7-hydroxy-1-indanone (VII) was obtained, m.p. 119.7–121.4°.

Anal. Calcd. for $C_9H_7ClO_2$: C, 59.20; H, 3.86; Cl, 19.42. Found: C, 59.16; H, 3.99; Cl, 19.50.

7-Chloro-4-indanol (III from VII).—A mixture of 450 g. (0.247 mole) of 4-chloro-7-hydroxy-1-indanone in 2 liters of toluene with 2 liters of acetic acid and 1500 g. of freshly amalgamated zinc (10 mesh) was heated with strong mechanical stirring under reflux at 90°, and 5 liters of hydrochloric acid was added during 4 hr. The heating and stirring were continued another 4 hr. with occasional additions of hydrochloric acid to a total of 7 liters.

The mixture was cooled and separated from undissolved zinc. The water layer was separated and washed with one liter of toluene. The combined toluene extracts were concentrated *in vacuo*. The residue was crystallized from 1 liter of "Skellysolve C" after decolorizing with charcoal yielding a 300 g. first crop of 7-chloro-4-indanole, m.p. 90–92°. By concentration and cooling and recrystallization a second crop of 35 g. was collected melting at the same point; total yield 335 g. (81%).

After recrystallization from 1.5 liters of ethylene dichloride, 310 g. of pure 7-chloro-4-indanol (II) was obtained, m.p. 91.2–92.8°.

Anal. Calcd. for C_9H_9ClO: Cl, 21.03. Found: Cl, 21.0.

A mixture melting point with the original sample of 7-chloro-4-indanol prepared by Method A was not depressed.

RENSSELAER, N. Y.

[CONTRIBUTION FROM THE LABORATORIES OF THE ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH]

Indole Carboxamidines and Aminomethylindoles as Antimetabolites of Serotonin

BY E. SHAW AND D. W. WOOLLEY[1]

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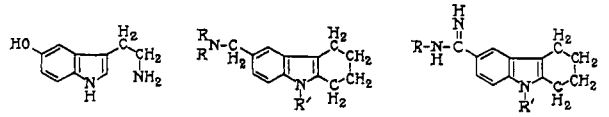
A number of antimetabolites of serotonin have been synthesized and studied in both isolated smooth muscles and in normal animals. These compounds were 1,2,3,4-tetrahydrocarbazoles (dialkylindoles) with $-CH_2-NR_2$ or $-C(=NR)-NH_2$ in the 6-position. Some had a benzyl group attached to the indole nitrogen as well. Methods for the synthesis of these compounds are described.

The early studies of the structural changes necessary to convert the hormone serotonin (I) into a specific antimetabolite of it had shown that one good way was to move the amino group from its position in the side chain of the hormone to position 5 in the indole nucleus.[2,3] The 5-amino-indoles, with alkyl groups in positions 3 (or 2 and 3) were active antiserotonins. However, they possessed the disadvantage that they were destroyed readily in living mammals. This defect apparently resided in the fact that they were substituted *p*-phenylenediamines which are liable to attack by some of the cytochrome-containing enzyme systems.[4] Since a basic group seemed to be needed somewhere in the molecule to confer high activity, the idea arose that the amino group of the aminoindoles might be protected from enzymic attack by placing a carbon atom between it and the indole nucleus. To test this postulate some 5-indolecarboxamidines and some 5-aminomethylindoles were synthesized and examined biologically for antiserotonin activity. These compounds contained either a $-C(=NH)-$ or a $-CH_2-$ between the basic nitrogen and the indole ring. For convenience in the practical syntheses, the alkyl groups in positions 2 and 3 were incorporated into a ring so that all of the compounds were 1,2,3,4-tetrahydrocarbazoles (II and III). Some of them proved to be relatively potent antimetabolites which were effective even in whole animals. Previous work had shown[5] that this was a rather rare property among antagonists of this hormone. The majority of existing antiserotonins were only effective on isolated tissues.



