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The Synthesis and Cleavage of Imidazo[2,3-a]phthalazine, a New Heterocyclic Ring System.

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Attempts to prepare 1-(2-mercaptoethylamino)-phthalazines from IVa or IVb gave instead the 2,3-dihydroimidazo[2,3-a]phthalazines (IIIa-b), a new heterocyclic ring system.

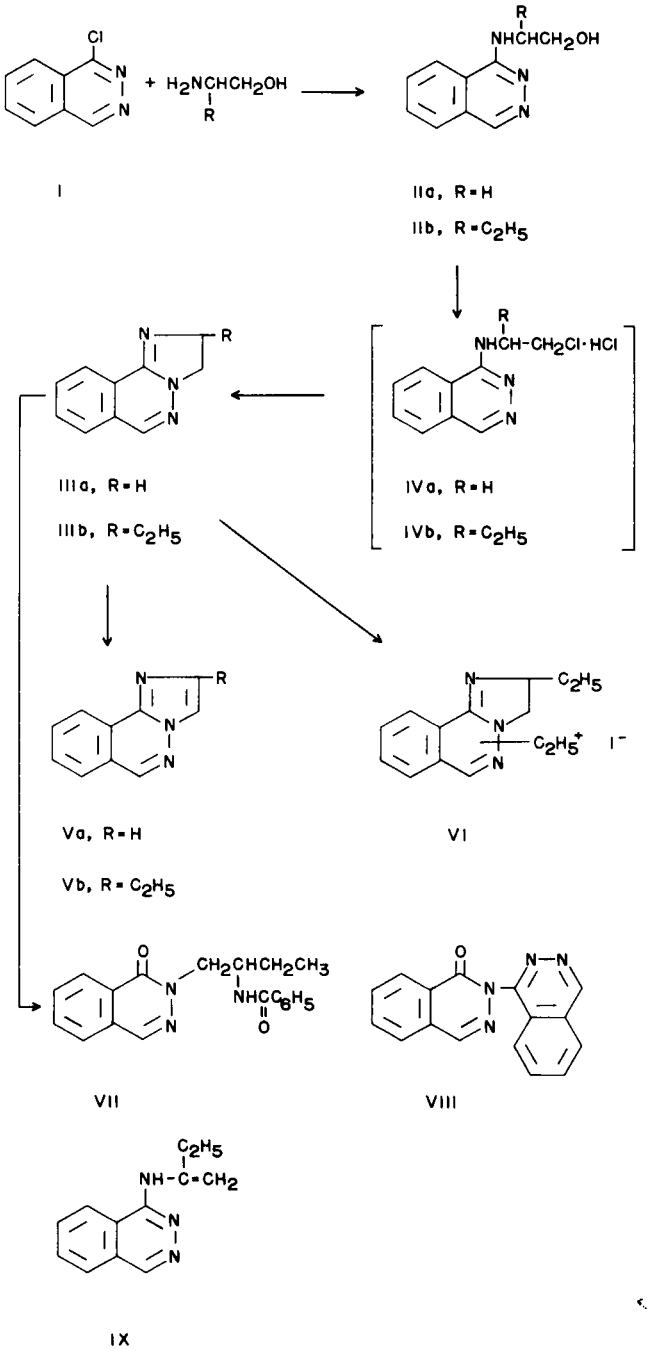
4-Chlorophthalazine (I) (3) was allowed to react with 2-aminoethanol or 2-amino-1-butanol. The products were 1-(2-hydroxyethylamino)phthalazine (IIa) and 1-(1-hydroxy-2-butylamino)phthalazine (IIb), respectively. During the preparation of IIb, a byproduct was obtained which has been assigned structure VIII [2-(1-phthalazyl)-1(2*H*)-phthalazinone] on the basis of elemental analyses and the spectroscopic data detailed in the experimental part (4). When either IIa or IIb was allowed to react with thionyl chloride, IVa or IVb was obtained. These compounds could be isolated but were not characterized. They were allowed to react immediately with potassium hydrosulfide and the products were 2,3-dihydroimidazo[2,3-a]phthalazine (IIIa) and 2-ethyl-2,3-dihydroimidazo[2,3-a]phthalazine (IIIb), respectively. Compounds IVa and IVb were also readily converted into IIIa and IIIb by allowing either IVa or IVb to react with potassium carbonate solution. Compound IIIb was readily converted into the ethiodide (VI).

