

## Synthesis, Separation and Structure of the Isomeric 6- and 7-Trifluoromethyl-1-chloro-4-methoxyphthalazines.

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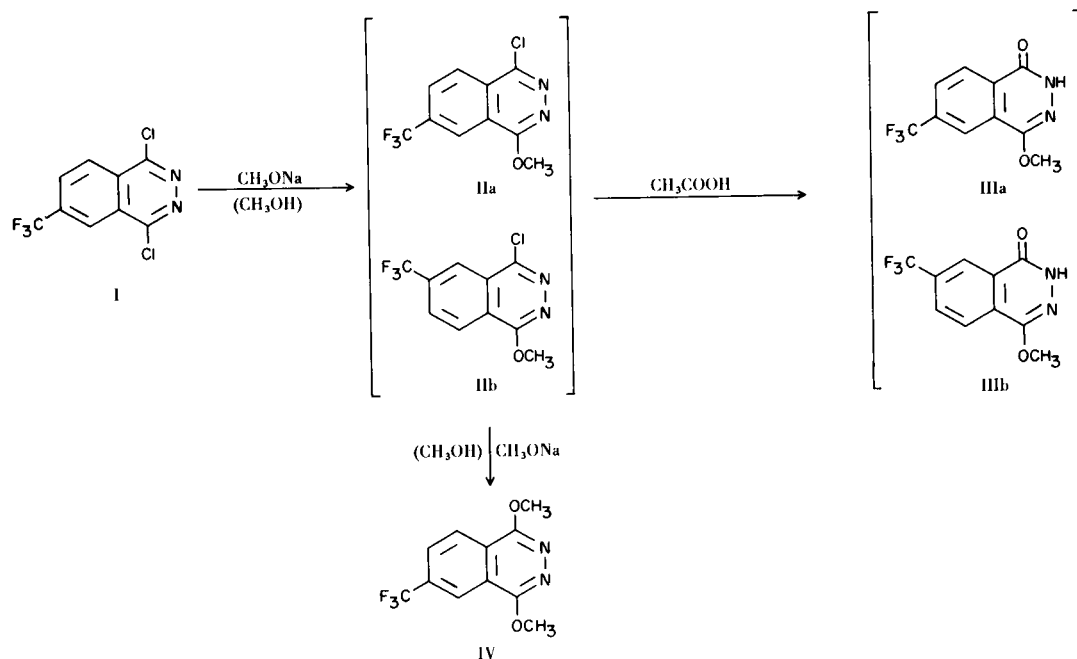
1-Chloro-4-methoxyphthalazines, obtained by the action of sodium methoxide on 1,4-dichlorophthalazines, have generally been used as intermediates for the synthesis of 1,4-dihydrazinophthalazines (1,2). When the benzene moiety is monosubstituted, two isomeric 1-chloro-4-methoxyphthalazines are obtained (3,4). The synthesis of 1,4-dihydrazino-6-trifluoromethylphthalazine by the action of hydrazine hydrate on the mixture of the two chloro-methoxytrifluoromethylphthalazines (IIa and IIb) was previously described (4). Since the final substitution of chloro- and methoxy- groups gives a single dihydrazino compound, the above isomers were not isolated.

The subject of the present paper is the isolation of the two isomers IIa and IIb and their structural assignment. The existence of two isomers in the reaction mixture mentioned above was shown by the presence of two methoxyl peaks in the NMR spectrum in pentadeuterio-pyridine. The isomers IIa and IIb were separated by preparative TLC but neither their NMR spectra nor their IR spectra in chloroform showed any appreciable differences, thus preventing their structure elucidation. The

mixture of IIa and IIb was then transformed by the action of glacial acetic acid into a mixture of the two 4-methoxy-1(2*H*)-phthalazinones IIIa and IIIb. These isomers were separated by preparative TLC and the assignment of the structure was made by means of their NMR spectra. Since the action of glacial acetic acid on IIa gave exclusively IIIa and IIb yielded only IIIb, the assignment of the correct structure to IIIa and IIIb also permits structural assignments to IIa and IIb. Compounds IIIa and IIIb exist either in the solid state or in solution in the oxo form as shown by a comparison of their IR and UV spectra with those of 4-methoxy-1(2*H*)-phthalazinone (5,6). By treating the mixture of IIa and IIb with an equivalent amount of sodium methoxide, 1,4-dimethoxy-6-trifluoromethylphthalazine (IV) was obtained.

