DERIVATIVES AND STEREOCHEMISTRY OF THE MATRINE ALKALOIDS

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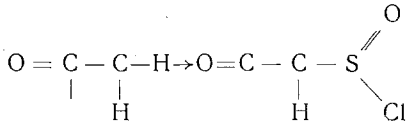
The study of the stereochemistry of the matrine alkaloids was begun by K. Tsuda and F. Bohlmann, who drew valuable conclusions on the configurations of these alkaloids from their experimental results [1, 2].

We have studied the possibility of using the methods of NMDR, ORD, and UV spectroscopy to establish the configuration of the isomeric matrines. For this purpose, various derivatives have been synthesized.

By the chlorination of matrine (I), sophoridine (II), leontine (III), and isosophoridine (IV) with a mixture of thionyl and sulfuryl chlorides we obtained the corresponding 14, 14-dichloro derivatives (V-VIII). The UV spectra of these compounds showed a displacement of the absorption maxima by 15-20 nm in the long-wave direction, which confirmed the presence of the halogen in the α position with respect to the carbonyl group.

The mass spectra of (V-VIII), unlike those of the starting materials (I-IV) (M^+ 248) exhibit peaks in the form of doublets showing the presence of the halogen in the molecule and peaks corresponding to the molecular ion (M^+ 315 and 317), and also ions formed by the elimination of the other rings (A, B, and C) but with the retention of ring D containing the halogen atoms. The fragments of the ions arising as the result of the decomposition and elimination of ring D accurately coincide with those for the initial bases [3].

In the chlorination of (I-IV), in addition to dichloro derivatives another product, giving a positive reaction for chlorine and sulfur, was formed in the reaction mixture in each case. By comparing their mass and IR spectra it has been established that the latter are the products of the condensation of (I-IV) with a thionyl chloride residue,  , and have mol. wt. 330.

The partial hydrogenation of (V-VIII) over platinum in ethanol led to the formation of the monochloro derivatives. From dichloromatrine, α-monochloromatrine was isolated and characterized completely; this has been sythesized previously by S. Okuda et al. [4]. In the case of dichlorosophoridine, however, two isomeric monochloro derivatives which passed into one another under the action of heat, were obtained.

The saponification of the monochloro derivatives takes place with difficulty and only from monochlorosophoridine did we isolate the 14-hydroxy derivative in an amount sufficient for recording its mass spectrum.

The treatment of monochloroisosophoridine with lithium carbonate and soium iodide gave dehydroisosophoridine with mp 98-99° C. A comparison of the mass spectra of the latter and of sophocarpine [3]

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showed that the double bond is in ring D, since all the fragments differ only in intensities. Their absorption maxima in the UV spectra are also identical and characteristic for the chromophore $-\overset{|}{N}-\overset{O}{\overset{\|}{C}}-\overset{|}{C}=\overset{|}{C}-$ (260 nm) [5].

In order to establish the orientation of the substituents at the α-carbon atom to the C = O group and unambiguously to identify the signals of the α-protons to the amide nitrogen atom, the NMR spectra of the alkaloids (I-IV) and also some of their monochloro and dichloro derivatives were studied.

Previously [6], the assignment of the signals of the protons at C_5, C_{11}, and C_{17} in the NMR spectra of (I) and (III) was made on the basis of a comparison with the spectrum of quinolizidone. In view of this, it appeared of interest to identify the signals of the protons mentioned in the alkaloids themselves using the double-resonance method.

In the NMR spectrum of (I) (Fig. 1), in the weak-field region there is a one-proton quartet with τ 5.64 ppm, J_1 = 12.5 and J_2 = 4.0 Hz, a multiplet with a center at τ 6.26 ppm, and a triplet at τ 7.00 ppm, $J_1 = J_2 = 12.5$ Hz.

Under double-resonance conditions, on irradiation of the quartet (τ 5.64 ppm) with ν = 300 Hz a singlet is obtained and conversely, the triplet (τ 7.00 ppm) with ν = 436 Hz is converted into a singlet.

