1-Ethynylphenethylamine[1]

ALFRED BURGER, STUART E. ZIMMERMAN,

Department of Chemistry, University of Virginia, Charlottesville, Virginia 22903

AND E. J. ARIËNS

Department of Pharmacology, University of Nijmegen, Nijmegen, The Netherlands

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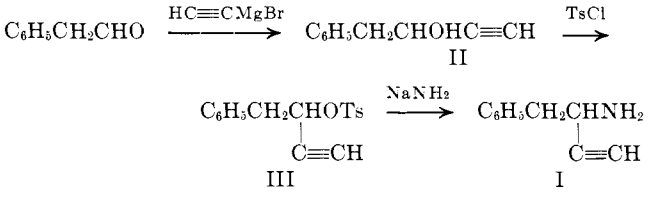
The synthesis of 1-ethynylphenethylamine is described. This acetylenic amine appears to protect phenethylamine from biological deamination and reveals the CNS activity of this compound.

A number of acetylenic amines have been found to possess MAO-inhibitory,[2] anticholinergic,[3] ganglionic blocking,[4] hypotensive,[4] and antimicrobial properties.[5] Only a few of these compounds contained an ethynyl group α to the amino function where, by its bulk and unsaturated character, the ethynyl could decisively affect the reactions of the amino group. The dimensions of the ethynyl group have been equated to those of the cyano group,[6] 3.2 (length) × 3.2 A (width), which compares with the corresponding dimensions of the methyl group, 3.3 × 2.0 A.[7] Thus ethynyl is shorter and more compact than ethyl and therefore amines containing the ethynyl group should offer less steric hindrance to fit at enzyme surfaces than the corresponding ethyl derivatives, which as a rule are considerably less biologically active than their methyl homologs.[8] We are reporting the synthesis and pharmacological study of the ethynyl analog of amphetamine, 1-ethynylphenethylamine (2-amino-1-phenyl-1-butyne, I).

The compound was synthesized by condensing phenylacetaldehyde with ethynylmagnesium bromide and treating the tosylate (III) of the resulting 1-ethynylphenethyl alcohol (II) with sodamide. Both the secondary alcohol and acetylenic amine exhibited in



their nmr spectra a downfield shift of the acetylenic protons of about 0.8 ppm ($CCl_4 \rightarrow$ DMSO-d_6); this is attributable to hydrogen bonding due to the triple bond,[9] and this feature suggests that the ethynyl group in I may simulate the hydrogen-bonding ability of the alcoholic hydroxyl in derivatives of phenylethanolamine.

Pharmacology.—1-Ethynylphenethylamine (I) hydrochloride was studied for its influence on the locomotor activity of mice as measured by means of a variation of Dew's light-beam method,[10] and for its action on the blood pressure of the cat.

Compound I was compared with a number of chemically related drugs, from the CNS stimulant, amphetamine, to the MAO inhibitor, pargyline (see Figure 1). Beside the individual effects of these compounds, their influence on the effect of a dose of phenethylamine given about 2–4 hr after their administration was recorded. Phenethylamine is practically devoid of CNS stimulant activity but, if protected against degradation by means of suitable MAO inhibitors, it induces a clear-cut increase in the locomotor activity of mice.[10] Figure 1 summarizes the main trend in the experimental results obtained with the various compounds in the test for their influence on locomotor activity. There was a gradual decrease in the activity as far as the primary influence on locomotor activity was concerned. With high doses of tranylcypromine (150 μmoles/kg) a slight increase in locomotor activity usually after a delay of about 30 min was observed. Subsequent doses of phenethylamine acted as a CNS stimulant. Tranylcypromine was much more effective in this sense, while pargyline, itself bearing an ethynyl group, was also active. In the series of compounds tested and at the doses used, a decrease in the CNS stimulant action was observed, and simultaneously the capacity of the drugs to promote the CNS stimulant action of phenethylamine increased. The influence on phenethylamine activity may be ascribed to the MAO-inhibitory properties of the compounds.

In tests for the effect on the blood pressure in the femoral artery of the cat under pentobarbital anesthesia, low intravenous doses of amphetamine (2.5 μmoles/kg), I·HCl (5 μmoles/kg), and 2-amino-1-phenylbutane (5 μmoles/kg) produced a rise in blood pressure of about 40 mm. It took about 15 min to reach the original

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(2) For references see C. L. Zirkle and C. Kaiser in "Psychopharmacological Agents," Vol. I, M. Gordon, Ed., Academic Press Inc., New York, N. Y., 1964, p 445.

