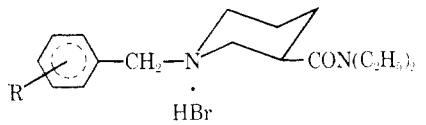
+2.767[13]), it is evident that the dissociation for our series is less sensitive to substituent influences than the dissociation for the anilinium series.[12] This is consistent with the observation[14] that the insertion of a methylene group between the aromatic ring and the reactive center results in a decrease in the ρ value. Based on data from several pairs of series, the average value for the ratio $\rho_{n=1}/\rho_{n=0}$ (where n is the number of methylene units between the ring and the reactive site) was found to be 0.410. If the ρ value for the dissociation of the substituted anilinium ions is assumed to be a reasonable approximation of that for a series of substituted 1-phenyl-3-(N,N-diethylcarbamoyl)piperidine hydrobromides, the ratio of ρ values (1.109/2.767) is equal to 0.401 which agrees well with the literature value.

TABLE III

APPARENT PARTITION COEFFICIENTS OF SUBSTITUTED 1-BENZYL-3-(N,N-DIETHYLCARBAMOYL)PIPERIDINE HYDROBROMIDES



Compd	R	App partition coefficient ($CHCl_3$–H_2O) ± SD[a]	π[b]
I	H	0.96 ± 0.02	0
II	*p*-OCH_3	1.99 ± 0.04	0.32
III	*m*-OCH_3	2.16 ± 0.12	0.35
IV	*p*-CH_3	3.22 ± 0.07	0.53
V	*m*-CH_3	5.56 ± 0.19	0.76
VI	*p*-Cl	2.52 ± 0.02	0.42
VII	*m*-Cl	2.12 ± 0.06	0.34
VIII	*p*-NO_2	0.99 ± 0.09	0.01
IX	*m*-NO_2	0.76 ± 0.02	−0.10

[a] Standard deviation. [b] $\pi = \log P_X - \log P_H$, where P_X is the partition coefficient of a derivative and P_H is that of the parent compound (I).[15]

Apparent partition coefficients ($CHCl_3$–water) for members of our series are summarized in Table III along with the corresponding calculated π values.[15] It should be noted that the π values for our derivatives decrease in the order $CH_3 > Cl > CH_3O > NO_2$ (for the *para* series) and $CH_3 > CH_3O$, $Cl > NO_2$ (for the *meta* series). These sequences tend to be consistent with Albert's classification of the pertinent substituents (*i.e.*, lipophilic, CH_3, Cl; slightly hydrophilic, CH_3O, NO_2)[16] considered along with the group moments[17] of these same substituents taken as an *approximate* measure of polarity.

Acknowledgments.—We wish to thank Dr. Andrew Lasslo for his interest in this work and for helpful discussions.

(13) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Holt, Rinehart, and Winston, Inc., New York, N. Y., 1959, p 222.

(14) H. H. Jaffé, *Chem. Rev.*, **53**, 191 (1953).

(15) T. Fujita, J. Iwasa, and C. Hansch, *J. Am. Chem. Soc.*, **86**, 5175 (1964).

(16) A. Albert, "Selective Toxicity," 3rd ed, John Wiley and Sons, Inc., New York, N. Y., 1965, pp 348–349.

(17) The group moments are CH_3, 0.4; CH_3O, 1.25; Cl, 1.58; NO_2, 3.98; C. P. Smyth, "Dielectric Behavior and Structure," McGraw-Hill Book Co., Inc., New York, N. Y., 1955, p 253.

Acetylenic Carbamates. II. Reactions of 1,1-Diaryl-2-propynyl Carbamates with Acids and Bases

ROBERT D. DILLARD, DONALD R. CASSADY, AND NELSON R. EASTON

The Lilly Research Laboratories, Indianapolis, Indiana 46206

Received March 18, 1967

It has recently been reported[1] that potent antitumor activity was found for a series of 1,1-diaryl-2-propynyl carbamates against a variety of experimental tumors in mice. Reactions of these compounds under acidic and basic conditions were investigated, and the products thus obtained were tested for antitumor activity to determine if any might be an active metabolite responsible for this activity. The reactions that the diaryl compounds undergo were compared with those reported for the 1,1-dialkyl-2-propynyl carbamates which were not effective as antitumor agents.