As a result of irradiation the quartet (τ 5.64 ppm) with ν = 287 Hz is converted into a doublet and the region of the signal at τ 7.13 ppm with ν = 436 Hz changes.

Thus, it follows from the double-resonance results that the quartet at τ 5.64 ppm is due to the C_{17} – H proton. With a large geminal spin-spin coupling constant (SSCC) (12.5 Hz) and with a small vicinal equatorial-axial constant (4.0 Hz), the latter interacts with the $C_5 - H_a$ proton, the signal of which appears at τ 7.13 ppm. This is also confirmed by the fact that in the spectrum of (XV) the signal in the weak field ($C_{17} - H_e$) consists of a doublet at τ 5.40 ppm with $J_{ae}^{gem} = 12.5$ Hz. Consequently, the triplet at 7.00 ppm relates to the $C_{17} - H_a$ proton the equivalence and magnitude of the SSCC of which shows that one of the constants is geminal and the other is due to diaxial vicinal coupling with the $C_5 - H_a$ proton. Consequently the $C_5 - H_a$ and the $C_{17} - H_a$ protons are trans-diaxial.

The one-proton multiplet in the spectrum of (I) at τ 6.26 ppm is due to the $C_{11} - H_a$ proton. The half width of this proton, equal to the sum of the SSCCs with the neighboring a-e protons is more than 35 Hz and shows that the proton at C_{11} has the axial orientation.

In the spectra of (III) and (IV) the SSCCs of $C_5 - H_a$ and $C_{17} - H_e$ are smaller than in (I), being 3.0 and 1.6 Hz, respectively. This fact, and also the absence of a signal from the proton at C_{11} in the weak field in the spectra of (III) and (IV) can be explained by a distortion of the conformation of ring C as compared with (I), which is reflected in the orientation of the $C_5 - H_a$ proton and in the screening of $C_{11} - H_a$.

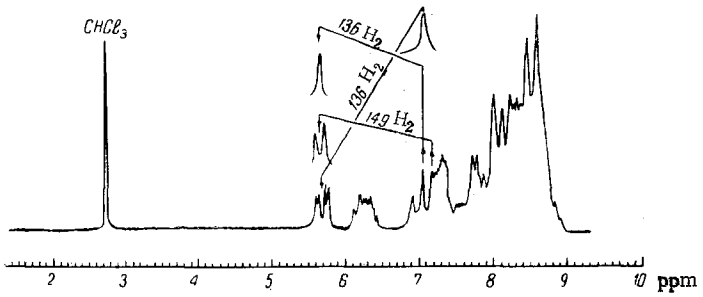

Fig. 1. NMR spectrum of matrine (I).

It is most interesting that in the NMR spectra of (II), its monochloro derivatives [(IX) oil and (X) crystalline], and its dichloro derivative (VI) the signals of the protons at C_{17} and C_{11} are absent in the weak-field region.

The appearance of the $C_{17} - H_e$ signal in the weak field in the spectra of (I) and (III). also is explained by the assumption that this proton is present in the plane of the lactam group in which descreening is a maximum [6]. The marked upfield shift of the C_{17}-H_e signal in the spectra of (II) and its derivatives can be explained by the fact that in (II), as compared with (I), the conformation of ring C is considerably distorted, as a result of which the C_{17}-H_e proton departs from the plane of the lactam ring and enters the cone of screening of the anisotropy of the diamagnetic susceptibility of the C = O group.

The oxidation of (II) with hydrogen peroxide gave the N-oxide of (II), in the NMR spectrum of which three is a quartet at τ 5.85 ppm with $J_1 = J_2 = 12.0$ Hz. This quartet obviously relates to the $C_6 - H$ proton and the equal values of its SSCCs with the protons at C_5 and C_7 show that they are mutually axial.