In order to eliminate IX as a possible structure for 2-ethyl-2,3-dihydroimidazo[2,3-a]phthalazine (IIIb), compound IIIb was allowed to heat under reflux with 85% sulfuric acid for 30 hours. The starting material was recovered unchanged, therefore structure IX was eliminated.

The fully aromatic imidazo[2,3-a]phthalazine (Va) and the 2-ethylimidazo[2,3-a]phthalazine (Vb) have been prepared from IIIa and IIIb, respectively by allowing IIIa or IIIb to react with palladium on charcoal in boiling *p*-cymene for 40 hours. The products were characterized by their ultraviolet spectra.

In order to establish the constitution of IIIa and IIIb, 2-ethyl-2,3-dihydroimidazo[2,3-a]phthalazine (IIIb) was subjected to the benzimidazole ring-opening method of Gerngross (5). Compound IIIb was converted into 2-(2-benzoylamino-1-butyl)-1(2*H*)-phthalazinone (VII). This compound was insoluble in 10% hydrochloric acid and had the ultraviolet spectral characteristics expected of a 2-substituted-1(2*H*)-phthalazinone. The spectrum of VII is compared with 1(2*H*)-phthalazinone in the experimental section.

All of the compounds had ultraviolet spectra consistent with the structures proposed.



EXPERIMENTAL (6)

1-Chlorophthalazine (I).

This compound was prepared from 1(2*H*)-phthalazinone (Eastman No. 7264) and phosphorus oxychloride, yield 99%, m.p. 121-123° (3).

1-(2-Hydroxyethylamino)phthalazine (IIa).

A mixture of 30.6 g. (0.186 mole) of 1-chlorophthalazine and 68 g. (1.12 moles) of 2-aminoethanol was heated at 95° for 40 hours. About 35 g. of 2-aminoethanol was removed by distillation under reduced pressure and the residue was allowed to stand for three days in the refrigerator. The crystalline solid that separated was filtered and recrystallized repeatedly from ethyl acetate. The 1-(2-hydroxyethylamino)phthalazine separated as colorless micro needles, yield 11.5 g. (44%), m.p. 133-136°.

U. V. λ max (95% ethanol), 208 (ε, 49,700); 220-234 sh (ε, 15,300-8,250); 256 (ε, 5,900); 313 mμ (ε, 9,000). U. V. λ max (10% HCl), 213.5 (ε, 32,300); 243 (ε, 15,400); 261 (ε, 14,900); 303.5 (ε, 7,250); 316 mμ (ε, 6,200).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.47; H, 5.86. Found: C, 63.48; H, 5.84.

1-(1-Hydroxy-2-butylamino)phthalazine (IIb).

A mixture of 36.1 g. (0.219 mole) of 1-chlorophthalazine and 57.7 g. (0.65 mole) of 2-amino-1-butanol was heated at 85° for 40 hours. To the reaction mixture was added 100 ml. of chloroform and 850 ml. of water and the entire heterogeneous mixture boiled a few minutes. The aqueous layer was separated. The chloroform layer was again heated with an additional 850 ml. of water and the aqueous layer separated. The combined aqueous extracts were reduced in volume to about 500 ml. by evaporation on a hot plate. After the aqueous extract was allowed to cool, colorless micro needles separated which were filtered, washed with a little water and recrystallized from ethanol, yield 27 g. (67%), m.p. 186-187°.

U. V. λ max (95% ethanol), 210 (ε, 47,600); 220 sh (ε, 11,300); 257 (ε, 6,000); 316 mμ (ε, 9,000). U. V. λ max (10% HCl), 213 (ε, 32,100); 244 (ε, 14,500); 262 (ε, 14,500); 304.5 (ε, 7,000); 317 mμ (ε, 6,000).

Anal. Calcd. for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96. Found: C, 66.24; H, 6.86.

2-(1-Phthalazyl)-1(2*H*)-phthalazinone (VIII).

This compound was obtained as an ethanol-insoluble byproduct during recrystallization of IIb above, m.p. 279-281°, yield 2.7 g. The infrared spectrum showed a strong carbonyl absorption at 1700 cm^{-1} assignable to an amide substituted with an aromatic group on the nitrogen atom (7). The NMR spectrum obtained in DMF-d_7 (TMS as external reference) showed a singlet at δ = 8.71 assignable to the proton on the 4-position of the phthalazinone ring, a singlet at δ = 9.89 assignable to the proton in the 4-position of the phthalazine ring and a complex benzenoid multiplet at δ = 7.5-8.4.

