TOTAL SYNTHESIS OF RACEMIC DIPTOCARPIDINE AND DIPTOCARPILINE

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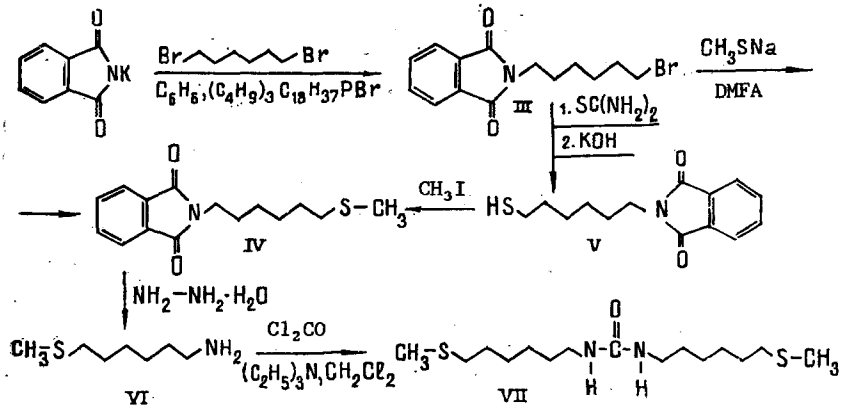
Convenient methods for the synthesis of racemic diptocarpidine and racemic diptocarpiline have been proposed on the basis of the readily available 6-phthalimidohexyl bromide and hept-6-enoic acid.

Among synthetic herbicides and pesticides used in agriculture, a special position is occupied by ureas. Possessing a broad spectrum of biological activity, they participate in various physiological processes responsible for the growth and the protective reactions of plants [1]. In this connection it is impossible not to turn one's attention to the fact that alkaloids of the urea type have been detected in plants. Thus, Yunusov, et al. [2] isolated from the plant Diptychocarpus strictus (family Cruciferae) the alkaloids diptocarpidine and diptocarpiline, which are sulfur-containing aliphatic ureas. Since this plant belongs to a rare species and its alkaloid content is extremely low [3], their production from plant raw material is a task difficult to perform.



Scheme 1

In view of the necessity for studying the biological properties of these compounds, we have developed several approaches enabling racemic diptocarpidine (I) and racemic diptocarpiline (II) to be obtained in a fairly simple manner. The first route was based on the transformation shown in Scheme 1. The alkylation of potassium phthalimide with 1,6-dibromohexane in the presence of tributyloctadecyl phosphonium bromide led to the bromide (III), the reaction of which with sodium methyl sulfide gave methyl 6-phthalimidohexyl sulfide (IV). However, a three-stage route from compound (III) to the sulfide (IV) proved to be more convenient: heating with thiourea gave the corresponding thiouronium salt of the bromide (III), the alkaline decomposition of which led to 6-phthalimidohexanethiol (V), the subsequent treatment of which with methyl iodide in the presence of tetrabutylammonium bromide gave compound (IV). By the action of hydrazine hydrate [4], the sulfide (IV) was converted into 7-thiaoctylamine (VI), the reaction of which with phosgene led to N,N'-di(7-thiaoctyl)urea (VII).*

We developed an alternative variant of the synthesis of urea (VII) from hept-6-enoic acid (Scheme 2). Its reaction with methanethiol under UV irradiation in the presence of

*The numbering of the carbon atoms in compounds (VII) and (I) (Schemes 1 and 2) has been done for convenience in assigning the signals of the ^{13}C NMR spectra.