In the spectra of the monochloro derivatives of (I) and (II), i.e., in the spectra of (IX), (X), and (XII), the signals of the protons on the α-carbon atom to the C = O group appear in the weak field at τ 6.63, 6.64, and 6.68 ppm, respectively. However, it is impossible from the values of the chemical shifts of these protons to deduce their axial or equatorial orientation. Consequently, we have made use of an important criterion of determining the orientation of protons for poorly-resolved signals – their half-width ($\Delta W_{1/2}$), which is equal to the sum of the SSCCs of the given proton with the neighboring ones. Usually $\Delta W_{1/2}$ of the signal of an axial proton is twice $\Delta W_{1/2}$ of the signal of an equatorial proton and amounts to 15-25 Hz [7].

In the spectra of (IX) and (XII), the half-width of the signal of the proton at C_{14} is approximately 7.0 Hz, which shows its equatorial orientation and the axial nature of the chlorine atom. In the case of (X), $\Delta W_{1/2}$ of the signal of the proton at C_{14} amounts to 13.5 Hz. Consequently, the proton is axial and the chlorine is equatorial.

In the IR spectra of (V-VIII), as compared with (I-III), the frequencies of the C = O vibrations are shifted in the high-frequency direction by ~20-30 cm^{-1}, and in the case of the monochloro derivatives, depending on the orientation of the chlorine, by from –10 to +15 cm^{-1} (this is the opposite of the α-halogeno ketones, since in the latter an equatorial halogen raises the frequency of the C = O vibrations by 20 cm^{-1}, and an axial halogen has no effect).

In the UV spectra of the dichloro derivatives (V-VIII), the absorption maxima are shifted in the long-wave direction by 18-25 nm. In the UV spectrum of (X) there is a hypsochromic shift and an increase in the extinction coefficient. In the other cases where the chlorine has the axial orientation a bathochromic shift of +7-13 nm is found, and the extinction coefficient is practically unchanged.

After the configuration of the α-halogen had been established, to determine the absolute configuration of the matrine alkaloids we studied the ORD curves both of the bases and of their dichloro and monochloro derivatives.

(+)-Matrine and dichloromatrine give simple curves with a positive Cotton effect (Fig. 2, a). This confirms the correctness of the conclusions of S. Okuda et al. [8] concerning the absolute configuration of matrine, i.e. the R configuration at C_{11} and not S as was stated by Cervinka [9]. In the spectrum of α-monochloromatrine there is a bathochromic shift (35 nm), which shows the possibility of using the axial rule for α-halogeno ketones in the case of α-halogeno amides, as well [10].

The ORD curve of leontine (Fig. 2, c) differs in shape and sign from that of matrine and possesses a negative Cotton effect consisting of two extremes. On considering models of matrine and leontine it can be seen that the greater contribution to the second extreme is made by rings A and B, in consequence of which the amplitude of the peak is far greater than that of the trough. A similar pattern is observed in the spectra of dichloro- and monochloroleontine. This shift confirms the axial position of the halogen, and the sign of the Cotton effect shows the S configuration at C_{11}. Hence, leontine has the 5R,6S,7S,11S configuration, which is confirmed by the formation of (–)-5-OH-$\Delta^{6,7}$-dehydromatrine from leontine.

However, the literature contains little information on the ORD of amides [11]. Consequently, it is difficult to deduce strictly the conformations of substituted amides from their ORD curves. Nevertheless, the results of our study of the ORD curves of amides of the sparteine series show that the conclusions on the conformation of the sparteines agree completely with chemical results [12]. At the same time, in the

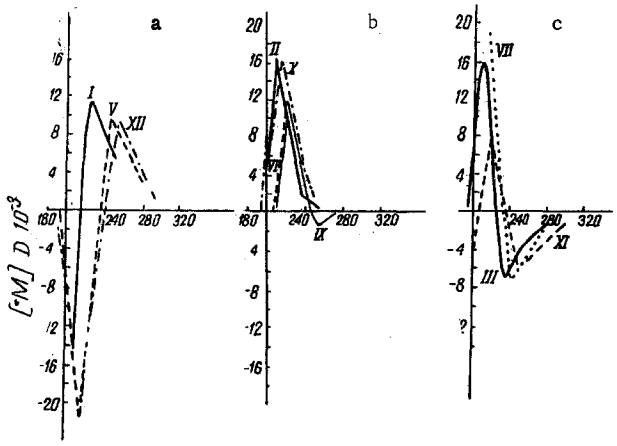

Fig. 2. ORD curves of compounds (I-XII).

