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ALKALOIDS OF *Haplophyllum dauricum*

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From the roots of *Haplophyllum dauricum* (L) G. Don., collected on the territory of the Uvur-Khangai aimak, Mongolian People's Republic, in the fruit-bearing stage have been isolated robustine, dictamnine, γ-fagarine, haplopine, skimmianine, 4-methoxy-N-methyl-2-quinolone, folimine, robustinine, and the new alkaloid daurine the structure of which has been established as 8-(γ,γ-dimethylallyloxy)-4-methoxy-N-methyl-2-quinolone.

Alkaloids of plants of the genus *Haplophyllum* (family *Rutaceae*) have been described in a large number of publications [1], but many representatives of this genus growing on the territory of the SSR and outside it have not yet been investigated. These plants include, in particular, *Haplophyllum dauricum* (L) G. Don., which is found in Siberia and is widely distributed in the steppe regions of Mongolia [2]. A report in the literature [3] is limited simply to a mention of the presence of alkaloids in the Mongolian species *H. dauricum*. This plant is used in folk medicine as an antipyretic and in the treatment of some forms of tumors.

We have studied the alkaloid composition of the epigeal part and roots of *H. dauricum* collected on the territory of the Uvur-Khangai aimak, Mongolian People's Republic, in the stage of incipient fruit bearing. In an investigation of the coumarin and lignan composition of this plant in which one of us took part, skimmianine and γ-fagarine were detected [4].

The comminuted raw material was extracted with methanol. The total alkaloids were obtained by the standard method, these making up 0.75% and 0.05% of the mass of the dry roots and epigeal part, respectively. The total alkaloids from the epigeal part, containing, according to TLC, skimmianine and γ-fagarine, were not studied because of their small amount. Column chromatography of the mixture of bases from the roots of *H. dauricum* gave robustine (I), dictamnine (II), skimmianine (III), and γ-fagarine (IV). The mother liquor after the isolation of the γ-fagarine was separated into phenolic and nonphenolic fractions. Haplopine (V) was obtained from the phenolic fraction. Rechromatography of the mixed fractions followed by crystallization yielded bases with mp 117-118°C (VI) and 100-101°C (VII), folamine (VIII), and robustinine (IX).

The alkaloid (VI) is new, and we have called it daurine. As the result of a study of spectral characteristics and also the formation of 8-hydroxy-4-methoxy-N-methyl-2-quinolone on the hydrolysis of (VI) in an acid medium, the structure of 8-(γ,γ-dimethylallyloxy)-4-methoxy-N-methy-2-quinoline has been established for daurine [5]. In contrast to all known alkoxy derivatives of the 2-quinolone series, the UV spectra of which do not change on acidification and alkalinization, the spectrum of daurine undergoes a change on the addition of a drop of hydrochloric acid to an ethanolic solution of (VI) (Fig. 1). A similar change in the absorption curve in an acid medium is observed in the spectrum of 8-hydroxy-4-methoxy-N-methyl-2-quinolone (X) (Fig. 1). This gave ground for assuming that in an acid medium

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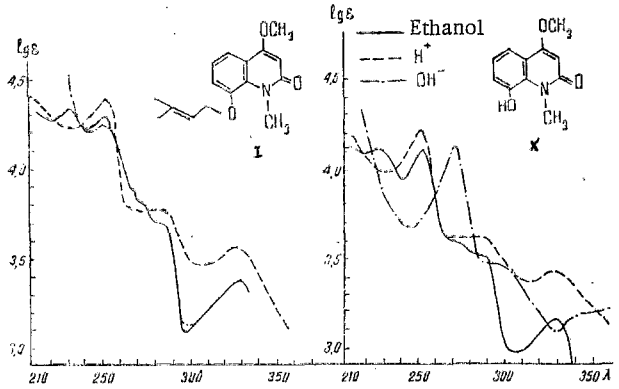

Fig. 1. UV spectra of daurine (I) and of 8-hydroxy-4-methoxy-2-quinolone (X).

daurine is readily hydrolyzed with the formation of (X). A confirmation of this was the isolation of (X) from an acidified solution of daurine. Consequently, the change in the absorption curve in an acid medium is due to the conversion of daurine into 8-hydroxy-4-methoxy-N-methyl-2-quinoline under the conditions of recording its UV spectrum.

According to its IR and UV spectra, compound (VII) was also a 2-quinolone derivative. Its PMR spectrum (CCl_4, 0 — HMDS) contained signals at 7.82 ppm (1H, quadruplet, J = 9 and 2.5 Hz, H_5), 7.28 ppm (3H, multiplet, $H_{6,7,8}$), 5.79 ppm (1H, singlet, H_3) and 3.87 and 3.47 ppm (singlets, 3H each, OCH_3 and NCH_3), indicating that (VII) has the structure of 4-methoxy-N-methyl-2-quinolone, which was first isolated from the plant *Hesperethusa crenulata* (family *Rutaceae*) [6].

The alkaloids robustine, dictamnine, skimmianine, γ-fagarine, haplopine, folamine, and robustine were identified by a direct comparison with authentic samples isolated from plants of the genus *Haplophyllum* [1].

Thus, five furanoquinoline alkaloids and four 4-methoxy-N-methyl-2-quinolone alkaloids have been isolated from the roots of *H. dauricum*.

This is the first time that 4-methoxy-N-methyl-2-quinolone has been isolated from plants of the genus *Haplophyllum*.

