Acknowledgment.—The authors would like to acknowledge financial support of this work from the National Cancer Institute under grant CY-4068.

The Formation and Subsequent Rearrangement of 7-Chloro-5-phenyl-3,1,4-benzoxadiazepin-2(1H)-one

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Received July 6, 1962

2-Amino-5-chlorobenzophenone α-oxime has been converted into 7-chloro-5-phenyl-3,1,4-benzoxadiazepin-2(1H)-one (II) by the action of phosgene. 2-Amino-5-chlorobenzophenone β-oxime afforded 6-chloro-4-phenyl-2(1H)-quinazolinone 3-oxide (VII). Compound II underwent a Beckmann rearrangement at its melting point to give 6-chloro-3-phenyl-2,4-(1H,3H)-quinazolinedione (V).

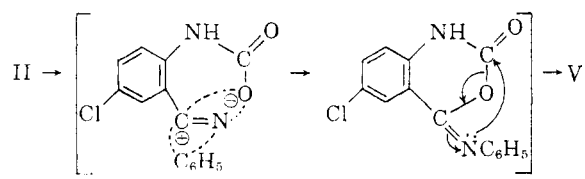
Compounds described in the literature as 3,1,4-benzoxadiazepines have been shown by Sternbach, Kaiser, and Reeder[1] to be quinazoline 3-oxides. Because 3,1,4-benzoxadiazepines have a structural similarity to 1,4-benzodiazepines in which we have been interested[2] we have prepared a 3,1,4-benzoxadiazepin-2-one and established its structure.

2-Amino-5-chlorobenzophenone α-oxime[3] (I) was treated with phosgene in benzene to afford 7-chloro-5-phenyl-3,1,4-benzoxadiazepin-3(1H)-one (II). Upon heating in ethanol II was converted into 2-carbethoxyamino-5-chlorobenzophenone α-oxime (III). In an attempt to obtain III alternatively from I and ethyl chloroformate, only 2-amino-5-chlorobenzophenone α-oxime, ethyl carbonate ester (IV), was obtained. Compounds III and IV could be distinguished by their infrared absorption spectra, the carbonyl stretching band of III appearing at 1735 cm.$^{-1}$ whereas that of IV appeared at 1769 cm.$^{-1}$. In addition IV showed the characteristic NH stretching absorptions of a primary amine (3350, 3435 cm.$^{-1}$).

Treatment of III with sodium hydroxide did not afford II, but returned unchanged III. Ried and Stahlhofen[4] reported the conversion of 2-carbethoxyaminobenzaldoxime into 3,1,4-benzoxadiazepin-2(1H)-one upon treatment with sodium hydroxide. Under the conditions employed by these authors II was actually converted into I.

The possibility that II was 6-chloro-4-phenyl-2-(1H)-quinazolinone 3-oxide (VII) could not be overlooked. The infrared absorption spectrum of II was not helpful, the carbonyl stretching band appearing at 1722 cm.$^{-1}$, a lower frequency than that of III or IV. The ultraviolet absorption spectrum of II had a peak at 315 mμ (ε 2,300) that might be attributable to the $C_6H_5—C(=N)—$ chromophore and was consistent with the spectrum of 7-chloro-5-phenyl-1,3-dihydro-2H-1,4-benzodiazepin-2-one[2] which has a peak at 314 mμ (ε 2,300). Although structure II could have resulted only from the α-oxime, structure VII could form from either the α- or β-oxime.[5] Therefore, 2-amino-5-chlorobenzophenone β-oxime (VI) was treated with phosgene and a product differing from II was obtained. The carbonyl stretching frequency (1771 cm.$^{-1}$) indicated an activated carbonyl function. The formulation of this product as 6-chloro-4-phenyl-2(1H)-quinazolinone 3-oxide (VII) was confirmed by its deoxygenation to 6-chloro-4-phenyl-2(1H)-quinazolinone (VIII) by means of phosphorus trichloride. Compound VIII was prepared for comparison by fusing 2-amino-5-chlorobenzophenone with urea. The ultraviolet absorption spectrum of VII did not show a peak at 315 mμ thus differing from that of II.

