EMDE DEGRADATION OF SOME RHOEADINE
AND ISORHOEADINE DERIVATIVES*

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Dedicated to Professor F. Šantavý on the occasion of his 60th birthday.

An analysis of the CD spectra showed that the products *IX* and *XII* of the Emde degradation of rhoeadine *(I)* and isorhoeadine *(V)* are diastereoisomers. The enantiomeric substances *XIV* and *XV* arise by degradation of rhoeageninediol *(VII)* and isorhoeageninediol *(VIII)*, which chemically confirms the configuration of isorhoeadine *(V)* at $C_{(5)}$.

Within the scope of a systematic study of the alkaloids from *Papaver rhoeas* L., we also paid attention[1-3] to the chiroptical properties of some degradation products of rhoeadine *(I)* and isorhoeadine *(V)*. The Emde degradation of rhoeadinemethiodide $(I.CH_3I)$ yielded[1] the substance *IX*. Recently, a paper[4] has been published on the degradation of the methiodides 1-epialpinine *(II)* and O-methylalpinigenine *(VI)*.** On degradation of the substance *II*, the main reaction product was the substance *X* and, on degradation of the substance *VI*, its enantiomer. Since the alkaloids rhoeadine *(I)* and 1-epialpinine *(II)* possess[6,7] the same absolute configuration, their degradation products should have analogous CD spectra. However, contrary to the substance *IX* which exhibits[1] two Cotton effects at 279 nm $(\Delta\varepsilon + 1\cdot39)$ and 296 nm $(\Delta\varepsilon - 3\cdot50)$ within the ^1L_b-band, the substance *X* shows[4] a Cotton effect at 282 nm $(\Delta\varepsilon - 1\cdot01)$. This discrepancy prompted us to study the course of the Emde degradation of rhoeadine alkaloids.

In addition to the previously described[1] substance *IX*, the polar fractions after the Emde degradation of rhoeadinemethiodide $(I.CH_3I)$ have given an optically inactive alcohol. Its PMR spectrum exhibits one proton $(4\cdot27$ p.p.m.$)$ which is exchangeable for deuterium. The singlet at $2\cdot27$ p.p.m. $(6$ H$)$ corresponds to protons of the dimethylamino group, the multiplet at $2\cdot1-3\cdot0$ $(4$ H$)$ is attributable to the fragment

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$ArCH_2CH_2N$. The chemical shift of the singlet at 2·82 (4 H) corresponds to aliphatic protons vicinal to the aryl and is assignable to the $ArCH_2CH_2Ar$ grouping. The singlet at 4·70 (2 H) is ascribed to the hydroxymethyl group on the aromatic nucleus. The two singlets at 5·88 (2 H) and 5·93 (2 H) are attributable to the methylenedioxy groups, the singlets at 6·58 (1 H), 6·65 (2 H) and 6·70 (1 H) to the aromatic protons. On the basis of these data, the isolated substance was assigned the structure *XIII* which was also confirmed by the interpretation of the PMR spectrum of its acetyl derivative. An attempt to convert the substance *IX* into the optically inactive compound *XIII* by reaction with sodium amalgam proved to be a failure, which indicates that the substance *XIII* arises by another mechanism than *via* the intermediary product *IX*. It was, however, obtained by the Emde degradation of all the studied substances.
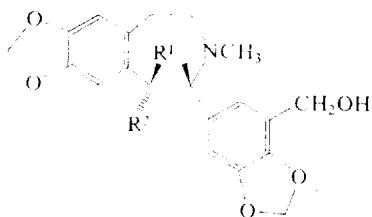
The Emde degradation of rhoeageninemethiodide (*III*.CH_3I) yielded the alcohol *XIII* besides the optically active diol. The structure *XIV* for this diol resulted from the interpretation of the PMR spectra of the diol and its diacetyl derivative. The same
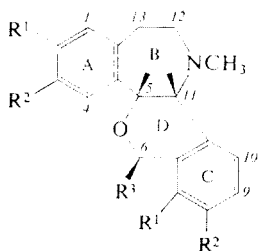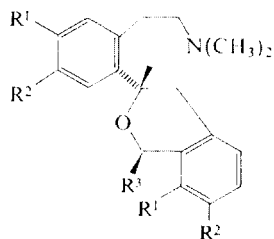