I II III

Experimental Part[6]

1,2,3,4-Tetrahydrocarbazole-6-carboxamide.—*p*-Aminobenzamide (7.0 g.) dissolved in water (55 ml.) and concentrated hydrochloric acid (20 ml.), was diazotized at −5° with sodium nitrite solution (3.5 g. in 25 ml. water). The filtered diazonium solution was poured into a cold solution of stannous chloride dihydrate (25 g.) in concentrated hydrochloric acid (25 ml.). After 15 minutes the tin complex was collected by suction filtration and converted to the hydrazine by treatment of a cold suspension in water (50 ml.) with 40% aqueous sodium hydroxide (20 ml.). *p*-Hydrazinobenzamide so obtained was combined with cyclohexanone in aqueous acetic acid in the usual manner. The crude hydrazone was refluxed in concentrated hydrochloric acid (20 ml. per g.) for 30 minutes. The resultant oil was dissolved in ethyl acetate which was washed with dilute alkali, dried and concentrated. The product crystallized in a yield of 45% (for the cyclization step) and had m.p. 217–219°.

Anal. Calcd. for $C_{13}H_{14}N_2O$: C, 72.89; H, 6.59; N, 13.08. Found: C, 73.41; H, 6.41; N, 12.83.

The intermediate hydrazine and hydrazone were too unstable to purify profitably.

1,2,3,4-Tetrahydrocarbazole-6-carboxhydrazide.—1,2,3,4-Tetrahydrocarbazole-6-carboxylic acid[7] was converted to the ethyl ester when refluxed for six hours with ten volumes of 2 *N* ethanolic hydrogen chloride. After recrystallization from ethanol, a 75% yield of ester, m.p. 117–119°, was obtained.

The ethyl ester (11.4 g.) was then refluxed in absolute alcohol (85 ml.) and 100% hydrazine hydrate (56 ml.) for 21 hours. The solution was concentrated in an air stream until crystals appeared; water was added and the product was filtered, washed with 50% aqueous alcohol and desiccated *in vacuo*. The material so obtained, 10.0 g. (93%), m.p. 197–199°, was used in the next step. An analytical sample crystallized from ethanol had m.p. 201–203°.

(1) With the technical assistance of C. Carter, G. Schaffner and E. Van Winkle.

(2) D. W. Woolley and E. Shaw, THIS JOURNAL, **74**, 2948 (1952).

(3) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **203**, 69 (1953).

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

(5) E. Shaw and D. W. Woolley, *ibid.*, **116**, 164 (1956).

(6) M.p.'s are uncorrected. Analyses were performed by S. Theodore Bella.

(7) W. M. Collar and S. G. P. Plant, *J. Chem. Soc.*, 808 (1926).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.09; H, 6.59; N, 18.33. Found: C, 68.51; H, 6.38; N, 18.94.

1,2,3,4-Tetrahydrocarbazole-6-carboxylic Acid Dimethylamide.—1,2,3,4-Tetrahydrocarbazole-6-carboxhydrazide (10 g.) in glacial acetic acid (150 ml.) was treated with aqueous sodium nitrite solution (3.5 g. in 10 ml. water) at 15°. The reaction mixture was then partitioned between ether (700 ml.) and water (200 ml.). After the ether layer had been washed with successive portions of aqueous bicarbonate, it was dried briefly with anhydrous sodium carbonate and filtered. A slow stream of dimethylamine was passed into the ethereal azide solution for six hours. Finally the mixture was evaporated to dryness in an air stream and the residue stirred with water and filtered. After recrystallization from ethyl acetate, 8.0 g., m.p. 188–190°, was obtained, a yield of 75%. In earlier runs a different crystalline modification was isolated with m.p. 150–151°. It could be converted to the higher melting form if its solutions were seeded with the latter.

Anal. Calcd. for $C_{15}H_{18}N_2O$: C, 74.35; H, 7.49; N, 11.56. Found: C, 74.47; H, 7.51; N, 11.64.

Amidation of the ester with dimethylamine failed.

