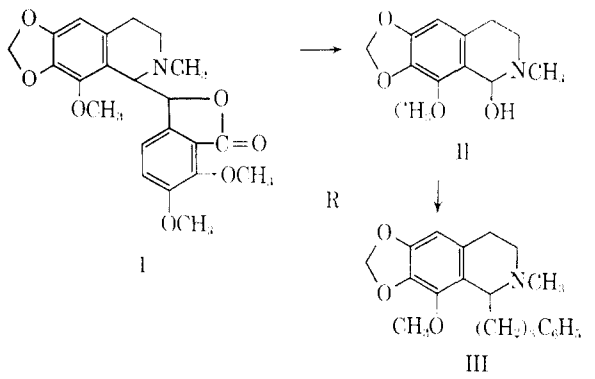
revealed activity against several microorganisms, among them a resistant strain of *Staphylococcus aureus*.



I II III

Experimental

1-(3-Phenylpropyl)-2-methyl-6,7-methylenedioxy-8-methoxy-1,2,3,4-tetrahydroisoquinoline (III) Hydrochloride.—3-Phenylpropylmagnesium bromide (0.18 mole) was prepared from 3-phenylpropyl bromide by the Grignard procedure and added (rapidly) to a vigorously stirred suspension of cotarnine[5] (II, 0.04 mole) in ether. The mixture was stirred for about 2 hr. and poured into a mixture of NH_4Cl, ice, and water. The aqueous solution was separated and washed with ether. The combined organic solution was extracted with dilute HCl, cooled in ice, and made basic with concentrated NH_4OH. Extraction with chloroform and ether, followed by drying over $MgSO_4$, gave about 17 g. of a red oil. The oil was dissolved in ether and a hydrochloride (HCl gas) was prepared. The solid was crystallized from acetone–methanol–ether to give III·HCl, 8.9 g. (60%), m.p. 182.5–183.5 or 193°, depending on its crystalline form.

Anal. Calcd. for $C_{21}H_{25}ClNO_3$: C, 67.28; H, 6.72; Cl, 9.45; N, 3.73. Found: C, 67.30; H, 6.91; Cl, 9.53; N, 3.82.

The infrared spectrum of III·HCl was consistent with the given structure; ν_{max}^{Nujol} 1370 and 930 (methylenedioxy), 1270 and 1060 (OCH_3), 900 and 790 (isolated phenyl hydrogen), 733 and 690 (monosubstituted benzene), and 2500 cm.$^{-1}$ (R_3N^+H). The n.m.r. spectrum was also fully consistent with the structure III.

(5) The cotarnine was obtained as a fragmentation product of narcotine by the general procedure of T. Anderson, *Ann.*, **86**, 179 (1853), as cited in the "Chemistry of the Opium Alkaloids," L. F. Small and R. E. Lutz, Government Printing Office, Washington, D. C., 1932, p. 49. We would like to thank the Mallinckrodt Chemical Works, St. Louis, Mo., for a generous supply of noscapine.

Structure–Activity Relationships in Antiinflammatory and Analgesic Compounds Chemically Related to α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide

G. PALA, S. CASADIO, T. BRUZZESE, E. CRESCENZI, AND E. MARAZZI-UBERTI

Research Laboratories of Istituto De Angeli S.p.A., Milan, Italy

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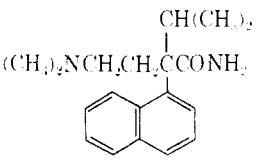
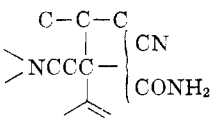
In previous papers we reported the pharmacological screening results of many naphthalene derivatives,[1] comparing them, in some cases, with corresponding benzene compounds. More specifically, 1-naphthylacetonitriles, 1-naphthylacetamides, and 1-naphthylmethyl ketones substituted in the α-position with basic radicals were studied. The most interesting result arising from these studies was the noteworthy antiinflammatory activity shown by the primary 1-naphthylacetamides, and in particular by α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide (**1**, naphthypramide),[2] a substance which is under clinical trial.



1

Some conclusions may be drawn about relationships between antiinflammatory and analgesic activities, and the structure of the above compounds and of the substances synthesized in this work. First, these activities are imparted to the compounds by the presence of a $CONH_2$ or CN group. Ketones and tertiary amides were poorly active or essentially inactive. Another important conclusion is that 1-naphthalene derivatives are, on the whole, more interesting than the corresponding benzene compounds. Substitution of the 1-naphthyl group with an isopropyl, 1-naphthylmethyl, or 2-naphthyl group leads in general to a noticeable reduction or, at most, to some retention of activity; however, the potency is never enhanced. For optimal activity, the α-methylene group in amides and nitriles must be disubstituted with an aminoethyl group along with an alkyl group. Disubstitution with two aminoethyls leads to poorly active compounds. Branching the alkyl chain is also required for the highest activity.

