residue was recrystallized four times from 1:2 methanol–ether to give 3.07 g. (8%), m.p. 247–250°.

Material from the mother liquors (17.5 g.), despite repeated crystallizations from various solvents, melted at 202–219°. We were unable to show this material to be different from the 3.07-g. fraction by elemental analyses, mixture melting point, infrared absorption, or thin layer chromatography, and its configuration at the spiro carbon remains in doubt.

β-*dl*-2,2-Dicyclohexyl-4-(2-piperidyl)-1,3-dioxolane Hydrochloride (30).—Compound **21** (17.3 g., 0.05 mole) was suspended in aqueous caustic and extracted into ether, and the ether was evaporated to give an oil. The oil was dissolved in 110 ml. of cold glacial acetic acid and 3 g. of 5% rhodium on alumina and hydrogenated for 26 hr. while the hydrogen pressure dropped 1.13 kg./cm.² (calcd. 0.88 kg./cm.²). The mixture was filtered and the solvent was distilled at reduced pressure leaving a residue which was neutralized with 50 ml. of 8% NaOH and extracted with ether. The combined extracts were dried ($MgSO_4$), filtered, and evaporated to an oil which crystallized on contact with dry ether. The 12 g. of crude product was dissolved in 200 ml. of ether and its hydrochloride was precipitated by adding 1.36 g (0.037 mole) of dry HCl in 24 ml. of 2-propanol. Recrystallization from 2-propanol gave 7.8 g. (44%) of product, m.p. 282° dec.

β-*dl*-4-(1-(Methyl-2-piperidyl)-2,2-diphenyl-1,3-dioxolane N-Oxide Hydrochloride (54).—Compound **27** (10 g., 0.028 mole) was suspended in aqueous caustic and extracted into ether, and the ether was evaporated to give an oil which was taken up in 100 ml. of methanol containing 14 ml. of 30% H_2O_2 in water. The reaction mixture stood for 2 weeks at +2° while a precipitate developed. The solvent was removed and the residue was taken up in 50 ml. of methanol, stirred with 100 mg. of PtO_2 until no further bubbles developed, and then filtered. Removal of the solvent gave a white solid which was recrystallized from ethyl acetate containing a trace of methanol. It was redissolved in fresh, dry methanol–ethyl acetate and treated with 0.7 g. of dry HCl in 5 ml. of 2-propanol to precipitate the hydrochloride, which was recrystallized from 75 ml. of butanol containing a trace of methanol and then from ethanol to give 4.2 g. (40%) of product, dec. pt. 190°.

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Notes

3-Indolylsuccinimides and 3-(3-Pyrrolidinyl)indoles

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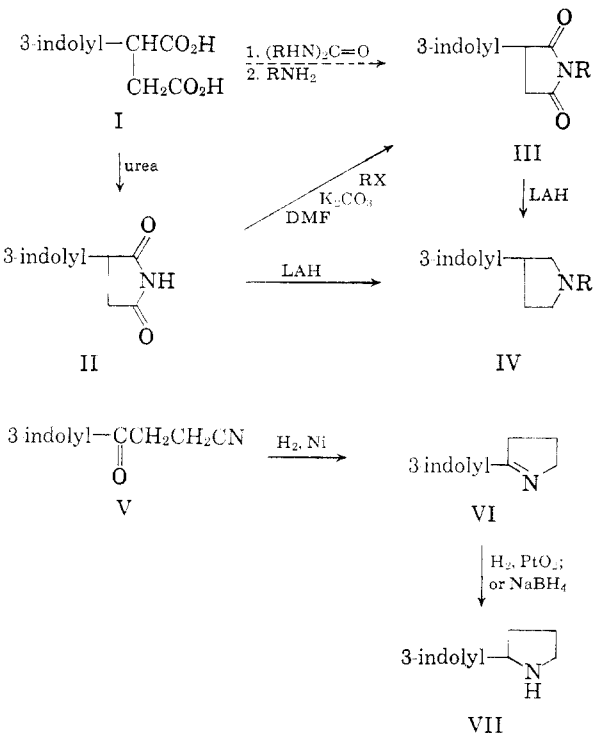
In a previous publication[2] we reported that 3-indolesuccinic acid (I) could be converted to 3-indolesuccinimide (II) by fusion with urea. Treatment of I with 1,3-dimethyl- and 1,3-diethylureas under the same conditions has given N-methyl- and N-ethyl-3-indolylsuccinimides (III, Scheme I). The same products have also been obtained by the reaction of 3-indolesuccinimide with methyl and ethyl iodides, respectively, in the presence of potassium carbonate in dimethylformamide. The reaction of potassium 3-indolesuccinimide with ethyl iodide in dimethylformamide gave N-ethyl-3-indolylsuccinimide in good yield.

