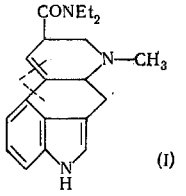
SYNTHESIS OF ANALOGS OF LYSERGIC ACID DIETHYLAMIDE

I. L. Kotlyarevskii and L. A. Mal'kova

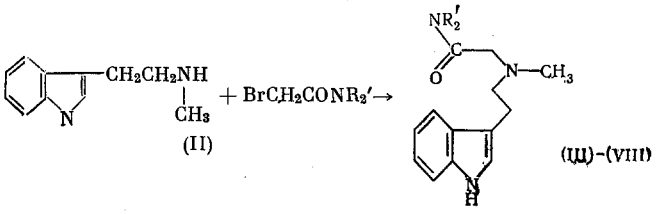
UDC 542.91:547.752

In a search for new medicinals, and also in order to ascertain the relation between the structure of LSD-25 (lysergic acid diethylamide, I) and the physiological activity, we synthesized some analogs of (I) [compounds (III)-(VIII)], which differed from (I) by the absence of two rings, the distance between the amide and amino groups, and the radicals attached to the nitrogen atom of the amide group



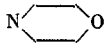
(I)

In order to accomplish these syntheses we selected the following scheme:



(II) (III)-(VIII)

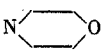
NR_2' = NMe_2 (III); NEt_2 (IV); NBu_2 (V); NPh_2 (VI);

 (VII);  (VIII)

The bromoacetic amides were synthesized by the condensation of bromoacetyl chloride with secondary amines

$$BrCH_2COCl + HNR_2' \rightarrow BrCH_2CONR_2'$$

NR_2' = NMe_2 (IX); NEt_2(X); NBu_2 (XI); NPh_2 (XII);

 (XIII);  (XIV)

The structure of amides (IX)-(XIV) was confirmed by the IR and NMR spectra, in which are present all of the bands that characterize the structure of these compounds, and also by their purity, as indicated by the presence of one spot during TLC in various systems of eluants.

The condensation of (II) with amides (IX)-(XIV) proceeds easily when equimolar amounts of the reactants are heated for 40-120 min at 110-120°C. Besides (III)-(VIII), which during TLC give spots with a high R_f value, the condensation products always contain another series of compounds, which remain at the start during TLC.

The question of the structure of (III)-(VIII) was solved by analyzing the NMR spectra. In the NMR spectra of N-methyltryptamine (II) are present two singlets in a 1:1 ratio. The singlet at δ 11.38 ppm (in D-pyridine, relative to HMDS) corresponds to the hydrogen attached to the nitrogen in the indole ring, while

Institute of Chemical Kinetics and Combustion, Siberian Branch of the Academy of Sciences of the USSR. Translated from Izvestiya Akademii Nauk SSSR, Seriya Khimicheskaya, No. 11, pp. 2613-2614, November, 1972. Original article submitted January 7, 1972.

TABLE 1

Amide No.	Time, h	Yield, %	Empirical formula	N, %		R_f	
				found	calc.	acetone	ether
III	1,5	20	$C_{15}H_{21}ON_3$	16,21	15,88	0,65	0,09
IV	2	35,4	$C_{17}H_{25}ON_3$	14,62	14,80	0,86	0,10
V	2,5	21,6	$C_{21}H_{33}ON_3$	12,32	12,23	0,90	0,08
VI *	1	40,0	$C_{25}H_{26}ON_3Br$	9,05	8,96	0,92	0,05
VII	0,5	29,2	$C_{18}H_{25}ON_3$	14,03	13,76	0,89	0,06

* Hydrobromide of (VI), mp 232-233°.

the singlet at δ 5.81 ppm corresponds to the hydrogen on the nitrogen in the side chain. This assignment was confirmed by the respective presence of singlets at δ 11.44 and 11.56 ppm in the spectra of β-(3-indolyl)ethanol and β-(3-indolyl)ethyl bromide (in D-pyridine). The position of the singlets depends on the solvent: in CCl_4 they are shifted upfield, while in D-pyridine and D-acetone, due to the formation of a hydrogen bond and the deshielding that is associated with this, they are shifted downfield. A singlet also appears downfield in the spectra of the condensation products, while the singlet, corresponding to the N–H of the side chain, is absent. This proves that the nitrogen in the side chain of N-methyltryptamine takes part in the reaction with the bromoacetic acid amides.

Methods for the synthesis of the other models, analogous to (III)-(VIII), but with a variation in the distance between the amino and amide groupings in the side chain, are being developed at the present time.

EXPERIMENTAL METHOD

Synthesis of Monobromoacetic Acid Morpholide (XVI). A solution of 15.7 g of monobromoacetyl chloride in 50 ml of dichloroethane was added at <–20° to 17.4 g of morpholine in 100 ml of dichloroethane. The mixture was stirred at –20° for 30 min, the morpholine hydrochloride was filtered rapidly, and the precipitate was washed with chilled dichloroethane, evaporated, and fractionally distilled in vacuo. The yield of amide (XIV) was 40%, bp 108° (0.5 mm), n_D^{20} 1.5342. On Al_2O_3 (II activity), R_f = 0.84 in ether, 0.26 in benzene, and 0.97 in acetone.

In a similar manner, from 7.8 g of the acid chloride and 16.9 g of diphenylamine was obtained amide (XII) in 65% yield, mp 115-116°, R_f = 0.78 in ether, 0.93 in acetone, and 0.20 in benzene.

The constants of amides (IX)-(XI) and (XIII) coincide with those of the compounds described in [1, 2].

Synthesis of N-methyl-N[β-(β-indolyl)ethyl]glycine Morpholide (VIII). A mixture of 2 g of N-methyltryptamine (II) and 2.39 g of amide (XIV) was heated at 110-120° for 2 h, and the product was dissolved in 10 ml of hot water, made weakly acid with HCl, washed with ether, the aqueous layer was made alkaline, and the product was extracted with ether. The extract after drying over K_2CO_3 was chromatographed on an Al_2O_3 column. Acetone was used to elute the reaction product (VIII), which was obtained as a glassy substance in 52% yield. Found: N 13.79%. $C_{17}H_{33}O_2N_3$. Calculated: N 13.91%. R_f = 0.84 in acetone, and 0.04 in ether.

Compounds (III)-(VII) were obtained in a similar manner. The data are given in Table 1.

CONCLUSIONS

A number of N-methyl-N[β-(β-indolyl)ethyl]glycine amides, representing analogs of lysergic acid diethylamide, were obtained.

LITERATURE CITED

1. E. W. Weaver and W. H. Whaley, J. Am. Chem. Soc., 69, 515 (1947).
2. I. Parrot, I. Hervieu, Y. Ursy, and M. Paty, Bull. Soc. Chim. France, 1063 (1964).