SYNTHESIS OF SOME NEW ALIPHATIC-AROMATIC SULFONAMIDE ANALOGS OF MELATONIN, 3,4-DIHYDRO-β-CARBOLINE, AND 1,2,3,4-TETRAHYDRO-β-CARBOLINE

D. R. Lagidze, L. Ya. Talakvadze, and R. M. Lagidze

UDC 547.759.3'829.07

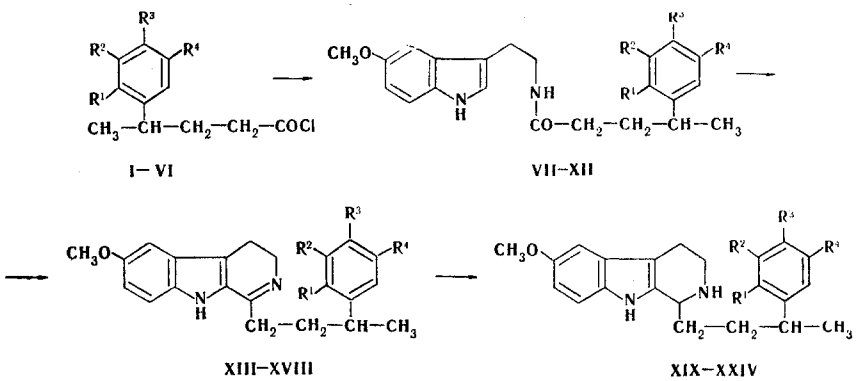
Aliphatic-aromatic sulfonamide analogs of melatonin were obtained by acylation of 5-methoxytryptamine with 4-(N,N-diethylsulfonamidoaryl)pentanoyl chlorides. It is shown that cyclization of the indicated amides under the conditions of the Bischler–Napieralski reaction leads to the formation of 3,4-dihydro-β-carbolines in good yields without involvement of the sulfonamido group. The corresponding 1,2,3,4-tetrahydro-β-carbolines were obtained by reduction of the latter with sodium metal in absolute methanol and were characterized.

Compounds containing arylalkyl groups with more than two to three carbon atoms in the side chain are rarely encountered among the numerous structural analogs of melatonin and β-carboline derivatives obtained from them. Moreover, the literature does not contain data on the analogous compounds with various sulfonamido groups in the aromatic ring [1].

In the present research for the first time we accomplished the acylation of 5-methoxytryptamine with 4-(N,N-diethylsulfonamidoaryl)pentanoyl chlorides [2] (I-VI). Cyclization of the resulting amides VII-XII under the conditions of the Bischler–Napieralski reaction leads to the formation of 6-methoxy-1-[2-(N,N-diethylsulfonamidoaryl)butyl]-3,4-dihydro-β-carbolines (XII-XVII) in good yields without involvement of the sulfonamido group in the side chain. The corresponding 1,2,3,4-tetrahydro-β-carbolines (XIX-XXIV) were obtained by reduction of the latter with sodium metal in absolute ethanol.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a DS-301 spectrometer. The UV spectra of ethanol solutions of the compounds were recorded with a Specord spectrophotometer. The PMR spectra of $CDCl_3$ solutions of the compounds were recorded with a Varian A-50/60 spectrometer. The molecular weights were determined by mass spectroscopy. The purity of all of the synthesized compounds was monitored by chromatography on a loose layer of "for-chromatography" aluminum oxide with chloroform as the solvent.



I, VII, XIII, XIX $R^1 = R^2 = R^4 = H$, $R^3 = SO_2N(C_2H_5)_2$; II, VIII, XIV, XX $R^1 = R^4 = H$, $R^3 = CH_3$, $R^2 = SO_2N(C_2H_5)_2$; III, IX, XV, XXI $R^2 = H$, $R^1 = R^4 = CH_3$, $R^3 = SO_2N(C_2H_5)_2$; IV, X, XVI, XXII $R^1 = H$, $R^2 = R^3 = CH_3$, $R^4 = SO_2N(C_2H_5)_2$, V, XI, XVII, XXIII $R^1 = H$, $R^2 = R^4 = CH_3$, $R^3 = SO_2N(C_2H_5)_2$; VI, XII, XVIII, XXIV $R^1 = R^4 = H$, $R^3 = C_2H_5$, $R^2 = SO_2N(C_2H_5)_2$.

Institute of Experimental and Clinical Surgery, Ministry of Public Health of the Georgian SSR, Tbilisi 380059. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1648-1650, December, 1977. Original article submitted March 28, 1977.

