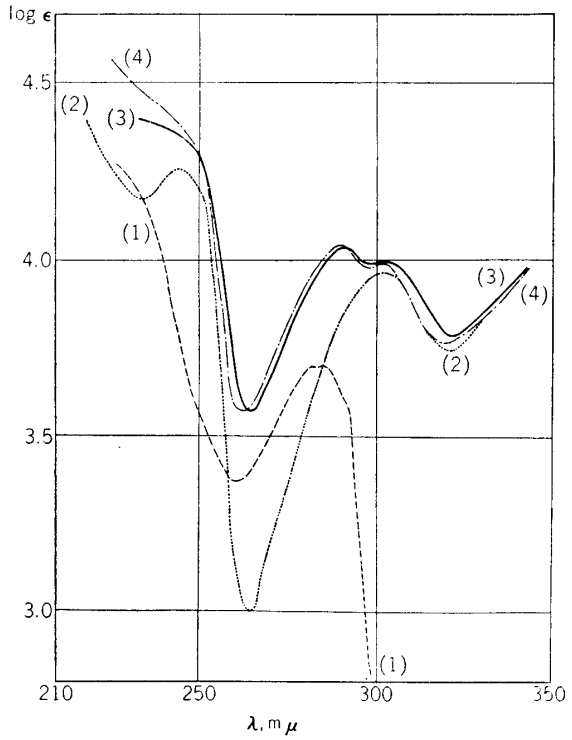

Fig. 2. Ultraviolet Absorption Spectra

(1) 1-Ethyl-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIe)

(2) 9,10-Dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium iodide (XII, X = I)

(3) 2′-Benzoyl-5,11b-dehydroemetinium perchlorate (IIIb) monohydrate

(4) The sum of (1) and (2)

and hydrogenation to the starting material after absorption of one molar equivalent of hydrogen. The above dehydrogenation took more than 20 minutes before mercurous acetate began to precipitate out and longer time was consumed to complete the reaction, as compared to that of benzoquinolizidine (XI). Judging from this result alone, the equatorial rather than the axial conformation of the hydrogen atom at C-11b of (−)-emetine seems likely, but contrary to this view and also to the earlier conclusion of Brossi, *et al.*,[3] there are strong evidences that this hydrogen occupies the axial position, which will be discussed in a forthcoming paper.

The mercuric acetate dehydrogenation of (−)-2′-acetylemetine (Ic) also gave the corresponding dehydro-2′-acetyl-5,11b-emetinium perchlorate (IIIc) as a crystalline tetrahydrate (white needles, m.p. 161~164°), whose ultraviolet absorption spectrum is shown in Fig. 3 along with the sum of spectra of 1-ethyl-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIf) and 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzoquinolizinium iodide

9) A. Brossi, H. Lindlar, M. Walter, O. Schnider : Helv. Chim. Acta, **41**, 119(1958).
10) Y. Ban, O. Yonemitsu, M. Terashima : This Bulletin, **8**, 194(1960).

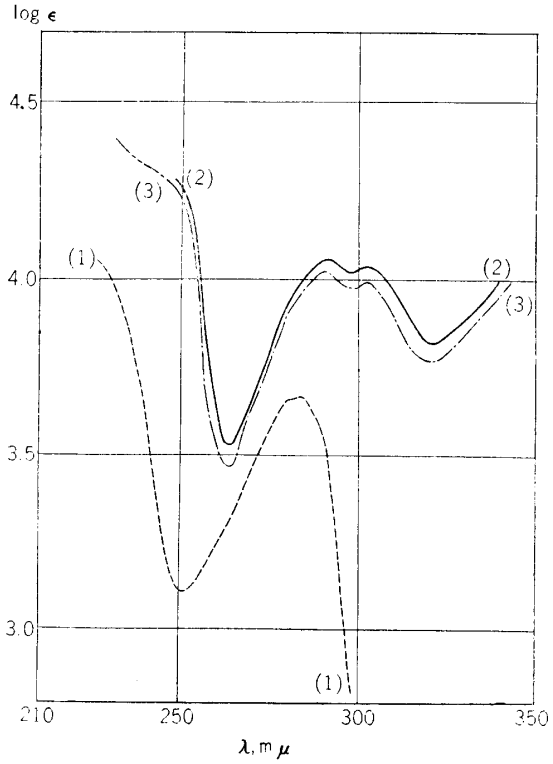

Fig. 3. Ultraviolet Absorption Spectra

(1) 1-Ethyl-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIf)

(2) 2′-Acetyl-5,11b-dehydroemetinium perchlorate (IIIc) tetrahydrate

(3) The sum of (1) in Fig. 3 and (2) in Fig. 2.

