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N-Alkylaminocarbazoles as Potential Anticonvulsant and Diuretic Agents†

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Carbazoles, in view of incorporating an indole nucleus in their structure and their close structural resemblance to phenothiazine, have been attracting increasing attention as pharmacodynamic agents.[1-5]

The present communication describes the synthesis and biological evaluation of *N*-alkylaminocarbazoles, tetrahydrocarbazoles, and those in which one of the phenyl rings has been enlarged to a seven-membered ring system.

Chemistry. The desired intermediate biphenyls were readily obtained by condensing the appropriate 2-bromonitrobenzene with the corresponding iodobenzene under Ullmann's conditions[6] and the products were purified by silica gel column chromatography.

The biphenyls were cyclized by refluxing with triethyl phosphite[7] to give the desired carbazoles. In cases where more than one product was expected, column chromatography in conjunction with tlc and nmr techniques was employed for isolation and characterization of the different isomers.

The synthesis of halogen-substituted tetrahydrocarbazoles and 6,7,8,9-10*H*-cyclohept[*b*]indoles was carried out by a Japp-Klingemann reaction on hydroxymethylcyclohexanone or -heptanone with aryldiazonium chloride followed by cyclization and Huang-Minlon reduction. The tetrahydrocarbazoles in turn were aromatized to carbazoles with chloranil. The corresponding N-alkylated compounds were obtained by reaction with the appropriate *tert*-aminoalkyl halides in the presence of NaH.

Biological Activity. CNS Activity. Acute toxicity, gross observational effects, and ability of the compounds to modify electroshock (SMES, 48 mA × 0.2 sec), pentylenetetrazole (80 mg/kg sc), and strychnine (1.5 mg/kg ip) induced seizures[8] were studied in male mice at the 0.2 ALD_{50} dose level. The end point employed in the SMES test was the abolition specifically of the hind limb tonic-extensor component of maximal seizure, while for the pentylene-

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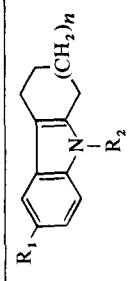
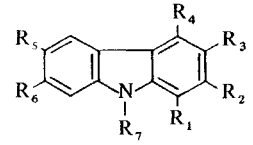
Table I



Compd no.	n	R_1	R_2	Mp, °C	Formula[a]	ALD_{50},[f] mg/kg ip	Gross effects at 0.2 ALD_{50}	SMES test, % protection at: 0.2 ALD_{50}, mg/kg ip	SMES test, % protection at: 0.1 ALD_{50}, mg/kg ip	Diuretic activity,[b] % urinary output at 0.25 ALD_{50}	Remarks
1	1	F	$(CH_2)_2N(CH_3)_2$	205	$C_{16}H_{21}FN_2 \cdot C_2H_2O_4$	100	↓[c]	0[e]		86	Depressant, diuretic
2	1	F	$(CH_2)_2N(C_2H_5)_2$	154–155	$C_{18}H_{25}FN_2 \cdot C_2H_2O_4$	300	0	0		81	Diuretic
3	1	F	$(CH_2)_2NC_4H_8$	192	$C_{18}H_{23}FN_2 \cdot C_2H_2O_4$	100	0	0		54	Diuretic
4	1	F	$(CH_2)_3N(CH_3)_2$	141–142	$C_{17}H_{23}FN_2 \cdot C_2H_2O_4$	150	0	0		87	Diuretic
5	1	Cl	$(CH_2)_2N(C_2H_5)_2$	140–141	$C_{18}H_{25}ClN_2 \cdot C_2H_2O_4$	100	0	0		52	Diuretic
6	1	Cl	$(CH_2)_2NC_4H_8$	170–171	$C_{18}H_{23}ClN_2 \cdot C_2H_2O_4$	100	0	0		16	
7	1	Cl	$(CH_2)_3N(CH_3)_2$	191–192	$C_{17}H_{25}ClN_2 \cdot C_2H_2O_4$	300	0	100	20	66	Anticonvulsant, diuretic
8	2	Cl	$(CH_2)_2N(CH_3)_2$	136	$C_{17}H_{25}ClN_2 \cdot C_2H_2O_4$	150	↓	0		–[d]	Depressant
9	2	Cl	$(CH_2)_2NC_4H_8$	220	$C_{19}H_{25}ClN_2 \cdot C_2H_2O_4$	100	↓	0		–	Depressant
10	2	CH_3O	$(CH_2)_2N(C_2H_5)_2$	126	$C_{20}H_{30}N_2O \cdot C_2H_2O_4$	200	0	0		–	
11	2	CH_3O	$(CH_2)_2NC_4H_8$	205	$C_{20}H_{28}N_2O \cdot C_2H_2O_4$	300	↓	0		–	Depressant