 0009-3122/77/1312-1316$07.50

TABLE 1. 4-(N,N-Diethylsulfonamidoaryl)pentanoyl Chlorides (I-VI)

Compound	bp, °C (10^{-2} mm)	n_D^{20}	Empirical formula	Cl, % found	Cl, % calc.	Yield, %
I	188—190	1,5235	$C_{15}H_{22}ClNO_3S$	10,5	10,7	85
II	210—211	1,5270	$C_{16}H_{24}ClNO_3S$	10,0	10,3	87
III	180—182	1,5241	$C_{17}H_{26}ClNO_3S$	9,7	9,9	83
IV	212—214	1,5240	$C_{17}H_{26}ClNO_3S$	9,7	9,9	82
V	208—210	1,5215	$C_{17}H_{26}ClNO_3S$	9,7	9,9	81
VI	176—178	1,5200	$C_{17}H_{26}ClNO_3S$	9,7	9,9	84

Absorption bands of an indole ring NH bond at 3380 cm^{-1}, an amide carbonyl group at 1160-1550 cm^{-1}, and two intense bands at 1340-1350 and 1150-1170 cm^{-1}, which correspond to the asymmetrical and symmetrical SO_2 vibrations, are observed in the IR spectra of VII-XII; this confirms the presence of a sulfonamido group. IR spectra of XIII-XVIII: 1220, 1640, and 3400 cm^{-1} (stretching vibrations of $ArOCH_3$ groupings, C=N bond of a six-membered ring, and indole ring NH bond, respectively).

The PMR spectra of XIII, XVI, and XIX contain the following signals: $N(CH_2\mathbf{CH_3})_2$ and $\mathbf{CH_3}CH$ multiplet at 1.0-1.3 ppm, CH_2 multiplet at 1.8-2.8 ppm, broad signal of the methylene protons of an $SO_2N(CH_2)_2$ group at 3.2 ppm, CH_3O singlet at 3.8 ppm, and multiplet of aromatic protons at 6.8-7.8 ppm.

In contrast to the spectra of XIII and XIX, a singlet of a CH_3 group attached to the aromatic ring at 2.25 ppm is observed in the PMR spectra of XVI.

The corresponding acid chlorides I-VI were obtained in good yields (Table 1) when 4-(N,N-diethylsulfonamidoaryl)pentanoic acids were refluxed with thionyl chloride (molar ratio 1:1.5).

4-[p-(N,N-Diethylsulfonamido)phenyl]pentanoic Acid 2-(5-Methyoxy-3-indolyl)ethylamide (VII). A solution of 2.58 g (0.007 mole) of 4-[p-(N,N-diethylsulfonamidophenyl]pentanoyl chloride (I) in 20 ml of benzene was added dropwise with stirring at about 20°C to a solution of 1 g (0.005 mole) of 5-methoxytryptamine in 20 ml of benzene and 10 ml of 0.5 N NaOH, and the mixture was refluxed for 1.5 h. It was then cooled, acidified with dilute hydrochloric acid, and extracted with chloroform (five 30-ml portions). The combined chloroform extracts were washed with water and dried over sodium sulfate, and the solvent was removed by vacuum distillation. The residual dark-yellow oil (2.1 g) was chromatographed with a column filled with Al_2O_3. Systems of solvents in the following sequence were used for elution: petroleum ether, petroleum ether–benzene (9:1, 8:2, and 7:3), benzene, and benzene–ether (1:1). Workup of the benzene eluate gave 2 g (76%) of VII with mp 38-40°C.

Compounds VII-XII were similarly obtained.

6-Methoxy-1-{2-[p-(N,N-diethylsulfonamido)phenyl]butyl}-3,4-dihydro-β-carboline (XIII). A 2.25-ml sample of $POCl_3$ was added to a solution of 1 g (0.002 mole) of amide VII in 50 ml of absolute benzene, and the mixture was refluxed for 1.5 h. The solvent was removed by vacuum distillation, and the residue was dissolved in the minimum amount of glacial acetic acid. The solution was heated on a water bath for 30 min, and the hot solution was filtered. The filtrate was cooled and treated with ammonium hydroxide, and the precipitate was extracted with chloroform (five 30-ml portions). The extract was dried over sodium sulfate and vacuum evaporated to dryness. The yellow residue (0.85 g) was purified by preparative chromatography on a plate with Al_2O_3 (elution with chloroform) to give 0.7 g (72%) of crystalline III with mp 78-80°C (from petroleum ether). UV spectrum (in alcohol), λ_{max} (log ε): 320 nm (3.8).

Compounds XIV-XVIII were similarly obtained.

6-Methoxy-1-{2-[p-(N,N-dimethylsulfonamido)phenyl]butyl}-1,2,3,4-tetrahydro-β-carboline (XIX). A 1.2-g sample of sodium metal was added to a solution of 0.35 g (0.006 mole) of XIII in 25 ml of absolute ethanol, and the mixture was refluxed for 30 min. It was then cooled and treated with 50 ml of water, and the solution was concentrated under low vacuum conditions to approximately half the volume of the solvents added. The concentrate was extracted with ether (three 30-ml portions), and the extract was dried over calcined potassium

TABLE 2. Arylalkylsulfonamide Derivatives of Melatonin (VII-XII), 3,4-Dihydro-β-carboline (XIII-XVIII), and 1,2,3,4-Tetrahydro-β-carboline (XIX-XXIV)

