Reissert Compound Studies. XXXV. Acid-Catalyzed Condensations of the Phthalazine Reissert Compound and Condensations of Phthalazine Reissert Compound Salt

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The phthalazine Reissert compound hydrofluoroborate undergoes condensation with alkynes to give pyrrolo[2,1-*a*]phthalazines and with alkenes to give 2-(1-phthalazyl)pyrroles. The phthalazine Reissert compound undergoes acid catalyzed condensations with some alkenes but the intermediate is of sufficient stability to be isolated. This same type of intermediate can also be isolated in the acid-catalyzed hydrolysis of the phthalazine Reissert compound.

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We reported (1) on the synthetic utility of the Reissert compound (**1**) from phthalazine in a variety of base-catalyzed reactions which made available a number of new phthalazine derivatives. We now report on the utility of reactions of **1** under acid-catalyzed conditions and on reactions of the hydrofluoroborate salt (**5**) (2) of **1**.

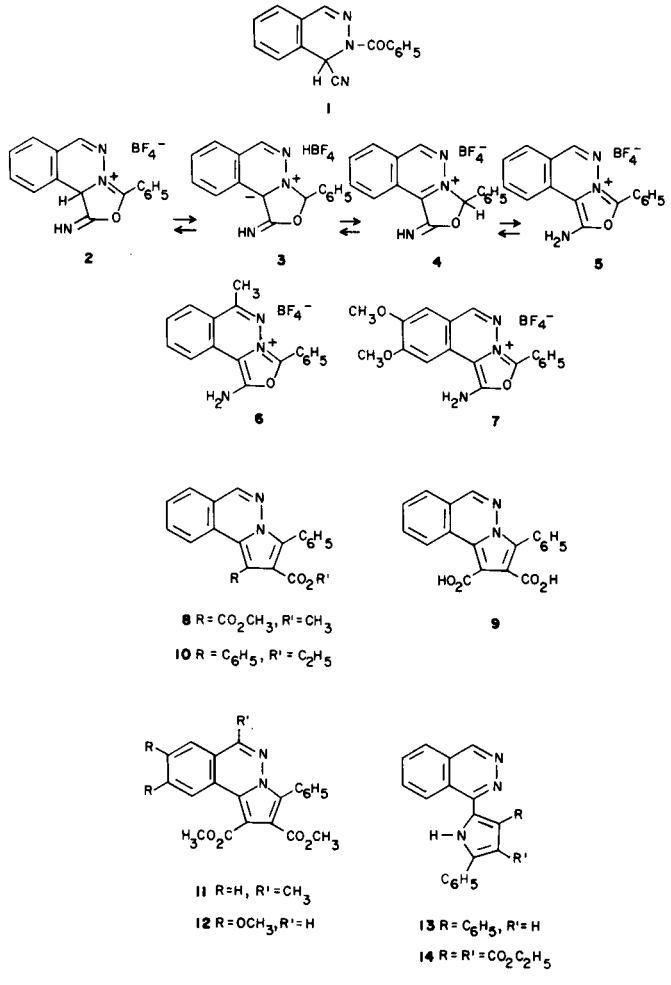
McEwen and coworkers (3) have reported in detail on the scope and synthetic utility of reactions of hydrofluoroborate salts of Reissert compounds with olefinic and acetylenic compounds. This paper reports on the extension of that work to the hydrofluoroborate salt (**5**) of the phthalazine Reissert compound.

Treatment of the phthalazine Reissert compound (**1**) with fluoroboric acid in glacial acetic acid gave the hydrofluoroborate salt which by analogy with work in the isoquinoline series (2) is assumed to consist of an equilibrium mixture of **2**, **4** and **5**, the latter being the major component. Also in the equilibrium are the original Reissert compound (**1**), the mesoionic compound (**3**) and fluoroboric acid. Similar hydrofluoroborate salts **6** and **7** have also been obtained from the Reissert compound of 1-methylphthalazine (1) and 6,7-dimethoxyphthalazine (4).

When equimolar quantities of the hydrofluoroborate salt (**5**) and dimethyl acetylenedicarboxylate were refluxed in methylene chloride-ethanol, dimethyl 3-phenylpyrrolo-[2,1-*a*]phthalazine-1,2-dicarboxylate (**8**) was obtained in 95% yield based on recovery of unreacted **5**. The same compound **8** could be obtained more efficiently by using the modified procedure (5) which involves reacting **5** with 1.5 equivalents of the alkyne in dimethylformamide at 100° for 24 hours. Hydrolysis of **8** by aqueous-ethanolic potassium hydroxide followed by acid treatment gave the corresponding dicarboxylic acid (**9**). Ethyl phenylpropiolate was also reacted with **5** to give **10** in 72% yield. The structures **8** and **10** were assigned in analogy to the work in the isoquinoline series (3). The hydrofluoroborate salts **6** and **7** also reacted smoothly with dimethyl acetylenedicarboxylate in anhydrous dimethylformamide at 100° to give the pyrrolo[2,1-*a*]phthalazines **11** and **12** respectively.

The phthalazine Reissert hydrofluoroborate (**5**), in analogy with the isoquinoline series was also reacted with alkenes to give 2-(1-phthalazyl)pyrroles. Thus **5** reacted with two equivalents of styrene and of diethyl maleate in anhydrous dimethylformamide at 150° to give 2-(1-phthalazyl)-3,5-diphenylpyrrole (**13**) and diethyl 2-(1-phthalazyl)-5-phenylpyrrole-3,4-dicarboxylate (**14**), respectively.

