Synthesis and Biological Activity of Some 5-, 6-, and 7-Aminomethyl-2,3-dimethylindoles

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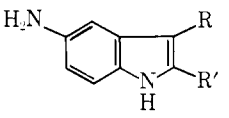
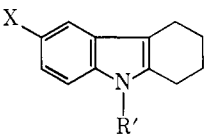
The syntheses of 5-, 6-, and 7-aminomethyl-, dimethylaminomethyl-, and benzylaminomethyl-2,3-dimethylindoles are reported. All the compounds were tested for toxicity to rats, for effect on the rectal temperature of rabbits, and for effect on the behavior of rats in the open field test. One compound (5-aminomethyl-2,3-dimethylindole) showed appreciable activity in the latter test.

Shaw and Woolley[2] demonstrated that 2,3-dialkyl-5-aminoindoles (I) had potent antiserotonin activity in *vitro* but were rapidly destroyed in *vivo*. They suggested that this was probably due to the fact that these compounds, being in effect substituted *p*-phenylenediamines, are liable to attack by cytochrome-containing enzyme systems. The same workers subsequently proposed[3] that the placing of a carbon atom between the amino group and the indole nucleus of the aminoindoles might protect the amino group from enzyme attack. To test this postulate they examined a number of 5-aminomethylindoles and 5-indolecarboxamidines in which the alkyl groups in positions 2 and 3 were, for convenience, incorporated into a ring giving the 6-substituted 1,2,3,4-tetrahydrocarbazoles (II, X = R_2NCH_2 or $RN{=}C(NH_2)$; R′ = H or $PhCH_2$). Shaw and Woolley studied the effect of these carbazoles on both isolated smooth muscle and on whole animals and found that all of the compounds had antiserotonin activity and some also affected the behavior of the experimental animals.



I

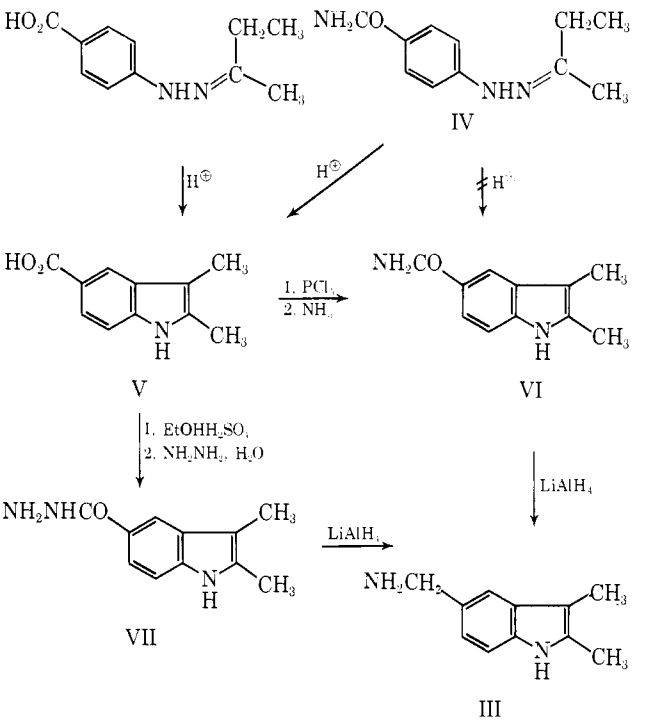


II

The purpose of the present work was to determine the effect on biological activity in whole animals of variation of the position of attachment of the aminomethyl group to the benzene ring of the indole nucleus and of variation of the nature of the substituents on the side-chain nitrogen.

