Quinazolines and 1,4-Benzodiazepines. XXII.[1] A Rearrangement of 5-Phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-ones[2]

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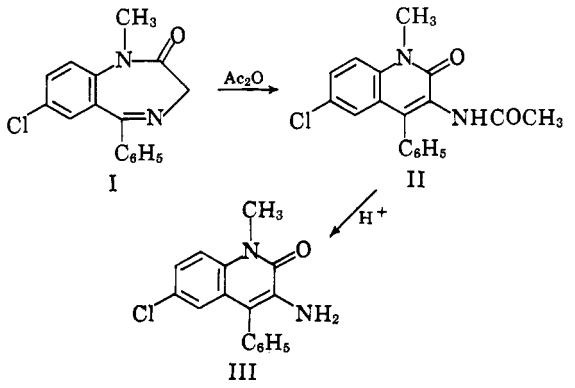
7-Chloro-1-methyl-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one (I) was shown to rearrange to 3-acetamido-6-chloro-1-methyl-4-phenyl-2(1H)quinolone (II) upon treatment with acetic anhydride. The corresponding desmethyl benzodiazepinone IV rearranged under the same conditions to give 6-chloro-2-methyl-9-phenyloxazolo[5,4-*b*]quinoline (V). The mechanism of the rearrangement is discussed.

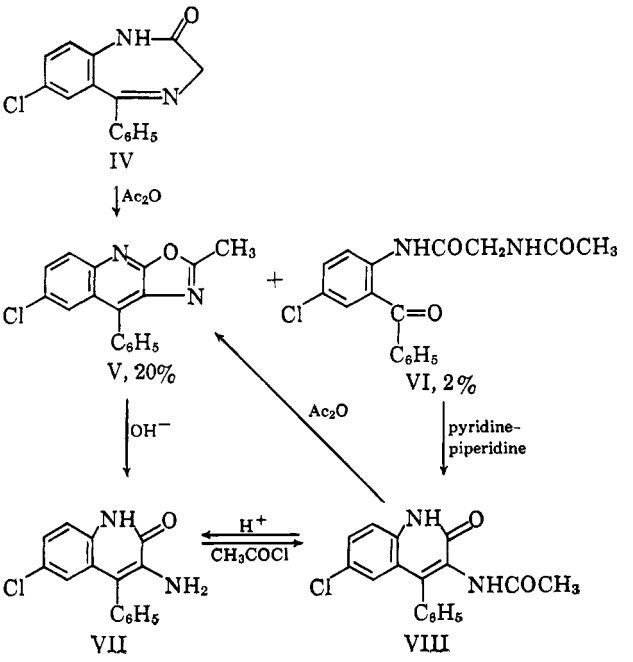
In the past few years several reports have appeared in the literature, of rearrangements and transformations of substituted 1,4-benzodiazepine 4-oxides to give derivatives of indoles,[3] quinazolines,[4-6] and quinoxalines.[7] We have found that substituted 1,4-benzodiazepin-2-ones undergo a ring contraction and rearrangement to give quinoline derivatives on treatment with acetic anhydride.

Treatment of 7-chloro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one (I) with acetic anhydride in the presence of sodium acetate led to the formation of 3-acetamido-6-chloro-1-methyl-4-phenyl-2(1H)-quinolone (II). This compound was hydrolyzed with 70% sulfuric acid to give the corresponding 3-amino quinolone III. A direct comparison of III with an authentic specimen prepared in conjunction with other work[8] showed the two compounds to be identical. 7-Chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (IV),



on treatment with acetic anhydride, also undergoes an intramolecular rearrangement to give the 2-methyl-9-phenyloxazolo[5,4-*b*]quinoline V as the major product. The structure of this compound was confirmed by the series of interconversions with 3-amino-6-chloro-4-phenyl-2(1H)-quinolone (VII)[8,9] and its corresponding 3-acetyl derivative VIII[8] shown below.

3-Acetamido-6-chloro-4-phenyl-2(1H)-quinolone (VIII) prepared from the acetamidobenzoylacetanilide VI,[8] when treated with acetic anhydride, cyclodehydrated readily to give V. Hydrolysis of this oxazoloquinoline with strong base gave a low yield of the aminoquinolone VII which was then converted to VIII by treatment with acetyl chloride. The minor product



isolated from the reaction of IV with acetic anhydride was the acetamidobenzoylacetanilide VI. This compound was shown to be identical with an authentic sample.[8] Since VI could not be converted to either V or to VIII with acetic anhydride,[10] two separate reaction mechanisms leading, respectively, to V and VI, would appear to exist.

The rearrangement of IV to V can be visualized as occurring from an acetylated ion such as IX. This ion can be formed either by direct acetylation of the N-4 atom of IV or with the help of XI, which is postulated below as an intermediate for the formation of VI. In connection with other work[11] we have shown that the hydrogen atoms at the 3-position are acidic; ring contraction could therefore occur, and the resulting unstable intermediate X would collapse to give the 3-acetamidoquinolone, VIII. Under the conditions used, VIII has been shown to cyclodehydrate to give V. The same mechanism would also be operable for the sequence I → II; the product in this case would be unable to form the oxazole ring.

