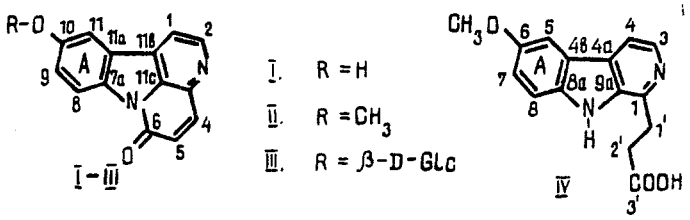
STRUCTURE OF THE ALKALOIDS OF Aerva lanata

G. G. Zapesochnaya, V. A. Kurkin, V. V. Okhanov,
L. N. Perzykh, and A. I. Miroshnilov

UDC 548.663:547.9

By the NOE method using ^{13}C NMR and UV spectra we have confirmed the structues of four new alkaloids isolated previously: 10-hydroxycanthin-6-one (ervine), 10-methoxycanthine-6-one (methylervine), 10-β-D-glucopyranosyloxycanthin-6-one (ervoside), and 6-methoxy-β-carbolin-1-ylpropionic acid (ervolanine).

We have previously [1] reported the isolation and a study of the structures of six β-carboline alkaloids from the herb Aerva lanata Juss. (Amaranthaceae). In the present paper we give additional information for the four new compounds of this series.



The structures of the new compounds (I-IV) had been established previously [1] on the basis of their UV, IR, ^1H NMR, and mass spectra. The close relationship and similar type of substitution of ring A of the compounds isolated was confirmed by their chemical transformations. Thus, ervoside (III) was readily hydrolyzed by β-glucosidase with the formation of ervine (I), which, on acetylation, formed a monoacetate and, on methylation with diazomethane, was converted into methylervine (II). Ervolanine (IV) was obtained from methylervine by selective hydrogenation followed by saponification. At the same time, an opinion was expressed on the necessity for revising the results of Arisawa et al. [2], who described as 10-hydroxy- and 10-hydroxycanthin-6-ones compounds which must now be regarded as 9-hydroxy- and 9-methoxycanthin-6-ones, respectively.

To confirm the structures of the new alkaloids (I-IV), we have carried out a series of experiments (Fig. 1) using the nuclear Overhauser effect (NOE). The NOE method has been used for determining the positions of substituents in analogous heteroaromatic systems [3]. The protons in positions 4 and 5 of β-carbolines (and the corresponding protons at C-1 and C-11 in the canthinones) are spatially close. In view of this, if the C-5 position is unsubstituted, irradiation of the proton at C-4 will lead to an increase in the intensity of the H-5 signal. A determination of the coupling constants of the perturbed signal will permit an unambiguous determination of the structures of substituted compounds. For example, in 2-methoxycanthin-6-one the signal of the N-11 proton increased by 3.5% when the singlet signal of H-1 was irradiated [4]. The absence of a NOE between the H-1 and H-11 protons gave grounds for the authors to assign the substituents to the 11-position in amarorine (11-hydroxycanthin-6-one) [4, 5] and amaroridine (11-methoxycanthin-6-one) [5].

Our NOE experiments showed that such conclusions are not always unambiguous. Thus, for compounds (II) and (IV) no Overhauser effects were observed for the above-mentioned protons at 200 Hz, but they were detected at 500 MHz (Fig. 1). When the H-11 proton (doublet with J = 2 Hz) was irradiated, the intensity of the signal of the H-1 proton increased (1%) for compound (II) at 500 MHz, while for compound (III) an analogous NOE (1%) was observed at 200 MHz (Fig. 1).

All-Union Scientific-Research Institute of Drugs Scientific–Production Association, Moscow. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 821-824, November-December, 1991. Original article submitted February 21, 1991.

0009-3130/91/2706-0725$12.50

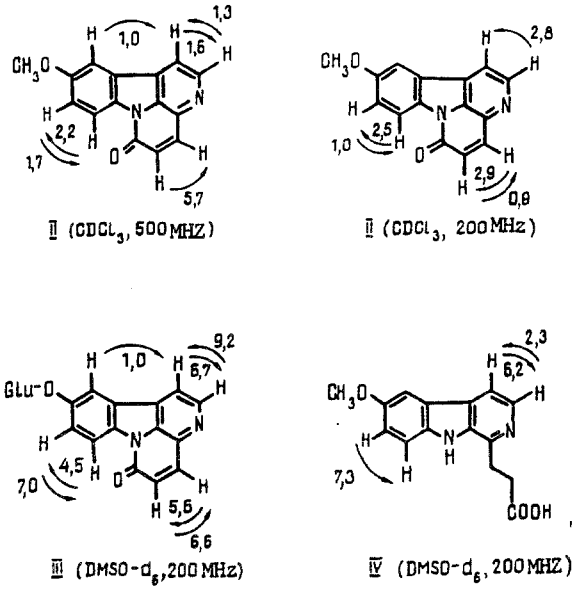


Fig. 1. Nuclear Overhauser effects (%) for methylervine (II), ervoside (III), and ervolanine (IV).

