SYNTHESIS AND STUDY OF THE BIOLOGICAL ACTIVITY OF AMINOALKYL DERIVATIVES IN THE CARBAZOLE SERIES

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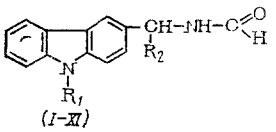
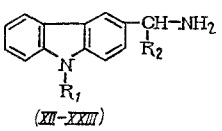
Many derivatives of carbazole and tetrahydrocarbazole are pharmacologically active with respect to the central nervous system [1-4]. Moreover, there is evidence that some of them have antivirus action [5, 6].

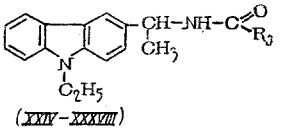
We have previously synthesized some 9-alkyl-3-[1-(formylamino)ethyl]carbazoles [7]; in the pharmacological testing of these compounds with respect to a number of indices which characterize the effect on the central nervous system, it was established that they had definite activity. It was of interest to study other compounds of this series. In this connection we have synthesized some series of formylaminoalkylcarbazoles (I-XI), aminoalkylcarbazoles (XII-XXIII), and acylaminocarbazoles (XXIV-XXXVIII) and have studied their biological activities.



(I-XI)



(XII-XXIII)



(XXIV-XXXVIII)

As the starting materials we used 9-alkyl-3-acylcarbazoles which had been synthesized by alkylation of carbazole with subsequent Friedel–Crafts acylation of the 9-alkyl derivatives obtained by known methods [8], except the starting 9-methylcarbazolealdehyde, which was prepared by the Vielsmeier process by treatment of 9-methylcarbazole with dimethylformamide and phosphorus oxychloride [9], and the starting 3-acetylcarbayole, which was prepared by the Fries–Rosenmund method [10].

The synthesis of I-XI (Table 1) was effected by the reaction of 9-alkyl-3-acylcarbazole derivatives with derivatives of formic acid, for example, with formamide or ammonium formate by the Leuckart reaction [11, 12]. Thereupon it was established that the greatest yield of formylamino derivative was achieved when formamide prepared from ammonium carbonate and formic acid was used, or a reagent containing small added amounts of formic acid.

Compounds XII-XXIII were obtained in 90-95% by hydrolysis of the formylamino derivatives with an aqueous alcoholic alkali solution (Table 2). It should be noted that acid hydrolysis of the Leuckart reaction products leads to their resinification. The amines were tested in the form of their hydrochlorides, which are readily soluble in water.

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TABLE 1. Formylaminoalkyl Derivatives of Carbazole

Compound	R_1	R_2	Yield, %	mp, deg	N found, %	Empirical formula	N calc., %
I	CH_3	H	60	163—64	11,55	$C_{15}H_{14}N_2O$	11,76
II	CH_3	CH_3	77	132—33	10,97	$C_{16}H_{16}N_2O$	11,11
III	C_2H_5	CH_3	75	114—15	10,34	$C_{17}H_{18}N_2O$	10,53
IV	n-C_3H_7	CH_3	70	115—16	9,88	$C_{18}H_{20}N_2O$	10,00
V	iso-C_3H_7	CH_3	40	109—10	9,84	$C_{18}H_{20}N_2O$	10,00
VI	C_4H_7	CH_3	70	112—13	9,36	$C_{19}H_{22}N_2O$	9,52
VII	iso-C_5H_{11}	CH_3	60	72—73	8,91	$C_{20}H_{24}N_2O$	9,09
VIII	$CH_2C_6H_5$	CH_3	60	160—61	8,37	$C_{22}H_{20}N_2O$	8,53
IX	C_2H_5	C_2H_5	60	118—19	9,85	$C_{18}H_{20}N_2O$	10,00
X	C_2H_5	C_3H_7	60	91—92	9,33	$C_{19}H_{22}N_2O$	9,52
XI	C_2H_5	C_6H_5	70	226—27	8,51	$C_{22}H_{20}N_2O$	8,53

Note. Compound VII was recrystallized from diethyl ether; XI, from acetone.

