Structure of Didehydroemetine and *O*-Methylpsychotrine

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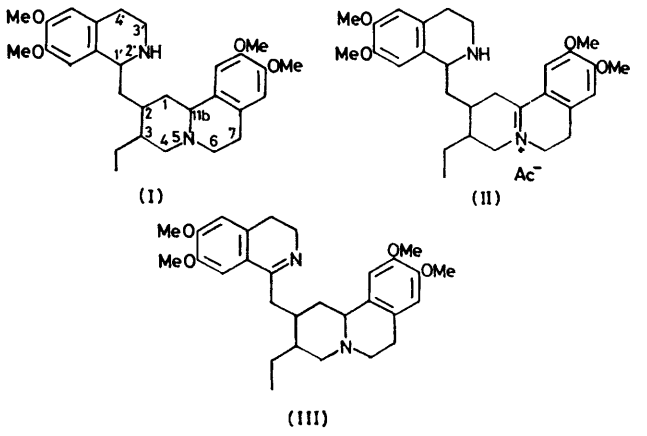
From an investigation of the didehydroemetine structure, it is concluded that the double bond is situated in the 1,2-position of the isoquinoline-moiety and not in the benzo[*a*]quinolizine moiety, as has generally been accepted up to now. The same position of the double bond is also found for the corresponding didehydrocephaeline. Consequently the double bond in *O*-methylpsychotrine and psychotrine must be situated exocyclic at the C(1) atom of the isoquinoline moiety. This is confirmed by deuterium-exchange experiments. It is shown that didehydroemetine and *O*-methylpsychotrine are tautomers.

ONE of the products isolated by us [1] in a qualitative investigation of the photochemical and thermochemical decomposition of emetine (I) conformed to the didehydroemetine ‡ described by Auterhoff and Jacobi [2] and Jacobi [3] who designated structure (II) to this compound. This didehydroemetine was synthesized according to Jacobi [3] by oxidation of emetine with mercuric acetate. On the basis of their u.v., i.r., and mass spectra and their t.l.c. behaviour the synthesized didehydroemetine and the above mentioned isolated product were identical. The mass spectrum of didehydroemetine (Jacobi) is, however, not that expected from structure (II), but, rather, that of *O*-methylpsychotrine.



(I) (II)

(III)

The latter compound, to which structure (III) is assigned in the recent literature, can be isolated from the mother-liquor obtained in the emetine isolation from ipecacuanha extract.[3,4] However the t.l.c. behaviour of the compounds is totally different. When using silica gel plates with chloroform–methanol–ammonia (80 : 20 : 1) as a developing medium, the R_F value of *O*-methylpsychotrine is 0.85 and that of didehydroemetine (Jacobi) is 0.10.

A detailed discussion of the mass spectra of ipecacuanha alkaloids is given by Budzikiewicz *et al.*,[5] and based hereupon, a simplified fragmentation pattern for *O*-methylpsychotrine is presented in Scheme 1.

Similarly a fragmention pattern for emetine, based on the work of Budzikiewicz *et al.*[5] is presented in Scheme 2 (see also Spiteller and Spiteller-Friedmann [6]).

It appears that of those ipecacuanha alkaloids, which, have a dihydroisoquinoline moiety, such as *O*-methylpsychotrine, the fragmention occurs by the α-route.

If a tetrahydroisoquinoline moiety is present in the molecule as in emetine itself, the fragmention routes α and β (and γ) can occur, of which the β-route is favoured (Budzikiewicz *et al.*[5]). In both the mass spectra of emetine and *O*-methylpsychotrine, a fragment can be detected with *m/e* 176, which is not mentioned by Budaiewicz *et al.*,[5] but could have originated from (1), *m/e* 191, by loss of a methyl radical.

In the above mentioned compounds there is always a hexahydrobenzo[*a*]quinolizidine moiety, from which the fragments e to i and p originate. If however an extra double bond is present in this part of the molecule, as in tetradehydroemetine (IV) this can be observed clearly in the fragmention pattern. When tetradehydroemetine is brought into the mass spectrometer as hydroxide, water is split off first by evaporation (see also Openshaw and Wood [7] and Fujii *et al.*[8] who have evidence of migration of this double bond in basic medium, in the given way). The fragmention pattern which is detected for tetradehydroemetine, synthesized according to Battersby and Openshaw,[9] is shown in Scheme 3 in a simplified form.