Shaw and Woolley[3] obtained 6-aminomethyl-1,2,3,4-tetrahydrocarbazole (II, R′ = H; X = NH_2CH_2) by the reduction of 1,2,3,4-tetrahydrocarbazole-6-carboxamide which had been prepared by the Fisher indole synthesis from *p*-hydrazinobenzamide and cyclohexanone. When this route was investigated as a means of preparing 5-aminomethyl-2,3-dimethylindole (III), it was found that, under the conditions required for the cyclization of the phenylhydrazone IV, hydrolysis of the amide group occurred, and the product was 2,3-dimethylindole-5-carboxylic acid (V). A low yield of the carboxamide VI was obtained from the acid V, *via* the acid chloride, and reduction of this amide with lithium aluminum hydride gave 5-aminomethyl-2,3-dimethylindole (III). It was more convenient, however, to obtain the carboxylic acid V by Fischer synthesis from *p*-hydrazinobenzoic acid. Conversion of the indole acid V into its ester and reaction of the latter with hydrazine hydrate gave the carboxhydrazide VII. Reduction of this hydrazide with lithium aluminum hydride in refluxing dioxane gave the amine III and not the hydrazine as would have been expected from the work of Kratzland and Berger[4] and Hinman.[5] This unusual reductive cleavage of a hydrazide thus provides a new route to amines from the corresponding carboxylic acids (see Scheme I).

SCHEME I



The 6- and 7-aminomethyl-2,3-dimethylindoles were similarly prepared, starting from *m*- and *o*-hydrazinobenzoic acid, respectively. The condensation of *m*-hydrazinobenzoic acid with ethyl methyl ketone gave a mixture of the 2,3-dimethylindole-6- and -4-carboxylic acids, the latter in low yield.[6]

Shaw and Woolley[3] prepared 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole (II, R′ = H; X =

(1) To whom inquiries should be addressed.

(2) E. Shaw and D. W. Woolley, *J. Pharmacol. Exptl. Therap.*, **108**, 87 (1953).

(3) E. Shaw and D. W. Woolley, *J. Am. Chem. Soc.*, **79**, 3561 (1957).

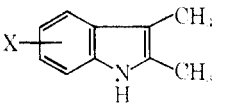
(4) K. Kratzland and K. P. Berger, *Monatsh.*, **89**, 83 (1958).

(5) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 1645 (1956).

(6) U. M. Brown, P. H. Carter, and M. L. Tomlinson, *J. Chem. Soc.*, 1843 (1958).

