INDOLE DERIVATIVES

LXIII.* PREPARATION OF 3-INDOLYLTAURINE

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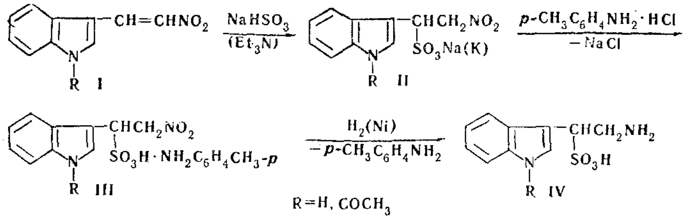
Salts of 2-nitro-1-(3'-indolyl)ethanesulfonic acid were obtained by the reaction of nitrovinylindole with potassium and sodium bisulfites. The salts were converted to the p-toluidine salt, which was reduced to 2-amino-1-(3'-indolyl)ethanesulfonic acid (3-indolyltaurine).

The addition of nucleophilic reagents to the carbon–carbon double bond of nitrovinylindole (I, R = H) and subsequent reduction of the nitro group opens a route to tryptamine derivatives containing substituents in the aliphatic chain. Aliphatic and aromatic compounds which contain a nitrovinyl group add bisulfites without catalysts [2, 3]. Nitrovinylindole reacts extremely slowly with sodium and potassium bisulfites under the usual conditions. However, in the presence of catalytic amounts of triethylamine the reaction proceeds rapidly. The resulting salts of 2-nitro-1-(3'-indolyl)ethanesulfonic acid (II, R = H) are rather unstable. The more stable p-toluidine salt (III, R = H) is reduced by hydrogen on a nickel catalyst to 3-indolyltaurine (IV, R = H). Similar transformations with N-acetylnitrovinylindole (I-IV, R = $COCH_3$) lead to more stable products.

Since indole and its 3-substituted derivatives are able to add bisulfites to form 2-sulfonic acids [4-7], the structure of IV required additional study.



The PMR spectrum of II (R = H) contains multiplet signals at δ 5.2 ppm (in CD_3OD) with an intensity of three proton units, which correspond to the $CH{-}CH_2$ group (ABC system), and a group of signals from the aromatic protons (7.0-7.7 ppm), among which the singlet of the C_2 proton of the indole ring (7.40 ppm) can be identified. On passing to the acetyl derivative (II, R = $COCH_3$, in D_2O), the positions of the signals from the $CH{-}CH_2$ group do not change. The signals from the C_2 proton of the indole ring and the protons of the acetyl group are observed as singlets at 7.71 and 2.53 ppm, respectively.

Since indolyltaurine is insoluble in water, the spectrum was obtained in D_2O containing Na_2CO_3. Despite appreciable decomposition of the compound, one can isolate the signals from the protons of the CH_2 group, which form an octet (AB portion of the ABX system) at 3.81 ppm with spin–spin interaction constants J_{AB} = 13.6 ± 0.2 Hz, J_{AX} = 4.2 ± 0.2 Hz, and J_{BX} = 9.5 ± 0.2 Hz. The signal of the CH proton is covered by signals from the solvent. It can be detected when the spectrum is obtained with a hot, deuterated

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[*] See [1] for communication LXII.

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TABLE 1. Chromatographic Characteristics of the Synthesized Compounds

Compound	R_f	Color during development		
		phosphomolybdic acid	p-Dimethylamino-benzaldehyde	Ninhydrin
II, R=H, Na- or K-salt	0,55	Dark-cherry	Rose	—
II, $R=COCH_3$, Na-salt	0,65	—†	—	—
III, R=H	0,55	Dark-cherry	Rose	—
	0,46*	—	Rose	—
III, $R=COCH_3$	0,65 †	—	—	—
	0,46	—	Yellow	—
IV, R=H	0,36	Dark-blue	Rose	Dark-violet
IV, $R=COCH_3$	0,42	Dark-blue	—	Dark-violet

* Ions of the salt are separated during chromatography; the spot with R_f 0.46 corresponds to p-toluidine.

† The dash indicates the absence of coloration during development.

dimethyl sulfoxide solution and is found as a quartet at 4.24 ppm (the X portion of the ABX system). The C_2 proton of the indole ring is observed at 7.46 ppm.

The PMR spectrum of acetylated 3-indolyltaurine was obtained in D_2O containing NaOD. The proton signals of the $CH{=}CH_2$ group were observed as two multiplets at 3.49 ppm (octet) and 4.43 ppm (quartet) (ABX system). The acetyl group and the C_2-proton of the indole ring form singlets at 1.94 and 7.43 ppm, respectively.

EXPERIMENTAL

The PMR spectra of 8-10% solutions of the compounds were obtained with a JNM-4H-100 spectrometer. The IR spectra of mineral oil suspensions were obtained with a UR-10 spectrometer.

Chromatography (see Table 1) was carried out on plates with a fixed layer of "Silufol UV_{254}" silica gel. The upper layer of a mixture of butanol with water and glacial acetic acid (4:5:1) was used for elution. The compounds were detected from their luminescence in UV light (all of the compounds give a violet color) and also by spraying the plates with alcohol solutions of phosphomolybdic acid, p-dimethylaminobenzaldehyde, and ninhydrin with subsequent heating at 90-110 deg.