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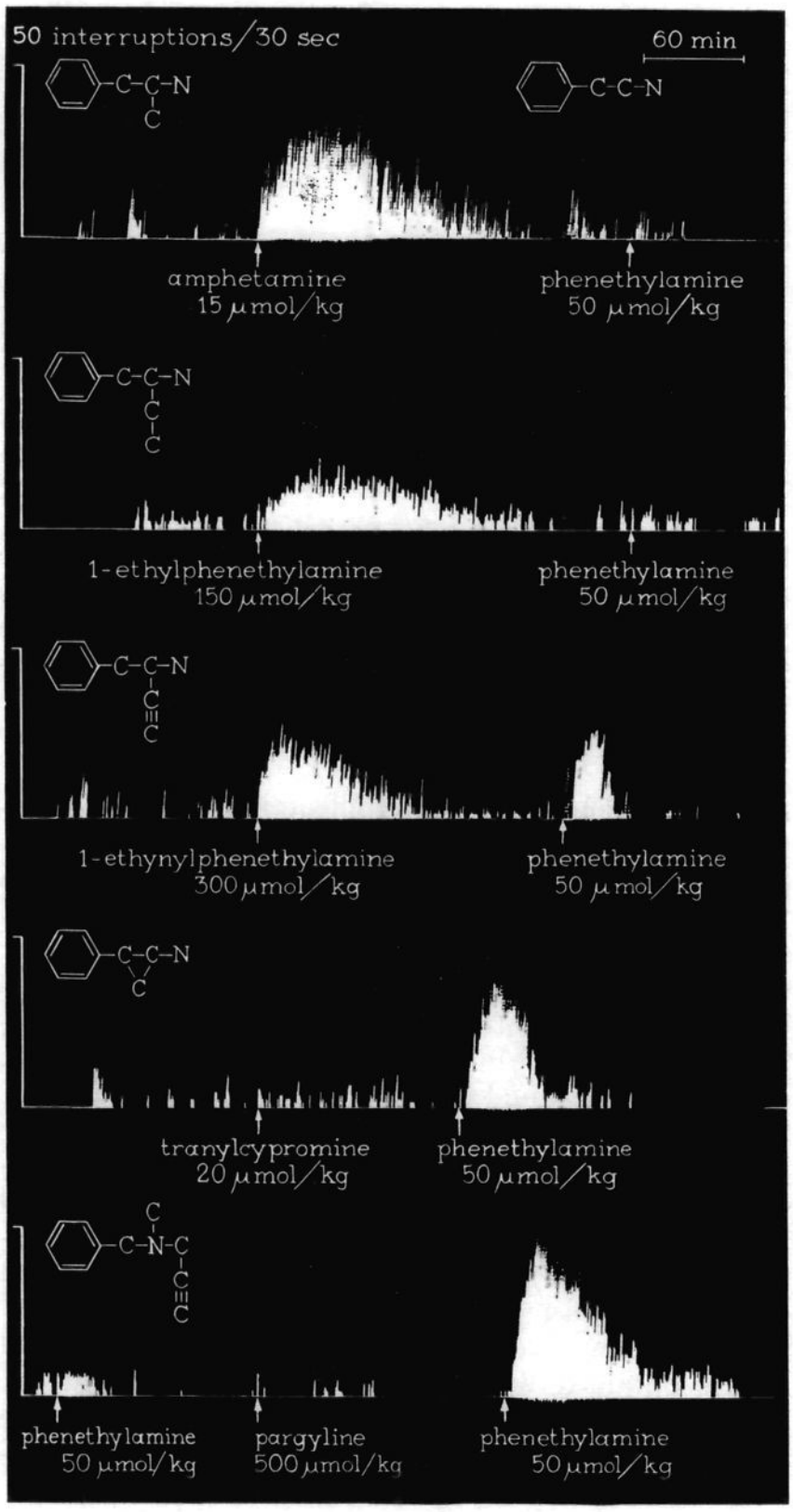

Figure 1.—Registrogram of the effect of a series of related compounds applied intraperitoneally on spontaneous locomotor activity of groups of six mice, and the effect on the locomotor activity of phenethylamine applied 2–4 hr after the various compounds. Ordinate: number of interruptions of the light beams/30 sec. Abscissa: time in minutes.[10] In the series of experiments presented there is a decrease in the primary effect on locomotor activity. There is an increase in the response obtained with phenethylamine given as a second drug, indicating an increase in the MAO-inhibitory activity of the drugs at the dose applied.

blood pressure level again. After 2 or 3 succeeding doses of amphetamine, a tachyphylaxis was observed which crossed over for both of the other compounds. The pressor effect of 2-amino-1-phenylbutane was reversed to a short-lasting depressor effect, while the pressor effect of I was abolished during tachyphylaxis.