Compound II was observed to resolidify just above its melting point. It was found that a rearrangement had taken place at the original melting point to give 6-chloro-3-phenyl-2,4-(1H,-3H)-quinazolinedione (V). This product was also obtained on heating III or IV above their melting points. The structure of V was established by an alternative preparation from 5-chloroanthranilic acid and phenylisocyanate. Compound V appears to be formed from II in a Beckmann rearrangement[6] with subsequent O → N migration of the carbonyl group.



(1) L. H. Sternbach, S. Kaiser, and E. Reeder, *J. Am. Chem. Soc.*, **82**, 475 (1960).

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

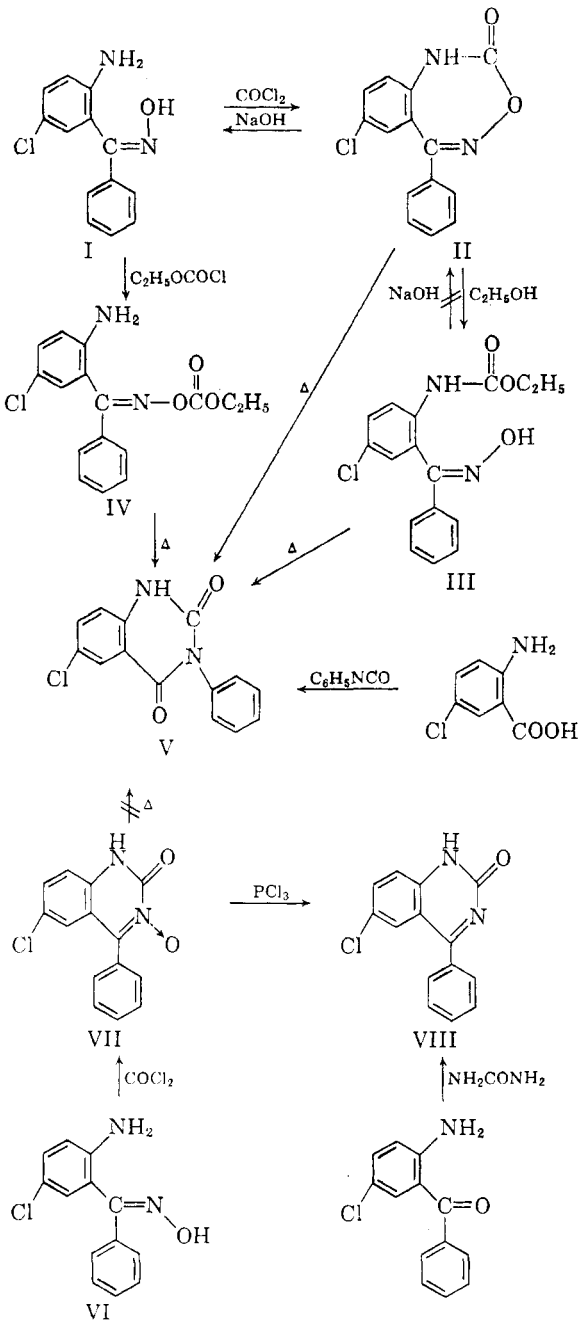
(3) The α-oxime is *syn* to the substituted phenyl.

(4) W. Ried and P. Stahlhofen, *Chem. Ber.*, **87**, 1814 (1954).

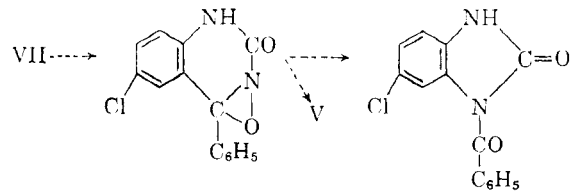
(5) 6-Chloro-2-methyl-4-phenylquinazoline 3-oxide has been formed from the α- or β-oxime of 2-amino-5-chlorobenzophenone by treatment with acetyl chloride (ref. 1).