TABLE 2. Aminoalkyl Carbazole Derivatives and Their Hydrochlorides

Compound	R_1	R_2	Bases		Hydrochlorides			
			mp, deg	bp,[1] deg	mp,[2] deg	N found, %	empirical formula[3]	N calc., %
XII	H	CH_3	—	—	211	11,31	$C_{14}H_{14}N_2 \cdot HCl$	11,34
XIII	CH_3	CH_3	70—71	210—13	200	10,65	$C_{15}H_{16}N_2 \cdot HCl$	10,74
XIV	C_2H_5	CH_3	35—36	185—90	140	10,00	$C_{16}H_{18}N_2 \cdot HCl$	10,20
XV	n-C_3H_7	CH_3	Oil	222—25	175	9,70	$C_{17}H_{20}N_2 \cdot HCl$	9,74
XVI	*изо*-C_3H_7	CH_3	Oil	205—10	165	9,62	$C_{17}H_{20}N_2HCl$	9,74
XVII	C_4H_9	CH_3	Oil	205—10	165	9,20	$C_{18}H_{22}N_2 \cdot HCl$	9,25
XVIII	n-C_6H_{11}	CH_3	Oil	226—28	143	8,75	$C_{19}H_{24}N_2HCl$	8,84
XX	iso-C_5H_{11}	CH_3	Oil	205—10	161	8,79	$C_{19}H_{24}N_2 \cdot HCl$	8,84
XX	$C_6H_5CH_2$	CH_3	67—68	220—25	—	9,25	$C_{21}H_{20}N_2$	9,33
XXI	C_2H_5	C_2H_5	Oil	220—25	175	9,63	$C_{17}H_{20}N_2 \cdot HCl$	9,25
XXII	C_2H_5	C_3H_7	Oil	225—27	173	9,15	$C_{18}H_{22}N_2 \cdot HCl$	9,25
XXIII	C_2H_5	C_6H_5	95—96	—	—	9,27	$C_{21}H_{20}N_2$	9,33

[1] At a presence of 4-5 mm.

[2] Melts with decomposition

[3] Compounds XX and XXIII were characterized in the form of the amines; their hydrochlorides were not prepared.

With the objective of studying the effect of the character of the acyl radical in the amino group on biological activity, we prepared a series of acylamino derivatives (Table 3) based on 9-ethyl-3-[1-(amino) ethyl]carbazole (XIV) and carboxylic acid halides.

Thin-layer chromatography was used to check the purity of the starting materials and compounds prepared.

In the IR spectra of compounds I-XI and XXIV-XXXVIII, two amide absorption groups each are observed: the first of these lies in the range 1625-1640 cm^{-1}; absorption in the 1529-1537 cm^{-1} region is typical of the second amide band.

For compounds XII-XXIII, two bands in the range 3483-3405 cm^{-1} are observed in the NH bond stretching region; the ratio of the wave numbers of these two absorption bands agrees well with the empirical equation [13]

$$\nu_s NH = 345.8 + 0.876\nu_{as}$$

Investigation of pharmacological activity was carried out on mice (18-20 g) and rats by a number of tests which are used to evaluate central neurotropic action. All the tested compounds were injected intraperitoneally.