I, $R^1 + R^2 = OCH_2O$, $R^3 = OCH_3$

II, $R^1 = R^2 = R^3 = OCH_3$

III, $R^1 + R^2 = OCH_2O$, $R^3 = OH$

IV, $R^1 + R^2 = OCH_2O$, $R^3 = H$
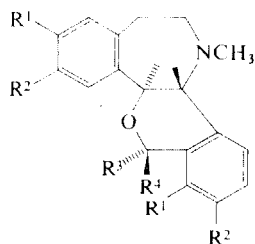
V, $R^1 + R^2 = OCH_2O$, $R^3 = H$, $R^4 = OCH_3$

VI, $R^1 = R^2 = R^4 = OCH_3$, $R^3 = H$

VII, $R^1 = H$, $R^2 = OH$

VIII, $R^1 = OH$, $R^2 = H$

IX, $R^1 + R^2 = OCH_2O$, $R^3 = OCH_3$

X, $R^1 = R^2 = R^3 = OCH_3$

XI, $R^1 + R^2 = OCH_2O$, $R^3 = H$

products (*XIII* and *XIV*) were obtained by Emde degradation of the rhoeagenine-diolmethiodide (*VII*.CH_3I). Emde degradation of rhoeageninemethiodide (*III*.CH_3I) probably proceeds in two steps. The first is reduction of the half-acetal group of *III*.CH_3I to the diol which is further degraded.

The Emde degradation of isorhoeadinemethiodide (*V*.CH_3I) and isorhoeagenine-diolmethiodide (*VIII*. CH_3I) takes place in a similar manner. In both cases there was isolated the optically inactive alcohol *XIII*. The optically active product of the Emde degradation of isorhoeadinemethiodide (*V*.CH_3I) was the substance *XII* which, on the basis of the value of the optical rotation is diastereoisomeric with the substance *IX*, obtained from rhoeadinemethiodide (*I*.CH_3I). The chemical shift of the proton at $C_{(5)}$ (4·95 q, $[J_{AX} + J_{BX}] = 15$ Hz) in the substance *XII* evidences[5] a *trans*-arrangement of the hydrogen H-5 and of the methoxyl group at $C_{(6)}$. In the compound *IX* (*cis*-arrangement), the signal of the proton at $C_{(5)}$ is shifted downfield (5·30 q, $[J_{AX} + J_{BX}] = 15·0$ Hz). The sum of the coupling constants of the proton H-5 in the compounds *IX* and *XII* indicates that in these two substances the ring A is equatorially oriented. The CD spectra of these two substances are mirror images (Fig. 1). Under the assumption[1] of a small contribution of the methoxyl group at $C_{(6)}$ to CD, the substances *IX* and *XII* have the same conformation of the ring D but a reverse helicity.

XII

XIII

XIV, $R^1 = OH$, $R^2 = H$
XV, $R^1 = H$, $R^2 = OH$

XVI
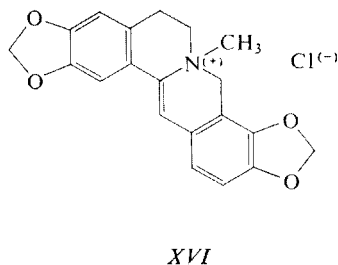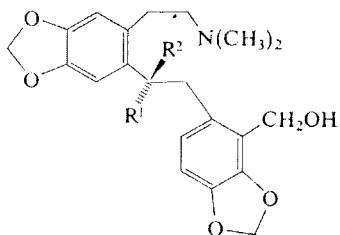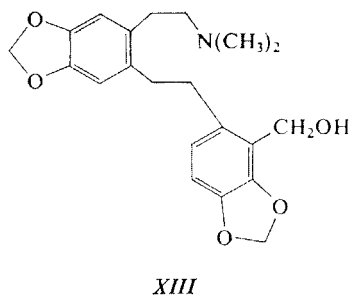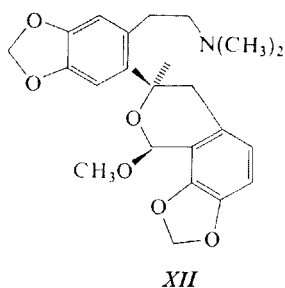
For the verification of the validity of this assumption, we prepared 6-demethoxy-rhoeadine (IV) by introduction of dry hydrogen chloride into a solution of rhoeagenine-ninediol (VII). The isolated by-product was isoprotopiniumchloride (XVI), the rise of which can be explained by substitution of the two hydroxyl groups of rhoeagenine-ninediol (VII) with chlorine and following cyclization and dehydrohalogenation under simultaneous rearrangement of the seven-membered ring B into a six-membered ring. 6-Demethoxyrhoeadine (IV) was already earlier prepared[8] by heating rhoeagenine-diol (VII) with 2M-HCl. The Emde degradation of 6-demethoxyrhoeadinemethiodide $(IV.CH_3I)$ yielded, in addition to the substance $XIII$, the substance XI possessing one center of chirality at $C_{(5)}$. Its CD in the region between $270-300$ nm $(^1L_b$ transition$)$ is almost identical with that of the substance IX (Fig. 1).
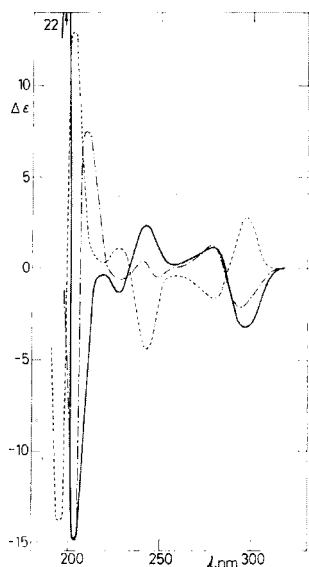
The Emde degradation of isorhoeageninediolmethiodide $(VIII.CH_3I)$ gave, besides the alcohol $XIII$, the diol XV which, on the basis of the value of the optical rotation and the CD spectrum, is enantiomeric with the diol XIV prepared from the methiodides of rhoe-agenine (III) and rhoeageninediol (VII). Thus it has chemically been confirmed that the alkaloids rhoeadine (I) and isorhoeadine (V) differ only by their configuration at $C_{(5)}$.

