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ALKALOIDS OF Reseda luteola

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Plants of the genus Reseda growing in the territory of the USSR have not previously been studied for their alkaloid content [1]. There is information on the isolation of sulfur-containing bases from some species of this genus [2]. We have previously reported the isolation of two new alkaloids – resedine, $C_9H_9NO_2$, and resedinine, C_9H_9NOS – from R. luteola L. [3]. We later developed methods for isolating and separating the combined alkaloids, and also obtained new chemical and spectral information confirming the structures of these alkaloids and their transformation products.

From the plant collected in the flowering period in the Samarkand oblast by the usual chloroform extraction we obtained a comparatively low yield (0.02%) of total alkaloids. The bulk of the alkaloids did not pass into the chloroform from the raw material, and another part was not extracted by organic solvents because of its high solubility in water, and therefore the raw material was extracted with a 1% solution of sulfuric acid. The extract was passed successively through KU-1 and KU-2 cation-exchange resins. The alkaloids were desorbed from the resins by means of an ethanolic solution of ammonia. The yield of combined alkaloids was 0.24%.

By separating the combined alkaloids according to their solubilities in organic solvents and by chromatography on a column of silica gel, we isolated four bases: resedine, resedinine, phenyl-β-naphthylamine, and β-hydroxyphenylethylamine.

The chemical transformations of resedine (I) and resedinine (II) gave a series of products which confirmed the structures proposed previously for these alkaloids [3]. The reduction of (I) in the presence of Raney nickel gave a base (III). The mass spectrum of (III) had the peaks of ions with c m/e 121 M^+ (3.3%) 91 (26.3%), 79 (2%), 77 (6%), 30 (100%) which agrees completely with the mass spectrum of phenylethylamine [4].

To confirm the structure and establish the site of attachment of the phenyl radical to the heterocyclic ring of resedine we reduced (I) with $LiAlH_4$ and obtained a mixture of products from which we isolated a liquid base (IV). The IR spectrum of (IV) contained absorption bands at 3200-3400 cm^{-1} (active hydrogen) and 710 and 770 cm^{-1} (monosubstituted benzene ring). The NMR spectrum of (IV) showed the signals of protons at 713 ppm (5 H, singlet, monosubstituted benzene ring), 4.60 ppm (1 H, triplet, $Ar-\underset{\underset{O-}{|}}{CH}-CH_2-$) 4.37 ppm (2 H, broadened singlet, =NH, OH), 2.40 (2 H, doublet, $=CH-\underline{CH_2}-$), and 2.18 ppm (3 H, singlet, $N-CH_3$). The mass spectrum of (IV) had the peaks of ions with c m/e 151 M^+ (10%), 107 (20%), 105 (40%), 79 (90%), 77 (95%), 44 (100%). An analysis of the spectra of (IV) leads to the structure of β-(hydroxyphenyl)-N-methylethylamine. The acetylation of (IV) with acetic anhydride in the presence of pyridine gave a O,N-diacetyl derivative (V), M^+ 235. In the IR spectrum of (V), the absorption band of active hydrogen had disappeared and the absorption bands of a carbonyl group had appeared at 1750 and 1670 cm^{-1}, which also confirms the structure for (IV) given above.

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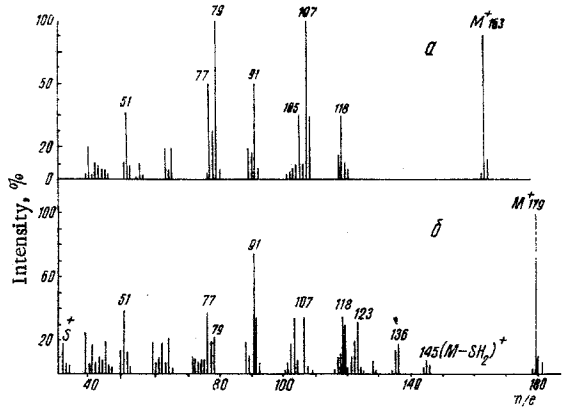


Fig. 1. Mass spectra of resedine (a) and resedinine (b).