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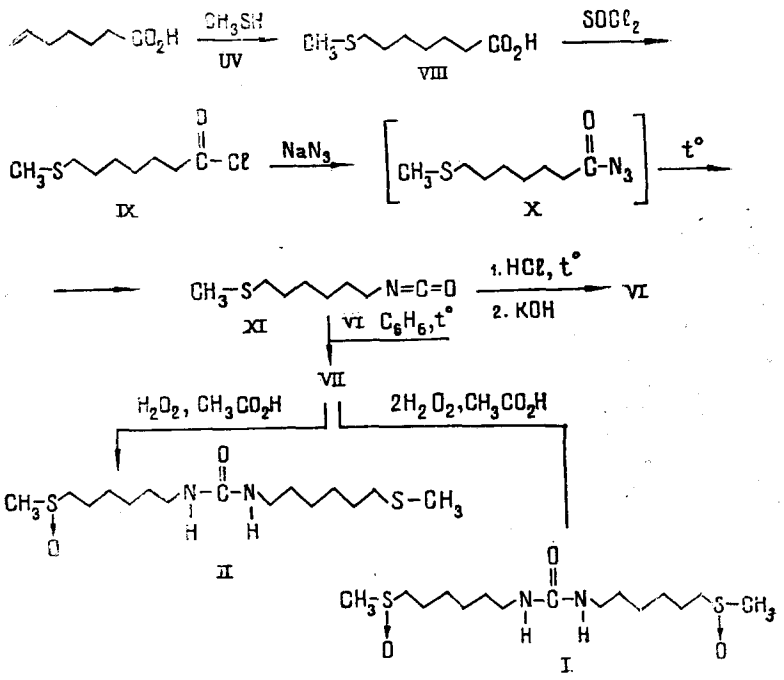

Scheme 2

catalytic amounts of azoisobutyronitrile led in quantitative yield to 8-thianonanoic acid (VIII), which was converted into the acid chloride (IX) by the action of thionyl chloride. The treatment of the acid chloride (IX) with the calculated amount of dry sodium azide followed by thermolysis of the intermediate amide (X) led to the isocyanate (XI). The interaction of compound (XI) with the amine (VI) gave the urea (VII), while treatment of the isocyanate (XI) with concentrated hydrochloric acid led to hydrochloride of the thiaamine (VI), from which the required amine (VI) was obtained. The synthesis of (±)-diptocarpidine (I) and (±)-diptocarpiline (II) was achieved by the oxidation of the sulfide precursor (VII) with the calculated amounts of hydrogen peroxide.

In the mass spectra of the ureas (VII), (II), and (I) the corresponding molecular ions were recorded. In a study of the negative-ion mass spectra of compounds (VII), (II), and (I) we detected the effect of an intramolecular interaction of the amide group with the S and SO groups, which indicates the presence of a folded conformation of the molecules of these compounds. Similar effects have been reported previously for esters of aliphatic ω-oxocarboxylic acids [5].

EXPERIMENTAL

IR spectra were obtained on a UR-20 instrument in Nujol or a thin layer and ^{1}H NMR spectra on a Tesla BS-567 B instrument with a working frequency of 100 MHz. Tetramethylsilane was used as the internal standard, and $CDCl_3$ as solvent. ^{13}C NMR spectra were recorded on a JEOl F X-90 Q instrument having a working frequency for ^{13}C of 22.5 MHz in $CDCl_3$, with tetramethyl silane as internal standard. The products of synthesis were 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), with detection by iodine vapor. For the identification and revelation of the main processes involved in the formation of the negative ions of compounds (I), (II), and (VII) we used the resonance electron-capture (REC) method of mass spectrometry. The REC spectra were obtained on a MI-1201 mass spectrometer reequipped for recording negative ions [6]. The scale of electron energies was calibrated from the curves of the effective yields SF_6^- from SF_6 and of NH_2^- from ammonia. Positive-ion mass spectra were obtained on a MKh-1320 instrument at ionizing voltages of 70, 22, and 20 eV with a temperature of the ionization chamber of 80°C.

6-Phthalimidohexyl Bromide (III). A mixture of 4.63 g ($2.5\cdot10^{-2}$ mole) of potassium phthalimide, 6.1 g ($2.5\cdot10^{-2}$ mole) of 1,6-dibromohexane, and 1 g ($2\cdot10^{-2}$ mole) of tributyloctadecylphosphonium bromide in 20 ml of benzene was stirred at 80°C for 4 h. After cooling, the reaction mixture was filtered. The filtrate was evaporated and the residue was

chromatographed on a column (with ether as eluent), with the collection of 250-ml fractions. After the ether had been driven off, 7.4 g of compound (III) was obtained. Yield 95%, mp 50-51°C. ^{1}H NMR (δ, ppm): 1.45 m (8 H, methylene protons); 3.39 t (2 H, CH_2Br, J = 6.8 Hz); 3.68 t (2 H, CH_2—N, J = 6.8 Hz); 7.75 m (4 H, aromatic protons). Found, %: C 54.19, H 5.16, Br 25.80, N 4.52. $C_{14}H_{16}BrNO_2$. Calculated, %: C 54.20, H 5.17, Br 25.80, N 4.36.