[a] All compounds were analyzed for C, H, and N except compounds **1–4** which were analyzed for N only. [b] Urinary output of chlorothiazide treated rats taken as 100. [c] ↓, CNS depressant. [d] –, not tested. [e] 0, no effect. [f] ALD_{50} = approximate LD_{50}.

Table II



Compd no.	R_1	R_2	R_3	R_4	R_5	R_6	R_7	Mp, °C	Formula[a]	ALD_{50},[f] mg/kg ip	Gross effects at 0.2 ALD_{50}	SMES test, % protection at 0.2 ALD_{50}, mg/kg ip	SMES test, % protection at 0.1 ALD_{50}, mg/kg ip	Diuretic activity,[b] % urinary output at 0.25 ALD_{50}	Remarks
12	H	H	F	H	H	H	$(CH_2)_2NC_4H_8$	190	$C_{18}H_{19}FN_2 \cdot C_2H_2O_4$	200	↓[c]	80	20	61	Anticonvulsant, depressant, diuretic
13	H	Cl	H	H	H	H	$(CH_2)_2N(CH_3)_2$	250	$C_{16}H_{17}ClN_2 \cdot HCl$	250	0[e]	100	80	–[d]	Anticonvulsant
14	H	Cl	H	H	H	H	$(CH_2)_2NC_4H_8$	237	$C_{18}H_{19}ClN_2 \cdot HCl$	300	↓	60	0	88	Anticonvulsant, depressant, diuretic
15	H	Cl	H	H	H	H	$(CH_2)_3N(CH_3)_2$	169	$C_{17}H_{19}ClN_2 \cdot C_2H_2O_4$	100	0	0		28	
16	H	H	Cl	H	H	H	$(CH_2)_2N(CH_3)_2$	182–183	$C_{16}H_{17}ClN_2 \cdot C_2H_2O_4$	300	0	100	0	36	Anticonvulsant
17	H	H	Cl	H	H	H	$(CH_2)_2NC_4H_8$	208	$C_{18}H_{19}ClN_2 \cdot C_2H_2O_4$	100	↓	0		130	Depressant, diuretic
18	H	H	Cl	H	H	H	$(CH_2)_3N(CH_3)_2$	160–161	$C_{17}H_{19}ClN_2 \cdot C_2H_2O_4$	200	↓	60	20	52	Anticonvulsant, depressant, diuretic
19	CH_3O	H	H	H	H	H	$(CH_2)_2N(CH_3)_2$	218–219	$C_{17}H_{20}N_2O \cdot C_2H_2O_4$	200	0	80	0	35	Anticonvulsant
20	CH_3O	H	H	H	H	H	$(CH_2)_2NC_4H_8$	217	$C_{19}H_{22}N_2O \cdot C_2H_2O_4$	300	↓	100	0	102	Anticonvulsant, depressant, diuretic
21	CH_3O	H	H	H	H	H	$(CH_2)_3N(CH_3)_2$	194	$C_{18}H_{22}N_2O \cdot C_2H_2O_4$	150	↓	0		–	Depressant
22	H	CH_3O	H	H	H	H	$(CH_2)_2N(CH_3)_2$	249	$C_{17}H_{20}N_2O \cdot HCl$	150	↓	100	0	178	Anticonvulsant, depressant, diuretic
23	H	CH_3O	H	H	H	H	$(CH_2)_2N(C_2H_5)_2$	192	$C_{19}H_{24}N_2O \cdot C_2H_2O_4$	200	0	0		–	
