Reissert Compound Studies. XXXIV. Base-Catalyzed Reactions of the Phthalazine Reissert Compound

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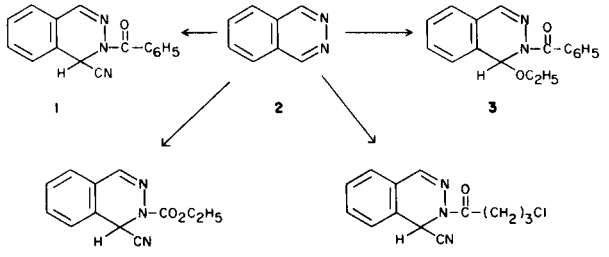
The phthalazine Reissert compound has been used to convert phthalazine to 1-benzylphthalazines, bisbenzylphthalazines, 1,4-disubstituted phthalazines, 1-cyanophthalazine, and a number of other phthalazine derivatives including the tricyclic compound **14**.

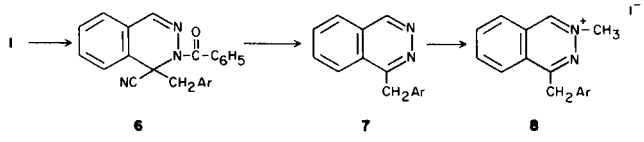
J. Heterocyclic Chem., **17**, 433 (1980).

Some time ago we reported (1) the preparation of a Reissert compound **1** from phthalazine (**2**). In view of the synthetic utility of quinoline and isoquinoline Reissert compounds (2,3), particularly the use of isoquinoline Reissert compounds in the synthesis of alkaloids, alkaloid analogs, and related compounds (4), it was decided to investigate the utility of the phthalazine Reissert compound as a general reagent for the preparation of new phthalazine derivatives.

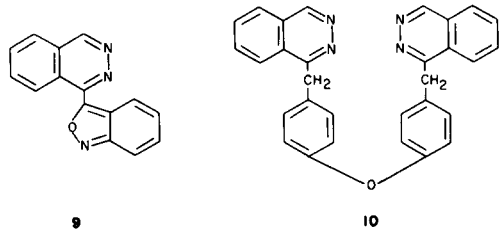
The yields and purity of **1**, obtained by the reaction of phthalazine, benzoyl chloride, and potassium cyanide in methylene chloride-water, were highly inconsistent. The product **1** was found to be contaminated by the pseudo-base which was isolated as **3** after recrystallization from ethanol (5). Pseudo-base formation has been previously noted in Reissert compound formation (3). Addition of a catalytic amount of the phase transfer agent, benzyltriethylammonium chloride, to the reaction mixture gave good yields of uncontaminated **1**. This same Reissert compound **1** as well as the Reissert analog **4** (1) could also be obtained in good yield by use of the trimethylsilyl cyanide method (6). Reissert compound **5** was prepared from phthalazine and 4-chlorobutyryl chloride using both the phase transfer and trimethylsilyl cyanide methods.



The anion of the iosquinoline Reissert compound has been alkylated (2,3) with a variety of benzyl halides to give alkaloids and alkaloid analogs (4). Treatment of the phthalazine Reissert compound **1** with benzyl halides and sodium hydride in dimethylformamide has given adducts of the type **6** which can be hydrolyzed with sodium hydroxide to **7**. Compounds **6**,**7** and the methiodides **8** are recorded in Table I. That the methiodides are alkylated on



N_3 rather than N_2 is supported by nmr evidence. The H_1 proton in isoquinoline is at δ 9.13 in phthalazine the H_1 and H_4 protons are at δ 9.68, and in 1-(3,4-dimethoxybenzyl)phthalazine the H_4 proton is at δ 9.36. In the methiodides, the isoquinoline methiodide H_1 proton shifts to δ 9.92, the phthalazine methiodide H_1 proton shifts to δ 10.62 and in the 1-(3,4-dimethoxybenzyl)phthalazine methiodide the proton at H_4 shifts to δ 10.54, indicating that methylation in the 1-substituted phthalazines had taken place at the nitrogen adjacent to C_4. We observed similar downfield shifts of H_4 with the methiodides of other 1-substituted phthalazine. Hydrolysis of **6** (Ar = 2-$NO_2C_6H_4$) by the usual method (2) gave what appears to be **9**. Cava and coworkers (7) reported a similar compound from hydrolysis attempts in the isoquinoline series. Using Cava's modification (7) for the hydrolysis gave the expected product **7** (Ar = 2-$NO_2C_6H_4$). Using the alkylation and hydrolysis sequence, we recently reported the synthesis of 3-azapapaverine (8). In a similar manner the Reissert compound of 6,7-dimethoxyphthalazine (8) has been converted to 1-methyl-6,7-dimethoxyphthalazine.