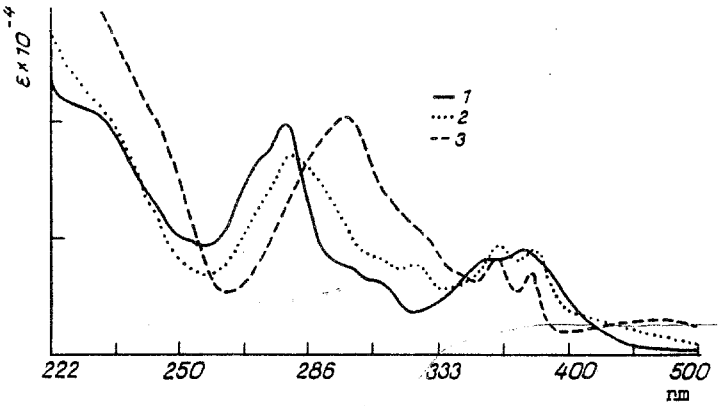


Fig. 2. UV spectra of ervine (I): 1) in EtOH; 2) in EtOH + HCl; 3) in EtOH + NaOMe.

The ^{13}C NMR spectra taken for two compounds under the regimes of complete and incomplete decoupling from protons likewise do not contradict the conclusions we have drawn concerning the structures of alkaloids (I)-(IV). In the spectrum of ervolanine (IV), for the assignment of the signals of the protonated carbon atoms we used the results of Aimi et al. [6] for an analogously substituted β-carboline (6-hydroxylyalosidic acid), and the signals of the quaternary carbons were assigned in accordance with Welti's paper [7]. In the assignment of the signals in the spectrum of methylervine (II) we also took into account the results of a study by Pettit et al. [4], who used the selective INEPT technique to confirm the assignment of the signals in 11-hydroxycanthin-6-one. It must be mentioned that the work of Welti [7], who made an unambiguous assignment of the ^{13}C NMR signals of harman (1-methyl-β-carboline) on the basis of INADEQUATE spectroscopy has created the necessity for a critical reconsideration both of the assignments made previously for harman [8, 9] and the assignments made on their basis in the ^{13}C NMR spectra of β-carbolines and canthinones (for example, in [10-12]).

The structures of compounds (I-IV) were also confirmed with the aid of UV spectroscopy. The UV spectra of ervine (I), methylervine (II), and ervoside (III) in ethanol are very similar to one another (Fig. 2). Their long-wave maximum (about 376 nm) differs appreciably from the results, agreeing with one another (λ_{max} about 352 nm), described for 9-methoxycanthin-6-one [13, 14] and 10-hydroxy- and 10-methoxycanthin-6-ones [2]. A change in the pH had practically no effect on the UV spectra of compounds (II) and (III). Only the UV spectra of ervine (I) changed sharply on the addition of NaOMe (Fig. 2) and the long-wave region (350, 376, 460 nm) differed considerably from that described in the paper by Arisawa et al. [2] for 10-hydroxy-canthin-6-one (356, 428 nm), which additionally indicates the necessity for a revision of these authors' results [2].

Thus, compounds (I-III) that we have described are the first representatives of the 10-substituted canthinones, since the 10-hydroxy- and 10-methoxycanthin-6-ones described by Arisawa et al. [2] must be assigned to the corresponding 9- isomers. Analogously substituted β-carbolines, to which ervolanine (IV) belongs, are also fairly rare. Only five such compounds have been described: 6-hydroxyharman, 6-methoxyharman [15], 6-bromoharman [16], cecilin (1-p-hydroxybenzyl-6-methoxy-β-carboline) [17], and 6-hydroxylyasolidic acid (the glucoside of a monoterpenoid β-carboline) [6].

