CHARACTERISTIC FEATURES OF THE NMR SPECTRA OF HYDROXYINDOLE ALKALOIDS OF THE EPIALLO AND ALLO SERIES

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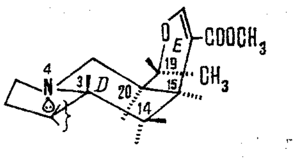
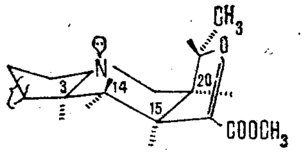
The pentacyclic hydroxyindole heteroyohimbine alkaloids of the epiallo series differ from those of the allo series by the configurations of the C_3 and N_4 centers. A simultaneous change in these centers leads to a conversion of ring D from one chain conformation to another [1, 2]. At the same time, the orientation of the C_3-H, $C_{15}-H$, and $C_{20}-H$ bonds change. These changes in stereochemistry are fundamentally reflected on the parameters of the NMR spectra of these alkaloids



epiallo



allo

Some features of the NMR spectra of alkaloids of the epiallo and allo series have been reported previously [1-7]. We give the results of a generalization of these features of the NMR spectra of the alkaloids of the series considered which permit their unambiguous stereochemical identification. The characteristics of the NMR spectra are given in Table 1 and in Fig. 1. The differences in the values of the chemical shifts (CSs) of the 19-CH_3, 19-H, 14-H^a, and $COOCH_3$ protons are explained by taking into account quantitative estimates (in the dipole approximation) of the contributions of the intramolecular anisotropic groups.

It can be seen from the table and figure that in the alkaloids of the epiallo series the signals in the 19-CH_3 and 19-H protons appear in a stronger field ($\Delta\delta = 0.16-0.17$ ppm) than those of the corresponding protons in the allo alkaloids. This difference in the values of the 19-CH_3 and 19-H signals is due mainly to the influence of the unshared electron pair (UEP) of the N_4 nitrogen atom on the screening of these protons, since on inversion (change in configuration) of the UEPs of the N_4, the distances (R) from the latter to the 19-H and 19-CH_3 protons change substantially. In the alkaloids of the epiallo series $R_{19-H} \approx 4.6$ Å and $R_{19-CH_3} \approx 6.0$ Å, and in the allo series $R_{19-H} \approx 2.1$ Å and $R_{19-CH_3} \approx 3.6$ Å. Therefore, obviously, in the alkaloids for the allo series an additional paramagnetic contribution $\Delta\delta \approx 0.16-0.17$ ppm to the CSs of the 19-CH_3 and 19-H protons is made by the electric field of the UEP of the N_4 nitrogen atom [7]. Quantitative evaluation by the Buckingham–Musher method [8] of the contribution of the electric field of the UEP of N_4 with the value that we have adopted for it of $\mu = 1.0$ D, to the CS of 19-H in the case of the allo series is in harmony with the experimentally observed difference.

In addition to the 19-H CS, in the spectra of the alkaloids considered the SSCCs of the 19-H and 20-H protons differ considerably: $J^{\text{epiallo}}_{19H-20H} = 1.5-2.0$ Hz and $J^{\text{allo}}_{19H-20H} = 9.0-11.0$ Hz [1, 2, 7]. This fact is a direct consequence of the conversion of ring D, leading to a change in the orientation of the proton at C_{20} from axial in the epiallo series to equatorial in the allo series and to the corresponding change in the dihedral angles φ in the $C_{19}H-C_{20}H$ fragment from approximately 80 to 170°.

