Alcoholation of the Trifluoromethyl Group. II. A Facile Synthesis of 6,12-Dimethoxydibenzo[*b*,*f*][1,5]diazocine from *o*-Aminobenzotrifluoride

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The novel conversion of 1- and 3-trifluoromethylphenothiazines to ortho esters of phenothiazinecarboxylic acids (1) [$CF_3 \rightarrow C(OCH_3)_3$] prompted us to investigate the stability of aminobenzotrifluorides in methanolic base.

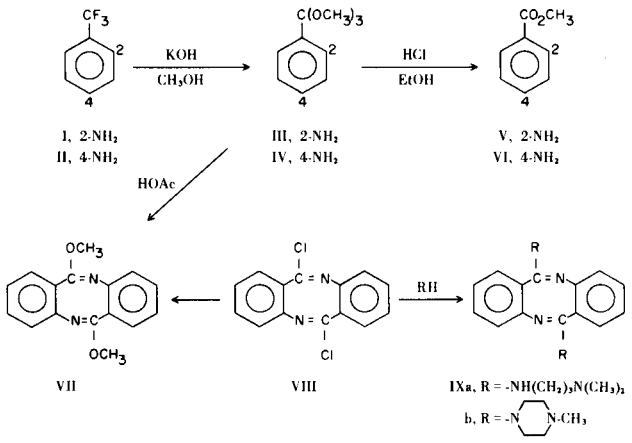
As previously described (2,3), CF_3 on a benzene ring activated by an *ortho* or *para* amino group readily loses fluoride ion under aqueous alkaline conditions to form the corresponding aminobenzoic acids. The trifluoromethyl group in the meta position relative to the amino group is stable even to hot concentrated alkali (2,4). This was further evident in the basic hydrolysis of 2,5-di(trifluoromethyl)aniline where CF_3 *ortho* to the amino function was hydrolyzed quantitatively, while the *m*-CF_3 group was unaffected, thus providing 4-trifluoromethylanthranilic acid (5).

We have now found that *o*- and *p*-aminobenzotrifluorides (I and II, Scheme I) are readily converted in good yield in methanolic base to trimethyl ortho-*o* and *p*-aminobenzoates (III and IV, respectively), the *m*-isomer being recovered unchanged. As expected, acid (hydrochloric acid) hydrolysis of III and IV produced methyl *o*- and *p*-aminobenzoates (V and VI, respectively). Interestingly, however, the ortho ester (III) in glacial acetic acid at ambient temperature afforded (81%) 6,12-dimethoxyphenhomazine (VII), a member of the dibenzo[*b*,*f*][1,5]-diazocine series. The *p*-isomer (IV) under similar conditions yielded a high melting insoluble polymer of unknown structure.

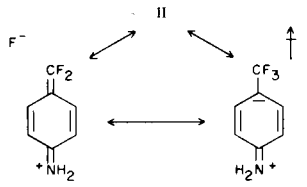
The facile conversion of III to VII was surprising since in the base-catalyzed self-condensation of methyl anthranilate (V) (6) the maximum yield of the dibenzodiazocine derivative (IX, R = OH or its tautomeride, dianthranilide) was only 4%. Synthesis of VII was previously accomplished (6) from anthraquinone in 4-steps *via* Beckmann rearrangement of the corresponding dioxime, chlorination of the resultant dianthranilide to VIII and subsequent methoxylation. The product prepared by the latter method was identical to that obtained by the ortho ester route.

Amination of VIII also provided diamines (IX a and b) which were investigated for antimalarial activity. Evaluation of compounds III, VII, IXa and b in *P. berghei* infected mice (7) revealed no antiplasmodial action at the highest dose, 640 mg/kg.

SCHEME I



The increased lability of fluorine in I and II may be represented by hyperconjugative and π-inductive structures of the type shown below for II. In the case of *o*-aminobenzotrifluoride (I), it has been postulated (2,8,9) that intramolecular hydrogen bonding may also play an important role in weakening the C-F bond. A recent critical analysis (10) of factors influencing the reactivity patterns of CF_3 aromatic systems concluded, moreover, that polar (inductive) effects best explain the behavior of CF_3.