(6) An analogous reaction has been observed in the formation of N-phenylphthalimide from 4-phenyl-1H-2,3-benzoxaxin-1-one. F. H. Thorp, *Ber.*, **26**, 1261, 1795 (1893).

(7) K. Dziewonski and L. Sternbach, *Bull. intern. acad. polonaise, Classe sci. math. nat.*, **1935A**, 333; *Chem. Abstr.*, **30**, 2971 (1936).



Another possible mechanism for this change [II → VII → V] was considered. It might be argued that VII in a Beckmann-type rearrangement ought to give 1-benzoyl-5-chlorobenzimidazolone (*trans* shift). Benzimidazole formation has indeed been observed from quinazoline 3-oxides.[7] More recent work, however, suggests oxaziridines as intermediates in nitrone rearrangements[8] with a consequent loss in stereospecificity.[9] This alternative mechanism was conclusively ruled out by the failure of VII to rearrange to V



under conditions sufficient to bring about the change of II into V.

The formation of V in a Beckmann rearrangement of II offers substantial confirmation of 7-chloro - 5 - phenyl - 3,1,4 - benzoxadiazepin - 2-(1H)-one as the structure of II.

Experimental[10]

7-Chloro-5-phenyl-3,1,4-benzoxadiazepin-2(1H)-one (II).—A solution of 12.3 g. of I (m.p. 170–173°) and 15 ml. of triethylamine in 150 ml. of ethyl acetate was cooled in an ice bath. The solution was stirred vigorously while 40 g. of 12.5% phosgene in benzene solution was added dropwise keeping the temperature below 10°. After addition was completed, the mixture was stirred 0.5 hr. at room temperature. The precipitated triethylamine hydrochloride was removed by filtration and the filtrate was concentrated *in vacuo*. After recrystallization from ethyl acetate, 5.0 g. of white crystalline solid was obtained, m.p. 195°, resolidifying, then remelting at 312°; $\lambda_{max}^{CHCl_3}$ 245, 315 mμ ε 12,500, 2,300.

Anal. Calcd. for $C_{14}H_9ClN_2O_2$: C, 61.66; H, 3.33; Cl, 13.00; N, 10.27. Found: C, 61.81; H, 3.34; Cl, 12.82; N, 10.23.

Six-tenths of a gram of II was warmed with 10 ml. of 1 *N* sodium hydroxide until a clear solution formed. The solution was cooled and acidified with glacial acetic acid until evolution of gas ceased. The precipitated solid was removed by filtration and washed thoroughly with water. After drying, 0.3 g. of white solid was obtained, m.p. 171–173°. A mixture melting point with I was undepressed.

6-Chloro-3-phenylquinazoline-2,4(1H,3H)-dione (V) from II.—One and one-half grams of II was heated at its melting point until a vigorous reaction ensued and the material solidified. The solid was recrystallized from ethanol with charcoal treatment. White needles (0.8 g.) were obtained, m.p. 312°.

Anal. Calcd. for $C_{14}H_9ClN_2O_2$: C, 61.66; H, 3.33; Cl, 13.00; N, 10.27. Found: C, 62.00; H, 3.37; Cl, 13.00; N, 10.02.

Compound V from 5-Chloroanthranilic Acid.—Phenyl isocyanate (3.0 g.) was added in one portion to a stirred solution of 4.3 g. of 5-chloroanthranilic acid in 50 ml. of ether. After stirring at room temperature for 1 hr., the precipitated solid was removed by filtration and recrystallized from ethyl acetate to afford 4.0 g. of 5-chloro-N-phenylcarbamylanthranilic acid, m.p. 199°.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_3$: C, 57.84; H, 3.81; Cl, 12.20; N, 9.64. Found: C, 57.69; H, 3.45; Cl, 12.0; N, 9.58.