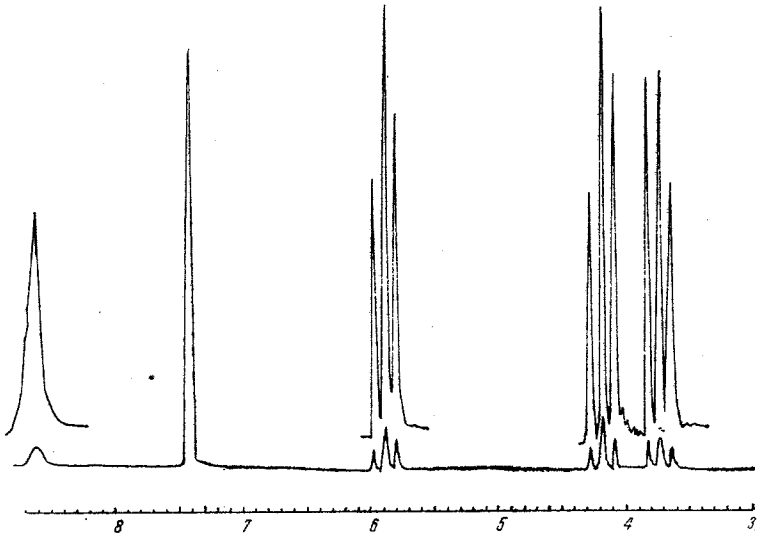
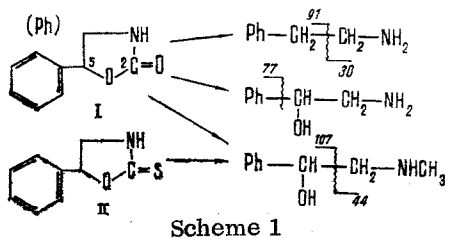


Fig. 2. NMR spectrum of resedinine.

We also obtained the base (IV) from the products of the reduction of (II) with $LiAlH_4$.

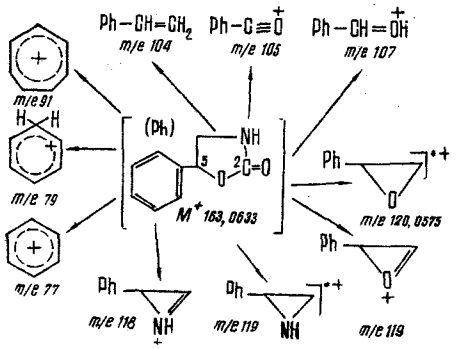
Thus, a correlation has been made of resedine with resedinine. When (I) was saponified with 20% KOH solution, a base (VI) was obtained with M^+ 137. The IR spectrum of (VI) showed absorption bands of active hydrogen at 3200-3400 cm^{-1} and bands at 710 and 760 cm^{-1} (monosubstituted benzene ring). On fragmentation under the conditions of mass spectrometry, ions were observed with m/e 137 M^+ (29%), 107 (87%), 79 (90%), 77 (97%), 30 (100%). Such a pattern of the spectrum shows that we were dealing with β-hydroxyphenylethylamine. The formation of these products confirms the fact that the phenyl radical is attached at position C_5 of the heterocyclic ring of oxazolidone (Scheme 1).



Scheme 1

A comparison of the mass spectra of (I), (III), (IV), and (VI) made obvious the origin of the peaks with m/e 105 and 107 in the spectrum of (I), which were obtained with the passage of a hydrogen atom to the charged or to the neutral fragment, respectively.

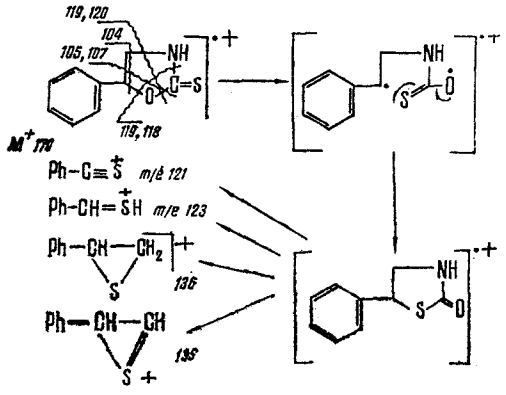
Since the mass spectra of oxazolidone derivatives has not been described in the literature, we have studied the fragmentation pathways of (I) and (II). After the action of electron impact on (I) the charge may be localized on either of the hetero atoms of the oxazolidone ring, in addition to the phenyl nucleus. In these circumstances, the fragmentation of the heterocycle takes place in several directions, which lead to oxygen-containing (or oxonium) and also to nitrogen-containing (or ammonium) ions (Scheme 2). The composition of some ions is confirmed by accurate mass measurements.