In the mass spectrum of tetradehydroemetine no fragmentation following the γ-route can be detected, as is the case for *O*-methylpsychotrine; the fragments k and l, originating from this γ-route, do not appear. In the spectrum of tetradehydroemetine the fragment *m/e* 190 originates from the fragment d, *m/e* 205, as proven by the appearance of a metastable peak at *m/e* 176.1 ($205^{+\cdot} \rightarrow 190^{+} + CH_3\cdot$); the metastable peak at *m/e* 147.7 is a proof for the decay: $205^{+\cdot} \rightarrow 174^{+} + OCH_3\cdot$.

From the foregoing it is obvious that if there is an extra double bond in the hexahydrobenzo[*a*]quinolizine moiety of the molecule, in comparison to emetine, the fragments originating from this moiety in the mass spectrum have *m/e* 2 units less than in the absence of this double bond, *e.g.* *m/e* 273—272 is shifted to *m/e* 271—270,

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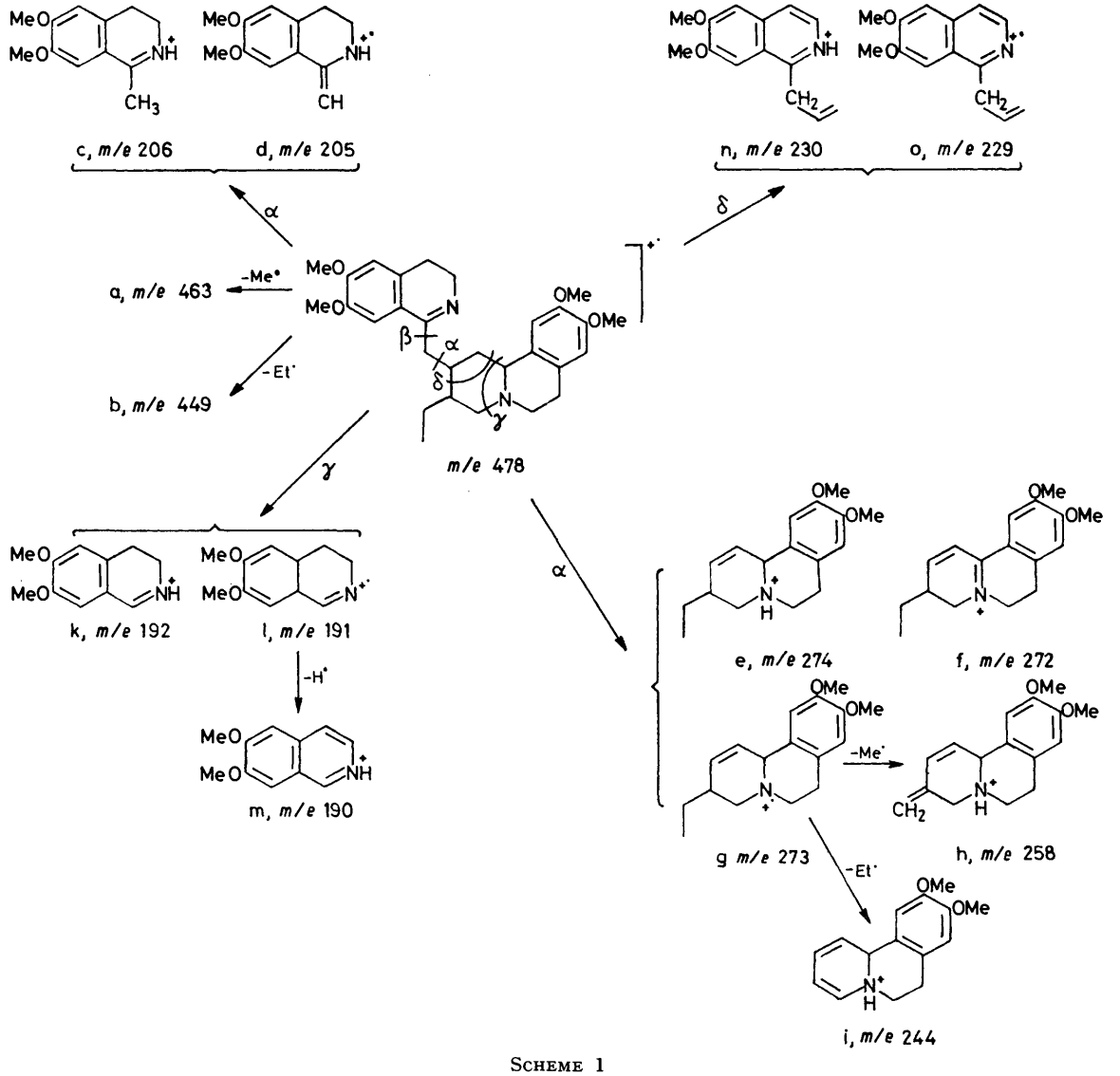
‡ In the literature the name assigned to this compound is ambiguous, because there are several other dihydroemetines, such as *O*-methylpsychotrine, *etc.* To prevent any confusion we refer to the compound as didehydroemetine (Jacobi).

