Synthesis and Pharmacology of a Pargyline Analog, *N*-3-(1-Butynyl)-benzylamine

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Abstract □ The synthesis of a structural isomer of pargyline was undertaken to test certain structure–activity relationships. *In vivo*, the new compound, *N*-3-(1-butynyl)-benzylamine, exhibited slight central stimulant effects but showed no MAO inhibitory activity *in vitro*.

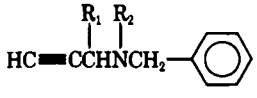
Keyphrases □ *N*-3-(1-Butynyl)-benzylamine (pargyline analog)—synthesis and pharmacology, structure–activity relationships □ Pargyline analog—synthesis and pharmacology of *N*-3-(1-butynyl)-benzylamine, structure–activity relationships □ MAO inhibitors—synthesis and pharmacology of pargyline analog, *N*-3-(1-butynyl)-benzylamine, structure–activity relationships

Pargyline (I*a*) is an MAO inhibitor which demonstrates antidepressant action and also serves as a clinically effective antihypertensive agent. Structure–activity relationships for the propynylamine series (I) indicate that when the R groups are larger than methyl, a decrease in both MAO inhibition and antidepressant activity is observed (1). The synthesis of *N*-3-(1-butynyl)-benzylamine (I*b*), a structural isomer of pargyline, was undertaken to determine whether the shift of the methyl group from the nitrogen to the adjacent carbon in the propynyl chain would greatly affect pharmacological activity. Compound I*b* was synthesized in two steps, beginning with the conversion of 1-butyn-3-ol to 3-chloro-1-butyne (in low yield) followed by condensation of the latter with benzylamine.

DISCUSSION

As an *in vivo* testing procedure, a method similar to that described by Everett and Wiegand (2) was employed. This procedure involves injection of the potential drug into mice followed by injection of dopa. The degree of increase in central activity is considered related to the effectiveness of MAO inhibition. The method has been utilized to determine indirectly MAO inhibition. Since both I*a* and I*b* have identical molecular weights, comparisons were made at equal weight dose levels. Although I*b* produced a slight increase in central activity, this increase was much less than that caused by pargyline. Even at higher toxic dose levels, this effect on the central activity was much less intense than that of pargyline. The overall results indicate that I*b* is at best a weak MAO inhibitor compared to pargyline.

Because I*b* was questionable as an MAO inhibitor, it was tested *in vitro*. Pargyline exhibited a straight-line log dose–response relationship with an ID_{50} (50% inhibition) of MAO at approximately 0.7 mcg./ml. Compound I*b* at concentrations up to 20 times the ID_{50} of pargyline demonstrated no MAO inhibitory activity. It is possible that the slight increase in central activity exhibited by I*b* was not due to MAO inhibition but rather some other unknown factor. However, the antidepressant encyprate was shown to be inactive *in vitro* but active *in vivo*, probably due to its metabolism to an active metabolite *in vivo* (3). Nevertheless, based on these results, it was concluded, in agreement with Swett *et al.* (1), that optimum activity is apparently associated with a small atom or groups of atoms, *i.e.*, hydrogen or methyl connected to the nitrogen atom, and that further *N*-alkylation or further substitution on the aliphatic chain tends to decrease activity.



I*a*: $R_1 = H$, $R_2 = CH_3$
I*b*: $R_1 = CH_3$, $R_2 = H$

EXPERIMENTAL

Pharmacology—The hydrochloride salts of both I*a* and I*b* were dissolved in distilled water. For testing *in vivo*, 152 male, albino mice (Swiss-Webster strain), weighing 20–32 g., were initially divided into groups of eight animals each. Each group was further separated into two subgroups of four mice each from which data were collected and pooled. According to a preset dosing schedule, all four mice in each group were administered various doses of the test drug intraperitoneally and placed in Plexiglas boxes, 12.7 × 12.7 × 12.7 cm. (5 × 5 × 5 in.) with adequate ventilation. At time intervals ranging from 15 min. to 4 hr. following drug administration, mice were injected with 200 mg./kg. i.p. of DL-dopa suspended in 0.25% agar-agar. Immediately following dopa administration and for the ensuing 30 min., the mice were observed as a group and behavioral changes were observed and rated similar to a procedure described by Everett and Wiegand (2). Each parameter received a numerical score: Straub tail = 1, salivation = 2, jumping = 3, and fighting = 4. The maximum total score for any group would be 10 (4 + 3 + 2 + 1), which would be related to a very high level of MAO inhibition.