Other N-substituted 3-indolylsuccinimides were prepared by the reaction of 3-indolesuccinic acid with amines in refluxing toluene, with azeotropic removal of the water formed. N-(2-Morpholinoethyl)-, N-(3-morpholinopropyl)-, and N-[2-(2-pyridyl)ethyl]-3-indolylsuccinimides were prepared in this manner (Scheme I) and are recorded in Table I.

Reduction of the N-substituted 3-indolylsuccinimides[3] with lithium aluminum hydride in dioxane or tetrahydrofuran produced the corresponding 3-(1-substituted 3-pyrrolidinyl)indoles[3] (IV, Table II). In some cases these products could not be obtained in pure form and are not reported here.

An approach to the synthesis of 3-(2-pyrrolidinyl)-indoles seemed possible through a procedure analogous

SCHEME I

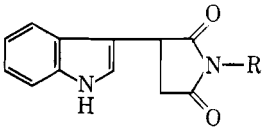


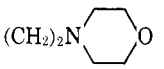
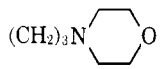
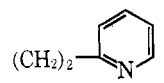
to that of Burckhalter and Short,[4] who hydrogenated β-aroylpropionitriles over Raney nickel catalyst to produce 2-arylpyrrolidines. Therefore, 3-(β-cyanopropionyl)indole[5] was hydrogenated in methanol over Raney nickel catalyst until hydrogen absorption had ceased. The uptake corresponded to 2 moles and the product was identified as 2-(3-indolyl)-1-pyrroline (VI), analogous to the 2-aryl-1-pyrrolines obtained by Burckhalter and Short when the hydrogenations of β-aroylpropionitriles were interrupted after the absorption of 2 moles of hydrogen. This compound was converted to the

(1) To whom inquiries concerning this manuscript should be addressed.
(2) Y. G. Perron and W. F. Minor, *J. Org. Chem.*, **24**, 1165 (1959).
(3) Y. G. Perron and W. F. Minor, U. S. Patent 3,109,844 (Nov. 5, 1963).
(4) J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1281 (1958).
(5) J. Szmuszkovicz, *J. Am. Chem. Soc.*, **82**, 1180 (1960).

TABLE I

3-INDOLYLSUCCINIMIDES

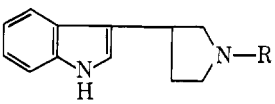


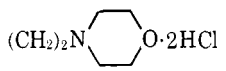
No.	R	Method[a]	Yield, %	M.p., °C.	Recrystn. solvent[b]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	LD_{50}, mg./kg. i.p.[c]
1	CH_3	A	71	175–176.5	A	$C_{13}H_{12}N_2O_2$	68.14	68.12	5.30	5.14	>1000
	CH_3	B	95	175–176.5							
2	C_2H_5	A	62	93.5–95.5	B	$C_{14}H_{14}N_2O_2$	69.40	69.30	5.83	5.75	>750
	C_2H_5	B	22	92.5–94.5							
	C_2H_5	C	50	92.5–95							
3		D	92	107–108.5	C	$C_{18}H_{21}N_3O_3$	66.03	66.65	6.47	6.46	
3a	Hydrochloride salt of 3			172.5–174.5	D–B	$C_{18}H_{22}ClN_3O_3$	59.50	59.31	6.16	5.82	424
4		D	73	138–139.5	E	$C_{19}H_{23}N_3O_3$	66.84	66.76	6.79	6.62	476
5		D	76	151–153	E	$C_{19}H_{17}N_3O_2$	71.45	71.25	5.37	5.42	>1200

[a] See Experimental Section. [b] A, acetonitrile; B, ether; C, ethyl alcohol; D, methyl alcohol; E, ethyl acetate. [c] Intraperitoneally in mice.