FIG. 1

CD Spectra of the Compounds IX (------),
XI (--·--·-·), and XII (— — —)

EXPERIMENTAL

The melting points were determined on a Kofler block and are uncorrected. Preparative column chromatography was carried out on alumina (activity II, Reanal, Hungary), thin-layer chromatography on silica gel G (Merck, Darmstadt) by using the solvent systems S_1 (cyclohexane–diethyl-amine 8 : 2) and S_2 (xylene–2-butanone–methanol–diethylamine 46 : 45 : 7 : 2). The PMR spectra were measured on a Varian T-60 in a 5% w/v concentration using tetramethylsilane as an internal standard in deuteriochloroform, the chemical shifts are given as δ (p.p.m.) values. The UV spectra were measured on a Unicam SP 700 spectrophotometer in 95% ethanol, the IR spectra on an Infrascan H-900 in chloroform, the optical rotations on a polarimeter Hilger-Watts, and the CD spectra on a Roussel-Jouan dichrograph (Model 185) at 20°C in cells of 0·01 to 2·00 cm thickness; all the values are given as λ_{max} $(\Delta\varepsilon)$. The starting material was rhoeadine (I), m.p.

251—253°C (ethyl acetate) (ref.[1]), isorhoeadine (*V*), m.p. 159—161°C (ether) (ref.[1]), rhoeagenine-diol (*VII*), m.p. 131—133°C (ethyl acetate) and isorhoeageninediol (*VIII*), m.p. 153—155°C (ether). The methiodides were prepared by boiling tertiary amine for eight hours with an excess of methyliodide in acetonitrile. The unreacted starting substance was separated chromatographically.

The Emde degradation of rhoeadinemethiodide (I.CH₃I). To the suspension of rhoeadinemethiodide (1 g) in 50 ml of 50% aqueous methanol, 4 g of 3% sodium amalgam was added. The mixture was left standing for 48 hours at room temperature. After concentration *in vacuo* to half of its volume and extraction with ether, a mixture of two substances (0·41 g) was obtained. Column chromatography with benzene–chloroform (9 : 1) yielded 0·27 g of the substance *IX*, m.p. 134—135°C (ethyl acetate) (ref.[1], m.p. 134—135°C), $[\alpha]_D^{24}$ +15° ± 3° (*c* 0·64 in methanol), +22° ± 2° (*c* 0·75 in chloroform). R_F 0·61 (S_1), 0·67 (S_2). Elution with chloroform gave 0·11 g of the substance *XIII*, m.p. 136—137°C (chloroform), optically inactive, λ_{max} 237 and 291 nm (log ε 3·96 and 3·94). For $C_{21}H_{25}NO_5$ (371·4) calculated: 67·91% C, 6·78% H, 3·77% N; found: 67·72% C, 6·78% H, 3·48% N.