(XII, X=I), but for the present purpose N-benzoylemetine (Ib) and its dehydro compound (IIIb) are preferable to the acetyl derivatives for easiness of characterization, which is important in stereochemical arguments.

Furthermore, all of these results seem to support strongly Openshaw's view[7b] about the structure of tetradehydroemetine (VII) which is obtained as an intermediate in the mercuric acetate dehydrogenation of emetine to rubremetine*6 (VI).

In connection with the experiments described above, 1-propyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIId) was dehydrogenated very readily by heating for 1.5 hours with mercuric acetate to afford the corresponding 3,4-dihydroisoquinolinium salt (X) in a good yield as the only isolable product, although Knabe obtained both 3,4-dihydro and aromatized products in similar dehydrogenation of laudanosine in the presence of ethylenediaminetetraacetate.[11]

Finally, 5,6,13,13a-tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (XIII) was dehydrogenated to a quaternary salt, which was assigned 5,6-dihydro-dibenzo[*a*,*g*]quinolizinium salt (XIV), since the dehydro compound is clearly distinguished from 5,6,8,13-tetrahydrodibenzo[*a*,*g*]-quinolizinium salt (XV) in melting point and ultraviolet absorption spectrum (Fig. 4), and this assignment is also supported by its convertibility to the starting material after absorption of two molar equivalents of hydrogen. This corresponds to formation of berberine from canadine by similar oxidation.[7h]

The ultraviolet and infrared absorption spectra which have been used for characterization in this work will be discussed in the following paper.[10]

*6 Additionally, the summed curve of ultraviolet absorption spectra of 9,10-dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium iodide (XII) and 1-propyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride is in close correspondence (λ_{max}^{EtOH} mμ(log ε): 244(4.49), 303(4.22), 352(4.20)), despite a little discrepancies in the intensities, with that of tetradehydroemetine given by Openshaw.[7b] One of the present authors (Y. B.), under the guidance of Prof. S. Sugasawa, succeeded in synthesizing *rac*-tetradehydroemetine (VII), but did not obtain it in a pure enough state for characterization.[7]

11) J. Knabe: Angew. Chem., **70**, 576(1958).

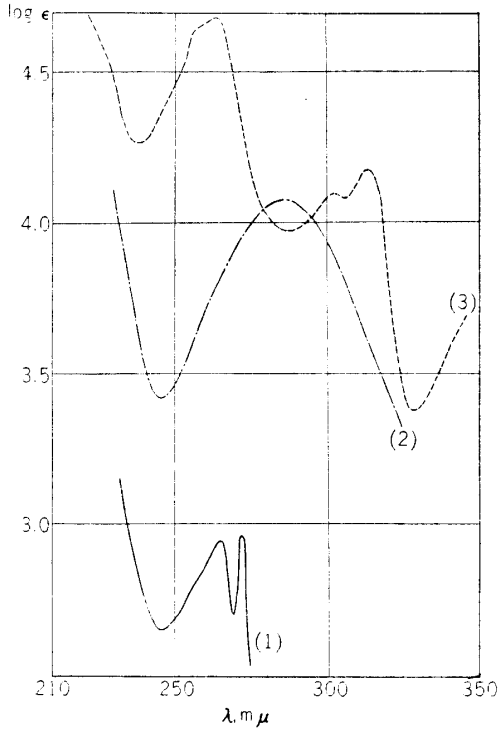

Fig. 4. Ultraviolet Absorption Spectra

(1) 5,6,13,13a-Tetrahydro-8*H*-dibenzo[*a*,*g*]-quinolizine (XIII)

(2) 5,6,8,13-Tetrahydro-dibenzo[*a*,*g*]quinolizinium iodide (XV)

(3) 5,6-Dihydro-dibenzo[*a*,*g*]quinolizinium iodide (XIV)

Further experiments are in progress with a view to clarifying the relationship between these dehydrogenations and stereochemical requirements.

