Quinazolines and 1,4-Benzodiazepines. XXVIII.[1] Substituted 2(3H)-Quinazolinones and -Quinazolinethiones

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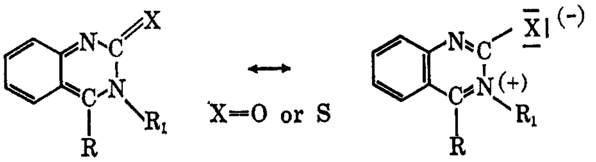
The reaction of 2-amino-5-chlorobenzophenone (I) with methylisocyanate and methylisothiocyanate gave quinoid quinazolone derivatives III. It was shown that these products easily undergo 1,4-additions. Compounds of type II, III, and IV were isolated and their interconversions were studied.

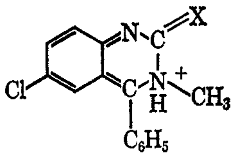
In a series of publications, Gheorghiu and his co-workers[2] described reactions of *o*-aminobenzaldehyde and *o*-aminobenzophenone with isocyanates and isothiocyanates, respectively. These reactions were reported to lead to quinazolone derivatives which on heating or addition of acids or metal halides gave highly colored products. A recent review referred to unpublished work[3] which seemed to confirm the assumption that the colored products are 3-substituted 2-(3H)-quinazolinones.[4]



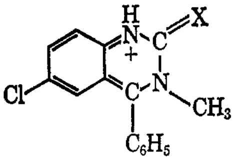
We studied the reaction of 2-amino-5-chlorobenzophenone I with methyl isocyanate and initially obtained a colorless product (IIa) which on heating was slowly converted to bright yellow needles (IIIa). This product was best obtained from IIa by high vacuum sublimation and could be reconverted to compounds of type II by addition of water or methanol.[5] This behavior is explained by assuming a 1,4 addition to the quinoid system of IIIa.

The yellow hydrochloride IVa which was isolated in crystalline form showed an ultraviolet absorption spectrum in tetrahydrofuran with a pattern identical with that found for an acidic solution of IIIa. The same ultraviolet absorptions were found for solutions of IIa and IIb in hydrochloric acid. The equilibrium constant for IIa $\rightleftarrows$ IVa was determined spectrophotometrically as $pK = 1.7 \pm 0.1$.[6]

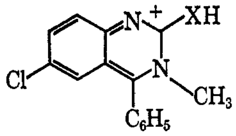
The infrared spectrum of IVa showed bands at 2700 cm^{-1} (ammonium salt $R_3\overset{+}{N}H$) and a strong band at 1760 cm^{-1} (carbonyl). These absorptions are not compatible with structure C. One might expect the protonation of IIIa to yield a salt of structure B rather than A. However, we favor structure A since an absorption around 1900 cm^{-1} indicating the presence of immonium salt ($-C{=}\overset{+}{N}H$, structure B) was not found.