TABLE I

2,3-DIMETHYLINDOLES



No.	Prepn procedure	X	Mp, °C (lit.)	Yield, %	Crystn solvent	Formula	% calcd C	% calcd H	% calcd N	% found C	% found H	% found N	Testing solvent
VIII	A	7-CONHNH$_2$	266–268 (256–258)[a]	94	EtOH	$C_{11}H_{13}N_3O$	65.00	6.45	20.68	65.19	6.49	20.58	
IX	A	6-CONHNH$_2$	242–243 (232–235)[a]	90	EtOH	$C_{11}H_{13}N_3O$	65.00	6.45	20.68	65.35	7.14	20.30	
VII	A	5-CONHNH$_2$	231–234 (231–234)[a]	80	EtOH	$C_{11}H_{13}N_3O$							
X	A	4-CONHNH$_2$	171.5–173	67	C$_6$H$_6$–MeOH	$C_{11}H_{13}N_3O$	65.00	6.45	20.68	65.03	6.56	20.70	
XI	B	7-CONMe$_2$	162–163	58	Petr ether[b]	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.46	8.03	12.55	
XII	B	6-CONMe$_2$	185–186	50	C$_6$H$_6$	$C_{13}H_{16}N_2O$	72.19	7.46	12.95	72.07	7.29	12.58	
XIII	B	5-CONMe$_2$	113 (112–114)[a]	60	C$_6$H$_6$	$C_{13}H_{16}N_2O$							
XIV	B	7-CONHCH$_2$Ph	147–149	83	Petr ether[b]	$C_{18}H_{18}N_2O$	77.67	6.52	10.07	77.64	6.68	10.39	
XV	B	6-CONHCH$_2$Ph	185–186	73	Petr ether[b]	$C_{18}H_{18}N_2O$	77.67	6.52	10.07	77.48	6.51	10.30	
XVI[c]	B	5-CONHCH$_2$Ph	143–144	85	Petr ether[b]	$C_{18}H_{18}N_2O$							
XVII	C[d]	7-CH$_2$NH$_2$	131–132	92	Cyclohexane	$C_{11}H_{14}N_2$	75.82	8.10	16.08	75.63	8.25	16.18	*a*
XVIII	C	6-CH$_2$NH$_2$	117–118	32	Cyclohexane	$C_{11}H_{14}N_2$	75.82	8.10	16.08	76.00	8.47	16.09	*a*
III	C	5-CH$_2$NH$_2$	153–155 (156–158)[a]	52[e] (42[f])	Cyclohexane	$C_{11}H_{14}N_2$	75.82	8.10	16.08	75.64	8.17	16.38	*a*
XIX	C	7-CH$_2$NMe$_2$	188–189[g]	79	Ethyl acetate	$C_{17}H_{22}N_2O_4$	64.13	6.97	8.80	64.60	7.24	9.07	*g*
XX	C	6-CH$_2$NMe$_2$	132–133	67.5	Ether	$C_{13}H_{18}N_2$	77.18	8.97	13.85	77.41	9.31	14.10	*a*
XXI	C	5-CH$_2$NMe$_2$	95–96 (96–98)[a]	62	Petr ether[h]	$C_{13}H_{18}N_2$							*a*
XXII	C	7-CH$_2$NHCH$_2$Ph	197–198[i]	93	C$_6$H$_6$–cyclohexane	$C_{18}H_{21}ClN_2$	71.87	7.04	9.31	72.53	7.28	9.55	*k*
XXIII	C	6-CH$_2$NHCH$_2$Ph	176.5–177[g]	48	C$_6$H$_6$–MeOH	$C_{22}H_{24}N_2O_4$	69.45	6.36	7.36	69.80	6.37	7.80	*j*
XXIV	C	5-CH$_2$NHCH$_2$Ph	92	52	Petr ether[h]	$C_{18}H_{20}N_2$	81.78	7.63	10.60	82.22	7.99	11.15	*l*

[a] Bp 80–100°. [b] Not possible to obtain analytically pure sample. [c] Refluxed for 21 hr. [d] Propylene glycol. [e] From the carboxhydrazide. [f] From the carboxamide. [g] 50% EtOH. [h] Maleate. [i] Bp 40–60°. [j] Hydrochloride. [k] N-Methylacetamide. [l] 50% N-Methylacetamide

Me_2NCH_2) by diazotizing 1,2,3,4-tetrahydrocarbazole-6-carboxhydrazide to give the azide, treating this with dimethylamine, and reducing the resultant amide. A similar route has been used by Hofmann and co-workers[7] for the preparation of N,N-disubstituted tryptamines. The 5-, 6-, and 7-dimethylaminomethyl- and benzylaminomethyl-2,3-dimethylindoles were prepared from the appropriate hydrazides by this method.

Terzyan and co-workers[8,9] have reported the preparation of a number of similar indoles including two described in the present paper, namely, 5-aminomethyl- and 5-dimethylaminomethyl-2,3-dimethylindole.

Brown and co-workers have mentioned[6] that they were not able to prepare 2,3-dimethylindole-4-carboxhydrazide by the method used for the other three isomers. There are no obvious reasons why this should be so, particularly as the same authors synthesized the 2,3-diphenylindole-4-carboxhydrazide. We have investigated the reaction between ethyl 2,3-dimethylindole-4-carboxylate and hydrazine hydrate and have obtained a product which had the correct elemental analyses for 2,3-dimethylindole-4-carboxhydrazide and which had an infrared spectrum consistent with that expected for this compound.

Pharmacology. Methods. A. Toxicity.—All the test materials (1 ml/kg of a solution of the compound in a suitable solvent) were injected subcutaneously into two male albino rats. The animals were observed for overt changes in behavior, signs of poisoning, or deaths and, in addition, were tested for their ability to climb a pair of inclined rods.[10] The dose used was 50 mg/kg or, where lack of solubility did not allow this to be given, the maximum possible dose.

