Intramolecular Rearrangements. V.[1] Formation and New Acyl Rearrangement of Isoindolo[2,1-*a*]quinazoline-5,11-dione to Isoindolo[1,2-*b*]quinazoline-10,12-dione

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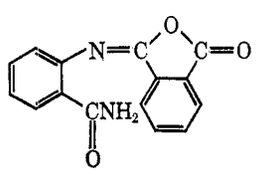
2′-Carbamoylphthalanilic acid (I) was prepared by the reaction of anthranilamide with phthalic anhydride; the treatment of I in acetic anhydride–pyridine has been shown to yield isoindolo[2,1-*a*]quinazoline-5,11-dione (III) and *o*-phthalimidobenzamide (II). The thermal treatment of III afforded isoindolo[1,2-*b*]quinazoline-10,12-dione (IV) by an intramolecular acyl rearrangement. New synthetic methods and the mechanism for the formation of IV were investigated.

The preparation of isoindolo[2,1-*a*]quinazoline-5,11-dione (III) by the reaction of anthranilamide with phthalic anhydride has been reported by Crippa and Caracci[2] in connection with the phthaloylation of amines. Recently, Gaudemaris, *et al.*,[3] reported the formation of III in connection with the synthesis of poly(isoindoloquinazolinediones). In the course of a study on ladder polymers,[4] the model reaction of anthranilamide with phthalic anhydride was reinvestigated. The spectral properties of the products and melting points appeared inconsistent for the reported structure III.[2,3] I wish to report that the correct structure of one of the products is that of isoindolo[1,2-*b*]quinazoline-10,12-dione (IV). We have prepared isoindolo[2,1-*a*]quinazoline-5,11-dione (III) by treatment of 2′-carbamoylphthalanilic acid (I) in acetic anhydride–pyridine, and studied its rearrangement to IV. Structures III and IV were assigned on the basis of nmr, infrared, ultraviolet, and elemental analyses. A similar study on 1,2,4-benzothiazine has been reported recently by Bell, *et al.*,[5] and Kratzl, *et al.*[6]

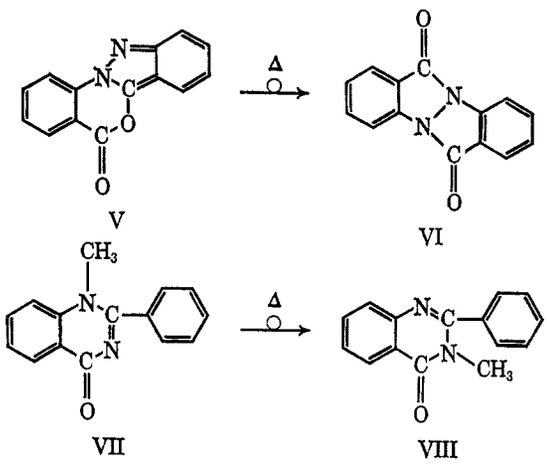
The reaction of anthranilamide with phthalic anhydride in N-methylpyrrolidone affords I as an initial condensation product (Scheme I). Compound I is subject to cyclization and yields IV when heated at 188°. Compounds II and III were isolated on treating I in acetic anhydride–pyridine under milder conditions. Cyclization of II to give IV was accomplished by heating at 260° or refluxing in acetic anhydride–pyridine. When heated at 260°, III rearranges to IV. The alternative isoimide formulation II′ for the imide II seems inconsistent with the infrared



II′

spectrum of the compound, which shows carbonyl absorption at 1780, 1720, and 721 cm^{-1} (normal imide). The spectrum of II′ would be expected to have two strong infrared absorptions at 1800 and 1710 cm^{-1}, attributed to stretching frequencies of the strained >C=O and >C=N– structure, respectively, and have no absorption at 721 cm^{-1}.[7]

The formation of compound IV from II was shown by ultraviolet and nmr methods to proceed in the sequence II → III → IV. This type of rearrangement is notable because bisanthranil, 5H-indazolo[2,3-*a*]-[3,1]benzoxazin-5-one (V), similarly rearranges to VI on heating,[8] and 1-methyl-2-phenyl-4(1H)-quinazolinone (VII) is converted on heating into 3-methyl-2-phenyl-4(3H)-quinazolinone (VIII).[1] Anthranilamide, upon strong heating with phthalic anhydride without solvent, affords IV, whereas Crippa[2] and Gaudemaris[3] reported the product as II but provided no spectral data to support their conclusions. These authors also reported that a product, mp 242°, prepared by thermal cyclization of II at 250° or refluxing II in acetic anhydride–pyridine was III. In a previous paper,[1] we have shown that, in the 4-quinazolinone system, the most thermally stable structure is that with a >C=N– bond fixed at a β,γ position to the carbonyl group.