Alkylation of the anion of **1** with 4,4'-oxydibenzyl bromide followed by hydrolysis gave **10** isolated as its methiodide. Using this same procedure, alkylation of the anion of **1** with **11** gave **12**. In a similar manner **13** was also prepared by bis-alkylation of **1**.

The above reactions indicate the synthetic utility of the phthalazine Reissert compound in the synthesis of phthalazine analogs of both the benzylisoquinolines and the bis-

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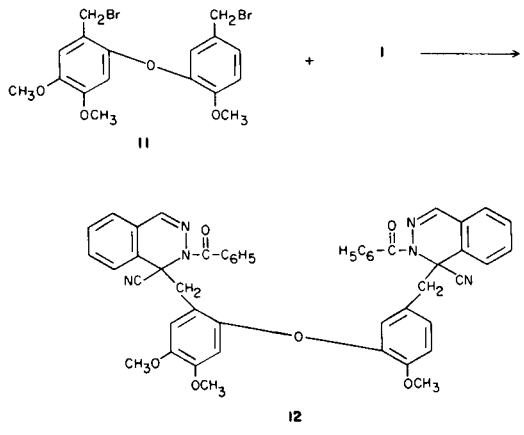
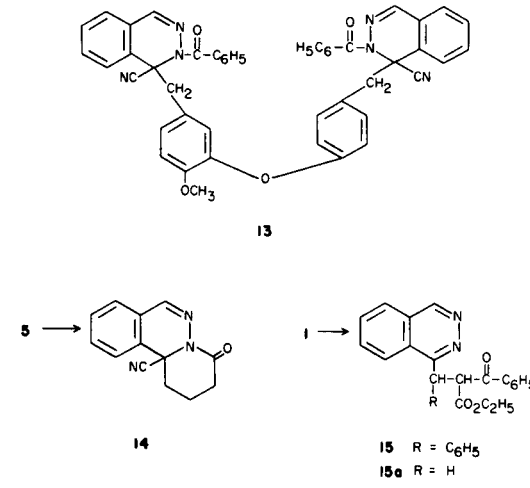




benzylisoquinolines.

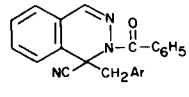
The phthalazine Reissert compound would also appear to be an attractive intermediate for the synthesis of tricyclic compounds starting with phthalazine. Treatment of the Reissert compound **5** with sodium hydride in dimethylformamide led to intramolecular alkylation, as in the isoquinoline case (9), to give **14**. Condensation of **1** with ethyl cinnamate in the presence of phenyl lithium in dioxane gave rise to the Michael addition product **15** rather than to a cyclization product. Ethyl acrylate also undergoes Michael addition under these conditions to give **15a**. Reaction of **1** with acrylonitrile in the presence of potassium *t*-butoxide in dimethyl sulfoxide, however, has been reported (10) to give a cyclic product.

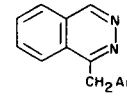
It is possible to use the Reissert alkylation sequence to prepare 1,4-disubstituted phthlazines. Both 1-methylphthalazine [prepared from **1** (1)] and **7** (Ar = 3,4-$(CH_3O)_2C_6H_3$) were converted into their Reissert compounds **16** (R = H) by the trimethylsilyl cyanide method. Alkylation of **16** (R = H, R′ = CH_3) with methyl iodide and sodium hydride in dimethylformamide gave **16** (R = R′ = CH_3) which was hydrolyzed to 1,4-dimethylphthalazine.