EXPERIMENTAL

The conditions for recording the UV, IR, PMR, and mass spectra have been described previously [7]. Column chromatography was carried out on silica gel L 100/160, and thin-layer chromatography on silica gel L 5/40 (Czechoslovakia) with the addition of 5% of gypsum in the following solvent systems: 1) toluene—ethyl acetate—acetic acid (5:4:1); 2) ethyl acetate; 3) cyclohexane—ethyl acetate (3:1); and 4) chloroform. The spots were revealed with Dragendorff's reagent.

Isolation and Separation of the Alkaloids. An evaporated methanolic extract obtained by treating the ground dry roots (1150 g) with methanol ten times, was diluted with water and extracted with chloroform. The alkaloids were extracted from the chloroform solution with 5% sulfuric acid and, immediately after alkalinization, they were reextracted with chloroform. Distillation of the dried and filtered chloroform extract gave a crystalline mixture of bases (8.63 g). Similar treatment of the epigeal part gave a noncrystalline mixture of alkaloids (0.95 g).

The mixture of alkaloids from the roots (863 g) was subjected to chromatographic separation on a column of silica gel (250 g). Elution was performed with ether and with an ether—chloroform gradient system. The ethereal eluates yielded alkaloids in the following sequence: robustine (1.56 g), mp 147-148°C (from ethanol); dictamnine (0.6 g), mp 132-133°C (from acetone); skimmianine (0.15 g), mp 177-178°C (from methanol); and γ-fagarine (1.51 g), mp 140-141°C (from aqueous acetone). The ethereal-chloroformic eluates contained a mixture of substances, according to TLC.

The γ-fagarine mother liquor was separated into phenolic and nonphenolic fractions. By chromatography, the phenolic fractions yielded haplopine, mp 202-203°C. Repeated rechromatography of the nonphenolic fraction and of the mixed ethereal-chloroformic eluates on silica

gel using hexane, ethyl acetate, and chloroform gave fractions having as their main components substances with R_f 0.57 and 0.46 (systems 1 and 2, respectively), 0.41 and 0.35, and 0.16 and 0.31, respectively.

The fractions containing the substance with R_f 0.57 and 0.46 (systems 1 and 2) were chromatographed on silica gel with elution by hexane and ethyl acetate. The ethyl acetate eluates yielded 10 mg of a base (VI). The fractions containing the substances with R_f 0.41; 0.35 and 0.16;0.31 (systems 1 and 2) (100 mg) were chromatographed on silica gel (10 g). Elution was performed with chloroform, 10-ml fractions being collected. The first eluates yielded γ-fagarine contaminated with substances (VII) and (VIII), fractions 4-6 a crystalline mixture of (VII) and (VIII) with mp 84°C (from hexane), and fractions 8-9 the base (IX). The crystals with mp 84°C were recrystallized from hexane. A crystalline mixture deposited which consisted of white warty crystals of (VII) (12 mg) and thin colorless needles of (VIII) (10 mg), which were separated mechanically.

Daurine (VI), mp 116-118°C (from hexane). Its spectral characteristics have been given previously [5].

Acid Hydrolysis of Daurine. A drop of concentrated hydrochloric acid was added to a solution of 3 mg of daurine in 1 ml of ethanol. The reaction mixture was left at room temperature. After 10 min, (X) was detected by GLC. On the following day, the ethanol was evaporated off and the residue was dissolved in 4% aqueous caustic soda. The alkaline solution was washed with ether acidified with acetic acid. The resulting precipitate (X) was washed with ethanol and dried. mp 220-222°C.

Mass spectrum, m/z (%): 205 (M^+, 100), 204 (9), 190 (18), 177 (4), 176 (9), 175 (4), 162 (10).

It was identical according to a mixed melting point and TLC with 8-hydroxy-4-methoxy-N-methyl-2-quinolone.

4-Methoxy-N-methyl-2-quinolone (VII), mp 100-101°C (from hexane), R_f 0.35 and 0.31 in systems 1 and 2, respectively. UV spectrum, nm: $\lambda_{max}^{C_2H_5OH}$ 229, 269, 279, 318, 330 (log ε 4.50, 3.64, 3.67, 3.56, 3.46). The spectrum did not change on acidification or alkalinization. IR spectrum (cm^{-1}): ν_{max}^{KBr}, 1645 (amide carbonyl), 1592, 1505 (aromatic system). Mass spectrum, m/z (%): 189 (M^+, 100), 174 (43), 146 (14), 132 (13), 77 (10).

Folamine (VII), mp 139-140°C (from hexane); R_f 0.35 and 0.31 in systems 1 and 2, respectively.

Robustine (IX), mp 139-140°C (from acetone), R_f 0.41 and 0.16 in systems 1 and 2, respectively. Mass spectrum, m/z (%): 205 (M^+, 100), 204 (75), 190 (20), 176 (35), 175 (33), 162 (11).

Substances (VI)-(IX) do not fluoresce in UV light.

The roots of *Haplophyllum dauricum* (L.) G. Don. have yielded dictamnine, robustine, γ-fagarine, haplopine, skimmianine, 4-methoxy-N-methyl-2-quinolone, robustine, folamine,and the new alkaloid daurine, the structure of which has been established as 8-(γ,γ-dimethylallyloxy)-4-methoxy-N-methyl-2-quinolone.

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