McEwen and coworkers have studied in detail the acid-catalyzed reaction of the isoquinoline Reissert compound with 1,1-diphenylethylene (6). We have reacted the



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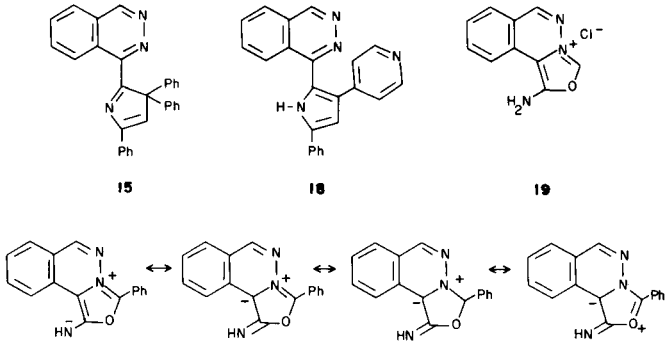
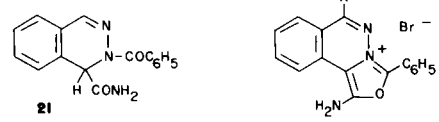
phthalazine Reissert compound (**1**) with 1,1-diphenylethylene in the presence of concentrated sulfuric acid in anhydrous dioxane to give in analogy to isoquinoline, 2-(1-phthalazyl)-3,3,5-triphenylpyrrolenine (**15**) as the major product. A high melting solid to which the structure **16** was assigned on the basis of elemental analysis, bright red color, and spectral characteristics (to be discussed below) was also obtained in this reaction. Further evidence for the structure **16** was obtained by reaction of **16** with dimethyl acetylenedicarboxylate in dimethylformamide to give **8** in high yield under exactly the same conditions that **5** yielded **8**. Although Reissert cations have been isolated as the halide (7) and, as noted above, as the hydrofluoroborate (**5**), this appears to be the first time that the conjugate base (2a) has been isolated.

Reaction of the phthalazine Reissert compound (**1**) with 4-vinylpyridine in the presence of concentrated hydrochloric acid, as described (8) for the isoquinoline Reissert compound, gave in addition to the expected 2-(1-phthalazyl)-3-(4-pyridyl)-5-phenylpyrrole hydrochloride (**17**) (which was isolated as the free base (**18**)), the conjugate base (**16**) which was identical with the material described above.



15 **18** **19**

16



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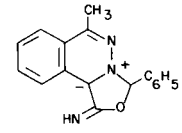
22 R=H
23 R=CH_3



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Reaction of cinnamonitrile with the phthalazine Reissert compound (**1**) in the presence of concentrated hydrochloric acid in dioxane (9) did not give any of the expected product but instead gave a 74% yield of the chloride (**19**). The same chloride could be obtained in comparable yield when the phthalazine Reissert compound (**1**) was reacted with concentrated hydrochloric acid in dioxane at room temperature in the absence of cinnamonitrile. The chloride was difficult to purify and it was unstable to store, being slowly converted to the phthalazine Reissert compound (**1**). This chloride had a great tendency to become solvated when recrystallized from a variety of solvents such as benzene, ethanol and methanol.

It was reported (9) that the isoquinoline Reissert compound reacts with acrylonitrile in the presence of concentrated hydrochloric acid to give 1-(1-isoquinolyl)-2-cyano-4-phenylpyrrole. Reaction of the phthalazine Reissert compound (**1**) with acrylonitrile under identical conditions, however, did not give the expected product. Instead, the munchone-type intermediate (**16**) was again obtained in 26.4% yield, together with a yellow compound (**20**), m.p. 322-324°, of undetermined structure and colorless flakes (**21**), m.p. 247°. Based on spectral information, the structure **21** was assigned to the latter product and was proven by the reaction of the phthalazine Reissert compound (**1**) with 30% hydrogen peroxide in acetone to give the same amide (**21**).

It appears that intermediates of the type **16** and **19** are much more stable in phthalazine series than in the isoquinoline series.

Phthalazine-1-carboxylic acid was reported (10) to be the product when the Reissert compound (**1**) was hydrolyzed with glacial acetic acid and hydrobromic acid-mixture by the method of Davis (11). In view of the above results this reaction was reinvestigated in detail. When the phthalazine Reissert compound (**1**) and the 1-methylphthalazine Reissert compound were treated with hydrobromic acid-glacial acetic acid at room temperature, the bromides **22** and **23** precipitated from the reaction mixture quite rapidly. The compounds **5**, **19**, **22** and **23** have similar spectral characteristics and can be converted to the respective Reissert compounds on base-treatment. The compounds **19**, **22** and **23** were reacted with dimethyl acetylenedicarboxylate in dimethylformamide at 100° to give **8** (from **19** and **22**) and **11** (from **23**) in good yields. When the phthalazine Reissert compound (**1**) was refluxed with hydrobromic acid-glacial acetic acid for a few minutes, phthalazine-1-carboxylic acid hydrobromide was obtained together with the conjugate base (**16**). A similar conjugate base (**24**) could also be isolated from 1-methylphthalazine Reissert compound under identical conditions. The compound **24** reacted with dimethyl acetylenedicarboxylate in dimethylformamide at 100° to give **11** in 90% yield.

The chloride (**19**) and the bromide (**22**) have identical ^1H nmr spectra with that of **5** in trifluoroacetic acid, lending further proof to the assigned structures of these compounds. The spectrum of the chloride (**19**) also shows clearly the presence of ethanol of crystallization in the compound. The bromide (**22**) and the hydrofluoroborate salt (**6**) have identical ^1H nmr spectrum taken in trifluoroacetic acid. The mesoionic compounds **16** and **24** had different types of splitting in the aromatic region when com-

pared to those of the hydrofluoroborate salts **5** and **6**, respectively.

Mass spectra of Reissert compounds have been studied in detail by Popp, *et al.*, (12) and also by Katritzky and his co-workers (2b). However, no study of the mass spectra of hydrofluoroborate salts of Reissert compounds and related compounds has appeared. The mass spectrum of the hydrofluoroborate salt (**5**) of the phthalazine Reissert compound (**1**) shows the molecular ion peak (M^+) at 262.0898 (1.5%; $C_{16}H_{12}N_3O$). In addition to this there are peaks at m/e's 261.0894 (7.9%, $C_{16}H_{11}N_3O$) and 260.0826 (11.3%, $C_{16}H_{10}N_3O$). The $C_{16}H_{11}N_3O$ fragment gives rise to $C_9H_6N_3$ and C_6H_5CO. The former then looses cyanide. In the bromide (**22**) the molecular ion appears at the expected value of 262 and other features are similar to **5**. Mass spectra of the mesoionic compounds **16** and **24** show the presence of the molecular ion peaks at m/e 261 and 275 corresponding to molecular formulas $C_{16}H_{11}N_3O$ and $C_{17}H_{13}N_3O$ respectively. The most characteristic feature of the mass spectral fragmentation of these two compounds is the loss of 43 amu, *i.e.*, isocyanic acid (HNCO) to give metastable peaks at m/e 218 and 232 respectively.

