Pharmacology.—The acute toxicity and the analgesic and anti-inflammatory activities were investigated by the techniques previously described.[1e] The highest dosage level which did not provoke an obvious toxic symptomatology in experimental animals was used for each test. Morphine and phenylbutazone were used as standards.

Acknowledgments.—The authors wish to thank Mr. G. Pinna and Mr. G. Bietti for their assistance in preparing the compounds, Dr. C. Turba and Mrs. L. Pozzi for their cooperation in performing the pharmacological tests, and Dr. G. Sekules for the microanalyses.

9-(2-Aminoethyl)-2,3-dihydro-1H-pyrrolo[1,2-*a*]-indoles, New Tryptamine Analogs

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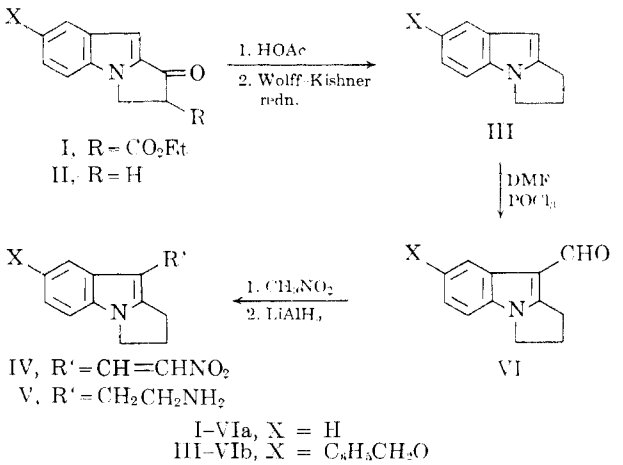
Following the initial studies of Woolley and Shaw on pharmacologically active analogs of serotonin,[1] a high interest in indoles related to tryptamine has been maintained.[2] In this paper we wish to report the preparation and properties of several new tryptamine analogs, 9-(2-aminoethyl)-2,3-dihydro-1H-pyrrolo-[1,2-*a*]indoles.

Studies in these laboratories on the synthesis of mitomycin analogs established a method for preparation of the pyrrolo[1,2-*a*]indole ring system,[3] and, in addition, furnished intermediates that appeared useful for the formation of tryptamine analogs. For example, it seemed likely that compounds such as 7-benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (IIIb)[4] could be converted to their 9-(2-aminoethyl) derivatives, *e.g.*, Vb, by one of the reaction sequences already established for the preparation of tryptamine from 3-unsubstituted indoles. The following series of transformations was therefore undertaken from IIIb. Vilsmeier–Haack formylation[5] afforded 9-formyl pyrrolo[1,2-*a*]indole VIb in good yield.[6] Condensation of VIb with nitromethane[8] gave 2-nitrovinyl derivative IVb, which was reduced with lithium aluminum hydride[9] to 9-(2-aminoethyl)pyrrolo[1,2-*a*]indole (Vb), isolated and characterized as its hydrochloride.



I–VIa, X = H
III–VIb, X = $C_6H_5CH_2O$

Having thus successfully prepared a 7-substituted pyrrolo[1,2-*a*]indole analog of tryptamine, we next undertook the synthesis of an analog with no substituent in the benzenoid ring, *e.g.*, Va. To obtain this analog, it was necessary to first prepare the appropriate 9-unsubstituted pyrrolo[1,2-*a*]indole (IIIa). Although the latter compound had already been reported by Laschtuvka and Huisgen,[10a] a more direct route to it was available by procedures developed in these laboratories.[3] Thus, condensation of ethyl 2-indolecarboxylate with ethyl acrylate afforded a pyrrolo-[1,2-*a*]indole β-keto ester (I) which was converted to IIIa by decarbethoxylation in acetic acid and subsequent Wolff–Kishner reduction (I → II → IIIa). The sample of IIIa prepared in this manner was identical by infrared absorption spectrum and mixture melting point with that reported by Laschtuvka and Huisgen.[10]

In addition to IIIa, Wolff–Kishner reduction of V gave a second product, a white crystalline solid $(C_{11}H_{10}N)_x$, that had m.p. 238–249° and a typical indole ultraviolet absorption spectrum.

Introduction of the 9-(2-aminoethyl) substituent into pyrrolo[1,2-*a*]indole IIIa was readily accomplished (IIIa → VIa → IVa → Va) by use of the same sequence employed in the 7-benzyloxy series, and tryptamine analog Va was characterized as its hydrochloride.