m/e 258 to *m/e* 256 and *m/e* 244 to *m/e* 242 (compare the mass spectra for the other ipecacuanha alkaloids given by Budzikiewicz *et al.*[5]).

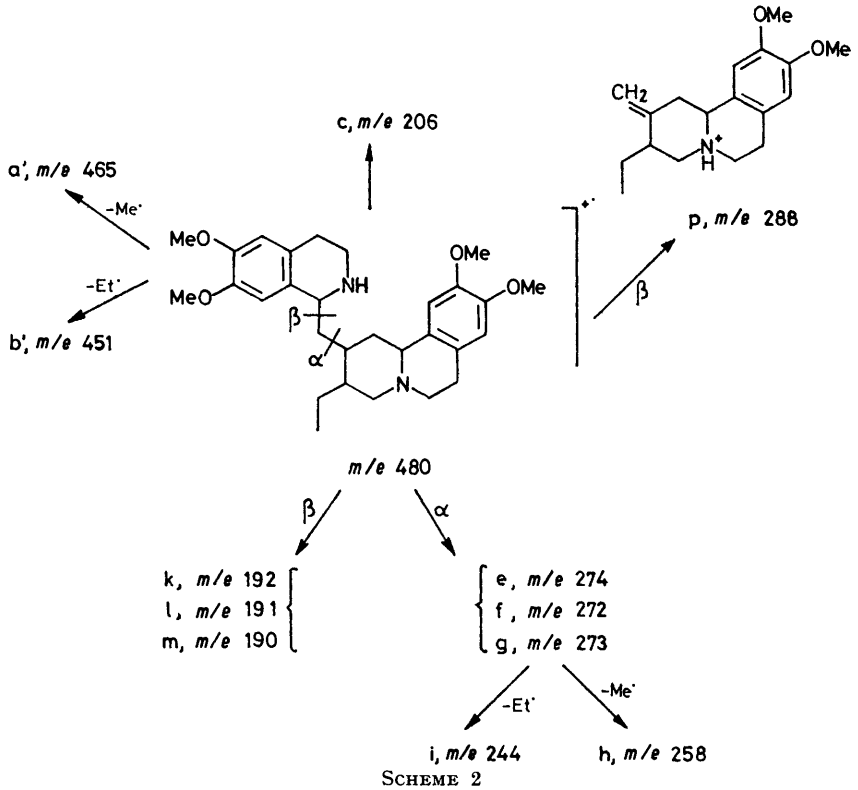
From the foregoing it is also obvious that when an extra double bond is present in the tetrahydroisoquinoline moiety of the molecule, in comparison to emetine, this can be detected in the mass spectrum.



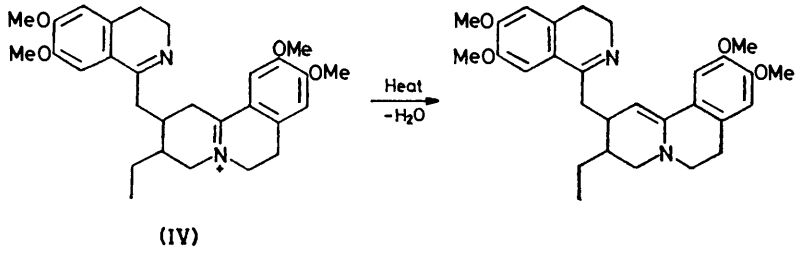
SCHEME 1

In the mass spectrum of didehydroemetine (Jacobi) the parent peak, at *m/e* 478, is two units less than that of emetine from which the first compound is formed, thus indicating the presence of an extra double bond. As the mass spectrum of didehydroemetine (Jacobi) contains fragments at *m/e* 274—272, *m/e* 258 and 244, it shows that the extra double bond is not situated in the hexahydrobenzo[*a*]quinolizine moiety of the molecule. The fragments originating from the isoquinoline-moiety of the molecule appear at the same positions as those of *O*-methylpsychotrine. These facts support a structure for didehydroemetine (Jacobi) in which this extra double bond is situated in the tetrahydroisoquinoline moiety and not in the hexahydrobenzo[*a*]quinolizine moiety, as was originally accepted by Auterhoff and Jacobi [2] and Jacobi.[3] The same is true for the corresponding didehydrocephaeline, which for reasons of comparison was synthesized from cephaeline with mercuric acetate (see also Kovar *et al.*,[10] Andreas [11]). The mass spectrum of didehydrocephaeline agreed with that of psychotrine.[5]