Potassium 2-Nitro-1-(3'-indolyl)ethanesulfonate (II, R = H). Triethylamine (0.2 g) was added at 14 deg to a suspension of 5.64 g (0.03 mole) of I (R = H) and 6.63 g (0.03 mole) of potassium metabisulfite in 60 ml of 50% alcohol. The solids gradually dissolved with stirring, and crystals began to precipitate from the almost colorless solution. After 45 min, the crystals were filtered and washed with 50% alcohol to give 7.94 g (85.8%) of a yellowish salt. Recrystallization from water gave 5.5 g of a salt which contained an insignificant amount of nitrovinylindole. Found %: C 36.60; H 3.53; N 8.73; S 8.96. $C_{10}H_9KN_2O_5S \cdot H_2O$. Calc. %: C 36.81; H 3.40; N 8.57; S 10.39. ν_{max} 3640, 3533 cm^{-1} (H_2O); 3430 cm^{-1} (NH); 1626 cm^{-1} (impurity); 1564, 1343 cm^{-1} (NO_2); 1250-1185, 1034 cm^{-1} (SO_3). Treatment of this salt with p-toluidine hydrochloride gave a toluidine salt which was identical to that obtained by the method described below.

p-Toluidine Salt of 2-Nitro-1-(3'-indolyl)ethanesulfonic Acid (III, R = H). Triethylamine (0.2 g) was added at 20 deg to a suspension of 7.52 g (0.04 mole) of I (R = H) and 7.6 g (0.04 mole) of sodium metabisulfite in 40 ml of 50% alcohol. A transparent solution formed after 20-25 min. A solution of 5.52 g (0.04 mole) of p-toluidine hydrochloride in 60 ml of water was added to it, and the mixture was allowed to stand in a refrigerator overnight. The resulting colorless, crystalline precipitate was filtered, washed with water and alcohol, and air-dried to give 11.75 g (79%) of a salt with mp 197-198 deg (from 20% alcohol). Found %: C 54.21; H 4.90; N 11.11; S 8.55. $C_{17}H_{19}N_3O_5S$. Calc. %: C 54.21; H 5.07; N 11.13; S 8.48. ν_{max} 3400 cm^{-1} (NH), 3200-2500 cm^{-1} (NH_3^+), 1560 cm^{-1} (NO_2), 1250-1140 cm^{-1} (SO_3).

2-Amino-1-(3'-indolyl)ethanesulfonic Acid (3-Indolyltaurine) (IV, R = H). A suspension of 6.63 g (0.018 mole) of III (R = H) in 100 ml of water and 50 ml of alcohol was shaken in a hydrogen atmosphere in the presence of 5 g of a Raney nickel catalyst. After 20 h, 1190 ml of hydrogen was absorbed. The catalyst was filtered and washed repeatedly with hot water. The filtrate and wash water were evaporated, and the residue was crystallized from water to give 2.4 g (55%) of colorless crystals that decomposed at 325 deg. Found %: C 50.35; H 4.95; N 11.93; S 13.12. $C_{10}H_{12}N_2O_3S$. Calc. %: C 49.98; H 5.03; N 11.65; S 13.34. ν_{max} 3445 cm^{-1} (NH), 3200-2500 cm^{-1} (NH_3^+), 1270-1150 cm^{-1} (SO_3).

Sodium 2-Nitro-1-(1'-acetyl-3'-indolyl)ethanesulfonate (II, R = $COCH_3$). Triethylamine (0.1 g) was added to a suspension of 4.6 g (0.02 mole) of I (R = $COCH_3$) and 3.8 g (0.02 mole) of sodium metabisulfite in 40 ml of 50% alcohol, the mixture was stirred at room temperature for 30 min, and the colorless suspension was vacuum-evaporated. The residue was extracted with hot absolute alcohol to give 5.33 g (72%) of yellowish crystals of the dihydrate of the sodium salt. Recrystallization from 96% alcohol gave a colorless product. Found %: C 38.64; H 3.99; N 7.53; S 8.86. $C_{12}H_{11}N_2NaO_6S \cdot 2H_2O$. Calc. %: C 38.92; H 4.08; N 7.56; S 8.64. ν_{max} 3480 cm^{-1} (H_2O); 1710 cm^{-1} (CO); 1557, 1337 cm^{-1} (NO_2); 1265-1180 cm^{-1} (SO_3).

p-Toluidine Salt of 2-Nitro-1-(1'-acetyl-3'-indolyl)ethanesulfonic Acid (III, R = $COCH_3$). Solutions of 3.7 g (0.01 mole) of II (R = $COCH_3$, sodium salt) in 13 ml of water and 1.43 g (0.01 mole) of p-toluidine hydrochloride in 10 ml of water were mixed, and the resulting suspension was placed in a refrigerator overnight. The mixture was filtered, and the solid was washed with water and alcohol and recrystallized from 175 ml of water to give 2.77 g (66%) of colorless crystals which decomposed at 235 deg. Found %: C 54.17; H 4.82; N 10.16; S 7.72. $C_{19}H_{21}N_3O_6S$. Calc. %: C 54.41; H 5.04; N 10.02; S 7.63. ν_{max} 2650-3250 cm^{-1} (NH_3^+); 1714 cm^{-1} (CO); 1557, 1334 cm^{-1} (NO_2); 1135-1260 cm^{-1} (SO_3).

2-Amino-1-(1'-acetyl-3'-indolyl)ethanesulfonic Acid (IV, R = $COCH_3$). A suspension of 3.6 g (0.0086 mole) of III (R = $COCH_3$) in 100 ml of 70% alcohol was hydrogenated at room temperature over ~ 4 g of a Raney nickel catalyst. The precipitate was filtered and washed repeatedly with hot water. The filtrate and wash water were evaporated, and the residue was recrystallized from 180 ml of water to give 1.8 g (74.5%) of colorless crystals that decomposed at 335 deg. Found %: C 51.35; H 4.90; N 9.96; S 11.18. $C_{12}H_{14}N_2O_4S$. Calc. %: C 51.06; H 4.99; N 9.92; S 11.33. ν_{max} 2650-3200 cm^{-1} (NH_3^+), 1728 cm^{-1} (CO), 1150-1260 cm^{-1} (SO_3).

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