Pharmacologically Active Acetylene Compounds. II. Propynyl-Substituted Indole Derivatives[1]

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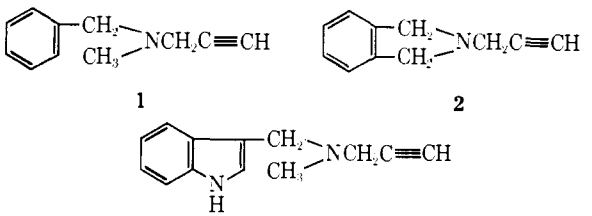
A number of novel acetylenic amines and amides attached to an indole and isoindoline nucleus have been synthesized. The compounds generally exhibited CNS depressant or stimulating effects at high dosage levels. Some of the compounds were found to be *in vitro* inhibitors of monoamine oxidase.

A large number of propynylamines have been prepared by Swett, *et al.*,[2] and evaluated as monoamine oxidase (MAO) inhibitors. Their investigations culminated in the clinically useful drug, pargyline hydrochloride, N-benzyl-N-methyl-2-propynylamine hydrochloride (**1**·HCl), a nonhydrazine MAO inhibitor that has been noted for its marked hypotensive action. We are primarily interested in exploring the pharmacological properties of propynylamines attached to an indole nucleus, a heterocyclic series which has been shown to convey pharmacologic activity to several classes of compounds.[3] We wish to report the synthesis and biological activity of a number of these substituted indoles and the preparation of N-(2-propynyl)isoindoline (**2**), a cyclized analog of pargyline (**1**).



1 **2**

3

The method of synthesis of 3-[N-methyl-N-(2-propynyl)aminomethyl]indole (**3**), a pargyline analog in which the benzene ring has been replaced by the indole moiety, is outlined in Scheme I. Indole-3-carboxaldehyde (**4**) was condensed with methylamine to give a Schiff base (**5**), which could be hydrogenated with Pd–C to yield 3-(methylaminomethyl)indole (**6**).[4] Compound **6**, characterized as the oxalate salt, was alkylated with propargyl bromide, and the resulting amine (**3**) was isolated as the oxalate salt. An alternate route to **3** was not explored because 3-bromomethylindole could not be prepared from 3-hydroxymethylindole.

The preparation of N,N-di(2-propynyl)tryptamine (**11**) (Scheme II) by a method that has been used successfully for a number of tryptamines[5] failed to yield **11** when applied to the acetylenic homologs. The glyoxylamines **9** could not be reduced by LAH in THF, and this route was abandoned in favor of a direct alkylation of 3-(2-bromoethyl)indole (**10**) with dipropargylamine.

N-2-(Propynyl)isoindoline (**2**) was obtained from the direct alkylation of isoindoline.[6]

Compounds **9** and **11** were screened in the reserpine ptosis test (prevention and reversal) in an attempt to elicit CNS stimulation, and in the hexobarbital potentiation and anticonvulsant (electroshock and pentylenetetrazole) screens for CNS-depressant activity and gross behavioral changes. The reserpine tests[7] were run at 1 and 10 mg/kg ip in mice. N,N-Di(2-propynyl)-indole-3-glyoxylamide (**9a**) both prevented and reversed reserpine ptosis at 10 mg/kg, but it was inactive at 1 mg/kg. The CNS-depressant screens were run at 10 mg/kg ip and *po*, 40 and 90 min after medication. 3-[N-Methyl-N-(2-propynyl)aminomethyl]indole (**3**) hydrogen oxalate, when screened in mice, exhibited a general activity decrease with an LD_{50} of 56 mg/kg and an MED_{50} of 10 mg/kg.

The insolubility of the glyoxylamides severely limited their *in vitro* testing as MAO inhibitors.[8] N,N-Di(2-propynyl)tryptamine hydrochloride (**11**·HCl), a soluble product, was only a weak inhibitor (Table I). None of the compounds tested was equivalent to pargyline (or superior to tranylcypromine, the other standard) in blocking MAO *in vitro*.

Experimental Section[9]

3-(Methylaminomethyl)indole (6).—A mixture of 3.6 g (0.025 mole) of indole-3-carboxaldehyde (Aldrich Chemical Co.) and 45 ml of $MeNH_2$ (40% in H_2O, Matheson Coleman and Bell) was heated to boiling in a water bath, and another 5 ml of $MeNH_2$ was added. The mixture was allowed to stand for at least 2 hr at room temperature. Saturated NaCl solution (50 ml) was then added, the mixture was centrifuged, and the H_2O was decanted from the Schiff's base. This intermediate, 3-(methyliminomethyl)indole (**5**) could be purified by recrystallization from C_6H_6–petroleum ether (bp 30–60°), mp 117–118°, followed by sublimation at 110° (2 mm). After sublimation, the imine melted at 116.5–117.5° (lit.[10] 123–124°).