U. V. λ max (95% ethanol), 208 (ε, 41,800); 243 mμ (ε, 61,000).

Anal. Calcd. for $C_{16}H_{10}N_4O$: C, 70.06; H, 3.67; N, 20.42. Found: C, 69.86; H, 3.68; N, 20.29.

2-Ethyl-2,3-dihydroimidazo[2,3-a]phthalazine (IIIb).
Method A.

Finely powdered 1-(1-hydroxy-2-butylamino)phthalazine (IIb) (8.6 g., 0.0394 mole) was added in small portions to 20 ml. of thionyl chloride with stirring and cooling (ice bath). The reaction mixture was allowed to stir at room temperature for 24 hours. To the mixture was added 20 ml. of chloroform and the entire mixture evaporated to dryness under reduced pressure at 40°. The intermediate hydrochloride (IVb) was not further purified but allowed to react as described below.

To a solution of potassium hydrosulfide (prepared from 12 g. of potassium hydroxide in 12 ml. of water and 108 ml. of ethanol into which an excess of hydrogen sulfide was bubbled with ice bath cooling) was added the above crude hydrochloride (IVb) in 100 ml. of ethanol while the mixture was stirred and cooled. The reaction mixture was allowed to stir at room temperature for 48 hours, then it was heated at 50-80° for 6 hours. The ethanol was removed under a stream of nitrogen and the residue was dissolved in 50 ml. of water and filtered. The pale brown filtrate was extracted three times with 100 ml. portions of benzene. The benzene extract was washed with saturated sodium chloride solution and dried (magnesium sulfate). Removal of the magnesium sulfate and the solvent left a yellow solid which was recrystallized from ether-petroleum ether to give 4.3 g. (55%) of yellow plates, m.p. 76-78°.

U. V. λ max (95% ethanol), 211 (ε, 48,000); 268 (ε, 13,000); 276 (ε, 18,100); 336 mμ (ε, 9,000). U. V. λ max (10% HCl), 216 (ε, 42,500); 237.5 (ε, 15,100); 272 (ε, 10,000); 296 mμ (ε, 8,000).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.55; H, 6.38; N, 21.18.

Method B.

Compound IIb (7.1 g., 0.0328 mole) was allowed to react as described in method A and 11.3 g. of the crude hydrochloride salt of IVb was obtained. The hydrochloride (IVb) (11.3 g.) was dissolved in 200 ml. of absolute ethanol and this solution was mixed with a solution containing 9.0 g. of potassium carbonate in 80 ml. of water. The mixture was shaken for 2 hours at room temperature then allowed to heat at reflux for 3 hours. After removal of the ethanol, the mixture was extracted with benzene, washed with saturated sodium chloride solution and dried over potassium carbonate. After removal of the potassium carbonate and evaporation of the solvent, 5.8 g. of yellow solid was obtained which was recrystallized from ether-petroleum ether. Yellow plates, m.p. 76-78° identical in all respects to that prepared by method A were obtained.

1,2-Dihydroimidazo[2,3-a]phthalazine (IIIa).
Method A.

Finely powdered 1-(2-hydroxyethylamino)phthalazine (IIa) (9.9 g., 0.05 mole) was added portionwise to 50 ml. of cold thionyl chloride with stirring. The reaction mixture was allowed to stir for an additional 2 hours and then allowed to stand overnight at room temperature. Fifty ml. of chloroform was added to the mixture and it was then evaporated to dryness at 40° under reduced pressure. The white mass (IVa) was dissolved in 250 ml. of absolute ethanol. This solution was poured into a solution containing 14 g. of potassium carbonate in 160 ml. of water. The mixture was shaken at room temperature for 2 hours and then heated to reflux for 3 hours. After removal of the ethanol, the mixture was extracted with benzene, washed with saturated sodium chloride solution and the benzene solution dried over potassium carbonate. Filtration of the potassium carbonate and evaporation of the solvent gave 5.0 g. of yellow solid which was purified by chromatography on alumina. Elution with benzene and subsequent recrystallization of the product from cyclohexane gave 4.7 g. (55%) of yellow needles, m.p. 103-104°.