24	H	CH_3O	H	H	H	H	$(CH_2)_2NC_4H_8$	234	$C_{19}H_{22}N_2O \cdot HCl$	150	0	100	0	204	Anticonvulsant, diuretic
25	H	CH_3O	H	H	H	H	$(CH_2)_3N(CH_3)_2$	178	$C_{18}H_{22}N_2O \cdot C_2H_2O_4$	300	0	100	100	121	Anticonvulsant, diuretic
26	H	H	CH_3O	H	H	H	$(CH_2)_2N(CH_3)_2$	221	$C_{17}H_{20}N_2O \cdot HCl$	400	↓	0		–	Depressant
27	H	H	CH_3O	H	H	H	$(CH_2)_2N(C_2H_5)_2$	155	$C_{19}H_{24}N_2O \cdot C_2H_2O_4$	150	0	0		–	
28	H	H	CH_3O	H	H	H	$(CH_2)_2NC_4H_8$	165–166	$C_{19}H_{22}N_2O \cdot C_2H_2O_4$	150	0	0		–	
29	H	H	CH_3O	H	H	H	$(CH_2)_3N(CH_3)_2$	156	$C_{18}H_{22}N_2O \cdot C_2H_2O_4$	400	0	80	0	18	Anticonvulsant
30	H	H	H	CH_3O	H	H	$(CH_2)_3N(CH_3)_2$	152	$C_{18}H_{22}N_2O \cdot C_2H_2O_4$	300	↓	80	0	36	Anticonvulsant, depressant
31	H	Cl	H	H	H	CH_3O	$(CH_2)_2N(CH_3)_2$	256–257	$C_{17}H_{19}ClN_2O \cdot HCl$	250	↓	100	50	35	Anticonvulsant, depressant
32	H	Cl	H	H	H	CH_3O	$(CH_2)_2N(C_2H_5)_2$	175	$C_{19}H_{23}ClN_2O \cdot C_2H_2O_4$	250	↓	80	20	14	Anticonvulsant, depressant
33	H	Cl	H	H	H	CH_3O	$(CH_2)_2NC_4H_8$	224	$C_{19}H_{21}ClN_2O \cdot HCl$	250	↓	100	60	23	Anticonvulsant, depressant
34	H	Cl	H	H	H	CH_3O	$(CH_2)_3N(CH_3)_2$	181	$C_{18}H_{21}ClN_2O \cdot C_2H_2O_4$	250	↓	80	20	33	Anticonvulsant, depressant
35	CH_3	CH_3O	H	H	H	H	$(CH_2)_2N(CH_3)_2$	245	$C_{18}H_{22}N_2O \cdot HCl$	200	↓	0		–	Depressant
36	CH_3	CH_3O	H	H	H	CH_3O	$(CH_2)_2N(CH_3)_2$	240	$C_{19}H_{24}N_2O_2 \cdot HCl$	>800	↓	0		–	Depressant
37	CH_3	CH_3O	H	H	H	CH_3O	$(CH_2)_2N(C_2H_5)_2$	223	$C_{21}H_{28}N_2O_2 \cdot HCl$	200	↓	0		–	Depressant
38	CH_3	CH_3O	H	H	H	CH_3O	$(CH_2)_2NC_4H_8$	172	$C_{21}H_{26}N_2O_2 \cdot HCl$	300	↓	0		–	Depressant
39	CH_3	CH_3O	H	H	CH_3O	CH_3O	$(CH_2)_2N(CH_3)_2$	120	$C_{20}H_{26}N_2O_3 \cdot HCl$	300	↓	0		–	Depressant

[a] All compounds were analyzed for C, H, and N except compound **12** which was analyzed for N only. [b] Urinary output of chlorothiazide treated rats taken as 100. [c] ↓, CNS depressant. [d] –, not tested. [e] 0, no effect. [f] ALD_{50} = approximate LD_{50}.