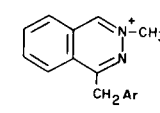
Treatment of the anion of the phthalazine Reissert compound **1** with benzaldehyde followed by base hydrolysis gave 1-phthalazylphenylcarbinol (1). Similar treatment of the anion of **1** with 3,4-dimethoxybenzaldehyde gave, after

Table I

Alkylation of Phthalazine Reissert Compounds

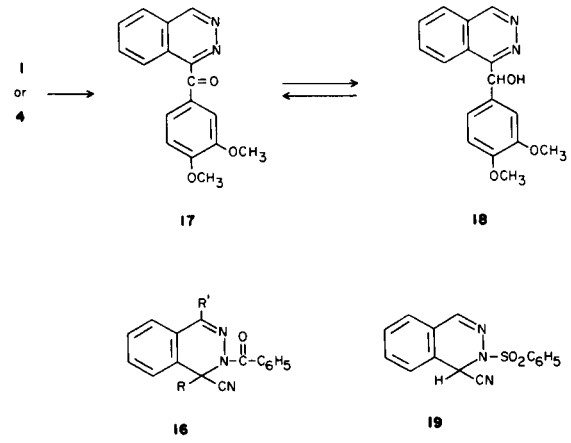






Ar	M.p., °C (a)	Yield %	Calcd. / *Anal.* Found C	H	N	M.p., °C (a)	Yield %	Calcd. / *Anal.* Found C	H	N	M.p., °C (b)	Calcd. / *Anal.* Found C	H	N
4-BrC_6H_4 (c)	146-147	78	64.19	3.75	9.76	132-133	33	60.22	3.71	9.36	221-224	43.56	3.20	6.35
			64.28	3.94	9.80			60.24	3.82	9.37		43.36	3.21	6.28
4-NO_2 (c)	178-179	67	69.69	4.07	14.13	176-178	70	67.91	4.18	15.84	191-193	47.19	3.47	10.32
			69.23	4.22	13.93			67.91	4.35	15.73		47.14	3.52	10.44
2,3-$(CH_3O)_2C_6H_3$ (c)	133-134	65	72.98	5.21		not purified					202-204	51.20	4.53	6.64
			73.05	5.14								51.21	4.49	6.63
3-CH_3O-4-(4-$CH_3C_6H_4O$)C_6H_3 (c)	not purified					not purified					175-178 (d)	60.37	4.86	2.81
												60.03	5.02	2.91
3,4-$(CH_3O)_2C_6H_3$	not purified					152-153 (e)	60	72.84	5.75	9.99	238-239 (f,g)			6.64
								72.64	5.74	10.09				6.64
2-$NO_2C_6H_3$	158-159	79	69.69	4.07		148-149 (f)	98	67.91	4.18	15.84	217-220 (f)	47.19	3.46	
			69.75	4.17				67.88	4.27	15.77		47.25	3.43	
6-NO_2-3,4-$CH_3O_2C_6H_3$	not purified					203-206 (h)	58	62.13	3.58	13.58	219-220	45.25	3.13	9.31
								61.98	3.73	13.31		45.16	3.18	9.26

(a) Recrystallized from ethanol unless otherwise noted. (b) Recrystallized from methanol-diethyl ether unless otherwise noted. (c) Some of these compounds were first prepared by F. D. Popp and H. R. Heller at Clarkson College of Technology. (d) Recrystallized from ethyl acetate-methanol-diethyl ether. (e) Nmr (deuteriochloroform): δ 9.36 (s, 1H), 8.1-7.66 (m, 4H), 6.9-6.75 (m, 3H), 4.63 (s, 2H), 3.77 (s, 6H). (f) Recrystallized from methanol. (g) Nmr (deuteriochloroform): δ 10.54 (s, 1H), 8.71-8.28 (m, 4H), 7.03 (s, 1H), 6.82 (s, 2H), 4.73 (s, 2H), 4.55 (s, 3H), 3.73 (s, 6H). (h) Recrystallized from chloroform-ethanol.



hydrolysis of the crude ester formed, the ketone **17** rather than the alcohol **18**. Such apparent oxidation during the workup has also been observed with this aldehyde in the isoquinoline series (11). Treatment of the Reissert analog **4** with 3,4-dimethoxybenzaldehyde and sodium hydride in dimethylformamide also led after workup, to **17**. Reduction of the ketone **17** with sodium borohydride gave the carbinol **18** which was oxidized back to **17** by chromium trioxide in pyridine at room temperature.