Experimental*7

1-Benzyl-1,2,3,4-tetrahydroisoquinoline (VIIIa)—This base (b.$p_{2.5}$ 163～169°) was prepared by hydrogenation of 1-benzyl-3,4-dihydroisoquinoline (IXa), b.$p_{2.5}$ 165～171° (reported[12] b.p_{12} 220°) [hydrochloride, m.p. 223～225° (reported[13] m.p. 227～229°); methiodide, m.p. 197～199° (reported[14] m.p. 197～199°)], in the usual fashion. The hydrochloride of this base was recrystallized from EtOH-Et_2O to give white needles, m.p. 170～172° (reported[15] m.p. 172～173°). The picrate was recrystallized from EtOH-Et_2O to orange-yellow crystals, m.p. 166～167° (reported[16] m.p. 166～167°).

1-Ethyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIb)—This base (b.p_4 162～164°) was also prepared almost quantitatively by hydrogenation of 1-ethyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IXb), b.p_2 146～150° (reported[17] b.p_1 170° (bath temp.)); picrate, m.p. 190～192° (reported[17] m.p. 195～196°).

The picrate of (VIIIb) was recrystallized from EtOH to yellow pillars, m.p. 182～184° (reported[18] m.p. 186°).

1-Propyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIc)—This base (b.p_4 163～167°) was obtained by hydrogenation of 1-propyl-6,7-dimethoxy-3,4-dihydroisoquinoline [(IXc), b.p_2 153～157° (reported[17] b.p_1 170～175° (bath temp.), picrate, m.p. 174～176° (reported[17] m.p. 180～181°)].

The picrate of (VIIIc) was recrystallized from EtOH to yellow prisms, m.p. 190～191° (reported[19] m.p. 192°). The hydrochloride was obtained after recrystallization from EtOH-Et_2O as white

*7 A Koken model DS-301 double-beam spectrophotometer equipped with NaCl optics was used for the determination of infrared spectra, and samples were run as Nujol mulls or as KBr disks. A Beckman Model DK-2 spectrophotometer was used for the determination of ultraviolet spectra. All melting points are uncorrected.

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13) W. M. Whaley, W. H. Hartung : J. Org. Chem., **14**, 650(1949).
14) A. Dobrowsky : Monatsh., **82**, 122(1951).
15) L. E. Craig, D. S. Tarbell : J. Am. Chem. Soc., **70**, 2783(1948).
16) R. Forsyth, C. I. Kelly, F. L. Pyman : J. Chem. Soc., **1925**, 1659.
17) E. Späth, N. Polgar : Monatsh., **51**, 190(1929).
18) B. B. Day, T. R. Govindachari : Arch. Pharm., **277**, 177(1939).
19) A. M. Barbier, P. Rumpt : Bull. soc. chim. France, **1953**, 293.

needles, m.p. 210～214° (reported[19] m.p. 212°).

1-Propyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIId)—The excess of MeI was added to 1-propyl-6,7-dimethoxy-3,4-dihydroisoquinoline (IXc) and the whole mixture was heated under gentle reflux on a water bath for 5 hr. After removal of the excess MeI, the residue was recrystallized from EtOH to yellow prisms, m.p. 167～169°, yield, 90%. *Anal.* Calcd. for $C_{15}H_{22}O_2NI$: C, 48.01; H, 5.91; N, 3.73. Found: C, 47.52; H, 5.90; N, 4.09.

This methiodide was converted to the corresponding chloride, which was subjected to hydrogenation to give 1-propyl-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIId) as colorless viscous oil, b.p_5 160～163°, in a 92% yield. The picrate of this base was recrystallized from EtOH to yellow prisms, m.p. 167～168.5°. *Anal.* Calcd. for $C_{21}H_{26}O_9N_4$: C, 52.71; H, 5.48; N, 11.71. Found: C, 52.98; H, 5.85; N, 11.95.