Treatment with Acids.—1,1-Diphenyl-2-propynyl carbamate (Ia) was used as a representative of the carbamate series. The carbamate Ia in aqueous ethanol, when treated with H_2SO_4 below 10°, gave the acetylenic ether IVa (Scheme I). It seems reasonable that the carbonium ion II is the intermediate in this reaction. Use of other primary and secondary alcohols as solvents gave the corresponding ethers. When tertiary alcohols were used, these products were not obtained. When Ia was heated at reflux temperature in the presence of H_2SO_4, the cinnamaldehyde VI was isolated. The formation of VI from I is related to the Meyer–Schuster rearrangement[2] with VI arising from the intermediate V. Supporting this type of rearrangement is the fact that the acetylenic ether (IV) under identical reaction conditions also gave VI.[3]

When Ia was treated with anhydrous HCl in an inert solvent, the 3,3-dichloro-1-propene (VIIIa) was isolated.[4] When anhydrous HBr was used, a product was obtained that was identical with 3,3-dibromo-1,1-diphenyl-1-propene prepared by Tani and Toda[5] from 1,1-diphenyl-2-propyn-1-ol and PBr_3. These dihalides, on treatment with water, gave the cinnamaldehyde VI.

The product IX[6] was isolated from the reaction mixture of Ia and concentrated HCl. This material could be formed from the dimerization of the proposed intermediate VII.

Cyclization involving addition of the carbonyl oxygen to the triple bond occurred to give XI[7] when 1,1-dialkyl-

(1) R. D. Dillard, G. Poore, D. R. Cassady, and N. R. Easton, *J. Med Chem.*, **10**, 40 (1967).

(2) K. H. Meyer and K. Schuster, *Ber.*, **55**, 819 (1922); H. Rupe and E. Kambli, *Helv. Chim. Acta*, **9**, 672 (1926).

(3) (a) G. F. Hennion and B. R. Fleck, *J. Am. Chem. Soc.*, **77**, 3253 (1955). (b) Hennion and Fleck found that 1,1-diaryl-2-propyn-1-ols, when treated under similar reaction conditions, gave IV and VI.

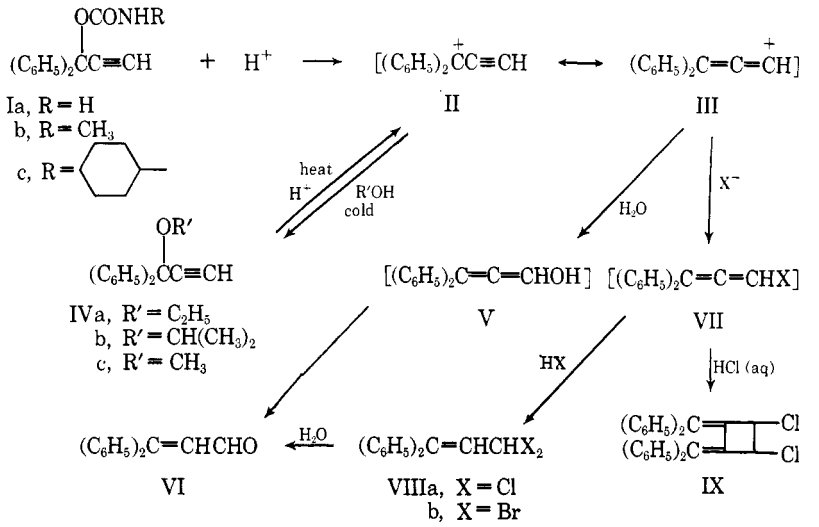
(4) It was reported by N. R. Easton, D. R. Cassady, and R. D. Dillard, *J. Org. Chem.*, **27**, 2746 (1962), that treatment of 1,1-diphenyl-2-propyn-1-ol with dry HCl gave 1,3-dichloro-3,3-diphenyl-1-propene. This product was identical with the one obtained on treating Ia with HCl. The ultraviolet spectra of these materials suggest that the correct structure for both products should be VIII; λ_{max}^{MeCN} 259 mμ (ε 15,150). In 95% EtOH, the material decomposed.