EXPERIMENTAL

General.

All melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratories. The infrared absorption spectra were determined with a Perkin-Elmer Model 710B spectrometer. ^1H nmr spectra were recorded either on a 60 MHz Hitachi Perkin-Elmer Model R-24B instrument or a 90 MHz CFT20 Varian spectrometer. Tetramethylsilane was used as an internal standard with deuteriochloroform and as an external standard with dimethylsulfoxide-d_6, acetone-d_6, deuterated trifluoroacetic acid and trifluoroacetic acid. Chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane. Mass spectra were recorded on Nuclide 1-90-G single focusing instrument, DS-50 high resolution mass spectrometer, and Jeol D-100 double focusing mass spectrometer with interface to a Texas Instrument Computer 980A. We thank the mass spectral laboratories at the University of Missouri-Rolla and the University of Nebraska-Lincoln for their assistance.

1-Cyano-2-benzoyl-1,2-dihydrophthalazine Hydrofluoroborate Salt (**5**).

A mixture of 5.0 g. (0.019 mole) of 1-cyano-2-benzoyl-1,2-dihydrophthalazine (**1**) and 21 ml. of glacial acetic acid was stirred with warming until solution was complete. The solution was cooled and before any solid could crystallize 20 ml. of 50% fluoroboric acid was added with stirring. The solution became orange-red, stirring was continued for half an hour and the mixture was chilled in an ice-water bath. The product was filtered, washed with ether several times and dried to give 6.25 g. (93.5%) of the fluoroborate (**5**), m.p. 225-227°, lit. (2a) m.p. 225-227°; ir (potassium bromide): 3420 (w), 3325 (m), 3200 (vw), 1655 (vs), 1620 (m), 1545 (m), 1245 (m), 1095 (vs), 1050 (s, broad); ^1H nmr (deuteriotrifluoroacetic acid): δ 8.69 (s, 1H), 8.49-8.33 (m, 2H), 7.97-7.55 (m, 7H) ^1H nmr (DMSO-d_6): δ 9.14 (s, 1H), 8.52-7.45 (m, 11H); ms: m/e 262.0939 ($^{12}C_{15}{}^{13}CH_{11}N_3O$, 18.08%), 261.0904 ($C_{16}H_{11}N_3O$, M^+, 100), 260.0828 ($C_{16}H_{10}N_3O$, 1.98), 157.0401 ($C_9H_5N_2O$, 3.19), 129.0453 ($C_8H_5N_2$, 16.39), 115.0421 (C_8H_5N, 5.87), 104.0498 (C_7H_6N, 26.57), 103.9425 (C_7H_5N, 42.88), 102.0345 (C_7H_4N, 10.80), 77.0390 (C_6H_5, 11.36).

1-Cyano-2-benzoyl-4-methyl-1,2-dihydrophthalazine Hydrofluoroborate Salt (**6**).

Compound **6** was prepared in 91% yield from 1-cyano-2-benzoyl-4-methyl-1,2-dihydrophthalazine by the above procedure, m.p. 198-203° (95% ethanol); ir (potassium bromide): 3400 (w), 3310 (m), 3205 (w), 1660 (vs), 1615 (w), 1600 (vw), 1545 (m), 1430 (w), 1395 (m), 1340 (m), 1305 (w), 1180 (w), 1115 (s), 1085 (s), 1060-1045 (s, broad), 1036 (m), 775 (s) cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 8.51-8.36 (m, 2H), 8.10-7.51 (m, 7H), 2.89 (s, 3H) ^1H nmr (DMSO-d_6): δ 8.47-7.51 (m, 11H), 2.84 (s, 3H);

Anal. Calcd. for $C_{17}H_{14}BF_4N_3O$: C, 56.22; H, 3.89; N, 11.57. Found: C, 55.88; H, 3.94; N, 11.37.

1-Cyano-2-benzoyl-6,7-dimethoxy-1,2-dihydrophthalazine Hydrofluoroborate Salt (**7**).

Compound **7** was also prepared by the above procedure from 1-cyano-2-benzoyl-6,7-dimethoxy-1,2-dihydrophthalazine and fluoroboric acid in glacial acetic acid in 83.5% yield, m.p. 170-171° (95% ethanol); ir (potassium bromide): 3400 (w), 3330 (m), 3220 (w), 3085 (vw), 1665 (s), 1620 (w), 1605 (m), 1545 (s), 1520 (w), 1475 (m), 1405 (vw), 1375 (m), 1305 (s), 1275 (s), 1175 (s), 1100-1005 (s, broad), 780 (m) cm^{-1};

Anal. Calcd. for $C_{19}H_{16}BF_4N_3O_3$: C, 52.84; H, 3.94; N, 10.27. Found: C, 52.65; H, 4.13; N, 10.23.

Dimethyl 3-Phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**8**).

(a) Methylene Chloride-Ethanol Method.

A mixture of 3.49 g. (0.01 mole) of 1-cyano-2-benzoyl-1,2-dihydrophthalazine hydrofluoroborate (**5**), 1.5 g. (0.01 mole) of dimethyl acetylenedicarboxylate and 50 ml. of methylene chloride was heated to reflux and 75 ml. of absolute ethanol added. The mixture was refluxed for 2.5 hours and evaporated to dryness. The residue was extracted several times with anhydrous ether. Concentration of the ether solution gave 0.8 g. of a pale yellow crystalline solid, m.p. 168-169° (95% ethanol) whose structure was assigned as dimethyl 3-phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**8**). In addition, 2.7 g. of unreacted fluoroborate salt was recovered. Based on the unrecovered starting material the yield was 95%; ir (potassium bromide): 2960 (w), 1720-1705 (vs, broad), 1620 (m), 1535 (m), 1460 (s), 1440 (s), 1415 (m), 1380 (m), 1275 (w), 1255 (s), 1235 (m), 1210 (vs), 1180 (vs), 1130 (w), 1060 (w), 1000 (w) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.91-8.77 (d, 1H), 8.29 (s, 1H), 7.66-7.28 (m, 8H), 3.93 (s, 3H), 3.71 (s, 3H); uv (ethanol): 251.42 (log ϵ 4.558), 270.27 (4.838), 279.07 (4.894), 323.08 mn (4.199).