Pharmacology.—None of the pyrrolo[1,2-*a*]indole analogs of tryptamine and intermediates described above exhibited significant hypotensive (no effect on the blood pressure of conscious normotensive rats at 100 mg./rat *p.o.*), diuretic (rejected at 25 mg./rat *p.o.*[11]), or antidepressant activity (rejected at maximum doses of 200–250 mg./kg. i.p.[12]), or had analgesic properties (rejected at 100 mg./kg. *p.o.* in mice[13]). The above tryptamines were inactive as monoamine oxidase inhibitors at the level tested (at 10^{-5} *M* no decrease in liberation of ammonia from dopamine by a preparation

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(4) G. R. Allen, Jr., and M. J. Weiss, *ibid.*, in press.

(5) A. Vilsmeier and A. Haack, *Ber.*, **60**, 119 (1927).

(6) The rate of formylation of IIIb under these conditions appeared to fall between the rates observed for the corresponding 1-ketopyrrolo[1,2-*a*]indole (7-benzyloxy II) and 1-ol acetate. Thus, formylation of the acetate at ice-bath temperature for 30 min. gave complete conversion to the 9-formyl derivative,[7] whereas IIIb was converted to VIb in 50% yield with 40% of starting material remaining. 7-Benzyloxy II was completely unreactive under these conditions, requiring steam-bath temperature to induce 9-formylation and then in low yield.[7]

(7) W. A. Remers, R. H. Roth, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 1612 (1964).

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(11) Procedure of J. R. Cummings, J. D. Haynes, L. M. Lipchuck, and M. A. Ronsberg, *J. Pharmacol. Exptl. Therap.*, **128**, 414 (1960).

(12) For testing procedure see V. G. Vernier, H. M. Hanson, and C. A. Stone, "Psychosomatic Medicine. The First Hahnemann Symposium," J. H. Nodine and J. H. Mayer, Ed., Lea and Febiger, Philadelphia, Pa., 1962, pp. 683–690.

(13) Method of E. Siegmund, R. Cadmus, and G. Lu, *Proc. Soc. Exptl. Biol. Med.*, **95**, 729 (1957).

in sucrose of the enzyme from mitochondria of guinea pig liver). It thus seems apparent that, within the limits of this study, the 1,2-trimethylene bridge of 2,3-dihydro-1H-pyrrolo[1,2-*a*]indoles has no beneficial pharmacological effect.

Experimental

General.—Melting points were determined on a hot stage microscope and are corrected. Ultraviolet spectra were determined in methanol with a Cary recording spectrophotometer, and infrared spectra were determined in KBr disks with a Perkin-Elmer Infracord spectrophotometer. Solutions were dried ($MgSO_4$) and were concentrated under reduced pressure on a rotary evaporator.

Ethyl 2,3-Dihydro-1-oxo-1H-pyrrolo[1,2-*a*]indole-2-carboxylate (I).—To a suspension of potassium *t*-butoxide (freshly prepared from 0.1 g.-atom of K and 100 ml. of *t*-butyl alcohol) in 200 ml. of benzene was added 18.9 g. (0.1 mole) of ethyl 2-indolecarboxylate. The mixture was stirred several minutes and treated with 10.0 g. (0.1 mole, 10.8 ml.) of ethyl acrylate. After the resulting mixture was stirred at reflux temperature for 3 days it was cooled, poured into water, and acidified with dilute HCl. The benzene layer was washed with water, dried, and concentrated to a viscous oil that crystallized on addition of methanol. In this manner was obtained 11.6 g. (48%) of ethyl 2,3-dihydro-1-oxo-1H-pyrrolo[1,2-*a*]indole-2-carboxylate (I): m.p 91–93°; λ_{max} 5.75, 5.90 μ; λ_{max} 242 mμ (ϵ 25,500), 320 (21,000). An analytical sample, recrystallized from methanol, had m.p. 100°.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.26, 68.27, 68.83; H, 5.92, 5.60, 5.55; N, 6.59, 5.75, 5.75.