In the course of a study of the herbage and roots of Aerva lanata we found considerable differences in their chemical compositions. Thus, in the herbage the dominating components were flavonoid O-acyl glycosides [18], which were practically absent from the roots, while no alkaloids of the β-carboline type were detected in them [1].

In a chemical study of the roots we isolated eight compounds for the first time, identifying them on the basis of chemical and spectral characteristics: the canthinones ervine (I), methylervine (II), and ervoside (III), the amides feruloyltyramine and feruloylhomovanillylamine, syringic and vanillic acids, and β-sitosterol. It must be mentioned that these compounds have been isolated previously from the herbage of A. lanata [1, 19].

EXPERIMENTAL

^{13}C NMR spectra were taken on a Bruker WM-250 instrument at 62.9 MHz using a concentration of 0.1 M in $CDCl_3$ (II) and in DMSO-d_6 (IV). UV spectra were taken on a Specord M40 spectrometer. The NOE experiments were conducted on Bruker WM-500 and Bruker MSL-200 instruments at 30°C using a concentration of the substances of 0.02 M. In all cases a positive effect was obtained; the solvents used were $CDCl_3$ (Fluka, 99.95% deuterated) and DMSO-d_6 (Merck, 99.8% deuterated) and the tubes had an internal diameter of 5 mm. The residual signal of the solvent was used as the internal standard, this being taken as 7.27 ppm in the case of chloroform and 2.49 ppm in the case of DMSO.

^{13}C NMR spectrum of compound (II) ($CDCl_3$), δ: 55.83 (q, CH_3O), 106.44 (d, C-11), 116.19 (d, C-8), 117.81 (d, C-9), 117.86 (d, C-1), 125.50 (s, C-11a), 128.86 (d, C-5), 130.12 (s, C-11b), 132.33 (s, C-11c), 133.66 (s, C-7a), 136.25 (s, C-3a), 139.06 (d, C-4), 145.52 (d, C-2), 157.82 (s, C-10), 159.05 (s, C-6).

^{13}C NMR spectrum of compound (IV) (DMSO-d_6), δ: 32.04 (t, C-1'), 35.37 (t, C-2'), 59.63 (q, CH_3O), 107.50 (d, C-5), 116.93 (d, C-4, C-8), 122.03 (d, C-7), 125.39 (s, C-4b), 131.06 (s, C-4a), 138.70 (s, C-9a), 139.34 (s, C-8a), 140.75 (d, C-3), 148.27 (s, C-1), 157.45 (s, C-6), 178.30 (s, C-3').

LITERATURE CITED

1. G. G. Zapesochnaya, L. N. Pervykh, and V. A. Kurkin, Khim. Prir. Soedin., No. 3, 388 (1991).
2. M. Arisawa, A. D. Kinghorn, G. A. Cordell, and N. R. Farnsworth, J. Nat. Prod., 46, No. 2, 222 (1983).
3. B. P. Roques, S. Combrisson, R. Oberlin, and J. Barbet, Tetrahedron Lett., No. 17, 1641 (1974).
4. G. R. Pettit, S. B. Singh, A. Goswami, and R. A. Nieman, Tetrahedron., 44, No. 11, 3349 (1988).
5. P. J. Clarke, K. Jewers, and H. F. Jones, J. Chem. Soc. Perkin Trans. I, 1614 (1980).
6. N. Aimi, H. Murakami, T. Tsuyuki, et al., Chem. Pharm. Bull., 34, No. 7, 3064 (1986).
7. D. H. Welti, Magn. Reson. Chem., 23, No. 10, 872 (1985).
8. H. Wagner, T. Nestler, and A. Neszmelyi, Tetrahedron Lett., No. 31, 2777 (1978).
9. C. A. Coune, L. J. C. Angenot, and J. Denoël, Phytochemistry, 19, No. 9, 2009 (1980).
10. T. Ohmoto, K. Kolke, and J. Sakamoto, Chem. Pharm. Bull., 29, No. 2, 390 (1981).
11. T. Ohmoto and K. Kolke, Chem. Pharm. Bull., 30, No. 4, 1204 (1982).
12. N. Fukamiya, M. Okano, T. Aratani, et al., J. Nat. Prod., 49, No. 3, 428 (1986).
13. A. M. Giesbrecht, H. E. Gottlieb, O. R. Gottlieb, et al., Phytochem., 19, No. 2, 313 (1980).
14. J. Polonsky, J. Gallas, J. Varenne, et al., Tetrahedron Lett., 23, No. 8, 869 (1982).
15. H. Rosler, H. Framm, and R. N. Blomster, J. Nat. Prod., 41, No. 4, 383 (1978).
16. A. Aiello, E. Fattorusso, S. Magno, and L. Mayol, Tetrahedron., 43, No. 4, 5929 (1987).
17. L. M. G. Aguiar, R. B. Filho, O. R. Gottlieb, et al., Phytochem., 19, No. 8, 1859 (1980).