Treatment of the Reissert analog **19** with base gave a convenient route to 1-cyanophthalazine. This is analogous to the similar conversion of isoquinoline to 1-cyanoisoquinoline.

EXPERIMENTAL

General.

All melting points were determined in a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses were performed by Spang Microanalytical Laboratories, Ann Arbor, Michigan. The infrared absorption spectra were determined with Perkin-Elmer Model 710B spectrometer and all ^1H nmr spectra were recorded on a 60 MHz R-24B Hitachi-Perkin-Elmer spectrometer.

1-Cyano-2-benzoyl-1,2-dihydrophthalazine (1).

a.

Reaction of potassium cyanide and phthalazine (**2**) in methylene chloride and water, with benzoyl chloride as previously described (1) gave in addition to **1**, m.p. 162-163° (from ethanol), reported (1) m.p. 163-164°; the compound **3**, m.p. 91° (from ethanol); ir (potassium bromide): 3000-2925, 1665, 1605 cm^{-1}; nmr (deuteriochloroform): δ 7.70-7.23 (m, 9H), 6.83 (s, 1H), 3.73 (q, 2H), 1.27-0.81 (t and s, 4H).

Anal. Calcd. for $C_{17}H_{16}N_2O_2$: C, 72.83; H, 5.75; N, 9.99. Found: C, 72.83; H, 5.75; N, 9.98.

b.

Using the above procedure (1) and adding 3% (by weight of potassium cyanide used) of benzyltriethylammonium chloride (4) gave a 65-70% yield of Reissert compound **1**; ir (potassium bromide): 2965, 1655, 1600 cm^{-1}; nmr (deuteriochloroform): δ 7.83-7.40 (m, 10H), 6.68 (s, 1H).

A mixture of 20.0 g. (0.154 mole) of phthalazine, 200 ml. of dry dichloromethane, a catalytic amount of anhydrous aluminum chloride and 30.45 g. (0.308 mole) of trimethylsilyl cyanide was stirred at room temperature and after 2 minutes, 43.2 g. (0.308 mole) of benzoyl chloride was slowly added. After stirring at room temperature for 24 hours, the mixture was washed with water, 5% hydrochloric acid, water, 5% sodium hydroxide and water. The organic phase was dried over sodium sulfate and evaporated *in vacuo* to give 35.2 g. (87.7%) of **1**.

1-Cyano-2-ethoxycarbonyl-1,2-dihydrophthalazine (**4**).

a.

Using the previously described procedure (1) with the addition of 3% (by weight of potassium cyanide used) of benzyltriethylammonium chloride gave a 37% yield of **4**, m.p. 137°, reported (1) m.p. 137-138°; ir (potassium bromide): 3000, 2950, 1700, 1575 cm^{-1}.

b.

Using the procedure described above 0.01 mole of phthalazine, a catalytic amount of anhydrous aluminum chloride, 0.011 mole of trimethylsilyl cyanide, and 0.0102 mole of ethyl chloroformate gave a 56.3% yield of **4**.

Reissert Compound **5**.

Using the standard procedure, 2.0 g. (0.0154 mole) of phthalazine, 4.0 g. (0.06 mole) of potassium cyanide, and 0.12 g. benzyltriethylammonium chloride in 25 ml. of methylene chloride and 6.2 ml. of water was treated with 8.46 g. (0.06 mole) of 4-chlorobutyryl chloride to give 1.75 g. (44%) of **7**, m.p. 115° (from ethanol); ir (potassium bromide): 2950, 1665, 1610 cm^{-1}; nmr (deuteriochloroform): δ 7.67 (s, 1H), 7.54-7.23 (m, 4H), 6.60 (s, 1H), 3.64 (t, 2H, J = 6.87 Hz), 3.11-2.87 (m, 2H), 2.19 (t, 2H, J = 6.67 Hz).