B. Hall's Open Field Test.[10,11]—All the compounds were tested for effects on rat behavior in this situation. Serially decreasing doses were used until an approximate minimal effective dose was reached.

C. Rabbit Rectal Temperature.—The method used has been previously described[10] and the doses used were 5 and 20 mg/kg. Changes in mean rectal temperature in the group of test animals were considered to be significant when they differed from the control level by more than 0.5°.

Results and Discussion

No compound was lethal or impaired the ability of rats to climb a pair of inclined rods at a dose of 50 mg/kg (33 mg/kg for XIX).

In Hall's open field test XIX and XXIV were inactive at the highest doses used (30 and 50 mg/kg, respectively). The approximate minimal effective doses for the remaining compounds were: III, 1 mg/kg; XVII, 50 mg/kg; XVIII, 45 mg/kg; XX, 10 mg/kg; XXI, 10 mg/kg; XXII, 10 mg/kg; and XXIII, 20 mg/kg.

It is considered that effects seen at doses of 10 mg/kg and above are of no particular behavioral significance. 5-Aminomethyl-2,3-dimethylindole (III) was active at 1 mg/kg but there were no consistent effects on behavior at different dose levels.

(7) A. Hofmann, F. Seeman, and F. Troxler, *Helv. Chim. Acta*, **42**, 2073 (1959).

(8) A. G. Terzyan and G. T. Tatevosyan, *Izv. Akad. Nauk Arm. SSR Khim. Nauk*, **13**, 193 (1960).

(9) A. G. Terzyan, Zh. G. Akopyan, and G. T. Tatevosyan, *ibid.*, **14**, 71 (1961).

(10) R. W. Brimblecombe, *Psychopharmacologia*, **4**, 139 (1963); R. W. Brimblecombe, D. F. Downing, D. M. Green, and R. R. Hunt, *Brit. J. Pharmacol.*, **23**, 43 (1964).

(11) C. S. Hall, *J. Comp. Psychol.*, **18**, 385 (1934).

It has been shown[12] that, within a series of lysergic acid derivatives, there is a marked parallelism between ability to produce a rise in the body temperature of rabbits and psychotomimetic activity in man. There has also been a suggestion[10] that the pyrogenic potency in rabbits of some simple tryptamines may parallel their ability to produce behavioral changes in rats. The nine indoles examined during this investigation only produced rises in rabbit rectal temperature at toxic dose levels. 5-Aminomethyl-2,3-dimethylindole did not affect rectal temperature at any dose level and so it seems improbable that the effect of this compound in the open field test was due to any psychotomimetic activity.

Among such relatively inactive compounds it is impossible to speculate concerning structure–activity relationships.

Experimental Section[13]

Ethyl 2,3-dimethylindole-4-, -5-, -6-, and -7-carboxylates were obtained by esterification of the appropriate indolecarboxylic acid prepared by the method reported by Brown, *et al.*[6]

2,3-Dimethylindole-5-carboxamide (VI).—A mixture of 2,3-dimethylindole-5-carboxylic acid (14 g), PCl_5 (19 g), and dry ether (350 ml) was stirred at room temperature for 18 hr and then filtered. The filtrate was concentrated to about 100 ml, petroleum ether (bp 40–60°) (1400 ml) was added, and the mixture again was filtered. The filtrate was refrigerated for 24 hr. The crystalline material which had separated was collected and then added to ethanol (30 ml) and saturated with NH_3 and the mixture was left at room temperature for 8 hr. The ethanol was removed by distillation and water was added to the residue yielding 2.5 g of crude VI, mp 176–178°. A further 2 g of crude product was obtained by passing NH_3 through the petroleum ether (bp 40–60°) filtrate; yield 4.5 g (32%). An analytical sample was obtained by recrystallization from ethyl acetate–petroleum ether (bp 60–80°), mp 182–183°, lit.[8] 170–172°.

Anal. Calcd for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.23; H, 6.51; N, 15.03.