A solution of 3.5 g. of the above urea and 1.5 g. of sodium hydroxide in 100 ml. of water was heated under reflux for 1 hr. The solution was cooled, acidified, and the precipitate was collected. After two recrystallizations from alcohol, 2.8 g. of white needles was obtained, m.p. 312°. A mixture melting point with V (prepared from II) was undepressed and the infrared spectra were identical. Compound V showed carbonyl stretching vibrations at 1656 cm.$^{-1}$ and 1736 cm.$^{-1}$.

Anal. Calcd. for $C_{14}H_9ClN_2O_2$: C, 61.66; H, 3.33; Cl,

(8) L. G. Donamura and W. A. Heldt, *Org. Reactions*, **11**, 48 (1960).

(9) N,α-Diphenylnitrone by way of an oxaziridine intermediate gives a mixture of benzanilide and diphenylformamide. J. S. Splitter and M. Calvin, *J. Org. Chem.*, **23**, 651 (1958).

(10) The melting points are uncorrected.

13.01; N, 10.27. Found: C, 61.68; H, 3.49; Cl, 13.0; N, 10.14.

2-Carbethoxyamino-5-chlorobenzophenone α-Oxime (III).—A heated solution of 2 g. of II in 30 ml. of ethanol was evaporated *in vacuo* to give an oil which solidified upon trituration with hexane. Recrystallization from a small volume of alcohol afforded 1.1 g. of III, m.p. 128°.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; Cl, 11.14; N, 8.79. Found: C, 60.30; H, 4.78; Cl, 11.1; N, 8.86.

One-half gram of III was heated at its melting point until the liquid solidified. After recrystallization from alcohol, 0.2 g. of V was obtained, m.p. 312°.

Compound III (0.6 g.) ws dissolved in 10 ml. of 1 *N* sodium hydroxide by warming on a steam bath.[4] The solution was acidified with glacial acetic acid and extracted with ethyl acetate. The organic layer was dried, concentrated, and the residue was triturated with hexane to obtain 0.4 g. of white solid, m.p. 126–128°. The melting point was not depressed upon mixing with III.

2-Amino-5-chlorobenzophenone α-Oxime, Ethyl Carbonate Ester (IV).—A solution of 6 g. of I and 3.5 ml. of triethylamine in 100 ml. of ethyl acetate was cooled to 5°. Ethyl chlorocarbonate (2.3 g.) was added in one portion and the mixture was stirred vigorously for 20 min. The mixture was filtered and the filtrate was evaporated *in vacuo*. Upon recrystallization of the residue from alcohol, 3.0 g. of white crystals of IV was obtained, m.p. 149–151°.

Anal. Calcd. for $C_{16}H_{15}ClN_2O_3$: C, 60.29; H, 4.74; Cl, 11.14; N, 8.79. Found: C, 60.39; H, 5.05; Cl, 12.0; N, 8.67.

6-Chloro-4-phenyl-2(1H)-quinazolinone 3-Oxide (VII).—A solution of 5 g. of VI (m.p. 130–133°) and 5.6 ml. of triethylamine in 75 ml. of ether was cooled to 5°. With stirring, 11.2 g. of 18% phosgene in benzene solution was added dropwise, keeping the temperature below 10°. After stirring for an additional 0.5 hr., the mixture was washed with water and concentrated *in vacuo*. Recrystallization of the residue from alcohol gave 2.1 g. of yellow solid, m.p. 270° dec. $\lambda_{max}^{CHCl_3}$ 242, 262(s), 322, 336, 345, 364, 380 mμ ε 19,500, 12,700, 6,000, 6,100, 6,120, 7,200, 6,900.

Anal. Calcd. for $C_{14}H_9ClN_2O_2$: C, 61.66; H, 3.33; Cl, 13.01; N, 10.27. Found: C, 61.69; H, 3.30; Cl, 12.90; N, 10.52.