Anal. Calcd. for $C_{13}H_{12}N_3ClO$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.61; H, 4.52; N, 16.08.

The trimethylsilyl cyanide method gave a 93% yield of **5**.

Preparation of Compounds in Table I.

The Reissert compound **1** was reacted with the appropriate benzyl halides using sodium hydride in dimethylformamide at room temperature as previously described for the alkylation of the isoquinoline Reissert compound (12). The compounds of the type **6** are included in Table I. Hydrolysis of **6** with alcoholic potassium hydroxide (12) gave the compounds of the type **7** in Table I. When this hydrolysis procedure was applied to **6** (Ar = 2-$NO_2C_6H_4$) a compound, m.p. 156-157° (from methanol), believed to be **9** was obtained in 39% yield.

Anal. Calcd. for $C_{15}H_9N_3O \cdot 0.33H_2O$: C, 71.14; H, 3.85; N, 16.59. Found: C, 71.37; H, 3.58; N, 16.48.

In order to obtain **7** (Ar = 2-$NO_2C_6H_4$) 0.005 mole of the appropriate **6** and 1.68 g. of potassium hydroxide in 42 ml. of methanol were refluxed for 10 minutes and poured into 200 ml. of ice water to give the product in an almost quantitative yield. This same procedure was used to prepare **7** (Ar = 6-NO_2-3,4-$CH_2O_2C_6H_2$).

The methiodides **8** shown in Table I were prepared in the conventional manner.

1-Cyano-1-methyl-2-benzoyl-1,2-dihydro-6,7-dimethoxyphthalazine.

A solution of 0.6 g. (0.00187 mole) of 1-cyano-2-benzoyl-6,7-dimethoxyphthalazine (8) and 0.27 g. (0.00187 mole) of methyl iodide in 10 ml. of anhydrous dimethylformamide was cooled to 5-10° and 0.09 g. (0.00187 mole) of 50% sodium hydride in oil was added. The mixture was stirred for 1.5 hours at room temperature and poured into 200 g. of crushed ice. Filtration gave a quantitative yield of the title compound, m.p. 165.5-167° (methylene chloride-ethanol); ir (potassium bromide): 2980, 2850, 1655, 1620, 1600, 1520, 1405, 1370, 1335, 1295, 1180 cm^{-1}; nmr (deuteriochloroform): δ 7.77-7.16 (m, 7H), 6.72 (s, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 1.97 (s, 3H).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.91; H, 5.15; N, 12.48.

1-Methyl-6,7-dimethoxyphthalazine.

A mixture of 0.40 g. (0.0012 mole) of the above alkylated Reissert compound and 4 g. of potassium hydroxide in 12 ml. of ethanol and 12 ml. of water was refluxed for 3 hours and worked up in the usual manner to give 0.20 g. (82%) of the title compound, m.p. 161-162° (methylene chloride-

ethanol); ir (potassium bromide): 1610, 1505, 1420, 1255, 1175 cm^{-1}; nmr (deuteriochloroform): δ 9.45 (s, 1H), 9.19 (s, 1H), 7.21 (s, 1H), 4.08 (s, 6H), 2.97 (s, 3H).

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 64.69; H, 5.92; N, 13.72. Found: C, 64.43; H, 5.85; N, 13.61.

Preparation of bis-Benzylphthalazines.

Using the procedure of Smith and Popp (14) 0.02 mole of **1**, 0.01 mole of 4,4'-oxydibenzyl bromide and 0.02 mole of 52% sodium hydride in oil were reacted in 50 ml. of dimethylformamide. The product, m.p. 137-140°; ir (potassium bromide): 3075, 2945, 1665, 1600, 1500, 1350, 1425 cm^{-1}; nmr (deuteriochloroform): δ 7.72-6.61 (m, 28H), 3.59 (q, 4H), was not purified but was used directly in the next step. The crude alkylation product was hydrolyzed using aqueous-alcoholic potassium hydroxide to give **10** ir (potassium bromide): 3450-3400, 1600, 1505 cm^{-1} in 61% overall yield from **1**. Treatment of the crude **10** with methyl iodide in methanol gave a methiodide, m.p. 166-170°.