2,3-Dimethylindolecarboxhydrazides (Table I, Procedure A).—The ethyl 2,3-dimethylindolecarboxylate (15.6 g, 0.07 mole) was refluxed with hydrazine hydrate (100 ml, 99–100%) for 2 hr. The reaction mixture was distilled under reduced pressure to remove some of the excess of hydrazine hydrate and then cooled. The precipitated hydrazide was collected by filtration, washed with water, and dried.

2,3-Dimethylindolecarboxamides (Table I, Procedure B).—Sodium nitrite (2 g, 0.029 mole) in water (20 ml) was added to a stirred, cold (0–5°) solution of the indolecarboxhydrazide (5.7 g, 0.028 mole) in glacial acetic acid (300 ml), and the mixture was stirred at 0–5° for 30 min. Water (1 l.) was added to the reaction mixture and the precipitated azide was collected, washed with water, and dried. The crude azide was then added to an excess of the appropriate amine (1 mole) at 0°, and the mixture was stirred at this temperature for 3 hr and added to water (400 ml). The precipitated amide was collected by filtration.

Preparation of the Amines (Table I, Procedure C).—The amines were prepared by adding a solution of the appropriate carboxhydrazide or carboxamide (0.03 mole) in dry dioxane (500 ml) to a stirred, refluxing suspension of $LiAlH_4$ (0.2 mole) in dry dioxane (150 ml) and refluxing the resultant mixture for 4 hr.

(12) A. Hofmann, *Svensk Kem. Tidskr.*, **72**, 12 (1960).

(13) Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus.

Hexahydropyrimidines. VII.[1] A Study of 2-Substituted 1,3-Bis(2-hydroxy-3-methoxybenzyl)hexahydropyrimidines and 2-Substituted 1,3-Bis(3,4-dimethoxybenzyl)hexahydropyrimidines as Antitumor Agents[2]

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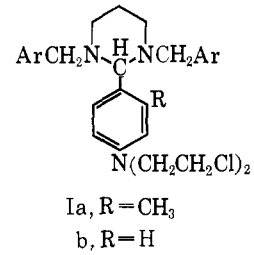
A series of 2-substituted 1,3-bis(2-hydroxy-3-methoxybenzyl)hexahydropyrimidines and 2-substituted 1,3-bis(3,4-dimethoxybenzyl)hexahydropyrimidines have been prepared and screened for antitumor activity. The tested compounds displayed no significant antineoplastic activity in tissue culture or animal studies.

In a previous study from this laboratory,[3] the synthesis and antitumor activity of a series of 1,2,3-substituted hexahydropyrimidines of the general structure I have been reported. One of these compounds, 2-{4-[N,N-Bis(2-chloroethyl)amino]-2-methylphenyl}-1,3-bis(*p*-methoxybenzyl)hexahydropyrimidine (Ia), exhibited appreciable amount of antitumor activity against Walker carcinoma 256 in preliminary test studies. A wide range of activity was observed by varying the substituents Ar in the structure Ia from *p*-methoxyphenyl (100% inhibition at 100 mg/kg) to *p*-chlorophenyl (71% inhibition at 100 mg/kg) to 2,4-dichlorophenyl (22% inhibition at 100 mg/kg). These substituents established the same relative order of activity in the Ib series. The markedly increased antitumor activity



Ia, R = CH_3

b, R = H

thus appeared to be related to the electron-donating ability of the substituents on N-1 and N-3 of the hexahydropyrimidine ring, although this ring is well separated from the nitrogen mustard group. Therefore, structure–activity relationship can be drawn.

The mechanism by which compounds of type II act in the biological systems is not well understood at this time. An attempt is, however, being made to determine whether the molecule as a whole is the effective

(1) Part VI: J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **8**, 540 (1965).

(2) This investigation was supported by a Public Health Service Research Grant No. CA-07227-02 from the National Cancer Institute.

(3) J. H. Billman and J. L. Meisenheimer, *J. Med. Chem.*, **7**, 115 (1964).