Chemistry of Natural Compounds, Vol. 32, No. 1, 1996

ISOLATION OF PEGANINE AND DEOXYPEGANINE FROM THE TOTAL ALKALOIDS OF *Peganum harmala* THROUGH THEIR COMPLEX SALTS

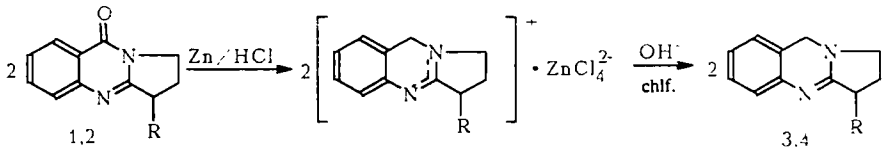
L. V. Molchanov, V. N. Plugar', A. L. D'yakonov, and Kh. N. Aripov

UDC 547.994+543.51

The possibility has been shown of combining the processes of the reduction of deoxyvasicinone and vasicinone to deoxypeganine and peganine and the isolation of the latter in the form of complex salts from the natural total mixture of alkaloids.

An extract of the total alkaloids isolated from the plant *Peganam harmala* (fam. Peganaceae) is used for the manufacture of the drug deoxypeganine hydrochloride [1, 2], for which a synthetic method of preparation has also been developed at the present time [3]. However, when the usual scheme of treating the plant material is employed, another alkaloid of practical interest — peganine — is lost [4, 5], being reduced under the given conditions to deoxypeganine. Nevertheless, peganine can be used as an intermediate in the synthesis of other, pharmacologically important, alkaloids [6].

A method that we have proposed for obtaining peganine and deoxypeganine is based on the reduction of the total quinazolone and quinazoline bases present in the plant extract with zinc and hydrochloric acid. We took into account the fact that, under these conditions, deoxyvasicinone (**1**) and vasicinone (**2**) are reduced to deoxypeganine (**3**) and peganine (**4**), respectively, with the formation of complex compounds of the latter with zinc chloride, as in [7], and they precipitate in an acid medium. This will permit them to be freed from the other alkaloids in the mixture from the plant.



To confirm this hypothesis we carried out the reduction of a model system A of the alkaloids (**1-4**) taken in identical amounts, as a result of which a mixture of complexes of deoxypeganine and peganine in various proportions was obtained (Table 1).

Further investigation was conducted with a 20% chloroform solution of alkaloid mixture B obtained from the plant raw material under experimental-industrial conditions. The reduction of this mixture with zinc dust in 15% hydrochloric acid (preliminary extraction of the chloroform fraction with acid of the given concentration) led to the formation of complex salts of deoxypeganine and peganine (see Table 1). Decomposition of the complexes with ammonia in aqueous solution at pH > 12 followed by extraction with chloroform gave a mixture of bases (**3**) and (**4**) in the ratio shown in the table, from which it can be seen that on extraction the amount of deoxypeganmine was higher than that of peganine. This is probably connected with a higher stability of the complex of the latter with zinc chloride. Alkaloids (**3**) and (**4**) can be separated either by the polybuffer distribution method [8], or by column chromatography [9], or by gas chromatography in combination with mass spectrometry (GC-MS method) [10].

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent, fax (3712) 89 14 75. Translated from Khimiya Prirodnykh Soedinenii, No. 1, pp. 70-73, January-February, 1996. Original article submitted April 5, 1994.

 0009-3130/96/3201-0056$15.00

TABLE 1. Amounts of Alkaloids (**1-4**) in Mixtures A and B

Compound	Mixture A			Mixture B		
	init., %	compl., %	bases, %, pH > 12	init., %	compl., %	bases, %, pH > 12
1	25	1	3	52	Сл.	2
2	25	1	2	15	1	2
3	25	48	50	8	58	62
4	25	50	44	25	39	36

This pair of alkaloids was separated on the basis of the different solubilities of their salts in certain solvents. It is known [11] that deoxypeganine readily forms a perchlorate that is insoluble in ethanol and acetone, while peganine perchlorate precipitates from these solvents with great difficulty: in order to confirm this we carried out the appropriate experiment with pure (±)-peganine. The perchlorate synthesized melted at 302-305°C (acetonitrile). However, peganine readily forms a nitrate [12], which can be isolated in practically quantitative yield. As the result of separation performed by the above-described scheme we obtained two fractions. The first contained a mixture of the perchlorates of (**3**) and (**4**) in a ratio of 3:1, and the second contained pure peganine nitrate (according to mass-spectrometric analysis).

The presence of very small amounts of compounds (**1**) and (**2**) in the bases isolated is due to the oxidation of bases (**3**) and (**4**) by atmospheric oxygen during the chloroform treatment, as has been observed repeatedly by various authors [13-15].

Thus, we have shown the possibility of obtaining peganine from the total alkaloids of *Peganum harmala* via its complex salt with zinc chloride.

EXPERIMENTAL

Semiquantitative Mass-Spectral Analysis. MS 25RF (Kratos) chromato-mass spectrometer with a DS90 data-processing system, a combined EI/CI ion source, an ionizing potential of 70 V, a collector current of 100 μA, an accelerating potential of 4 kV, temperature of the direct injection system 100-250°C (complete evaporation), and temperature of the ion source 300°C.