U. V. λ max (95% ethanol), 209 (ε, 44,750); 266 (ε, 10,300); 274 (ε, 15,500); 335 mμ (ε, 6,500). U. V. λ max (10% HCl), 215 (ε, 40,400); 237 (ε, 14,250); 272 (ε, 8,900); 298 mμ (ε, 7,350).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.16; H, 5.30; N, 24.54. Found: C, 70.56; H, 4.98; N, 24.67.

Method B.

Compound IIIa was also prepared by the sodium hydrosulfide method described as method A under the preparation of IIIb.

1,2-Dihydroimidazo[2,3-a]phthalazine Dihydrochloride.

Compound IIa (9.9 g., 0.05 mole) was allowed to react with thionyl chloride (50 ml.) as described above under method A. After removal of the excess thionyl chloride, the resulting hydrochloride was recrystallized from ethanol to give colorless prisms, m.p. 335-336° dec. The ultraviolet spectrum of this compound in distilled water was identical with that of IIIa in 10% hydrochloric acid solution.

Anal. Calcd. for $C_{10}H_{11}Cl_2N_3$: C, 49.20; H, 4.54. Found: C, 49.34; H, 4.24.

The Reaction of 2-Ethyl-1,2-dihydroimidazo[2,3-a]phthalazine with 85% Sulfuric Acid.

A mixture containing 1.99 g. of 2-ethyl-1,2-dihydroimidazo[2,3-a]-phthalazine and 20 ml. of 85% sulfuric acid was allowed to heat under reflux for 30 hours. During the reflux period the reaction mixture darkened. After the mixture was allowed to cool, it was poured into 40 ml. of water, treated with charcoal and filtered. The colorless filtrate was made alkaline with 10% sodium hydroxide solution and extracted with chloroform. The chloroform extract was washed with saturated sodium chloride solution and dried over potassium carbonate. Removal of the potassium carbonate and chloroform gave a pale yellow solid, m.p. 71° which after recrystallization from a petroleum ether-ether mixture gave yellow plates, m.p. 73° (1.5 g.) which was identical with the starting material. The results of this experiment preclude structure IX as a possible formula for IIIb.

Imidazo[2,3-a]phthalazine (Va).

A mixture containing 0.6 g. of 2,3-dihydroimidazo[2,3-a]phthalazine (IIIa), 0.5 g. of 5% palladium on charcoal, 0.5 g. of methyl cinnamate and 20 ml. of *p*-cymene was allowed to heat under reflux for 40 hours. After the mixture was allowed to cool, it was diluted with 50 ml. of chloroform and filtered. The filtrate was extracted with 15% hydrochloric acid and the aqueous acid solution was washed well with ether and then decolorized with activated charcoal. The charcoal was removed by filtration, the filtrate was made alkaline with ammonium

hydroxide and extracted with chloroform. The chloroform extract was washed with saturated sodium chloride solution and dried over potassium carbonate. Filtration of the potassium carbonate and evaporation of the solvent gave a white solid which was recrystallized from benzene-cyclohexane. There was obtained 0.4 g. of colorless needles, m.p. 96-97°. The ultraviolet spectrum was clearly different from that of the starting material, compound IIIa.

U. V. λ max (95% ethanol), 245 (ε, 38,500); 252 (ε, 42,000); 270.5 (ε, 8,900); 281 (ε, 9,450); 292 (ε, 6,800); 333 mμ (ε, 3,050). U. V. λ max (10% HCl), 240 (ε, 44,250); 263 (ε, 10,200); 273 (ε, 10,250); 283 mμ (ε, 8,950).

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.83. Found: C, 70.78; H, 3.75; N, 24.69.

2-Ethylimidazo[2,3-a]phthalazine (Vb).

2-Ethyl-2,3-dihydroimidazo[2,3-a]phthalazine (IIIb) (0.9 g.) was allowed to react with the same amounts of reagents as described for Va above. There was obtained 0.36 g. of colorless micro needles of Vb, m.p. 87-88° after recrystallization from cyclohexane. The ultraviolet spectrum was different from the starting material (IIIb).

U. V. λ max (95% ethanol), 207 (ε, 17,900); 238 (ε, 24,900); 257.5 (ε, 43,550); 286 (ε, 10,000); 298 (ε, 8,050); 336 mμ (ε, 3,250). U. V. λ max (10% HCl), 212.5 (ε, 17,100); 244 (ε, 45,040); 248.5 (ε, 47,070); 271 (ε, 11,000); 280 (ε, 11,650); 291 mμ (ε, 11,850).

