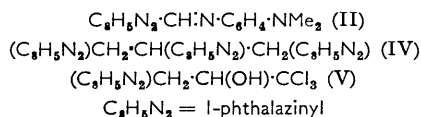
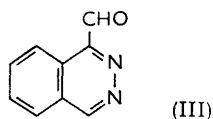
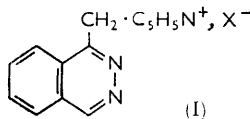


355. Heterocyclic Nitrogen Compounds. Part V.¹ Some Derivatives of Phthalazine-1-aldehyde.

By EMILY F. M. STEPHENSON.

1-Methylphthalazine has been prepared by catalytic dechlorination of 1-chloro-4-methylphthalazine and converted into the anil (II) by Kröhnke's method. Other derivatives of the aldehyde have been prepared from this anil.

THE preparation of phthalazine-1-aldehyde (III) was investigated as part of a scheme to prepare simple phthalazine derivatives as reference compounds. After exploratory work summarised below 1-methylphthalazine was converted into *N*-(1-phthalazinylmethyl)-pyridinium iodide (I; X = I) by heating it with iodine and pyridine, and the iodide was converted into the perchlorate² (I; X = ClO₄).² Treatment of the perchlorate with *NN*-dimethyl-*p*-nitrosoaniline and alkali³ gave *NN*-dimethyl-*N'*-1'-phthalazinylmethylene-*p*-phenylenediamine (II). Free phthalazine-1-aldehyde (III) has not been isolated



but the anil (II) was converted directly into the semicarbazone, thiosemicarbazone, phenylhydrazone, and 2,4-dinitrophenylhydrazone. Nitrones, and not anils, are the usual products of the Kröhnke synthesis and the formation of our anil is being investigated further.

1-Methylphthalazine reacted readily with selenium dioxide but the only crystalline product isolated (in small yield) was 1,2,3-tri-1'-phthalazinylpropane (IV). 1-Methylphthalazine reacted with mercuric oxide and aqueous sodium hydroxide, to give a mercury derivative (cf. Reissert's procedure⁴ for preparation of *o*-nitrobenzaldehyde from *o*-nitrotoluene), but attempts to obtain an aldehyde by hydrolysis of this derivative failed. 1-(3,3,3-Trichloro-2-hydroxypropyl)phthalazine⁵ (V) was readily obtained from 1-methylphthalazine and chloral, but attempts to convert it into the aldehyde (III) through β-1-phthalazinylacrylic acid were abortive, as were attempts to condense 1-methylphthalazine and *NN*-dimethyl-*p*-nitrosoaniline to give the anil (II) and/or the corresponding nitrone.

In connexion with the catalytic dechlorination of 1-chloro-4-methylphthalazine,

¹ Part IV, Stephenson, *J.*, 1954, 2354.

² Cf. King, *J. Amer. Chem. Soc.*, 1944, **66**, 894, 1612; Ried and Bender, *Chem. Ber.*, 1956, **89**, 1893; Ried and Gross, *ibid.*, 1957, **90**, 2646.

³ Kröhnke, *Ber.*, 1938, **71**, 2585; *Angew. Chem.*, 1953, **65**, 612.

⁴ Reissert, *Ber.*, 1907, **50**, 4216; D.R.-P., 182,217; 182,218; 186,881; Alford and Schofield, *J.*, 1952, 2105.

⁵ Gabriel and Eschenbach, *Ber.*, 1897, **30**, 3022.

further studies have been made with phthalazine and 3-chloroindazole. With hydrogen and a platinum catalyst the nitrogen–nitrogen bond of phthalazine is cleaved, but 3-chloroindazole was converted into indazole in good yield.

EXPERIMENTAL

Microanalyses were made by the Australian Microanalytical Service (Dr. K. W. Zimmerman and Staff). Ultraviolet spectra were measured for ethanol solutions on an S.P. 700 Unicam instrument and infrared spectra marked * were determined for potassium chloride discs on a model 137 Perkin-Elmer Infracord by Mr. W. R. C. Stevenson. M. p.s marked * were determined on a Kofler hot-stage microapparatus. Temperatures quoted for sublimations refer to the heating bath.

