means of a Dean–Stark trap. The solution was decanted from a small amount of gum and allowed to stand for 12 hr. at 25°. The crystalline product was collected and combined with a second crop obtained by concentration of the mother liquor: yield 30.2 g. (92%), m.p. 103.5–108°. Recrystallization from ethyl alcohol gave **3** of m.p. 107–108.5°: infrared (KBr, cm.$^{-1}$), 3230 (NH), 1750 and 1670 (C=O), 1110 (ether).

The **hydrochloride** of **3,** prepared by treatment of a sample in methanol with excess methanolic HCl, was recrystallized from methanol–ether; m.p. 172.5–174.5°.

3-(1-Methyl-3-pyrrolidinyl)indole (7).—A solution of 22.8 g. (0.10 mole) of N-methyl-3-indolylsuccinimide in dioxane was added to a heated suspension of 15.2 g. (0.40 mole) of lithium aluminum hydride in 400 ml. of dioxane at a rate which maintained reflux. The mixture was refluxed for 21 hr., cooled in ice, and treated carefully with ice water until a white solid was obtained. Filtration and evaporation of the filtrate *in vacuo* gave a pale yellow oil which slowly crystallized; yield 17.0 g. (85%). It was recrystallized from ethyl acetate to give a white product of m.p. 111.5–113°; infrared (CCl_4 cm.$^{-1}$), 3550 (NH).

2-(3-Indolyl)-1-pyrroline (VI).—A suspension of 19.8 g. (0.10 mole) of 3-(β-cyanopropionyl)indole[5] (V) in 250 ml. of methanol was hydrogenated at an initial pressure of 3 atm. over Raney nickel catalyst. After 2.5 hr. 2 moles of hydrogen had been absorbed. Continued hydrogenation for 3 days produced no further absorption, even after substitution of fresh catalyst. Removal of the catalyst and concentration *in vacuo* gave a crystalline solid which was triturated in ether and filtered to yield 15.6 g. (85%) of buff-colored material, m.p. 180.5–182.5° dec. An analytical sample was recrystallized from acetone then acetonitrile; m.p. 183–184.5° dec.; lit.[7] m.p. 182.5–183.5°; infrared ($CHCl_3$, cm.$^{-1}$), 3470 (NH).

Anal. Calcd. for $C_{12}H_{12}N$: C, 78.23; H, 6.57; N, 15.21. Found: C, 78.00; H, 6.50; N, 15.27.

3-(2-Pyrrolidinyl)indole (VII). A. By Hydrogenation of VI.—A suspension of 3.7 g. (0.02 mole) of VI in 100 ml. of methanol was hydrogenated at 40° and 3 atm. over 0.2 g. of platinum oxide, the theoretical amount of hydrogen being absorbed in 16 hr. Removal of the catalyst and concentration under reduced pressure left a white crystalline solid which was recrystallized from acetonitrile to give 2.0 g. (54%) of VII, m.p. 138–140°. A sample was recrystallized again from acetonitrile and had m.p. 140–142°; lit. m.p. 145.8–146.6°,[6] 141–143°[7]; infrared (KBr, cm.$^{-1}$), 3280 (NH).

Anal. Calcd. for $C_{12}H_{14}N_2$: C, 77.38; H, 7.58; N, 15.04. Found: C, 77.50; H, 7.64; N, 15.19.

B. By Reduction of VI with Sodium Borohydride.—A solution of 3.7 g. (0.02 mole) of VI in 100 ml. of absolute methanol was treated with 1.5 g. (0.04 mole) of sodium borohydride in portions during 5–10 min. The solution was refluxed for 1 hr., cooled, and treated with 27 ml. of 6 *N* NaOH then 200 ml. of water. After 16 hr. a white crystalline solid was collected and dried *in vacuo* over P_2O_5; yield 2.1 g. (57%), m.p. 139.5–141°. After recrystallization from acetonitrile, the material had m.p. 141.5–142.5° alone or when mixed with VII obtained by catalytic reduction of V. Its infrared spectrum was superimposable on that of the material from A.

Acknowledgment.—We are indebted to Mr. David Whitehead and staff for the infrared data, to Mr. R. M. Downing and Mrs. C. Kalinowski for the elemental analyses, and to Mr. R. B. Babel for the preparation of several of the necessary intermediates.

