SYNTHESIS OF ISOTRYPTAMINES AND TETRAHYDRO-γ-CARBOLINES FROM 2-INDOLYLACETIC ACID DERIVATIVES

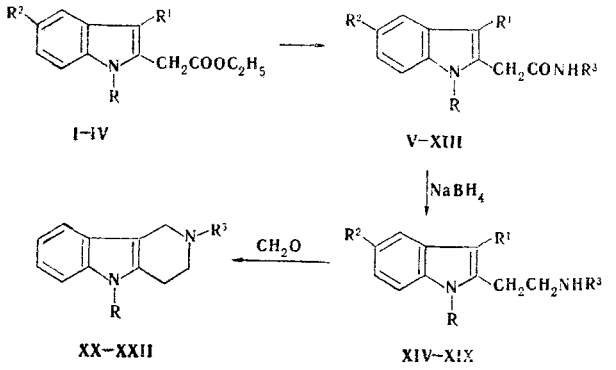
F. A. Trofimov, V. I. Garnova,
A. N. Grinev, and N. G. Tsyshkova

UDC 547.755.757.759.3

The reaction of ethyl 2-indolylacetate with alkylamines gave the corresponding amides, which were reduced with sodium borohydride to isotryptamines. The latter were converted to 1,2,3,4-tetrahydro-γ-carboline derivatives by condensation with formaldehyde.

2-Indolylacetamides are attracting attention as possible intermediates in the synthesis of isotryptamine derivatives. The latter, in turn, through reaction of the amino group with carbonyl compounds, form condensed systems, including tetrahydro-γ-carbolines [1], which have a broad spectrum of pharmacological activity [2]. However, the known methods for the synthesis of isotryptamines are multistep processes, are based on the use of indole-2-carboxylic acids [3-9] and lithium derivatives of indole [10] and require a large excess of lithium aluminum hydride for the reduction of nitrovinyl derivatives.

We have previously shown that 3-carbethoxy-2-indolylacetamides are readily formed at room temperature by reaction of the esters with primary amines with $pK \geq 10$. However, comparative experiments showed that 2-indolylacetic acid esters that do not have a carbethoxy group in the 3 position do not form amides under similar conditions. In this connection, to obtain alkylamides of 2-indolylacetic acid (V-XIII) from esters I-IV we used excess amounts of primary amines as the amidating agents and carried out the reaction in ethylene glycol at 140-160°C. Amides V-VII and IX-XI were then reduced to 2-alkylaminoethylindoles (isotryptamines) XIV-XIX in 55-88% yields. The preparatively convenient sodium borohydride–acetic acid complex in dioxane was used as the reducing agent for the amide group. Isotryptamines XV-XVII and XIX with a free β position in the indole ring form 1,2,3,4-tetrahydro-γ-carbolines (XX-XXIII) on treatment with formaldehyde in acetic acid at room temperature. It should be noted that the presence of a methoxy group in the 5 position of the indole ring prevents the formation of a carboline. A similar observation was also made in the case of cyclization of amides of indole-2-carboxylic acid aminoacetal to β-carboline derivatives [13].



I $R=CH_3$, $R^1=SCH_3$, $R^2=H$; II $R=CH_3$, $R^1=R^2=H$; III $R=CH_3$, $R^1=H$, $R^2=OCH_3$; IV $R=CH_2C_6H_5$, $R^1=R^2=H$

Scientific-Research Institute of Medicinal Radiology, Academy of Medical Sciences of the USSR, Obninsk 249020. S. Ordzhonikidze All-Union Scientific-Research Pharmaceutical-Chemistry Institute, Moscow 119021. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 1, pp. 72-74, January, 1979. Original article submitted April 18, 1978.