Table III. Comparative Data of Acute Toxicity and Anticonvulsant Activity of 25 and 33

Compd	LD_{50}, mg/kg ip (95% fiducial limits)[a]	ED_{50}, mg/kg ip (95% fiducial limits)
25	263 (205–323)	23.5 (20.9–26.2)
33	263.1 (190–427)	20.3 (10–27)
Dillantin	150	7.1

[a] D. J. Finney, "Probit Analysis," Cambridge University Press, New York, N. Y., 1952.

tetrazole test inhibition of the clonic convulsions was the end point.

Compounds showing depressant effect on the central nervous system were also studied for their effect on the forced locomotor activity in mice using the method of Kinnard and Carr.[9] Compounds having no gross effect on the central nervous system at 0.2 ALD_{50} were studied for their monoamine oxidase (MAO) inhibitor activity using the method of Brodie, *et al.*[10]

Out of 39 compounds tested, 16 compounds afforded protection against maximal electroshock seizures in mice. Their anticonvulsant activities at 0.2 and 0.1 ALD_{50} are given in Tables I and II. The maximum protection was observed in compounds **25** and **33**. Other doses of these compounds were, therefore, tested to establish a dose-response relationship to find out the ED_{50}. Both these compounds were, however, less active than dillantin which was used as a reference standard (Table III).

None of the compounds studied showed protection against pentylenetetrazole- or strychnine-induced convulsions. They were also devoid of MAO inhibitor activity and of any effect on forced locomotor activity.

Diuretic Activity. Diuretic activity of the compounds was tested in groups of five rats each, loaded orally with normal saline equal to 5% of their body weight. All compounds were administered orally and were tested at 0.25 ALD_{50}. Chlorothiazide (125 mg/kg oral) was used as a reference standard. The urinary output was measured after 4 hr and the results were expressed as percentage urinary output taking chlorothiazide activity as 100%. The maximum diuresis was obtained with compounds **17**, **22**, **24**, and **25** (Table II).

Results and Discussion

The results listed in Tables I and II show that *N*-alkylaminocarbazoles possess significant anticonvulsant and diuretic activity. From the limited data available it would appear that the corresponding tetrahydrocarbazoles **(1–7)** and cycloheptindoles **(8–11)** are less active.

Introduction of the dimethylaminopropyl chain at the N atom seems to enhance the anticonvulsant activity in combination with CH_3O at positions 2, 3, and 4 **(25, 29,** and **30)**. Shortening of the chain by one carbon atom or incorporating a cyclic moiety (pyrrolidinoethyl), however, results in the retention of the activity when CH_3O is at positions 1 and 2 only **(19, 20, 22,** and **24)**. Compounds with 2- and 3-carbon atom chain and Cl at positions 2 or 3 are also active **(13, 16,** and **18)**. Substitution with both Cl and CH_3O at positions 2 and 7 demonstrates a good order of activity **(31–34)** while the CH_3 at position 1 reduces the activity **(35–39)**.

Experimental Section

All melting points are uncorrected. The compounds were routinely checked by ir and nmr spectroscopy.

4-Chloro-4′-methoxy-2′-nitrobiphenyl (40). An intimate mixture of 4-chloroiodobenzene (47.7 g, 0.2 mol), 4-methoxy-2-nitrobromobenzene (46.4 g, 0.2 mol), and copper bronze (100 g) was heated at 200–230° for 4 hr, followed by extraction of the cooled reaction mixture with hot EtOAc. The residue, after removal of the solvent, was chromatographed over a silica gel column (1 kg), which on elution with 10% C_6H_6 in hexane furnished the product: mp 79°; yield 57%. *Anal.* ($C_{13}H_{10}ClNO_3$) C, H, N.