The imine (crude or purified) was dissolved in 250 ml of MeOH (EtOH and i-PrOH were also satisfactory) and 2 g of 10% Pd–C

(1) Previous paper in this series: J. L. Neumeyer, U. V. Moyer, J. A. Richman, F. J. Rosenberg, and D. A. Teiger, *J. Med. Chem.*, **10**, 615 (1967).

(2) L. R. Swett, W. B. Martin, J. D. Taylor, G. M. Everett, A. A. Wykes, and Y. C. Gladish, *Ann. N. Y. Acad. Sci.*, **107**, 891 (1963).

(3) For a recent review, see R. V. Heinzelman and J. Szmuszkovicz, *Progr. Drug Res.*, **6**, 75 (1963).

(4) This indole derivative has been reported by S. H. Mudd [*Nature*, **189**, 489 (1961)] as a constituent of barley, but no physical constants were reported for this compound. We have characterized this indole derivative as its oxalate salt but were unable to isolate the free base.

(5) M. E. Speeter and W. C. Anthony, *J. Am. Chem. Soc.*, **76**, 6208 (1954).

(6) J. L. Neumeyer, *J. Pharm. Sci.*, **53**, 981 (1964).

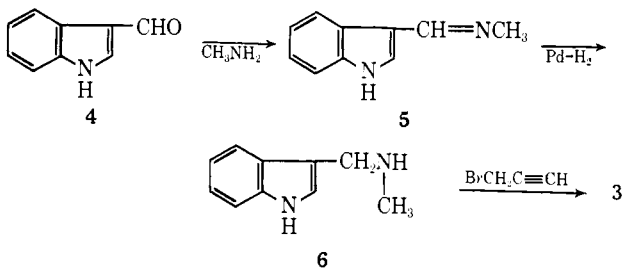
(7) M. D. Aceto and L. S. Harris, *Toxicol. Appl Pharmacol.*, **7**, 329 (1965).

(8) The method was a modification of the procedure of R. J. Wurtman and J. Axelrod, *Biochem. Pharmacol.*, **12**, 1439 (1963), employing rat liver homogenate as substrate and tryptamine-2-^{14}C bisuccinate.

(9) All melting points were taken on a Thomas–Hoover melting point apparatus and are uncorrected. The microanalyses were performed by Dr. S. M. Nagy of the Massachusetts Institute of Technology. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of theoretical values. In conducting the research reported herein, the investigators adhered to the "Principles of Laboratory Animal Care" as established by the National Society for Medical Research.

(10) E. Wenkert, J. H. Udelhofen, and N. K. Bhattacharyya, *J. Am. Chem. Soc.*, **81**, 3763 (1959).

SCHEME I



SCHEME II

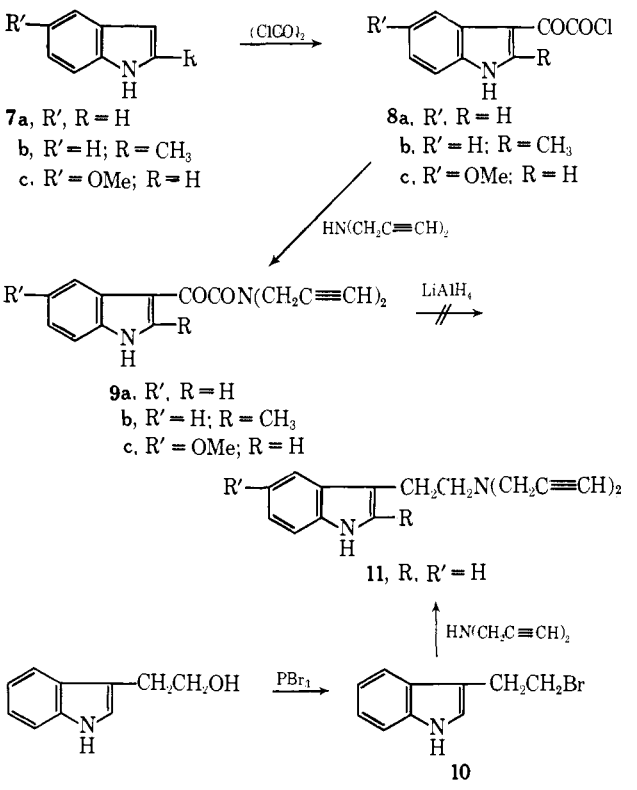


TABLE I

MONOAMINE OXIDASE INHIBITION[a]