Anal. Calcd. for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.97; H, 4.45; N, 7.78.

(b) DMF at 100° Method.

A mixture of 2.0 g. (0.0057 mole) of the hydrofluoroborate salt (**5**) and 1.22 g. (0.0086 mole) of dimethyl acetylenedicarboxylate in 40 ml. of anhydrous dimethylfromamide was heated to 100° slowly and kept at that temperature for 24 hours. The mixture was cooled and poured onto 500 g. of crushed ice, stirred well, the precipitated solid was filtered, and dried to give 1.7 g. (82.48%) of pure **8**, m.p. 168-169° (95% ethanol).

3-Phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylic Acid (**9**).

To a warm solution of 8 g. of potassium hydroxide in 13 ml. of water, a hot suspension of 0.23 g. of the diester (**8**) in 13 ml. of ethanol was added and the mixture was refluxed for 1 hour, cooled, poured into 10% hydrochloric acid, and filtered to give 0.18 g. of the diacid (**9**), m.p. 248-250° (methylene chloride-ethanol); ir (potassium bromide): 3300-2800 (w, broad), 1715 (s), 1680 (s), 1615 (m), 1530 (w), 1490 (w), 1455 (m), 1285 (m), 1260 (m), 1200 (s), 1180 (s) cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.89 (d, 1H, J = 7.8 Hz), 8.67 (s, 1H), 8.01-7.32 (m, 8H).

Anal. Calcd. for $C_{19}H_{12}N_2O_4$: C, 68.67; H, 3.64; N, 8.43. Found: C, 68.74; H, 3.73; N, 8.35.

Ethyl 1,3-Diphenylpyrrolo[2,1-*a*]phthalazine-2-carboxylate (**10**).

To 1.15 g. (0.0033 mole) of the hydrofluoroborate salt (**5**) in 25 ml. of

anhydrous dimethylformamide was added, 1.14 g. (0.00655 mole) of ethyl phenylpropiolate. The mixture was warmed to 150° and kept at 150-153° for 24 hours. The reaction mixture was then cooled and poured into 500 g. of crushed ice. The mixture was extracted several times with chloroform, the extract was washed with water, dried over anhydrous magnesium sulfate, evaporated and the residue was chromatographed over alumina. Elution with chloroform afforded a yellow solid which was crystallized from chloroform-hexane to give 0.93 g. (72.2%) of **10**, m.p. 151-151.5°; ir (potassium bromide): 3055 (w), 2985 (w), 2905 (w), 1695 (vs), 1610 (m), 1490 (w), 1455 (s), 1425 (s), 1280 (s), 1255 (s), 1200 (s), 1155 (s), 765 (s), 705 (s) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.22 (s, 1H), 7.41-7.28 (m, 14H), 3.92 (q, 2H, J = 7.2 Hz), 0.83 (t, 3H, J = 7.2 Hz).

Anal. Calcd. for $C_{26}H_{21}N_2O_2$: C, 79.36; H, 5.38; N, 7.12. Found: C, 79.24; H, 5.17; N, 7.08.

Dimethyl 4-Methyl-3-phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**11**).

A mixture of 0.6 g. (0.001728 mole) of 1-cyano-2-benzoyl-4-methyl-1,2-dihydrophthalazine hydrofluoroborate (**6**) in 10 ml. of anhydrous dimethylformamide and 0.37 g. (0.002606 mole) of dimethyl acetylenedicarboxylate was slowly heated to 100° in an oil bath and kept at that temperature for 24 hours. The mixture was cooled and poured into 200 g. of ice-water mixture, stirred well and the precipitated solid was collected by filtration and dried. Recrystallization from 95% ethanol gave 0.54 g. (83.47%) of dimethyl 4-methyl-3-phenylpyrrolo[2,1-*a*]phthalazine 1,2-dicarboxylate (**11**), m.p. 175°; ir (potassium bromide): 3010 (vw), 2955 (m), 1720 (s), 1695 (s), 1600 (m), 1510 (m), 1440 (s), 1370 (s), 1345 (m), 1250 (s), 1200 (vs), 1165 (vs), 1135 (s), 1055 (m), 1000 (m), 950 (w), 850 (w), 765 (m) cm^{-1}; ^1H (deuteriochloroform): δ 8.9 (d, 1H, J = 7.8 Hz), 7.86-7.30 (m, 8H), 3.94 (s, 3H), 3.75 (s, 3H), 2.62 (s, 3H).

Anal. Calcd. for $C_{22}H_{18}N_2O_4$: C, 70.58;H, 4.85; N, 7.48. Found: C, 70.64; H, 4.79; N, 7.48.

Dimethyl 6,7-Dimethoxy-3-phenylpyrrolo[2,1-*a* phthalazine-1,2 dicarboxylate (**12**).

A mixture of 0.6 g. (0.001466 mole) of 1-cyano-2-benzoyl-6,7-dimethoxy-1,2-dihydrophthalazine hydrofluoroborate (7) and 0.31 g. (0.002183 mole) of dimethyl acetylenedicarboxylate in 5 ml. of anhydrous dimethylformamide was heated at 100° for 24 hours and the product was isolated in the same way as described above. The crude product was crystallized from chloroform-95% ethanol to give 0.48 g. (77.9% yield) of dimethyl 6,7-dimethoxy-3-phenylpyrrolo[2,1-*a*]phthalazine-1,2-dicarboxylate (**12**), m.p. 183°; ir (potassium bromide): 3125 (vw), 3025 (w), 2950 (m), 2870 (w), 1730 (s), 1700 (s), 1625 (m), 1500 (s), 1450 (s), 1395 (m), 1285 (m), 1265 (s), 1255 (s), 1210 (s), 1440 (vs), 1060 (m), 930 (w), 855 (w), 795 (m) cm^{-1}; ^1H nmr (deuteriochloroform): δ 8.94 (s, 1H), 8.29 (s, 1H), 7.63-7.32 (m, 5H), 7.06 (s, 1H), 4.08 (s, 3H), 3.98 (s, 3H), 3.90 (s, 3H), 3.75 (s, 3H).

