A STUDY OF Rosmarinus officinalis

IV. ISOROSMARICINE

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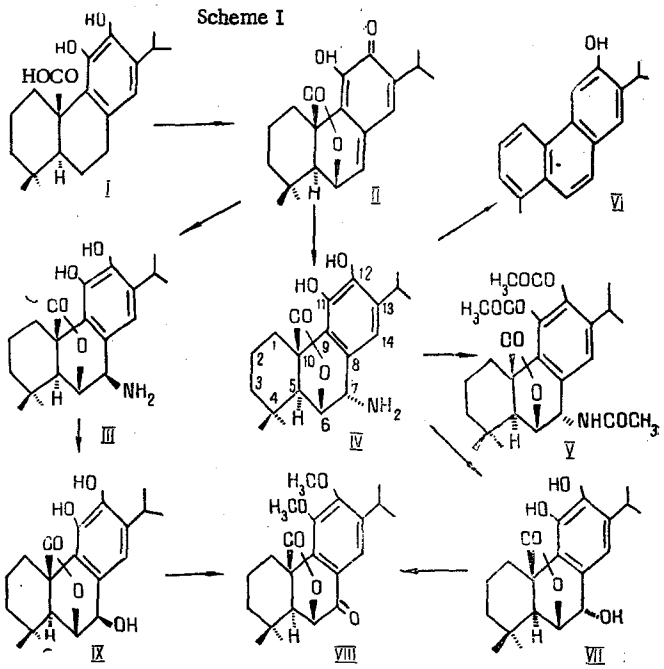
Carnosic acid (I) – the main terpene component of Rosmarinus officinalis L. (rosemary) – readily undergoes various transformations with the formation of a six-membered lactone ring. In particular, in air this acid undergoes oxidative transformations with the formation of carnosol [1]. In the presence of ammonia, the main products of the reaction are rosmaricine (III) and a base 2 [2], which we have called isorosmaricine.

The present paper gives the results of a study of the structure of isorosmaricine (IV).

Isorosmaricine has the same elementary composition as rosmaricine – $C_{20}H_{27}NO_4$ – and contains a γ-lactone grouping (IR spectrum: 1760 cm^{-1}), a $C-(CH_3)_2$ group, and four labile hydrogen atoms. On acetylation, isorosmaricine forms a N,O,O-triacetate (V), and on treatment with nitric acid an oxydesamino derivative. The dehydrogenation of isorosmaricine with selenium leads to retenol (VI) (Table 1 and Scheme 1).

Scheme I



The methylation of oxydesaminoisorosmaricine (VII) with dimethyl sulfate in an alkaline medium and subsequent oxidation with potassium permanganate gave di-O-methyloxydesaminoisorosmaricine (VII), containing two methoxy groups, a ketone carbonyl, and a γ-lactone group.

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TABLE 1. Physicochemical Properties of Rosmaricine and Isorosmaricine and Their Derivatives

Compound	Formula	Rosmaricine	Isorosmaricine
		mp, °C	
Base	$C_{20}H_{27}NO_4$	199–200(decomp.) $[\alpha]_D^{20}$ + 137° (ethanol)	197–198 (decomp.) $[\alpha]_D^{20}$ + 36° (ethanol)
Sulfate	$C_{20}H_{27}NO_4 \cdot {}^1/_2H_2SO_4$	—	188–190 (decomp.)
Hydrochloride	$C_{20}H_{27}NO_4 \cdot HCl$	197–198 (decomp.)	214–216 (decomp.)
N, O_9 O-Triacetate	$C_{26}H_{33}NO_7$	217–219 (decomp.)	291–292 (decomp.)
Oxydesamino derivative	$C_{20}H_{26}O_5$	172–175 (decomp.)	178–180 (decomp.)
Di-O-methyl, oxydesamino derivative	$C_{22}H_{28}O_5$	121–122	121–122

TABLE 2. Chemical Shifts and Spin-Spin Coupling Constants and the NMR Spectra of Rosmaricine and Isorosmaricine Triacetates

Compound	Group							
	$C_4-(CH_3)_2$							
	axial	equatorial	C_5-H	C_6-H	C_7-H	$C_{13}-CH(\underline{CH_3})_2$	OAc	NHAc
Rosmaricine triacetate (X)	0,92 s *	0,94 s	2,07 s	4,70 d (3,0) †	5,47 q (3,0 and 10)	1,13 d (7) 1,20 d (7)	2,27 s 2,31 s	2,06 s
Isorosmaricine triacetate (V)	0,92 s	0,82 s	1,97 s	4,69 d (3,3)	5,17 q 3,3 and 7)	1,14 s 1,20 s	2,26 s 2,30 s	2,02 s

*s)-singlet; d)-doublet; q)-quartet;

† The values of the spin-spin coupling constants in Hz are given in brackets (the chemical shifts are given in the δ scale).

Similar transformations of rosmaricine (III) (treatment with nitrous acid, methylation with dimethyl sulfate, oxidation with potassium permanganate) gave di-O-methyloxydesaminorosmaricine, identical with (VIII). The IR spectra of the two substances coincided, and a mixture of them gave no depression of the melting point. Since in these transformations the asymmetric center at C_7 disappears and no other asymmetric centers of the molecule are affected, the formation of one and the same substance (VIII) from rosmaricine (III) and from isorosmaricine (IV) shows that (III) and (IV) are epimers at C_7. The β position of the amino group at C_7 has previously been established for rosmaricine [1]. Consequently, in isorosmaricine the amino group at C_7 occupies the α position.