From these considerations the tentative conclusion may be drawn that, in the series investigated, the skeleton **2** represents the best structure for high-potency antiinflammatory and analgesic compounds.



2

Experimental[3]

Chemistry.—The new compounds are listed in Table 1, along with yields, physical constants, and analytical data.

α,α-Diisopropyl-α-(2-dimethylaminoethyl)acetonitrile (I).—Ferric nitrate [$Fe(NO_3)_3 \cdot 9H_2O$] (0.37 g.) and then sodium (13.53 g., 0.59 g.-atom) were added, in small portions and with stirring, to anhydrous liquid ammonia (265 ml.), making certain that between additions the solution's color changed from blue to gray. The mixture was then stirred for an additional 15 min.; after that α,α-diisopropylacetonitrile[4] (36.7 g., 0.293 mole) and 308 ml. (0.588 mole) of a 20.5% ethereal solution of 2-(N,N-dimethylamino)-1-chloroethane were added. The solution was then stirred for 30 hr. at the reflux temperature of liquid ammonia, using a reflux condenser cooled with Dry Ice–acetone. The ammonia was then evaporated on a water bath, and the residue was cautiously decomposed with water and extracted with ether.

(1) (a) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *Farmaco* (Pavia), *Ed. Sci.*, **19**, 731 (1964); (b) G. Pala, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **19**, 933 (1964); (c) S. Casadio, G. Pala, E. Crescenzi, T. Bruzzese, E. Marazzi-Uberti, and G. Coppi, *J. Med. Chem.*, **8**, 589 (1965); (d) S. Casadio, G. Pala, T. Bruzzese, E. Crescenzi, E. Marazzi-Uberti, and G. Coppi, *ibid.*, **8**, 594 (1965).

(2) S. Casadio, G. Pala, E. Marazzi-Uberti, and G. Coppi, *Experientia*, **20**, 457 (1964).

(3) Boiling points are uncorrected. Melting points are corrected and were taken on a Büchi capillary melting point apparatus.

(4) M. S. Newman, T. Fukunaga, and T. Miwa, *J. Am. Chem. Soc.*, **82**, 873 (1960).

TABLE I

Compd.	Yield, %	B.p. (mm.) or m.p., °C.	Formula	Calcd., % C	Calcd., % H	Calcd., % N	Found, % C	Found, % H	Found, % N
α,α-Diisopropyl-α-(2-dimethylaminoethyl)acetonitrile (I)	81[a]	72–75 (0.08)	$C_{12}H_{24}N_2$	73.41	12.32	14.27	73.51	12.36	14.13
α,α-Diisopropyl-α-(2-dimethylaminoethyl)acetamide (II)	82[b]	111–112	$C_{12}H_{26}N_2O$	67.24	12.23	13.07	67.29	12.33	12.91
α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylpropionitrile (III)	62[a]	151–153 (0.15)	$C_{20}H_{26}N_2$	81.58	8.90	9.58	81.74	8.87	9.40
α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylpropionamide (IV)	67[b]	128.5–129.5	$C_{20}H_{28}N_2O$	76.88	9.03	8.97	76.74	8.94	8.93
α-(2-Dimethylaminoethyl)-2-naphthylacetonitrile (V)	73[a]	154–155 (0.3)	$C_{16}H_{18}N_2$	80.63	7.61	11.76	80.69	7.65	11.64
α-Isopropyl-α-(2-dimethylaminoethyl-2-naphthylacetonitrile (VI)	81[a]	142–144 (0.1)	$C_{19}H_{24}N_2$	81.38	8.63	9.99	81.25	8.56	10.05
α-Isopropyl-α-(2-dimethylaminoethyl)-2-naphthylacetamide (VII)	63[b]	122.5–123.5	$C_{19}H_{26}N_2O$	76.47	8.78	9.39	76.38	8.85	9.32
α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide methobromide (VIII)	96[b]	171–173	$C_{20}H_{29}BrN_2O$	61.06	7.43	7.12	61.12	7.33	7.08
1-Dimethylamino-3-phenyl-4-hexanone[c] (IX)	61[a]	97–99 (0.5)	$C_{14}H_{21}NO$	76.66	9.65	6.39	76.78	9.73	6.39

[a] Once distilled. [b] Crude product. [c] Reported by F. F. Blicke and E.-P. Tsao, *J. Am. Chem. Soc.*, **75**, 5587 (1953), b.p. 90–92° (0.5 mm.), yield 51.2%.