Anal. Calcd. for $C_{32}H_{28}N_4I_2O$: C, 52.05; H, 3.82; N, 7.59. Found: C, 51.76; H, 4.11; N, 7.30.

In a similar manner **1** and **11** with sodium hydride in dimethylformamide gave a 73.5% yield of **12**, m.p. 139-142° (from ethanol); ir (potassium bromide): 3625-3400, 2950, 2850, 1670-1660, 1610, 1510 cm^{-1}; nmr (deuteriochloroform): δ 7.75-5.90 (m, 25H), 3.82-3.20 (m, 13H, 2-CH_2 and 3-OCH_3).

Anal. Calcd. for $C_{49}H_{38}N_6O_6 \cdot C_2H_5OH$: C, 71.81; H, 5.20; N, 9.85. Found: C, 71.67; H, 4.81; N, 9.44.

Also prepared in a similar manner from **1** and 4',5-dichloromethyl-2-methoxydiphenyl ether was **13** (66% yield), m.p. 148-151° (ethanol); ir (potassium bromide): 3065, 2950, 1670, 1615, 1510, 1350, 1285, 920 cm^{-1}; nmr (deuteriochloroform): δ 7.73-6.11 (m, 27H), 3.68-3.37 (m, 7H, 2-CH_2 and OCH_3).

Anal. Calcd. for $C_{47}H_{34}N_6O_4$: C, 75.59; H, 4.58; N, 11.25. Found: C, 75.44; H, 4.67; N, 11.06.

Cyclization of **5** to **14**.

A mixture of 0.01 mole of **5** and 0.01 mole of 52% sodium hydride in oil in 42 ml. of dimethylformamide were treated as described (9) to give a 59% yield of **14**, m.p. 172-174° (methanol); ir (potassium bromide): 3030, 2980, 1680, 1605 cm^{-1}; nmr (deuteriochloroform): δ 8.1 (s, 1H), 7.52-7.20 (m, 4H), 3.25-2.15 (m, 6H).

Anal. Calcd. for $C_{13}H_{11}N_3O$: C, 69.32; H, 4.92; N, 18.66. Found: C, 69.28; H, 4.85; N, 18.56.

A small amount of highly insoluble material, m.p. > 300°; ir (potassium bromide): 1680 cm^{-1}, was also obtained but not characterized.

Condensation with Ethyl Cinnamate.

A solution of 1.5 g. (0.0058 mole) of **1** in 30 ml. of anhydrous dioxane and 30 ml. of anhydrous ether was cooled to −20° with stirring and 4.8 ml. of a 1.75 *M* solution of phenyllithium in ether and benzene was introduced slowly under a nitrogen atmosphere. The temperature was not allowed to rise beyond −10°. After 5-10 minutes a solution of 1.1 ml. (0.0062 mole) of ethyl cinnamate in 3.5 ml. of dioxane was added slowly. The mixture was stirred and allowed to attain room temperature slowly. After stirring for 10 hours, 15 g. of dry ice and 15 g. of water were added and the mixture was extracted with ether. The aqueous layer was again extracted with chloroform and the extracts were combined. Some ethanol was added and on standing 0.93 g. (38%) of a α-carbethoxy-β-(1-phthalazyl)-β-phenylpropiophenone (**15**), m.p. 161° from benzene-hexane, was obtained; ir (potassium bromide): 1720, 1675, 1600, 1450 cm^{-1} nmr (deuteriochloroform): δ 9.1 (s, 1H), 8.3-7.1 (m, 14H), 6.32-5.75 (m, 2H), 4.1-3.68 (m, 2H), 1.15-0.78 (m, 3H).

Anal. Calcd. for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40. Found: C, 76.19; H, 5.54.

A red compound was also obtained in trace amounts together with unreacted **1**.

Condensation with Ethyl Acrylate.