EXPERIMENTAL

Melting points were determined with an electrically heated Thiele-Dennis apparatus and are uncorrected. Elemental analyses were performed by Schwartzkopf Microanalytical Laboratory, Woodside, N. Y. and Microanalysis, Inc., Wilmington, Del. Ir

spectra were recorded on a Perkin-Elmer Model 137 Spectrophotometer. The aminobenzotrifluorides were purchased from Pierce Chemical Co., Rockford, Ill.

Trimethyl Ortho-*o*-aminobenzoate (III).

To a stirred solution of *o*-aminobenzotrifluoride (I) (5 g., 0.031 mole) in methanol (160 ml.) was added potassium hydroxide (120 g.) in water (80 ml.). The reaction was heated at reflux for 17 hours, reduced to half its volume, diluted with water and filtered to give III (83%) as white crystals from 90-120° ligroin, m.p. 56-57°; ir (nujol mull): 2.9-3.1 (NH), 9.05-9.55 μ (OCH_3, (broad).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.09. Found: C, 61.19; H, 7.69; N, 6.69.

Hydrolysis of the ortho ester (III) with 10% hydrochloric acid in ethanol provided (83%) the hydrochloride salt of methyl anthranilate, m.p. 178° dec. Mixture melting point with an authentic sample was not depressed and ir spectra were identical.

Trimethyl Ortho-*p*-aminobenzoate (IV).

p-Aminobenzotrifluoride (II) was treated as above to provide the corresponding ortho ester in 64% yield. Recrystallization from 90-120° ligroin yielded IV as white needles, m.p. 112.5-113.5°; ir (nujol mull): 2.85-3.05 (NH), 9.1-9.5 μ (OCH_3, broad).

Anal. Calcd. for $C_{10}H_{15}NO_3$: C, 60.90; H, 7.67; N, 7.09. Found: C, 61.15; H, 7.59; N, 7.06.

Hydrochloric acid and IV followed by basification in the cold gave methyl *p*-aminobenzoate whose ir spectrum was identical with authentic material.

Treatment of IV with glacial acetic acid as described below afforded a pale yellow insoluble solid, m.p. >345°; ir (nujol mull): 6.05 (C=N), 6.24 (C=C), 9.07 μ (OCH_3).

6,12-Dimethoxydibenzo[*b*,*f*][1,5]diazocine (VII).

The ortho ester (III) (7.9 g., 0.04 mole) was dissolved in glacial acetic acid (25 ml.) and stirred at room temperature for 1.5 hours. The resultant precipitate was filtered and recrystallized from ethanol producing (81%) VII as white crystals, m.p. 162.5-163.5° [lit. m.p. 161-162° (6)]; ir (nujol mull): 6.0 (C=N), 9.2 μ (OCH_3); identical with the product synthesized from anthraquinone as described in reference (6).

6,12-Di-(3-dimethylaminopropylamino)dibenzo[*b*,*f*][1,5]diazocine (IXa) and the Di-(*N*-methylpiperazinyl) Derivative (IXb).

A stirred mixture of VIII (2.75 g., 0.01 mole), sodium carbonate (2.12 g., 0.02 mole) and 3-dimethylaminopropylamine (4.1 g., 0.04 mole) in dimethylformamide (50 ml.) was heated at reflux for 5.5 hours, filtered hot and the filtrate brought to dryness *in vacuo*. Trituration of the residue with ether(20-40°)-petroleum-ether (1:4) yielded (60%) IXa as white solid from hexane, m.p. 135-135.5°; ir (nujol mull): 2.95-3.05 (NH, doublet), 6.2 μ (C=N).

Anal. Calcd. for $C_{24}H_{34}N_6$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.75; H, 8.30; N, 20.50.

The di-(*N*-methylpiperazinyl) derivative (IXb) was prepared in an analogous manner as white crystals from benzene, m.p. 186-187°; ir (nujol mull): 6.2 μ (C=N).

Anal. Calcd. for $C_{24}H_{30}N_6$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.59; H, 7.45; N, 20.83.

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