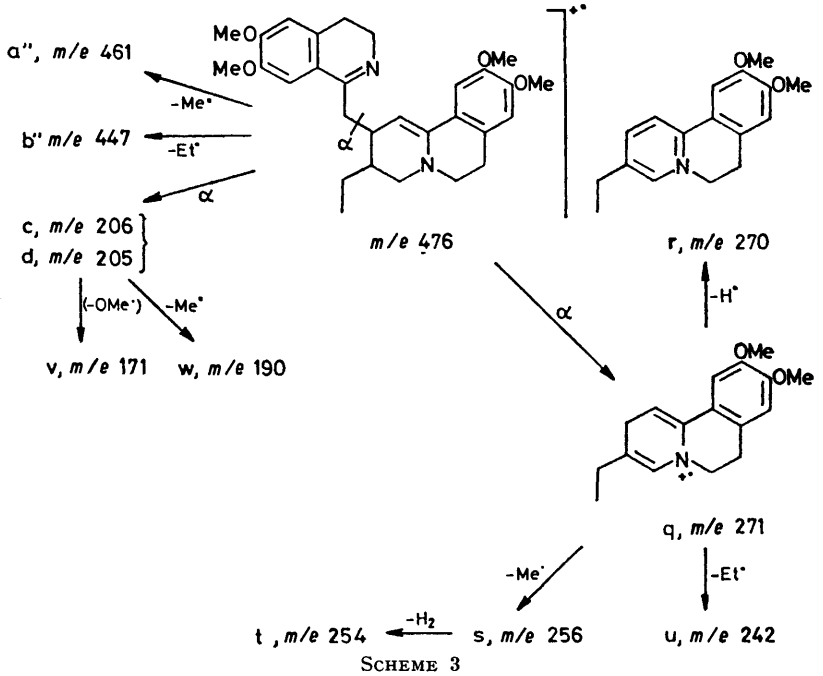
To determine the exact position of the afore-mentioned double bond in didehydroemetine (Jacobi), 1-ethyl-1,2,3,4-tetrahydro-6,7-dimethoxyisoquinoline (V), which is comparable with the tetrahydroisoquinoline moiety of the emetine molecule, was converted into the didehydro-compound (VI). This was performed under the same conditions as the oxidation of emetine into didehydroemetine (Jacobi), namely with mercuric acetate. Compound (V) was obtained by reduction of



SCHEME 2

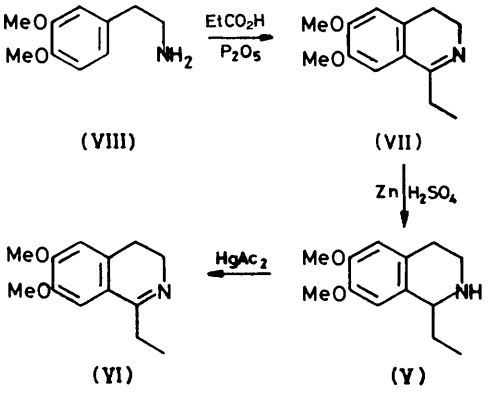


(IV)



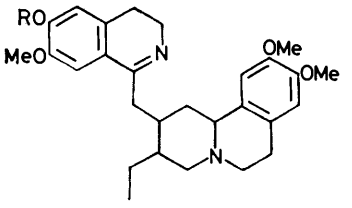
SCHEME 3

the corresponding 3,4-dihydro-compound (VII) with zinc in sulphuric acid;[12] (VII) was synthesized from homoveratrylamine (VIII) and propionic acid [13] (Scheme 4) according to the Bischler–Napieralski reaction.[14]



SCHEME 4

Compounds (VI) and (VII) have identical u.v., i.r., and mass spectra and their t.l.c. behaviour is also identical. From their n.m.r. spectra, the position of the double bond is also shown to be identical for the two compounds. The foregoing facts support the structure represented by (IXa) for didehydroemetine (Jacobi) and the structure represented by (IXb) for the corresponding didehydrocephaeline.