Compd	I_{50} 10^{-5} M	Comments
9a	>3[b]	At 10^{-4} M, compound precipitated from solution
9b	>10[b]	
9c		Weak, 9% inhib at 10^{-4} M
11		20% inhib at 10^{-4} M, but 16% stim at 10^{-5} M
2	8.4	
5		17% inhib at 10^{-4} M
Pargyline	0.017	
Tranylcypromine	0.027	

[a] Reference 8. [b] Inactive at this concentration.

was added. The mixture was hydrogenated in a Parr low-pressure hydrogenator until the theoretical amount of H_2 was absorbed (about 5 min) and then was filtered through Celite, to yield a solution of 3-(methylaminomethyl)indole.

The **oxalate salt** was prepared by adding an equimolar amount of solid oxalic acid (as dihydrate or anhydrous) to a hot solution of the amine in EtOH. Et_2O equal to about half the volume of EtOH was added, and cooling caused the oxalate salt to crystallize. The yield was 60% from indole-3-carboxaldehyde. The salt was slightly hydroscopic and discolored on standing in the air or upon heating. In the melting point apparatus, it changed color to red, mp 126–128°, then resolidified, melting again at 150–165° dec. The ir and nmr spectra agree with the assigned structure.

The analytical sample of the oxalate was obtained after recrystallization from *i*-PrOH–Et_2O, under N_2; nmr ($CDCl_3$–CF_3COOH), δ 2.93 (3 H triplet), 4.62 (2 H multiplet), 7.1–7.7 (multiplet). *Anal.* ($C_{12}H_{14}N_2O_2$) C, H, N.

3-[N-Methyl-N-(2-propynyl)aminomethyl]indole Hydrogen Oxalate (3·Salt).—A solution of 3-(methylaminomethyl)indole (**6**) in 250 ml of MeOH was stirred with an excess of anhydrous K_2CO_3 while an equimolar amount of propargyl bromide was added dropwise. After the mixture had been stirred overnight, the solvent was removed under reduced pressure and the residue was redissolved in 500 ml of C_6H_6 and 100 ml of H_2O. The C_6H_6 layer was washed (50 ml of saturated NaCl solution) and the aqueous layers were washed (100 ml of $CHCl_3$). An equimolar quantity of oxalic acid in EtOH was added to the $CHCl_3$–C_6H_6 solution, causing the propynylamine to precipitate as the oxalate, mp 130–131°. No suitable solvent could be found for this salt for an nmr spectrum. An ir spectrum was consistent with the proposed structure. *Anal.* ($C_{15}H_{16}N_2O_4$) C, H, N.

3-Indoleglyoxylyl Chlorides (8a).—A solution of 54 g (0.428 mole) of oxalyl chloride in 150 ml of dry Et_2O was added to a solution of 25 g (0.214 mole) of indole in 500 ml of dry Et_2O. After the mixture had stood at room temperature for 12 hr, the solid was collected and dried to yield 39.8 g (90%) of **8a**, mp 128°.

Similarly prepared were **8b** and **8c**.

2-Methyl-3-indoleglyoxylyl chloride (8b) (17.7 g, 80%), mp 147–147.5°, was obtained from 13.1 g (0.1 mole) of 2-methylindole (Aldrich Chemical Co.) and 25.4 g (0.2 mole) of oxalyl chloride.

5-Methoxy-3-indoleglyoxylyl chloride (8c) (15 g, 81%), mp 118–119° dec, was obtained from 10 g (0.068 mole) of 5-methoxyindole (Aldrich Chemical Co.) and 17.2 g (0.136 mole) of oxalyl chloride.

N,N-Di(2-propynyl)indole-3-glyoxylamide (9a).—A solution of 22.5 g (0.108 mole) of 3-indolylglyoxylyl chloride (**8a**) in 300 ml of anhydrous THF was cooled to 0° and a solution of 10 g (0.108 mole) of di-2-propynylamine (Aldrich Chemical Co.) and 11 g (0.108 mole) of Et_3N in 150 ml of THF was added dropwise with cooling. A white precipitate formed. The mixture was stirred at room temperature for 12 hr. The precipitate was filtered and washed (THF), and the combined filtrates were evaporated. The residual solid was recrystallized from *t*-BuOH–petroleum ether, yielding 21.8 g (76%) of yellow needles of **9a**, mp 158–159°. The analytical sample (from EtOH) had the same melting point. *Anal.* ($C_{16}H_{12}N_2O_2$) C, H, N.