0009-3122/79/1501-0063$07.50

TABLE 1. 2-Indolylacetic Acid Amides

Compound	R	R^1	R^2	R^3	mp, °C*	Found, %			Empirical formula	Calc., %			Yield, %
						C	H	N		C	H	N	
VI	CH_3	H	H	$(CH_2)_3OH$	75—77	68,0	7,3	11,5	$C_{14}H_{18}N_2O_2$	68,3	7,4	11,4	81
VII	CH_3	H	H	$C(CH_3)_2CH_2OH$	117—120	69,2	8,0	11,3	$C_{15}H_{20}N_2O_2$	69,2	7,7	10,8	76
VIII	CH_3	H	H	$CH_2C_6H_5$	130—131	77,8	6,4	9,8	$C_{18}H_{18}N_2O$	77,7	6,5	10,1	40
IX	CH_3	H	OCH_3	CH_2CH_2OH	139—141	64,2	6,8	10,6	$C_{14}H_{18}N_2O_3$	64,1	6,9	10,7	81
X	$CH_2C_6H_5$	H	H	CH_2CH_2OH	123—125	74,0	6,6	9,0	$C_{19}H_{20}N_2O_2$	74,0	6,5	9,1	87
XI	CH_3	SCH_3	H	CH_2CH_2OH	132—135	60,4	6,2	10,1	$C_{14}H_{18}N_2O_2S$	60,4	6,5	10,1	90
XII	CH_3	SCH_3	H	$(CH_2)_3OH$	107—110	61,1	6,8	—	$C_{15}H_{20}N_2O_2S$	61,6	6,9	—	65
XIII	CH_3	SCH_3	H	$CH_2C_6H_5$	173—174	70,3	6,4	8,7	$C_{19}H_{20}N_2OS$	70,4	6,2	8,7	56

*The compounds were recrystallized: VI, IX-XI, and XIII from benzene, XII from carbon tetrachloride, and VII and VIII from petroleum ether–benzene.

TABLE 2. Isotryptamines and Tetrahydro-γ-carbolines

Compound	R*	R^2	R^3	mp, °C†	Found, %			Empirical formula	Calc., %			Yield, %
					N	H	C		N	H	C	
XV	CH_3	H	CH_2CH_2OH	167—168	61,2	7,4	10,9	$C_{13}H_{18}N_2O \cdot HCl$	61,3	7,5	11,0	86
XVI	CH_3	H	$(CH_2)_3OH$	159—160	62,4	7,9	10,5	$C_{14}H_{20}N_2O \cdot HCl$	62,6	7,9	10,4	75
XVII	CH_3	H	$C(CH_3)_2CH_2OH$	141	73,1	9,2	11,7	$C_{15}H_{22}N_2O$	73,2	9,0	11,4	54
XVIII	CH_3	OCH_3	CH_2CH_2OH	195—196	59,3	7,5	9,9	$C_{14}H_{20}N_2O_2 \cdot HCl$	59,0	7,4	9,8	88
XIX	$CH_2C_6H_5$	H	CH_2CH_2OH	196	68,9	7,0	8,7	$C_{19}H_{22}N_2O \cdot HCl$	69,0	7,0	8,5	61
XXI	CH_3	H	$(CH_2)_3OH$	169—170	73,6	8,5	11,7	$C_{15}H_{20}N_2O$	73,7	8,2	11,5	86
XXII	CH_3	H	$C(CH_3)_2CH_2OH$	223	64,7	7,9	9,4	$C_{16}H_{23}N_2O \cdot HCl$	64,9	8,2	9,5	72
XXIII	$CH_2C_6H_5$	H	CH_2CH_2OH	205—206	70,0	6,8	8,3	$C_{20}H_{22}N_2O \cdot HCl$	70,1	6,8	8,2	44

*R^1 = H.

†The compounds were recrystallized: XV, XVI, XVIII, XIX, XXII, and XXIII from absolute alcohol, XVII from benzene, and XXI from petroleum ether with absolute alcohol.

EXPERIMENTAL

The IR spectra of KBr pellets of the compounds were recorded with a UR-10 spectrometer. The individuality of the compounds was monitored by thin-layer chromatography (TLC) on activity II Al_2O_3 in a benzene–alcohol system (10:1).

Ethyl 1-Methyl-3-methylthio-2-indolylacetate (I) and Ethyl 1-Methyl-2-indolylacetate (II). These compounds were obtained by the method in [14]. A similar procedure was used to obtain ethyl 1-methyl-5-methoxy-2-indolylacetate (III), with mp 42°C (from hexane), in 58% yield. Found: C 68.6; H 7.1%. $C_{14}H_{17}NO_3$. Calculated: C 68.0; H 6.9%. Ethyl 1-benzyl-2-indolylacetate, with mp 57°C (from alcohol), was obtained in 78% yield. Found: C 78.0; H 6.7; N 5.0%. $C_{19}H_{19}NO_2$. Calculated: C 77.8; H 6.5; N 4.8%.