(IX)
a; R = Me
b; R = H

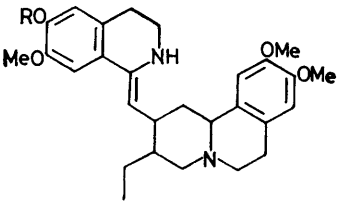
From the t.l.c. behaviour of didehydroemetine (Jacobi) (IXa) and *O*-methylpsychotrine, it can be concluded that these compounds differ, although their mass spectra are identical. Both compounds possess an extra double bond as compared to emetine.

Reduction of *O*-methylpsychotrine gives emetine and isoemetine (Dietz,[4] Auterhoff and Merz,[15] Merz,[16] and the references mentioned in these publications).

Since emetine and isoemetine are stereoisomeric at C-1′ the double bond in *O*-methylpsychotrine must be located here. As a consequence of this and bearing in mind the structure of didehydroemetine (Jacobi), *O*-methylpsychotrine has to be represented by structure (Xa), and psychotrine by (Xb).

Up to now there has been confusion about the location of this double bond in *O*-methylpsychotrine. Pyman [17] synthesized a *N*-benzoyl derivative of *O*-methylpsychotrine, while Karrer *et al.*[18] and Hazlett and McEwen [1] could obtain *N*-derivatives of *O*-methylpsychotrine. These facts gave rise to the assumption that the double bond must be exocyclic as in (Xa).

However Brossi *et al.*[20] showed that successful *N*-acylation need not necessarily be proof of the absence of an endocyclic double bond in which the N-atom would be tertiary, since double bond migration to the exocyclic position could occur during acylation. Openshaw and Wood [7] and Battersby *et al.*[21] concluded from u.v. spectral data that the double bond must be exocyclic although Evstigneeva and Preobrazhensky [22] had shown that the u.v. spectra permit no differentiation between an endo- and exo-cyclic double bond. Further, Battersby *et al.*[21] found no absorption originating from a NH-bond in the i.r. spectrum, which points towards the presence of an endocyclic double bond. Evstigneeva and Preobrazhensky [22] reported similar negative results for *O*-methylpsychotrine, although a reference compound,



(X)
a; R = Me
b; R = H

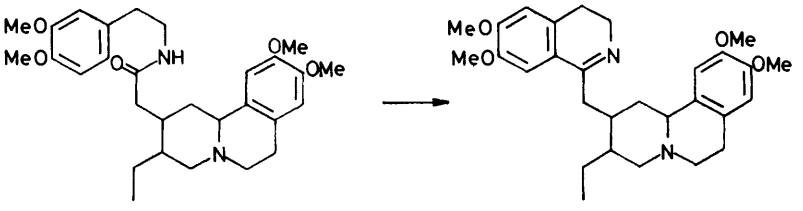
dihomoveratrylamine, showed NH absorption at 3 293.5 cm^{-1}. They drew no conclusion concerning the location of the double bond from this however since *O*-methylpsychotrine contains water of crystallization which would obscure very small NH stretching in this region. Similarly, negative results were obtained upon deuterium exchange for *O*-methylpsychotrine. Unfortunately the same was true for dihomoveratrylamine, although the absorption between 1 200 and 1 700 cm^{-1} led them to conclude that an NH-bond was absent. However, this is an area in which the difference between *O*-methylpsychotrine, didehydroemetine (Jacobi), and emetine is not easily observed, so that the presence of this absorption cannot be considered as a proof.

An attempt was also made to locate the position of the double bond by synthesis of *O*-methylpsychotrine *via* a Bischler–Napieralski reaction. Thus, the hexahydrobenzo[*a*]quinolizine moiety was pre-synthesized after which the ring closure is carried out *via* the amide, resulting in the isoquinoline moiety of the molecule (Scheme 5).

Although in the Bischler–Napieralski reaction the double bond formed is usually endocyclic, this is certainly not always the case.[14] Thus the synthetic pathway cannot be used as a proof for the location of the double bond.