Scheme 2

We have shown previously that resedinine differs from resedine by the presence of a thiocarbonyl group in place of an amide carbonyl group [3]. In the mass spectrum of (II) there is the peak of the molecular ion with m/e 179, which is 16 m/e greater than in the mass spectrum of (I). The nature of the distribution of the intensities of the peaks of the molecular ion corresponds to the presence of one sulfur atom [5] (Fig. 1). The mass spectrum of (II) shows the peaks of fragmentary ions the masses of which coincide completely with those of the fragmentary ions of (I). However, there are also peaks of ions with m/e 121, 123, 135, and 136, the structures and compositions of which do not agree with the proposed structure (II) [3]. Such a nature of the spectrum of (II) indicates the presence of phenylthiazolid-2-one, since in the decomposition of the 2-thiooxazolidone ring the sulfur should depart with the ejected fragment. Since the substance was purified by repeated recrystallization and the IR spectrum of (II) lacked a band for a CO group, compound (II) must consist only of phenyl-2-thiooxazolidone, and the presence of the thiazolidone as an impurity in (II) is excluded.

Thus, the sulfur-containing ions in the mass spectrum must appear after a rearrangement of the molecular ion in which the 2-thiooxazolidone nucleus changes into a thiazolidone nucleus (Scheme 3). It must be mentioned that analogs of the sulfur-containing ions are also present in the mass spectrum of 5-vinyl-2-thiooxazolidone [6].



Scheme 3

The NMR spectrum of resedine has signals from five aromatic protons of a monosubstituted benzene ring in the form of a singlet at 7.70 ppm (5 H) and a broadened singlet at 6.85 ppm from the proton of the NH group. In addition, there are three one-proton triplets at 5.52, 3.90, and 3.45 ppm with spin–spin coupling constants J = 7 Hz from the three protons of the oxazolidone ring. The nature of the splitting and the various CSs of the signals show the nonequivalence of the protons at C_4. This is due to the fact that the protons in a

saturated five-membered ring are present in axial or equatorial orientations. We assigned the triplet in the weakest field (5.52 ppm) to the proton at C_5, since this proton is attached to a carbon atom connected with a phenyl radical and with an electronegative oxygen atom.

The NMR spectrum of resedinine is similar to that of resedine. Triplets in the spectrum of resedinine resonate in a weaker field, i.e., at 5.82, 4.10, and 3.65 ppm, and the signal of the proton of the NH group is observed at 8.52 ppm (Fig. 2).

Continuing the separation of the combined ether-soluble material [3], we isolated a base of which the spectral characteristics, the Rf value, and the melting point coincided with those of β-hydroxyphenylethylamine. A mixture with an authentic sample gave no depression of the melting point. To confirm the native nature of the alkaloid, (I) was dissolved in a 10% ethanolic solution of ammonia and the solution was boiled on the water bath for 6 h. No formation of (VI) was observed under these conditions.

EXPERIMENTAL

The UV spectra were taken on a Hitachi spectrophotometer, the IR spectra on a UR-20 instrument (tablets with KBr), the mass spectra on an MKh-1303 instrument with a system for the direct introduction of the sample at 90-100°C and with an ionizing voltage of 40 V, and the NMR spectra on a JNM-4H 100/100 MHz spectrometer. The accurate ion masses were measured on a Varian MAT-311 mass spectrometer by R. Razakov.

Isolation and Separation of the Combined Alkaloids. The comminuted raw material (17 kg) was extracted with 1% sulfuric acid. The extract was passed continuously through KU-1 and KU-2 cation-exchange resins at the rate of 10 liters/h. After the end of extraction, the resins were washed with water and ethanol. The alkaloids were desorbed from the resins with a 1% ethanolic solution of ammonia. The ammoniacal ethanolic solution was concentrated under vacuum and the alkaloids were extracted successively with petroleum ether, diethyl ether, and chloroform. The total yield of combined alkaloids was 40.92 g (0.24%).

The combined petroleum-ether-soluble material (5.7 g) was chromatographed on a column of silica gel (1:20). Elution with petroleum ether yielded phenyl-β-naphthylamine [7]. When the combined diethyl-ether-soluble material (20 g) was concentrated, β-hydroxyphenylethylamine precipitated. The mother solution was separated by chromatography in a column of silica gel (1:20). Elution with petroleum ether gave 5 mg of phenyl-β-naphthylamine, and benzene fractions yielded 3.4 g of resedinine. Further elution with a mixture of benzene and chloroform (95:5) gave 6.0 g of resedine. The combined chloroform-soluble material (15 g), on chromatography in a column of silica gel (1:40) yielded 50 mg of resedinine and 0.5 g of resedine.

Reduction of Resedine in the Presence of Raney Nickel. The hydrogenation of 100 mg of (I) was performed in 10 ml of ethanol in the presence of Raney nickel at room temperature. This gave 70 mg of (III) with mp 192-194°C (chloroform), M^+ 121.