1-Chloro-4-methylphthalazine.—The procedure of Gabriel and Neumann⁶ was modified. A mixture of methylphthalazine (8 g.) and redistilled phosphoryl chloride (22 ml.) was refluxed for 2 min. with exclusion of moisture and then left with occasional shaking for 4 min. Addition of (iron-free) 2M-sodium hydroxide (735 ml.) and ice (735 ml.) then yielded a pale cream precipitate of 1-chloro-4-methylphthalazine (7.8 g.), m. p. 129–130° (Found: C, 60.4; H, 3.95; N, 15.0. Calc. for C₉H₇ClN₂: C, 60.5; H, 3.9; N, 15.7%).

1-Methylphthalazine.—1-Chloro-4-methylphthalazine (0.05 mole), 10% palladium-charcoal (2.5 g.), "AnalaR" 5M-sodium hydroxide (12 ml.), and ethanol (195 ml.) were shaken with hydrogen at 1 atm. until 0.98–0.99 mol. had been absorbed. The catalyst and solvent were removed and the residue was mixed with 1:1 sodium chloride—"Supercel" (2–3 g.) and sublimed at 125–150°/0.05 mm. The sublimate was dissolved in concentrated hydrochloric acid (6 ml.) and water (12 ml.), and a small amount of insoluble oil was extracted with benzene and discarded. The aqueous solution of 1-methylphthalazine hydrochloride was evaporated to dryness and all the excess of acid was removed under reduced pressure over sodium hydroxide. The hydrochloride was digested with boiling propan-2-ol (16 ml. per g.). The white salt was converted into the base with a small excess of sodium hydroxide solution. After removal of water and mixing with sodium chloride—"Supercel," 1-methylphthalazine sublimed at 125–135°/0.05 mm. The white crystalline hygroscopic sublimate, m. p.* 70.5–71.5°, was obtained in 64–68% overall yield (Found: C, 75.0; H, 5.7; N, 19.7. Calc. for C₉H₉N₂: C, 75.0; H, 5.6; N, 19.4%) and had λ_{max} 217 (ε 76,500) and 263 mμ (ε 5000). Paper chromatography in butan-1-ol-acetic acid-water (8:1:1) showed only one spot (R_F 0.83). The hydrochloride formed prisms (from propan-2-ol), m. p.* 204–205° (decomp.) (slow heating) (Found: C, 60.0; H, 4.75; Cl, 20.1; N, 14.9. Calc. for C₉H₉ClN₂: C, 59.8; H, 5.0; Cl, 19.6; N, 15.5%). The *hydroxymide* formed prisms (from butan-1-ol), m. p.* 280–282° (decomp.) (Found: C, 48.0; H, 4.0; Br, 36.3; N, 12.1. C₉H₉BrN₂ requires C, 48.0; H, 4.0; Br, 35.5; N, 12.45%). For both these salts it is essential to remove all the free acid under reduced pressure over solid sodium hydroxide before crystallisation. The *perchlorate* (from water) had m. p. 241–242° (decomp.) (Found: C, 44.25; H, 3.9; Cl, 14.9; N, 11.3; O, 26.3. C₉H₉ClN₂O₄ requires C, 44.2; H, 3.7; Cl, 14.5; N, 11.5; O, 26.2%).

N-(1-Phthalazinylmethyl)pyridinium Iodide (I; X = I) and Perchlorate.—Iodine (12.7 g.) was added to a solution of 1-methylphthalazine (7.2 g.) in dry "AnalaR" pyridine (40 ml.) and the mixture warmed with shaking for several minutes until the iodine dissolved and separation of the iodide began. The mixture was then heated on a water-bath for 4 hr. Benzene (40 ml.) was added and the mixture cooled. The precipitate was stirred with cold water (70 ml.) to remove pyridinium hydriodide.

N-(1-Phthalazinylmethyl)pyridinium iodide (15 g.), m. p. 220° (decomp.), formed a red powder.