From a comparison of the signals in Fig. 1 and the figures of Table 1 it can clearly be seen that the multiplicity and CS of the signal corresponding to the 14-H^a axial proton differ considerably in the spectra of the

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TABLE 1. Characteristic Chemical Shifts (CSs) and Spin–Spin Coupling Constants (SSCCs) of a Series of Protons of Alkaloids of the Epiallo and Allo Series

Series, group, and absolute configuration	CSs (δ, ppm)					SSCC (J, Hz)			
	19–CH$_3$	19–H	14–H^a	17–H	COOCH$_3$	19H–20H	17H–15H	14H^a–15H	19H–CH$_3$
epiallo-B 7R, 3R, 4S, 15S, 19S, 20S	1,20–1,23 d	4,16–4,20 o	1,07 sex.	7,40–7,71 d	3,58–3,60 s	1,5–2,0	2,0	5,0	6,5
epiallo-A 7S, 3R, 4S, 15S, 19S, 20S	1,22–1,26 d	4,15–4,22 o	1,60 sex	7,31–7,37 d.	3,32–3,43 s	1,5–2,0	2,0	5,0	6,5
allo-B 7R, 3S, 4R, 15S, 19S, 20S	1,35–1,38 d	4,30–4,53 o	1,40 q	7,41–7,70 s	3,55–3,58 s	9,0–11,0	0	12,0	6,5
allo-A 7S, 3S, 4R, 15S, 19S, 20S	1,37–1,40 d	4,30–4,36 o	0,91 q	7,40–7,72 s	3,56–3,58 s	9,0–11,0	0	12,0	6,5

Note. CDCl$_3$, internal standard TMS, δ scale [1-7], s) singlet; d) doublet; q) quartet; sex) sextet; o) octet.

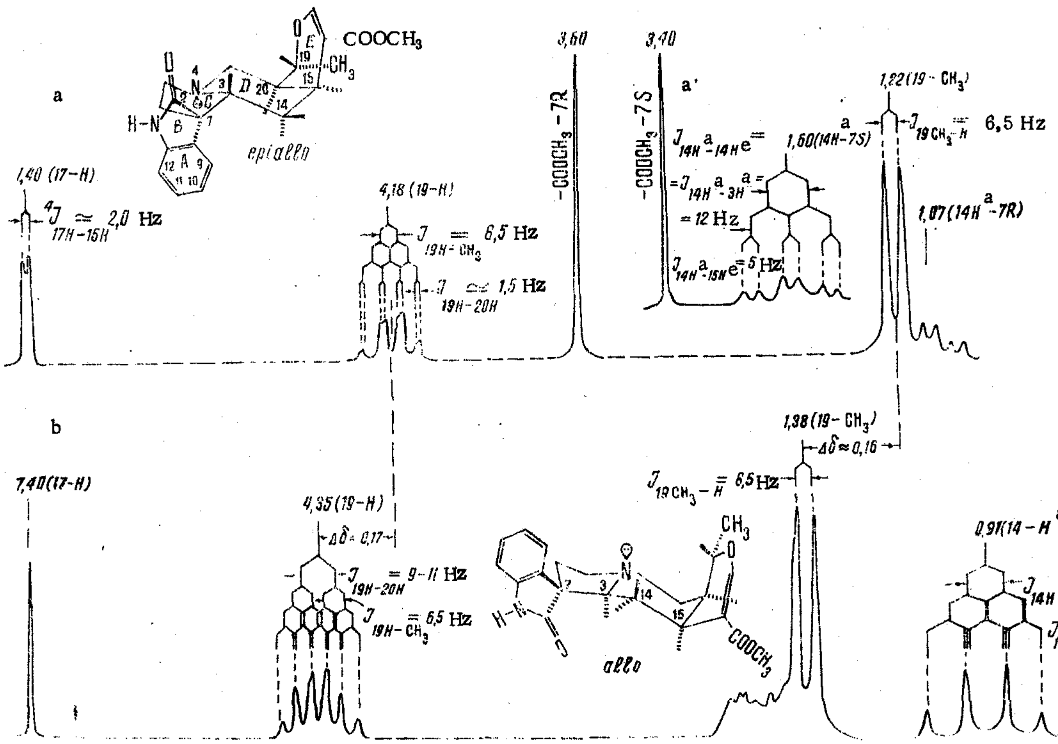

Fig. 1. Fragments of the NMR spectra of hydroxyindole alkaloids of the epiallo and allo series.

alkaloids under discussion [7]. We have established that the values of the vicinal SSCCs and the multiplicities of the 14-H^a signal in these series are due to the reorientation of the proton at C_{15} (15-H) from the equatorial position (epiallo) to the axial position (allo) in relation to 14-H^a (see Fig. 1a and b).

