Quinazolines and 1,4-Benzodiazepines (VIII).[1] The Photoisomerization of 7-Chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-Oxide[2]

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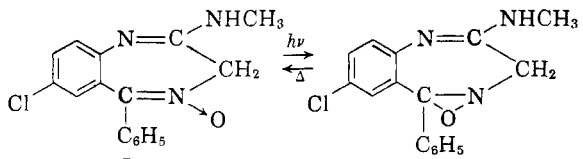
It was found that there was a radical change in the ultraviolet absorption spectra of dilute isopropyl alcohol solutions of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide[2] (I) on exposure to daylight. The two maxima at 245 and 265 mμ (ε 30,000 and 32,100), present in the spectrum of compound I, disappeared and were replaced by a single peak of lower intensity at 278 mμ (ε 18,000).

Since it had been reported[3] that irradiation of nitrones could result in a rearrangement to oxaziridines, we suspected that such a change had also taken place in this case and that our irradiation product was 7-chloro-4,5-epoxy-4,5-dihydro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (II).



I II

In order to verify this assumption we carried out preparative experiments and investigated the irradiation product.

When an open capillary tube containing a sample of this material was introduced into an oil bath preheated to 160°, a melting point of 167–170° was observed; the material then solidified immediately and remelted at 236–236.5°, the melting point of compound I. The infrared and ultraviolet spectra of the light yellow, high melting product, and the mixed melting point with an authentic sample of chlordiazepoxide established that quantitative reconversion into I had occurred. Isomerization also took place in dilute hydrochloric acid at room temperature, and when a solution of the oxaziridine in isopropyl alcohol was refluxed for a short time. This thermal reconversion of II into I parallels the behavior of oxaziridines described in the literature.[4]

(1) Paper VII, *Helv. Chim. Acta*, **45**, 2226 (1962).

(2) The generic name of this compound is chlordiazepoxide.

(3) M. J. Kamlet and L. A. Kaplan, *J. Org. Chem.*, **22**, 576 (1957); J. S. Splitter and M. Calvin, *ibid.*, **23**, 651 (1958); R. Bonnett, V. M. Clark, and Sir A. Todd, *J. Chem. Soc.*, 2102 (1959). See also F. Kröhnke, *Ann.*, **604**, 203 (1957).

(4)(a) W. D. Emmons, *J. Am. Chem. Soc.*, **78**, 6208 (1956); **79**, 5739 (1957). (b) M. F. Hawthorne and R. D. Strohn, *J. Org. Chem.* **22**, 1263 (1957). (c) L. Horner and E. Jürgens, *Ber.*, **90**, 2184 (1957).

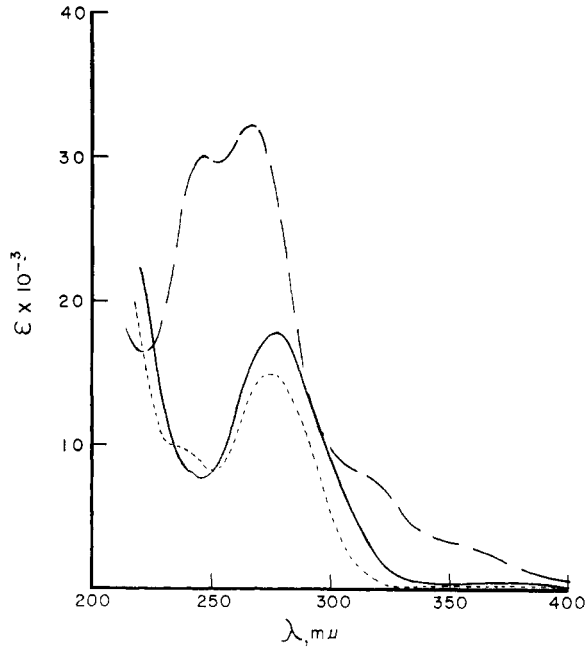
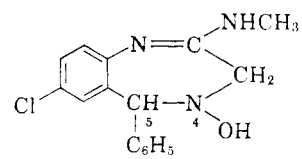


Fig. 1.—Ultraviolet absorption spectra in isopropyl alcohol.
I. — — —
II. ——
III. - - - -

Similarly to other oxaziridines, compound II exhibited oxidizing properties and liberated iodine from a potassium iodide solution.[4a,c,5] The corresponding nitrone I does not show this behavior.