Reduction of Resedine with $LiAlH_4$. In portions, 200 mg of $LiAlH_4$ was added to a solution of 100 mg of (I) in 30 ml of absolute ether. Compound (IV) was obtained in the form of an oil; yield 30 mg, M^+ 151.

Saponification of Resedine. A solution of 50 mg of (I) in 15 ml of 20% KOH solution was boiled for 8 h. This gave 30 mg of (VI), M^+ 137.

SUMMARY

1. The separation of a mixture of bases from the epigeal part of Reseda luteola L. has given four alkaloids: resedine, resedinine, phenyl-β-naphthylamine, and β-hydroxyphenylethylamine.

2. A study of the chemical properties and spectral characteristics of resedine and resedinine has confirmed the structure put forward for them previously.

3. It has been shown that under the conditions of the mass spectrometry of resedinine the 2-thiooxazolidone nucleus rearranges into a thiazolidone nucleus.

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CIRCULAR DICHROISM OF SOME STEROID ALKALOIDS

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In the present paper we consider the interconnection between the nature of the circular dichroism (CD) curves and the stereochemical features of steroid alkaloids: imperialine (I), eduardine (II), isogermine (III), veralodine (IV), and veralomidine (V). The structures of the compounds investigated have been established previously [1-6]. As can be seen from Fig. 1, for the C-nor-D-homosteroid alkaloids (I-III), there are two Cotton effects (CEs) in the CD spectra, in the 290 and 200 nm regions.

The sign and amplitude of the CE in the 290 nm region, due to a $n \rightarrow \pi^*$ transition in the carbonyl chromophore, confirms the trans-linkage of rings A/B in compounds (I-III) [7]. In the hydroxy ketone isogermine (III) the Cotton effect connected with the carbonyl chromophore is hypsochromically shifted in comparison with the usual position in 4-ketosteroids. Such a shift indicates the equatorial β orientation of the OH group at C_3. This is also confirmed by the fact that the intensity of the CE of (III) is almost the same as that of the unsubstituted 4-oxo compound [7]; in the case of an axial orientation of the OH group the amplitude of the CE should be considerably higher.

The CD spectra of compounds (I-III) contain, in addition to the long-wave CE, an intense CE in the 200 nm region caused by a $n \rightarrow \sigma^*$ transition in the C–N bond. This band disappears almost completely on acidification, which can be explained by the protonation of the nitrogen (Table 1). An analysis of the CD spectra of (I-III) has shown that the nature of the substituents of the closest asymmetric center at C_{20} has a substantial influence on the shortwave CE. Thus, the replacement of the hydrogen atom at C_{20} in (II) by a hydroxy group (I, III) causes a change in the sign of the CE. A negative CE in the 200 nm region may be connected with a 20R configuration (II) and a positive CE with a 20S configuration in compounds (I) and (III).

In the CD spectrum of veralodine (IV) (Fig. 2a) there are three CEs. Two of them, at 315 and 240 nm, are due to $n \rightarrow \pi^*$ and $\pi \rightarrow \pi^*$ transitions, respectively (R and K bands) in the α,β-unsaturated carbonyl chromophore, and the CE in the 205 nm region is connected with the lactam carbonyl. The nature of the CD spectrum of (IV) in the region of the R and K bands is the same as that of testosterone [7], which confirms the trans-linkage of rings BC and the $8\beta,9\alpha$ configuration in veralodine. A positive lactam CE at 205 nm is characteristic for the trans-linkage of rings E/F.

When a methanolic solution of (IV) was acidified, another (+)CE appeared in the CD spectrum at about 370 nm and the CE at 315 nm simultaneously decreased in intensity (see Fig. 2a). We assumed that in an acid medium dehydration takes place with the appearance of another double bond between C_6 and C_7 which increases the size of the system of conjugation and bathochromically shifts the $n \rightarrow \pi^*$ Cotton effect.

The CD spectrum of veralomidine (V) (Fig. 2b) is characterized by two negative CEs at 203 and 195 nm. On the acidification of a methanolic solution, the first CE decreases in intensity and the second remains unchanged, and on this basis the first CE is ascribed to a $n \rightarrow \sigma^*$ transition of the secondary amino group and the CE in the 195 nm region to a $\pi \rightarrow \pi^*$ transition of the C = C bond. By analogy with piperidine derivatives [8], the negative CE in the 203 nm region may be connected with the R configuration of the asymmetric center closest to the NH group, i.e., in the case of veralomidine, with the 22R configuration. In order to confirm the possibility of the use of the CE in the 200 nm region to determine the configuration of the asymmetric center

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