DL-2-Amino-4-(4-pyridyl)butyric Acid

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Received August 10, 1965

The Michael addition products of acylamidomalonates or acylamidocyanoacetates with acrylonitrile,[2a–c] methyl methacrylate,[2c,d] acrylamide,[2c] acrolein,[3] methyl vinyl ketone,[4] and methyl vinyl sulfone[5] have proved to be useful intermediates for the preparation of amino acids. We report in this communication the successful basic-resin catalyzed addition of ethyl acetamidomalonate to another activated α,β-olefinic system, 4-vinylpyridine, and hydrolysis of the addition product to the new, unnatural, basic amino acid, DL-2-amino-4-(4-pyridyl)butyric acid dihydrochloride (**1**). Compound **1** was found to have no inhibitory effects *in vitro* against standard strains of *Mycobacterium tuberculosis*, bacteria, and fungae.

Experimental Section[6]

DL-2-Amino-4-(4-pyridyl)butyric Acid Dihydrochloride.—A mixture of 21.7 g. (0.1 mole) of diethyl acetamidomalonate, 11.6 g. (0.11 mole) of 4-vinylpyridine, 10 g. of Amberlite 400 (OH form), and 50 ml. of absolute ethanol was heated at 60–70° (stirring) for 20 hr. The mixture was filtered and concentrated *in vacuo* to a heavy syrup which did not crystallize; yield 24 g.

The crude malonate (24 g.) was refluxed for 12 hr. with 6 *N* HCl. The reaction mixture was concentrated to dryness *in vacuo*. The crystalline residue was extracted twice with boiling ethanol (reflux) and recrystallized from methanol–ether; yield 12.5 g. (49.4% over-all), m.p. 223–224°. A second recrystallization from methanol did not change the melting point.

Anal. Calcd. for $C_9H_{14}Cl_2N_2O_2$: C, 42.71; H, 5.58; N, 11.07. Found: C, 43.02; H, 5.78; N, 10.84.

(1) To whom inquiries should be addressed at Psychopharmacology Service Center, National Institute of Mental Health, Bethesda, Md. 20014.

(2) (a) W. E. Hanby, S. G. Waley, J. Watson, and E. J. Ambrose, *J. Chem. Soc.*, 3239 (1950); (b) N. F. Albertson and S. Archer, *J. Am. Chem. Soc.*, **67**, 2043 (1945); (c) K. Shimo and S. Wakamatsu, *J. Org. Chem.*, **26**, 3788 (1961); (d) H. R. Snyder, J. F. Shekleton, and C. D. Lewis, *J. Am. Chem. Soc.*, **67**, 310 (1945).

(3) D. T. Warner and O. A. Moe, *ibid.*, **70**, 2765 (1948); J. W. Cornforth, R. Cornforth, C. E. Dahlgleisch, and A. Neuberger, *Biochem. J.*, **48**, 591 (1957).

(4) H. Gershon and A. Scala, *J. Org. Chem.*, **26**, 2347 (1961); F. Leonard and W. Tschannen, *J. Med. Chem.*, **8**, 287 (1965).

(5) T. Kaneko and T. Inui, *Nippon Kagaku Zasshi*, **76**, 306 (1955); *Chem. Abstr.*, **51**, 17747 (1957).

(6) Microanalyses were performed by Mr. J. Deonorine of these laboratories. All melting points were determined on a Thomas–Hoover melting point apparatus and are corrected.

5-Nitro- and 5-Aminogramines

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As part of a program designed to detect physiological activity in organic compounds, we have prepared a series of 5-nitro- and 5-aminogramines. Previous work has shown that gramine compounds can exert a variety of physiological actions in animals including antiserotonin activity,[1,2] hypotension,[3] and oxytocic activity.[3–6]

(1) E. N. Shaw and D. W. Woolley, *J. Pharmacol. Exptl. Therap.*, **116**, 164 (1956).

(2) G. Ehrhart and I. Hennig, *Arch. Pharm.*, **294**, 550 (1961).

(3) D. K. DeJongh and E. G. Van Proosdij-Hartzema, *J. Pharmacol. Exptl. Therap.*, **105**, 130 (1952).

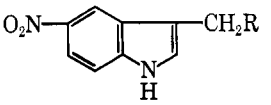
(4) E. G. Van Proosdij-Hartzema and D. K. DeJongh, *Arch. Intern. Pharmacodyn.*, **98**, 335 (1954).