A



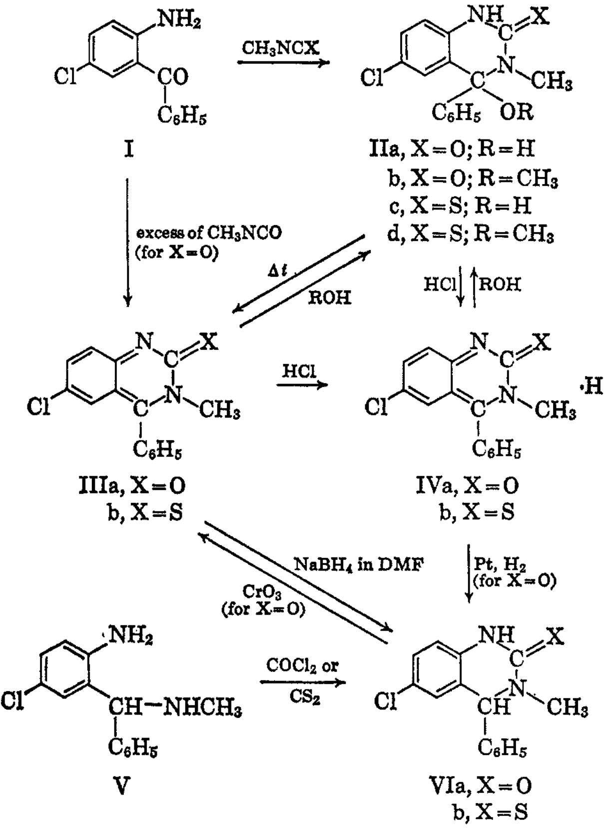
B



C

The equilibria between the quinone IIIa and its salt IVa, respectively, with the adducts IIa and IIb are indicated in Chart I.

CHART I



Proof for the quinoid structure of IIIa was obtained by reduction to the quinazolinone VIa with sodium borohydride. The same product was obtained in good yield by a catalytic hydrogenation of a solution of the hydrate IIa in hydrochloric acid (IIa → IVa → VIa). The ultraviolet spectra of VIa and the adducts

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[1] Paper XXVII: A. Stempel, E. Reeder, and L. H. Sternbach, *J. Org. Chem.*, **30**, 4267 (1965).

[2] (a) C. V. Gheorghiu, *Ber.*, **76**, 994 (1943) and earlier papers. (b) T. A. Williamson, "Heterocyclic Compounds," Vol. 6, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1957, p 371.

[3] W. L. F. Armarego, "Advances in Heterocyclic Chemistry," Vol. 1, A. R. Katritzky, Ed., Academic Press Inc., New York, N. Y., 1963, pp 268, 275.

[4] For the proposal of a quinoid quinazolone structure, see also A. Reissert and H. Schaaf, *Ber.*, **59**, 2494 (1926).

[5] By using an excess of methyl isocyanate in refluxing benzene compound IIIa was obtained directly from I, presumably by dehydration of the intermediate IIa.

[6] This constant describes the equilibrium of the protonated quinoid form with its neutral hydrate and not with the neutral quinoid form.

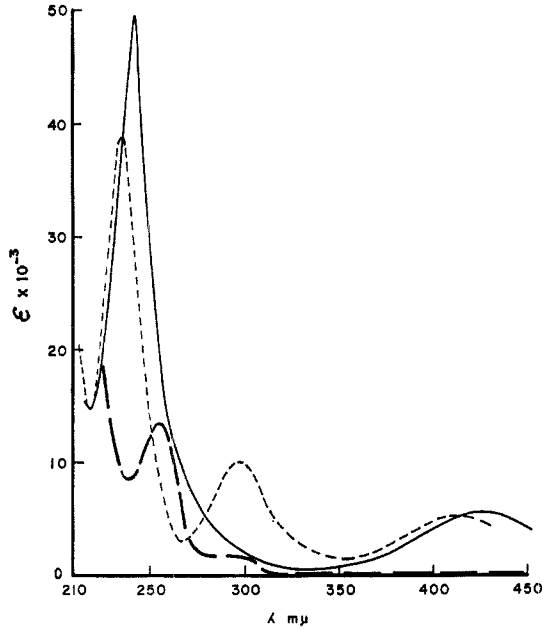

Figure 1.—Ultraviolet spectra of IIIa: ———, in isopropyl alcohol; — —, in 1 N HCl; and — —, in 0.1 N KOH.

