Synthesis and MAO Inhibitory Activity of 6-(2-Propynyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine

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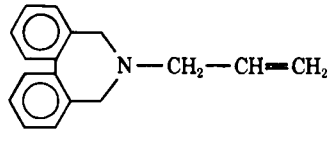
Abstract □ A propynyl dibenzazepine was synthesized with a view to design a compound that would possess the structural features essential for biological activity present in the antiadrenergic compound azapetine and in the MAO inhibitor pargyline, both of which have been used as antihypertensives. The new compound possesses MAO-inhibiting activity weaker than that of pargyline.

Keyphrases □ 6-(2-Propynyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine—synthesized and screened as potential MAO inhibitor □ MAO inhibitors, potential—synthesis and screening of 6-(2-propynyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine □ Dibenzazepines—synthesis and screening of 6-(2-propynyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine as MAO inhibitor

Various dibenzazepine derivatives were described by Randall and Smith (1), of which azapetine[1] (I) was the most potent antiadrenergic compound. It was subsequently marketed for clinical use in hypertensive and vascular disorders. Both the allyl group and the dibenzazepine tricyclic arrangement in azapetine appear to be essential for its biological activity.

Another series of compounds that possesses strong MAO-inhibiting activity led to the clinically used antihypertensive pargyline[2] (II), the inhibiting property being not necessarily related to the hypotensive property (2). The synthesis and evaluation of several MAO inhibitors structurally related to pargyline have indicated the importance of the propargyl or 2-propynyl group to the activity of these compounds (3, 4).

The 2-propynyl or propargyl derivative of the dibenz[*c*,*e*]azepine ring system may provide a compound with desirable or even more potent antihypertensive activity than either of the two clinically tried agents, I and II. Synthesis of such a compound, 6-(2-propynyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (III), and its MAO-inhibiting activity are reported in this paper while the antiadrenergic and antihypertensive properties of the compound will be reported later.



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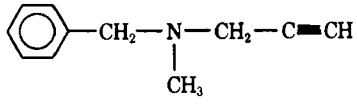

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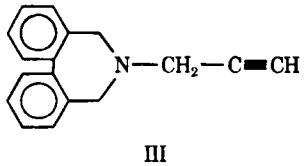

III

[1] Ilidar, Roche.
[2] Eutonyl, Abbott.

Table I—*In Vitro* Inhibition of Liver MAO by III as Compared with Other Known Inhibitors

Inhibitor	Concentration, *M*	Velocity Constant *K*, $\times 10^{-2}$ min.$^{-1}$ S_1[a]	S_2	K_i
Dibenzazepine derivative (III)	4.6×10^{-5}	6.02	4.20	4.9×10^{-5}
	9.3×10^{-5}	3.03	2.35	
	2.2×10^{-4}	2.66	1.69	
	3.5×10^{-4}	1.61	1.17	
Iproniazid	1.4×10^{-5}	8.88	6.66	1.5×10^{-5}
	2.8×10^{-5}	6.48	4.62	
	5.6×10^{-5}	5.33	3.08	
Pargyline (II)	0.7×10^{-8}	4.50	—	1.7×10^{-7}
	2.0×10^{-8}	—	31.2	
	3.9×10^{-8}	4.00	29.0	
	2.0×10^{-7}	2.70	—	
	3.9×10^{-7}	2.20	1.30	

[a] S_1 (2.0×10^{-3} *M*) and S_2 (8.9×10^{-4} *M*) are the two concentrations of tyramine used as substrate.

Compound III was prepared by the lithium aluminum hydride reduction of *N*-(2-propynyl)diphenimide. The latter was obtained by the alkylation of potassium diphenimide with 2-propynyl bromide. Diphenimide was prepared from diphenic acid by methods reported in the literature (5, 6), involving diphenic anhydride and diphenamic acid as intermediates.

EXPERIMENTAL[3]

The following were used: diphenic acid[4]; diphenic anhydride, prepared according to the method of Roberts and Johnson (5); and diphenimide, prepared according to the method of Underwood and Kochmann (6).