Anal. Calcd. for $C_{23}H_{20}N_2O_6$: C, 65.71; H, 4.80; N, 6.66. Found: C, 65.78; H, 4.77; N, 6.70.

2-(1-Phthalazyl)-3,5-diphenylpyrrole (**13**).

A mixture of 2.0 g. (0.0057 mole) of the hydrofluoroborate salt (**5**), 1.19 g. (0.0114 mole) of freshly distilled styrene and 20 ml. of anhydrous dimethylformamide was heated at 150° for 24 hours, cooled, poured into 500 ml. of water and the aqueous suspension was extracted with chloroform. The chloroform extract after drying over anhydrous magnesium sulfate and evaporation was chromatographed over alumina. Elution with benzene-chloroform removed some unidentified material and elution with chloroform-10% methanol gave **13**. Recrystallization from chloroform-ethanol gave 1.04 g. (52.5%) of **13**, m.p. 250.5-251°; ir (potassium bromide): 3430 (w), 3075 (m), 2915 (w), 1600 (m), 1585 (m), 1505 (m), 1490 (m), 1470 (s), 1410 (m), 1350 (s), 1235 (w), 1035 (w), 770 (s) cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.19 (s, 1H), 7.84-6.77 (m, 16H).

Anal. Calcd. for $C_{24}H_{17}N_3$: C, 82.97; H, 4.93; N, 12.10. Found: C, 82.75; H, 5.11; N, 11.91.

Diethyl 2-(1-Phthalazyl)-5-phenylpyrrole-3,4-dicarboxylate (**14**).

To 2.3 g. (0.0066 mole) of **5** in 30 ml. of anhydrous dimethylformamide was added 3.38 g. (0.02 mole) of diethyl maleate. The mixture was stirred magnetically and heated slowly to 150° in an oil bath and kept at that temperature for 50 hours. The mixture became dark red. It was cooled and poured into ice-water, and was extracted with chloroform. The chloroform extract was dried over anhydrous magnesium sulfate, the solvent was removed *in vacuo* and the residue was chromatographed over alumina. Elution with 5% methanol in chloroform gave 0.89 g. (32%) of diethyl 2-(1-phthalazyl)-5-phenylpyrrole-3,4-dicarboxylate (**14**), m.p. 192.5-193° (95% ethanol); ir (potassium bromide): 3410 (s), 3190 (w, broad), 3000 (w), 1720 (s), 1690 (s), 1645 (s), 1585 (m), 1550 (m), 1495 (m), 1455 (s), 1385 (s), 1340 (s), 1220 (s), 1170 (s), 1110 (s), 1035 (m), 900 (m), 775 (s) cm^{-1}.

Anal. Calcd. for $C_{24}H_{21}N_3O_4 \cdot H_2O$: C, 66.50; H, 5.35; N, 9.69. Found: C, 66.85; H, 5.38; N, 9.69.

Reaction of the Phthalazine Reissert Compound (**1**) with 1,1-Diphenylethylene in Presence of Concentrated Sulfuric Acid.

To a solution of 2.5 g. (0.0096 mole) of 1-cyano-2-benzoyl-1,2-dihydrophthalazine (**1**) and 2.5 g. (0.014 mole) of 1,1-dimethylethylene in 50 ml. of pure, anhydrous dioxane was added slowly, with vigorous stirring, 5 ml. of cold concentrated sulfuric acid. The mixture was stirred at room temperature for 12-14 hours and was then poured into a large amount of ice-water. The solid was collected by filtration, dried, boiled with a mixture of chloroform and ethanol (50 ml.) and filtered hot. The filtrate after concentration and cooling afforded 1.21 g. (29.8%) of light yellow crystals of 2-(1-phthalazyl)-3,3,5-triphenylpyrrolenine (**15**), m.p. 237-238° (chloroform-ethanol); ir (potassium bromide): 3070 (w), 3456 (w), 1605 (s), 1575 (m), 1550 (m), 1495 (s), 1450 (s), 1370 (s), 1305 (w), 1220 (m), 1070 (m), 935 (m), 880 (m), 765 (s), 705 (s) cm^{-1}; ^1H nmr (deuteriochloroform): δ 9.37 (s, 1H), 8.59-6.97 (m, 20H).

Anal. Calcd. for $C_{30}H_{21}N_3$: C, 85.08; H, 5.00; N, 9.92. Found: C, 84.73; H, 4.97; N, 9.84.

The residue obtained after boiling the crude solid with chloroform-ethanol was purified by recrystallization from a large volume of chloroform-ethanol to give 0.83 g. (33.1%) of a red solid (**16**), m.p. 265-266°; ir (potassium bromide): 2950, 2600-2505 (m), 1625 (s), 1600, 1550, 1450, 1415, 1380, 1260, 1215, 1135, 1070, 930, 775 cm^{-1}; ms: (70 eV; 140°) m/e 263 (1.5%), 262 (18.08), 261 (100), 260 (1.98), 259 (0.76), 232 (0.89), 218.8 (3.86), 217.98 (48.06), 216.97 (0.56), 211.9 (1.56), 207 (0.70), 190 (0.84), 158 (0.65), 157 (3.19), 131 (2.7), 130.54 (8.28), 130 (16.09), 129 (16.39), 128 (0.62), 116 (0.76), 115 (5.87), 114 (0.58), 105 (2.12), 105 (1.12), 104 (26.57), 103 (42.88), 102 (0.57), 102 (10.00), 101 (0.89), 101 (0.73), 89 (0.81), 88 (0.66), 78 (0.78), 77 (11.36), 77 (0.58), 76 (9.09), 76 (1.66), 75 (4.53), 75 (0.71), 74 (1.06), 63 (1.38), 62 (0.89), 52 (0.99), 52 (0.56), 50.98 (4.48), 49.97 (0.79), 39 (1.48).