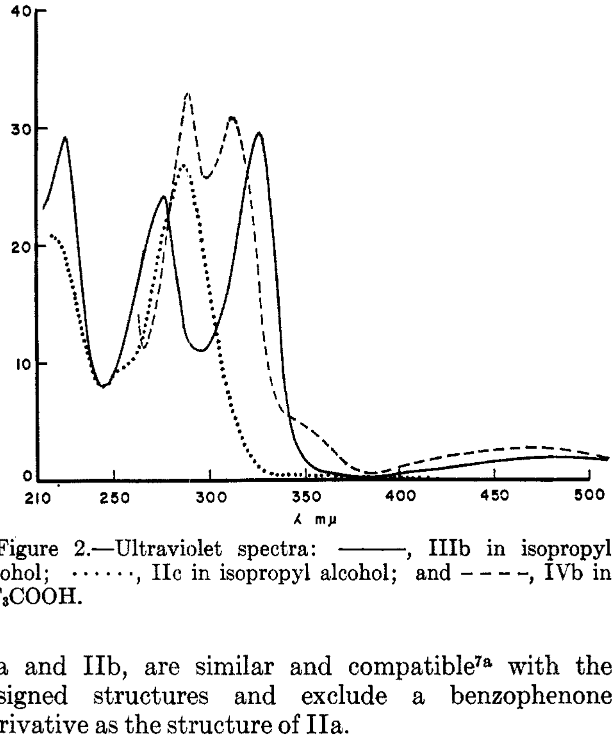

Figure 2.—Ultraviolet spectra: ———, IIIb in isopropyl alcohol; ······, IIc in isopropyl alcohol; and - - - -, IVb in CF_3COOH.

IIa and IIb, are similar and compatible[7a] with the assigned structures and exclude a benzophenone derivative as the structure of IIa.

Compound VIa was also obtained by condensation of the amine V with phosgene in analogy to a known procedure.[7b] Finally, compound VIa was reoxidized with chromium oxide and isolated as IIIa (Figure 1) or in the form of its hydrate IIa depending on the work-up conditions.

Reaction of 2-amino-5-chlorobenzophenone with methylisothiocyanate gave a colorless product to which structure IIc was assigned. It was converted to the oxygen analog IIa by oxidation with hydrogen peroxide. As described for similar substituted quinazoline thiones,[2] compound IIc gave colorless solutions in xylene which turned deep red on heating and became colorless on cooling. However, on prolonged heating and removal of water by azeotropic distillation, a deep red crystalline compound was obtained, to which the quinoid structure IIIb was assigned. Since this compound readily adds water or methanol to give the colorless adducts IIc or IId, the color phenomenon described above can be explained by assuming an equilibrium between compound IIc and the quinoid quinazoline-2-thione IIIb.

As in the oxygen series, salts were formed with acids from IIc as well as directly from IIIb as indicated by the characteristic changes of the ultraviolet absorption (Figure 2). The equilibrium constant governing IIc $\rightleftarrows$ IVb was determined spectrophotometrically as $pK = 0.3 \pm 0.1$.[6] The hydrochloride was isolated in crystalline form from a nonaqueous medium and showed an infrared absorption at 1880 cm^{-1} ($C{=}\overset{+}{N}H$) which permits assignment of structure B as one of its possible resonance forms. Reduction of IIIb with sodium borohydride gave VIb which was also obtained from V in analogy to a known route.[2]

Experimental Section

All melting points are corrected. The infrared spectra were determined using a Beckman IR-9 spectrophotometer. The ultraviolet spectra were determined using a Cary Model 14M spectrophotometer. Compounds were identified by comparison of spectral properties and mixture melting point.

6-Chloro-3,4-dihydro-4-hydroxy-3-methyl-4-phenyl-2(1H)-quinazolinone (IIa). A. From I.—A solution of 15 g (0.065 mole) of 2-amino-5-chlorobenzophenone (I)[8] and 15 ml of methyl isocyanate in 100 ml of methylene chloride was refluxed for 15 hr. The crystalline precipitate was collected on a filter and washed with ether to give 14.3 g (76%) of white needles (IIa) which on heating above 200° were slowly converted to yellow needles which melted at 307–309° (IIIa). The properties of IIa follow: ν_{CO}^{KBr} 1660 cm^{-1}; $\lambda_{max}^{i\text{-}PrOH}$ 255 mμ, ε 13,500, 300 mμ, ε 1500.

Anal. Calcd for $C_{15}H_{13}ClN_2O_2$: C, 62.40; H, 4.45; N, 9.70. Found: C, 62.30; H, 4.78; N, 9.87.