(5) H. Tani and F. Toda, *Chem. Ind.* (London), 1083 (1963).

(6) (a) P. D. Landor and S. R. Landor, *J. Chem. Soc.*, 2707 (1963). (b) Landor and Landor obtained IX on treating 1,1-diphenyl-2-propyn-1-ol with thionyl chloride in pyridine.

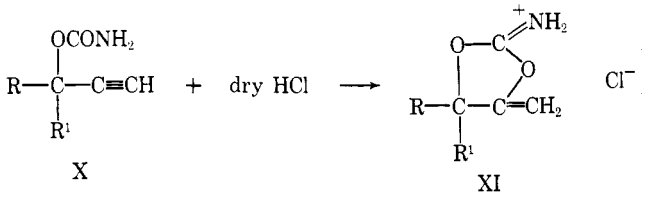
(7) D. R. Cassady and N. R. Easton, *J. Org. Chem.*, **29**, 2032 (1964).

SCHEME I



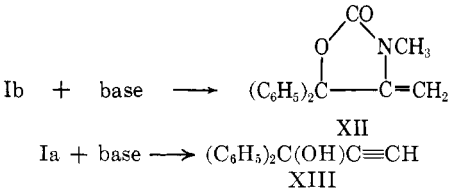
2-propynyl carbamates are treated with HCl (Scheme II). The 1,1-diaryl compounds did not undergo this type of cyclization with acids, but the initial step with all acids used involved the cleavage of the C–O bond that gave rise to the proposed carbonium ion intermediates.

SCHEME II



Treatment with Bases.—An intramolecular cyclization of 1,1-diphenyl-2-propynyl N-methylcarbamate (Ib) was accomplished using sodium ethoxide in ethanol to give XII (Scheme III). This type of cyclization has been previously reported[7] for 1,1-dialkyl-2-propynyl carbamates. When the primary carbamate was used, the acetylenic alcohol (XIII) was obtained. Aqueous hydrolysis also gave XIII. When Ia was treated with Na or NaH in an inert solvent, XIII and sodium cyanate were isolated. The dialkyl compounds also undergo this reaction.

SCHEME III



All of the acid- and base-catalyzed reaction products were tested for antitumor activity[1] and were found to be inactive.

Experimental Section

All melting points are uncorrected and were obtained in an open capillary tube. The infrared spectra were determined in $CHCl_3$ with a Perkin-Elmer spectrophotometer, Model 21. The nmr spectra were detrmined in $CDCl_3$ on a Varian A-60 nmr spectrometer using tetramethylsilane as an internal standard. Data are given in cycles per second.

3,3-Diphenyl-3-ethoxy-1-propyne (IVa).—A solution of 25 ml of concentrated H_2SO_4, 50 ml of water, and 100 ml of ethanol was added dropwise to 12.55 g (0.05 mole) of Ia in 250 ml of ethanol while maintaining a temperature of 0° with external cooling. Stirring and cooling were maintained for 3 hr and the reaction mixture was diluted with water and extracted with ether. The ether was washed three times with H_2O, dried ($MgSO_4$), and distilled. The fraction boiling at 87–88° (0.06 mm) weighed 9 g (76%); nmr, 74 (3 H, triplet J = 7 cps, ethyl), 167 (1 H, singlet, C≡CH), 212 (quartet, J = 7 cps, ethyl), 438 cps (10 H, multiplet, phenyl). The infrared spectrum showed the characteristic acetylenic C–H peak at 3.02 μ.

