SYNTHESIS OF GOEBELINE

B. Sadykov, S. Iskandarov,
and S. Yu. Yunusov

UDC 547.944/945

We have previously proposed a biomolecular structure [1] for the alkaloid goebeline isolated from the still residues from the production of pachycarpine. In order definitively to confirm the site of attachment of the two residues in the goebeline molecule and also to establish the configuration of the asymmetric centers, we have performed the Wurtz and Ullman reactions [2, 3]. Matrine was used as the starting material. When it was chlorinated with a mixture of thionyl chloride and sulfuryl chloride, 14,14-dichloromatrine was obtained [4], and the partial catalytic hydrogenation of this formed a mixture of the isomeric 14α- and 14β-monochloromatrines [5].

The mixture of monochloride was dissolved in anhydrousxylene, and the solution was boiled in the presence of metallic sodium and passed through a column of silica gel. Elution with chloroform gave a viscous pale yellow oil crystallizing on standing with mp 197-199°C. The R_f values of the synthetic product in a thin layer of silica gel and on paper differed from those for dihydrogoebeline. However, a comparison of the IR spectrum of the base with the spectrum of the derivatives showed that it contained characteristic absorption bands of a lactam carbonyl (1640 cm^{-1}) and of a trans-quinolizidine (2765, 2800 cm^{-1} (Fig. 1)). The mass spectrum of the products obtained showed, in addition to the peak of the molecular ion with m/e 494 (20.9%), strong peaks of ions with m/e 248 (100%), 219 (22.5%), 205 (60%), 192 (8.3%), 150 (11.0%) 98 (30.5%), and 96 (12.4%).

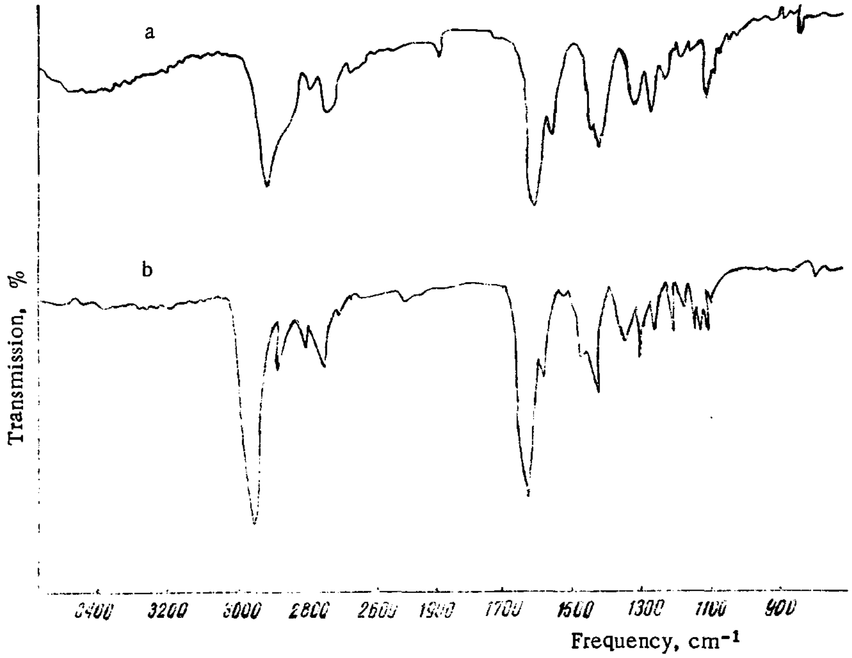

Fig. 1. IR spectrum of dihydrogoebeline (a) and of isodihydrogoebeline (b).

Institute of the Chemistry of Plant Substances, Academy of Sciences of the Uzbek SSR. Translated from Khimiya Prirodnykh Soedinenii, No. 5, pp. 606-610, September-October, 1975. Original article submitted June 17, 1974.

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The intensities of the peaks with m/e 494 (20.6%) and 248 (20.8%) in the spectrum of dihydrogoebeline were similar. In the spectrum of the synthetic products, the intensities of the peaks of these ions differed somewhat (20% and 100%, respectively,) which shows a steric difference of these compounds solely at the position of linkage of the two matrine residues.