TABLE II

3-(1-SUBSTITUTED 3-PYRROLIDINYL)INDOLES



No.	R	Yield, %	M.p., °C.	Recrystn. solvent[a]	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	—LD_{50}, mg./kg.— I.p.[b]	Oral[b]
6	H	51	102–104.5	A	$C_{12}H_{14}N_2$[c]	77.38	77.25	7.58	7.63		<300
7	CH_3	66	111.5–113	E	$C_{13}H_{16}N_2$	77.96	77.94	8.05	8.00	100	244
										107[d]	413[d]
8	C_2H_5	31	67–68	F	$C_{14}H_{18}N_2$[e]	78.46	78.67	8.47	8.66	66	<300
											<100[d]
9		75	256.5–257	D	$C_{18}H_{26}Cl_2N_3O$	58.00	58.19	7.30	7.36	254	1071
										276[d]	1577[d]

[a] A, acetonitrile; B, ether; C, ethyl alcohol; D, methyl alcohol; E, ethyl acetate; F, petroleum ether (b.p. 60–68°). [b] In mice. [c] *Anal.* Calcd.: N, 15.04. Found: N, 15.01. [d] In rats. [e] *Anal.* Calcd.: N, 13.07. Found: N, 13.00.

desired 3-(2-pyrrolidinyl)indole (VII) by further low-pressure hydrogenation over platinum oxide or by reduction with sodium borohydride. This compound had been previously reported by Fuhlhage and Vander Werf[6] from the reaction of indole and 1-pyrroline. After the completion of our work, it was also reported by Youngdale and co-workers.[8]

Pharmacological Methods

Unless otherwise noted the compounds were administered orally as aqueous suspensions or solutions (depending on individual solubility characteristics) for evaluation of their pharmacologic properties.

Acute Toxicity.—The test compounds were suspended in either 0.9% saline, 2% aqueous acacia, an aqueous lecithin, span, Tween 80-carboxymethylcellulose medium (LST-CMC), or placed into solution with the aid of dilute acids prior to oral or intraperitoneal administration to mice or rats. Doses were increased logarithmically and the 72-hr. LD_{50} was determined, where possible, by the method of Litchfield and Wilcoxon[8] or Weil.[9]

Central Nervous System Activity. A. Stimulation or Depression.—Mice treated orally were observed in an undisturbed condition for signs of depression or stimulation, and also checked for their reaction to selected stimuli.

B. Reflex Depression.—The presence or absence of the righting, pinna, and corneal reflexes were determined. The last two were elicited by a fine wire, while the righting reflex was considered to be depressed if the mice, when placed on their backs, did not right themselves within 30 sec.

C. Muscle Relaxation.—Abdominal and limb tone were subjectively evaluated by gently pressing the abdomen and flexing the hind limbs by gentle pressure. Limb tone and grip strength were further checked by placing the mice on a vertical pole. Their inability to climb the pole or to maintain themselves on it indicated a reduction of these parameters.

D. Spinal Depression.—This test was carried out according to be method of Bastian and Ridlon.[10] An increase of >30% in the time between cervical decapitation and onset of clonic convulsions, as compared to that obtained with controls, was considered a significant depression of the spinal reflex.

(6) D. W. Fuhlhage and C. A. Vander Werf, *J. Am. Chem. Soc.* **80**, 6249 (1958).

(7) G. A. Youngdale, *et al.*, *J. Med. Chem.*, **7**, 415 (1964).

(8) J. T. Litchfield, Jr., and F. Wilcoxon, *J. Pharmacol. Exptl. Therap.* **96**, 99 (1949).

(9) C. S. Weil, *Biometrics*, **8**, 249 (1952).

(10) J. W. Bastian and S. A. Ridlon, *Federation Proc.*, **17**, 1367 (1958).

E. Analgesia.—Analgesic activity was determined by the method of Siegmund, Cadmus, and Lu.[11] A reduction of >30% in the number of writhing movements induced by phenyl-*p*-quinone alone was considered significant activity.

Monoamine Oxidase Inhibition and Antidepressant Activity.—Three hours after oral administration of the test compound reserpine was injected intravenously at a dose of 5 mg./kg. Increased motor activity, profuse salivation, and reversal of ptosis indicated monoamine oxidase inhibitory activity. Reversal of only the reserpine-induced ptosis suggested antidepressant activity without enzyme inhibition.

Edema Inhibition in the Rat Paw.—Rats were injected subcutaneously in the plantar aponeurosis of one hind paw with 0.1 ml. of an edema-inducing agent in 0.9% saline. The contralateral paw was similarly injected with 0.9% saline and served as the control. The degree of edema was determined by fluid displacement. A reduction of >30% in the degree of edema seen in the treated animals, as compared to a control group, was considered significant. The edema-inducing agents were 2% yeast, 1% carrageenin, and 0.01% serotonin. Evaluation for the above agents was at 1 hr., 3 hr., and 20 min. post injection of the paw, respectively.