Compound	mp, °C	Found, %				Empirical formula	Calc., %				Yield, %
		C	H	N	S		C	H	N	S	
VII	38—40	64,6	7,2	8,4	6,5	$C_{26}H_{35}N_3O_4S$	64,3	7,2	8,6	6,5	76
VIII	44—46	63,8	7,2	8,4	6,6	$C_{27}H_{37}N_3O_4S$	64,1	7,4	8,4	6,4	85
IX	53—56	65,4	7,6	8,1	5,8	$C_{28}H_{39}N_3O_4S$	65,5	7,6	8,2	6,2	74
X	56—58	65,8	7,6	7,8	6,4	$C_{28}H_{39}N_3O_4S$	65,5	7,6	8,2	6,2	77
XI	30—32	65,5	7,7	8,0	6,3	$C_{28}H_{39}N_3O_4S$	65,5	7,6	8,2	6,2	76
XII	32—35	65,3	7,6	8,1	6,2	$C_{28}H_{39}N_3O_4S$	65,5	7,6	8,2	6,2	80
XIII	78—80	66,8	7,3	8,9	6,5	$C_{26}H_{33}N_3O_3S$	66,8	7,1	9,0	6,8	72
XIV	97—99	67,5	7,4	8,6	6,4	$C_{27}H_{35}N_3O_3S$	67,8	7,3	8,4	6,6	75
XV	89—92	68,42	7,3	8,3	6,2	$C_{28}H_{37}N_3O_3S$	68,7	7,5	8,4	6,5	73
XVI	94—97	68,6	7,5	8,4	6,8	$C_{28}H_{37}N_3O_3S$	68,7	7,5	8,4	6,5	74
XVII	99—101	68,5	7,4	8,4	6,4	$C_{28}H_{37}N_3O_3S$	68,7	7,5	8,4	6,5	75
XVIII	98—100	68,6	7,5	8,2	6,1	$C_{28}H_{37}N_3O_3S$	68,7	7,5	8,4	6,5	74
XIX	100—101	66,4	7,4	8,7	6,5	$C_{26}H_{35}N_3O_3S$	66,5	7,5	8,9	6,8	70
XX	85—86	66,9	7,4	8,6	7,4	$C_{27}H_{37}N_3O_3S$	67,1	7,7	8,8	6,6	67
XXI	93—94	67,7	7,9	8,7	6,5	$C_{28}H_{39}N_3O_3S$	67,6	7,8	8,4	6,4	69
XXII	98—99	67,5	7,7	8,2	6,1	$C_{28}H_{39}N_3O_3S$	67,6	7,8	8,4	6,4	72
XXIII	102—103	67,6	7,9	8,2	6,6	$C_{28}H_{39}N_3O_3S$	67,6	7,8	8,4	6,4	71
XXIV	106—108	67,6	7,9	8,3	6,5	$C_{28}H_{39}N_3O_3S$	67,6	7,8	8,4	6,4	73

carbonate and evaporated to dryness to give 0.24 g (70%) of XIX with mp 100-101°C (from petroleum ether). UV spectrum (in alcohol), λ_{max} (log ε): 300 nm (3.6).

Compounds XX-XXIV were similarly obtained.

LITERATURE CITED

1. M. Protiva, L. Lilek, E. Hachova, L. Novak, Z. Vejdelek, and E. Adlerova, Chem. Listy, No. 5, 1915 (1957).
2. D. R. Lagidze and L. Ya. Talakvadze, Soobshch. Akad. Nauk Gruz. SSR, 72, 97 (1973).

CHEMISTRY OF HETEROCYCLIC N-OXIDES AND RELATED COMPOUNDS. IX.* DEHYDROGENATION OF THE HANTZSCH ESTER BY NITRO AND CARBOXY DERIVATIVES OF PYRIDINE N-OXIDE

A. S. Kurbatova, Yu. V. Kurbatov, and D. A. Niyazova

UDC 547.821:547.826:542.941.8'942.7

The dehydrogenating activity of 4-nitropyridine N-oxide and picolinic, nicotinic, isonicotinic, and quinolinic acid N-oxides was studied in the case of the reaction with the Hantzsch ester.

In a continuation of our study of the dehydrogenating capacity of N-oxides of pyridine bases it seemed of interest to study pyridine N-oxide derivatives with electronegative substituents, since the introduction of the latter into the N-oxide molecule sharply increases the redox potential [2]. In the present research in the case of the dehydrogenation of the Hantzsch ester (I) we studied the dehydrogenating activity of N-oxides of picolinic (II), nicotinic (III), isonicotinic (IV), and quinolinic (V) acids and 4-nitropyridine (VI).

Pyridinecarboxylic acid N-oxides dehydrogenate the Hantzsch ester at lower temperatures than the unsubstituted pyridine N-oxide, and better results are obtained when oxide II is used.

*See [1] for communication VIII.

A. Navoi Samarkand State University, Samarkand 703000.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 12, pp. 1651-1653, December, 1977. Original article submitted October 19, 1976.

0009-3122/77/1312-1318$07.50