Similarly prepared were **9b** and **9c**.

N,N-Di(2-propynyl)-2-methylindole-3-glyoxylamide (9b).—A 78% yield of **9b**, mp 147–150° (from EtOH), was obtained from 2-methyl-3-indoleglyoxylyl chloride and di-2-propynylamine. The analytical sample, mp 149–150°, was recrystallized from EtOH–petroleum ether. *Anal.* ($C_{17}H_{14}N_2O_2$) C, H, N.

N,N-Di(2-propynyl)-5-methoxyindole-3-glyoxylamide (9c).—The 5-methoxy derivative (11 g, 72%), mp 199–201° (from EtOH), was obtained from 12.7 g (0.054 mole) of 5-methoxy-3-indoleglyoxylyl chloride and 5 g (0.054 mole) of di-2-propynylamine (Aldrich Chemical Co.). *Anal.* ($C_{17}H_{14}N_2O_3$) C, H, N.

3-(2-Bromoethyl)indole (10).—PBr_3 (3.6 g, 0.0133 mole) was added to a solution of 3 g (0.0186 mole) of tryptophol (prepared by LAH reduction of ethyl 3-indoleglyoxylate)[11] in 225 ml of dry C_6H_6 containing a few drops of pyridine. The solution was then refluxed under dry N_2 overnight. An orange-brown precipitate formed. The supernatant solution was decanted into 100 ml of cold H_2O. The mixture was stirred vigorously and neutralized with 100 ml of 5% $NaHCO_3$. The C_6H_6 layer was separated, washed (5% $NaHCO_3$, saturated NaCl), and dried ($MgSO_4$). After evaporation of the solvent, 3.5 g (80%) of **10** was obtained as a pale yellow solid, mp 97–98° (lit.[12] mp 100–102°).

N,N-Dipropynyltryptamine (11).—A solution of 4.16 g (0.04 mole) of dipropynylamine (Aldrich Chemical Co.) in 50 ml of *i*-PrOH was added to 5 g (0.02 mole) of 3-(2-bromoethyl)indole in 75 ml of *i*-PrOH and the mixture was stirred at reflux for 4 hr, cooled, and filtered. The filtrate was evaporated and the solid remaining was extracted (Et_2O). A solid was recovered from the Et_2O upon evaporation. It was recrystallized from EtOAc–petroleum ether to yield 2.4 g (46%) of **11** as yellow needles, mp 92–93°. *Anal.* ($C_{16}H_{16}N_2$) C, H, N. The HCl salt was pre-

(11) Upjohn Co., British Patent 778,823 (July 10, 1957); *Chem. Abstr.*, **52**, 1265 (1958).

(12) M. S. Fish, N. M. Johnson, and E. C. Horning, *J. Am. Chem. Soc.*, **78**, 3668 (1956).

pared in Et_2O. It was recrystallized (Et_2O–EtOH) as white needles, mp 143–144°. *Anal.* ($C_{16}H_{17}ClN_2$) C, H, N.

N-(2-Propynyl)isoindole (2) Hydrochloride.—A solution of 11.9 g (0.1 mole) of 3-bromopropyne in 25 ml of Et_2O was added dropwise at 0° to a solution of 23.8 g (0.2 mole) of isoindoline[6] in 200 ml of anhydrous Et_2O. The mixture was allowed to stir in an ice bath for 3 hr and at room temperature overnight. Isoindoline hydrobromide was filtered off, and the Et_2O solution was dried (Na_2CO_3) and evaporated. The resulting orange oil was distilled at 65° (0.3 mm), resulting in 8.6 g (55%) of **2** as a slightly yellowish oil, $n^{25}D$ 1.5520. *Anal.* ($C_{11}H_{11}N$) C, H, N.

The **hydrochloride** of **2** was formed in Et_2O. It melted at 189–190° (from EtOH, dissolved at room temperature and cooled to −20°). *Anal.* ($C_{11}H_{12}ClN$) C, H, N.

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β-Adrenergic Blocking Agents. IV. Variation of the 2-Naphthyl Group of Pronethalol [2-Isopropylamino-1-(2-naphthyl)ethanol]

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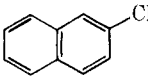
In attempts to improve the potency of the adrenergic β-receptor antagonist pronethalol [2-isopropylamino-1-(2-naphthyl)ethanol] the 2-naphthyl group has been replaced by, for example, 1-naphthyl, tetrahydro-2-naphthyl, 5-indanyl, and various tricarbocyclic groups. Analogs have also been made with substituents other than *i*-Pr on N. Structure–activity relationships are discussed. Several of the compounds described have the same level of potency as pronethalol.