The ultraviolet spectrum of compound II gave additional evidence for the oxaziridine structure. The spectrum of II showed, as mentioned above, only a single absorption peak at 278 mμ. The position and intensity of this maximum are, as can be seen in Fig. 1, very similar to those exhibited by compound III,[6] which also lacks the double bond in the 4,5-position.



III

Experimental

7-Chloro-4,5-epoxy-4,5-dihydro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (II).—A solution of 10 g. of 7-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine 4-oxide (I) in 1000 ml. of isopropyl alcohol was exposed in a borosilicate glass flask for 12 days to diffused daylight. The end point was determined spectrophotometrically. The solvent was evaporated at low temperature and the irradiation product was separated from small amounts of compound I by fractional crystallization from a mixture of ether and petroleum ether (evaporations were carried out *in vacuo*), in which the new product was considerably more soluble. It

(5) H. Krimm, *Ber.*, **91**, 1057 (1958).

(6) L. H. Sternbach and E. Reeder, *J. Org. Chem.*, **26**, 1111 (1961).

was isolated in 65% yield in the form of colorless prisms, m.p. 167–170° (bath preheated to 160°). Found: C, 64.14; H, 5.06. Calc. for $C_{16}H_{14}ClN_3O$: C, 64.11; H, 4.71.

The Isomerization of II to the Nitrone I. Method A.—A spectrophotometric study of a solution of the oxaziridine II in an excess of 0.1 *N* hydrochloric acid (room temperature) indicated that after 26 hr. a 99% conversion into the nitrone I had occurred.

Method B.—A 1.5% isopropyl alcohol solution of the oxaziridine II, which was refluxed for 50 min., was shown spectrophotometrically to contain 90% of the nitrone I. The mixture was refluxed for an additional 3 hr., concentrated under reduced pressure, cooled, and allowed to crystallize. Ninety per cent of the nitrone I was recovered; m.p. and mixed m.p. 236–236.5°.

Acknowledgment.—We are indebted to Dr. V. Toome and Dr. A. Motchane for most of the spectrophotometric determinations, and to Dr. Al Steyermark and his staff for the microanalyses.

Nonclassical Antimetabolites. X.[1,2] A Facile Synthesis of 4-Quinazolone-2-carboxylic Acid and the Structure of Bogert's Ammonium Salt

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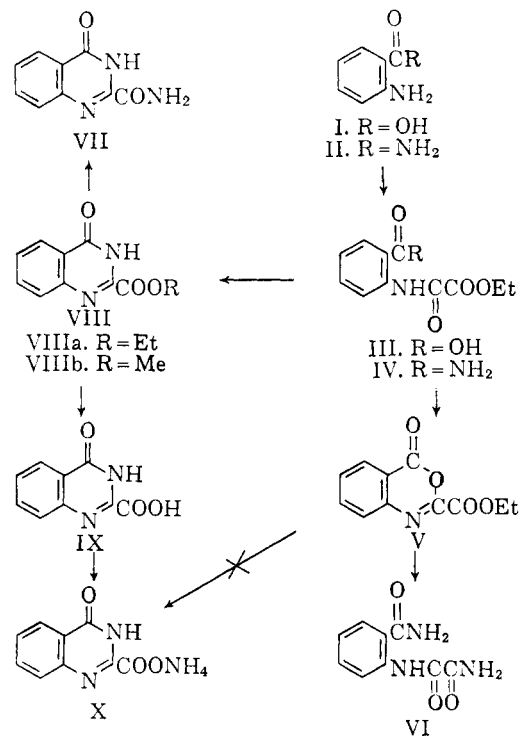
Recently, we presented[3,4] strong experimental evidence to support the concept[5] of a new class of irreversible inhibitors that operate by exo-alkylation. A properly designed compound, such as 4-(iodoacetamido)salicyclic acid, can complex reversibly with an enzyme such as glutamic dehydrogenase, then become irreversibly bound within the complex adjacent to the active site. A number of factors can influence the rate at which the reversibly complexed inhibitor can become covalently bound to the enzyme such as (1) the ability of the reversibly bound inhibitor to bridge to a nucleophilic site on the enzyme,[6,7] (2) the nucleophilic character of the enzymic group,[2] (3) the reactivity of the group on the inhibitor forming the bond, and (4) the K_i of the reversibly bound inhibitor.