The ethereal layer was extracted with 10% HCl, the acid solution was treated with charcoal, filtered, made basic to phenolphthalein with 30% NaOH, and the separated oil was extracted with ether. The ethereal solution was dried ($MgSO_4$), and the solvent was removed under reduced pressure. Distillation of the residue at 72–75° (0.08 mm.) yielded a colorless liquid.

α,α-Diisopropyl-α-(2-dimethylaminoethyl)acetamide (II).—Hydrolysis of I (23 g., 0.11 mole), accomplished by heating for 18 hr. at 90–95° with 85% H_2SO_4 (70 ml.), yielded a solid which after crystallization from ethyl acetate gave colorless crystals, m.p. 111–112°.

α-Carbethoxy-α-isopropyl-1-naphthylpropionitrile.—Ethyl α-isopropylcyanoacetate[5] (155.2 g., 1 mole) was added with stirring to a solution of sodium (25.3 g., 1.1 g.-atoms) in anhydrous ethanol (600 ml.). After the exothermic reaction had subsided, the mixture was refluxed overnight, and then cooled. The NaCl was filtered off, and the solvent was removed under reduced pressure. The oily residue was dissolved in ether, and the solution was washed with water and dried (Na_2SO_4). The solvent was removed under reduced pressure and the residue was distilled at 162–164° (0.3 mm.) to give 233.4 g. (79%) of a viscous colorless oil.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.26; H, 7.17; N, 4.74. Found: C, 77.32; H, 7.23; N, 4.80.

α-Isopropyl-1-naphthylpropionitrile.—α-Carbethoxy-α-isopropyl-1-naphthylpropionitrile (233.4 g., 0.79 mole) was hydrolyzed by refluxing for 32 hr. with ethanol (70 ml.) and 35% KOH (565 g.). The mixture was then diluted with water (500 ml.), washed with ether, and acidified with 1:1 HCl. The precipitated pasty product was extracted with ether, and the extract was washed with water and dried ($MgSO_4$). Removal of the solvent under reduced pressure yielded 191 g. (90.6%) of crude α-carboxy-α-isopropyl-1-naphthylpropionitrile, which was decarboxylated without purification by heating at 200° in the presence of powdered copper (1 g.). After about 10 hr. the evolution of CO_2 practically ceased; the residue was distilled at 134–135° (0.15 mm.) to give 149.2 g. (93.4%) of a viscous colorless oil.

Anal. Calcd. for $C_{16}H_{17}N$: C, 86.05; H, 7.67; N, 6.27. Found: C, 86.16; H, 7.70; N, 6.24.

α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylpropionitrile (III).—α-Isopropyl-1-naphthylpropionitrile (149.2 g., 0.668 mole) was alkylated with 2-(N,N-dimethylamino)-1-chloroethane (143.6 g., 1.336 moles) in the presence of sodium (30.7 g., 1.336 g.-atoms) dissolved in liquid ammonia (1.2 l.), following a procedure quite similar to that described for I. The reaction time was 30 hr., and the product obtained was a colorless oil, b.p. 151–153° (0.15 mm.).

α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylpropionamide (IV).—Hydrolysis of III (29.4 g., 0.1 mole), accomplished by refluxing for 16 hr. with a 1:1:1 mixture (114.5 ml.) of concentrated H_2SO_4, glacial acetic acid, and water, yielded a solid which after crystallization from ligroin (b.p. 75–120°) gave colorless crystals, m.p. 128.5–129.5°.

α-(2-Dimethylaminoethyl)-2-naphthylacetonitrile (V).—Alkylation of 2-naphthylacetonitrile[6] (50.1 g., 0.3 mole) with 2-(N,N-dimethylamino)-1-chloroethane (32.3 g., 0.3 mole), carried out by refluxing for 4 hr. in benzene (300 ml.) and in the presence of sodamide (11.7 g., 0.3 mole), gave a colorless oil, b.p. 154–155° (0.3 mm.).

α-Isopropyl-α-(2-dimethylaminoethyl)-2-naphthylacetonitrile (VI).—Alkylation of V (40 g., 0.168 mole) with 2-bromopropane (22.77 g., 0.185 mole), carried out by refluxing for 5 hr. in ether (400 ml.) and in the presence of sodamide (7.22 g., 0.185 mole), gave a colorless oil, b.p. 142–144° (0.1 mm.).