The NMR spectra agree well with the conclusions drawn on the basis of the chemical transformations of rosmaricine and isorosmaricine. The NMR spectra of (III) and (IV), and also of their triacetates, are almost identical, which shows that the structures of these compounds are similar.

In addition to this, the chemical shifts of the signals of the NH and C_7-H protons for the triacetate of isorosmaricine differ significantly from the chemical shifts of the corresponding protons in the triacetate of rosmaricine. There is also a difference in the positions of the signals of the protons of the gem-dimethyl grouping. While the signals of the protons of the axial methyl groups at C_4 of rosmaricine triacetate (X) and of isorosmaricine triacetate (V) have extremely similar chemical shifts (Table 2), the signal of the equatorial methyl group at C_4 of (V) is in a stronger field than that for (X) by 0.12 ppm.

It follows from an analysis of the NMR spectra that the configuration of the N-acetyl group in (V) differs from that in (X). As a consideration of molecular models has shown, for the β configuration the N-acetyl group and the equatorial methyl group at C_4 are spatially close, which, in all probability, is the

cause of the upfield shift of the signal of the latter. Because of the steric interaction of the N-acetyl group and the lactone ring in (X), the preferred configuration must be that in which the protons at C_7 and on the nitrogen atom are in the transoid position with respect to one another. However, for (V) the configuration in which the N-acetyl group and the equatorial methyl group are spatially close is energetically unfavorable. This view is supported by the decrease in the vicinal constant J (NH – C_7-H) on passing from (X) (J = 10 Hz) to (V) (J = 7 Hz).

Thus, the NMR spectra confirm the configuration of the amino group in isorosmaricine as the α configuration.

A consideration of the mechanism of the conversion of carnosic acid into rosmaricine enabled American authors to suggest a scheme of reactions through the intermediate substance (II) [1]. Apparently, the formation of rosmaricine and of isorosmaricine takes place by a common mechanism through substance (II) with the addition of a molecule of ammonia as the result of attack at the C_7-C_8 double bond from both sides of the plane of the molecule. The different screenings of this double bond explains the dissimilar ease of approach of the amono group and also the different amounts of rosmaricine and isorosmaricine formed by these reactions.

EXPERIMENTAL

The elementary analyses of isorosmaricine and all subsequent substances corresponded to the calculated figures.

Separation of Rosmaricine (III) and Isorosmaricine (IV). Unrecrystallized rosmaricine [3] (1.1 g) was heated with 30 ml of 5% H_2SO_4. The hot solution deposited crystals of isorosmaricine sulfate (0.37 g), the melting point of which after recrystallization from aqueous methanol was 188-190° C (decomp.).

Found %: N 3.29; 3.36; S 3.57; 3.82. $C_{20}H_{27}NO_4 \cdot {}^1/_2\, H_2SO_4$. Calculated %: N 3.54; S 4.05.

Rosmaricine sulfate remained in solution. Isorosmaricine, $C_{20}H_{27}NO_4$ (IV) obtained from the sulfate had, after recrystallization from toluene, mp 197-198° C (decomp.).

The hydrochloride of (IV), $C_{20}H_{27}NO_4 \cdot HCl$, mp 214-216° C (decomp., from water).

The N,O,O-triacetyl derivative of (IV). $C_{26}H_{33}NO_7$ (V), mp 291-292° C (decomp., from methanol).

Desamination of Isorosmaricine (IV). The diazotization of 0.90 g of (IV) was performed in 100 ml of 5% HCl with 0.75 g of $NaNO_2$. The yellow precipitate was recrystallized from ether, giving 0.25 g of oxydesaminoisorosmaricine, $C_{20}H_{26}O_5$ (VII) with mp 178-180° C (decomp.).

Dehydrogenation of Isorosmaricine. A mixture of 1.5 g of (IV) and 1.5 g of selenium was heated at 330-340° C for 2 h. The product was chromatographed on Al_2O_3 (activity grade II), and 200 ml of benzene and 2 ml of methanol eluted 0.8 g of (VI) with mp 177-178° C, giving no depression of the melting point in admixture with a sample of reten-12-ol [4].

Methylation and Oxidation of Oxydesaminoisorosmaricine (VII). Powdered potassium permanganate was added in 0.4-g to 0.5-g portions together with 1 ml of glacial acetic acid for each portion to a solution of 1.1 g of (VII) in 50 ml of acetone at 20° C. A total of 5.5 g of potassium permanganate and 13 ml of glacial acetic acid was added. Then the reaction mixture was filtered and the filtrate was evaporated to dryness in vacuum. The residue was boiled with ether. The extract yielded 0.47 g of (VIII), with the composition $C_{22}H_{28}O_5$, mp 120-121° C (from petroleum ether), IR spectrum 1790, 1709 cm^{-1}.

SUMMARY

The structure of isorosmaricine has been established on the basis of chemical reactions and NMR spectroscopy. It has been shown that isorosmaricine is the α epimer of rosmaricine with respect to the position of the amino group at C_7.

LITERATURE CITED

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