Experimental Section

1-Ethynylphenethyl Alcohol (II).—A solution of ethylmagnesium bromide, prepared from 24 g (1 g-atom) of magnesium and 108 g (1 mole) of ethyl bromide in 500 ml of tetrahydrofuran (THF) was added dropwise (1 hr) with gentle refluxing to 300 ml of THF saturated with a stream of purified acetylene.[11] Phenylacetaldehyde (monomer) in an equal volume of THF was then added dropwise with gentle refluxing. The flow of acetylene was arrested and stirring was continued at 23° for 14 hr. The mixture was decomposed with a solution of 75 g (1.4 moles) of NH_4Cl in 200 ml of water and worked up. Distillation furnished 11 g of slightly impure II, bp 167–174.5° (0.04 mm), and 16 g of purified II as a light yellow mobile liquid: bp 175° (0.03 mm); ν_{max}^{film} 3275 (OH), 3250 (≡CH), 2105 cm^{-1} (C≡C); nmr, δ (CCl_4, TMS) 3.03 (OH), 4.40 (CH; broad), 2.25 (≡CH; doublet, $J \sim 1.8$ cps), 2.92 (CH_2; doublet, $J \sim 6.6$ cps), 7.17 (phenyl); δ (deuterated DMSO, TMS) 5.45 (OH; doublet, $J \sim 6.0$ cps), 3.03 (≡CH; doublet, $J \sim 1.8$ cps), 4.37 (CH; multiplet). This alcohol gave a white precipitate with both ammoniacal $AgNO_3$ and alkaline HgI_2 reagent, and a yellow precipitate with ammoniacal Cu_2Cl_2.[12]

1-Ethynylphenethyl Tosylate (III).—To 19.1 g (0.1 mole) of purified *p*-toluenesulfonyl chloride[13] in 25 ml of pyridine was added dropwise with stirring 14.0 g (0.096 mole) of 1-ethynylphenethyl alcohol.[14] Stirring was continued overnight at ambient temperature, 30 ml of water was added dropwise with cooling and stirring, and the solution was extracted with ether. The combined etheral extracts were washed (5% H_2SO_4, saturated $NaHCO_3$, H_2O), dried ($MgSO_4$), decolorized with charcoal, concentrated, and diluted with absolute ethanol and petroleum ether (bp 30–60°). Cooling produced crystals which were filtered off, washed with petroleum ether, and dried under vacuum to yield 5.50 g (19%) of white crystals. An analytical sample was prepared by recrystallization from ethanol; mp 63–64°; ν_{max}^{KBr} 3235 (≡CH), 2115 cm^{-1} (C≡C); nmr, δ (CCl_4, TMS) 2.38 (CH_3), 7.1–7.8 (tosylate phenyl; 4 peaks), 5.13 (CH; triplet, $J \sim 6.6$ cps; split; doublet, $J \sim 1.8$ cps), 2.33 (≡CH; doublet $J \sim 1.8$ cps), 3.07 (CH_2; doublet, $J \sim 6.6$ cps), 7.18 (phenyl).

Anal. Calcd for $C_{17}H_{16}O_3S$: C, 67.86; H, 5.37. Found: C, 67.92; H, 5.46.

III gave a white precipitate with ammoniacal $AgNO_3$ in ethanol.

1-Ethynylphenethylamine (I).—To a solution of 0.56 g (0.025 mole) of sodium in 100 ml of liquid NH_3, cooled in acetone–Dry Ice was added, dropwise (45 min) with stirring and cooling, a solution of 7.35 g (0.025 mole) of 1-ethynylphenethyl tosylate in 40 ml of anhydrous ether.[15] More anhydrous ether (100 ml) was added, stirring was discontinued, and the mixture was allowed to stand overnight without further cooling. It was treated with ice water and ether, and the combined ethereal extracts were dried ($MgSO_4$) and distilled to yield 3.1 g (88%) of a colorless mobile liquid: bp 60° (0.01 mm); ν_{max}^{film} 3325 (NH_2), 3250 (≡CH), 2090 cm^{-1} (C≡C); nmr, δ (CCl_4, TMS) 1.47 (NH_2), 3.70 (CH; triplet, $J \sim 7.8$ cps; split, doublet, $J \sim 1.8$ cps), 2.13 (≡CH; doublet, $J \sim 1.8$ cps), 7.20 (phenyl); δ (deuterated DMSO, TMS) 2.13 (NH_2), 2.93 (≡CH; doublet, $J \sim 1.8$ cps). The amine gave white precipitates with both ammoniacal $AgNO_3$ and alkaline HgI_2 reagents, and a yellow precipitate with ammoniacal Cu_2Cl_2.

An ethereal solution of I was treated with dry HCl, the minute crystals which separated were removed by filtration, dissolved in absolute ethanol, and decolorized with charcoal. Dilution with excess anhydrous ether produced small crystals which were filtered off and dried *in vacuo* to yield analytically pure I·HCl: mp 220.5° dec (sealed tube); ν_{max}^{KBr} 2800 (NH_3^+), 3245 (≡CH), 2100 cm^{-1} (C≡C).

Anal. Calcd for $C_{10}H_{11}N \cdot HCl$: C, 66.11; H, 6.66; N, 7.71. Found: C, 66.09; H, 6.60; N, 7.73.

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