6-Chloro-4-phenyl-2(1H)-quinazolinone (VIII) from VII.—A mixture of 1.4 g. of VII, 3.5 ml. of phosphorus trichloride and 20 ml. of chloroform was heated under reflux for 1 hr. The solvent was evaporated *in vacuo*. The residue was triturated with saturated sodium bicarbonate solution and recrystallized from ethanol yielding 0.85 g. of yellow VIII, m.p. 310–312°. Upon mixing with an authentic sample (below) of 6-chloro-4-phenyl-2(1H)-quinazolinone the m.p. was undepressed. The infrared spectra were identical.

Compound VIII from 2-Amino-5-chlorobenzophenone.—Two grams of 2-amino-5-chlorobenzophenone and 0.5 g. of urea were heated at 195° until the mixture solidified. The solid was triturated with hexane and recrystallized from alcohol to yield 1.3 g. of VIII, m.p. 312°.

Anal. Calcd. for $C_{14}H_9ClN_2O$: C, 65.50; H, 3.53; Cl, 13.82; N, 10.91. Found: C, 65.54; H, 3.70; Cl, 13.48; N, 11.08.

The Stereochemistry of the Hydrogenation of *cis*- and *trans*-1-Nitro-2-phenylcyclohexane Using W-2 Raney Nickel Catalyst

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Received July 2, 1962

Hydrogenation of *cis*-1-nitro-2-phenylcyclohexane over W-2 Raney nickel occurs with retention of configuration if conditions are used that avoid epimerization of the nitro compound prior to reduction.

Hydrogenation over W-2 Raney nickel catalyst has proved, in our experience, to be one of the most effective methods of reducing a nitro group in a β-nitro acetate to an amino group. To use this reaction as a means of establishing the configuration of certain β-nitro acetates[2] it became necessary to establish its stereochemical course. The reduction of *cis*- and *trans*-1-nitro-2-phenylcyclohexanes was chosen as a model system since both the nitro compounds[3] and the corresponding amines[4] have been well characterized and are closely analogous to the systems in question.[2]

trans-1-Nitro-2-phenylcyclohexane was found to yield *trans*-1-amino-2-phenylcyclohexane on hydrogenation over W-2 Raney nickel catalyst or on reduction using zinc and sulfuric acid in methanol.

The nature of the product formed by hydrogenation of *cis*-1-nitro-2-phenylcyclohexane was found to depend on the conditions used. When the nitro compound was dissolved in warm (60° to 70°) alcohol, W-2 Raney nickel added, and the mixture hydrogenated (the conditions used for the *trans* isomer) a mixture of *cis*- and *trans*-1-amino-2-phenylcyclohexanes resulted. On the other hand, when *cis*-1-nitro-2-phenylcyclohexane was added to cold (0–20°) ethanol, W-2 Raney nickel added, and the mixture hydrogenated, the product was *cis*-1-amino-2-phenylcyclohexane. The thioureide derivative, prepared for purposes of identification, did not possess bands at 9.35, 10.27, and 13.19 μ that are present in the spectrum of the corresponding derivative of the *trans* isomer. The reduction was stereospecific to the extent of at least 86%, judging from the absence of these bands.

Hydrogenation of *cis*-1-nitro-2-phenylcyclohexane over palladium on charcoal in methanol containing a few drops of sulfuric acid also proceeded with retention of configuration, as did

(1) National Science Foundation Cooperative Fellow, 1961–1962.

(2) Paper IV, F. G. Bordwell and E. W. Garbisch, Jr., *J. Org. Chem.*, in press.

(3) H. E. Zimmerman and T. E. Nevins, *J. Am. Chem. Soc.*, **79**, 6559 (1957).

(4) R. T. Arnold and P. N. Richardson, *ibid.*, **76**, 3649 (1954).