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Fluoro Derivatives of Phenarsazine

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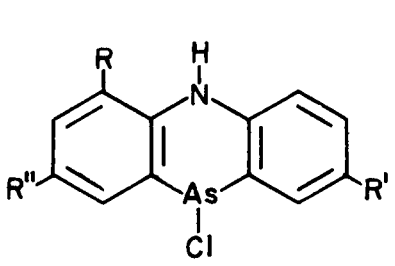
Several fluorinated derivatives of phenarsazine and benzophenarsazines, bearing various additional substituents in their molecule, have been prepared from arsenic trichloride and the appropriate N,N'-diarylamines. These compounds showed strong irritant and sternutatory properties.

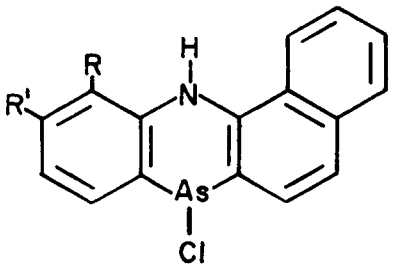
10-Chloro-5,10-dihydrophenarsazine (I; R, R', R'' = H), readily prepared by condensation of arsenic trichloride with diphenylamine (1), acquired fame during World War I as a potent sternutatory agent, and several of its derivatives also display strong irritant activity towards the mucous membranes. More recently, some angular polysubstituted dihydrobenzophenarsazines have been found to possess weak, but definite tumor-producing properties on the skin of mice (2). Further, fluorine substitution very often maintains or even enhances various types of biological activity, such as in the case of the azobenzene derivatives that are carcinogenic for the liver (3), and the angular benzacridines, that are carcinogenic for the skin and connective tissue (4). We were thus led to prepare, for biological investigation, a number of fluoro and trifluoromethyl derivatives of 10-chloro-5,10-dihydrophenarsazine, and of 7-chloro-7,12-dihydrobenzo[c]- (II; R, R' = H) and 7-chloro-7,12-dihydrobenzo[a]-phenarsazine (III; R, R' = H).

These compounds were readily obtained by condensing arsenic trichloride with the appropriate substituted diphenylamines and N-phenylnaphthylamines in solution in *o*-dichlorobenzene; several of these secondary amines were prepared for the first time. The diphenylamines were prepared by Goldberg's method (5), *i.e.* condensing a fluoroacetanilide with the appropriate aryl bromide, and hydrolyzing the N-acetyldiarylamine thus formed; it is to be noted that the condensation of *o*-bromochlorobenzene with *p*-fluoroacetanilide readily yielded N-acetyl-2-chloro-4'-fluorodiphenylamine (IV). This amine failed to give any sizable amount of reaction-product with arsenic trichloride, even on prolonged heating. The N-arylnaphthylamines were obtained by the Knoevenagel technique, involving the condensation of α- or β-naphthol with the appropriate aniline in the presence of iodine (6); *o*-trifluoromethylaniline failed to undergo this reaction.

The phenarsazine derivatives thus prepared possess strong sternutatory properties, and their vapors are highly irritant for the mucous membranes. Their antibacterial and antifungal activities are being investigated.



I



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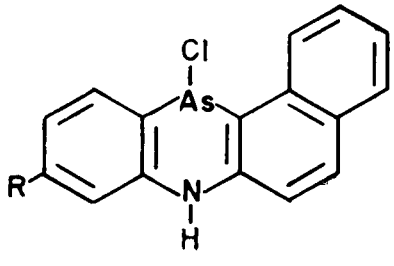
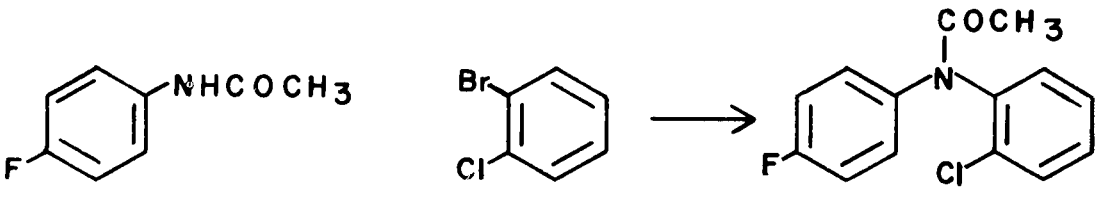