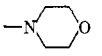
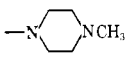
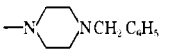
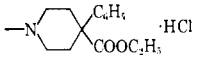
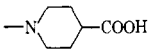
(5) A. M. Akkerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

(6) A. M. Akkerman, D. K. DeJongh, and H. Veldstra, *ibid.*, **70**, 899 (1951).

TABLE I

5-NITROGRAMINES

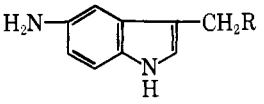


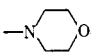
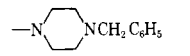
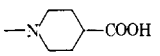
R	M.p., °C.	Yield, %	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	LD_{50}, mg./kg. i.v.	Remarks[a]
$N(CH_3)_2$[b]									2.00	CNS depression, ataxia
$N(C_2H_5)_2$	135–137.5	49	63.1	6.93	17.0	63.5	6.81	17.2	8.91	CNS depression, low carriage, muscle depression
$N(C_3H_7)_2$	96–99	68	65.4	7.69	15.3	65.4	7.45	15.2	20.0	Muscle depression
$N(C_4H_9)_2$	80–93	3[c]	67.3	8.31	13.8	67.0	8.18	14.1	22.4	CNS depression, decreased muscle tone
	161–163	82	63.7	6.16	17.1	63.9	6.36	17.0	3.55	CNS depression
	150–152	72	64.9	6.61	16.2	64.8	6.68	15.9	1.78–2.24	CNS depression, low carriage
	150–153	33	59.8	5.78	16.1	59.8	5.86	15.9	8.91–14.1	Decreased activity, low carriage
	92–94	78	60.3	6.69	20.1	60.0	6.67	20.0	56.2	Ataxia, low carriage
	108–112	9[c]	68.6	6.34	16.0	68.5	6.34	15.8	39.8	Hind-limb ataxia, tremors, weakness
	240–242	30	62.2	5.95	9.48	62.3	6.18	9.60	11.2	CNS depression
	262–264	44	59.6	5.34	13.9	59.5	6.01	13.6	>200	CNS depression, muscle depression, mydriasis

[a] In conducting the research reported herein, the investigators adhered to the "Guide for Laboratory Animal Facilities and Care," U. S. Public Health Service Publication No. 1024, Revised 1965. [b] See ref. 7. [c] The low yields are due to difficulty of separation from polymeric material.

TABLE II

5-AMINOGRAMINES



R	M.p., °C.	Yield, %	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N	LD_{50}, mg./kg. i.v.	Remarks
$N(CH_3)_2$	131–133	43	69.8	7.99	22.2	70.1	7.79	21.6	50.1	CNS depression
	126–128	38	72.5	79.6	19.5	72.5	7.81	19.3	25.1	CNS depression, ataxia, motor deficit
	90–93	7[a]	73.4	8.36	18.3	73.3	8.47	18.1	35.5	Motor deficit
	148–150	68	67.5	7.41	18.2	67.6	7.25	18.1	>100	CNS depression, ataxia, motor deficit
	147–149	65	75.0	7.55	17.5	74.5	7.56	17.1	56.2	CNS depression
	190–193	48	64.3	7.33	16.1	64.8	7.00	15.6	>200	CNS stimulation

[a] The low yield is due to difficulty of separation from polymeric material.

The 5-nitrogramines were prepared by the usual Mannich procedure with 5-nitroindole, formaldehyde, and a secondary aliphatic amine in aqueous acetic acid according to Cavallini and Ravenna,[7] who prepared 5-nitrogramine itself. The 5-aminogramines were prepared by platinum oxide catalyzed hydrogenation of the nitro compounds at atmospheric pressure. No hydrogenolysis of the dialkylaminomethyl group to form skatoles was observed as reported by Merchand.[8]

The 5-nitrogramines (Table I and II), when tested in the general behavioral screen with mice, showed mainly CNS depression. However, the toxicities of these compounds were rather high. It is interesting that an increase in the carbon-chain length lowers the toxicity as seen in the first four compounds of Table I. The 5-aminogramines also showed a decrease in toxicity, but in general the compounds were not sufficiently active to be of interest.

(7) G. Cavallini and F. Ravenna, *Farmaco* (Pavia), *Ed. Sci.*, **13**, 105 (1958).

(8) B. Merchand, *Chem. Ber.*, **95**, 577 (1962).

