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#### SYNTHESIS OF THE RACEMIC ALKALOID DIPTALINE

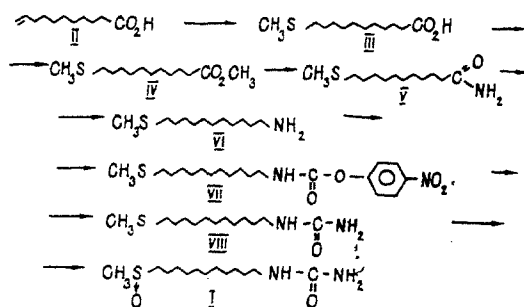
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The isolation from the plant *Dipthychocarpus strictus* (Cruciferae) of the optically active base diptaline, identified as N-(11-methylsulfinylundecyl)urea, has been reported [1]. A synthesis of the racemic form of this alkaloid has now been achieved.

In the development of investigations on the total synthesis of racemic alkaloids of the urea type [2-4], we have devised a rational approach to the synthesis of achiral diptaline (I) based on the transformation of the readily available undec-10-enoic acid (II). Its thiylation at the  $\Delta^{10}$  double bond with methyl mercaptan under UV irradiation gave a 74% yield of 12-thiatridecanoic acid (III), the methyl ester (IV) of which was converted by treatment with ammonia in methanolic solution in 74% yield into the amide (V), and this was reduced by the action of  $\text{LiAlH}_4$  to the key 12-thiatridecylamine (VI) (85%). The reaction of the amine (VI) with bis(4-nitrophenyl) carbonate in  $\text{CH}_2\text{Cl}_2$  solution at  $-10^\circ\text{C}$  [5] led with a yield of 57% to the intermediate carbamate (VII), the interaction of which with ammonia under the same conditions gave an 82% yield of the sulfide precursor (VIII) of alkaloid (I). Oxidation of compound (VIII) with hydrogen peroxide completed the synthesis of racemic diptaline (I). This, unlike the native product, is a crystalline substance, which is apparently explained by the optically inactive form of the synthetic alkaloid. The overall yield of ( $\pm$ )-diptaline calculated on the initial acid (II) was 14%.

In the PMR spectrum of the sulfide precursor (VIII) the signals of the protons of the  $\text{CH}_3$  and  $\text{CH}_2$  groups adjacent to the sulfur atom were observed in the form of a singlet ( $\delta$  2.08 ppm) and a triplet ( $\delta$  2.48 ppm,  $J = 7.2$  Hz), respectively. In the case of ( $\pm$ )-diptaline (I) the signals of the protons of the analogous groups appeared in a weaker field ( $\delta$  2.56 and 2.72 ppm) because of the descreening influence of the SO group.



The mass spectra of compounds (I) and (VIII) contained the peaks of molecular ions corresponding to the assumed empirical compositions ( $\text{C}_{13}\text{H}_{28}\text{N}_2\text{OS}$ ,  $\text{C}_{13}\text{H}_{28}\text{N}_2\text{O}_2\text{S}$ ) and the peaks of  $(M + 2)^+$  ions corresponding to the natural distribution of the isotope  $^{34}\text{S}$  for the pres-

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ence of one sulfur atom in the molecular ion. The characteristic ions [ $M - CH_3S^{1+}$ ,  $M - CH_3-S(O)CH_2^{1+}$ ,  $M - C_9H_{18}S(O)CH_3^{1+}$ ,  $M - C_{10}H_{20}S(O)CH_3^{1+}$ ,  $M - CH_3^{1+}$ ,  $M - CH_2NHCONH_2^{1+}$ ,  $C_2H_4S(O)-CH_3^{1+}$ ,  $CH_2S(O)CH_3^{1+}$ , and  $HS(O)CH_3^{1+}$ ] were formed according to [6] by simple bond cleavage.

#### EXPERIMENTAL

IR spectra were taken on a UR-20 spectrometer in Nujol or in a thin layer. PMR spectra were obtained on a Tesla BS-567 B instrument with a working frequency of 100 MHz.  $^{13}C$  NMR spectra were recorded on a JEOL FX-90 Q instrument with a working frequency of 22.5 MHz, using  $CDCl_3$  as solvent and TMS as internal standard. Positive-ion mass spectra were obtained on a MKh-1320 instrument at a temperature of the ionization chamber of 30-50°C and ionizing energies of 70 and 16 eV, using a SVP-5 direct-inlet system. The products of synthesis were separated by column chromatography on silica gels L 40/100 and L 100/160 (Czechoslovakia). The analyses of all the compounds corresponded to the calculated figures.