Methyl 6-Phthalimidohexyl Sulfide (IV). a) A solution of 0.74 g ($1\cdot10^{-2}$ mole) of sodium methyl sulfide obtained beforehand by the passage of methanethiol through a suspension of 0.42 g ($1\cdot10^{-2}$ mole) of NaOH in 5 ml of DMFA, was treated with a solution of 3.3 g ($1\cdot10^{-2}$ mole) of the bromide (III) in 2 ml of dry DMFA. The reaction mixture was stirred at room temperature for 24 h and was then diluted with ethyl acetate and washed with water (3 × 25 ml). The organic layer was separated off and dried with $MgSO_4$. The solvent was distilled off and the residue was chromatographed on a column with hexane—ethyl acetate (7:3) as eluent. The yield of the sulfide (IV) was 15%. ^{1}H NMR spectrum (δ, ppm): 1.45 m (8 H, methylene protons); 2.07 s (3 H, S—CH_3); 2.49 t (2 H, CH_2—S, J = 6.8 Hz); 3.68 t (2 H, CH_2—N, J = 7 Hz); 7.74 m (4 H, aromatic protons). Found, %: C 58.25, H 6.15, N 4.53, S 10.35, $C_{15}H_{19}NO_2S$. Calculated, %: C 58.27, H 6.18, N 4.49, S 10.32.

b) A solution of 0.6 g ($1.5\cdot10^{-2}$ mole) of NaOH in 10 ml of water was added to a mixture of 2.63 g ($1\cdot10^{-2}$ mole) of the thiol (V) (for its preparation, see below), 1.42 g ($1\cdot10^{-2}$ mole) of methyl iodide, and 0.32 ($1\cdot10^{-3}$ mole) of tetrabutylammonium bromide in 10 ml of benzene, and the mixture was stirred at 20°C for 6 h. The organic layer was separated off, washed with water (3 × 10 ml), and dried with $MgSO_4$. The solvent was distilled off and the residue was chromatographed on a column. The yield of product (IV) was 70%.

6-Phthalimidohexanethiol (V). A mixture of 8.6 g ($2.8\cdot10^{-2}$ mole) of the bromide (III) and 2 g ($2.8\cdot10^{-2}$ mole) of thiourea in 10 ml of ethanol was boiled for 5 h. Then a solution of 1.7 g ($4.2\cdot10^{-2}$ mole) of NaOH in 10 ml of water was added and the new mixture was boiled for 2 h. After this, it was acidified with 10% HCl solution and was extracted with benzene. The combined extracts were dried with Na_2SO_4. The solvent was distilled off, and the residue was chromatographed on a column with hexane—ethyl acetate (7:3) as eluent. Yield 54%, mp 33-34°C. ^{1}H NMR spectrum (δ, ppm): 1.31-1.82 m (8 H, methylene protons; 1 H, SH); 2.46 t (2 H, CH_2—SH, J = 7 Hz); 3.65 t (2 H, CH_2—N, J = 6.9 Hz); 7.77 m (4 H, aromatic protons).

7-Thiaoctylamine (VI). a) A mixture of 1 g ($3\cdot10^{-3}$ mole) of the sulfide (IV) and 0.4 g ($6.8\cdot10^{-3}$ mole) of 85% hydrazine hydrate in 10 ml of methanol was boiled for 15 h. After cooling, the reaction mixture was diluted with 5 ml of water and the methanol was distilled off in the vacuum of a water pump. The aqueous solution was treated with 5 ml of concentrated HCl and the mixture was heated at 100°C for 5 h. Then it was cooled to 0°C and the precipitate that deposited was filtered off. The filtrate was brought to pH 10-12 with NaOH and was saturated with NaCl. The amine (VI) that had been formed was extracted with ether (10 × 10 ml). The combined extracts were dried with $MgSO_4$. The ether was distilled off, and the yield of crystalline amine (VI) was 32%, mp 88-90°C. IR spectrum (cm^{-1}): 1380 (C—S); 1580 (NH_2); 3300-3360 (NH_2).