2,3-Dihydro-1H-pyrrolo[1,2-*a*]indol-1-one (II).—A mixture of 11.16 g. (0.46 mole) of I and 250 ml. of 95% aqueous acetic acid was stirred at reflux temperature for 22 hr. It was then cooled and diluted with water until no further crystallization occurred. The crystals were washed thoroughly with water and dissolved in methylene chloride, and this solution was dried and concentrated on a steam bath as acetone was added. When the first crystals appeared, the solution was cooled to afford 2.13 g. of II: m.p. 141–142°; λ_{max} 5.9 μ; λ_{max} 239 mμ (ϵ 25,000), 315 (21,000). An additional 3.63 g. (total yield 73%) of II, m.p. 142–144°, was obtained by concentration of the above mother liquor with concomitant addition of hexane. An analytical sample, recrystallized from acetone, had m.p. 145–146°.

Anal. Calcd. for $C_{11}H_9NO$: C, 77.17; H, 5.30; N, 8.18. Found: C, 77.08; H, 5.58; N, 8.18.

2,3-Dihydro-1H-pyrrolo[1,2-*a*]indole (IIIa).—A mixture of 5.42 g. (31.7 mmoles) of II, 5.61 g. (excess) of KOH, 4.3 ml. (excess) of hydrazine hydrate, and 100 ml. of diethylene glycol was heated at reflux temperature for 1.5 hr. It was then cooled and treated with water and methylene chloride. The methylene chloride layer was washed with water, dried, and concentrated. A benzene solution of the residue was passed through a Florisil[14] column (16 × 200 mm.) with benzene as eluent. The residue from concentration of the eluate solidified on standing. It was extracted with boiling methanol and this extract was filtered to remove some insoluble white solid. Concentration and cooling of the extract afforded first a yellow oil. The supernatant was decanted and cooled, yielding in several crops 2.36 g. (48%) of IIIa: white prisms, m.p. 72–75°; λ_{max} 280, 289, 297 mμ. An analytical sample, purified by sublimation at 150°, had m.p. 74–75° (lit.[10a] m.p. 79–80°). On our Kofler hot stage microscope a sample of IIIa from Huisgen[10b] had m.p. 74–75°, and a mixture melting point with our sample was undepressed. These two samples had infrared absorption spectra that were superimposable.

The methanol-insoluble white solid was recrystallized from chloroform–cyclohexane to give 140 mg. of white plates: m.p. 238–249°; λ_{max} 280, 289, 297 mμ.

Anal. Calcd. for $(C_{11}H_{10}N)_n$: C, 84.58; H, 6.45; N, 8.97. Found: C, 84.76; H, 6.05; N, 8.11.

7-Benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (VIb).—To 0.5 ml. of ice-cooled dimethylformamide was added 71 mg. (0.47 mmole) of freshly distilled $POCl_3$. The mixture was stirred and cooled for 15 min. and treated with a suspension of 122 mg. (0.47 mmole) of 7-benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (IIIb)[4] in 2 ml. of dimethylformamide. The resulting yellow solution was stirred at 35° for 1 hr. and poured onto ice. A pink solid that formed was collected on a filter. It was starting material. The filtrate was made alkaline with dilute NaOH solution and the pale yellow solid that formed was washed with water and dried. In this manner was obtained 65 mg. (48%) of VIb: m.p. 157°; λ_{max} 3.6, 3.8, 6.1 μ; λ_{max} 257 mμ (ϵ 20,000), 276 (14,000), 308 (12,000).

Anal. Calcd. for $C_{19}H_{17}NO_2$: C, 78.33; H, 5.88; N, 4.81. Found: C, 78.16; H, 6.06; N, 5.13.

When the above reaction was run at 60° for 80 min., the yield of VIb was increased to 74%; however, some decomposition occurred and it was necessary to purify this product by passing a methylene chloride solution of it through a magnesia–silica gel adsorbent.

2,3-Dihydro-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (VIa).—Treatment of 2,3-dihydro-1H-pyrrolo[1,2-*a*]indole (IIIa) in the manner described in the preparation of VIb afforded, after crystallization from methanol, 59% of VIa as pale yellow needles: m.p. 145–151°; λ_{max} 6.10 μ; λ_{max} 248 mμ (ϵ 20,000), 265 (15,000), 307 (19,000). An analytical sample, recrystallized from methanol, had m.p. 151–154°.

Anal. Calcd. for $C_{12}H_{11}NO$: C, 77.81; H, 5.99; N, 7.56. Found: C, 77.86, 77.82; H, 5.93, 6.36; N, 7.40.