The assignment of the structure to IIIa and IIIb was made by means of the NMR spectra in pentadeuterio-pyridine solution. The signals of the aromatic hydrogens are reported in Fig. 1 together with their proton assignments. These assignments are based on the fact that the tautomeric oxo form is predominant in solution, as well

SCHEME I



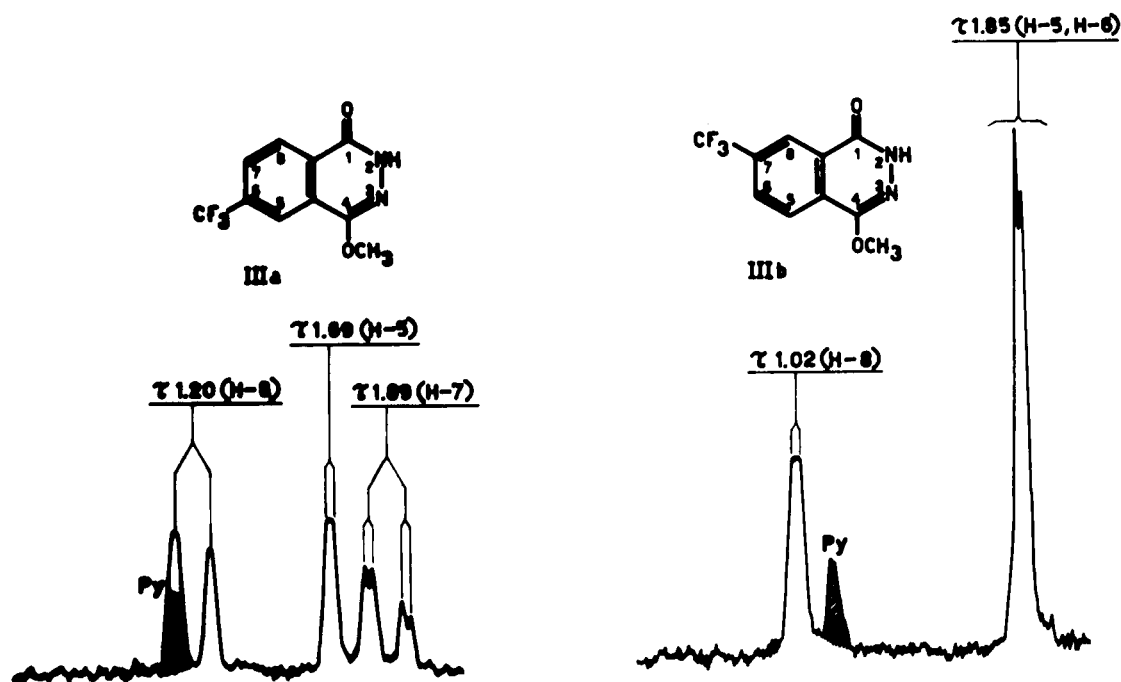


Figure 1. NMR spectra of the aromatic hydrogens of IIIa and IIIb in pentadeuteriopyridine solution.

as on the effect that the substituents have on the chemical shift of the aromatic hydrogens and on the analysis of the splitting patterns (7). It is to be noted that the NMR data can be interpreted only on the basis of the existence of the compounds in the oxo form. From the known strong deshielding effect of a cyclic C=O group on the hydrogen in a *peri* position (8) and from the deshielding effect of the trifluoromethyl group on the *ortho* hydrogen (about 0.4 ppm. in the case of 4-trifluoromethylphthalic acid (9)) the doublet at  $\tau$  1.20 ( $J_{ortho} = 8$  Hz) (11) is attributed to H-8 of IIIa (which is deshielded by the *peri* situated carbonyl group) and the doublet at  $\tau$  1.02 ( $J_{meta}$  assumed about 2 Hz) (12) to H-8 of IIIb (which is subjected to the additive effect of the trifluoromethyl group in the *ortho* position). The signal at  $\tau$  1.85 of compound IIIb is attributed to H-5 and H-6, while the doublet at  $\tau$  1.69 ( $J_{meta} = 2$  Hz) (12) and the pair of doublets at  $\tau$  1.89 ( $J_{ortho} = 8$  Hz,  $J_{meta} = 2$  Hz) of IIIa are attributed to H-5 and to H-7, respectively. Consequently, structure IIa is assigned to the phthalazine giving compound IIIa and structure IIb to that giving compound IIIb.