It was established that I-XI are compounds of low toxicity. In the experiments on mice, the LD_{50} (daily) for compounds I, II, and IV-XI was approximately 1000 mg/kg; for compound III, 700 mg/kg. In doses amounting to $^1/_5$ or $^1/_{10}$ of the LD_{50}, the indicated carbazole derivatives caused a reduction in rectal temperature and breakdown in motor coordination (rotating rod test [14]), and increased the duration of

TABLE 3. 9-Ethyl-3-[1-(acylamino)ethyl]carbazoles

Compound	R_3	Yield, %	mp, deg	N found, %	Empirical formula	N calc., %
XXIV	CH_3	64	102—03	9,98	$C_{18}H_{20}N_2O$	10,00
XXV	C_2H_5	82	122—23	9,45	$C_{19}H_{22}N_2O$	9,52
XXVI	C_3H_7	73	117—19	9,02	$C_{20}H_{24}N_2O$	9,09
XXVII	C_6H_5	80	127—28	8,28	$C_{23}H_{22}N_2O$	8,18
XXVIII	o-BrC_6H_4	65	128—29	6,67 -	$C_{23}H_{21}BrN_2O$	6,65
XXIX	m-BrC_6H_4	61	138—39	6,55	$C_{23}H_{21}BrN_2O$	6,65
XXX	p-BrC_6H_4	85	188—89	6,59	$C_{23}H_{21}BrN_2O$	6,65
XXXI	o-ClC_6H_4	61,4	118—19	7,48	$C_{23}H_{21}ClN_2O$	7,43
XXXII	m-ClC_6H_4	80	124—25	7,31	$C_{23}H_{21}ClN_2O$	7,43
XXXIII	o-$NO_2C_6H_4$	83	164—65	10,78	$C_{23}H_{21}N_3O_3$	10,87
XXXIV	p-$NO_2C_6H_4$	83	167—68	10,80	$C_{23}H_{21}N_3O_3$	10,87
XXXV	m-$NO_2C_6H_4$	80	164—65	10,86	$C_{23}H_{21}N_3O_3$	10,87
XXXVI	3,4,5-$(CH_3O)_3C_6H_2$	80	210—11	6,58	$C_{26}H_{28}N_2O_4$	6,64
XXXVII	m-$NH_2C_6H_4$	63	155—56	11,71	$C_{23}H_{23}N_3O$	11,79
XXXVIII	C_6H_4CH-CH	83	174—75	7,70	$C_{25}H_{24}N_2O$	7,61

TABLE 4. Neurotropic Activity of Formylaminoalkyl Derivatives of Carbazole

Compound	Dose for mice, mg/kg	Change in rectal temp. (deviation from original), deg	No. of animals with destroyed motor coordination (%)	Effect on duration of chloral hydrate-induced sleep (deviation from control) (%)	Effect on convulsive dose of corazole (deviation from threshold dose in %)	Ability to cause catalepsy in rats (ED_{50} in mg/kg)
I	200	—3,1	17	0	0	300
II	100	—6,0	100	+130	+30	58 (32—104)
	200	—6,8	100	+400		
III	70	—2,6	90	0	+30	135 (87—211)
	140	—6,2	100	+70		
IV	100	—3,4	90	0	+30	84 (49—144)
	200	—6,5	100	+100		
VI	100	—5,2	100	+113	+30	175 (95—320)
	200	—6,5	100	+170		
VII	100	—6,1	100	+300	+70	153 (76,5—306)
	200	—6,8	100			
VIII	100	—3,6	90	+100	0	0
	200			+260		
IX	200	—2,1	34	0	0	200
X	200	—1,0	0	0	0	230 (109—483)
XI	200	—2,7	34	0	0	0

sleep caused by chloral hydrate (300 mg/kg intraperitoneally) and the threshold of corazole convulsive action. Part of the compounds in this series caused a state of catalepsy in rats (Table 4). The formylaminoalkyl derivatives of carbazole did not exert an effect on the central effects of 5-hydroxytryptophane (head shaking test [15]).

None of the other carbazole derivatives (XII-XXXVIII) has a clear neurotropic activity.

Antibacterial activity of the compounds was evaluated from the value of the minimum bacteriostatic concentration (MBsC) as obtained by the method of successive twofold dilutions in a liquid growth medium. As the test organisms we used staphylococci, streptococci, pneumococci, E. coli, Pseudomonas pyocyanea, proteus, anthrax spores, the dysentery bacillus, typhoid bacillus, and also two strains of tuberculosis mycobacterium of the human type: $H_{37}Rv$ and Academia.