When two molecules of matrine are condensed, the formation of three types of isomers is possible: 14e-14'e, 14a-14'a, and 14e-14'a. The isomers with the axial orientation of the substituents are energetically less stable than the isomers with the equatorial position of the substituents. If it is recognized that the matrine molecule is a voluminous substituent, the formation of the 14e-14'a and 14e-14'e isomers is favoured. The last-mentioned is preferable and, apparently, the Wurtz reaction forms mainly this product. It might be assumed that the production of a particular amount of isomer would depend on the conditions of performing the reaction. In actual fact, in the Ullman reaction when a mixture of monochloromatrines was heated with freshly prepared copper at 220-250°C for 2 h, in addition to the substance described above another product was formed. However, the mixture of these isomers could be separated only by paper chromatography. The molecular weight of the mixture determined mass spectrometrically was 494. Its mass spectrum was identical with that of the substance obtained by the Wurtz reaction.

Having synthesized an isomer of dihydrogoebeline from matrine, we attempted to condense two sophocarpine residues, starting from the following considerations: in the sophocarpine molecule there is a double bond, as a consequence of which the hydrogen atom at C_{14} is mobile. The results of dimerization starting from monochloromatrine permit the assumption that goebeline is a product of the condensation of two molecules of sophocarpine, since the isolation of pachycarpine from the total alkaloids under factory conditions takes place at a high temperature and under reduced pressure, and the thermal treatment of the combined material lasts for a long time.

Several samples of sophocarpine were heated in retorts under various conditions, both the temperature and the pressure being varied. A base was found in the reaction mixture which had R_f values in a thin layer and on paper coinciding with those of goebeline.

The best yield of the dimer was observed when sophocarpine was treated under vacuum at 200-350°C for a long time. After two preparative separations of the reaction mixture in a thin layer of silica gel and purification, a base was isolated with mp 228-230°C which was identified as goebeline by means of a mixed melting point, and its IR and mass spectra.

The possibility of the formation of goebeline from sophocarpine on thermal treatment induced us to undertake investigations of the alkaloids of the epigeal part of *Sophora pachycarpa*. It was necessary to find whether goebeline was present in the total alkaloids obtained from the plant. The epigeal part of *S. pachycarpa* collected in June, 1971, in a section of the Turkestan division of the "Darmina" sovkhoz [state farm], Chimkent oblast, contained 2.2% of total alkaloids.

Part of the combined alkaloids was separated according to the solubility of the perchlorates, and pachycarpine, matrine, and sophocarpine were isolated. The same alkaloids were obtained from the mother liquors by preparative separation on silica gel. As the result of the repeated chromatrography of the individual eluates with a marker, the absence of goebeline from the total alkaloids was established.

Another part of the combined alkaloids was heated as in the thermal treatment of sophocarpine. After the reaction, the mixture of bases was separated preparatively and, by the chromatography of the individual eluates, a product was detected the R_f values of which in a thin layer and on paper coincided with those of goebeline. The melting point of the base isolated from the individual eluates was 228-230°C.

EXPERIMENTAL

The following systems were used for chromatography: 1) isobutanol—concentrated hydrochloric acid—water (50 : 7.5 : 13.5) (paper chromatography — PC); 2) silica gel—gypsum (9:1) chloroform—methanol (2:1) (thin-layer chromatography — TLC); 3) butanol—concentrated hydrochloric acid—water (50 : 7 : 13.5) (radial paper chromatography — RPC).

Di- and monochloromatrines were obtained by published methods [4, 5].

Wurtz Condensation of Monochloromatrine. A solution of monochloromatrine (0.7 g) in 700 ml of absolute xylene was placed in a dry two-necked flask with a reflux condenser and a calcium chloride tube. The mixture was heated in the presence of metallic sodium at 135-137°C for 1 h. The filtered solution was treated with 5% sulfuric acid and made alkaline with concentrated ammonia solution, and the bases were extracted with ether. Yield 0.6 g; Rf 0.65, 0.79, and 0.85 (trace) (system 1). The combined ether-soluble material was chromatographed on a column of silica gel and eluted with chloroform. Eluates 2-7 yielded a viscous oil which crystallized on standing, mp 197-198°C. The base was readily soluble in chloroform, methanol, and ethanol and sparingly soluble in diethyl ether and petroleum ether; $[\alpha]_D$ − 132°C (c 0.2; ethanol); R_f 0.65 (system 1); mol. wt. 494 (mass spectrometrically); IR spectrum (cm^{-1}): 1640 (lactam carbonyl), 2765, 2800 (trans-quinolizidine). The perchlorate had mp 262-263°C (acetone), and the picrate mp 177-179°C (ethanol).

