RING–CHAIN TAUTOMERISM OF SPIRO AMINO KETAL ALKALOIDS

L. D. Yakhontova, M. N. Komarova,
O. N. Tolkachev, and M. E. Perel'son

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We have previously reported the isolation from *Hypecoum erectum* L. of two new alkaloids — hypecorine and hypecorinine — and the determination of their structure [1] and have observed that the action of acetic anhydride on hypecorine leads to the cleavage of the spiro amino ketal grouping with the opening of rings B and C.

A further study of the chemical properties of hypecorine has shown that the action on it of acids (for example, hydrochloric acid) also leads to a reaction with the participation of the spiro amino ketal group. In this case, only the —C—O— bond in ring C is cleaved, with the retention of the —C—N— bond, and the quaternary dihydroisoquinoline derivative (II), is formed. The structure of (II) follows from its IR, UV, and NMR spectra. In the UV spectrum of (II) (λ_{max} in ethanol 247, 295, 365 nm; log ε 4.22, 3.94, 3.96), unlike that of hypecorine, a considerable bathochromic shift of the long-wave band (which is located at 290 nm in hypecorine) is observed, which shows the appearance of an additional double bond conjugated with an aromatic ring.

The NMR spectrum confirms the structure of compound (II) (Table 1). The methylene groups in positions 5 and 6 give two triplets at 3.30 and 4.24 ppm, and the chemical shift of the weak-field triplet shows the attachment of one of the methyl groups to a quaternary nitrogen atom. The signals from the 15-CH_2, 1-H, and 4-H protons are shifted downfield in comparison with the corresponding signals of hypecorine. This fact, and also the presence of four methylene groups in (II) (see Table 1), unambiguously fixes the 7-8 position of the double bond.

Thus, compound (II) is the salt of an acyclic tautomer of hypecorine with a $-(C=\overset{+}{N})$ endocyclic double bond — pseudohypecorine chloride. The action of strong bases on the latter led to the splitting out of hydrogen chloride with the regeneration of the tetracyclic system of hypecorine. The ease of transition in the (I) $\rightleftarrows$ (II) system explains why the alkaloid is isolated from the plant in the racemic form.

The reduction of (II) with sodium tetrahydroborate in methanol or zinc dust in hydrochloric acid led to the saturation of the C=N multiple bond and the formation of the tertiary isoquinoline derivative (III). UV spectrum: λ_{max} in ethanol 240 and 294 nm; log ε 4.93 and 4.98. The parameters of the NMR spectrum of (III) (see Table 1) agree completely with the structural formula given in the scheme.

When compound (III) was boiled with acetic anhydride, the tetrahydroisoquinoline ring opened and an unsaturated O,N-diacetyl derivative of the stilbene series (IV) was formed. In the NMR spectrum of (IV) there are the signals of O- and N-acetyl groups, and the signal from 15-CH_2 is absent. In the aromatic region additional signals of two protons on an ethylenic double bond appear. Becasue of the hindrance to rotation around the N—Ac bond the spectrum contains satellites of the signals from the N—CH_3, the N—$COCH_3$, and the aromatic protons. It can be seen from the ratio of the intensities that 60% of the molecules are present in one form and 40% in the other. The presence of satellites prevented the analysis of the region of aromatic protons, but the value of the total intensity of the signals, namely 6, and the absence of a signal from the 15-CH_2 protons confirm the diphenylethylene nature of the double bond. In deuteropyridine at 100°C, the signals of the protons mentioned above coalesce.

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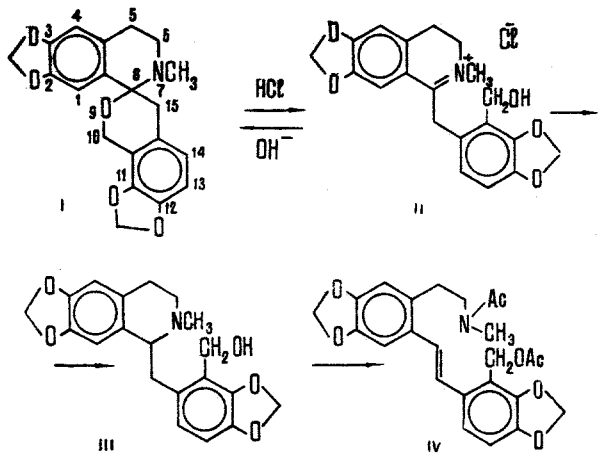
TABLE 1. Characteristics of the NMR Spectra of Hypecorine and Its Derivatives