9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XI)[11]—This was prepared by following the details given by Sugasawa, *et al.*;[8] and several intermediates which are necessary for the present purpose, were particularly checked and given analytical data as follows:

i) 1-(3,4-Dimethoxyphenethyl)-2(1*H*)-pyridone: A viscous syrup, obtained by $K_3Fe(CN)_6$ oxidation of 1-(3,4-dimethoxyphenethyl)pyridinium bromide, solidified when it was allowed to stand in hexane. The crude product was recrystallized from hexane to colorless needles, m.p. 78～80°. Yield, 4.2 g. (52.5%). *Anal.* Calcd. for $C_{15}H_{17}O_3N$: C, 69.48; H, 6.61; N, 5.40. Found: C, 69.13; H, 6.22; N, 5.89.

ii) 1-(3,4-Dimethoxyphenethyl)-2-piperidone: A mixture of 2.5 g. of the foregoing pyridone and 1.5 g. of Raney Ni (W-2) in 50 cc. of EtOH was subjected to hydrogenation at a room temperature. This was worked up in the usual way and a viscous syrup (2.6 g.) was obtained which was used in the next cyclization without further purification.

iii) 9,10-Dimethoxy-1,2,3,4,6,7-hexahydrobenzo[*a*]quinolizinium Iodide (XII, X=I): A solution of 2.1 g. of the foregoing crude piperidone and 10.5 g. of $POCl_3$ in 10 cc. of benzene was refluxed for 2.5 hr. Benzene and the excess $POCl_3$ were evaporated *in vacuo* to yield a brown viscous syrup (2.0 g.), which was dissolved in a small amount of water, and saturated with solid KI. The precipitate was collected by filtration (yield, 2.1 g. or 70%) and recrystallized from EtOH to yellow needles, m.p. 203～205° (reported[20] m.p. 210～212°). *Anal.* Calcd. for $C_{15}H_{20}O_2NI$: C, 48.26; H, 5.40; N, 3.76. Found: C, 48.30; H. 5.38; N, 3.88.

The corresponding picrate formed readily in EtOH and was obtained after recrystallization from EtOH as yellow scales, m.p. 183～185° (reported[20] 185～186°). *Anal.* Calcd. for $C_{21}H_{22}O_9N_4$: C, 53.16; H, 4.68; N, 11.81. Found: C, 52.77; H, 5.13; N, 12.21.

iv) 9,10-Dimethoxy-1,2,3,4,6,7-hexahydro-11b*H*-benzo[*a*]quinolizine (XI): The foregoing iodide (1.2 g.) was converted to the corresponding chloride in the usual way and the chloride was hydrogenated over Adams' catalyst in EtOH at a room temperature. One molar equivalent of H_2 (ca. 80 cc.) was taken up in 1.5 hr. After removal of the catalyst and solvent, the residue was dissolved in a small amount of water, made alkaline with $NaHCO_3$, and extracted with benzene. Benzene was evaporated to leave a colorless syrup, which solidified when triturated by a glass rod in petr. ether. This was recrystallized from petr. ether to furnish colorless plates, m.p. 57～59.5° (reported[20] m.p. 59～60°), whose picrate was obtained after recrystallization from EtOH as yellow prisms, m.p. 170～172° (reported[18] m.p. 167～168°). The hydrochloride was purified from EtOH-Et_2O to m.p. 230～232° (reported[20] m.p. 235～237°), and the perchlorate was recrystallized from water to white needles, m.p. 180～183° (reported[21] m.p. 179～180°).

5,6,13,13a-Tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine (XIII)[22]—i) 5,6,8,13-Tetrahydro-dibenzo[*a*,*g*]-quinolizinium iodide (XV): A solution of 5 g. of (VIIIa) in 3 g. of anhyd. HCOOH was refluxed in an oil bath kept at 200° for 3 hr. and excess HCOOH was removed *in vacuo* to leave a viscous syrup (5.5 g.), which was dissolved in 70 cc. of tetralin. To this solution was added 17 g. of P_2O_5, the whole was refluxed for 10 min. Further 17 g. of P_2O_5 was added and heated under reflux for additional 15 min. On cooling, about 200 cc. of ice water was added to the reaction mixture, acidified with HCl, and the supernatant tetralin layer was separated. The aqueous layer was extracted thoroughly with benzene, the benzene layer was discarded, the aqueous layer was filtered, and then saturated with solid KI. There separated 4.9 g. (60.5%) of the crude iodide (XV: X=I), m.p. 178～181°, which was recrystallized from 90% EtOH to yellow needles, m.p. 193～194°. *Anal.* Calcd. for $C_{17}H_{16}NI$: C, 56.52; H, 4.46; N, 3.88. Found: C, 56.82; H, 4.66; N, 4.11.