Ullman Condensation of Monochloromatrine. A mixture of 0.2 g of monochloromatrine, 0.1 g of purified sand, and 0.2 g of freshly prepared copper was heated at 220-250°C for 2 h. Then it was cooled and was treated with 5% sulfuric acid, and the solution was made alkaline with 25% ammonia solution and extracted with ether. The residue from the evaporation of the ether was a viscous oil which did not crystallize from various solvents; R_f 0.65, 0.75 (system 1); mol. wt. 494 (mass spectrometrically).

Condensation of Sophocarpine. Sophocarpine (20 g) was placed in a retort connected with a long (40 cm) glass tube and was heated under vacuum (4-5 mm) for 80 h, with variation of the pressure and of the temperature in the range from 200 to 350°C. Sometimes the process was performed at atmospheric pressure. The reaction mixture was separated preparatively in a thin layer of silica gel and, by chromatographing the individual fractions, a product was detected the R_f values of which in a thin layer and on paper coincided with those of goebeline. After preparative separation once more, a base was obtained which melted at 228-230°C; R_f 0.3 (system 1), 0.8 (system 2), 0.4 (system 3); $[\alpha]_D$ −13.2 (ethanol).

IR spectrum (cm^{-1}): 2770, 2750, 2680 (trans-quinolizidine), 1670 (double bond), 1660, 1645 (lactam carbonyls); mol. wt. 492 (mass spectrometrically). A mixture of the base with goebeline gave no depression of the melting point (the mixture melted at 229-230°C). Their IR and mass spectra were identical.

Isolation of Alkaloids from the Epigeal Part of *Sophora pachycarpa*. By the usual chloroform extraction 3 kg of the plant yielded 66 g (2.2%) of combined alkaloids (mixture of 9 or 10 bases); R_f 0.04, 0.13, 0.30, 0.52, 0.66, 0.75, 0.80, 0.92, 0.95.

Pachycarpine. The combined alkaloids (40 g) were dissolved in acetone and the solution was acidified with perchloric acid. The perchlorates were separated into those which did and did not pass into chloroform. From those that passed into chloroform, pachycarpine perchlorate with mp 168-170°C was isolated.

Sophocarpine and Matrine. The perchlorates that had not passed into the chloroform (15 g) were converted into the bases. The resulting combined bases (11.3 g) were passed through a column of alumina and eluted with ether and then with chloroform. From the ethereal eluates were isolated sophocarpine (2.3 g), R_f 0.55 (system 3) and matrine (4.0 g), R_f 0.6 (system 3). The separate ethereal and chloroform eluates were chromatographed in a thin layer of silica gel and on paper. No goebeline was detected.

Separation of the Combined Alkaloids after Thermal Treatment. The combined alkaloids (25 g) were heated under the conditions for the thermal treatment of sophocarpine and were then dissolved in 40 ml of chloroform, and the solution was treated with 10% sulfuric acid. The acid solution was made alkaline with 10% NaOH solution and the bases were extracted with diethyl ether, petroleum ether, benzene, and, finally, chloroform. This gave 5.2 g of ether fraction, 3.5 g of petroleum ether fraction, 5.8 g of benzene fraction, and 10.0 g of chloroform fraction. Each fraction was separated preparatively in a thin layer of silica gel, and the separate eluates were chromatographed. In the benzene and chloroform fractions a base was found which had the same R_f value as goebeline (0.33 in system 1 and 0.8 in system 2). When the mixture was again separated preparatively, a base was isolated with mp 228-230°C. A mixture of this base with goebeline gave no depression of the melting point.

SUMMARY

14,14'-Bimatridine has been obtained by the Wurtz and Ullman reactions. Goebeline has been synthesized from sophocarpine; it is an artefact and is formed in the thermal treatment of the combined alkaloids under factory conditions.

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