V VI

VII VIII

Compound III had carbonyl absorption peaks at 1760 (five-membered carbonyl) and 1680 cm^{-1} (six-membered carbonyl), and a >C=N– absorption peak at 1620 cm^{-1}, whereas IV had carbonyl peaks at 1780 (five-membered carbonyl) and 1700 cm^{-1} (six-membered carbonyl), and >C=N– absorption peak

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(2) G. B. Crippa and R. Caracci, *Gazz. Chim. Ital.*, **68**, 109 (1938).

(3) G. Rabilloud, B. Sillion, and G. de Gaudemaris, *Makromol. Chem.*, **108**, 18 (1967).

(4) M. Kurihara and Y. Yoda, *J. Polym. Sci., Part B*, **6**, 875 (1968).

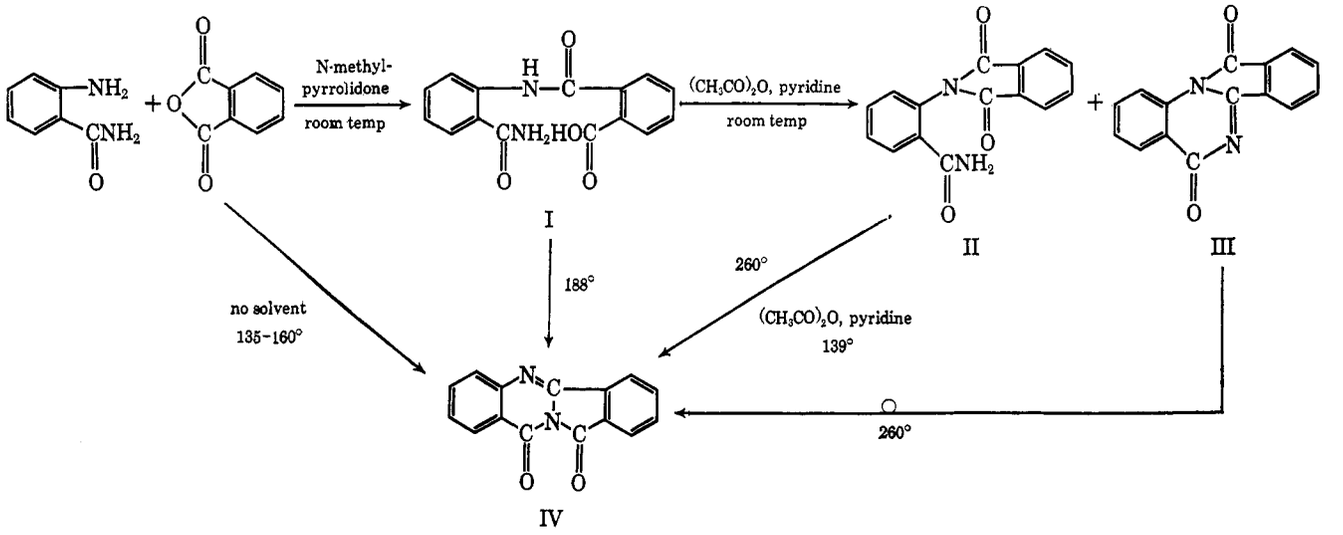
(5) (a) C. S. Bell, P. H. L. Wei, and S. T. Childress, *J. Org. Chem.*, **29**, 3206 (1964); (b) S. C. Bell, and G. Conklin, *J. Heterocycl. Chem.*, **5**, 183 (1968).

(6) K. Kratzl and H. Ruis, *Monatsh. Chem.*, **96**, 1596 (1965); *ibid.*, **96**, 1586 (1965).

(7) (a) R. A. Dine-Hart and W. W. Wright, *J. Polym. Sci., Part A-1*, **11**, 609 (1967); (b) A. L. Laszlo, U. S. Patent 3,179,633 (1965); (c) R. J. Angelo, U. S. Patent 3,282,898 (1966).