(1) Paper XXI: R. I. Fryer, J. V. Earley, and L. H. Sternbach, *J. Org. Chem.*, **30**, 521 (1965).

(2) Presented in part at the XIXth Congress of the International Union of Pure and Applied Chemistry, London, July 1963.

(3) W. Metlesics, G. Silverman, and L. H. Sternbach, *J. Org. Chem.*, **29**, 1621 (1964).

(4) S. C. Bell and S. J. Childress, *ibid.*, **27**, 1691 (1962).

(5) S. C. Bell, C. Gochman, and S. J. Childress, *ibid.*, **28**, 3010 (1963).

(6) L. H. Sternbach, E. Reeder, A. Stempel, and A. I. Rachlin, *ibid.*, **29**, 332 (1964).

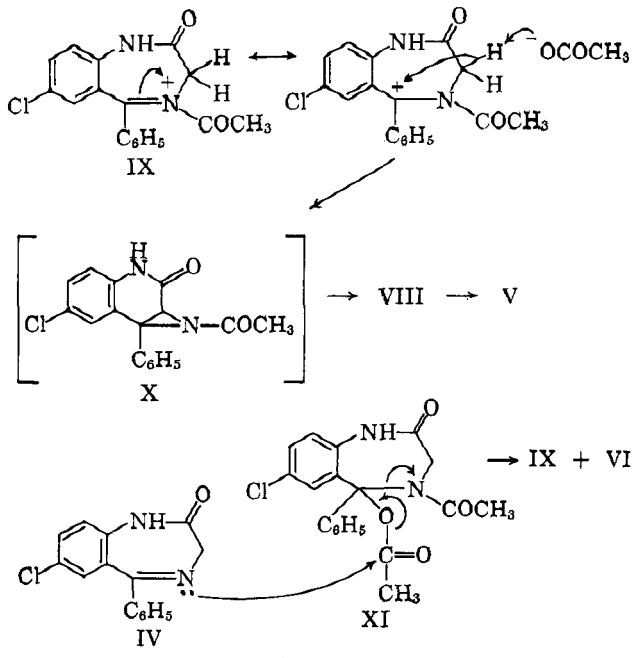
(7) S. C. Bell and S. J. Childress, *ibid.*, **29**, 506 (1964).

(8) R. I. Fryer, B. Brust, and L. H. Sternbach, *J. Chem. Soc.*, 3097 (1964).

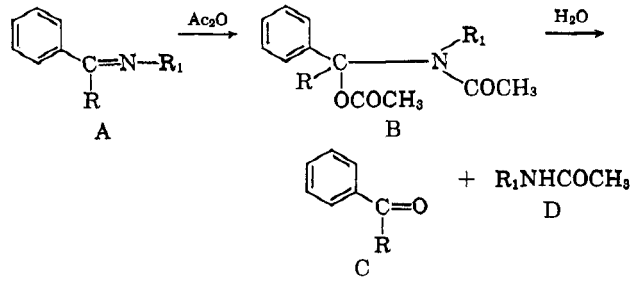
(9) S. C. Bell, T. S. Sulkowski, C. Gochman, and S. J. Childress, *J. Org. Chem.*, **27**, 562 (1962).

(10) VI was, however, readily cyclized to VIII in a pyridine–piperidine mixture; see ref. 8.

(11) R. Ian Fryer and L. H. Sternbach, unpublished results.



The formation of small amounts of an addition compound of type XI, which would parallel the "normal" reaction between a Schiff base and acetic anhydride,[12] would account for the formation of VI.



Compound VI could be obtained either by hydrolysis of XI on decomposition with water,[12] or by acetylation of additional 1,4-benzodiazepinone IV by XI which would give VI directly along with the ion IX.

A less plausible explanation for the formation of VI would be given either by the hydrolysis of the azomethine bond of IV, followed by acetylation of the free amine, or by hydrolysis of the ion IX. In general, 1,4-benzodiazepinones are stable to hot glacial acetic acid[11] and we were never able to isolate XI from the reaction mixture. Furthermore, we always obtained small amounts (*ca.* 2%) of VI even when anhydrous conditions were used in the work-up. It is apparent from the comparative yields of V and VI (20% and 2%, respectively) that the reaction sequence IV + XI → IX is of minor importance when compared with the formation of IX by the direct acetylation of IV with acetic anhydride.

Experimental

All melting points were determined microscopically on a hot stage and were corrected.