Replacing ethyl cinnamate by ethyl acrylate in the above procedure gave a white solid (**15a**), m.p. 152-154° (benzene-hexane); ir (potassium bromide): 1730, 1675, 1601, 1580, 1450 cm^{-1}; nmr (deuteriochloroform): δ 9.25 (s, 1H), 8.18-8.0 (m, 5H), 7.82-7.77 (m, 4H), 5.70 (t, 1H), 4.29-3.97 (m, 4H), 1.13 (t, 3H, J = 7.5 Hz).

Anal. Calcd. for $C_{20}H_{18}N_2O_3 \cdot 0.5C_6H_6$: C, 73.97; H, 5.67; N, 7.50. Found: C, 73.63; H, 5.79; N, 7.56.

A trace of red solid was also obtained.

1-Cyano-2-benzoyl-4-methyl-1,2-dihydrophthalazine (**16**, R' = CH_3, R = H).

As described above 2.0 g. (0.014 mole) of 1-methylphthalazine (1), 0.42 g. of trimethylsilyl cyanide, a catalytic amount of anhydrous aluminum chloride, and 5.86 g. (0.042 mole) of benzoyl chloride in 30 ml. of anhydrous methylene chloride gave 3.2 g. (84%) of **16** (R = H, R' = CH_3), m.p. 147-148° (ethanol); ir (potassium bromide): 3050, 3020, 2970, 1655, 1600, 1570, 1495, 1455, 1395, 1360, 1310, 1120, 880, 785 cm^{-1}; nmr (deuteriochloroform): δ 7.79-7.28 (m, 9H), 6.60 (s, 1H), 2.41 (s, 3H).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.16; H, 4.76; N, 15.27. Found: C, 74.54; H, 4.80; N, 15.33.

1-Cyano-2-benzoyl-4-(3',4'-dimethoxybenzyl)-1,2-dihydrophthalazine (**16**, R = H, R' = 3,4-$(CH_3O)_2C_6H_3CH_2$).

Using the above trimethylsilyl cyanide method with 1-(3',4'-dimethoxybenzyl)phthalazine (**7**, Ar = 3,4-$(CH_3O)_2C_6H_3$) gave an 89% yield of **16** (R = H, R' = 3,4-$(CH_3O)_2C_6H_3CH_2$), m.p. 139-140° (ethanol); ir (potassium bromide): 1655, 1600, 1520 cm^{-1}, nmr (deuteriochloroform): δ 7.80-7.27 (m, 9H), 6.75 (broad s, 3H), 6.62 (s, 1H), 4.04 (s, 2H), 3.78 (s, 3H), 3.72 (s, 3H).

Anal. Calcd. for $C_{25}H_{21}N_3O_3$: C, 72.98; H, 5.15; N, 10.21. Found: C, 73.03; H, 5.18; N, 10.18.

1-Cyano-1,4-dimethyl-2-benzoyl-1,2-dihydrophthalazine (**16**, R = R' = CH_3).

To a mixture of 1.6 g. (0.0058 mole) of **16** (R = H, R' = CH_3), and 0.82 g. (0.0058 mole) of methyl iodide in 25 ml. of anhydrous dimethylformamide was added 0.28 g. of sodium hydride (50% dispersion in oil) and the mixture was stirred at room temperature for 1.5 hours and poured onto ice. Filtration gave 1.4 g. (83.4%) of **16** (R = R' = CH_3), m.p. 172-173° (ethanol); ir (potassium bromide): 1650, 1600, 1450 cm^{-1}; nmr (deuteriochloroform): δ 7.73-7.26 (m, 9H), 2.26 (s, 3H), 1.92 (s, 3H).

Anal. Calcd. for $C_{18}H_{15}N_3O$: C, 74.72; H, 5.23; N, 14.53. Found: C, 74.55; H, 5.26; N, 14.53.

1,4-Dimethylphthalazine.

A mixture of 1.10 g. (0.0038 mole) of **16** (R = R' = CH_3) in 30 ml. of hot ethanol and 10 g. of potassium hydroxide in 30 ml. of water was refluxed for 2 hours. Addition of water and concentration gave after extraction with chloroform 0.42 g. (70%) of 1,4-dimethylphthalazine, m.p. 107-108° (benzene-petroleum ether), reported (15) m.p. 106-107°; ir (potassium bromide): 1600, 1575, 1445, 1390 cm^{-1}; nmr (deuteriochloroform): δ 8.1-7.6 (m, 4H), 2.84 (s, 6H).