B. From IIIa.—A solution of IIIa in methylene chloride was shaken with water. White needles were obtained which were identified as IIa.

C. From IIc.—A suspension of 1 g of IIc in 7 ml of ethanol was added to a chilled solution of 0.75 g of potassium hydroxide in 8 ml of 30% aqueous hydrogen peroxide. The mixture was stirred for 6 hr at 25° and the solid preciptate was collected on a filter. A yield of 0.7 g (75%) of IIa was obtained.

6-Chloro-3,4-dihydro-4-methoxy-3-methyl-4-phenyl-2(1H)-quinazolinone (IIb).—A suspension of 15 g of IIIa in 150 ml of methanol was refluxed for 20 min. On cooling a white precipitate was collected which, after recrystallization from a mixture of tetrahydrofuran and petroleum ether (bp 40–50°) gave 11.6 g (69%) of white prisms melting at 194–197° (dec) (IIb): $\nu_{CO}^{CHCl_3}$ 1670 cm^{-1}; $\lambda_{max}^{i\text{-}PrOH}$ 253 mμ, ε 16,000, 300 mμ, ε 2000. On heating above the melting point the sample resolidified and melted at 305–307° (IIIa).

Anal. Calcd for $C_{16}H_{15}ClN_2O_2$: C, 63.62; H, 4.99; OCH_3, 10.25. Found: C, 63.92; H, 5.24; OCH_3, 10.77.

6-Chloro-3,4-dihydro-4-hydroxy-3-methyl-4-phenyl-2(1H)-quinazolinethione (IIc). A. From I.—A solution of 92.8 g (0.4 mole) of I[8] and 80 g (1.1 mole) of methyl isothiocyanate in 500 ml of ethanol was refluxed for 16 hr. The solution was concentrated and the residue, on recrystallization from a mixture of methylene chloride and ether, gave 79.3 g (65%) of white prisms melting at 200–202° (dec): $\lambda_{infl}^{i\text{-}PrOH}$ 255 mμ, ε 9500, $\lambda_{max}^{i\text{-}PrOH}$ 287 mμ, ε 27,000.

Anal. Calcd for $C_{15}H_{13}ClN_2OS$: C, 59.11; H, 4.30; N, 9.19. Found: C, 58.80; H, 4.16; N, 9.37.

B. From IIIb.—A suspension of IIIb in water was heated to reflux for 1 hr. Colorless prisms were obtained and identified as IIc.

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(7) (a) For ultraviolet spectrum of *p*-chloro-N-acetylaniline, λ_{max}^{EtOH} 253 mμ, ε 15,900, and shoulder at 278 mμ, ε 1260, see P. Grammaticakis, *Bull. Soc. Chim. France*, 534 (1951). (b) See ref 2, p 347.

(8) F. D. Chattaway, *J. Chem. Soc.*, **85**, 344 (1904).

6-Chloro-3,4-dihydro-4-methoxy-3-methyl-4-phenyl-2(1H)-quinazolinethione (**IId**).—A suspension of 1.5 g of IIIb in 4 ml of of methanol was treated with a catalytic amount of ethereal hydrogen chloride. A white precipitate was collected on a filter, and after recrystallization from a mixture of methylene chloride and methanol, gave 1.0 g (60%) of white prisms melting at 167–170° (dec): $\lambda_{\max}^{i\text{-PrOH}}$ 252 mμ, ε 9000, $\lambda_{\max}$ 288 mμ, ε 31,500.

Anal. Calcd for $C_{16}H_{15}ClN_2OS$: C, 60.27; H, 4.74; OCH_3, 9.73. Found: C, 59.91; H, 4.96; OCH_3, 9.88.

6-Chloro-3-methyl-4-phenyl-2(3H)-quinazolinone (**IIIa**). **A. From I.**—A solution of 20 g (0.086 mole) of 2-amino-5-chlorobenzophenone I[8] and 20 ml of methylisocyanate in 125 ml of benzene was refluxed for 16 hr. The solution was cooled and the yellow precipitate was collected on a filter. Recrystallization from dimethylformamide gave 14.5 g (62%) of yellow needles melting at 307–309°: $\nu_{\text{CO}}^{\text{KBr}}$ 1670 cm^{-1}; $\lambda_{\max}^{i\text{-PrOH}}$ 242 mμ, ε 50,000, 425 mμ, ε 6000.