6-Dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole.—The preceding N,N-dimethylamide (5.7 g.) was stirred overnight with a suspension of lithium aluminum hydride (2.5 g.) in dry ether (750 ml.). The excess hydride was cautiously decomposed in the usual way with aqueous sodium potassium tartrate and the product extracted from the ether layer with several 50-ml. portions of 0.5 *N* hydrochloric acid. The base was precipitated by addition of alkali to the acid extracts and was recrystallized from ethanol in a yield of 70%, m.p. 161–163°.

Anal. Calcd. for $C_{16}H_{20}N_2$: C, 78.91; H, 8.83; N, 12.27. Found: C, 78.72; H, 8.82; N, 12.35.

6-Aminomethyl-1,2,3,4-tetrahydrocarbazole Hydrochloride.—1,2,3,4-Tetrahydrocarbazole-6-carboxamide (2.0 g.) was reduced with lithium aluminum hydride (1.0 g.) in dry ether (250 ml.) as in the preceding example. The product was extracted from the ether solution with 0.5 *N* HCl (3 × 30 ml.). When the acid extracts were made alkaline, the base crystallized, 0.65 g., m.p. 142–145°. For convenience, it was converted to the hydrochloride, m.p. 255–257° dec.

Anal. Calcd. for $C_{13}H_{17}N_2Cl$: C, 65.95; H, 7.23. Found: C, 65.54; H, 6.93.

9-Benzyl-6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole Hydrochloride.—A solution of 1,2,3,4-tetrahydrocarbazole-6-N,N-dimethylcarboxamide (10 g.) in benzene was added to a suspension of sodium hydride (1.5 g.) in benzene (400 ml.) in an atmosphere of nitrogen. The mixture was refluxed for one-half hour. Benzyl chloride (5.2 ml.) was added and the refluxing was continued overnight. To decompose excess hydride, absolute ethanol (10 ml.) was introduced. The benzene layer was washed with water, dried and evaporated to dryness. The benzylated amide was not crystallized. Instead the residue was taken up in anhydrous ether and added to a suspension of lithium aluminum hydride (4.0 g.) in ether (1 liter). After the mixture had been stirred for two days, the excess hydride was decomposed in the usual way with aqueous sodium potassium tartrate and the product was extracted from the ether layer with *N* hydrochloric acid (2 × 100 ml.). The hydrochloride of the product which had crystallized immediately in the acid extracts was filtered, washed with dilute hydrochloric acid, and desiccated *in vacuo* with moistened pellets of sodium hydroxide. The hydrochloride thus isolated always had a characteristic m.p. of 84–87° but was hydrated to a variable degree in different preparations. After recrystallization from water, lustrous flakes, 7.0 g., of the same m.p. were obtained. After drying for several hours at 65° and 1 mm. this material was analytically pure as anhydrous hydrochloride[8] and represented a yield of 50% for the two steps. Recrystallization from absolute alcohol gave a product with a m.p. of 198–199°.

Anal. Calcd. for $C_{22}H_{27}N_2Cl$: C, 74.45; H, 7.67; N, 7.89. Found: C, 74.34; H, 7.48; N, 7.98.

This anhydrous high melting form was reconverted to the form melting at 84–87° by recrystallization from water.

This same compound was prepared by direct benzylation of 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole in liquid ammonia in the presence of sodamide. The yield was 46%.

p-Hydrazinobenzamidine Dihydrochloride.—*p*-Aminobenzamidine dihydrochloride was prepared by low pressure hydrogenation of *p*-nitrobenzamidine[9] in ethanol with palladized charcoal. The filtrate was concentrated to a small volume and the product precipitated by the addition of concentrated hydrochloric acid. Yields of 85%, m.p. 290–291°, resulted. Although lit. m.p. is 320° cor.,[10] the material obtained was analytically pure.

Anal. Calcd. for $C_7H_{11}N_3Cl_2$: Cl^-, 34.1; N, 20.19. Found: Cl^-, 34.4; N, 20.44.