Experimental Section

5-Nitro-3-dialkylaminomethylindoles.—These compounds were prepared from 5-nitroindole by the general procedure of Cavallini and Ravenna,[7] who prepared 5-nitrogramine. The amines were separated from accompanying polymeric material either by extraction into hot 6 *N* HCl, followed by precipitation with ammonia, or by recrystallization from toluene or ethanol.

5-Amino-3-dialkylaminomethylindoles.—The corresponding aminogramines were prepared by low-pressure hydrogenation of the nitro compounds over platinum oxide in ethanol. The amino compounds were somewhat unstable and difficult to obtain pure. For this reason not all of the nitrogramines were successfully converted to their amino analogs. The 5-amino compounds were recrystallized from benzene and cyclohexane mixtures. No tendency towards hydrogenolysis of the dialkylamino moiety was observed as evidenced by the consumption of only 3 equiv. of hydrogen in each case.

Melting points, yields, and analytical data for all the new compounds prepared are presented in Tables I and II.

Acknowledgment.—We wish to thank Dr. Samuel Ferguson and his staff for the mouse behavioral data and toxicities.

Substitution in the Hydantoin Ring. III. Bicyclo[3.3.0]octane Derivatives

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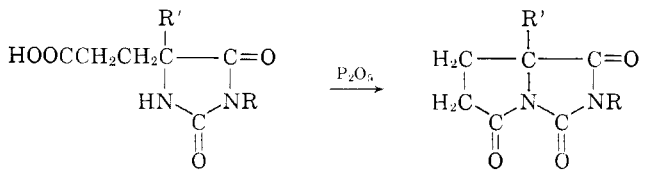
Received August 13, 1965

The dehydration of 4-methyl- and 4-phenyl-2,5-dioxo-4-imidazolidinepropionic acid (Ia[1] and Ib) with phosphorus pentoxide produced the cyclized products 7,7a-dihydro-7a-methyl- and 7a-phenyl-1H-pyrrolo[1,2-*c*]-imidazole-1,3,5(2H,6H)-trione (IIa and IIb). That



Ia, R = H; R′ = CH_3
b, R = H; R′ = C_6H_5

IIa, R = H; R′ = CH_3
b, R = H; R′ = C_6H_5
c, R = $CH_2NHC_6H_5$; R′ = CH_3
d, R = $CH_2NHC_6H_5$; R′ = C_6H_5

the cyclization occurred at the N-1 amide and not the N-3 imide position of the hydantoin ring was suggested by several observations. (a) IIa and IIb were readily soluble in dilute sodium hydroxide. (b) IIa showed a bathochromic shift in the ultraviolet spectrum upon changing from a neutral or acidic medium to an alkaline one.[2] Thus, in methanol or acidified methanol, the ultraviolet absorption maximum occurred at 207 mμ, whereas in alkaline methanol this maximum occurred at 223 mμ. (c) Ia and Ib each exhibited two pK_a values attributable to the carboxylic acid and imide functional groups, whereas IIa and IIb each exhibited one pK_a value attributable to the imide functional group. (d) IIa and IIb readily underwent condensation with formaldehyde and aniline to form IIc and IId, respectively. The condensation of hydantoins which are unsubstituted in the N-3 imide position with formaldehyde and amines to produce N-3 aminomethyl derivatives has received extensive investigation recently.[3-5] (e) Dehydration of 2,5-dioxo-4-imidazolidinepropionic acid has previously been shown to occur at the amide position to produce 7,7a-dihydro-1H-pyrrolo[1,2-*c*]imidazole-1,3,5(2H,6H)-trione.[6]

Pharmacology.—Several chemotherapeutic and pharmacologic tests on compounds IIa and IIb were conducted by Merck Sharp and Dohme Research Laboratories, Division of Merck and Co., Inc. The *Escherichia coli in vitro* assay, tests for effects on the nervous system in mice, and antiinflammatory activity were determined as described previously.[7] In the *E. coli in vitro* assay the compounds were inactive at 1 mg./ml. No significant effects on the nervous system were observed. In the antiinflammatory test, IIb was inactive at 100 mg./kg.