1-Phthalazyl 3,4-Dimethoxyphenyl Ketone (**17**).

a.

To a mixture of 2.0 g. (0.0077 mole) of **1** and 1.29 g. (0.0077 mole) of 3,4-dimethoxybenzaldehyde in 40 ml. of anhydrous dimethylformamide was added 0.36 g. (0.0077 mole) of sodium hydride (52% dispersion in oil) and the mixture was stirred for 6 hours and poured into ice. A crude ester; ir (potassium bromide): 1710 cm^{-1}, was obtained and used directly in the next step.

The crude ester was dissolved in 75 ml. of ethanol and refluxed for 2 hours with 12 g. of potassium hydroxide in 75 ml. of water. The mixture was diluted with water and concentrated. Extraction with chloroform gave, after washing with water, drying, and concentration, an oil that was finally crystallized from chloroform-methanol to give 0.86 g. (38%) of **17**, m.p. 214-215°; ir (potassium bromide): 1650, 1595, 1550, 1515, 1460, 1420, 1345, 1275, 1210 cm^{-1}; nmr (deuteriochloroform): 9.53 (s, 1H), 7.95-6.72 (m, 7H), 3.95 (s, 6H).

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.80; N, 9.52. Found: C, 68.96; H, 5.01; N, 9.43.

b.

Reaction of **4** with 3,4-dimethoxybenzaldehyde as described above gave a 51% yield of **17**, m.p. 212-213° (ethanol), identical in all respects with the solid obtained from **1**.

Anal. Calcd. for $C_{17}H_{14}N_2O_3$: C, 69.38; H, 4.80; N, 9.52. Found: C, 69.14; H, 5.08; N, 9.49.

1-Phthalazyl 3,4-Dimethoxyphenyl Carbinol (**18**).

A suspension of 0.20 g. (0.00068 mole) of the ketone **17** in 15 ml. of methanol was cooled to 0-5° and 0.25 g. of sodium borohydride was added in small poritons. The mixture was stirred in the cold until a clear solution was obtained and then was stirred for 30 minutes at room temperature. A 5% hydrochloric acid solution was added and the methanol was removed *in vacuo*. After the addition of 25 ml. of water the mixture was extracted with chloroform. Removal of the chloroform gave 0.145 g. (72%) of **18**, m.p. 235-236° (from ethanol); ir (potassium bromide): 3425, 2980, 1590, 1515, 1270, 1165, 1040, 810, 780 cm^{-1}.

Anal. Calcd. for $C_{17}H_{16}N_2O_3 \cdot 0.5C_2H_5OH$: C, 67.69; H, 6.00; N, 8.77. Found: C, 67.80; H, 5.97; N, 8.59.

Oxidation of Alcohol **18** to Ketone **17**.

A mixture of 90 mg. (0.0003 mole) of the alcohol **18**, 200 mg. of chromium trioxide, and 5 ml. of pyridine was stirred overnight at room temperature and poured into 30 ml. of cold water. The mixture was extracted with ether and the ether was washed with 10% sodium carbonate solution and with water, and dried over anhydrous magnesium sulfate. Removal of the ether and trituration with ethanol gave 68 mg. (77%) of **17**, m.p. 214-215°, identical in all respects with the compound reported above from both **1** and from **4**.

1-Cyanophthalazine.

A mixture of 0.60 g. (0.002 mole) of **19** (1) and 0.096 g. of sodium hydride in 10 ml. of xylene was refluxed for 1 hour, cooled, sodium benzenesulfinate was removed by filtration, and the filtrate was concentrated to give 0.28 g. (90%) of 1-cyanophthalazine, m.p. 156° (ether), reported (16) m.p. 156-157°; ir (potassium bromide): 2250 (w), 1605, 1410 cm^{-1}; nmr (deuterichloroform): δ 9.61 (s, 1H), 8.35-8.02 δ (m, 4H).

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