Diazotization of *p*-aminobenzamidine dihydrochloride (5.0 g.) in 2 *N* hydrochloric acid (80 ml.) was carried out at −10° with a solution of sodium nitrite (1.75 g.) in water (5 ml.). A cold solution of stannous chloride dihydrate (25 g.) in concentrated hydrochloric acid (25 ml.) was added. After 20 minutes, the tin complex was filtered with suction and washed with ice-water. The precipitate in water (125 ml.) was treated with hydrogen sulfide and the filtrate concentrated to a small volume with reduced pressure until the appearance of crystals. After refrigeration, the product was collected. It was recrystallized from water (15 ml.) by the addition of *N* ethanolic HCl (60 ml.) in the form of long needles, m.p. 269–270° dec., 2.9 g.

Anal. Calcd. for $C_7H_{12}N_4Cl_2$: C, 37.68; H, 5.42; N, 25.11. Found: C, 37.80; H, 5.34; N, 25.14.

1,2,3,4-Tetrahydrocarbazole-6-carboxamidine Hydrochloride.—*p*-Hydrazinobenzamidine dihydrochloride (3.0 g.) in water (90 ml.) was treated with cyclohexanone (2 ml.). The yellow solution was made strongly alkaline with 6 *N* sodium hydroxide whereupon the hydrazone separated as an oil which crystallized. After the mixture was chilled, the product was filtered, washed with water and desiccated *in vacuo*. The crude hydrazone melted at 225–226° dec. Purification proved unprofitable.

The hydrazone (2.2 g.) was refluxed for 30 minutes in concentrated hydrochloric acid (22 ml.). The hydrochloride of the product which formed as an oil crystallized on standing. It was dissolved in hot water (20 ml.). The solution was cooled for four hours, filtered from an insoluble impurity and crystallized from the filtrate by addition of 6 *N* hydrochloric acid (2 ml.) to yield 1.6 g. (44%), m.p. 193–195°. It was recrystallized from hot 0.5 *N* hydrochloric acid.

Material dehydrated at 100° *in vacuo* was hygroscopic; satisfactory analyses were obtained on anhydrous material allowed to hydrate in a moist atmosphere until no further gain in weight occurred. The uptake indicated a monohydrate.

Anal. Calcd. for $C_{13}H_{16}N_3Cl \cdot H_2O$: C, 58.30; H, 6.72; N, 15.69. Found: C, 58.93; H, 6.71; N, 15.88.

The free base was obtained as a gum by treatment of the hydrochloride with aqueous NaOH. In some preparations, this gum was obtained crystalline by solution in ethanol and partial evaporation of the solvent. Occasionally the gum could not be induced to crystallize. The free base melted at 171–173°.

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.20; H, 7.09; N, 19.70. Found: C, 73.16; H, 6.75; N, 19.52.

6-Cyano-1,2,3,4-tetrahydrocarbazole.—The hydrazone from cyclohexanone and *p*-cyanophenylhydrazine[11] formed in the usual manner (m.p. 174–175°) was refluxed in concd. hydrochloric acid (15 ml. per g.) for 15 minutes. Longer refluxing hydrolyzed the nitrile. The precipitated gum was dissolved in ethyl acetate which was then washed with aqueous sodium carbonate, dried and evaporated. The dried residue was freed of some contaminating amide by extraction with ether in which the amide was insoluble. Evaporation of the ether gave crystalline nitrile in a yield of about 70%. This was generally used without further purification. The pure nitrile, after repeated crystallization from benzene and hexane, had a m.p. of 117–119°.

Anal. Calcd. for $C_{13}H_{12}N_2$: C, 79.56; H, 6.16; N, 14.28. Found: C, 79.24; H, 6.31; N, 14.23.

Attempts to convert the nitrile to an imino ether in ether

(8) The m.p. of this anhydrous material was considerably lower than that of the anhydrous material obtained by crystallization from alcohol.

(9) A. Pinner and F. Gradenwitz, *Ann.*, **298**, 47 (1897).

(10) A. P. T. Easson and F. L. Pyman, *J. Chem. Soc.*, 2991 (1931).

(11) A. Weissburger, H. P. Porter and W. A. Gregory, THIS JOURNAL, **66**, 1851 (1944).

or chloroform resulted only in the formation of a hydrochloride of the starting material. Amidines were therefore prepared by alternate routes.