The Emde degradation of rhoeageninemethiodide (III.CH₃I). The procedure as described for the Emde degradation of rhoeadinemethiodide yielded 0·52 g of a mixture of two substances from rhoeageninemethiodide (1 g). Chromatography with chloroform gave 0·33 g of the compound *XIII*. Elution with chloroform–ethanol (9 : 1) gave 0·14 g of the substance *XIV*, m.p. 135—136°C (ethyl acetate-ethanol), $[\alpha]_D^{24}$ +112° ± 3° (*c* 0·87 in methanol), +63° ± 3° (*c* 0·98 in chloroform). PMR: 2·10 s (N(CH₃)₂); 2·3—3·3 m (ArCH₂CH₂N, —CH₂CH(OH)—); 4·92 q, [J_{AX} + J_{BX}] = = 13·5 Hz (—CH(OH)CH₂—); 4·70 s (—CH₂OH); 5·93 s and 5·97 s (2 O—CH₂—O); 6·58 s (Ar—H); 6·67 bs (2 Ar—H); 7·02 s (Ar—H). λ_{max} 237 and 292 nm (log ε 3·92 and 3·91). For $C_{21}H_{25}NO_6$ (387·4) calculated: 65·10% C, 6·50% H, 3·62% N; found: 65·02% C, 6·45% H, 3·45% N.

Acetylation of the compounds XIII *and* XIV. The compound *XIV* (0·10 g) in pyridine (2 ml) and acetic anhydride (2 ml) were left standing at room temperature for 24 h. Pyridine and acetic anhydride were distilled off *in vacuo*, the residue was dissolved in chloroform and the solution shaken with 10% NaHCO₃. After evaporation of the chloroform layer, the yield gave 0·072 g of the oily diacetylderivative of the substance *XIV*, $[\alpha]_D^{24}$ +64° ± 3° (*c* 0·68 in methanol). PMR: 1·98 s and 2·07 s (2 CH₃CO); 2·23 s (N(CH₃)₂); 2·3—3·3 m (ArCH₂CH₂N, —CH₂CH. . (OCOCH₃)—); 5·08 s (—CH₂OCOCH₃); 5·90 s and 5·92 s (2 O—CH₂—O); 6·08 q, [J_{AX} + + J_{BX}] = 14·0 Hz (—CH(OCOCH₃)CH₂—); 6·57 s (Ar—H); 6·40 d and 6·63 d, J_{ortho} = = 8·0 Hz (2 Ar—H); 6·87 s (Ar—H).

The acetyl derivative of the substance *XIII*, m.p. 71—73°C (n-hexane), was prepared in an analogous manner. PMR: 2·07 s (CH₃CO); 2·27 s (N(CH₃)₂); 2·2—3·0 m (ArCH₂CH₂N); 2·77 s (ArCH₂CH₂Ar); 5·13 s (—CH₂COCH₃); 5·90 s and 5·98 s (2 O—CH₂—O); 6·63 s (Ar—H); 6·68 bs (2 Ar—H); 6·72 s (Ar—H). For $C_{23}H_{27}NO_6$ (413·5) calculated: 66·81% C, 6·58% H, 3·39% N; found: 66·50% C, 6·40% H, 3·40% N.

The Emde degradation of isorhoeadinemethiodide (V.CH₃I). By application of the method described for rhoeadinemethiodide, the degradation of isorhoeadinemethiodide (0·087 g) gave 0·065 g of a mixture of two substances. Chromatography with benzene afforded 0·023 g of an oily substance *XII*, $[\alpha]_D^{24}$ +39° ± 3° (*c* 0·92 in methanol), +91° ± 3° (*c* 1·76 in chloroform), R_F 0·56 (S_1), 0·71 (S_2). PMR: 2·25 s (N(CH₃)₂); 2·2-3·3 m (ArCH₂CH₂N, —CH₂CH(O)—); 3·53 s (OCH₃); 4·95 q, [J_{AX} + J_{BX}] = 15·0 Hz (—CH(O)CH₂—); 5·93 bs (—CH(OCH₃)O—, O—CH₂—O); 5·98 q, J_{gem} = 1·5 Hz (O—CH₂—O); 6·57 d and 6·75 d, J_{ortho} = 8·5 Hz (2 Ar—

—H); 6·63 s (Ar—H); 7·08 s (Ar—H). λ_{max} 238 and 291 nm (log ε 3·95 and 3·88). For $C_{22}H_{25}NO_6$ (399·4) calculated: 66·15% C, 6·31% H, 3·51% N; found: 66·45% C, 6·65% H, 3·42% N. Elution with chloroform gave 0·027 g of the compound *XIII*.