#### EXPERIMENTAL

Melting points were determined in capillary tubes and are uncorrected. IR spectra were obtained with a Perkin-Elmer model 157 spectrophotometer, as Nujol mulls or chloroform solutions. UV spectra were recorded with a Unicam S.P.800 spectrophotometer. NMR spectra were obtained with a Varian A-60 spectro-

meter in pentadeuteriopyridine using TMS as an internal reference ( $\tau = 10.00$  ppm.). Analytical thin-layer chromatographic (TLC) separations were performed on Silica-gel HF/UV<sub>254</sub> to a distance of 10.0 cm. The spots were detected by visual examination under UV light and after spraying with a 0.1 *N* solution of iodine followed by concentrated sulfuric acid. Preparative TLC was performed on glass plates (20 x 20 cm.) coated with about 1 mm. layer of Silica-gel HF/UV<sub>254</sub> applying about 60 mg. of the mixture and developing the plates to a distance of 15.0 cm.; zones were visualized under UV light.

1-Chloro-4-methoxy-6-trifluoromethylphthalazine (IIa) and 1-Chloro-4-methoxy-7-trifluoromethylphthalazine (IIb).

1,4-Dichloro-6-trifluoromethylphthalazine (I) (2.9 g.) was treated with sodium methoxide in methanol as previously described (4) and 2.2 g. (77%) of product (m.p. 135°) was obtained.

Anal. Calcd. for C<sub>10</sub>H<sub>6</sub>ClF<sub>3</sub>N<sub>2</sub>O: C, 45.73; H, 2.30; Cl, 13.50; F, 21.70; N, 10.67. Found: C, 45.55; H, 2.50; Cl, 13.18; F, 21.78; N, 10.40.

According to TLC (developed twice with isopropyl ether) a mixture of two compounds with  $R_f$  0.52 and  $R_f$  0.64 ( $R_f$  relative to phthalide 1.15 and 1.45), had been formed.

Separation of Compounds IIa and IIb.

The above product was recrystallized from 60 ml. of isopropyl ether and the first crop of crystals (880 mg.) was subjected to preparative TLC. A solution of 500 mg. of the product in 8 ml. of chloroform was applied to eight plates and developed with a 1:1 mixture of benzene and isopropyl ether. The silica-gel corresponding to three zones with  $R_f$  0.28-0.50 (a),  $R_f$  0.50-0.60 (b) and  $R_f$  0.60-0.73 (c) were separately collected from all plates, combined and eluted with 100 ml. of a 9:1 mixture of chloroform and methanol. From (a) and (b) 320 mg. and 110 mg. of product, respectively, were collected. These were found to be again mix-

tures of the two isomers. Fraction (c) yielded 55 mg. of compound IIa, (m.p. 123-127°) which gave only one spot on TLC ( $R_f = 0.64$ ); IR (chloroform), 1550 ( $\nu$  C=N), 1320 and 1140 ( $\nu$  C-F), 1140 ( $\nu$  C-O), 870 and 840  $\text{cm}^{-1}$  ( $\gamma$  C-H aromatic); NMR,  $\tau$  5.76 (s, 3H, CH<sub>3</sub>O),  $\tau$  2.0-1.5 (m, 3H, H aromatic). The product obtained from (a) was rechromatographed on five plates by applying the same procedure and three zones with  $R_f$  0.52 (d),  $R_f$  0.52-0.64 (e) and  $R_f$  0.64 (f) were detected. Elution of (d) gave 80 mg. of compound IIb, (m.p. 139-140°) which gave only one spot on TLC ( $R_f$  0.52); IR (chloroform), 1550 ( $\nu$  C=N), 1340 and 1140 ( $\nu$  C-F), 1140 ( $\nu$  C-O), 870 and 850  $\text{cm}^{-1}$  ( $\gamma$  C-H aromatic); NMR,  $\tau$  5.77 (s, 3H, CH<sub>3</sub>O),  $\tau$  1.8-1.5 (m, 3H, H aromatic). An additional 55 mg. of compound IIa was obtained from the fraction (f).

4-Methoxy-6-trifluoromethyl-1(2H)-phthalazinone (IIIa) and  
4-Methoxy-7-trifluoromethyl-1(2H)-phthalazinone (IIIb).

A solution of 1.1 g. of unseparated IIa and IIb in 10 ml. of glacial acetic acid was refluxed for 2 hours. After cooling, water was added and the precipitate was collected and crystallized from isopropyl ether, yielding 0.87 g. (85%) of product (m.p. 185-187°).

*Anal.* Calcd. for C<sub>10</sub>H<sub>7</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 49.18; H, 2.88; F, 23.24; N, 11.47. Found: C, 48.95; H, 2.48; F, 23.67; N, 11.47.