b) A solution of 1 g ($9.2\cdot10^{-3}$ mole) of the isocyanate (XI) [see the preparation of the urea (VII) by method b)] in 10 ml of benzene was treated with 2 ml of concentrated HCl and the mixture was heated at 80°C for 1 h. After cooling, the mixture was washed with water (5 × 10 ml). The combined aqueous fractions were brought to pH 10-12 with NaOH and were extracted with ether. The ethereal extracts were dried with $MgSO_4$ and the solvent was distilled off. The yield of amine (VI) was 70%, calculated on the acid chloride (IX).

N,N'-Di(7-thiaoctyl)urea (VII). a) To a stirred solution of 1 g ($6.8\cdot10^{-3}$ mole) of the amine (VI) in 10 ml of dry CH_2Cl_2 was added 0.9 g ($6.8\cdot10^{-3}$ mole) of freshly distilled Et_3N, and the temperature was lowered to −20°C. Then a solution of 0.34 g ($3.4\cdot10^{-3}$ mole) of phosgene in 2 ml of dry CH_2Cl_2 cooled to −25°C was added over 5 min. The resulting mixture was kept at −20°C for 0.5 h, after which the temperature was raised to that of the room. The reaction mixture was diluted with water and the organic layer was separated off, washed with saturated NaCl solution, and dried with $MgSO_4$. The solvent was distilled off and the residue was chromatographed on a column with chloroform—methanol (9:1) as eluent. Yield 40%, mp 55-57°C. IR spectrum (cm^{-1}): 1380 (S—CH_3), 1580, 1630 (CONH), 3325-3380 (N—H). ^{1}H NMR spectrum (δ, ppm): 1.12-1.89 m (16 H, methylene protons), 2.09 s (6 H, 2 CH_3—S); 2.48 t (4H, 2 CH_2—S, J = 7 Hz); 3.11 t (4 H, 2 CH_2N, J = 7 Hz); 4.71 m (2 H, 2 NH). ^{13}C NMR

spectrum (δ, ppm): 15.50 q (C-8, C-16), 26.49 t (C-2, C-10), 28.44 t (C-3, C-11), 28.99 t (C-5, C-13), 30.18 t (C-4, C-12), 34.19 t (C-6, C-14), 40.47 t (C-1, C-9), 158.36 s (C-17). Mass spectrum, m/z (%) M^+ 320(0.33), 305(14.16), 290(10.41), 258(100), 202(10.90), 174(10.83), 159(12.50), 146(7.08), 143(12.50), 132(22.50), 131(26.66), 128(8.33), 115(12.08), 111(15.41), 101(5.20), 100(29.16), 98(12.50), 87(10.41), 86(10.83), 83(25.41), 81(22.08), 75(11.25), 61(62.50). REC mass spectrum (m/z)*: 319 $(M-H)^-$ 2.0% (1.2 eV), 0.5% (4.0 eV), and 0.9% (5.9 eV); 305 $(M-CH_3)^-$ 1.2% (0.95 eV), 0.5% (4.0 eV), and 1.1% (5.95 eV); 273 $(M-SCH_3)^-$ 1.7% (3.4 eV) and 0.4% (5.9 eV); 259 $(M-SC_2H_5)^-$ 0.2% (3.4 eV) and 0.3% (6.3 eV); 189 $CH_3S(CH_2)_6-NHCONH^-$ 5.1% (6.3 eV); 174 $CH_3S(CH_2)_6-NHCO^-$ 3.0% (6.4 eV); 146 $CH_3S(CH_2)_6NH^-$ 0.4% (4.15 eV) and 0.7% (6.4 eV); 59 H_2NCONH^- 1% (0.9 eV), 1.2% (3.75 eV), and 2.0% (6.25 eV); 47 CH_3S^- 2.6% (0.7 eV), 37.1% (3.75 eV), and 100% (6.25 eV); 42 CON^- 68.1% (1.2 eV) and 21.6% (6.35 eV). Found, %: C 56.27, H 10.00; N 8.75, S 20.00. $C_{15}H_{32}N_2OS_2$. Calculated, %: C 56.25, H 9.98, N 8.72, S 20.10.