The next important criterion of the distinction of the epiallo from the allo alkaloids according to their NMR spectra may be regarded as the value of the long-range SSCC of the 17-H olefinic proton with the 15-H proton. We originally assigned the one-proton doublet in the weak field at 7.40 ppm in the spectra of the epiallo alkaloids vinerine and vineridine to the H_{12} aromatic proton [7]. Then it was found by the double-resonance method on a JNM-4H-100/100-MHz instrument that this double at 7.40 ppm ($J \approx 2$ Hz) is due to the 17-H olefinic proton,[*] since on irradiation with $\nu_2 = 240$ Hz (the 15-H signal), the doublet at 7.40 ppm is converted into a sharp singlet. Thus, we have established that the doublet splitting with $J \approx 2.0$ Hz of the signal at 7.40 ppm in the epiallo alkaloids is due to the long-range (allyl) interaction of the 17-H olefinic proton with the 15-H proton. At the same time, the signal of the 17-H proton in the allo alkaloids is observed in the form of a singlet, i.e., $J_{17H-15H} \approx 0$. This difference in the values of J_{al} in the alkaloids of the epiallo and allo series is obviously due to the stereospecificity of the allyl SSCCs, which depend on the angle θ between the plane of the $C_{16}=C_{17}$ double bond and the neighboring $C_{15}-H$ bond [9]:

$$ {}^4J_{al} = \begin{cases} < 0.5 \text{ Hz} & \text{at } 20° > \theta > 170° \\ 1.3-3.1 \text{ Hz} & \text{at } \theta = 60-110° . \end{cases} $$

The value of the angle θ measured on stereomodels for the epiallo alkaloids is approximately 100° and corresponds to the experimentally observed SSCC $J_{al} \approx 2.0$ Hz, and for the allo alkaloids $\theta \approx 20°$ and $J_{al} \approx 0$. Consequently, changes in the values of the SSCCs of the 17-H and 15-H protons from 2.0 to 0 Hz on passing from epiallo to allo are explained completely by the reorientation of the $C_{15}-H$ bond in them on the conversion of ring D.

In addition to the features of the NMR spectra of the epiallo and allo alkaloids that have been mentioned, characteristic differences are also observed within each series according to the configuration of the C_7 center. We have shown previously that in the epiallo alkaloids of group A (7-S), a paramagnetic shift of the signal of the 14-H^a proton by 0.53 ppm in comparison with the CS of the 14-H^a proton of the alkaloids of group B (7-R) takes place which is connected with the influence of the anisotropy of the lactam $C=O$ group [7]. The chemical shift of the signal of the protons of the $-COOCH_3$ methyl group in the epiallo-B alkaloids is displaced downfield by 0.20-0.30 ppm in comparison with the corresponding signal in the alkaloids of the epiallo-A series, and the hypothesis has been put forward of a screening of the H_3CO- protons by the benzene ring in the latter [2]. In actual fact, contribution of the calculation of the anisotropy of the benzene ring to the CS of the H_3CO- protons according to Johnson and Bovey [10] in the case of the epiallo-A alkaloids gives a value $\Delta\delta \approx 0.30$ ppm upfield, which agrees well with the experimental values [4]. In the spectra of the alkaloids of both series, the CS of the signal of the H_9 aromatic proton depends on the mutual orientation of the UEP of the N_4 nitrogen atom and of the lactam $C=O$ group [1, 7]. Where they have the anti orientation the H_9 signal is shifted downfield by 0.20-0.30 ppm, probably because of the influence of the UEP of the N_4 on H_9, as compared with their syn arrangement. Furthermore, the CSs of the N-H protons measured under identical conditions [7] are found in a weaker field by 0.80 ppm in the spectra of the epiallo-A alkaloids than in those of the epiallo-B alkaloids, which is apparently explained by the influence of the N_4 UEP on the lactam $C=O$ group.