ii) 5,6,13,13a-Tetrahydro-8*H*-dibenzo[*a*,*g*]quinolizine[22] (XIII): Cyclization of (VIIIa) with HCOOH was carried out in the usual way, the reaction mixture was poured into ice water, to which was added 35 cc. of conc. HCl and 10 g. of Zn dust, and the mixture was heated on a water bath for 3 hr., becoming almost colorless. After filtration of excess Zn dust, the filtrate was basified with $NaHCO_3$, extracted

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21) S. Sugasawa, S. Akaboshi, M. Yamada: Yakugaku Zasshi, **71**, 1341(1951).
22) W. Leithe: Ber., **63**, 2343(1930).

with $CHCl_3$, washed, dried, and the solvent was evaporated. The residue was recrystallized from hexane to pale yellow needles, m.p. 82~85° (reported[22] m.p. 85°); yield, 2.2 g. (41.8%).

The picrate was recrystallized from ethanol to yellow needles, m.p. 148~150° (reported[22] m.p. 151°).

1-Ethyl-2-acetyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIf)—A mixture of 1 g. of (VIIb) and 4 cc. of Ac_2O was heated under reflux in an oil bath for 30 min., cooled, the whole mixture was poured into ice-water, and made alkaline with $NaHCO_3$. Benzene extraction followed by usual drying and concentration gave a colorless viscous syrup which solidified when allowed to stand in hexane. Yield, 0.95 g. Recrystallization from hexane gave colorless pillars, m.p. 78~80°. *Anal.* Calcd. for $C_{15}H_{21}O_3N$: C, 68.41; H, 8.04; N, 5.32. Found : C, 68.44; H, 8.09; N, 5.37.

1-Ethyl-2-benzoyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (VIIIe)—A mixture of 1 g. of (VIIb), 30 cc. of 10% NaOH solution, 3 cc. of BzCl, and 15 cc. of Et_2O was vigorously shaken for 30 min. The combined ether extracts gave 1.10 g. of a crude product, which was recrystallized from hexane to colorless pillars, m.p. 104~106°. *Anal.* Calcd. for $C_{20}H_{23}O_3N$: C, 73.82; H, 7.12; N, 4.30. Found : C, 73.32; H, 7.20; N, 4.66.

Dehydrogenation of 1-Benzyl-1,2,3,4-tetrahydroisoquinoline with Mercuric Acetate—The procedure was similar to that employed with quinolizidine by Leonard, *et al.*[6] To a solution of 0.30 g. of 1-benzyl-1,2,3,4-tetrahydroisoquinoline in 5 cc. of 5% AcOH, a solution of 2.20 g. of $(AcO)_2Hg$ in 10 cc. of 5% AcOH was added and the whole mixture was heated in a water bath kept at 90~95°. In about 20 min., AcOHg began to precipitate out, and AcOHg was collected after 3 hr. from the cooled solution by filtration, then washed with 5 cc. of 5% AcOH. The filtrate was saturated with H_2S at 100° to remove excess Hg^{2+} as HgS. After filtration while warm, the filtrate was basified with $NaHCO_3$, extracted with benzene, and the usual drying and concentration of the extract gave a viscous syrup, which was converted to 0.20 g. (33%) of a picrate, m.p. 165~170°. Recrystallization from EtOH gave 0.16 g. (26%) of yellow prisms, m.p. 175~176°, which was identified with authentic 1-benzyl-3,4-dihydroisoquinoline by mixed m.p. test and by a good agreement of ultraviolet and infrared spectra of the two samples.

Dehydrogenation of (VIIIb) with Mercuric Acetate—The procedure was also similar to that described above. A solution of 0.6 g. of $(AcO)_2Hg$ and 0.1 g. of (VIIb) in 10 cc. of hydr. AcOH was heated in a water bath kept at 90~95°. AcOHg began to precipitate out in 1 hr. and heating was continued for additional 2.5 hr. When cool, the reaction mixture was worked up as described above and a base was obtained which was converted to the picrate. This was recrystallized from EtOH to 0.13 g. of yellow needles, m.p. 190~192°, which was identical in all respects in melting point and infrared absorption spectrum with an authentic picrate of (IXb).