Evstigneeva and Preobrazhensky [22] suggest the possibility of tautomerism between the endocyclic and the exocyclic compound, a proposal supported by other workers.[15,16,24-26] We showed that such tautomerism

existed between *O*-methylpsychotrine and didehydroemetine (Jacobi) because one of the products formed on irradiating *O*-methylpsychotrine was didehydroemetine (Jacobi), the reverse occurring upon the irradiation of didehydroemetine (Jacobi).[1] This tautomerism is not catalysed by acid or base. Our conclusion that *O*-methylpsychotrine has to be represented by structure (Xa) and didehydroemetine (Jacobi) by (IXa) and that they are tautomeric forms of each other is supported by the results of deuterium experiments. After recording the mass spectrum of emetine, D_2O was introduced into the mass spectrometer and a mass spectrum was recorded again. As expected, it appeared that deuterium exchange had taken place, the peak at *m/e* 481 being much enhanced; it could be calculated that *ca.* 30% deuterium exchange had taken place. When mass spectra were recorded for *O*-methylpsychotrine in the same way, it appeared that in this case deuterium exchange had also occurred since the peak at *m/e* 479 was much enhanced; *ca.* 32% exchange had taken place. Thus in these experiments *O*-methylpsychotrine reacted in the same way as emetine, indicating a free NH and an exocyclic double bond. When mass spectra of didehydroemetine (Jacobi) were recorded before and after the introduction of D_2O it appeared that only very weak enhancement of the peak at *m/e* 479 had taken place (*ca.* 4%); thus in this case there is no free NH. This experiment was repeated after heating didehydroemetine (Jacobi) for a much longer time at 200 °C in the mass spectrometer; now it appeared that the deuterium exchange had taken place for a greater part (*ca.* 12%), which agrees with the above mentioned tautomerism.



(XI) (XII)

SCHEME 5

EXPERIMENTAL

T.l.c. was carried out on DC-Fertigplatten silica gel GF_{254} (Merck) with chloroform–methanol–ammonia (25%) (80 : 20 : 1) for development; detection was by means of u.v. light at 254 or 366 nm. For column chromatography Silica gel 60 (Merck) (0.062—0.200 mm) was used with the same solvent system for development as that used for t.l.c. U.v. spectra were recorded by means of a Perkin-Elmer EPS-3T spectrometer; methanol acidified with 2N-hydrochloric acid was used as solvent. A Jeol PS-100 spectrometer was used for recording the n.m.r. spectra and and AEI MS-902 mass spectrometer (with D_2O *via* cold inlet) for the mass spectra. The n.m.r. signals are given in p.p.m. (δ).

The thermochemical decomposition of emetine was carried out in aqueous solution at 100 °C. The photochemical decomposition of emetine was carried out in aqueous solution in a quartz vessel with a Rayonet Photochemical Reactor (RPR 208) equipped with 8 lamps which emit light of 254 nm (RUL 2 537 Å).

Didehydroemetine.—This was synthesized according to the method of Jacobi.[3] U.v. maxima at 290, 302, and 355 nm were in agreement with literature values.[10,27]

Didehydrocephaeline.—This was synthesized in a similar way to that described for didehydroemetine. U.v. maxima at 295, 303, and 355 nm were in agreement with Kovar *et al.*[10]

Tetradehydroemetine.—This was synthesized according to the method of Battersby and Openshaw.[9] U.v. maxima at 245, 308, 358 nm were in agreement with the data of Battersby and Openshaw [9] and Kovar.[27]

1-*Ethyl*-3,4-*dihydro*-6,7-*dimethoxyisoquinoline* (VII).—This was synthesized according to the method of Spath and Polgar [13] (see Ban *et al.*[28]). U.v. maxima at 246, 305, and 365 nm. N.m.r.: singlets at 6.96 (1 H), 6.63 (1 H), and 3.84 (6 H); triplets at 3.56—3.70 (2 H) and 1.15—1.29 (3 H); and a multiplet at 2.32—2.84 (4 H).

1-*Ethyl*-1,2,3,4-*tetrahydro*-6,7-*dimethoxyisoquinoline* (V) was synthesized according to the method of Dey and Govindachari.[12] U.v. maxima at 235 and 284 nm. N.m.r.: singlets at 6.60 (1 H), 6.54 (1 H), 3.83 (6 H), and 2.26 (1 H, broad); triplet at 0.94—1.08 (3 H); quartet at 1.68—1.90 (2 H); multiplet at 2.64—3.29 (5 H).

Oxidation of (*V*).—This was carried out with mercuric acetate as described in the synthesis of didehydroemetine. The purification was carried out by means of column chromatography; on t.l.c. only one spot could be detected with an R_F value equal to that of (VII) (*ca.* 0.85). The u.v. and the n.m.r. spectra were equal to those of (VII) (see also Ban *et al.*[28]).

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