b) At 10°C, over 5 min, 0.7 g ($1\cdot10^{-2}$ mole) of dry NaN_3 was added to a vigorously stirred solution of 2 g ($1\cdot10^{-2}$ mole) of the acid chloride (IX) (for its preparation, see below) in 10 ml of dry C_6H_6. Then the reaction mixture was carefully heated in the oil bath at 80°C for 1 h. The course of the rearrangement of the azide (X) was followed from the evolution of nitrogen and by the TLC method. The resulting 7-thiaoctyl isocyanate (XI) was treated with a solution of 1.6 g ($1\cdot10^{-2}$ mole) of the amine (VI) in 5 ml of dry C_6H_6, and the mixture was heated for 1 h. Then it was cooled and was washed with 10% HCl and with saturated NaCl solution. The organic layer was separated off and dried with $MgSO_4$. The solvent was distilled off and the residue was chromatographed on a column. The yield of compound (VII) was 85%, calculated on the acid chloride (IX).

8-Thianonanoic Acid (VIII). A quartz-glass flask was charged with 4 g ($3.1\cdot10^{-2}$ mole) of hept-6-enoic acid, and 0.05 g of azoisobutyronitrile and was cooled to −20°C. In one portion, but carefully, 2.97 g ($6.2\cdot10^{-2}$ mole) of methanethiol was added. The flask was tightly sealed and, with stirring and cooling, (−20°C) the reaction mixture was irradiated by a UV lamp for 3 h. After the elimination of the excess of methanethiol, the 8-thianonanoic acid was purified via the sodium salt. The yield was quantitative. IR spectrum (cm^{-1}): 1325 (C–S), 1710 (C), 2400-3500 (C(=O)–OH). ^1H NMR spectrum (δ, ppm): 2.08 s (3H, CH_3–S), 2.26 t (2H, CH_2–S, J = 7 Hz); 2.46 t (2H, $-CH_2-CO_2H$, J = 7 Hz), 10.67 s (H, –C–OH).

8-Thianonanoyl Chloride (IX). At room temperature, 2.7 g ($2.3\cdot10^{-2}$ mole) of freshly distilled thionyl chloride was added over 15 min to a stirred solution of 4 g ($2.3\cdot10^{-2}$ mole) of the acid (VIII) in 10 ml of dry C_6H_6. Then the mixture was heated at 80°C for 0.5 h. The acid chloride (IX) so formed was purified by vacuum distillation in an atmosphere of argon. Yield 60%, mp 117-118°C/1 mm Hg. IR spectrum (cm^{-1}): 1320 (C–S); 1790-1800 (–COCl).

N,N'-Di(6-methylsulfinylhexyl)urea – (±)-Diptocarpidine (I). At room temperature, 0.7 g ($6.2\cdot10^{-3}$ mole) of 30% H_2O_2 was added to a stirred solution of 1 g ($3.1\cdot10^{-3}$ mole) of compound (VII) in 5 ml of glacial CH_3CO_2H. The reaction mixture was allowed to stand for 2 h and was then diluted with 10 ml of $CHCl_3$ and was neutralized with saturated Na_2CO_3 solution. The organic layer was separated off, and the aqueous layer was extracted with $CHCl_3$ (3 × 10 ml). The combined extracts were dried with $MgSO_4$. The solvent was distilled off and the residue was chromatographed on a column with chloroform–methanol (9:1) as eluent. The yield of (I) was 70%, mp 101-102°C. ^{13}C NMR spectrum (δ, ppm): 22.43 t (C-5, C-13), 26.39 t (C-2, C-10), 28.28 t (C-3, C-11), 29.96 t (C-4, C-12), 38.58 q (C-8, C-16), 39.93 t (C-1, C-9), 54.45 t (C-6, C-14), 158.75 s (C-17). The characteristics of the IR and ^1H NMR spectra of compound (I) were identical with those given in the literature [3].