Semiquantitative mass-spectral analysis was carried out by the method of reconstructing the ion current curve with the aid of the DS90 data-processing system. It has been shown previously [16] that the individual sensitivities of a mass spectrometer to the components of the mixture differ only slightly. The ratios of alkaloids (**1-4**) were determined by integrating the curves of the currents of the M^+ ions of the mixtures.

Reduction of a Model Mixture of Alkaloids. A mixture of 0.01 mole each of the hydrochlorides of (**1-4**) was dissolved in 15 ml of 15% hydrochloric acid, and 0.03 g-atom of zinc dust was added in portions at 90-95°C with constant stirring. When the whole amount of zinc had been added, the solution was filtered in the hot state. After cooling, the crystals of the mixture of complex salts that had precipitated was filtered off. The precipitate was alkalinized with 10% aqueous ammonia to pH 12 and was extracted with chloroform (3 × 50 ml). The solvent was distilled off, leaving a crystallized residue consisting of a mixture of bases (**3**) and (**4**) in a ratio of 1:1.

Reduction of the Total Alkaloids from *Peganum harmala*. The chloroform fraction of the *Peganum harmala* alkaloids (500 ml), obtained by the procedure of [2], was extracted with 15% hydrochloric acid (2 × 150 ml). The combined acid extracts were heated to 90-95°C, and zinc dust was added in 1- to 2-g portions. After the addition of 72 g of zinc, the solution was boiled with 6 g of activated carbon for 0.5 h. It was filtered in the hot state and the 108 g of the complexes of peganine and deoxypeganine that deposited when the mother solution cooled was filtered off.

Isolation of Peganine from Its Mixture with Deoxypeganine. A mixture of 30 g of the complexes of (**3**) and (**4**) in a ratio of 58:39 (see Table 1) was dissolved in 240 ml of 10% aqueous ammonia and extracted with chloroform (3 × 100 ml). The solvent was distilled off and the residue was treated with 100 ml of acetone. The part insoluble in acetone consisted of a mixture of peganine and deoxypeganine in a ratio of 2:1. With heating, 1 g of this mixture was treated with methanol and the resulting solution was made strongly acid with 56% perchloric acid. The resulting precipitate was filtered off with suction and was recrystallized from ethanol to give 0.35 g of a mixture of perchlorates (first fraction). The alcoholic mother solutions were combined and were treated with conc. nitric acid. The precipitate of peganine nitrate (second fraction) was separated off and recrystallized from methanol, mp 168-169°C, yield 0.43 g.

TLC was conducted on Silufol UV-254 plates in the chloroform–methanol–ammonia (5:4:0.1) system. For deoxypeganine R_f 0.071, and for peganine R_f 0.134.

REFERENCES

1. T. T. Shakirov, E. K. Dobronravova, A. Kh. Sattarova, and A. I. Glushenkova, FS [Pharmaceutical Specification] 42-2418-86.
2. B. K. Mirzakhmedov, Kh. N. Aripov, T. T. Shakirov, M. V. Telezhenetskaya, M. N. Sharakhimov, and S. Yu. Yunusov, USSR Inventors' Certificate 878,295 (1981); Byull. Isobret., No. 6 (1975).
3. K. D. Sargazakov, Kh. N. Aripov, L. V. Molchanov, and B. N. Plugar', Khim. Prir. Soedin., 506 (1990).
4. Kh. M. Khashimov, M. V. Telezhenetskaya, N. M. Sharakhimov, and S. Yu. Yunusov, Khim. Prir. Soedin., 382 (1971).
5. B. K. Mirzakhmedov, Kh. N. Aripov, and T. T. Shakirov, Khim. Prir. Soedin., 432 (1975).
6. N. Tulyaganov, The Pharmacology of Natural Substances [in Russian] Fan, Tashkent (1978), p. 56.
7. K. D. Sargazakov, L. V. Molchanov, B. Tashkhodzhaev, and Kh. N. Aripov, Khim. Prir. Soedin., 862 (1991).
8. B. K. Mirzakhmedov, B. Kh. Zharekeev, M. V. Telezhenetskaya, and Kh. N. Aripov, Khim. Prir. Soedin., 404 (1976).
9. N. I. Koretskaya, Zh. Obshch. Khim., **27**, 3361 (1957)
10. I. Laakso, P. Virkajarvi, H. Airaksinen, and E. Varis, J. Chromatogr., **505**, 424 (1990).
11. Kh. N. Khashimov, M. V. Telezhenetskaya, and S. Yu. Yunusov, Khim. Prir. Soedin., 456 (1969).
12. Kh. N. Khashimov, M. V. Telezhenetskaya, Ya. V. Rashkes, and S. Yu. Yunusov, Khim. Prir. Soedin., 453 (1970).
13. D. R. Mehta, J. S. Naravane, and R. M. Desai, J. Org. Chem., **28**, 445 (1963).
14. L. Skursky, Collect. Czech. Chem. Commun., **30**, 2080 (1965).
15. B. K. Chowdhury, Indian J. Chem., Sect. B, **26**, 688 (1987).
16. V. N. Plugar', Ya. V. Rashkes, and N. Tulyaganov, Khim. Prir. Soedin., 201 (1981).