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.31. Found: C, 73.22; H, 5.32; N, 21.48.

2-Ethyl-2,3-dihydroimidazo[2,3-a]phthalazine Ethiodide (VI).

2-Ethyl-2,3-dihydroimidazo[2,3-a]phthalazine (IIIb) (0.99 g., 0.005 mole) was dissolved in 5 ml. (excess) ethyl iodide and the mixture was allowed to stand in a sealed tube at room temperature for 19 hours. The resultant yellow mass was recrystallized from ethanol to give yellow crystals (1.5 g.) m.p. 207-208° dec.

U. V. λ max (95% ethanol), 216 (ε, 50,000); 240-248 sh (ε, 14,500-12,000); 276.5 (ε, 10,900); 306 mμ (ε, 8,750). U. V. λ max (10% HCl), 217 (ε, 47,400); 278 (ε, 9,750); 306 mμ (ε, 8,150).

Anal. Calcd. for $C_{14}H_{18}IN_3$: C, 47.34; H, 5.11. Found: C, 47.22; H, 4.91.

The Gerngross Benzimidazole Ring-opening Reaction Applied to 2-Ethyl-2,3-dihydroimidazo[2,3-a]phthalazine. 2-(2-Benzoylamino-1-butyl)-1-phthalazinone (VII).

To a mixture containing 0.5 g. of 2-ethyl-2,3-dihydroimidazo[2,3-a]-phthalazine (IIIb), 0.9 g. of sodium carbonate and 15 ml. of water was added 1.9 ml. of benzoyl chloride. The mixture was shaken for 2 hours at room temperature and then 15 ml. of chloroform was added. After shaking for one additional hour at room temperature, the mixture was heated for 1 hour on the steam bath. After cooling, the mixture was extracted with chloroform, the extract washed with 5% hydrochloric acid and dried over potassium carbonate. Filtration of the potassium carbonate and evaporation of the chloroform gave a pale yellow solid which was recrystallized from benzene-cyclohexane to give 0.7 g. of colorless needles, m.p. 149.5°. Unlike the starting material, the product (VII) was insoluble in 10% hydrochloric acid.

U. V. λ max (95% ethanol), 209 (ε, 45,000); 222-240 sh (ε, 29,500-14,000); 252 sh (ε, 10,500); 287.5 mμ (ε, 9,350). The spectrum of 1-phthalazinone is repeated for comparison. U. V. λ max (95% ethanol) 206 (ε, 35,500); 222 sh (ε, 18,400); 240 (ε, 9,100); 249 (ε, 9,250); 280 mμ (ε, 7,850).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 71.01; H, 5.96; N, 13.08. Found: C, 71.25; H, 5.71; N, 13.22.

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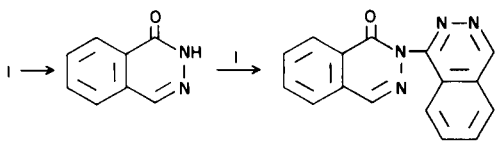
REFERENCES

(1) To whom inquiries should be directed.

(2) Present address: Tohoku University, Sendai, Japan.

(3) S. Gabriel and A. Neumann, *Ber.*, 26, 525 (1893).

(4) The authors are indebted to Dr. Gary M. Singerman of this laboratory for the proof of structure VIII. Dr. Singerman isolated VIII as a byproduct in the synthesis of 1-(3-hydroxypropoxy)phthalazine which was prepared by the interaction of 1-chlorophthalazine (I) and the monosodium salt of 1,3-propanediol. It is possible that VIII may arise by the following sequence of reactions in the presence of traces of moisture.



VIII

(5) O. Gerngross, *Ber.*, 46, 1908 (1913).

(6) All melting points were taken in capillary tubes either in a heated copper block or a stirred bath and are uncorrected. The ultraviolet spectra were taken on the Bausch and Lomb Spectronic 505 spectrophotometer in the solvent indicated. The infrared spectra were taken in potassium bromide discs with a Perkin-Elmer 337 spectrophotometer. The NMR spectra were taken with a Varian A-60 A spectrometer in the solvent indicated in the experimental section.

(7) L. J. Bellamy, "The Infra-red Spectra of Complex Molecules," 2nd Ed., John Wiley and Sons, Inc., New York, N. Y., 1958, p. 213.

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