The iodide (15 g.) was dissolved in hot water (875 ml.) and filtered hot. 2M-sodium perchlorate (160 ml.) was added. After 3 hr. the precipitate was collected, dissolved in hot water (790 ml.), cooled to 40–45°, filtered, and treated with 2M-sodium perchlorate (160 ml.). After 2 hr. the precipitated *perchlorate* (10.2 g.) was collected. It formed bright orange crystals, m. p. 245–246° (decomp.) (Found: C, 52.3; H, 3.9; Cl, 10.9; N, 13.0; O, 20.2. C₁₄H₁₂ClN₃O₄ requires C, 52.3; H, 3.8; Cl, 11.0; N, 13.1; O, 19.9%).

NN-Dimethyl-N'-1'-phthalazinylmethylene-p-phenylenediamine (II).—To a mixture of *N*-(1-phthalazinylmethyl)pyridinium perchlorate (0.64 g.), *NN*-dimethyl-*p*-nitrosoaniline (0.3 g.), and ethanol (10 ml.) at –4°, M-sodium hydroxide (3.6 ml.) was added rapidly with stirring. The

* Gabriel and Neumann, *Ber.*, 1893, **26**, 709.

temperature rose temporarily to 4°. The mixture was kept in an ice-bath for 3 hr. with stirring, then water (60 ml.) was added to precipitate the product (240 mg.). After digestion with a little methanol *NN-dimethyl-N'-1'-phthalazinylmethylene-p-phenylenediamine* (II) sublimed at 125—150°/0.01 mm. and had m. p.* 136—137° (Found: C, 73.9; H, 6.1; N, 20.05). $C_{17}H_{16}N_4$ requires C, 73.9; H, 5.8; N, 20.3%, λ_{\max} 445 μ (ϵ 17,500), shoulder at 290 μ , ν_{\max} 1587, 1515, 1439, 1361, 1235, 1164, and 823 cm^{-1} . The anil (II) exists in a yellow and a red form which appear to differ little in stability. Earlier preparations gave the yellow form, but the red form appeared during purification and thereafter the yellow form was never obtained free from the red form.

Phthalazine-1-aldehyde Semicarbazone.—The foregoing Schiff base (0.276 g.) and *N*-hydrochloric acid (5 ml.) were heated for 10 min. on a water-bath, semicarbazide hydrochloride (0.157 g.) and water (7 ml.) were added, and heating continued for 5 min. with stirring. After addition of water (7 ml.) and cooling, the product (195 mg.) was precipitated by adjustment of the pH to ~5 by successive addition of sodium hydrogen carbonate and acetic acid. After digestion with boiling benzene to remove traces of an orange impurity, the *semicarbazone* crystallised from water in pale cream needles, m. p.* 229—231° (decomp.) (Found: C, 55.8; H, 4.1; N, 32.4; O, 7.7). $C_{10}H_9N_5O$ requires C, 55.8; H, 4.2; N, 32.5; O, 7.4%, λ_{\max} 228 (ϵ 37,600) and 315 μ (ϵ 18,500).

Similar reactions gave the cream-coloured *thiosemicarbazone*, m. p. 234—235° (decomp.), very sparingly soluble in alcohols, hydrocarbon, and chlorinated hydrocarbon solvents (Found: C, 51.2; H, 4.1; N, 30.45; S, 13.65). $C_{10}H_9N_5S$ requires C, 51.9; H, 3.9; N, 30.3; S, 13.8%, ν_{\max} 1600, 1515, 1460, 1351, 1220, 1072, 943, 844, and 823 cm^{-1} , and the yellow *phenylhydrazone* m. p.* 205.0—205.5° (decomp.) (from butan-1-ol) (Found: C, 72.1; H, 5.0; N, 22.3). $C_{15}H_{12}N_4$ requires C, 72.6; H, 4.9; N, 22.6%, ν_{\max} 1563, 1481, 1307, 1256, 1163, and 1070 cm^{-1} .