7-Benzyloxy-2,3-dihydro-3-(2-nitrovinyl)-1H-pyrrolo[1,2-*a*]indole (IVb).—A mixture of 500 mg. of 7-benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (VIb),[4] 120 mg. of ammonium acetate, and 1.0 ml. of nitromethane was heated on a steam bath for 30 min. The yellow crystals that formed on cooling were washed with 20 ml. of hot water, dissolved in methylene chloride, and dried. The resulting solution was concentrated on a steam bath and treated with methanol until the first crystals appeared. Cooling afforded yellow needles, m.p. 154–164°. Recrystallization from methanol gave 300 mg. (52%) of IVb: golden prisms, m.p. 169–171°; λ_{max} 6.22, 6.60, 7.6 μ; λ_{max} 420 mμ.

Anal. Calcd. for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.81; H, 5.77; N, 8.22.

2,3-Dihydro-9-(2-nitrovinyl)-1H-pyrrolo[1,2-*a*]indole (IVa).—Treatment of 2,3-dihydro-1H-pyrrolo[1,2-*a*]indole-9-carboxaldehyde (VIa) in the manner described in the preparation of IVb gave a 73% yield of IVa as orange prisms: m.p. 182–184°; λ_{max} 6.22, 6.60, 7.60 μ; λ_{max} 285, 425 mμ.

Anal. Calcd. for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.40; H, 5.51; N, 11.95.

9-(2-Aminoethyl)-7-benzyloxy-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole Hydrochloride (5-Benzyloxy-1,2-trimethylenetryptamine Hydrochloride, Vb).—To a stirred suspension of 630 mg. (16.6 mmoles) of $LiAlH_4$ in 25 ml. of tetrahydrofuran was added a suspension of 708 mg. (2.1 mmoles) of 7-benzyloxy-2,3-dihydro-3-(2-nitrovinyl)-1H-pyrrolo[1,2-*a*]indole (IVb) in 20 ml. of tetrahydrofuran. After this addition was complete (10 min.), the mixture was stirred 1 hr. and treated with water. The resulting mixture was filtered, and the solids were washed with tetrahydrofuran. The combined filtrate and wash was concentrated, and the residue was treated with water and CH_2Cl_2. After drying, the methylene chloride solution was concentrated and the yellow oily residue was dissolved in ether and treated with anhydrous HCl until no further amine hydrochloride precipitated. This precipitate was washed with ether and dried. In this manner was obtained 550 mg. (77%) of Vb, m.p. 80° dec. This sample was somewhat unstable to heat and air oxidation and was hygroscopic. A suitable recrystallization solvent could not be found.

Anal. Calcd. for $C_{20}H_{23}ClN_2O$: C, 70.03; H, 6.76; Cl, 10.34; N, 8.17. Found: C, 69.87; H, 6.89; Cl, 10.31; N, 7.76.

9-(2-Aminoethyl)-2,3-dihydro-1H-pyrrolo[1,2-*a*]indole Hydrochloride (1,2-Trimethylenetryptamine Hydrochloride, Va).—Treatment of 2,3-dihydro-9-(2-nitrovinyl)-1H-pyrrolo[1,2-*a*]indole (IVa) in the manner described in the preparation of Vb afforded 570 mg. (45%) of Va: m.p. 210–220° dec.; λ_{max} 275, 283, 292 mμ. This sample was hygroscopic and somewhat unstable to air oxidation. A suitable recrystallization solvent could not be found.

Anal. Calcd. for $C_{13}H_{17}ClN_2$: C, 65.97; H, 7.24; Cl, 14.98; N, 11.84. Found: C, 66.24; H, 7.25; Cl, 15.41; N, 11.62.

(14) Floridin Co., magnesia–silica gel adsorbent.

Acknowledgment. The authors are indebted to Mr. W. Fulmor and staff for spectral data; to Mr. L. Brancone and staff for microanalyses; to Dr. J. L. Fedrick, Mr. E. K. Norton, and Mr. R. Zambrano for large-scale preparation of certain intermediates; to Drs. A. C. Osterberg and J. R. Cummings and associates and Mrs. E. Markley for evaluation of the biological activity of compounds described herein; and to Drs. E. Cohen and S. M. Gadekar for helpful discussions.