The Emde degradation of isorhoeageninediol methiodide (*VIII*.CH$_3$I). Degradation of isorhoeageninediolmethiodide (0·13 g) afforded 0·072 g of a mixture of two substances. Chromatography with chloroform gave 0·045 g of the substance *XIII*. Elution with chloroform–ethanol (9 : 1) yielded 0·025 g of the substance *XV*, m.p. 135—136°C (ethyl acetate–ethanol), $[\alpha]_D^{24}$ —110° ± 3° (*c* 0·91 in methanol), —61° ± 3° (*c* 0·89 in chloroform). The PMR spectrum of the substance *XV* was identical with that of the substance *XIV*.

6-Demethoxyrhoeadine (IV). Rhoeageninediol (1·9 g) was dissolved in 40 ml of chloroform. After addition of 1 g of powdered calcium chloride, the solution was bubbled through with hydrogen chloride for 4 h. The reaction mixture was filtered, evaporated, and the residue crystallized from methanol–acetone. Yield 1·17 g of hydrochloride, m.p. 199—203°C which after conversion into a free base yielded 6-demethoxyrhoeadine (*IV*), m.p. 117—118°C (ether) (ref.[8], m.p. 117—119°C), which on the basis of the IR spectrum is identical with the substance prepared according to ref.[8]. After crystallization of the hydrochloride, the mother liquors were chromatographed. Elution with chloroform–ethanol (1 : 1) gave 0·045 g of a substance of the m.p. 176 to 180°C (decomp.) which, on the basis of the IR spectrum, was identical with the isoprotopinium chloride (*XVI*) prepared according to ref.[9].

The Emde degradation of 6-demethoxyrhoeadinemethiodide (*IV*.CH$_3$I). Degradation of 6-demethoxyrhoeadinemethiodide (0·50 g) afforded, similarly to rhoeadinemethiodide, 0·37 g of a mixture of two substances. Chromatography with benzene gave 0·16 g of the substance *XI*, m.p. 125—127°C (n-hexane), $[\alpha]_D^{24}$ —85° ± 3° (*c* 0·73 in methanol), —73° ± 3° (*c* 0·96 in chloroform). PMR: 2·25 s (N(CH$_3$)$_2$); 2·2—3·0 m (ArCH$_2$CH$_2$N, —CH$_2$CH(O)—); 4·77 q, [J_{AX} + + J_{BX}] = 14·0 Hz (—CH(O)CH$_2$—); 4·92 q, J_{gem} = 15·0 Hz (ArCH$_2$O); 5·88 s and 5·92 s (2 O—CH$_2$—O); 6·55 d and 6·70 d, J_{ortho} = 8·0 Hz (2 Ar—H); 6·62 s (Ar—H); 6·97 s (Ar—H). λ_{max} 238 and 289 nm (log ε 3·96 and 3·88). For $C_{21}H_{23}NO_5$ calculated: 68·28% C, 6·28% H, 3·79% N; found: 68·39% C, 6·21% H, 3·58% N. Elution with chloroform gave 0·15 g of the compound *XIII*.

CD Spectra

Compound *IX*: ethanol: 296 (—3·50), 279 (+1·39), 241 (+2·74), 227 (—0·87), 204 (—15·43), 195 (+21·8); ethanol–HCl: 297 (—2·10), 279 (+0·97), 243 (+1·50), 230 (—0·90), 204 (—13·24), 196 (+19·42) (ref.[1]). Compound *XI*: ethanol: 294 (—2·24), 278 (+1·22), 248 (—0·56), 241 (+0·32), 230 (—0·55), 210 (+7·45), 203 (—14·9); ethanol–HCl: 294 (—1·82), 278 (+1·27), 246 (—0·69), 232 (—1·63), 220 (+0·50), 210 (+5·50), 205 (—2·20), 198 (+6·6). Compound *XII*: ethanol: 297 (+2·72), 280 (—1·64), 243 (—4·42), 228 (+1·01), 203 (+12·96), 195 (—13·82); ethanol–HCl: 296 (+1·60), 280 (—1·47), 243 (—1·30), 230 (+1·21), 204 (+8·64), 197 (—22·5). Compound *XIV*: ethanol: 296 (+2·29), 242 (+5·90), 205 (+8·45); ethanol–HCl: 296 (+3·82), 238 (+5·95), positive at shorter wavelengths. Compound *XV*: ethanol: 296 (—1·97), 242 (—4·54), 205 (—7·75); ethanol–HCl: 296 (—3·02), 238 (—4·66), 206 (—22·9), 197 (+12·5).

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