TLC of this material, developed with a 1:1 mixture of benzene and ethyl ether, showed the presence of two components ( $R_f$  0.30 and  $R_f$  0.37;  $R_f$  relative to phthalide 0.55 and 0.70).

Separation of IIIa and IIIb.

By recrystallization from isopropyl ether a first crop of compound IIIb (250 mg.) with m.p. 226-227° was obtained. TLC showed a single spot at  $R_f$  0.37; IR (nujol), 3160 ( $\nu$  N-H), 1660 ( $\nu$  C=O), 1610 ( $\nu$  C=N), 1320 and 1120 ( $\nu$  C-F), 1160 ( $\nu$  C-O), 850 and 785  $\text{cm}^{-1}$  ( $\gamma$  C-H aromatic); NMR,  $\tau$  5.99 (s, 3H, CH<sub>3</sub>O),  $\tau$  1.85 (2H, H-5 and H-6),  $\tau$  1.02 (d,  $J_{meta} = 2$  Hz, 1H, H-8); UV (ethanol),  $\lambda$  max,  $m\mu$  ( $\epsilon$ ): 307 (5400), 265 (4600) and 256 (3700).

Concentration of the mother liquors and finally evaporation to dryness gave a mixture of isomers. A solution of 250 mg. of the latter was applied on five plates and developed once with a 1:1 mixture of benzene and ethyl ether and then three times with a 4:1 mixture of benzene and ethyl ether. Two zones with  $R_f$  0.52-0.70 (a) and  $R_f$  0.70-0.80 (b) were visualized. Chloroform and methanol (9:1) eluted 48 mg. of compound IIIb from (b) and 100 mg. of IIIa (m.p. 222°;  $R_f$  0.30) from (a). IR (nujol), 3150 ( $\nu$  N-H), 1670 ( $\nu$  C=O), 1600 ( $\nu$  C=N), 1300 and 1120 ( $\nu$  C-F), 1120 ( $\nu$  C-O), 860 and 790  $\text{cm}^{-1}$  ( $\gamma$  C-H aromatic); NMR;  $\tau$  5.97 (s, 3H, CH<sub>3</sub>O),  $\tau$  1.89 (two d,  $J_{ortho} = 8$  Hz and  $J_{meta} = 2$  Hz, 1H, H-7),  $\tau$  1.69 (d,  $J_{meta} = 2$  Hz, 1H, H-5),  $\tau$  1.20 (d,  $J_{ortho} = 8$  Hz, 1H, H-8); UV (ethanol),  $\lambda$  max,  $m\mu$  ( $\epsilon$ ): 303 (5000), 267 (2600) and 256 (2400).

Reactions of IIa and IIb with Acetic Acid.

(a) By treating IIa (96 mg.) with glacial acetic acid (2 ml.) as described above 25 mg. of compound IIIa (m.p. 222°) was

obtained. Its identity with the compound isolated by preparative TLC was confirmed by IR and NMR spectroscopy.

(b) When fraction IIb (150 mg.) was worked up in a similar manner, 100 mg. of compound IIIb (m.p. 226°) was obtained and was shown to be identical (IR and NMR spectra) with the product isolated by preparative TLC.

1,4-Dimethoxy-6-trifluoromethylphthalazine (IV).

A solution of the mixture of compounds IIa and IIb (1.0 g.) in methanol (80 ml.) was added with stirring to a solution of sodium (0.090 g.) in methanol (20 ml.). After refluxing for one hour, the solvent was evaporated *in vacuo* and the residue was extracted with isopropyl ether. The extract was filtered, treated with charcoal and concentrated to crystallization, yield 0.83 g. (83%) of compound IV (m.p. 176°; TLC developed twice with isopropyl ether  $R_f$  0.40, relative to phthalide 0.87).

*Anal.* Calcd. for C<sub>11</sub>H<sub>9</sub>F<sub>3</sub>N<sub>2</sub>O<sub>2</sub>: C, 51.16; H, 3.51; F, 22.07; N, 10.84. Found: C, 51.04; H, 3.53; F, 21.68; N, 11.10.

IR (chloroform), 1570 ( $\nu$  C=N), 1360 and 1140 ( $\nu$  C-F), 1140 ( $\nu$  C-O), 870 and 850  $\text{cm}^{-1}$  ( $\gamma$  C-H aromatic); NMR,  $\tau$  5.78 and  $\tau$  5.76 (two s, 6H, CH<sub>3</sub>O),  $\tau$  7.9-7.4 (m, 3H, H aromatic).

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