Dehydrogenation of (VIIIc) with Mercuric Acetate—(VIIc) was also dehydrogenated with $(AcO)_2Hg$ very readily in a similar manner to furnish 1-propyl-6,7-dimethoxy-3,4-dihydroisoquinoline as its picrate, m.p. 165~168°, in 85% yield, which was recrystallized from EtOH to yellow needles, m.p. 174~176° (yield, 79%). This was identical in all respects with an authentic specimen of a picrate of (IXc).

Dehydrogenation of (VIIId) with Mercuric Acetate—Dehydrogenation of 0.25 g. of (VIId) with $(AcO)_2Hg$ was carried out the same as above. After the removal of HgS, the UV spectrum of the filtrate was qualitatively examined and was found to have maxima at 247 and 306 mμ, which suggested that the solution contained only 3,4-dihydroisoquinolyl cation, and no trace of aromatized product. Thus, there was obtained 0.31 g. (82.7%) of an iodide, which was recrystallized from EtOH to yellow needles, m.p. 167~169°. This iodide was identified with an authentic sample of (X, X=I) by mixed m.p. test, and IR and UV spectra (λ_{max}^{EtOH} mμ (log ε) : 247 (4.29), 306 (4.01)).

Action of Mercuric Acetate on (VIIIe)—In 20 cc. of 5% AcOH was suspended 0.5 g. (1.15 m. moles) of (VIIe), to which was added 2.5 g. (7.83 m. moles) of $(AcO)_2Hg$. The whole mixture was heated in a water bath kept at 95° for 3 hr., during which time the benzoyl compound separated as an oil, without any precipitation of AcOHg. When cool, the mixture was extracted thoroughly with benzene, the benzene extract was dried, and evaporated to furnish 0.45 g. of a solid, which was recrystallized from hexane to white pillars, m.p. 104~106°. This product was identified with the starting material by mixed m.p. test.

Action of Mercuric Acetate on (VIIIf)—i) In 25 cc. of 5% AcOH 0.5 g. (1.90 m. moles) of (VIIf) was suspended and 3 g. (9.50 m. moles) of $(AcO)_2Hg$ was added. The whole mixture was heated in a water bath kept at 95° for 2.5 hr., during which time the acetyl compound separated as a pale yellow oil without any precipitation of AcOHg. When cool, the mixture was extracted with benzene, the benzene extract was washed with $NaHCO_3$ solution, dried, and evaporated *in vacuo* to give 0.42 g. of viscous oil, which solidified when it was triturated in hexane. This was recrystallized from hexane to white pillars, m.p. 77~78°, which was identified with the initial compound by mixed m.p. test.

ii) In the above-mentioned procedures for testing the sensibility of (VIIe) and (VIIf) to $(AcO)_2Hg$, conditions similar to the dehydrogenation of (−)-2′-acylemetines were adopted, but in this case, (VIIe) and

(VIIIf) did not dissolve in such a dilute AcOH on account of their non-basicity. Thus, the following experiments were carried out :

To a solution of 100 mg. of (VIIIf) in 1 cc. of glacial AcOH, a solution of 600 mg. of $(AcO)_2Hg$ in 1 cc. of water was added and the resulting homogeneous solution was heated in a water bath kept at 95° for 9 hr., during which time no change was observed. On standing the mixture overnight, there separated 9 mg. of AcOHg, which was collected, washed with 50% AcOH, and the filtrate was saturated with H_2S to remove excess Hg ions. After filtration of HgS, the filtrate was made alkaline with $NaHCO_3$, and extracted with benzene, which was dried over Na_2SO_4 and evaporated *in vacuo* to leave 120 mg. of a syrup, which solidified on standing. The UV and IR absorption spectra of the crude product were almost identical with those of an authentic sample. The crude substance (85 mg.) was recrystallized from hexane to yield 58 mg. of a pure product, which was completely identical with an authentic sample, m.p. and mixed m.p. 78~80°.

Additionally, it was found that a similar treatment of $(AcO)_2Hg$ in ca. 50% AcOH at 95° for 9 hr. without the acyl compound afforded the same amount of AcOHg.