12-Thiatridecenoic Acid (III). A quartz-glass flask was charged with 9.22 g ( $5 \cdot 10^{-2}$  mole) of undecenoic acid and 0.01 g of azobis(isobutyronitrile), and it was cooled to 5°C. After the careful addition in one portion of 3.6 g ( $7.5 \cdot 10^{-2}$  mole) of methyl mercaptan, the mixture was stirred at 5°C with irradiation by a UV lamp (PRK-4) for 1 h. The excess of methyl mercaptan was eliminated, and the acid (III) was purified via the sodium salt. The yield of the acid (III) was 8.6 g (74%), in the form of crystals with mp 36-38°C (hexane). IR spectrum ( $\nu$ ,  $cm^{-1}$ ): 1380 (CS), 1710 (C=O), 2400-3550 (OH). PMR spectrum ( $\delta$ , ppm): 1.29-1.62 (16H, m,  $8CH_2$ ), 2.09 (3H, s,  $CH_3-S$ ), 2.35 (2H, t,  $S-CH_2$ ,  $J = 7.5$  Hz), 2.49 (2H, t,  $CH_2-CO_2^-$ ,  $J = 7.2$  Hz), 10.72 (1H, br. s, -OH).  $^{13}C$  NMR spectrum ( $\delta$ , ppm): 15.52 ( $CH_3-S$ ), 24.68, 28.80, 29.05, 29.20, 29.34, 29.43 ( $8CH_2$ ), 34.11 ( $S-CH_2$ ), 34.34 ( $CH_2-CO_2^-$ ), 180.18 (C=O). Mass spectrum,  $m/z$  (%): 232 ( $M^+$ , 60), 217(7), 185(13), 103(16), 75(23), 73(30), 61(100), 60(27), 47(10), 45(12).

Methyl 12-Thiatridecenoate (IV). A mixture of 13 g ( $5.6 \cdot 10^{-2}$  mole) of the acid (III), 0.25 g of p-toluenesulfonic acid, and 250 ml of anhydrous methanol was stirred for 24 h. The solvent was evaporated off, the residue was dissolved in 100 ml of ether, the solution was washed with 5%  $NaHCO_3$  solution ( $2 \times 50$  ml), the organic layer was dried with  $MgSO_4$  and evaporated, and the residue was chromatographed [hexane-ethyl acetate (7:3)]. This gave 10 g (80%) of the ester (IV) in the form of an oil,  $R_f$  0.5. IR spectrum ( $\nu$ ,  $cm^{-1}$ ): 1375 (CS), 1745 (C=O). PMR spectrum ( $\delta$ , ppm): 1.28-1.69 (16H, m,  $8CH_2$ ), 2.09 (3H, s,  $CH_3-S$ ), 2.32 (2H, t,  $S-CH_2$ ,  $J = 7.2$  Hz), 2.52 (2H, t,  $CH_2-CO_2^-$ ,  $J = 7.2$  Hz), 3.67 (3H, s,  $OCH_3$ ).  $^{13}C$  NMR spectrum ( $\delta$ , ppm): 15.53 ( $CH_3-S$ ), 25.00, 28.85, 29.24 ( $8CH_2$ ), 34.07 ( $S-CH_2$ ), 34.34 ( $CH_2-CO_2^-$ ), 51.37 ( $OCH_3$ ), 174.16 (C=O). Mass spectrum,  $m/z$  (%): 246 ( $M^+$ , 72), 231(21), 215(28), 199(100), 173(25), 171(18), 167(29), 125(11), 103(18), 87(42), 74(59), 61(48), 59(10), 47(9).