Mass spectrum, m/z (%): M^+ 352 (0.33), 337 (10.47), 289 (20.95), 275 (7.61), 274 (16.19), 273 (7.85), 260 (5.29), 246 (3.33), 225 (15.71), 211 (6.19), 210 (8.09), 190 (100); 175 (31.42), 174 (9.04), 172 (15.23), 164 (45.23), 162 (24.76), 149 (7.14), 147 (2.14), 146 (3.33), 144 (3.57), 142 (4.28), 137 (5.95), 131 (8.09), 128 (6.66), 126 (28.57), 119 (14.76), 117 (57.14), 103 (15.47), 101 (8.57), 100 (69.04), 87 (6.19), 86 (10.59), 63 (20.47), 61 (24.28). REC mass spectrum (m/z): 351 $(M-H)^-$ 0.1% (0.55 eV), 321 $(M-OCH_3)^-$ 0.3% (0.55 eV), 275 $(M-SOC_2H_5)^-$ 1.9% (0.55 eV), 259 $(M-SO_2C_2H_5)^-$ 0.7% (0.55 eV), 63 CH_3SO^- 34.4% (1.1 eV), 7.7% (4.4 eV), and 8.6% (7.25 eV), 59 H_2NCONH^- 8.7% (0.55 eV), 48 SO^- 100% (4.2 eV), 47

*Here and below, the mass number and the empirical formula of the negative ion, the intensity of the ion as a percentage and, in parentheses, the energy of the resonance maximum of the yield of the ions.

CH_3S^- 10.4% (4.4 eV) and 11.5% (7.2 eV), 42 CON^- 62.8% (1.6 eV), 6% (4.4 eV), and 9.8% (7.3 eV).

N-(6-Methylsulfinylhexyl)-N'-(7-thiaoctyl)urea – (±)-Diptocarpiline (II). At room temperature, 0.096 g ($7.8 \cdot 10^{-4}$ mole) of 30% H_2O_2 was added to a stirred solution of 0.25 g ($7.8 \cdot 10^{-4}$ mole) of compound (VII) in 1 ml of glacial CH_3CO_2H, and the mixture was left to stand for 1 h. After the working-up procedure [see the preparation of diptocarpidine (I)], the compound (II) was purified by column chromatography with chloroform–methanol (9:1) as eluent. Yield 65%, mp 91°C. The IR and ^1H NMR spectra of compound (II) were identical with those given in the literature [3]. Mass spectrum, m/z (%): M^+ 336 (2.50), 321 (5.00), 320 (12.00), 306 (19.00), 290 (10.50), 276 (7.05); 275 (19.00), 274 (63.08), 273 (5.53), 260 (15.12), 258 (22.12), 256 (13.00), 232 (9.06), 218 (14.01), 212 (11.21), 210 (46.00), 205 (6.00), 190 (13.50), 188 (13.50), 175 (100), 164 (56.00), 147 (37.00), 146 (13.00), 142 (20.00), 131 (17.00), 128 (13.50), 126 (10.00), 117 (19.00), 111 (24.00), 103 (15.00), 101 (8.00), 100 (75.00), 98 (32.50), 87 (11.00), 86 (10.00), 83 (95.00), 63 (15.00), 61 (25.00). REC mass spectrum (m/z): 335 $(M-H)^-$ 0.2% (0.35 eV), 305 $(M-OCH_3)^-$ 6.7% (0.35 eV), 291 $(M-OC_2H_5)^-$ 0.9% (0.35 eV), 275 $(M-SC_2H_5)^-$ 100% (0.35 eV) and 1.5% (7.1 eV), 63 CH_3SO^- 8.9% (1.1 eV), 6.9 (4.5 eV), and 24.7% (7.05 eV), 59 H_2NCONH^- 3.0% (0.35 eV), 48 SO^- 62% (4.25 eV); 47 CH_3S^- 11.3% (0.35 eV), 8.2% (3.7 eV), 12% (4.65 eV), and 18.9% (7.1 eV), 42 CON^- 91.3% (0.65 eV) and 4.5% (7.1 eV).

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CONCLUSIONS

Convenient approaches to the synthesis of racemic diptocarpiline and racemic diptocarpine from the readily accessible 6-phthalimidohexyl bromide and hept-6-enoic acid have been developed.

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