9-Benzyl-6-cyano-1,2,3,4-tetrahydrocarbazole.—6-Cyano-1,2,3,4-tetrahydrocarbazole (2.0 g.) in benzene (75 ml.) was converted to a sodium salt with sodium hydride (0.25 g.) followed by dimethylformamide (5 ml.). Benzyl chloride (1.2 ml.) was then introduced and the reaction mixture was refluxed for two hours. After decomposition of unreacted hydride with ethanol the benzene solution was washed, dried and concentrated. The residue in a small volume of benzene was applied to a column of alumina (3.4 × 30 cm.) and eluted with the same solvent containing 2% ethanol. The first fraction which emerged crystallized on removal of the solvent. The crystals were thinned with alcohol and water for filtration and provided 1.6 g., 56% of product melting at 117–118°. The analytical sample obtained from the same solvents had m.p. 120–121°.

Anal. Calcd. for $C_{20}H_{18}N_2$: C, 83.87; H, 6.34; N, 9.78. Found: C, 84.02; H, 6.38; N, 9.99.

1,2,3,4-Tetrahydrocarbazole-6-N-phenylcarboxamidine Hydrochloride.[12]—6-Cyano-1,2,3,4-tetrahydrocarbazole (3.1 g.) and aniline *p*-toluenesulfonate (4.3 g.) were heated for one hour at 220° and the cooled melt was partitioned between chloroform and *N* sodium hydroxide. The chloroform layer was washed with water followed by 3 *N* hydrochloric acid which precipitated the amidine hydrochloride as a gum. The latter was either crystallized from 80% ethanol or, with smaller losses, purified as the picrate, m.p. 258–259°, in a yield of 49%. The hydrochloride had a m.p. of 266–267°.

Anal. Calcd. for $C_{19}H_{20}N_3Cl$: C, 70.04; H, 6.18; N, 12.90. Found: C, 70.33; H, 6.05; N, 12.63.

9-Benzyl-1,2,3,4-tetrahydrocarbazole-6-N-phenylcarboxamidine Hydrochloride.[12]—9-Benzyl-6-cyano-1,2,3,4-tetrahydrocarbazole (1.5 g.) was heated with aniline *p*-toluenesulfonate (1.4 g.) for one hour at 200° and worked up as in the preceding example. Saturated sodium chloride solution was added to help break emulsions in the extraction step. When the chloroform layer was shaken with *N* hydrochloric acid (20 ml.) the product remained dissolved in the chloroform layer as the hydrochloride. The chloroform was dried and concentrated to a small volume whereupon the product crystallized. After recrystallization from alcohol and ether, the hydrochloride was obtained in a yield of 50%, m.p. 272–273°.

Anal. Calcd. for $C_{26}H_{26}N_3Cl$: C, 75.09; H, 6.30; N, 10.10. Found: C, 74.85; H, 6.03; N, 10.44.

Pharmacological Results

Antiserotonin Activity as Measured on Artery Rings.—The method of Woolley and Shaw[3] was used, which depended on the measurement of the concentration of the analog required to overcome the contraction caused in ring-shaped segments of carotid arteries by a fixed amount of serotonin. The results of these tests are shown in Table I where it can be seen that most of the analogs possessed activity. The increased potency of the dimethylaminomethyl over the aminomethyltetrahydrocarbazole was noteworthy. One would expect the latter to be deaminated readily, and this may explain partly the observed difference.

Antiserotonin Activity on Isolated Rat Uterus.—The method introduced by Erspamer[13] was used in the manner previously described from this Laboratory.[5] The results of these tests are also shown in Table I. The variation in relative potency of a single compound on the two tissues is noteworthy. Clearly, most of the analogs were antimetabolites on the uterus as well as on the carotid artery.

Antiserotonin Activity as Measured against the

(12) *Cf.* general method of Oxley and Short, *J. Chem. Soc.*, 147 (1946).

(13) V. Erspamer, *Ricerca Sci.*, **22**, 1568 (1952).