In the course of our synthetic program[1] aimed at improving the potency of the adrenergic β-receptor antagonist 2-isopropylamino-1-(2-naphthyl)ethanol (pronethalol)[2] we have prepared the analogs described in



pronethalol

Table I. The 2-naphthyl group of pronethalol has been replaced by for example 1-naphthyl,[3] tetrahydro-2-naphthyl,[4] 5-indanyl,[4] and various tricarbocyclic groups[5] to provide a series of 16 compounds having an isopropylaminoethanol side chain. Analogs have also been made with substituents other than isopropyl on N. The compounds were prepared mainly by three of the methods described in part I.[1a]

In method A, an intermediate aminomethyl ketone (Table II) was reduced by $NaBH_4$ in good yield.

$$RCOCH_2X + R^1R^2NH \xrightarrow{B} RCOCH_2NR^1R^2 \xrightarrow[NaBH_4]{A} RCH(OH)CH_2NR^1R^2$$

X = Br or Cl

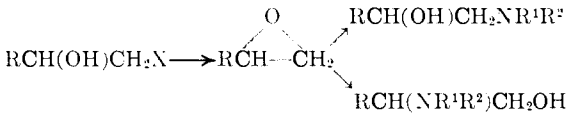
Several specific methods are described for the isolation of the salts of the aminomethyl ketones, in addition to the general method B. Yields were usually in the region 20–30% except for **48** (53%). Most of the intermediate halomethyl ketones were known. The orientation of 4-methyl-1-acetonaphthone,[6] obtained by acylation of 1-methylnaphthalene and used to prepare bromomethyl 4-methyl-1-naphthyl ketone, was checked by oxidation *via* 4-methyl-1-naphthoic acid to naphthalene-1,4-dicarboxylic acid.[7] Chloromethyl 1,2,3,4-tetrahydro-2-naphthyl ketone (**65**) was prepared by the following route.

$$RCOCl \longrightarrow RCOCHN_2 \longrightarrow RCOCH_2Cl$$

65

R = 1,2,3,4-tetrahydro-2-naphthyl

In method C an intermediate halohydrin was treated with an amine to give (*via* an epoxide) a mixture of



position isomers, which largely consisted of the desired secondary alcohol isomer. Purification by fractional crystallization gave the required isomer. Samples of **4**, **13**, and **15** obtained by method C were identical with those produced unambigously by method A. The structures of those compounds prepared only by method C were confirmed by nmr and, in particular, by the chemical shift of the proton –CH(O)– which in pronethalol (CCl_4) is τ 5.15 (X part of ABX). For those compounds in which there was no fused-ring junction at a ring carbon atom adjacent to the one bearing the side chain, *i.e.*, for **34**, **35**, and **42**, the chemical shift was τ 5.1–5.25. For those with an adjacent fused ring, *i.e.*, the α-naphthyl analogs **1**, **3**, **6**, **8**, **11**, and the phenanthrene **37**, the chemical shift was τ 4.35–4.5. For the ring-substituted compounds **17** and **18** the chemical shifts were τ 5.3 and 4.7 (nmr spectra in $CDCl_3$, except for **6**, **11**, and **18** which were measured in DMSO-d_6).

(1) (a) Part I: R. Howe, A. F. Crowther, J. S. Stephenson, B. S. Rao, and L. H. Smith, *J. Med. Chem.*, 11, 1000 (1968); (b) part II: A. F. Crowther and L. H. Smith, *ibid.*, 11, 1009 (1968); (c) part III: R. Howe and B. S. Rao, *ibid.*, 11, 1118 (1968).

(2) Alderlin®.

(3) J. S. Stephenson and B. J. McLoughlin, British Patent 998,524 (1965).

(4) R. Howe, L. H. Smith, and J. S. Stephenson, British Patent 1,005,026 (1965).

(5) R. Howe, British Patent 984,291 (1965).

(6) (a) R. D. Haworth and C. R. Marvin, *J. Chem. Soc.*, 2720 (1932); (b) J. Sauer, R. Huisgen, and A. Hauser, *Ber.*, 91, 1461 (1958).

(7) F. Mayer and A. Sieglitz, *ibid.*, 55, 1835 (1922).