12-Thiatridecenamide (V). A mixture of 10 g ( $4.1 \cdot 10^{-2}$  mole) of the methyl ester (IV) and 400 ml of a saturated solution of anhydrous ammonia in methanol was kept at 5°C for 10 days. The solvent and the excess of ammonia were evaporated off, and the residue was crystallized from methanol-ether. This gave 7 g (74%) of the amide (V) in the form of crystals with mp 96-98°C. IR spectrum ( $\nu$ ,  $cm^{-1}$ ): 1640 ( $\delta$   $NH_2$ ), 1648 (C=O), 3392 (NH). PMR spectrum ( $\delta$ , ppm): 1.29-1.69 (16H, m,  $8CH_2$ ), 2.09 (3H, s,  $CH_3-S$ ), 2.23 (2H, t,  $S-CH_2$ ,  $J = 7.2$  Hz), 2.49 (2H, t,  $CH_2-CO_2^-$ ,  $J = 7.2$  Hz), 5.76 (2H, m,  $NH_2$ ).  $^{13}C$  NMR spectrum ( $\delta$ , ppm): 15.54 ( $CH_3-S$ ), 25.52, 28.85, 29.84 ( $8CH_2$ ), 34.33 ( $S-CH_2$ ), 34.93 ( $CH_2-CO_2^-$ ), 175.91 (C=O). Mass spectrum,  $m/z$  (%): 231 ( $M^+$ , 53), 216(14), 184(73), 173(48), 114(11), 103(19), 72(70), 61(73), 59(100), 47(10), 44(62).

12-Thiatridecylamine (VI). In three portions, 2.4 g ( $7.02 \cdot 10^{-2}$  mole) of  $LiAlH_4$  was added to a stirred suspension of 6.11 g ( $2.8 \cdot 10^{-2}$  mole) of the amide (V) in 50 ml of anhydrous ether. The reaction mixture was heated (30°C) for 12 h and was cooled, and then 0.49 g ( $1.3 \cdot 10^{-2}$  mole) of  $LiAlH_4$  was added and it was stirred at room temperature for 2 h. After the careful addition of 100 ml of dry ether and then 10 ml of a saturated aqueous solution KOH, the precipitate was filtered off, the organic layer in the filtrate was separated off, and the aqueous layer was extracted with ether ( $2 \times 10$  ml). The combined extracts were dried with  $Na_2SO_4$  and evaporated, and the residue was chromatographed [ $SiO_2$ , chloroform-methanol (9:1)] to give 4.84 g (85%) of the amine (VI) in the form of an oil with  $R_f$  0.185. IR spectrum ( $\nu$ ,  $cm^{-1}$ ): 1350 (CS), 1560-1640, 3342 (NH). PMR spectrum ( $\delta$ , ppm): 1.28-1.66 (18H, m,  $9CH_2$ ), 2.09 (3H, s,  $CH_3-S$ ), 2.55 (2H, t,  $S-CH_2$ ,  $J = 7.2$  Hz), 2.69 (2H, t,  $CH_2-N$ ,  $J = 7.2$  Hz), 3.62 (2H, m,  $NH_2$ ). Mass spectrum,  $m/z$  (%): 217 ( $M^+$ , 39), 202(100), 170(82), 156(31), 86(49), 72(39), 61(28), 47(8), 44(54), 30(50).

4-Nitrophenyl N-(12-Thiatridecyl)carbamate (VII). In drops, a solution of 2.17 g ( $1 \cdot 10^{-3}$  mole) of the amine (VI) in 10 ml of  $\text{CH}_2\text{Cl}_2$  was added (0.5 h) to a stirred mixture of 3.04 g ( $1 \cdot 10^{-3}$  mole) of bis(4-nitrophenyl)carbonate and 50 ml of anhydrous  $\text{CH}_2\text{Cl}_2$  at  $-10^\circ\text{C}$ . The reaction mixture was stirred at  $-10^\circ\text{C}$  for 2 h, and, after it had been washed with 20%  $\text{NaHCO}_3$  solution ( $4 \times 25$  ml) and saturated  $\text{NaCl}$  solution (30 ml), it was dried with  $\text{MgSO}_4$  and evaporated, and the residue was crystallized from methanol. The yield of the carbamate (VII) was 2.19 g (57%), in the form of crystals with mp  $80-82^\circ\text{C}$  (methanol). IR spectrum ( $\nu$ ,  $\text{cm}^{-1}$ ): 1375 (CS), 1680 (C=O), 3325 (NH). PMR spectrum ( $\delta$ , ppm): 1.26-1.42 (14H, m,  $7\text{CH}_2$ ), 1.60 (2H, m,  $2\text{CH}_2$ ), 2.09 (3H, s,  $\text{CH}_3\text{-S}$ ), 2.48 (2H, t,  $\text{S-CH}_2$ ,  $J = 7.2$  Hz), 3.26 (2H, m,  $\text{CH}_2\text{-N}$ ), 5.22 (H, br.s, NH), 7.38 (2H, d, Ar,  $J = 9.1$  Hz), 8.27 (2H, d, Ar,  $J = 9.1$  Hz).  $^{13}\text{C}$  NMR spectrum ( $\delta$ , ppm): 15.56 ( $\text{CH}_3\text{-S}$ ), 26.73, 28.82, 29.23, 29.49, 29.72 ( $9\text{CH}_2$ ), 34.40 ( $\text{S-CH}_2$ ), 41.48 ( $\text{CH}_2\text{N}$ ), 121.90, 125.09, 144.77, 153.12 (Ar), 156.14 (C=O).