***N*-(2-Propynyldiphenimide)**—A solution of alcoholic potassium hydroxide (1.5 g. potassium hydroxide in 1.5 ml. water, *q.s.* to 5 ml. with absolute ethanol) was added with stirring to a hot (65–70°) solution of diphenimide (5.0 g., 22.4 mmoles) in 130 ml. of absolute ethanol. After removing the solvent *in vacuo*, the residue was triturated with anhydrous ether–acetone to yield a white solid potassium salt, which was collected by filtration and used without further purification. A solution of 2-propynyl bromide (2.7 g., 22.5 mmoles) in 10 ml. of dimethylformamide was added slowly with stirring to a solution of potassium diphenimide in 50 ml. of dimethylformamide. The mixture was heated for 4 hr. under gentle reflux and poured into water. The gray-white precipitate (5.0 g., 85%) was collected, m.p. 169–171°. Decolorization[5] and recrystallization from ethanol–water gave a colorless product, m.p. 175–176°.

[3] All melting points were determined with a Fisher melting-point apparatus and are uncorrected. IR spectra were recorded with a Perkin-Elmer model 700 grating spectrophotometer and were as expected. Microanalyses were performed by Galbraith Laboratories, Knoxville, Tenn.
[4] Aldrich Chemical Co. Milwaukee, Wis.
[5] With Norite.

Table II—*In Vivo* Inhibition of Hepatic MAO in Mice by III and Iproniazid

Treatment	Inhibition of MAO at 10 min. after Incubation, %: Acute (0.1 mmole/kg. i.p., 2 hr. before Assay)	Chronic (0.01 mmole/kg. i.p., Daily for 7 days)
Dibenzazepine derivative (III)	25	10
Iproniazid	64	28

Anal.—Calc. for $C_{17}H_{11}NO_2$: C, 78.14; H, 4.24; N, 5.36. Found: C, 78.25; H, 4.34; N, 5.12.

6-(2-Propynyl)-6,7-dihydro-5*H*-dibenz[*c*,*e*]azepine (III)—*N*-(2-Propynyl)diphenimide (7.0 g., 27 mmoles) was placed in a soxhlet extraction apparatus above a stirred suspension of lithium aluminum hydride (5.5 g., 146 mmoles) in 300 ml. of anhydrous ether. Extraction was continued for 72 hr., after which time only a slight residue remained in the thimble. The excess hydride was decomposed by the cautious addition of water followed by 5 ml. of 20% sodium hydroxide. The resulting mixture was filtered and the ethereal layer was separated and dried over anhydrous sodium sulfate. The hydrochloride salt of III (5.5 g., 75%) was precipitated by mixing the dried ether layer with ethereal hydrogen chloride. The salt was recrystallized from 2-butanone, m.p. 201–203°.

Anal.—Calc. for $C_{17}H_{16}ClN$: C, 75.68; H, 5.97; N, 5.19. Found: C, 75.23; H, 6.13; N, 5.25.

MAO Inhibition—Inhibition of MAO was determined by a modification of the method of Snyder and Hendley (7), which employs tyramine as the substrate and homovanillic acid as the fluorescence generating reagent. Mouse liver was homogenized in ice-cold 0.1 *M* phosphate buffer, pH 7.8 (1:20 dilution) and centrifuged at 14,500×*g* and −5° in a refrigerated centrifuge[6] to obtain a cell-free supernate which served as the source of enzyme. Iproniazid[7] and pargyline[2] were used as standard inhibitors for comparison.

The inhibition constants (K_i) were determined by the method of Dixon (8). For *in vitro* inhibition studies, the drugs were incubated with the mouse liver enzyme prior to addition of the substrate. For acute *in vivo* inhibition studies, mice were given single intraperitoneal doses of the drugs 2 hr. prior to the removal of liver for determination of enzyme activity. In the case of chronic *in vivo* studies, however, the drugs were given once daily for 7 days and the livers were removed for the enzyme determination 4–6 hr. following the administration on the last day.

[6] Sorvall, RC2-B.
[7] Roche.

RESULTS AND DISCUSSION

Table I includes the data on the *in vitro* inhibition of the mouse liver MAO produced by varying concentrations of III and two known inhibitors, iproniazid and pargyline. Both the data and the K_i values show that III is a much weaker inhibitor of MAO than is pargyline.

The results of *in vivo* inhibition studies in both acute and chronically treated animals are shown in Table II. In these studies also, III appears to be a weaker MAO inhibitor.

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