Anal. Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.83. Found: C, 86.26; H, 7.11.

3,3-Diphenyl-3-isopropoxy-1-propyne (IVb).—In a similar manner using 2-propanol as solvent, Ia was converted to IVb, bp 95–96° (0.01 mm), 60% yield.

Anal. Calcd for $C_{18}H_{18}O$: C, 86.36; H, 7.25. Found: C, 86.52; H, 7.21.

3,3-Diphenyl-3-methoxy-1-propyne (IVc).—Compound Ic in methanol was converted to IVc, bp 86–88° (0.05 mm), yield 71%.

Anal. Calcd for $C_{16}H_{14}O$: C, 86.45; H, 6.35. Found: C, 86.55; H, 6.54.

β,β-Diphenylacrolein (VI). A.—Concentrated H_2SO_4 (25 ml) in 50 ml of H_2O was added dropwise to 12.5 g (0.05 mole) of Ia in 250 ml of ethanol; the resulting solution was heated at reflux temperature for 2 hr. After cooling, the mixture was diluted with H_2O and extracted with ether. After washing with H_2O and drying, the ether was distilled. The fraction boiling at 114–115° (0.08 mm), 8.5 g (79%), solidified; nmr, 395 (1 H, doublet, J = 8 cps, ethylenic), 440 (10 H, multiplet, phenyl), 570 cps (1 H, doublet, J = 8 cps, aldehyde). The infrared spectrum of this material was identical with that reported by Hennion and Fleck.[3a]

Anal. Calcd for $C_{15}H_{12}O$: C, 86.51; H, 5.81. Found: C, 86.27; H, 5.90.

B.—A solution of Ia (0.05 mole) in *t*-amyl alcohol was treated with H_2SO_4 as described for IVa and the product, 5 g, bp 110–120° (0.05 mm), was identified as a mixture of 1,1-diphenyl-2-propyn-1-ol (40%) and β,β-diphenylacrolein (60%).

C.—An ethanolic solution of 8 g of IVa, treated with H_2SO_4 as described under method A, gave 6.3 g of VI.

3,3-Dichloro-1,1-diphenyl-1-propene (VIIIa).—Anhydrous HCl was bubbled into 250 ml of toluene containing 10 g (0.04 mole) of Ia for 30 min. The cooled mixture was filtered. The filtrate was distilled to give 8 g (76%) of colorless oil: bp 108° (0.06 mm); nmr, 368 (1 H, doublet, J = 10 cps), 386 (1 H, doublet, J = 10 cps), 438 cps (10 H, multiplet).

Anal. Calcd for $C_{15}H_{12}Cl_2$: C, 68.46; H, 4.60; Cl, 26.95. Found: C, 68.64; H, 4.79; Cl, 26.68.

Using anhydrous HBr, 0.1 mole of Ia was converted to 24 g (68%) of XIIIb, mp 81–82.5° (lit.[4] mp 82°), after recrystallizing from petroleum ether (bp 60–71°).

1,2-Dichloro-3,4-bis(diphenylmethylene)cyclobutane (IX).—A mixture of 10 g (0.04 mole) of Ia and 100 ml of concentrated HCl was heated on a steam bath for 0.5 hr and left at room

temperature overnight. The product was extracted from the reaction mixture with CH_2Cl_2; yield 45%, mp 191–192° after two recrystallizations from aqueous acetone (lit.[8a] mp 191–192°).

5,5-Diphenyl-3-methyl-4-methyleneoxazolidone (XII).—1,1-Diphenyl-2-propynyl N-methylcarbamate (10 g, 0.04 mole) and 0.22 mole of NaOEt in 150 ml of ethanol were refluxed for 2 hr. After cooling, the reaction mixture was diluted with H_2O and extracted with ether. After drying ($MgSO_4$), the ether was distilled. A fraction, bp 148–158° (0.05 mm), was recrystallized from petroleum ether (bp 60–71°) giving 7.7 g (66%) of white solid: mp 92–94°; nmr, 181 (3 H, singlet, NCH_3), 250 (1 H, doublet, J = 3 cps), 269 (1 H, doublet, J = 3 cps), 441 cps (10 H, multiplet).