N-(12-Thiatridecyl)urea (VIII). A mixture of 0.38 g ( $1 \cdot 10^{-3}$  mole) of the carbamate (VII), 0.1 g ( $5 \cdot 10^{-3}$  mole) of liquid ammonia, and 10 ml of anhydrous  $\text{CH}_2\text{Cl}_2$  was stirred at  $0^\circ\text{C}$  for 4 h. Then it was washed with 5%  $\text{HCl}$  ( $2 \times 5$  ml) and with saturated  $\text{NaHCO}_3$  solution ( $2 \times 3$  ml) and was dried with  $\text{Na}_2\text{SO}_4$  and evaporated, and the residue was crystallized from methanol-ether. This gave 0.2 g (80%) of the urea (VIII) in the form of crystals with mp  $98-100^\circ\text{C}$  (ether). IR spectrum ( $\nu$ ,  $\text{cm}^{-1}$ ): 1375 (CS), 1600 (NH), 1650 (C=O), 3342 (NH). PMR spectrum ( $\delta$ , ppm): 1.20-1.62 (18H, m,  $9\text{CH}_2$ ), 2.08 (3H, s,  $\text{CH}_3\text{-S}$ ), 2.48 (2H, t,  $\text{CH}_2\text{-S}$ ,  $J = 7.2$  Hz), 3.14 (2H, m,  $\text{CH}_2\text{-N}$ ), 4.24-4.70 (3H, m, NH,  $\text{NH}_2$ ). Mass spectrum,  $m/z$  (%): 260 ( $\text{M}^+$ , 20), 245(30), 217(6), 216(5), 213(100), 202(15), 199(6), 101(11), 87(17), 73(41), 61(30), 44(15), 30(70).

N-(11-Methylsulfinylundecyl)urea - ( $\pm$ )-Diptaline (I). At  $25^\circ\text{C}$ , 0.13 g ( $1.4 \cdot 10^{-3}$  mole) of 30%  $\text{H}_2\text{O}_2$  was added to a stirred mixture of 0.29 g ( $1.1 \cdot 10^{-3}$  mole) of the sulfidourea (VIII), 5 ml of glacial acetic acid, and 5 ml of acetone. After 2 h, the reaction mixture was diluted with 10 ml of  $\text{CHCl}_3$  and was washed with a saturated solution of  $\text{NaHCO}_3$  to eliminate traces of acid; it was then dried with  $\text{Na}_2\text{SO}_4$  and evaporated, and the residue was chromatographed [chloroform-methanol (9:1)]. This gave 0.22 g (70%) of ( $\pm$ )-diptaline (I) in the form of crystals with mp  $122-124^\circ\text{C}$  (according to the literature [1]: an oil). IR spectrum ( $\nu$ ,  $\text{cm}^{-1}$ ): 1045 (S=O), 1375 (CS), 1550 (NH), 1680 (C=O), 3340 (NH). PMR spectrum ( $\delta$ , ppm): 1.22-1.75 (18H, m,  $9\text{CH}_2$ ), 2.56 (3H, s,  $\text{CH}_3\text{-SO}$ ), 2.72 (2H, t,  $\text{OS-CH}_2$ ,  $J = 7.2$  Hz), 3.12 (2H, q,  $\text{CH}_2\text{-N}$ ,  $J = 6.4$  Hz), 4.65 and 5.20 (3H, m, NH,  $\text{NH}_2$ ).  $^{13}\text{C}$  NMR spectrum ( $\delta$ , ppm): 22.54, 26.84, 28.69, 29.09, 29.12, 29.21, 29.35, 29.73, 30.16 ( $9\text{CH}_2$ ), 38.50 ( $\text{CH}_3\text{-SO}$ ), 40.65 ( $\text{CH}_2\text{N}$ ), 54.88 ( $\text{OS-CH}_2$ ), 159.18 (C=O). Mass spectrum,  $m/z$  (%): 276 ( $\text{M}^+$ , 3), 261(11), 218(13), 216(15), 213(22), 199(8), 189(11), 170(18), 73(31), 64(22), 63(4), 44(21), 43(36), 30(100).

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