Pretreatment of mice with I*b* at 40–160 mg./kg. 1 hr. prior to DL-dopa did not produce symptoms suggesting significant MAO inhibitory activity. A dose of 320 mg./kg. of I*b* resulted in a 100% mortality within 5 min.; I*a* resulted in a dose-dependent relationship, with the maximal effect occurring at the 80-mg./kg. dose. When administered by themselves, neither drug caused any of the behavioral characteristics being measured.

When DL-dopa was administered at various time intervals following intraperitoneal injection of 240 mg./kg. of I*b*, pronounced effects were observed. At the 15-min. time interval, when the increase in central activity was maximal, I*b* appeared to be one-third to one-sixth as potent as pargyline. However, the lethal effects of I*b* were evident within 30 min. and all of the animals were dead within the 4-hr. period.

For *in vitro* testing, the procedure of Lovenberg *et al.* (4) was employed, using tryptamine as a substrate. The MAO enzyme was obtained fresh from rat liver. Pargyline was tested at concentrations from 0.1 to 1.6 mcg./ml., and I*b* was tested at concentrations of 0.1 to 13 mcg./ml.

Chemistry[1]—*3-Chloro-1-butyne*—A procedure similar to that described by Hennion and coworkers (5, 6) was employed. A mixture of 1-butyn-3-ol (14.0 g., 0.20 mole), pyridine (0.3 g.), and freshly distilled thionyl chloride (23.8 g., 0.20 mole) was gently refluxed for 30 min., cooled, and poured onto 60 g. of ice water. The mixture was extracted with 30 ml. of ether, and the organic phase was washed successively with water (2 × 5 ml.), 5% aqueous sodium bicarbonate (2 × 5 ml.), and finally again with water (2 × 5 ml.). After drying the ether solution for 2 days over calcium chloride, it was distilled through a 10 × 200-mm. Vigreaux column and 3.15 g. of the frac-

[1] Melting points were taken on a Thomas-Hoover apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer Infracord spectrophotometer. NMR spectra were recorded on a Varian Associates A-60 spectrometer using spectroquality carbon tetrachloride as a solvent; chemical shifts are reported in parts per million (δ) relative to tetramethylsilane as an internal standard. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Mich.

tion distilling at 60–61.5° was collected. Longer or shorter reaction times and higher or lower temperatures failed to produce a yield in excess of 18%. Vapor phase chromatographic analysis of the products from various experiments indicated a purity of 70–90%. Redistillation of the 60–61.5° fraction afforded little additional purity. This material was used in the reaction with benzylamine. The purest sample was employed in spectral studies; IR (neat): 2150 (—C≡CH) cm.$^{-1}$; NMR (CCl_4): 1.65 (d, 3, C—CH_3), 2.43 (d, 1, —C≡CH), and 4.50 (quartet of doublets, 1, Cl—CH).

N-3-(1-Butynyl)-benzylamine Hydrochloride—Similar to a procedure described by Hennion and Nelson (7), a mixture of the above chloro compound (2.5 g.), benzylamine (13.1 g.), and water (3.2 ml.) was stirred at room temperature for 60 hr. At the end of this time, an equal volume of water (15 ml.) was added and two phases formed. The upper layer (organic phase) was separated, and the bottom layer (aqueous phase) was diluted again with an equal volume of water. Again two phases formed and the upper layer was combined with the first. Ether (25 ml.) was added, this solution was washed with water (2 × 5 ml.) and dried over potassium hydroxide, and the ether was removed *in vacuo*. The residue was distilled through a Vigreaux column, and the fraction distilling at 168–172°/17 mm. Hg was collected; IR (neat): 3400 (>NH) and 2150 (—C≡CH) cm.$^{-1}$; NMR (CCl_4): 1.31 (d, 3, C—CH_3), 2.16 (d, 1, —C≡CH), 3.38 (quartet of doublets, 1, N—CH), 3.88 (d, 2, $ArCH_2$), and 7.22 (s, 5, ArH). This fraction was dissolved in 50 ml. of anhydrous ether, and hydrogen chloride gas was passed through the solution, giving 1.2 g. of a white solid (22% yield based on pure 3-chloro-1-butyne). Several crystallizations from benzene afforded an analytically pure sample, m.p. 210.5–211.5°.