3-Acetamido-6-chloro-1-methyl-4-phenyl-2(1H)-quinolone (II).—A mixture of 10 g. of 7-chloro-1,3-dihydro-1-methyl-5-phenyl-2H-1,4-benzodiazepin-2-one,[13] 10 g. of sodium acetate hydrate, and 20 ml. of acetic anhydride was heated under reflux for 2 hr. and then poured over 500 g. of crushed ice. The products were extracted into dichloromethane (three 100-ml. portions). The combined organic layers were washed with three 100-ml. portions of dilute sodium hydroxide solution and three 100-ml. portions of water, and were then dried over sodium sulfate and concentrated. The residual oil was dissolved in a small amount of benzene and chromatographed over 50 g. of Woelm grade I neutral alumina. Concentration of the ether eluates and recrystallization of the residue from an ether–petroleum ether mixture gave 6.7 g. of starting material, m.p. 130–133°. The eluent was changed to methanol, which gave, on evaporation of solvent, 2.1 g. of an oil. Crystallization from benzene gave 900 mg. (23%, based on benzodiazepinone consumed) of II as white prisms, m.p. 233–234°.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.16; H, 4.63. Found: C, 66.22; H, 4.59.

3-Amino-6-chloro-1-methyl-4-phenyl-2(1H)-quinolone (III).—A mixture of 1 g. of II, 3 ml. of glacial acetic acid, and 20 ml. of 70% (v./v.) sulfuric acid was heated under reflux for 5 hr. The resulting solution was cooled, poured over 100 g. of ice, made basic (pH 8) with sodium hydroxide solution, and filtered. The precipitate was washed with water and recrystallized from an acetone–petroleum ether (b.p. 30–60°) mixture to give 700 mg. of pure III, m.p. and m.m.p. 133–135°.

7-Chloro-2-methyl-9-phenyloxazolo[5,4-*b*]quinoline (V) and 2-Acetamido-2′-benzoyl-4′-chloroacetanilide (VI).—A solution of 40 g. of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one[13] in 100 ml. of acetic anhydride was treated with 2 drops of concentrated sulfuric acid and heated under reflux for 3 hr. The reaction mixture was poured over 500 g. of ice and diluted to 1 l. with water. The aqueous mixture was extracted with three 200-ml. portions of dichloromethane. The organic layers were combined and washed first with 3 *N* sodium hydroxide solution until the washes were basic, and then with water until the washes were neutral. The dichloromethane solution was dried over sodium sulfate, treated with Norit, filtered, and concentrated to an oil. Crystallization from methanol gave 10.8 g. of V, m.p. 228–229°. Recrystallization from acetone gave 10.0 g. (23%) of the pure product as white needles, m.p. 228–229°.

Anal. Calcd. for $C_{17}H_{11}ClN_2O$: C, 69.28; H, 3.76; N, 9.51. Found: C, 69.56; H, 3.61; N, 9.77.

The mother liquors were concentrated, dissolved in benzene, and chromatographed over Woelm grade III neutral alumina. The benzene fraction was discarded and the eluent changed to ether, which, after evaporation yielded 1 g. of pure VI, m.p. and m.m.p. 137–139°.

3-Amino-6-chloro-4-phenyl-2(1H)-quinolone (VII).—A solution of 500 mg. of V in 25 ml. of methanol was treated with 2.5 g. of sodium hydroxide and heated under reflux for 4 hr. The reaction mixture was cooled, acidified with dilute hydrochloric acid, and filtered. The precipitate was recrystallized from acetone to give 100 mg. of pure VII, m.p. and m.m.p. 239–242°.

3-Acetamido-6-chloro-4-phenyl-2(1H)-quinolone (VIII).—A suspension of 1 g. of VII[8] in 10 ml. of benzene was treated with 1 equiv. of acetyl chloride and heated under reflux for 1 hr. The solution was cooled and filtered. The precipitate was recrystallized from dilute methanol to give 900 mg. (77%) of pure VIII,[14] m.p. and m.m.p. 210–214°, reset m.p. 280–284°.

The Cyclodehydration of 3-Acetamido-6-chloro-4-phenyl-2(1H)-quinolone (VIII).—A solution of 900 mg. of VIII in 15 ml. of acetic anhydride was treated with 1 drop of concentrated sulfuric acid and heated under reflux for 2 hr. The reaction mixture was poured over 200 g. of ice and made basic with sodium hydroxide; the product was extracted with three 50-ml. portions of dichloromethane. The organic layers were combined, washed with water, dried over sodium sulfate, and filtered over a small amount of Woelm grade I neutral alumina. The alumina was washed well with dichloromethane and all the eluates were combined and evaporated. Recrystallization of the residue from acetone gave 700 mg. of V, m.p. 233–234°.

Acknowledgment.—We are indebted to Dr. Al Steyermark and his staff for the microanalyses and to Dr. V. Toome and Mr. S. Traiman for the determination of ultraviolet and infrared spectra.

(12) See G. N. Walker and M. A. Moore [*J. Org. Chem.*, **26**, 432 (1961), and references cited therein] for reaction sequences corresponding to A → B → C + D.

(13) L. H. Sternbach and E. Reeder, *ibid.*, **26**, 4936 (1961).

(14) Isolated as the hemihydrate, see ref. 8.