Thus, the use of the criteria given for distinguishing NMR parameters permits an unambiguous stereochemical identification of the alkaloids of the epiallo and allo series.

SUMMARY

On the basis of an analysis and generalization of the characteristics of the NMR spectra of the pentacyclic hydroxyindole alkaloids of the epiallo and allo series, criteria have been found for distinguishing between the CSs and SSCCs of a number of protons which permit unambiguous stereochemical identification on such alkaloids.

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[*] Accordingly, the signals at 6.47 and 6.55 ppm in their spectra relate to the H_{12} aromatic proton, and the paramagnetic shift of the H_{12} signal on the acetylation of the N-H group of vinerine amounts to 1.40 ppm [7].

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THE STRUCTURE OF KESSELRINGINE

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UDC 547.944.6

We have previously reported the isolation from the epigeal parts of Colchicum kesselringii Rgl. of a new base kesselringine and its partial structure [1, 2]. From the nature of its UV spectrum, this compound differs considerably from the homoproaporphine and proaporphine bases with a dienone ring [3, 4]. Its IR spectrum (Fig. 1) shows the absorption bands of a hydroxy group (3530 cm^{-1}), a benzene ring (1600, 900–800 cm^{-1}), and methylene groups (1460 cm^{-1}).

The NMR spectrum of the alkaloid (Fig. 2) shows three-proton singlets at 2.32 and 3.32 ppm of N-methyl and O-methyl groups, respectively, and a one-proton singlet at 6.42 ppm corresponding to the C_3 proton of the benzene ring.

According to its mass spectrum, which has the peaks of the following main ions: m/e 331 (M^+, 42%), 330 $(M-1)^+$ (100%), 316, 288 $(M-43)^+$, 256, 244, 242, 238, 230, 228, 165, kesselringine is close to the proaporphine alkaloids of the type of amuramine [5], and probably has the basic skeleton I.

From the spectral characteristics and the elementary composition, it may be concluded that kesselringine is a homoproaporphine compound highly reduced in the dienone ring and is the first representative of substances with a spirocyclohexane ring.

Diazomethane methylates the phenolic hydroxy group of ring A of kesselringine with the formation of O-methylkesselringine (II, Scheme 1).

Judging from the value of its chemical shift (CS) in the PMR spectrum, the methoxy group of kesselringine is located in an alicyclic ring. The base is inert to the action of ammonia and alkalis, but it is readily hydrolyzed by heating in dilute acids, changing into norkesselringine (III). The hydrolysis of O-methylkesselringine forms O-methylnorkesselringine (IV), which is isomeric with kesselringine. These two compounds differ by the positions of the hydroxy and methoxy groups. The hydrolysis of the alicyclic methoxy group in the formation of O-methylnorkesselringine is shown by the absence of the corresponding CS (three-proton singlet at 3.32 ppm)

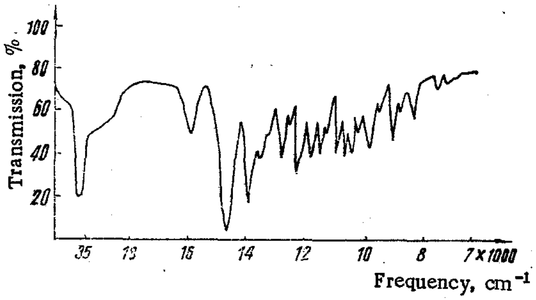

Fig. 1. IR spectrum of kesselringine (in paraffin oil).

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