The latter phenomenon would be important in chemotherapy, since the lower the K_i, the less intracellular concentration of inhibitor will be needed to inactivate a given enzyme. Compounds bearing 1,2- or 1,3-oxo (or hydroxyl) and carboxyl groups usually give good reversible inhibition of lactic and glutamic dehydrogenases; in fact, 1-hydroxy-2-naphthoic acid,[8] coumarin-3-carboxylic acid,[9] and 2-hydroxycinchoninic acid,[9] can reversibly bind to these enzymes much more effectively than salicylic acid and in some cases even better than the substrate. Since 4-quinazolone-2-carboxylic (IX) has the proper relationship of oxo and carboxyl functions, this compound has been resynthesized for evaluation as an inhibitor; however, it was found to bind less effectively than salicylic acid (I_{50} about 20)[8] since IX had $I_{50} = 31$ for glutamic dehydrogenase and $I_{50} = 33$ for lactic dehydrogenase. Thus, IX was not suitable for conversion to a potent irreversible inhibitor.



Among the routes available[10,11] for synthesis of 4-quinazolone-2-carboxylic acid, the route (I→III→V→X→IX) described by Bogert and Gortner[10] seemed attractive in view of past use[12] of anthranils such as V for synthesis of a variety of 4-quinazolones. Preparation of the anthranil, V, and reaction with ethanolic ammonia according to the described procedure[10] gave a compound iden-

(1) This work was generously supported by Grant CY-5867 of the National Cancer Institute, U. S. Public Health Service.

(2) For paper IX of this series see B. R. Baker and R. P. Patel, *Biochem. Biophys. Res. Comm.*, **9**, 199 (1962).

(3) B. R. Baker, W. W. Lee, E. Tong, and L. O. Ross, *J. Am. Chem. Soc.*, **83**, 3713 (1961); paper III of this series.

(4) B. R. Baker, W. W. Lee, and E. Tong, *J. Theor. Biol.*, **3**, 458 (1962); paper VI of this series.

(5) B. R. Baker, *Cancer Chemotherapy Repts.*, No. **4**, 1 (1959), published by the National Cancer Institute; paper I of this series.

(6) B. R. Baker, *J. Med. Pharm. Chem.*, **5**, 654 (1962); paper VII of this series.

(7) B. R. Baker, *Biochem. Pharm.*, in press; paper VIII of this series.

(8) B. R. Baker, W. W. Lee, W. A. Skinner, A. P. Martinez, and E. Tong, *J. Med. Pharm. Chem.*, **2**, 633 (1960); paper II of this series.

(9) B. R. Baker, W. W. Lee, E. Tong, L. O. Ross, and A. P. Martinez, *J. Theor. Biol.*, **3**, 446 (1962); paper V of this series.

(10) M. T. Bogert and R. A. Gortner, *J. Am. Chem. Soc.*, **32**, 123 (1910).

(11) A. Reissert and F. Grube, *Ber.*, **42**, 3713 (1909).

(12) B. R. Baker, M. V. Querry, A. F. Kadish, and J. H. Williams, *J. Org. Chem.*, **17**, 35 (1952), and following papers.