PREPARATION OF N,N'-DI(7-THIAOCTYL)UREA — A SULFIDE PRECURSOR OF THE ALKALOIDS DIPTOCARPIDINE AND DIPTOCARPILINE

O. V. Tolstikova, A. G. Tolstikov, and S. F. Aripova

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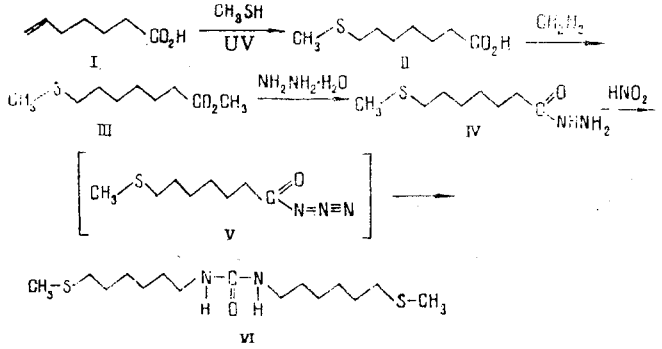
A convenient synthesis is given of a key sulfide precursor of the alkaloids diptocarpidine and diptocarpiline from hept-6-enoic acid.

Sulfur-containing low-molecular-weight alkaloids of plant origin are interesting substances for medicobiological investigations. This comparatively small class of substances includes diptocarpiline and diptocarpidine, which are produced by the fairly rare plant *Diptychocarpus strictus* [1-3]. Only a limited amount of it is gathered, which complicates the problem of producing the alkaloids from the plant raw material. However, the chemical structures of diptocarpiline and diptocarpidine permit simple schemes for their synthesis to be developed.



In the present communication we give a simple method for obtaining the key sulfide precursor (VI) of these alkaloids (scheme). Using a known method for adding thiols to olefins [4], the 8-thianonanoic acid (II) was prepared in quantitative yield by the reaction of methyl mercaptan with hept-6-enoic acid (I) under UV irradiation. The reaction of the methyl ester of (III) with a small excess of hydrazine hydrate led to the hydrazide (IV) with a yield of 80%. The azide of the acid (V) was synthesized by the action of nitrous acid prepared in situ on compound (IV) in diethyl ether solution at 0°C. Taking into consideration the fact that many azides of lower carboxylic acids are explosion-hazardous and tend to undergo spontaneous rearrangements into esters of isocyanic acids [5] with the formation of amines and symmetrical ureas in moist inert solvents, all the operations with the azide (V) were performed in a single reaction vessel without the isolation of the intermediate compounds. When the azide of 8-thianonanoic acid (V) was heated in moist acetone, we obtained N,N'-di(7-thiaoctyl)urea (VI) with a yield of 60%.

EXPERIMENTAL

IR spectra were taken on a UR-20 instrument with the substances in Nujol or in the form of a thin layer. ^{1}H NMR spectra were recorded on a Tesla BS-576B instrument with a working frequency of 100 MHz. Tetramethylsilane was used as the internal standard, and $CDCl_3$ as solvent. The products of synthesis was separated by column chromatography on silica gels L 40/100 and L 100/160 (Czechoslovakia). The products were analyzed by TLC on Silufol UV-254 plates (Czechoslovakia), and were detected with iodine vapor.

Institute of Chemistry of the Bashkir Branch of the USSR Academy of Sciences, Ufa. Institute of Chemistry of Plant Substances of the Uzbek SSR Academy of Sciences, Tashkent.
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8-Thianonanoic Acid (II). A quartz-glass flask was charged with 3.4 g (0.02 mole) of hept-6-enoic acid and 0.05 g of azoisobutyronitrile (AIBN), and was cooled to −20°C. Carefully, 1.90 g (0.03 mole) of methyl mercaptan was added in one portion. The flask was tightly closed and, with stirring and cooling (CO_2—acetone, −20°C), the flask was irradiated with a UV lamp for 3 h. After the elimination of the excess of methyl mercaptan, the 8-thianonanoic acid was purified via the sodium salt. The yield was quantitative. IR spectrum (cm^{-1}): 1325 (C—S), 1710 (C=O), 2400—3550 (C(=O)—OH). ^1H NMR spectrum (δ, ppm): 2.08 s (3H, CH_3—), 2.26 t (2H, CH_2—S, J = 7 Hz), 2.46 t (2H, CH_2—CO, J = 7 Hz), 10.67 s (H, CO_2H).

Methyl 8-Thianonanoate (III). Compound (III) was obtained by treating the acid (II) with an ethereal solution of diazomethane. IR spectrum (cm^{-1}): 1250 (C—O), 1320 (C—S), 1740 (C(=O)—O). ^1H NMR spectrum (δ, ppm): 2.11 s (3H, CH_3), 2.28 t (2H, CH_2—S, J = 7 Hz), 2.45 t (2H, CH_2—CO, J = 7 Hz), 3.68 s (3H, $\overline{CO_2CH_3}$).

8-Thianonanoic Acid Hydrazide (IV). A flask containing 200 ml of ethanol was charged with 4.08 g (0.02 mole) of compound (III) and 3.2 g (0.06 mole) of 85% hydrazine hydrate. The reaction mixture was boiled for 1.5 h, the solvent was distilled off, and the residue was recrystallized from ethanol. The yield of product (IV) was 80%. mp 62-64°C. IR spectrum (cm^{-1}): 1320 (S—CH_3), 1540 (N—H), 1645 (CONH), 3300-3350 (NH—NH_2) ^1H NMR spectrum (δ, ppm): 1.18-1.97 m (8H, methylene protons), 2.10 s (3H, CH_3—), 2.25 t (2H, CH_2—S, J = 7.5 Hz), 2.49 t (2H, CH_2—CO, J = 7Hz), 3.74-3.90 m (3H, NH—NH_2). Found, %: C 50.80, H 9.41, S 16.74, N 14.92. Calculated, %: C 50.50, H 9.50, S 16,80, N 14.73.

N,N'-Di(7-thiaoctyl)urea (VI). A flask was charged with 3 g (0.014 mole) of the hydrazide (IV), a solution of 0.6 g (0.016 mole) of concentrated HCl in 1 ml of water was added, and, after cooling to 0°C, 30 ml of ether was run in. A saturated solution of 1.1 g (0.016 mole) of $NaNO_2$ was added to the stirred reaction mixture at such a rate that the temperature did not rise above 10°C. The ethereal layer was separated off and concentrated, the residue was diluted with 10 ml of acetone containing 0.5 ml of water, and the mixture was heated at 50°C for 6 h. After the elimination of the solvent, the residue was subjected to chromatography on a column of SiO_2. The eluent was chloroform—methanol (9:1), R_f 0.65. mp 55°C. Yield 60%. IR spectrum (cm^{-1}): 1325 (S—CH_3), 1580 (NH), 1640 (CONH), 3320-3370 (N—H). ^1H NMR spectrum (δ, ppm): 1.11-1.90 m (16 H, methylene protons), 2.80 s (6H, $2CH_3$), 2.43 t (4H, $2CH_2$—S, J = 7 Hz), 2.63 t (4H, $2CH_2$—N, J = 7.5 Hz), 5.03 m (2H, 2NH). Found, %: C 56.26, H 9.95, N 8.70, S 20.10. Calculated, %: C 56.27, H 10.00, N 8.75, S 20.00.

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CONCLUSIONS

A convenient method for synthesizing from hept-6-enoic acid a key sulfide precursor of the alkaloids diptocarpidine and diptocarpiline has been developed.

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