Anal. Calcd. for $C_{16}H_{11}N_3O$: C, 73.54; H, 4.24; N, 16.08. Found: C, 73.81; H, 4.22; N, 15.98.

Reaction of **3** with Dimethyl Acetylenedicarboxylate in Dimethylformamide at 100°.

A mixture of 0.8 g. (0.0031 mole) of the red crystalline compound (**16**) and 0.65 g. (0.0046 mole) of dimethyl acetylenedicarboxylate in 20 ml. of anhydrous dimethylformamide was slowly heated to 100° in an oil bath and kept at that temperature for 24 hours. The reaction mixture was cooled, poured into 300 g. of crushed ice, the solid was filtered, washed several times with water and dried. Recrystallization from ethanol gave 1.03 g. (93.3%) of **8** to be identical in all respects to the compound prepared from the hydrofluoroborate salt (**5**) and dimethyl acetylenedicarboxylate in dimethylformamide at 100°.

Reaction of the Phthalazine Reissert Compound (**1**) with 4-Vinylpyridine in the Presence of Concentrated Hydrochloric Acid.

A mixture of 2.61 g. (0.01 mole) of the phthalazine Reissert compound (**1**) and 1.05 g. (0.01 mole) of 4-vinylpyridine in 30 ml. of freshly distilled dioxane was cooled and 10 ml. of concentrated hydrochloric acid was added over 10 minutes. The mixture was then allowed to stir at room

temperature for 36 hours during which time an orange-yellow precipitate was obtained. After cooling the orange-yellow solid (3.3 g.) was filtered on fractional crystallization from chloroform-ethanol 0.92 g. (35.25%) of the red solid (**16**) and another yellow compound, to which structure **17** was assigned, could be separated. The yellow compound (**17**) was triturated with 50% aqueous sodium hydroxide, diluted with water, and neutralized carefully with dilute hydrochloric acid. The solid was filtered washed several times with water, dried, and recrystallized from ethanol to afford another yellow compound (**18**), m.p. 236-237° in 21.1% yield; ir (potassium bromide): 3075 (s), 3025 (m), 2950-2600 (m, broad), 1605 (m), 1590 (vs), 1500 (vs), 1495 (vs), 1350 (s), 1160 (m), 820 (w), 800 (w), 765 (vs), 710 (w) cm^{-1}.

Anal. Calcd. for $C_{23}H_{16}N_4$: C, 79.28; H, 4.63; N, 16.08. Found: C, 78.94; H, 4.72; N, 16.03.

The residue obtained after boiling the crude solid with chloroform-ethanol was purified by recrystallization from a large volume of chloroform-ethanol mixture to give 0.92 g. (35.2/yield) of a red solid (**16**), m.p. 265-268°, identical with that reported above; ^1H nmr (DMSO-d_6): δ 8.59 (s, 1H), 8.35-7.38 (m, 10H); ms: m/e 262.0898 ($C_{16}H_{12}N_3O$, M^+, 1.52%), 261.0894 ($C_{16}H_{11}N_3O$, 7.89), 260.0826 ($C_{16}H_{10}N_3O$, 11.3), 218.0848 (1.5), 157.0593 ($^{12}C_8{}^{13}CH_6N_3$, 2.71), 157.0404 ($C_9H_5N_2O$, 7.22), 156.0562 ($C_9H_6N_3$, 25.61), 130.0497 (3.82), 129.0452 ($C_8H_5N_2$, 9.6), 106.0377 ($^{12}C_6{}^{13}CH_5O$, 7.40), 105.0345 (C_7H_5O, 100), 77.0387 (C_6H_5, 30.8).

Anal. Calcd. for $C_{16}N_{11}N_3O$: C, 73.54; H, 4.24; N, 16.08. Found: C, 73.81; H, 4.22; N, 15.98.

Reaction of the Phthalazine Reissert Compound (**1**) with Cinnamonitrile in the Presence of Concentrated Hydrochloric Acid in Dioxane.

To a well-cooled mixture of 1.3 g. (0.005 mole) of the phthalazine Reissert compound and 0.645 g. (0.005 mole) of cinnamonitrile in 15 ml. of freshly distilled dioxane was added 5 ml. of concentrated hydrochloric acid. The mixture was stirred at room temperature for 24 hours and the orange precipitate was filtered, washed with ether, then with benzene and dried to give 1.13 g. (73.63% yield) of **19**. An analytical sample, m.p. 168-169°, was obtained by several recrystallizations from absolute ethanol. Samples were also recrystallized from methanol and from benzene; ir (potassium bromide): 3400 (w), 3010 (m), 1645 (s), 1610 (m), 1545 (m), 1425 (w), 1305 (m), 1245 (m), 1225 (w), 1155 (vw), 1030 (vw), 780 (m) cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid or trifluoroacetic acid): same as that of **5**; in addition a quartet of δ 4.49 and a triplet at δ 1.43 were present in the sample recrystallized from ethanol; ms: m/e 261.0894 ($C_{16}H_{11}N_3O$, M^+, 0.5%), 156.0561 ($C_9H_6N_3$, 36), 130.0511 ($C_8H_6N_2$, 3.3), 105.0344 (C_6H_5CO, 100).

Anal. Calcd. for $C_{16}H_{12}ClN_3O \cdot 0.2C_2H_5OH$: C, 64.17; H, 4.33; N, 13.69. Found (recrystallized from ethanol): C, 64.01; H, 4.33; N, 13.74.

Anal. Calcd. for $C_{16}H_{12}ClN_3O \cdot 1.5CH_3OH$: C, 60.78; H, 5.25; N, 12.15; Cl, 10.25. Found (recrystallized from methanol): C, 61.25; H, 4.64; N, 12.28; Cl, 10.30.

Anal. Calcd. for $C_{16}H_{12}ClN_3O \cdot 0.33C_6H_6$: C, 66.77; H, 4.36; N, 12.98; Cl, 10.95. Found (recrystallized from benzene): C, 66.45; H, 4.34; N, 12.58; Cl, 10.85.