Isomeric Benzyldiaminodihydrotriazines

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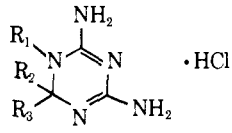
Interest in dihydrodiaminotriazines of type I[2] developed over a decade ago when the antimalarial



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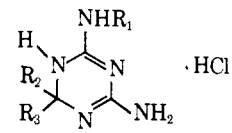

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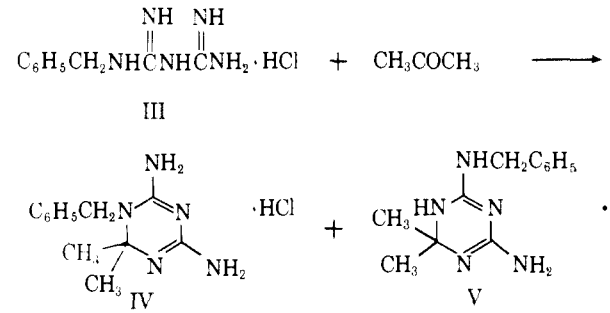
I II

metabolite, 4,6-diamino-1-*p*-chlorophenyl-1,2-dihydro-2,2-dimethyl-*s*-triazine (I, R_1 = *p*-chlorophenyl; R_2 = R_3 = CH_3) was isolated from the urine of rabbits and humans receiving doses of the antimalarial chlorguanide.[3] Besides antimalarial activity, antitumor,[4] anticoccidial,[5,6] antibacterial,[7,8] and anthelmintic[9] activity have been reported for a number of different 4,6-diamino-1-aryl-dihydro-*s*-triazines, as well as synergistic action with sulfonamide drugs.[5,8,10]

Synthetic routes to compounds of type I in which R_1 = aryl and R_2 and R_3 are either both alkyl, or aryl and hydrogen were developed independently by workers at ICI in England[3,11] and by Modest, *et al.*, in the United States.[12-14] These involved the reaction of either an arylbiguanide hydrochloride and a ketone or aromatic aldehyde (method A), or the reaction of an arylamine hydrochloride, dicyandiamide, and the carbonyl component (method B). In both of these methods an excess of mineral acid was used. These two methods were used to prepare a large number of analogs of the antimalarial metabolite I (R_1 = *p*-chlorophenyl; R_2 = R_3 = CH_3). The exclusive product from either of the two methods were compounds of type I; compounds of type II, which *a priori* might have been expected, were not observed. This is a particularly interesting result in view of the ease with which compounds of type I are isomerized to those of type II,[13] indicating the latter to be thermodynamically more stable.

With regard to the preparation of *alkyl* diaminodihydrotriazines, Furukawa[15a] reported the failure of alkylbiguanides to react according to method A. More recently, 1-alkyl-2,2-dimethyldiaminodihydrotriazines (I, R_1 = alkyl; R_2 = R_3 = CH_3) were reportedly isolated from the reaction of alkylbiguanide hydrochlorides and acetone[15b] essentially according to this method. No mention was made of the formation of the isomeric compounds of type II. In contrast, we have found (before the appearance of the work cited in ref. 15b) that under the conditions of method A, benzylbiguanide hydrochloride (III) reacts with acetone to give IV and V in roughly equal amounts. That V was formed directly rather than by rearrange-

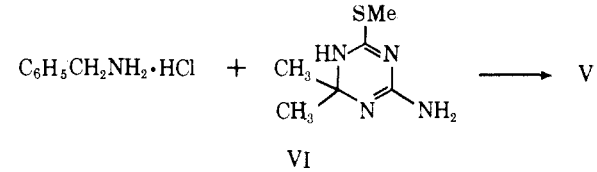


III IV V

ment of the initially formed IV was demonstrated by the recovery of I unchanged after exposure to the reaction conditions of method A.

Increasing the temperature of the reaction to 110° (sealed tube) resulted in exclusive formation of V after 20 hr., while after 5 hr. the ratio of IV to V was roughly 1:2. It appeared probable that at this elevated temperature IV does rearrange to V, and this was, indeed, found to be the case. Thus, exposure of IV to these reaction conditions for 17.5 hr. resulted in its complete transformation to V. This isomerization was also effected in base.[13]

The structure of V was unequivocally established by independent synthesis from 2,2-dimethyl-4-amino-1,2-dihydro-6-methylthio-*s*-triazine (VI) and benzylamine hydrochloride according to the procedure of Birtwell,



VI

(1) Lederle Laboratories Division, American Cyanamid Co., Pearl River, N. Y.

(2) The tautomeric form indicated is done so arbitrarily. There is no evidence to date which favors this one over the other alternatives.

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