Anal.—Calc. for $C_{11}H_{11}ClN$: C, 67.52; H, 7.16; N, 7.16. Found: C, 67.37; H, 6.97; N, 7.00.

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Synthesis and Antifungal Activity of Polyhalophenyl Esters of Pyridyl- and 4-Quinolylcarbamic Acids IV

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Abstract □ Polyhalophenyl esters of 2-, 3-, and 4-pyridyl- and 2-phenyl-4-quinolylcarbamic acids were synthesized. All prepared compounds inhibited the growth of *Candida albicans* at 50-mcg./ml. concentration.

Keyphrases □ Pyridylcarbamic acid, polyhalophenyl esters—synthesis, antifungal activity □ 2-Phenyl-4-quinolylcarbamic acid, polyhalophenyl esters—synthesis, antifungal activity □ Carbamic acid esters—synthesis, antifungal activity □ Antifungal agents, potential—polyhalophenyl esters of pyridyl- and 2-phenyl-4-quinolylcarbamic acids

In a continuation of the studies on the chemistry and antifungal activity of substituted carbamic acid esters (1–3), polyhalophenyl esters of 2-, 3-, and 4-pyridyl- and 2-phenyl-4-quinolylcarbamic acids were synthesized by interaction of the appropriate azide and polyhalophenol (Scheme I).

$$RCOCl \rightarrow RCON_3 \rightarrow RNHCO_2Ar$$

R = 2-, 3-, or 4-pyridyl or 2-phenyl-4-quinolyl
Ar = 2,4,6-tribromophenyl, 2,4,6-trichlorophenyl, 2,4,6-triiodophenyl, or pentachlorophenyl

Scheme I

EXPERIMENTAL[1]

Picolinyl azide was prepared according to Meyer and Mally (4). Nicotinyl azide was prepared by the method of Curtius and Mohr (5). Isonicotinyl azide was synthesized according to Yoshikowa (6). 2-Phenyl-4-quinolylcarboxazide was obtained by the method of John *et al.* (7).

2-Pyridylcarbamic Acid Pentachlorophenyl Ester—2-Pyridyl azide, 0.74 g. (5 mmoles), and 1.33 g. (5 mmoles) of pentachlorophenol in 30 ml. of dry toluene were gently refluxed for 30 min. After evaporation of the solvent under reduced pressure, the residue was recrystallized from 80% ethanol to give 1.16 g. (60%), m.p. 135°; *m/e* 384, 386, 388, and 390; ν_{max}: 2900, 1710, 1620, 1540, 1470, 1440, 1410, 1360, 1320, 1250, 1150, 995, 980, 880, 778, and 715 cm.$^{-1}$.

3-Pyridylcarbamic Acid 2,4,6-Triiodophenyl Ester—This compound was prepared in a similar manner to its pentachlorophenyl analog; *m/e* 592; ν_{max}: 3300, 1750, 1580, 1550, 1480, 1420, 1200, 1060, 1020, 850, 810, 780, 740, and 703 cm.$^{-1}$.

4-Pyridylcarbamic Acid 2,4,6-Triiodophenyl Ester—This compound was prepared in a similar manner to its pentachlorophenyl analog; *m/e* 592; NMR (dimethyl sulfoxide): τ 7.9–8.1 (d, 2H,

[1] Melting points were taken on a Kofler hot-stage microscope and are uncorrected. The IR spectra were determined with a Leitz model III spectrograph. NMR spectra were obtained on a Varian A60A instrument. Mass spectra were determined with a Varian Mat 111 instrument.