Similar results were obtained using a 10 fold excess of cinnamonitrile.

Reaction of the Phthalazine Reissert Compound with Concentrated Hydrochloric Acid in Dioxane.

To a cold, well-stirred solution of 1.0 g. (0.0038 mole) of the phthalazine Reissert compound (**1**) in 10 ml. of freshly distilled dioxane was added 5 ml. of concentrated hydrochloric acid slowly. The mixture was allowed to stir overnight and the orange-yellow solid was filtered, washed well with ether, and dried to obtain 1.07 g. of crude **19**. This was finally crystallized from ethanol to obtain pure **19**, m.p. 168-169°. This was found to be identical to the chloride (**19**) in all respects.

Reaction of the Phthalazine Reissert Compound (**1**) with Acrylonitrile in the Presence of Concentrated Hydrochloric Acid.

To a cold, well-stirred solution of 2.61 g. (0.01 mole) of the phthalazine Reissert compound (**1**), 0.53 g. (0.01 mole) of acrylonitrile in 30 ml. of freshly distilled dioxane, 10 ml. of concentrated hydrochloric acid was added over 10 minutes. The mixture was allowed to stir at room temperature for 36 hours, cooled, and the yellow solid was filtered. After drying, the solid was boiled with 100 ml. of chloroform and filtered hot. The residue (0.87 g.) was crystallized from boiling glacial acetic acid several times to get an analytical sample (**20**) m.p. 322-324°; ir (potassium bromide): 3400 (m), 3190 (m), 1635 (s), 1605 (s), 1510 (w), 1460 (m), 1405 (s), 1350 (w), 1255 (m), 1210 (m), 915 (w), 810 (w), 770 (m) cm^{-1}; ^1H nmr (deuteriotrifluoroacetic acid): δ 8.94 (d, 1H, J = 7.8 Hz), 8.60 (s, 1H), 8.01-7.25 (m, 9H); ms: (70 eV; 200°) m/e 288 (20.3%), 287 (100), 286 (5), 272 (10.5), 271 (51.5), 270 (5.71), 269 (21.4), 268 (6.9), 267 (2.9), 244 (4.7), 243 (10.9), 242 (10.9), 241 (3.0), 216 (3.6), 215 (1.7), 214 (3.8), 213 (3.2), 190 (1.3), 189 (1.9), 144 (1.2), 141 (4.2), 140 (32.1), 139 (3.9), 135 (4.5), 129 (2.0), 122 (1.3), 121 (6.5), 115 (6.8), 114 (7.2), 113 (9.0), 108 (1.3), 107 (3.1), 104 (2.0), 103 (4.0), 102 (0.0), 95 (2.1), 89 (6.0), 88 (6.0), 87 (5.3), 86 (3.4), 77 (7.2), 76 (6.1), 75 (5.4), 74 (3.8), 63 (11.5), 51 (9.2), 50 (6.1), 44 (13.0), molecular ion 287.105 ($C_{18}H_{13}N_3O$).

Anal. Calcd. for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.62. Found: C, 75.11; H, 4.74; N, 14.49.

From the filtrate, after fractional crystallization from chloroform-ethanol mixture, were isolated 0.69 g. (26.4%) of the imine (**16**) and 0.3 g. (10.7%) of a colorless flaky solid, m.p. 247° (95% ethanol). The latter compound was found to be identical with an authentic sample of 1-amido-2-benzoyl-1,2-dihydrophthalazine (**21**) prepared from the phthalazine Reissert compound as noted below.

1-Amido-2-benzoyl-1,2-dihydrophthalazine (**21**).

This was synthesized following the procedure of Walters (13) for the preparation of 1-amido-2-benzoyl-1,2-dihydroisoquinoline. To a suspension of 2.0 g. (0.0077 mole) of 1-cyano-2-benzoyl-1,2-dihydrophthalazine (**1**) and 0.8 g. of sodium bicarbonate in 50 ml. of acetone, cooled to an ice-bath, was added 30 ml. of 30% hydrogen peroxide over a period of half an hour. The mixture was stirred at room temperature and 1.2 ml. of 5% sodium bicarbonate solution was added. After stirring for an additional half an hour, the white flaky solid was filtered, washed with acetone and dried to give 1.92 g. (89.4%) of crude **21**. A small amount was crystallized from 95% ethanol to get a pure compound, m.p. 246-247° ir (potassium bromide): 3435 (m), 3310 (m), 1670-1640 (s, broad), 1620 (m), 1585 (m), 1495 (w), 1460 (w), 1390 (s), 1360 (m), 1330 (w), 1280 (w), 1260 (w), 1165 (w), 1120 (m), 940 (m), 910 (w), 885 (w), 860 (w), 780 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ 7.78-7.29 (m, 11H), 7.00 (s, 1H, broad), 6.07 (s, 1H); ms: (70 eV; 105°) m/e 236 (4.8%), 235 (27.5), 131 (3.0), 130 (4.5), 106 (6.6), 105 (100), 103 (3.8), 102 (1.9), 78 (3.9), 77 (53.8), 76 (7.6), 75 (2.1), 51 (14.5).

Anal. Calcd. for $C_{16}H_{13}N_3O_2$: C, 68.80; H, 4.69; N, 15.05. Found: C, 68.62; H, 4.57; N, 15.26.

Reaction of Reissert Compounds with Hydrobromic Acid-Acetic Acid at Room Temperature.

To a suspension of 1.3 g. (0.005 mole) of the phthalazine Reissert compound (**1**) in 5 ml. of glacial acetic acid, 1 ml. of 48% hydrobromic acid was added slowly with vigorous stirring. The mixture turned orange immediately and after a few minutes a clear orange solution was obtained. When the stirring was continued for a few more hours an orange solid was obtained. The mixture was cooled, filtered and finally crystallized from glacial acetic acid to obtain 1.43 g. (83.58% yield) of the bromide (**22**), m.p. 205-207°; ir (potassium bromide): 3200 (w), 3010 (m), 1650 (s), 1605 (s), 1540 (s), 1405 (w), 1240 (w), 1215 (w), 920 (vw), 780 (m) cm^{-1}; ^1H nmr trifluoroacetic acid): same as that of **5**; ms: (70 eV at 150°) m/e 263 (6.47%), 262 (33.16), 261 (5.39), 236 (13.42), 235 (77.09), 207 (17.16), 181 (8.29), 157 (9.95), 156 (82.9), 131 (28.77), 130 (6.88), 128 (5.63), 127 (5.72), 106 (28.93), 105 (100), 102 (9.36), 101 (7.71), 82 (10.20), 80 (11.52), 78 (11.77), 77 (100), 76 (20.72), 75 (18.32), 74 (10.52), 63 (9.1).