Compound	1-H*	4-H	14-H	13-H	5-CH_3 6-CH_3	15-CH_3	2,3-O-CH_2-O	11,12-O-CH_2-O	10-CH_3	N-CH_3	Other protons	Solvent; temperature, °C
Hypecorine	6,74 s; 1H	6,40 s; 1H	6,52 d; 8,0 1H	6,38 d; 8,0 1H	2,35–3,35 m; 6H		5,79 s; 2H	5,86 s; 2H	4,61; d 15,0; 1H 4,65; d 15,0; 1H	2,19 s; 3H	—	CCl_4; 33°
II	7,34 s; 1H	6,96 s; 1H	6,67 d; 8,0 1H	6,29 d; 8,0 1H	3,20; t 7,5; 2H 4,13; t 7,5; 2H	4,61 ur 2H or 4,72	6,08 s; 2H	5,96 s; 2H	4,72; s 2H or 4,61	3,69 s; 3H	—	CD_3OD; 20°
	7,45 s; 1H	7,07 s; 1H	6,77 d; 8,0 1H	6,39 d; 8,0 1H	3,30; t 7,5; 2H 4,24; t 7,5; 2H	4,84; s 2H or 4,72	6,10; s 2H	6,07 s; 2H	4,72; ur 2H or 4,84	3,80 s; 3H	—	CD_3OD + 5 drops of CF_3COOH; 20°C
III	6,68 s; 1H	6,52 s; 1H	6,70 d; 8,0 1H	6,60 d; 8,0 1H	2,4–3,2 m; 6H		5,90 s; 2H	5,95 m; 2H	4,60; d 11,0; 1H 4,46; d 11,0; 1H	2,20 s; 3H	8-H 3,57; t $\varepsilon J = 12$; 1H	$CDCl_3$; 20°
IV	6,66–7,34; 6H				2,95 m; 2H 3,47 m; 2H	—	5,90; s; 2H 5,96; s; 2H		5,22 s; 2H	2,88 s 1,8H 2,86 s; 1,2H	$\underline{OCOCH_3}$ 2,00; s; 3H N–$\underline{COCH_3}$ 1,98; s; 1,8H 1,77; s; 1,2H	CD_3OD; 20°
	—				2,89 m; 2H 3,60 m; 2H	—	5,97; ur 4H		5,51 s; 2H	2,89 s; 3H	$OCOCH_3$ N–$COCH_3$ 1,99; s; 3H –2,04; s; 3H	C_5D_5N; 100°

*For compounds (II)-(IV) an arbitrary numbering of the atoms corresponding to that of (I) is given.

Thus, the product of the acetylation of reduced pseudohypecorine chloride has the structure (IV), which is confirmed by the bathochromic shift of the longwave band in the UV spectrum in the transition (III) → (IV). The results of the investigations performed show the ease of opening of rings B and C in the hypecorine molecule and the possibility of a transition from the spiro amino ketal system of type (I) to the benzyldihydroisoquinoline system of type (II) and to compounds of the type of protopine and protoberberine.

Compound (III) that we obtained is apparently a racemate of the optically active alkaloid corydalisol obtained by Japanese workers [2]. The alkaloid corydalispirone described in the same paper is obviously identical with the hypecorinine described by us previously [1].



EXPERIMENTAL

The NMR spectra were obtained on an HA-100D (100 MHz) instrument, O — TMS. The IR spectra were taken on a UR-10 spectrophotometer and the UV spectra on an EPS-3T instrument.

The analyses of all the compounds corresponded to the calculated figures.

Pseudohypecorine Chloride (II). A solution of 0.5 g of hypecorine in 20 ml of chloroform was treated with 20 ml of ethanol saturated with hydrogen chloride. After concentration to ~15 ml, the solution was allowed to stand for crystallization. The pseudohypecorine chloride, $C_{20}H_{19}NO_5 \cdot HCl$ was obtained in the form of yellow crystals with mp 240-242°C (decomp., from ethanol); yield 0.38 g.