Antihistaminic Activity.—This activity was initially determined on isolated guinea pig ileum by the Magnus[12] method. Activity was compared with phenyltoloxamine and expressed as a fraction of its potency. Guinea pigs were exposed to a 1% histamine aerosol in a confined chamber. If no anoxic symptoms were observed within 5 min., the animals were considered protected.

Antiserotonin Activity.—Besides the serotonin-induced edema in the rat paw test, inhibition of 5-hydroxytryptophan-induced diarrhea in mice according to the method of Woolley[13] was employed. The determination of antiserotonin activity by the isolated strip from the fundic portion of the rat stomach[14] was also attempted. Treated guinea pigs were also exposed to a 2% serotonin aerosol in a confined chamber. Evaluation was the same as for the histamine-aerosol.

Antihypersensitivity.—Mice were sensitized to horse serum according to the method of Malkiel and Hargis.[15] Following treatment, the mice were challenged by the intravenous injection of 0.5 ml. of horse serum. Death was taken as the end point, with <40% deaths being the level of significant protection.

Guinea pigs were sensitized to ovalbumin and challenged intravenously with an ovalbumin solution.[16] Evaluation was the same as stated above with sensitized mice. An "anaphylactoid" response was also used. White rats, weighing 130 ± 10 g. were adrenalectomized. After 24 hr., animals were treated and 1 hr. later injected with 0.3 ml. of a 6% dextran solution. Evaluation was the same as for the two previous sensitivity tests.

Cardiovascular.—Direct blood pressure measurements were obtained using anesthetized dogs, cats, and rats. The same was accomplished in unanesthetized rats by means of an indwelling polyethylene cannula in the carotid artery. Recording was by means of a Statham P23Gb transducer with suitable recorder, or kymographically with a mercury manometer or double-membrane tambour.

Charcoal Meal.—Treated mice were given 0.5 ml. of a 5% charcoal suspension in 2% acacia by gavage. One hour later the animals were sacrificed and the entire small intestine was removed. The distance traveled by the charcoal in the small intestine was determined.

Results

Compounds **1–5** were without effect in any of the experimental tests following oral doses of 100–300 mg./kg. This lack of activity cannot be ascribed solely to poor absorption or to low dosage levels, since the compounds were also devoid of activity when tested *in vitro*. The acute toxicity of these compounds, as summarized in Table I, also reflected a low level of pharmacological response. The intraperitoneal LD_{50} values ranged from 424 to >1200 mg./kg. in mice.

Reduction of the N-substituted 3-indolylsuccinimides (Table I) to the corresponding 3-(1-substituted 3-pyrrolidinyl)indoles (Table II) produced significant changes in pharmacological properties, which are summarized in Table III. The LD_{50} values were decreased (Table II). The LD_{50} of VI was >250 but <500 mg./kg. i.p. and <300 mg./kg. orally in mice; for VII it was 198 mg./kg. i.p. and <300 mg./kg. orally in mice. The toxicity data also indicate relatively complete oral absorption, with the exception of **9**, since the difference between intraperitoneal and oral toxicity is small. By *in vitro* methods **6–9** were effective antihistaminic agents. This was confirmed in dogs, following intravenous administration, by their inhibition of histamine depressor responses. Except **9** these same compounds, as well as VI and VII, were spasmogenic to guinea pig ileum. Following oral administration, **6–9** and VII inhibited serotonin-induced edema in the raw paw. Muscle relaxant, spinal depressant, analgesic, monoamine oxidase inhibitory, and antidepressant activity, singly or in combination, were seen with **6–9**, VI, and VII. However, as can be seen in Table III, any activity seen was at high doses and was considered to be referable to toxicity.

3-(1-Methyl-3-pyrrolidinyl)indole (**7**) was selected for more extensive pharmacological study because of its significant, combined antihistamine–antiserotonin activity. Being insoluble in water, it was employed as a suspension in 1% aqueous acacia or placed into solution with acid. For the latter, dilute acetic acid was used or CO_2 was bubbled through a fine, aqueous suspension. The pH of solutions varied from 7.4–8.4, depending on the concentration.