Anal. Calcd for $C_{15}H_{11}ClN_2O$: C, 66.55; H, 4.10; N, 10.35. Found: C, 66.52; H, 4.09; N, 10.66.

B. From IIa.—Compound IIIa was also obtained as a sublimate on heating of IIa at 250 (0.2° mm).

C. From VIa.—Compound IVa (0.27 g) was oxidized using 0.07 g of chromium trioxide in 7 ml of acetic acid at 100° to give 0.2 g of IIIa.

6-Chloro-3-methyl-4-phenyl-2(3H)-quinazolinethione (**IIIb**).—A stirred solution of 20 g (0.066 mole) of IIc in 300 ml of xylene was refluxed for 60 hr. Water was removed with a Dean–Stark apparatus. On cooling, 13.1 g (70%) of dark red needles melting at 246–248° were obtained: $\lambda_{\max}^{i\text{-PrOH}}$ 225 mμ, ε 29,000, 276 mμ, ε 24,000, 326 mμ, ε 29,700, 485 mμ, ε 2000.

Anal. Calcd for $C_{15}H_{11}ClN_2S$: C, 62.82; H, 3.87; N, 9.77. Found: C, 63.05; H, 3.68; N, 9.77.

Hydrochloride of IIIa.—To a solution of 1 g of IIIa in methylene chloride was added a solution of hydrogen chloride in ether. A yellow powder was obtained which after recrystallization from a mixture of methanol and ether gave yellow prisms melting at 267–269° (dec): $\nu_{R_3\overset{+}{N}H}^{\text{KBr}}$ 2700 cm^{-1}, $\nu_{\text{CO}}^{\text{KBr}}$ 1760 cm^{-1}; $\lambda_{\max}^{\text{THF}}$ 235 mμ, ε 34,000, 296 mμ, ε 8000, 412 mμ, ε 4500; $pK = 1.7 \pm 0.1$[9] (IVa).

Anal. Calcd for $C_{15}H_{11}ClN_2O \cdot HCl$: Cl, 23.08. Found: Cl, 22.75.

Hydrochloride of IIIb.—To a solution of 0.5 g of IIIb in methylene chloride was added an ethereal solution of hydrogen chloride. Red prisms were obtained which after recrystallization from a mixture of methanol and ethereal hydrogen chloride melted at 217–222° (dec): $\nu_{C-\overset{+}{N}H}^{\text{KBr}}$ 2500, 1880 cm^{-1}; $\lambda_{\max}^{CH_3COOH}$ 289 mμ, ε 33,000, 312 mμ, ε 31,000, 470 mμ, ε 2700; $pK = 0.3 \pm 0.1$[9] (IVb).

Anal. Calcd for $C_{15}H_{11}ClN_2S \cdot HCl$: C, 55.73; H, 3.74; Cl, 21.94. Found: C, 55.77; H, 3.89; Cl, 21.74.

2-Amino-5-chloro-N-methylbenzhydrylamine (V).[10]—To a solution of 23.4 g (0.1 mole) of 2-amino-5-chlorobenzhydrol[11] in 250 ml of methylene chloride was added 2 drops of pyridine and 14.5 ml of thionyl chloride. The mixture was refluxed for 30 min and stirred at 25° for 2 hr. The solution was concentrated *in vacuo* and the residue was dissolved in 250 ml of methylene chloride. The solution was cooled and an excess of gaseous methylamine was introduced. The mixture was stirred for 2 hr at 25°, washed with water, dried, concentrated, and the residue was dissolved in ether. This solution was shaken with 2 *N* aqueous hydrochloric acid, and the extract was basified. Extraction with ether gave 9.5 g (38.5%) of an oil (V) which was used for further reactions.