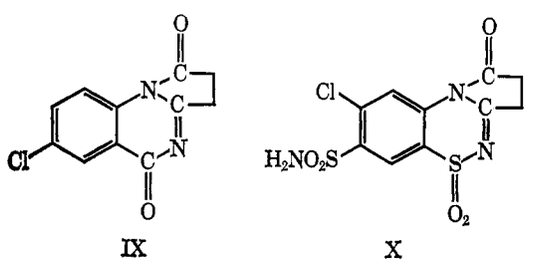
(8) (a) G. Heller, *Chem. Ber.*, **49**, 523 (1916); (b) W. L. Mosby, *Chem. Ind.* (London), 17 (1967); (c) G. K. J. Gibson and A. S. Lindsey, *J. Chem. Soc., C*, 1792 (1967).

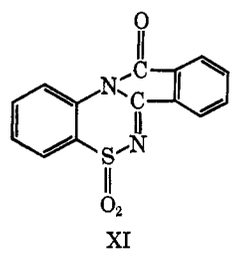
SCHEME I



at 1640 cm^{-1}, the shift to a higher wave number being attributed to the CONCO grouping. This result is in good agreement with the previous data.[1] Carbonyl groups with an α,β-conjugated –N=C< double bond absorb at lower wave numbers than those with a β,γ-unsaturated carbonyl group. These results are also observed in the absorption band of a >C=N– double bond in the 4-quinazolinone system. The difference in absorption bands dissociated with the six-membered carbonyl group and >C=N– double bond of III and IV is 20 cm^{-1}. From these infrared measurements, it is concluded that compounds III and IV are isoindolo[2,1-*a*]quinazoline-5,11-dione (III) and isoindolo[1,2-*b*]quinazoline-10,12-dione (IV), respectively. This conclusion is also supported by the comparison of uv spectra. Compound III has λ_{max} at 255 mμ (ϵ 19,400), 310 (4340), whereas IV has λ_{max} at 275 mμ (ϵ 10,170). We have reported[1] that the spectrum of β,γ-unsaturated 4(3H)-quinazolinone derivatives had a distinct absorption at 277–280 mμ, whereas that of α,β-conjugated 4(1H)-quinazolinone at about 255 and 310 mμ.

Furthermore, a comparison of the nmr spectra of III and IV revealed a considerable difference in the aromatic region. In IV, the aromatic proton adjacent to the 5-nitrogen had a normal value of δ 7.65, whereas in III the corresponding *ortho* proton was shifted downfield to δ 8.77. Analogous 7-chloro-2,3-dihydropyrrolo[1,2-*a*]quinazoline-1,5-dione (IX),[5b] pyrrolo[2,1-*c*][1,2,4]benzothiadiazine (X),[5b] and 11-oxo-11H-isoindolo[1,2-*c*][1,2,4]benzothiadiazine 5,5-dioxide (XI)[6] also had a large downfield shift (δ 8.90, 8.95) for the corresponding *ortho* proton.





This downfield shift of an *ortho* proton due to the orientation of a carbonyl group toward the benzene ring has recently been reported.[5] Thus the large downfield shift in III, produced by the deshielding from the adjacent carbonyl group, verified that III is isoindolo[2,1-*a*]quinazoline-5,11-dione.

Experimental Section[9]

2′-Carbamoylphthalanilic Acid (I). Method A.—A mixture of 1.36 g (0.01 mol) of anthranilamide and 1.48 g (0.01 mol) of phthalic anhydride was added to 20 ml of N-methylpyrrolidone at 10° and stirred for 5 hr at 10°. After disappearance of the carbonyl absorption of phthalic anhydride at 1880 cm^{-1}, 1780 cm^{-1} in the infrared spectrum of the solution, N-methylpyrrolidone was removed under reduced pressure (10^{-1} mm) at 70° to yield white crystals melting at 140°. The yield was 3.8 g (theoretical amount was 2.84 g). This compound was presumed to be a 2′-carbamoylphthalanilic acid–N-methylpyrrolidone complex. Recrystallization from ethanol yielded I as white crystals: mp 186 (lit.[3] mp 212°); ir 1705, 1690, 1665 cm^{-1} (C=O); uv_{max} 253 mμ (ϵ 13,760), 303 (5480).

Anal. Calcd for $C_{15}H_{21}O_4N_2$: C, 63.38; H, 4.26; N, 9.86. Found: C, 63.13; H, 4.42; N, 9.80.