The acute oral and intraperitoneal LD_{50} values were determined in mice and rats using a suspension in 1% aqueous acacia. In mice these values, with 95% confidence limits, were 97 (85–117) mg./kg. i.p. and 244 (217–276) mg./kg. orally, while in rats they were 107 (82–140) mg./kg. and 417 (288–592) mg./kg, respectively. Good oral absorption is indicated by these results. Grossly observed symptoms at toxic dose levels were due to a marked central nervous system stimulation. The animals displayed a general muscular rigidity with the hind limbs assuming a "spread-eagle" effect. A semi-Straub position of the tail was seen, excessive salivation occurred, reactions to stimuli of sound or touch were pronounced, and respiration was increased.

Antiserotonin activity was evidenced by several methods. The minimally effective oral dose which significantly inhibited serotonin-induced edema in the rat paw was 6.25 mg./kg. Inhibition of the diarrhea produced in mice by the intraperitoneal injection of 5-hydroxytryptophan was achieved at oral doses down to 50 mg./kg. In relation to this latter test it was determined that **7**, at the same dose, also reduced the distance a charcoal meal traveled along the gastrointestinal tract. This effect could reflect its spasmogenic activity as it had no anticholinergic effect. No specific antiserotonin action could be determined on the isolated fundic strip prepared from the rat stomach because of

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

(12) R. Magnus, *Arch. Ges. Physiol.*, **102**, 123 (1904).

(13) D. W. Woolley, *Proc. Soc. Exptl. Biol. Med.*, **98**, 367 (1958).

(14) J. R. Vane, *Brit. J. Pharmacol.*, **12**, 344 (1957).

(15) S. Malkiel and B. J. Hargis, *Proc. Soc. Exptl. Biol. Med.*, **81**, 109 (1952).

(16) D. H. Campbell, J. S. Garvey, N. E. Cremer, and D. H. Sussdorf, "Methods in Immunology," W. A. Benjamin Inc., New York, N. Y., 1963, p. 217.

TABLE III

INITIAL PHARMACOLOGICAL TESTING (ORAL)[a]

No.	Muscle relax. MED[b]	Spinal depression MED[b]	Analgesia MED[b]	MAO inhib. MED[b]	Anti-depressant MED[b]	Antihistamine phenyltoloxamine index	Antiserotonin foot edema MED[b]
6	150	...[c]	...	150	150	1/50	12.5
7	...	...	...	50	50	1.0	6.2
8	100	100	25	...	100	1/10	12.2
9	300	...	...	...	...	1/5	50.0
VI	...	...	...	...	100	<1/200	150.0
VII	...	150	75	...	...	<1/200	25.0

[a] All doses shown are milligrams per kilogram. [b] Minimal effective dose. [c] Dots indicate that no significant activity was seen.

the compound's spasmogenicity. It was observed that such a strip, placed into spasm with serotonin, could be relaxed by introduction of compound **7**. At 33 mg./kg. i.p. in guinea pigs, **7** afforded protection against the anoxic seizures produced by aerosolization of a 2% serotonin solution into a confined chamber. It was also effective intravenously in preventing the rise in blood pressure induced by intravenous serotonin.

Antihistaminic activity was demonstrated on the isolated guinea pig ileum and by its inhibition of the depressor response induced by histamine in anesthetized dogs. Doses of 33 mg./kg. i.p. and 60 mg./kg. orally protected guinea pigs from fatal seizures when histamine was aerosolized into a confined chamber. By these tests, compound **7** proved as effective as phenyltoloxamine.

Because of its combined antihistaminic–antiserotonin activity, compound **7** was tested in several laboratory models where this type of compound has proven to be effective. At 60 mg./kg. orally and 4.2 mg./kg. i.p. it reduced the edema induced in the rat paw by yeast. At 33 mg./kg. i.p., **7** prevented anaphylactic death in mice sensitized to horse serum, but orally it was not effective. Poor and variable results in protecting guinea pigs against anaphylactic death were obtained, but effective protection against dextran-induced anaphylactoid death in adrenalectomized rats was seen.

Compound **7** resembled serotonin in being a smooth muscle spasmogen. Also, it produced a decrease of blood pressure in cats and rats, while in dogs an elevation in pressure was seen as with serotonin. The blood pressure effects were more prolonged than those with serotonin.

The 1-benzyl analog of serotonin (BAS) was also examined in the antiserotonin tests along with **7**. As reported,[13] BAS was quite effective in blocking the 5-hydroxytryptophan-induced diarrhea, as was **7**, but BAS showed no activity in the other tests where **7** was effective.