Dehydrogenation of (XI) with Mercuric Acetate—Procedure similar to those of the foregoing dehydrogenation was also used in this reaction. To a solution of 0.3 g. of (XI) in 5 cc. of 5% AcOH a solution of 1.8 g. of $(AcO)_2Hg$ in 15 cc. of 5% AcOH was added and the whole mixture was heated in a water bath kept at 95°. In a few minutes, AcOHg began to precipitate out. After 1.5 hr. AcOHg was removed from the cooled solution by filtration and the filtrate was worked up in the usual way. There was obtained a quaternary iodide, m.p. 196°, which was recrystallized from EtOH to white pillars, m.p. 204~206°. Yield, 0.41 g. (91.6%). These were shown both by IR and UV (λ_{max}^{EtOH} mμ(log ε): 244(4.26), 302(3.97)) spectral comparison, and by a mixed m.p. determination to be identical with an authentic sample of (XII, X = I).

Dehydrogenation of (XIII) with Mercuric Acetate—Dehydrogenation of 0.95 g. of (XIII) with $(AcO)_2Hg$ yielded 1.09 g. (75.2%) of 5,6-dihydro-dibenzo[*a*,*g*]quinolizinium iodide (XIV : X = I), in a similar way, and was recrystallized from 80% EtOH to yellow needles, m.p. 239~241° (reported[23] m.p. 232° (decomp.)). UV λ_{max}^{EtOH} mμ(log ε) : 264(4.68), 302(4.10), 313(4.18) (cf. Fig. 4).

The picrate was purified from EtOH to yellow pillars, m.p. 191~192° (reported[23] m.p. 192~193°). *Anal.* Calcd. for $C_{23}H_{16}O_7N_4$: C, 60.00; H, 3.50; N, 12.17. Found : C, 59.66; H, 3.85; N, 12.12.

In order to confirm the structure of (XIV), catalytic hydrogenation was carried out. After 0.72 g. of (XIV: X = I) was converted to the corresponding chloride in the usual way, it was subjected to hydrogenation over Adams' catalyst in EtOH at a room temperature and 2 mol. equiv. of H_2 (94 cc., 105% of the calculated amount) was taken up in 2 hr. After filtration of the catalyst and evaporation of the solvent, the resultant residue was dissolved in 20 cc. of water, made alkaline with $NaHCO_3$ and extracted with benzene. The solvent was evaporated *in vacuo* to leave 0.45 g. of solid, which was recrystallized from hexane to yellow needles, m.p. 85°; yield, 95.7%. This was shown both by ultraviolet spectral comparison (λ_{max}^{EtOH} mμ(log ε) : 265(2.95), 272(2.96)) and by mixed m.p. determination to be identical with an authentic sample of (VIII).

The picrate was recrystallized from EtOH to yellow needles, m.p. 148~150°, which was identified with an authentic sample by mixed m.p. determination.

Dehydrogenation of (−)-2′-Acetylemetine (Ic) with Mercuric Acetate—The starting material, (−)-2′-acetylemetine (Ic) was prepared from natural (−)-emetine according to the method of Reichstein, *et al.*,[24] and was recrystallized from Et_2O to white prismatic needles, m.p. 97~99° (reported[24] m.p. 97~99°).

To a solution of 1 g. of (Ic) in 10 cc. of 5% AcOH a solution of 1.47 g. of $(AcO)_2Hg$ in 5 cc. of 5% AcOH was added and the whole was heated in a water bath kept at 90~95°. In about 30 min., AcOHg began to precipitate out and heating was continued for 2 hr. From the cooled reaction mixture, AcOHg was collected by filtration and washed with 5% AcOH. The filtrate was heated on a water bath at 100° and saturated with H_2S to remove excess Hg ion as HgS. After filtration while warm, the filter cake was washed thoroughly with hot 5% AcOH. The combined filtrate was concentrated *in vacuo* to ca. 10 cc. and excess of 30% $HClO_4$ was added. When the whole mixture was allowed to stand at a room temperature, there separated amorphous white solid, which was collected by filtration, washed with water and Et_2O, and dried. Yield, 0.9 g. This product was recrystallized from tetrahydrofuran containing a small amount of MeOH to furnish white prisms. When dried at a room temperature for 2 days over P_2O_5 *in vacuo*, it melted at 161~164°. *Anal.* Calcd. for $C_{31}H_{41}O_9N_2Cl \cdot 4H_2O$: C, 53.71; H, 7.07; N, 4.04. Found : C, 53.28; H, 6.66; N, 3.87. UV : λ_{max}^{EtOH} mμ (log ε) : 291 (4.06), 302(4.04); λ_{min}^{EtOH} mμ(log ε) : 264(3.53), 320(3.83). IR $\nu_{C=N}$ 1643 cm^{-1}.