Method B.—Products prepared in a mixed solvent system of chloroform, benzene, and methanol were identical with those obtained by method A in 90% yield with mp 186°.

o-Phthalimidobenzamide (II).—A 200-mg portion of 2′-carbamoylphthalanilic acid (I) was dissolved in a mixture (1:1) of 80 ml of acetic anhydride and pyridine and the solution was kept for 12 hr at room temperature. The solvent was removed under reduced pressure (10^{-4} mm at 25°) and the residue was washed with ether. The yield was 140 mg (75.2%), mp 237°. One recrystallization from ethanol then raised the melting point to 239° (lit. mp 225,[2] 239[3]): ir 1780, 1700, 1650 cm^{-1} (C=O); uv_{max} 218 mμ (ϵ 35,700), 282 (5190).

Anal. Calcd for $C_{15}H_{10}O_3N_2$: C, 67.66; H, 3.79; N, 10.52. Found: C, 67.44; H, 3.56; N, 10.80.

(9) All melting points were taken on a Büchi melting point apparatus and were uncorrected. The microanalyses were carried out by the Microanalytical Section of these laboratories. The infrared spectra were recorded with a Hitachi Model EPI-S recording spectrophotometer, using a potassium bromide disk. The ultraviolet spectra were recorded with a Cary Model 14 recording spectrophotometer in 99.5% ethanol. The nmr spectra were obtained on a Varian A-60 spectrometer using 15% dimethyl sulfoxide-d_6 solutions; chemical shifts are given in parts per million downfield from tetramethylsilane.

Isoindolo[2,1-*a*]quinazoline-5,11-dione (III).—To a mixture (1:1) of 40 ml of acetic anhydride and pyridine was added 2.0 g of 2′-carbamoylphthalanilic acid (I). The solution was stirred slowly for 23 hr at room temperature, during which time yellow solids separated out. The crystals were collected: yield 0.25 g (14.3%); mp 246°. Recrystallization from ethanol gave III: mp 247°; ir (KBr) 1760, 1680 (C=O), 1620 cm^{-1} (C=N); uv_{max} 230 mμ (ε 26,500), 245 (18,690), 255 (19,400), 265 (15,500), 283 (9060), 310 (4,340); nmr δ 8.78 (d) 8.20 (m), 7.64.

Anal. Calcd for $C_{15}H_8O_2N_2$: C, 72.57; H, 3.25; N, 11.27. Found: C, 72.37; H, 3.12; N, 11.39.

From the filtrate, on addition of ethyl ether, there was obtained 1.40 g (74.8%) of *o*-phthalimidobenzamide (II), mp 220°. Recrystallization from ethanol yielded pure II, mp 239°.

Isoindolo[1,2-*b*]quinazoline-10,12-dione (IV). Method A. Cyclization of 2′-Carbamoylphthalanilic Acid (I).—A 2.84-g portion of 2′-carbamoylphthalanilic acid (I) was heated at 188° for 20 min to obtain white crystals. Sublimation at 260° yielded white crystals melting at 233°. The yield was 2.50 g (99%): ir (KBr) 1780, 1700 (C=O), 1640 cm^{-1} (C=N); uv_{max} 275 mμ (ε 10,170), 303 (7690), 315 (5750); nmr δ 8.16 (d) 7.20, 8.00 (m).

Anal. Calcd for $C_{15}H_8O_2N_2$: C, 72.57; H, 3.25; N, 11.27. Found: C, 72.58, H, 3.29; N, 11.45.

Method B. Cyclization of *o*-phthalimidobenzamide (II). a.—By the treatment of *o*-phthalimidobenzamide (II) at 260° for 1 hr, isoindolo[1,2-*b*]quinazoline-10,12-dione (IV) was obtained quantitatively, mp 233°. The structure was confirmed by the comparison of its infrared spectrum with those of an authentic sample of IV prepared directly from 2′-carbamoylphthalanilic acid by the thermal cyclization.

b.—To a mixture (1:1) of 10 ml of acetic anhydride and pyridine was added for 200 mg of *o*-phthalimidobenzamide (II). The solution was refluxed for 2 hr. By removal of the solvent under vacuum, there was obtained 180 mg of IV, mp 225°, recrystallization from ethanol yielded III as pure yellow crystals, mp 233°.