case of d-sophoridine (II) the ORD curves do not agree with the chemical results, namely: on dehydrogenation with mercuric acetate d-sophoridine gives (–)-5-OH-$\Delta^{6,7}$-dehydromatrine (XV) while (+)-matrine gives (+)-5-OH-$\Delta^{6,7}$-dehydromatrine; the signs of the ORD curves of d-sophoridine and (+)-matrine and their derivatives coincide (Fig. 2, a, b).

Furthermore, the chemical shifts (CS) of $C_{17} - H_e$ and $C_{17} - H_a$ of the protons in matrine are found in the weak field and the relative chemical shift a – e at C_{17} and C_{11} in them is 0.5-0.6 ppm, while in the case of sophoridine the CSs of the protons mentioned are shifted strongly upfield. If we start from a C/D-cis linkage [13], we should expect the CS of the $C_{11} - H_e$ signal in the weak field, which is not the case for the NMR spectrum of sophoridine. At the same time, in the case of the oxosparteines with cis-linked rings the signals of O=C—N—C—He are found in the weak field [14]. Consequently, the ORD and NMR characteristics show that the conformation of ring C is considerably distorted as compared with the other isomers.

EXPERIMENTAL

The following systems of solvents were used for chromatography: 1) butan-1-ol–conc. HCl–water (50 : 7.5 : 13.5, M-1 paper); 2) benzene–methanol [5 : 2; TLC in silica gel–gypsum (9 : 1)]; and 3) chloroform–methanol [2 : 1; TLC in silica–gypsum (9 : 1)].

The NMR spectra were obtained on a JNM-4H-100/100 MHz instrument in $CDCl_3$ with HMDS as internal standard, and the ORD curves on a Cary-60 instrument with methanol as the solvent.

Dichlorosophoridine (VI). A solution of 4.9 g of (II) in a mixture of 6 ml of $SOCl_2$ and SO_2Cl_2 was boiled in the water bath for 1 h. The dry residue after the distillation of the excess of the reagents was made alkaline with 5% ammonia solution and extracted with ether and chloroform. The ethereal fraction (3 g) was chromatographed on a column of silica gel. The chloroform-methanol (20 : 1) eluates yielded substance (VI). Yield 1.9 g. Mp. 128-130° C (ether) $[\alpha]_D$ + 19° (c 0.37; ethanol). UV spectrum: λ_{max} 222 nm (log ε 3.77).

The chloroform eluate yielded a substance with R_f 0.95 (1), mol. wt. 330.

Dichloroleontine (VII) was obtained by the method described above from 0.5 g of (III) and 4 ml of a mixture of $SOCl_2$ and SO_2Cl_2. Yield 0.25 g. Mp 158-159° C (ether). UV spectrum: λ_{max} 220 nm (log ε 3.7).

Dichloromatrine (V) was isolated from 3 g of (I) as described by Okuda et al. [8]. Yield 1.4 g. UV spectrum: λ_{max} 230 nm (log ε 3.78).

Dichloroisosophoridine (VIII) was formed by boiling 0.9 g of (IV) with a mixture of 5 ml of $SOCl_2$ and SO_2Cl_2 for 3 h. The residue after evaporation was dissolved in 1% hydrochloric acid, and the solution was made alkaline with 25% ammonia and extracted with ether.

The light-colored oil (1.1 g) obtained after the distillation of the ether was crystallized (dry ether). Yield of (VIII) 0.5 g. Mp 152° C, $[\alpha]_D$ – 114.8° (c 0.48; ethanol), R_f 0.21 (3), 0.95 (1). Mol. wt. 315 (from the mass spectrum). UV spectrum: 223 nm (log ε 3.76).