The summation of UV spectra of (XII) and (VIIIf) gave a spectrum remarkably similar to that of the above product, as shown in Fig 2. This was the main reason why 5,11b-dehydro-2′-acetyl-

23) S. N. Chakravarti, R. D. Haworth, W. H. Perkin, Jr. : J. Chem. Soc., **1927**, 2275.
24) A. Ahl, T. Reichstein : Helv. Chim. Acta, **27**, 366(1944).

emetinium perchlorate tetrahydrate (IIIc) was assigned to this compound. Its infrared absorption spectrum also supported this assignment, which will be discussed in the following paper.[10]

Additionally, in order to raise the yield of this product (IIIc), the foregoing procedure was modified as follows: A solution of 10 g. of 2′-acetylemetine and 16 g. of $(AcO)_2Hg$ in 180 cc. of glacial AcOH was heated in a water bath kept at 60°. In 30 min., AcOHg began to precipitate out and heating was continued for 7 hr. The reaction mixture was worked up as described above to give 13 g. (98%) of crude product of (IIIc).

Dehydrogenation of (−)-2′-Benzoylemetine (Ib) with Mercuric Acetate—(−)-2′-Benzoylemetine was prepared from natural emetine according to the method of Späth, *et al.*[30] and was recrystallized from dehyd. EtOH to white prismatic needles, m.p. 181~182° (reported[25] m.p. 185~186°).

A solution of 5 g. of (Ib) and 6 g. of $(AcO)_2Hg$ in 90 cc. of 10% AcOH was heated in a water bath kept at 60~70°. In about 30 min., AcOHg began to precipitate out and heating was continued for 2 hr. The reaction mixture was treated in the usual fashion to furnish 5.9 g. (98%) of a quaternary perchlorate, which was recrystallized from EtOH to white needles. When dried at a room temperature for 2 days over P_2O_5 *in vacuo*, it melted at 163~165°. *Anal.* Calcd. for $C_{36}H_{43}N_9Cl \cdot H_2O$: C, 61.66; H, 6.47; N, 4.00. Found: C, 61.26; H, 6.47; N, 4.06. UV λ_{max}^{EtOH} mμ(log ε): 291(4.04), 302(3.99); λ_{max}^{EtOH} mμ(log ε): 265(3.56); 322(3.77). IR $\nu_{C=N}$ 1644 cm^{-1}.

The summation of UV sbsorption spectra of (XII) and (VIIIe) gave a spectrum remarkably similar to that of the above product as shown in Fig. 2.

The authors wish to express their gratitude to Professor Emeritus S. Sugasawa of the University of Tokyo, for his encouragement throughout this work. Thanks are also due to Mr. K. Narita of the Central Analysis Room of this Institute, and to Mrs. F. Hisamichi and Messrs. T. Yoda and T. Kono of Tokyo Research Laboratories, Tanabe Seiyaku Co., Ltd., for elemental analyses. A part of expenses for the present work was defrayed by the Grant-in-Aid for Developmental Scientific Researches from the Ministry of Education, which is gratefully acknowledged.

Summary

Mercuric acetate dehydrogenation of (−)-2′-acylemetines, which have the same configuration as (−)-emetine, was found to afford 5,11b-dehydro-2′-acylemetines. In preliminary experiments, it was shown that 1-alkyl-1,2,3,4-tetrahydroisoquinoline derivatives are dehydrogenated with the same reagent to afford 3,4-dihydro compounds, but the corresponding 2-acyl compounds resisted similar dehydrogenation. These results seem to strongly support Openshaw's view about the structure of tetradehydroemetine.

(Received July 31, 1959)

25) E. Späth, W. Leithe: Ber., **60**, 697(1927).