Reduction of Pseudohypecorine Chloride. A. The reduction of 0.15 g of (II) with sodium tetrahydroborate in methanol yielded 0.09 g of dihydropseudohypecorine, $C_{20}H_{21}NO_5$ (III), mp 145-146°C (from ethanol).

B. A solution of 0.20 g of (II) in 5% hydrochloric acid was reduced with zinc dust at 20°C overnight. The yield of (III) was 0.15 g, mp 146-147°C (from ethanol).

Acetylation of (III). When 0.2 g of (III) was boiled with an excess of acetic anhydride for 8 h, a colored diacetate (0.12 g) with mp 134-135°C (from ethanol) was obtained. IR spectrum: 1645 and 1740 cm^{-1}. UV spectrum; λ_{max} in ethanol: 225 (shoulder), 313; log ε 4.46 and 4.13.

SUMMARY

Under the action of acids, the spiro amino ketal grouping of hypecorine opens. The structure of the pseudohypecorine chloride so formed has been confirmed by spectroscopy and by its reduction to the corresponding dihydro derivative. When the latter was treated with boiling acetic anhydride, the tetrahydroisoquinoline nucleus opened and a O,N-diacetyl derivative was formed.

LITERATURE CITED

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THE STRUCTURE OF ANHYDROLUPININE

A. I. Begisheva, K. Inoyatova,
A. A. Abduvakhabov, Kh. A. Aslanov,
and A. S. Sadykov

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The product of the dehydration of lupinine — anhydrolupinine — obtained by various methods [1-6] has widely differing specific rotations. This has led to the assumption that anhydrolupinine may exist in the form of two structural isomers readily changing into one another (I and II).

The anhydrolupinine obtained by heating lupinine with a mixture of sulfuric and glacial acetic acids [6] is a very unstable substance which rapidly oxidizes in the air. Judging from the fact that the product obtained is optically inactive, structure (II), having no asymmetric carbon atoms, has been proposed for it. In the separation of the alkaloids of *Anabasis aphylla* by the sulfuric acid method, we observed that the hydrolysis of lupinine sulfate formed a secondary product identical with the anhydrolupinine obtained by the method described by Willstätter and Fourneau [6].

The IR spectrum of the base taken immediately after its isolation showed a low-intensity absorption band in the 2800-2700 cm^{-1} region (trans-quinolizidine), a band in the 1650-cm^{-1} region, and a less intense band in the 1730-cm^{-1} region. The spectrum of the anhydro product that had been allowed to stand for a day retained the trans band, but the bands in the 1650- and 1730-cm^{-1} regions had acquired equal intensities, Apparently, anhydrolupinine consists of a mixture of two α,β-unsaturated isomeric compounds differing by the position of the double bond. At the moment of isolation, in all probability, one of them is present in predominating amount, and after a day an equilibrium is set up between these forms. On the basis of the characteristics of the IR spectra, it may be assumed that the isomeric mixture consists of forms (II) and (III).

The NMR spectrum, taken in benzene, of the anhydrolupinine obtained showed the following signals doublet at 1.07 ppm and singlets at 1.7 and 4.5 ppm. The doublet at 1.07 ppm is due to the protons of a methyl group bound in the form of $>CH-CH_3$, and the singlet in the weaker field at 1.7 ppm is due to the protons of a methyl group on an unsaturated carbon atom. The ratio of the intensities of the signals of the two methyl groups shows that the substance consists of the two isomers (II and III) in a ratio of 7:3, and the downfield shift of the singlet signal is caused by the anisotropic influence of the double bond on the protons of the methyl group. The upfield shift of the signal of the proton on the double bond may be due to the delocalization of the electrons of the unshared pair of the nitrogen into the π-orbital of the double bond. The signals of the protons of a $=CH_2$ group are not observed in the NMR spectrum, which shows the absence of form (I).

On analyzing the IR and NMR spectra, it may be concluded that anhydrolupinine is a mixture of two isomers (II) and (III) which can pass into one another, form (I) being completely absent from the mixture and form (II) amounting to about 70%. The production of these two forms in the dehydration of lupinine by the method of Willstätter and Fourneau [6] can be explained by the following scheme:

V. I. Lenin Tashkent State University. Division of Bioorganic Chemistry, Academy of Sciences of the Uzbek SSR, Tashkent. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 495-497, July-August, 1976. Original article submitted November 11, 1975.