2-Chloro-7-methoxycarbazole (41). 4-Chloro-4′-methoxy-2′-nitrobiphenyl (30 g) was heated with triethyl phosphite (60 ml) at 160° for 9 hr, followed by removal of the solvent under vacuum. The residue was crystallized from C_6H_6–EtOAc: mp 258°; yield 80%. *Anal.* ($C_{13}H_{10}ClNO$) C, H, N.

Cyclohexane-1,2-dione 1-(4-Fluoro)phenylhydrazone (42). 4-Fluorobenzenediazonium chloride (prepared from 4-fluoroaniline, 33.3 g, 0.3 mol) in water was added during 25 min with vigorous stirring to a cooled solution of 2-formylcyclohexanone (37.8 g, 0.3 mol) in MeOH containing NaOAc (55 g) when a compound separated out. After additional stirring for 1 hr, it was diluted with water and the precipitated product was collected by filtration and recrystallized from EtOAc: mp 147–148°; yield 75%. *Anal.* ($C_{12}H_{13}FN_2O$) C, H, N.

1-Oxo-1,2,3,4-tetrahydro-6-fluorocarbazole (43). To the foregoing hydrazone (30.8 g, 0.14 mol) dissolved in warm glacial HOAc (300 ml) was carefully added concentrated HCl (55 ml) and the mixture heated for 10 min at 120°. After cooling it was diluted with H_2O and the precipitate collected and crystallized from C_6H_6: mp 205°; yield 48%. *Anal.* ($C_{12}H_{10}FNO$) C, H, N.

6-Fluoro-1,2,3,4-tetrahydrocarbazole (44). A mixture of **43** (13.2 g, 0.06 mol), hydrazine hydrate (90%, 10 ml), and KOH pellets (13.3 g) was warmed in diethylene glycol (100 ml) on a water bath until most of the KOH dissolved. The mixture was refluxed for 1 hr and distilled until the temperature of the reaction mixture rose to 175°. It was again refluxed for 3 hr, cooled, and poured on cold dilute HCl. The precipitated material was filtered, washed well with water, dried, and crystallized from petroleum ether: mp 102–103°; yield 65% (lit.[11] mp 103–104°).

3-Fluorocarbazole (45). A mixture of **44** (4.72 g, 0.025 mol) and chloranil (6.15 g, 0.025 mol) in dry xylene (30 ml) was refluxed for 1 hr. The solvent was removed and the residue after column chromatography over silica gel (80 g, solvent 20% C_6H_6 in hexane) gave the product which crystallized from C_6H_6–hexane: mp 203°; yield 78% (lit.[11] mp 202–203°).

3-Fluoro-9-(2-pyrrolidinoethyl)carbazole Oxalate (12). A mixture of **45** (1.85 g, 0.01 mol) and NaH (0.48 g, 0.02 mol) was refluxed in dry xylene for 1 hr. After cooling, a solution of 2-pyrrolidinoethyl chloride (2.67 g, 0.02 mol) in dry ether (15 ml) was added and the mixture boiled for additional 4 hr. It was then cooled, diluted cautiously with cold water, and thoroughly extracted with 2 *N* HCl (40 ml). The acid extract was washed with ether, basified (K_2CO_3), and reextracted with ether. The ethereal layer was washed with water and dried ($MgSO_4$), and the solvent was removed. The residue was dissolved in minimum quantity of MeOH and treated with a methanolic solution of oxalic acid. The precipitated oxalate salt was filtered, washed with ether, and crystallized from MeOH: mp 190°; yield 87%.

By adopting a similar procedure, other *N*-alkylaminocarbazoles, tetrahydrocarbazoles, and cycloheptindoles were prepared (Tables I and II).

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