Phthalazine-1-aldehyde 2,4-Dinitrophenylhydrazone.—The Schiff base (0.31 g.) was added rapidly to a warm solution of 2,4-dinitrophenylhydrazine (0.198 g.) in concentrated hydrochloric acid (2 ml.) and ethanol (20 ml.) and kept at 70° for 10 min. with stirring. After collection, the product was stirred with concentrated sodium acetate solution. The 2,4-dinitrophenylhydrazone (315 mg.) formed yellow prisms, m. p. 282—283° (decomp.), from ethyl benzoate (Found: C, 53.4; H, 3.1; N, 24.5; O, 19.4). $C_{15}H_{10}N_6O_4$ requires C, 53.25; H, 3.0; N, 24.85; O, 18.9%.

1,2,3-Tri-1'-phthalazinylpropane (IV).—In most experiments freshly prepared and sublimed selenium dioxide was used but there was no apparent difference in results when this dioxide had been stored for some months. Reactions were run in ethanol, benzene, and acetic anhydride with the theoretical or half the theoretical amount of dioxide required for conversion of CH_2 into CHO. A pure product was obtained (in small yield) from the oxidation in benzene, the yield being improved slightly by refluxing the crude product with acetic anhydride. Selenium dioxide (0.06 g.) was added in portions to methylphthalazine (0.14 g.) in boiling benzene (12 ml.) during 1 hr. After 5 hours' refluxing the benzene was removed and the residue refluxed with acetic anhydride (8 ml.) for 5 hr. After being stirred with an excess of sodium hydroxide solution to remove acetic anhydride, and storage (12 hr.), solidification of the product was complete. The product was chromatographed in benzene on alumina, then dissolved in warm 5*N*-hydrochloric acid containing 20% of acetic acid. 1,2,3-Tri-1'-phthalazinylpropane was precipitated on basification of the filtrate and sublimed at 160—170°/0.05 mm. to give cream needles, m. p.* 190—192° (Found: C, 74.9; H, 4.3; N, 19.7). $C_{27}H_{20}N_6$ requires C, 75.7; H, 4.7; N, 19.6%, which, as a potassium bromide disc, had no absorption band at or near 960—970 cm^{-1} .

The Action of Mercuric Oxide and Alkali on 1-Methylphthalazine.—1-Methylphthalazine (1.44 g.) was added in 20 min. to a stirred mixture of yellow mercuric oxide (4.34 g.) and sodium hydroxide (0.4 g.) in water (30 ml.) at 100—110° (bath-temperature), and heating and stirring were continued for 5 hr. The pale yellow precipitate (4.5 g.) of *mercury derivative* decomposed above 220° (Found: C, 19.2; H, 1.5; Hg, 68.4; N, 4.4; O, 6.7). $C_9H_6Hg_2N_2O_2 \cdot H_2O$ requires C, 18.7; H, 1.4; Hg, 69.5; N, 4.85; O, 5.5%.

Hydrogenation of Phthalazine.—Phthalazine (0.005 mole) was shaken with Adams platinum oxide (100 mg.), ethanol (25 ml.), and hydrogen at 1 atm. Uptake was steady, then slowed, and stopped after absorption of 1.5 mol. Copious amounts of ammonia were formed. The initially colourless solution yielded only tars. No phthalazine or *o*-xylylenediamine was detected.

Indazole.—3-Chloroindazole (1.53 g.), 20% palladium-charcoal (1.8 g.), ethanol (35 ml.), and "AnalaR" 5M-sodium hydroxide (2.4 ml.) were shaken with hydrogen at 1 atm. until 1 mol. of hydrogen had been absorbed. After removal of the catalyst and ethanol the residue was dissolved in 3N-hydrochloric acid (35 ml.). Basification of the filtrate with ammonia gave indazole (0.96 g.). After crystallisation from water and sublimation at 110—120°/0.05 mm. this had m. p.* 147.0—147.5° (Found: C, 71.5; H, 4.9; N, 23.5. Calc. for $C_7H_6N_2$: C, 71.2; H, 5.1; N, 23.7%).

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