Anal. Calcd for $C_{17}H_{15}NO_2$: N, 5.28. Found: N, 5.13.

Treatment of Ia with NaOH in Aqueous Ethanol.—An ethanolic solution of 5 g (0.02 mole) of Ia and 20 ml of 20% NaOH was refluxed 3.5 hr. After diluting with H_2O, the mixture was extracted with ether, and the ether was dried and distilled. The product, bp 117–118° (0.3 mm), 2.7 g (68%), was identical with an authentic sample of 1,1-diphenyl-2-propyn-1-ol (infrared, nmr).

Treatment of Ia with Sodium Methoxide in Ethanol.—An ethanolic solution of 0.04 mole of Ia and 0.02 mole of NaOEt was stirred 16 hr at 20°. After isolation as described above, 7 g of distillate, identified as 1,1-diphenyl-2-propyn-1-ol, was obtained.

Reaction of Ia with Sodium.—A xylene dispersion of Na (1.4 g, 0.06 mole) and 5 g (0.02 mole) of Ia were stirred at 25° for 16 hr. The excess Na was decomposed with ethanol (25 ml), and H_2O was added. The organic layer was separated and dried, and the solvent was removed at reduced pressure. An oily residue (4 g) remained (infrared and nmr spectra identical with those of 1,1-diphenyl-2-propyn-1-ol). Water was removed from the aqueous layer; the residue was a mixture of NaOH and NaCNO (strong band at 4.5 μ in the infrared spectrum).

Acknowledgment.—The microanalyses were performed by Messrs. William Brown, Howard Hunter, Charles Ashbrook, and David Cline. Many of the intermediates were prepared by Mr. Lawrence White.

Some 2,3,6,8-Tetrasubstituted Quinazolone Hydrazides as Monoamine Oxidase Inhibitors[1a]

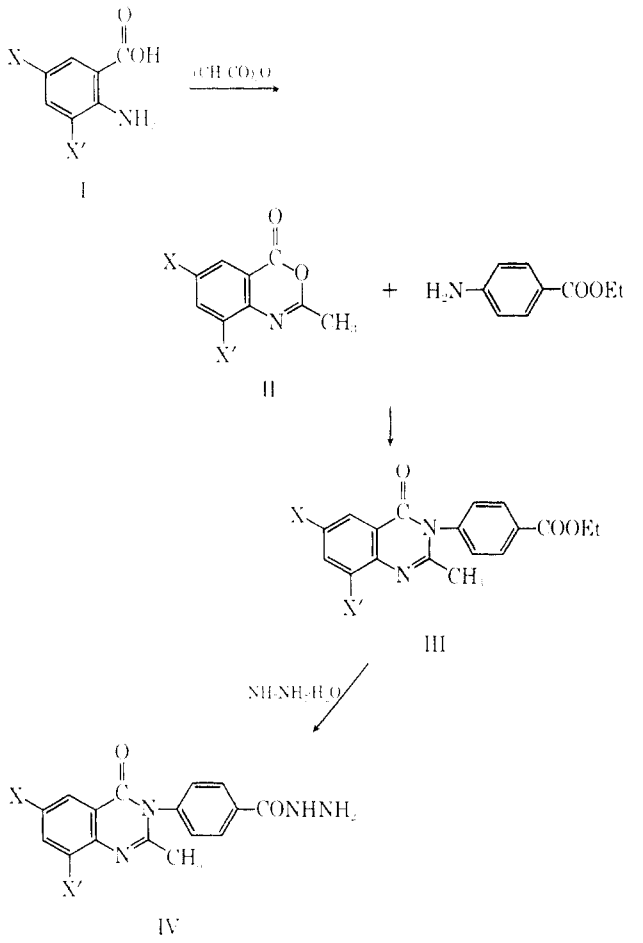
SURENDRA S. PARMAR[1b] AND R. C. ARORA[1c]