1-Methyl-2-indolylacetic Acid 2-Hydroxyethylamide (V). A solution of 2.17 g (0.01 mole) of ester II and 10 ml of 2-aminoethanol was refluxed for 5 h, after which the excess amine was removed by distillation, and water was added to the residue. The resulting precipitate was removed by filtration to give 2 g (86%) of a product with mp 110-112°C (from benzene) and R_f 0.30. IR spectrum: 1670 and 1530 (amide I and II C=O); 3370 cm^{-1} (NH). Found: C 67.2; H 7.0; N 12.2%. $C_{13}H_{16}N_2O_2$. Calculated: C 67.2; H 7.0; N 12.1%. Amides VI-XIII were similarly obtained (Table 1).

1-Methyl-2-[2-(β-hydroxyethyl)aminoethyl]-3-methylthioindole (XIV). A 1.5-g (0.025 mole) sample of glacial acetic acid was added with cooling (ice water) in the course of 5 min to a stirred suspension of 0.95 g (0.025 mole) of sodium borohydride and 1.4 g (0.005

of amide XI in 15 ml of dioxane, and the mixture was refluxed with stirring for 2 h. It was then evaporated to dryness, and the residue was treated with water. The aqueous mixture was extracted with chloroform, and the extract was dried with anhydrous sodium sulfate. The chloroform was removed by vacuum distillation, and the residue was dissolved in a mixture of absolute alcohol and ether. An ether solution of dry hydrogen chloride was added to the solution, and the mixture was worked up to give 1.2 g (80%) of the hydrochloride with mp 188-190°C (from absolute alcohol). Found: C 56.0; H 7.0; N 9.1%. $C_{14}H_{20}N_2OS \cdot HCl$. Calculated: C 55.9; H 7.1; N 9.3%. Isotryptamines XV-XIX were similarly obtained (Table 2).

3-(2-Hydroxyethyl)-9-methyl-1,2,3,4-tetrahydro-γ-carboline (XX) Hydrochloride. A mixture of 0.7 g (0.0032 mole) of isotryptamine XV, 3 ml of glacial acetic acid, and 0.3 ml of 33% formaldehyde solution was allowed to stand at room temperature for 24 h, after which 10 ml of water was added, and the mixture was made alkaline with 10% sodium hydroxide solution and extracted with benzene. The extract was dried with sodium sulfate and treated with an ether solution of dry hydrogen chloride, and the resulting precipitate was removed by filtration to give 0.7 g (82%) of the hydrochloride with mp 232-236°C (dec., from absolute alcohol). Found: C 62.2; H 7.2; N 10.3%. $C_{14}H_{18}N_2O \cdot HCl$. Calculated: C 63.0; H 7.2; N 10.5%. Carbolines XXI-XXIII were similarly obtained (Table 2).

LITERATURE CITED

1. A. N. Kost, M. A. Yurovskaya, and F. A. Trofimov, Khim. Geterotsikl. Soedin., No. 3, 291 (1973).
2. K. S. Shadurskii, T. Yu. Il'yuchenok, F. A. Trofimov, and A. N. Kost, Farmakol. Toksikol., No. 4, 482 (1969).
3. Japanese Patent No. 7207788; Chem. Abstr., 77, 5325 (1972).
4. S. P. Hiremath and M. G. Purohit, Indian J. Chem., 10, 984 (1972).
5. G. A. Bhat and S. Siddappa, J. Indian Chem. Soc., 51, 427 (1974).
6. G. A. Bhat and S. Siddappa, J. Indian Chem. Soc., 52, 335 (1975).
7. S. P. Hiremath and S. S. Kaddargi, Indian J. Chem. Soc., 53, 71 (1976).
8. S. P. Hiremath and M. G. Purohit, J. Indian Chem. Soc., 53, 71 (1976).
9. V. Sniekus and K. S. Bhandari, Tetrahedron Lett., No. 39, 3375 (1969).
10. I. Kebrle, A. Rossi, and K. Hoffman, Helv. Chim. Acta, 42, 907 (1959).
11. F. A. Trofimov, V. I. Ryabchenko, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 10, 1343 (1975).
12. F. A. Trofimov, V. I. Nozdrich, A. N. Grinev, and V. I. Shvedov, Khim.-farm. Zh., No. 7, 22 (1967).
13. R. C. Elderfield (editor), Heterocyclic Compounds, Vol. 7, Wiley-Interscience (1961).
14. F. A. Trofimov, N. G. Tsyshkova, V. I. Garnova, and A. N. Grinev, Khim. Geterotsikl. Soedin., No. 9, 1254 (1975).