Anal. Calcd. for $C_{16}H_{12}BrN_3O$: C, 56.15; H, 3.53; N, 12.28; Br, 23.35. Found: C, 56.33; H, 3.61; N, 12.17. Br, 23.37.

1-Cyano-2-benzoyl-4-methyl-1,2-dihydrophthalazine was similarly converted to the compound **23**, m.p. 198-201° dec (95% ethanol) in 86.2% yield; ir (potassium bromide): 3400 (w), 3190 (w), 3015 (m), 1645 (s), 1610 (m), 1560 (w), 1540 (w), 1420 (w), 1385 (w), 1335 (w), 1330 (w), 1165 (w),

1050 (w), 770 (m) cm^{-1}; ^1H nmr (trifluoroacetic acid): same as that of **6**; ms: (70 eV at 65°) m/e 277 (1.61%), 276 (9.11), 250 (4.19), 249 (24.76), 171 (6.21), 170 (51.61), 145 (5.4), 116 (4.5), 116 (16.85), 106 (13.46), 106 (100), 89 (5.53), 82 (6.61), 77 (80.64), 76 (7.18), 75 (5.32), 51 (35.32).

Anal. Calcd. for $C_{17}H_{14}BrN_3O + 0.25C_2H_5OH$: C, 57.15; H, 4.25; N, 11.43; Br, 21.73. Found: C, 56.81; H, 4.42; N, 11.15; Br, 22.02. In another run the product was crystallized from aqueous acetic acid and a compound, m.p. 209-211° was isolated.

Anal. Calcd. for $C_{17}H_{14}BrN_3O \cdot 0.5H_2O$: C, 55.90; H, 4.14; N, 11.51; Br, 21.88. Found: C, 56.20; H, 4.10; N, 11.05; Br, 21.88.

Reaction of **19**, **22** and **23** with Base.

Trituration of 0.3 g. (0.00098 mole) of the chloride (**19**) with 50% sodium hydroxide resulted in the formation of a thick paste and the deep orange starting material was converted to a colorless solid. It was diluted with water, the solid was filtered, washed thoroughly with water and dried. Finally it was crystallized from 95% ethanol to give the Reissert compound (**1**) almost quantitatively.

The expected Reissert compounds were similarly obtained from the bromides **22** and **23**, respectively in nearly quantitative yields.

Reaction of **19**, **22** and **23** with Dimethyl Acetylenedicarboxylate in Anhydrous Dimethylformamide at 100°.

A mixture of 0.5 g. (0.00146 mole) of the bromide (**22**) and 0.31 g. (0.00219 mole) of dimethyl acetylenedicarboxylate in 5 ml. of anhydrous dimethylformamide were slowly heated to 100° in an oil bath. The mixture was kept at that temperature for 24 hours, cooled and poured into 300 g. of ice-water. The solid was collected by filtration, dried and crystallized from 95% ethanol to give 0.38 g. (72.22% yield) of **8**.

The compounds **19** and **23** were similarly converted to **8** and **11** in 64.5% and 76.17% yields, respectively.

Reaction of **22** with Refluxing Hydrobromic Acid-Glacial Acetic Acid Mixture.

A mixture of 1.0 g. (0.0038 mole) of the phthalazine Reissert compound (**1**) 5 ml. of glacial acetic acid and 1 ml. of 48% hydrobromic acid were refluxed for 2 hours, cooled and filtered. The solid was washed with ether and dried to yield 0.96 g. of a yellow solid. This was boiled with 75 ml. of chloroform and filtered hot. The residue after further purification was found to be phthalazine-1-carboxylic acid hydrobromide, m.p. 196-198° dec, reported (10) m.p. 198-200°. The mother liquor was evaporated to dryness and crystallized from 95% ethanol to give 0.18 g. of the munchnone imine (**16**).

Similar results were obtained when the Reissert compound of 1-methylphthalazine was refluxed with a mixture of 48% hydrobromic acid and glacial acetic acid. In this case, however, the crude 1-methylphthalazine-4-carboxylic acid hydrobromide could not be adequately purified. Only the munchnone imine (**24**) could be isolated and purified, m.p. 277-281° (crystallized first from ethanol and then from glacial acetic acid); ir (potassium bromide): 2970-2915 (w), 2750-2250 (m, broad), 1620 (s), 1605 (s), 1550 (m), 1455 (s), 1420 (s), 1395 (m), 1320 (w), 1240 (m), 1215 (w), 1030 (w), 890 (w), 770 (m) cm^{-1}; ^1H nmr (DMSO-d_6): δ 8.42-7.37 (m, 10H), 2.68 (s, 3H); ms: m/e 276.1094 ($^{12}C_{16}{}^{13}CH_{13}N_3O$, 18.57%), 275.1061 ($C_{17}H_{13}N_3O$, M^+, 100), 274.0978 ($C_{17}H_{12}N_3O$), $(M-1)^+$, 4.93), 232.1001 ($C_{16}H_{12}N_2$, loss of HNCO from $C_{17}H_{13}N_{3O}$, 14.76), 129.0538 ($C_4H_7N_3O$, 25.59), 104.0501 (C_7H_6N, 15.91), 103.0422 (C_7H_5N, 25.59), 102.0348 (C_7H_4N, 8.60).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.26. Found: C, 74.30; H, 4.78; N, 15.30.

Reaction of **24** with Dimethyl Acetylenedicarboxylate in Dimethylformamide at 100°.

Using the procedure by which **15** was converted to **8**, the compound **11** was obtained from **24** in 89.5% yield.

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