18. A. M. Zadorozhnyi, G. G. Zapesochnaya, L. N. Pervykh, A. N. Shchavlinskii, L. S. Kovtun, and N. V. Svanidze, Khim.-farm. Zh., 20, No. 7, 855 (1986).
19. G. G. Zapesochnaya, V. A. Kurkin, and L. N. Pervykh, Khim. Prir. Soedin., 694 (1990).

SYNTHESIS AND STRUCTURE OF NEW PHENYL- AND DIPHENYLPHOSPHINE DERIVATIVES OF ANABASINE AND THEIR INFLUENCE ON THE ACTIVITY OF MOUSE LIVER MICROSOMAL CYTOCHROME-P-450-DEPENDENT MONOOXYGENASES

D. N. Dalimov, S. N. Moralev, B. N. Babaev, B. N. Kormilitsyn, N. K. Prokhorenko, A. A. Abduvakhov, and F. G. Kamaev

UDC 541.69:542.91:577.150.4

A series of alkyl N-β-hydroxypropylanabasinyl and alkyl N-but-2-ynylanabasinyl phenylphosphonates and also N-β-hydroxypropylanabasinyl and N-but-2-enylanabasinyl diphenylphosphinates possessing considerable antimonooxygenase activity, exceeding that of the standard inhibitor SKF-525A with respect both to an insecticide (paraoxon) and to a medicinal drug (aminopyrine), have been synthesized.

Microsomal (M) cytochrome-P-450-dependent monoxygenases (MMs) take an active part in the mechanism of xenobiotics, especially pesticides and drugs. MM inhibitors can be used as insecticide synergists and for prolonging the action of drugs.

Many groups of compounds capable of suppressing the activity of MMs are known – in particular, pyridine derivatives, tertiary amines, and acetylene-containing compounds [1]. In order to find effective MM inhibitors we have synthesized phosphorylated derivatives of anabasine and have investigated their influence on the rate of oxidation of various compounds under the action of mouse liver MMs in vitro: standard MM substrates – p-nitroanisole and aminopyrine [2] – and also paraoxon, which we selected as a model insecticide. The efficacy of the compounds investigated was also evaluated in vivo from their influence on the duration of hexobarbital soluble sleep of mice. The lowering of the rate of decomposition of hexobarbital soluble by the MM system of the liver leads to a prolongation of its action.

All stages in the prepration of alkyl phenylphosphonochloridates and diphenylphosphinic chloride have been described in the literature [3-6]. N-β-Hydroxypropylanabasine was obtained by condensing anabasine with propylene oxide in ethanol [7]. N-(4-Hydroxybut-2-ynyl)-anabasine was synthesized by the interaction of anabasine, propargyl alcohol, and paraformaldehyde in dioxane [8]. The final substances, alkyl N-β-hydroxypropylanabasinyl phenylphosphonates, alkyl N-but-2-ynylanabasinyl phenylphosphonates, N-β-hydroxypropylanabasinyl diphenylphosphinate, and N-but-2-ynylanabasinyl diphenylphosphinate were obtained by the reactions of alkyl phenylphosphonochloridates or diphenylphosphinic chloride with the appropriate amino alcohols in absolute ether in accordance with the scheme given below.

The structures of the compounds were confirmed by the results of elementary analysis and by IR and PMR spectroscopy.

In the IR spectrum of pentyl N-β-hydroxypropylanabasinyl phenylphosphonate chracteristic bands of the following functional groups were observed (ν, cm^{-1}): (P–OC_5H_{11}) 980-1000, (P=O) 1250, (C–H) 1450, (N–C) 1540, (P–C_6H_5) 1640.

A. S. Sadykov Institute of Bioorganic Chemistry, Uzbek Academy of Sciences, Tashkent. I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, Leningrad. Translated from Khimiya Prirodnykh Soedinenii, No. 6, pp. 824-828, November-December, 1991. Original article submitted March 18, 1991; revision submitted June 25, 1991.

 0009-3130/91/2706-0728$12.50