Among the aminoalkyl derivatives of carbazole, substances were discovered which possessed activity with respect to certain gram-positive and gram-negative microorganisms. Thus, the MBsC of compounds XV, XVII, XVIII, and XIX with respect to staphylococcus and streptococcus is in the range 1.5-25 μg/ml; with respect to Flexner dysentery bacillus (except XIX), 17-50 μg/ml; and with respect to the typhoid bacillus (except XV), 25-42 μg/ml.

Compounds XIII, XV, XVII, XVIII, XIX, XXI, and XXII possess high antitubercular activity: the MBsC with respect to the H_{37} Rv strain is 4-16 μg/ml; with respect to the Academia strain, 8-62 μg/ml, regardless of the presence of serum in the growth medium.

Among the acyl derivatives of carbazole studied, no substances were observed with definite activity with respect to gram-positive or gram-negative bacteria: the MBsC in almost all cases was 200 μg/ml or more. Compounds XXV, XXVI, and XXVIII had a high antituberculosis activity; their MBsC was 8-40 μg/ml.

EXPERIMENTAL

The IR spectra were taken in an IKS-22 instrument, using tablets with potassium bromide.

9-Methyl-3-[1-(formylamino)ethyl]carbazole (II). A mixture of 12 g of ammonium carbonate and 13.6 g of 85% formic acid was gradually heated to 165°. Then 10 g of 9-methyl-3-acetylcarbazole was added and heating was continued at 175-180°. At the end of the reaction, after 45-50 min, the reaction mixture was cooled, and the solid was washed with water, dried, and purified by a double recrystallization from benzene. A yield of 3.7 g (77%) was obtained, mp 132-133°. The other derivatives in this series were prepared similarly, and are shown in Table 1.

9-Methyl-3-[1-(amino)ethyl]carbazole (XIII). To a solution of 10 g of II in 20 ml of ethanol was added 20 ml of an aqueous-alcoholic solution (1 : 1) containing 2.1 g of potassium hydroxide, and the mixture obtained was boiled under reflux for 2 h. After this, the alcohol was distilled off, the organic layer was extracted with ether, the ether was distilled off, and the residue was subjected to vacuum distillation. At 210-213° (4-5 mm) there was obtained 8 g (92%) of XIII in the form of a colorless oil which crystallized on standing. The amine hydrochloride was obtained by passing dry hydrogen chloride through an ether solution of the amine; it was purified by reprecipitation from alcohol with ether. The amines shown in Table 2 were prepared similarly.

9-Ethyl-3-[1-(benzoylamino)ethyl]carbazole (XXVII). Into a solution of 4.76 g of XIV in 30 ml of benzene was introduced 1.65 g of a 50% aqueous potassium carbonate solution and, while stirring at 18-20°, 2.81 g of benzoyl chloride in 10 ml of benzene was added dropwise. After 20-25 min the reaction mixture was diluted with 50 ml of water, the organic layer was separated, and the product was washed with water to a neutral reaction; the solid was filtered off, dried, and purified by crystallization from benzene. The yield was 5.47 g (80%), mp 127-128°. The remaining compounds shown in Table 3 were prepared similarly, except compound XXXVII, which was prepared by the method described below.

9-Ethyl-3-[1-(m-aminobenzoylamino)ethyl] carbazole (XXXVII). To a mixture of 2 g of XXXV, 28 ml of alcohol, 7 ml of benzene, and 6 ml of concentrated hydrochloric acid, were added with vigorous stirring zinc dust in the amount of 1.64 g. After 30 min the mixture was filtered from the unreacted zinc and the filtrate was diluted with water; after basification it was extracted with ether. The solvent was distilled off, and the product was crystallized from alcohol. The yield was 1.16 g (70%), mp 155-156°.

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