Monochlorosophoridines (IX, X). A solution of 1.9 g of (VI) in 25 ml of ethanol was shaken in an atmosphere of hydrogen with 0.4 g of PtO_2. After 5 h, 130 ml of hydrogen (0.96 mole) had been absorbed. The catalyst was separated off, the solvent was distilled, and the residue (1.8 g) was chromatographed on silica gel. It was eluted with chloroform–methanol (30 : 1), (20 : 1). The first fractions gave an oily base (IX). Yield 0.23 g, $[\alpha]_D$ + 17° (c 0.6; ethanol), R_f 0.86 (1), 0.52 (2), Mol. wt. 282 (from the mass spectrum). UV spectrum: λ_{max} 201 nm (log ε 3.9).

The second fractions deposited the crystalline base (X). Yield 0.9 g. Mp 140-141° C (ether), $[\alpha]_D$ + 30° (c 1.34; ethanol), R_f 0.84 (1), 0.40 (2), mol. wt. 282 (from the mass spectrum). UV spectrum: λ_{max} 210 nm (log ε 3.27).

Monochloroleontine (XI) was obtained by shaking 0.2 g of (VII) in 10 ml of ethanol with 0.05 g of PtO_2 in an atmosphere of hydrogen for 1 h, followed by chromatography on silica gel and elution with chloroform–methanol (12 : 1) and also by crystallization from ether. Yield 0.12 g. Mp 139-140° C, $[\alpha]_D$ – 17° (c 0.1; ethanol), R_f 0.81 (1). Mol. wt. 282 (from the mass spectrum). UV spectrum: λ_{max} 212 nm (log ε 3.97).

α-Monochloromatrine (XII). A solution of 1.4 g of (V) in 20 ml of ethanol was shaken in an atmosphere of hydrogen with 0.5 g of PtO_2 for 4 h. The residue after the separation of the catalyst gave a perchlorate with mp 240-241° C (ethanol). The base from the perchlorate was crystallized (ether). Yield 0.64 g. Mp 106-107° C, $[\alpha]_D$ + 29° (c 0.9; ethanol). Mol. wt. 282 (from the mass spectrum). UV spectrum: λ_{max} 218 nm (log ε 4.0).

Monochloroisosophoridine (XIII) was obtained by shaking for 3 h 0.5 g of (VIII), in the form of the hydrochloride with mp 272-275° C, in 15 ml of ethanol in the presence of the platinum from 0.12 g of PtO_2 in an atmosphere of hydrogen. Yield 0.28 g. The base (XIII) was liquid, $[\alpha]_D$ – 75° (c 0.64; ethanol), R_f 0.24 (3), mol. wt. 282 (from the mass spectrum).

Dehydroisosophoridine (XIV). A mixture of 0.2 g of (XIII), 0.3 g of sodium oidide, and 0.15 g of lithium carbonate in 20 ml of dimethylformamide was heated in the water bath for 2 h. After cooling, the reaction mixture was passed through a column of alumina, the solvent was distilled off, and the residue was chromatographed on silica gel. Elution with chloroform–methanol (10 : 1) gave a base R_f 0.14 (3) crystallizing from dry ether. Yield 0.1 g. mp 97-98° C, $[\alpha]_D$ + 50° (c 0.2; ethanol). Mol. wt. 246 (from the mass spectrum). UV spectrum: λ_{max} 255 nm (log ε 3.37).

Hydroxysophoridine (XV). A mixture of 0.14 g of (X) and 20 ml of 5% caustic soda solution was heated in the water bath for 3 h. After cooling, the base was extracted with ether. The residue was chromatographed on silica gel, and the chloroform–methanol (100 : 8) fractions yielded substance (XV) with R_f 0.23; mol. wt. 264 (from the mass spectrum).

SUMMARY

α-Substituted derivatives of the isomeric matrines and a new isomer of sophocarpine–13, 14-dehydroisosophoridine–have been synthesized.

The possibility of using rotatory dispersion to establish the absolute configuration of the matrine alkaloids has been shown.

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