α-Isopropyl-α-(2-dimethylaminoethyl)-2-naphthylacetamide (VII).—Hydrolysis of VI (28.0 g., 0.1 mole) by refluxing for 72 hr. with 1:1:1 mixture (109 ml.) of concentrated H_2SO_4, glacial acetic acid, and water yielded a solid which after crystallization from petroleum ether (b.p. 40–70°) gave colorless crystals, m.p. 122.5–123.5°.

α-Isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide Methobromide (VIII).—A solution of methyl bromide (19 g., 0.2 mole) and α-isopropyl-α-(2-dimethylaminoethyl)-1-naphthylacetamide[id] (10 g., 0.033 mole) in benzene (100 ml.) gave, upon standing for 2 days at room temperature, a colorless crystalline solid, m.p. 171–173°.

TABLE II

PHARMACOLOGICAL DATA

Compd.	Approx. LD_{50} (mouse), mg./kg. i.p.	Analgesic act. (mouse) Reaction time, inc., %	Analgesic act. (mouse) mg./kg. i.p.	Antiinflammatory act. (rat) Edema inhib., %	Antiinflammatory act. (rat) mg./kg. p.o.
I	120–150	18	25	39	25
II	380–400	48	200	34	200
III	250–300	160	50	30	50
IV	120–140	109	100	42	100
V	130–160	47	25	18	25
VI	110–140	61	25	21	25
VII	40–70	30	25	20	25
VIII	100–130	17	25	Inactive	25
IX	110–140	36	25	11	25
Morphine·HCl		67	5		
Phenylbutazone				18	100

(5) J. C. Hessler, *J. Am. Chem. Soc.*, **35**, 990 (1913).

(6) M. S. Newman, *J. Org. Chem.*, **9**, 518 (1944).

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

WILLIAM A. REMERS AND MARTIN J. WEISS

Organic Chemical Research Section, Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York

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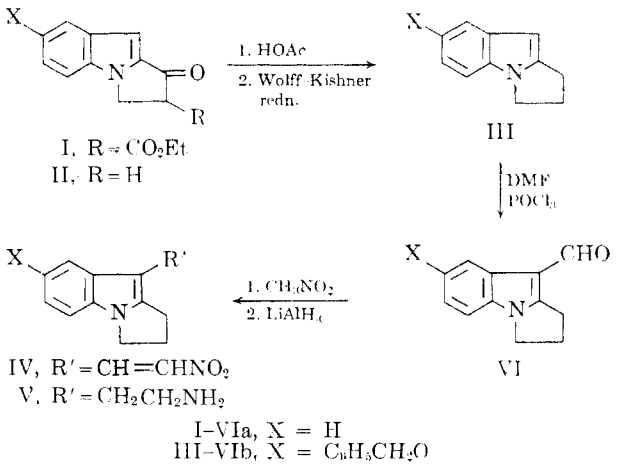
Following the initial studies of Woolley and Shaw on pharmacologically active analogs of serotonin,[1] a high interest in indoles related to tryptamine has been maintained.[2] In this paper we wish to report the preparation and properties of several new tryptamine analogs, 9-(2-aminoethyl)-2,3-dihydro-1H-pyrrolo-[1,2-*a*]indoles.

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 $(C_{11}H_{10}N)_n$, 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

(1) D. W. Woolley and E. Shaw, *J. Biol. Chem.*, **203**, 69 (1953); *J. Pharmacol. Exptl. Therap.*, **108**, 87 (1953); E. Shaw and D. W. Woolley, *ibid.*, **111**, 43 (1954).

(2) E. Shaw, *J. Am. Chem. Soc.*, **77**, 4319 (1955); E. Shaw and D. W. Woolley, *J. Pharmacol. Exptl. Therap.*, **116**, 164 (1956); **121**, 13 (1957); B. B. Brodie, A. Pletscher, and P. A. Shore, *ibid.*, **116**, 9 (1956); R. B. Barlow and I. Khan, *Brit. J. Pharmacol.*, **14**, 553 (1959); V. Erspamer in "Progress in Drug Research," Vol. 3, E. Jucker, Ed., Birkhäuser Verlag, Basel, Switzerland, 1961.

(3) (a) C. R. Allen, Jr., J. F. Poletto, and M. J. Weiss, *J. Am. Chem. Soc.*, **86**, 3877 (1964); (b) *J. Org. Chem.*, in press.

(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**, 4612 (1964).

(8) E. H. P. Young, *J. Chem. Soc.*, 3493 (1958).

(9) R. F. Nystrom and W. G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

(10) (a) E. Laschtuvka and R. Huisgen, *Ber.*, **93**, 81 (1960). (b) We wish to thank Professor Huisgen for kindly providing a sample of this compound.

(11) Procedure of J. R. Cummings, J. D. Haynes, L. M. Lipelmick, and M. A. Rousberg, *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).