Department of Pharmacology and Therapeutics, King George's Medical College, Lucknow University, Lucknow, India, and Biochemical Research Laboratory, Boston University, Veterans Administration Hospital, Brockton, Massachusetts 02401

Received June 21, 1967

Inhibitors of monoamine oxidase (MAO) have been shown to possess pronounced anticonvulsant properties.[2] The effectiveness of 2-methyl-3-(4-benzhydrazide)-4-quinazolone in inhibiting this enzyme was found to be significantly increased by the introduction of a substituent at position 6 of the quinazolone nucleus.[3] For that reason, corresponding 2-methyl-3-(4-benzhydrazide)-4-quinazolones with substituents at positions 6 and 8 have now been synthesized as potential hypnotics and anticonvulsants.[4,5] In the present study, attempts have also been made to investigate the role of such substituents on the ability of quinazolone hydrazides to inhibit rat liver MAO. The quinazolone hydrazides have been synthesized according to Scheme I (X or X′ = H, Cl, Br, or I).

SCHEME I



Experimental Section[6]

Anthranilic Acids (I).—Substituted anthranilic acids were synthesized according to the methods reported in the literature. The anthranilic acids used were 3,5-dichloro-,[7] 3,5-dibromo-,[8] and 3,5-diiodoanthranilic acids.[9]

Acetanthranils (II).—Appropriate anthranilic acids (1 mole) were refluxed with Ac_2O (2 moles) for 1 hr. After excess Ac_2O was distilled, the acetanthranils separated as solid masses and were used without further purification. 3,5-Dibromoacetanthranil had been reported earlier.[10] **3,5-Dichloroacetanthranil,** mp 145–146°, and **3,5-diiodoacetanthranil,** mp 185–187°, were obtained in 80 and 70% yields, respectively.

Anal. Calcd for $C_9H_5Cl_2NO_2$: C, 46.9; H, 2.2; N, 6.1. Found: C, 46.7; H, 2.0; N, 5.9.

Anal. Calcd for $C_9H_5I_2NO_2$: C, 26.2; H, 1.2; N, 3.4. Found: C, 25.9; H, 1.5; N, 3.2.

(1) (a) The authors wish to express their thanks to Dr. Sabit Gabay and Dr. J. P. Barthwal for their advice and encouragement and to Dr. M. L. Dhar and Dr. Nitya Anand from Central Drug Research Institute, Lucknow, for providing facilities for microanalysis. Grateful acknowledgment is made to the Council of Scientific and Industrial Research, New Delhi, for providing financial assistance. (b) Visiting Scientist, Biochemical Reseach Laboratory, Boston University, Veterans Administration Hospital, Brockton, Mass. (May–Aug 1965). (c) Senior Research Fellow of the Council of Scientific and Industrial Research, New Delhi.

(2) J. P. Darwin, A. Shore, and B. B. Brodie, *Ann. N. Y. Acad. Sci.*, **80**, 643 (1959).

(3) S. S. Parmar and R. C. Arora, *Can. J. Chem.*, **44**, 2100 (1966).

(4) M. L. Gujral, R. P. Kohli, and P. N. Saxena, *J. Assoc. Physicians*, **2**, 29 (1955).

(5) M. L. Gujral, P. N. Saxena, and R. P. Kohli, *Indian J. Med. Res.*, **45**, 207 (1957).

(6) Melting points were taken in open capillary tubes and are corrected.

(7) M. M. Endicott, B. B. Alden, and M. L. Sherill, *J. Am. Chem. Soc.*, **68**, 1303 (1946).

(8) A. S. Wheeler and W. M. Oats, *ibid.*, **32**, 770 (1910).

(9) C. J. Klemme and J. H. Hunter, *J. Org. Chem.*, **5**, 227 (1940).

(10) J. S. Shukla, H. H. Singh, and S. S. Parmar, *Can. J. Chem.*, in press.