Method C. Intramolecular Acyl Rearrangement of Isoindolo[2,1-a]quinazoline-5,11-dione (III) to Isoindolo[1,2-b]quinazoline-10,12-dione (IV) by Heating.—Isoindolo[2,1-*a*]quinazoline-5,11-dione (III, 200 mg) was heated in a test tube at 260° for 30 min and cooled, affording 188 g of a precipitate, mp 225°. One sublimation raised the melting point to 232°. The infrared, ultraviolet, and nmr spectra are in good agreement with those of an authentic sample.

Anal. Calcd for $C_{15}H_8O_2N_2$: C, 72.57; H, 3.25; N, 11.27. Found: C, 72.38; H, 3.19; N, 11.25.

Method D. Reaction of Anthranilamide with Phthalic Anhydride without Solvent.[3]—A mixture of 2.72 g (0.02 mol) of anthranilamide and 2.96 g (0.02 mol) of phthalic anhydride was heated at 135–160° for 2.5 hr by the method of Crippa and Caracci,[2] cooled, and 4.5 g of the product (90.8% yield, mp 225°) was obtained. Recrystallization from ethanol gave pure IV, mp 234°. A previous paper[2] reported that this product was II. The infrared, ultraviolet, and nmr data are identical with those of pure IV.

Registry No.—I, 18257-54-0; II, 18257-55-1; III, 18257-78-8; IV, 19910-55-5.

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Equilibration Studies. 2-Methylthiopyridine–N-Methyl-2-thiopyridone

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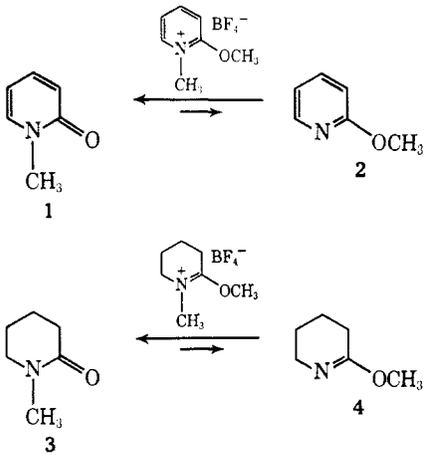
Equilibration of N-methyl-2-thiopyridone (**7**) with 2-methylthiopyridine (**9**) through the catalytic action of N-methyl-2-methylthiopyridinium fluoroborate at 145–188° indicates that **9** is favored in the liquid phase by an enthalpy of 2.6 ± 1.3 kcal/mol. Conversion of this enthalpy difference to the gas phase with correction for differences in kinetic and zero-point energies gives a difference in chemical binding energy between **7** and **9** of 7.6 ± 4.3 kcal/mole in favor of **9**. This order of stabilities is contrasted with those observed for the analogous protomeric and oxygen-substituted systems.

Relative chemical binding energies have been obtained for amide–imidate isomer pairs by measurements of liquid-phase enthalpies, extrapolations to the gas phase, and estimates of differences in kinetic and zero-point energies.[1] For the pairs N-methyl-2-pyridone (**1**)–2-methoxypyridine (**2**) and N-methyl-2-piperidone (**3**)–O-methylvalerolactim (**4**) the amides are the more stable isomers in chemical binding energies by 8.0 ± 3.5 and 14.1 ± 3.5 kcal/mol, respectively. Extension of the equilibration procedure and estimates of differences in binding energies to the corresponding thioamides–thioimidates is of interest for determination of the relative stabilities of these isomeric functionalities, comparison of the chemical-binding abilities of sulfur and oxygen, and insight into the relative stabilization energies of pyridine–pyridone isomer pairs.



Few thioamide–thioimidate equilibrations have been reported. However, at least one system which has a formal resemblance to a simple thioamide–thioimidate pair has been equilibrated; 2-thiobenzothiazoles (**5**) may be transformed to the isomeric 2,3-dihydro-3-thiobenzothiazoles (**6**) under equilibrating conditions.[2]

(1) P. Beak, J. Bonham, and J. T. Lee, Jr., *J. Am. Chem. Soc.*, **90**, 1569 (1968).

(2) D. J. Fry and J. D. Kendall, *J. Chem. Soc.*, 1716 (1951); J. J. D'Amico, S. T. Webster, R. H. Campbell, and C. E. Twine, *J. Org. Chem.*, **30**, 3628 (1965).