A sample of the oily product was dissolved in methanolic hydrogen chloride, ether was added, and the precipitate was recrystallized from a mixture of methanol, acetonitrile, and ether to give white prisms melting at 150–160°.

Anal. Calcd for $C_{14}H_{15}ClN_2 \cdot 2HCl$: C, 52.60; H, 5.36. Found: C, 52.70; H, 5.50.

6-Chloro-3,4-dihydro-3-methyl-4-phenyl-2(1H)-quinazolinone (**VIa**). **A. From IIIa.**—To a solution of 0.6 of IIIa in 10 ml of dimethylformamide was added 0.1 g of sodum borohydride. The solution was kept at room temperature for 30 min and poured onto ice. Extraction with ether gave white needles which, after recrystallization from a mixture of methylene chloride and petroleum ether, melted at 224–226°: $\nu_{\text{CO}}^{CHCl_3}$ 1670 cm^{-1}; $\lambda_{\max}$ 260 mμ, ε 11,000, 300 mμ, ε 2000.

Anal. Calcd for $C_{15}H_{13}ClN_2O$: C, 66.06; H, 4.80; N, 10.27. Found: C, 66.10; H, 4.62; N, 10.56.

B. From IIa.—A suspension of 21.7 g (0.075 mole) of IIa and 1 g of platinum oxide in 375 ml of 27% hydrochloric acid was shaken in an atmosphere of hydrogen. The hydrogen uptake stopped after 4 hr when 2500 cc had been consumed. A white solid which had precipitated during the hydrogenation was filtered from the solution and separated from the platinum with methylene chloride. This material after recrystallization from a mixture of methylene chloride and petroleum ether gave 15 g (73% of theory) of white needles melting at 224–226° (VIa).

C. From V.—A solution of 1.2 g of V and 0.8 ml of pyridine in 25 ml of a 12.5% solution of phosgene in benzene was kept at 25° for 3 hr. Methanol (*ca.* 100 ml) was added, the mixture was stirred for 16 hr, and the solvents removed *in vacuo*. The residue was partitioned between methylene chloride and an aqueous sodium bicarbonate solution. From the methylene chloride solution 0.8 g (60%) of VIa was obtained.

6-Chloro-3,4-dihydro-3-methyl-4-phenyl-2(1H)-quinazolinethione (**VIb**). **A. From IIIb.**—To a solution of 0.3 g of IIIb in 10 ml of dimethylformamide was added 0.15 g of sodium borohydride. The solution was poured into ice–water and the crystalline precipitate was collected on a filter. Recrystallization from a mixture of methylene chloride and methanol gave white prisms melting at 245–247°: $\lambda_{\max}^{i\text{-PrOH}}$ 290 mμ, ε 23,000.

Anal. Calcd for $C_{15}H_{13}ClN_2S$: C, 62.38; H, 4.54. Found: C, 62.45; H, 4.53.

B. From V.—A solution of 15 g of V and 6 g of potassium hydroxide in 50 ml of ethanol and 50 ml of carbon disulfide was heated to reflux for 16 hr. The solution was concentrated; the residue was brought to pH 5 and extracted with methylene chloride. The methylene chloride solution was concentrated and the residue, on recrystallization from a mixture of methylene chloride and methanol, gave 4 g (23%) of VIb melting at 245–247°.

Acknowledgment.—We are indebted to Mr. S. Traiman for infrared spectroscopy and Dr. Al Steyermark and his staff for microanalyses. We wish to thank Professor G. Büchi and Professor W. G. Dauben for valuable discussions.

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[9] Determined spectrophotometrically as described by A. Albert and E. P. Serjeant in "Ionization Constants of Acids and Bases," Methuen and Co. Ltd., London, 1962, p 72.

[10] Prepared by the method described by R. I. Fryer, G. A. Archer, B. Brust, W. Zally, and L. H. Sternbach, *J. Org. Chem.*, **30**, 1308 (1965).

[11] G. N. Walker, *ibid.*, **27**, 1929 (1962).