Experimental Section[8]

7,7a-Dihydro-7a-methyl-1H-pyrrolo[1,2-*c*]imidazole-1,3,5-(2H,6H)-trione (IIa).—Three grams (0.02 mole) of Ia[1] was dissolved in 50 ml. of hot 1,1,2,2-tetrachloroethane, and 1.5 g. (0.01 mole) of P_2O_5 was added quickly. The mixture was refluxed 2 hr. and then filtered from the charred residue. Upon cooling the filtrate, IIa precipitated in 85% yield. After recrystallization from tetrachloroethane and vacuum drying, it melted at 210.5°. The product was very soluble in dilute NaOH and somewhat soluble in water and ethanol; $\lambda_{max}^{CH_3OH}$ 207 mμ (ε 10,593), $\lambda_{max}^{CH_3OH-HCl}$ 207 mμ (ε 10,392), $\lambda_{max}^{CH_3OH-KOH}$ 223 mμ (ε 12,998). Potentiometric titration of IIa (4.15 mg./100 ml. of water) with 0.005 *N* NaOH gave a pK_a of 6.80. The starting reagent, Ia (53.5 mg./100 ml. of water and titrated with 0.025 *N* NaOH), had pK_{a_1} = 4.40 and pK_{a_2} = 8.55.

Anal. Calcd. for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66; mol. wt., 168.2. Found: C, 50.40; H, 4.96; N, 16.64; mol. wt., 167.6.

Attempts to effect the cyclization in either dilute HCl or $POCl_3$ in dioxane resulted only in the recovery of unreacted hydantoin. Cyclization was effected in polyphosphoric acid, but the yield of IIa was low.

2,5-Dioxo-4-phenyl-4-imidazolidinepropionic Acid (Ib).—The preparation of Ib from benzoylethene has been described previously.[9] In this study the compound was prepared from 3-benzoylpropanoic acid, $(NH_4)_2CO_3$, and KCN in 60% ethanol in a manner similar to that described by Goodson.[10] The reaction medium was maintained at 60° for 24 hr. The product was recrystallized from ethanol; yield 80%, m.p. 216–217.5°. Additional recrystallizations raised the melting point to 219° (lit.[9] m.p. 215°).

7,7a-Dihydro-7a-phenyl-1H-pyrrolo[1,2-*c*]imidazole-1,3,5-(2H,6H)-trione (IIb).—Ib (2 g., 0.008 mole) and 1 g. (0.007 mole) of P_2O_5 were suspended in 50 ml. of *m*-xylene and refluxed for 3 hr. The insoluble substances were filtered hot and the residue was washed with aqueous $NaHCO_3$ to give IIb (78%). It was insoluble in water but was soluble in dilute NaOH. After recrystallization from ethanol it melted at 265.5–266.5°; $\lambda_{max}^{CH_3OH}$ 263, 258.5 mμ (ε 276, 405); $\lambda_{max}^{CH_3OH-HCl}$ 262.5, 258.5 mμ (ε 424, 553).

(1) K. Pfister, W. J. Leanza, J. P. Conbere, H. J. Becker, A. R. Matzuk, and E. F. Rogers, *J. Am. Chem. Soc.*, **77**, 697 (1955).

(2) R. E. Stuckey, *J. Chem. Soc.*, 331 (1947).

(3) M. B. Winstead, D. E. Barr, C. R. Hamel, D. J. Renn, H. I. Parker, and R. M. Neumann, *J. Med. Chem.*, **8**, 117 (1965).

(4) O. O. Orazi and R. A. Corral, *Tetrahedron*, **15**, 93 (1961).

(5) J. N. Coker and M. Fields, *J. Org. Chem.*, **27**, 2226 (1962).

(6) J. L. Szabo and J. V. Karabinos, *J. Am. Chem. Soc.*, **66**, 650 (1944).

(7) M. B. Winstead and C. R. Hamel, *J. Med. Chem.*, **8**, 120 (1965).

(8) Melting points were determined in a Mel-Temp apparatus and are corrected. Infrared and ultraviolet spectrograms of the compounds reported appear in the "Sadtler Standard Spectra Catalog," Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1965. Nitrogen analyses are by the semimicro Kjeldahl method. Other analyses were determined by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Potentiometric titrations were conducted with a Beckman Zeromatic pH meter using a glass electrode and a reference electrode saturated with potassium chloride.

(9) H. R. Henze and R. E. Leslie, *J. Org. Chem.*, **14**, 602 (1949).

(10) L. H. Goodson, I. L. Honigberg, J. J. Lehman, and W. H. Burton, *ibid.*, **25**, 1920 (1960).