TABLE I

ANTISEROTONIN ACTIVITIES OF THE ANALOGS AS MEASURED WITH ISOLATED TISSUE IN VITRO

1,2,3,4-Tetrahydrocarbazoles	Inhibition index in sheep arteries[a]	Inhibition index in rat uterus[b]
6-Carboxamidine	6	25
6-N-Phenylcarboxamidine[c]	200	50
6-Aminomethyl	20	..
6-N,N-Dimethylaminomethyl	2	10
9-Benzyl 6-N,N-dimethylaminomethyl[c]	..	300

[a] These values represent the number of mg. of analog required to antagonize the contracting action of 1 mg. of serotonin creatinine sulfate and were determined from the point of half maximal effect. The concentration of serotonin in the bath was 0.2 γ/ml. [b] Inhibition index has the same connotation as above. The amount of serotonin in the bath was 0.05 γ/ml. The analog was left in contact with the tissue for two minutes before addition of serotonin. [c] These analogs endowed the tissues with an insensitivity to serotonin that persisted long after washing. The acetyl choline response was not affected by them.

Pressor Action in Dogs.—The compounds were examined according to the methods previously described.[4,5] When given by the intravenous route two of the compounds (the dimethylaminomethyltetrahydrocarbazole and the tetrahydrocarbazole N-phenylcarboxamidine) proved to be quite effective. Data are summarized in Table II. By the oral route, however, the former was without demonstrable antiserotonin action on dogs. Daily doses of 45 mg. per kg. for 4 days failed to protect against the pressor effect of serotonin. In fact this compound given orally potentiated serotonin. The N-phenylcarboxamidine fed at 3.5 and 7.5 mg. per kg. per day partially protected 2 dogs but in one the effect was slight.

Hypotension Caused by the 1,2,3,4-Tetrahydrocarbazole 6-N-Phenylcarboxamidine in Dogs.—When given intravenously in doses of 2–7 mg. per kg. to anesthetized dogs the tetrahydrocarbazole 6-N-phenylcarboxamidine caused a sharp fall in arterial blood pressure (usually about 20 mm. of Hg). In two of five animals, however, the hypotension was very severe, and in one of these the pressure fell to zero with 9 mg. per kg. Sometimes the hypotension persisted for an hour or more. This kind of action has been rare among antiserotonins, but was noted recently with the benzyl analog of bufotenin.[14]

Behavioral Changes Caused by 9-Benzyl-6-dimethylaminomethyl - 1,2,3,4 - tetrahydrocarbazole.—Although the dimethylaminomethyltetrahydrocarbazole did not cause any noticeable behavioral changes when fed to normal dogs or mice, the corresponding benzyl derivative, *viz.*, 9-benzyl-6-dimethylamino-methyl-1,2,3,4-tetrahydrocarbazole brought about an alteration which might be called a psychosis. Dogs fed daily 25 mg. per kg. of this analog mixed with their food ate it readily for 3 or 4 days. They then developed a most pronounced aversion to the taste of it, whereas in the first days they did not object at all. This aversion was so great that the animals refused to touch any food containing the drug. At the time that this distaste arose, the attitude and behavior

(14) E. Shaw and D. W. Woolley, *Proc. Soc. Exptl. Biol. Med.*, **93**, 217 (1956).

TABLE II

AMOUNTS OF ANALOGS REQUIRED BY THE INTRAVENOUS AND BY THE ORAL ROUTE TO PROTECT DOGS FROM THE PRESSOR ACTION OF SEROTONIN

1,2,3,4-Tetrahydrocarbazoles	No. of dogs	I.V. dose,[a] mg./kg. Av.	Extreme range	Oral dose, mg./kg./day
6-Carboxamidine	1	No effect at 6	.....	.....
6-N-Phenylcarboxamidine	4	0.4[b]	0.14–0.5	.....
	2	..	.....	Some protection at 3.5 and 7.5 but not complete
6-N,N-Dimethylaminomethyl	4	1.6	0.7–2.7	.....
	2	..	.....	No protection at 45[c]
9-Benzyl 6-N,N-dimethylaminomethyl	1	..	Less than 2.5	.....
	4	..	....	Partial at 25[d]