Oral administration of 10–30 mg./kg. in cats and dogs produced bizarre, central nervous system effects. These doses exerted no important effects upon consciousness or motor function. In these species the same pattern of muscle rigidity seen in mice and rats was evident. However, a marked alteration in "personality" occurred. Normally social and affectionate animals became notably unfriendly and hostile. In some instances they exhibited signs similar to LSD-induced "sham rage," responding to approach by hissing or howling, wild-eyed excitement or fear, and aggressiveness. At other times the animals appeared as though they were having hallucinations, inasmuch as these symptoms occurred spontaneously, no stimulus being apparent. At these doses emesis was occasionally seen, indicating central nervous system stimulation also.

General Comments.—Combined antihistaminic–antiserotonin activity was demonstrated for **6–9** in animal experimentations. Upon further pharmacological testing of the most active of these compounds, **7**, it was found that unusual central nervous sytem manifestations were also inherent in this compound. Separation of these two main areas of activity was not readily achieved on the basis of dose.

Experimental Section[17]

Preparation of 3-Indolylsuccinimides.—The following examples illustrate the methods used to prepare the compounds described in Table I.

Synthesis of N-Methyl-3-indolylsuccinimide (1). A. By Reaction of 3-Indolesuccinic Acid (I) with 1,3-Dimethylurea.—A mixture of 11.7 g. (0.05 mole) of I[2,3] and 13.4 g. (0.15 mole) of 1,3-dimethylurea in a round-bottomed flask was introduced into an oil bath at 165°. The bath temperature was raised to 185° during 10 min. and maintained at 180–190° for 1 hr. The hot melt was diluted with several times its volume of cold water, cooled, and filtered. Recrystallization of the crude product from acetonitrile gave 8.0 g. (71%) of **1**: m.p. 175–176.5°; infrared (KBr, cm.$^{-1}$), 3320 (NH), 1762 and 1680 (C=O).

B. By Alkylation of 3-Indolylsuccinimide with Methyl Iodide.—A mixture of 5.4 g. (0.025 mole) of II,[2,3] 3.5 g. (0.025 mole) of anhydrous K_2CO_3, and 6.2 g. (0.05 mole) of iodomethane in 40 ml. of dimethylformamide (DMF) was stirred for 7.5 hr. at 25° and diluted to 250 ml. with water. The crystalline product was collected, washed with water, and dried *in vacuo* over P_2O_5; yield 5.4 g. (95%), m.p. 174.5–176.5°. Recrystallization from acetone gave **1**, m.p. 174.5–176° alone or in mixture with that from A. Its infrared spectrum was superimposable on the spectrum of the material prepared in A.

C. N-Ethyl-3-indolylsuccinimide (2).—A solution of 2.14 g. (0.01 mole) of II in 50 ml. of hot ethyl alcohol was added to 0.65 g. (0.01 mole) of 85% KOH in 0.6 ml. of water and 1.8 ml. of ethyl alcohol. After 18 hr. at 5°, the solution was evaporated to dryness under reduced pressure, and the white foam was triturated in ether and filtered to yield, after drying, 2.28 g. (90.5%) of crude potassium 3-indolylsuccinimide. This in 16 ml. of DMF was treated with 3.12 g. (0.02 mole) of iodoethane, stirred for 0.5 hr. at 25°, and poured into 100 ml. of water. The crude product was recrystallized from ether; yield 999 mg. (50.4%); m.p. 92.5–95°; infrared (KBr, cm.$^{-1}$), 3320 (NH), 1762 and 1680 (C=O). This product gave no melting point depression when mixed with N-ethyl-3-indolylsuccinimide prepared by procedure A. The aqueous mother liquor was extracted three times with $CHCl_3$. The combined extracts were washed, dried, and concentrated *in vacuo* to give a gum which crystallized, on trituration in water, to 420 mg. (21%) of crude II.

D. N-[2-(Morpholino)ethyl]-3-indolylsuccinimide (3).—A mixture of 23.3 g. (0.10 mole) of I and 13.0 g. (0.10 mole) of N-(2-aminoethyl)morpholine in 300 ml. of dry toluene was refluxed for 20 hr., 3.7 ml. (0.20 mole) of water being separated by

(17) Melting points were determined on a Mel-Temp aluminum-block apparatus, or in open capillaries on a Hershberg apparatus, and are corrected. All chemical intermediates were obtained from commercial sources unless otherwise specified. Analyses are recorded in Tables I and II if they do not appear in the text. The infrared spectra were recorded on a Beckman IR 9 spectrometer.

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.

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

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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.

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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]

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