[a] Amount required to reduce to half the pressor response of the standard dose of serotonin (usually 50 gamma per kg.). [b] Complete protection was not achieved in some of the dogs with doses ten times this amount, although partial protection was always seen. [c] Both dogs showed an increase in the pressor effect of serotonin after eating this compound. [d] Two dogs showed only slight protection; one showed good protection; and one showed no protection but instead there was augmentation of the pressor response

of the animals became quite changed. Some raced around the room excitedly and without obvious purpose. One animal was so distracted that in running constantly about the room he would bump into articles of furniture. The behavioral changes varied from animal to animal, but of the 4 dogs tested all showed the slow onset and the delayed development of distaste for food mixed with the analog. In all, the symptoms could be summarized as marked excitement. A further sign was seen in all, *viz.*, constant slow movement of the head from side to side in a horizontal plane. This motion was continued regularly for hours.

When dogs exhibiting the influence of this compound were anesthetized with Nembutal, the sleeping time was always prolonged so that they would not awaken for about 24 hours. When ingestion of the compound was stopped, the behavior of the animals returned to normal within a few days.

In mice, the intraperitoneal injection of this compound (30 mg. per kg.) brought about neurological changes similar to those seen in dogs. Chief of these were the excitement, and the turning of the head from side to side regularly and rhythmically. In a mouse it is not as easy to recognize behavioral changes which can be called psychotic with any assurance, and none which could be so labeled were observed. The walking backwards as seen in mice given lysergic acid diethylamide[15] was never seen. However, just as in dogs, the sleeping time caused by a standard dose of Nembutal was markedly increased.

Curious Prolonged Action of 9-Benzyl-6-dimethylaminomethyl - 1,2,3,4 - tetrahydrocarbazole as an Antipressor Agent in Dogs.—When dogs were fed this compound for 4 days (25 mg. per kg. per day) and then tested for their protection against the pressor effects of serotonin, the results were not dramatic. Only partial protection could be found (*cf.* Table II). When the feeding of the compound was then stopped, and the dogs were challenged at long intervals thereafter, their protection was sometimes found to have lasted or even increased. This effect was noticeable for periods ranging (in various dogs) from a few days to many weeks. The dimethylaminomethyltetrahydrocarbazole which lacked the benzyl group did not cause this prolonged and progressive effect.

(15) D. W. Woolley, *Proc. Natl. Acad. Sci.*, **41**, 338 (1955).

Discussion

Although a basic group seems to be necessary in a serotonin analog for it to show marked antiserotonin activity, the results of the present study illustrate the degree of freedom which may be enjoyed in the location of this group. The insertion of a carbon atom between the indole ring and the basic nitrogen has resulted in the attainment of compounds which are much more potent than the corresponding aminoindoles.

The fact that these new antimetabolites were relatively inactive as antipressor agents when fed, or at least, were not as active as when injected intravenously, should be borne in mind. The reason why this should be so is unknown. Compounds such as 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole have had incorporated in them the features designed to protect them from destruction by deamination or from a variety of oxidative enzyme systems, and yet they failed to act by the oral route. Perhaps they may have been excreted too rapidly, or may have been destroyed in unsuspected ways.

The pronounced effects of 9-benzyl-6-dimethylaminomethyl-1,2,3,4- tetrahydrocarbazole are noteworthy for 2 reasons. Firstly, the abnormal behavior which it caused lends support to the idea first proposed by Woolley and Shaw[16] that serotonin plays a role in mental processes.

The second point of interest about this compound was that 6-dimethylaminomethyl-1,2,3,4-tetrahydrocarbazole, which differed from it only in lacking the benzyl group, did not call forth the abnormal behavior. Neither did it exhibit the curious delayed and prolonged action as an antipressor agent. Recently, the conferment of striking properties on another antiserotonin by introduction of a benzyl group has been illustrated by comparison of BAS with the corresponding unbenzylated analog.[5,17] In both cases prolonged action and increased potency resulted from introduction of the benzyl group.

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(16) D. W. Woolley and E. Shaw, *ibid.*, **40**, 228 (1954).

(17) D. W. Woolley and E. Shaw, *Science*, **124**, 34 (1956).