III



IV

Table

Derivatives of 5,10-Dihydrophenarsazine

Substituent	Molecular formula	M.p., °C.	Chlorine, % Calcd.	Chlorine, % Found	Nitrogen, % Calcd.	Nitrogen, % Found
4-Fluoro-8-methyl- (I; R = F, R' = CH_3, R'' = H)	$C_{13}H_{10}AsClFN$	207	11.4	11.4	4.5	4.5
4-Fluoro-8-methoxy- (I; R = F, R' = OCH_3, R'' = H)	$C_{13}H_{10}AsClFNO$	204	10.8	10.8	4.3	4.2
8-Fluoro-4-methoxy- (I; R = OCH_3, R' = F, R'' = H)	$C_{13}H_{10}AsClFNO$	191	10.8	11.0	4.3	4.6
2-Fluoro-8-methyl- (I; R = H, R' = CH_3, R'' = F)	$C_{13}H_{10}AsClFN$	237	11.4	11.0	4.5	4.4
2-Fluoro-8-methoxy- (I; R = H, R' = OCH_3, R'' = F)	$C_{13}H_{10}AsClFNO$	227	10.8	10.5	4.3	4.3
11-Fluorobenzo[c]- (II; R = F, R' = H)	$C_{16}H_{10}AsClFN$	196	10.3	10.7	4.1	4.2
10-Fluorobenzo[c]- (II; R = H, R' = F)	$C_{16}H_{10}AsClFN$	268	10.3	10.0	4.1	4.1
10-Trifluoromethylbenzo[c]- (II; R = H, R' = CF_3)	$C_{17}H_{10}AsClF_3N$	252	9.0	8.7	3.5	3.8
9-Trifluoromethylbenzo[a]- (III; R = F)	$C_{17}H_{10}AsClF_3N$	300	9.0	8.7	3.5	3.7

EXPERIMENTAL

2-Fluoro-4'-methyldiphenylamine.

A well-stirred mixture of 15.3 g. of *o*-fluoroacetanilide, 34.3 g. of *p*-bromotoluene, 13.8 g. of anhydrous potassium carbonate, and 20 ml. of anhydrous nitrobenzene was refluxed for 17 hr. on a sand-bath with 6 g. of a catalyst mixture made up of copper powder (2 g.), cuprous iodide (2 g.), potassium iodide (2 g.), and iodine (0.2 g.). After cooling, water was added, and the *p*-bromotoluene in excess was removed with steam, along with the nitrobenzene. The reaction-product was taken up in ether, and the residue from distillation of the solvent was hydrolyzed by heating 3 hrs. with 100 ml. of a 20% solution of potassium hydroxide in ethanol; 100 ml. of a saturated aqueous solution of sodium chloride was added, the free amine was then taken up in ether, the ethereal solution was dried over sodium salfate, the solvent removed, and the residue vacuum-fractionated. The portion b.p. 185-187°/20 mm. crystallized from methanol in colorless prisms, m.p. 53°; yield, 65%.

Anal. Calcd. for $C_{13}H_{12}FN$: C, 77.6; H, 6.0; N, 7.0. Found: C, 77.9; H, 5.9; N, 7.0.

2-Fluoro-4'-methoxydiphenylamine.

Similarly prepared, in 70% yield, from *o*-fluoroacetanilide and *p*-bromoanisol, this product b.p. 218-220°/24 mm., crystallized from ethanol in colorless prisms, m.p. 91°.

Anal. Calcd. for $C_{13}H_{12}FNO$: C, 71.9; H, 5.5; N, 6.5. Found: C, 72.0; H, 5.3; N, 6.6.

2-Chloro-4'-fluorodiphenylamine.

Prepared in 72% yield from *o*-bromochlorobenzene and *p*-fluoroacetanilide, this product was a pale yellow oil, b.p. 166-168°/12 mm., n_D^{20} 1.6321.

Anal. Calcd. for $C_{12}H_9ClFN$: C, 65.0; H, 4.1; N, 6.3. Found: C, 65.2; H, 4.1; N, 6.2.

4-Fluoro-2'-methoxydiphenylamine.

This compound was obtained as a pale yellow, viscous oil, b.p. 178-179°/12 mm., n_D^{20} 1.6233; yield: 80%.

Anal. Calcd. for $C_{13}H_{12}FNO$: C, 71.9; H, 5.5; N, 6.5. Found: C, 71.6; H, 5.5; N, 6.2.

4-Fluoro-4'-methoxydiphenylamine.

This compound crystallized from methanol in colorless prisms, m.p. 59°, b.p. 204°/18 mm.; yield: 65%.

Anal. Calcd. for $C_{13}H_{12}FNO$: C, 71.9; H, 5.5; N, 6.5. Found: C, 71.8; H, 5.5; N, 6.5.

4-Fluoro-4'-methyldiphenylamine.

This product crystallized from methanol in colorless prisms, m.p. 54°, b.p. 186-187°/24 mm.; yield: 75%.

Anal. Calcd. for $C_{13}H_{12}FN$: C, 77.6; H, 6.0; N, 7.0. Found: C, 77.9; H, 5.9; N, 7.0.

N-*m*-Fluorophenyl-α-naphthylamine.

The Knoevenagel reaction of *o*- and *p*-fluoroaniline with α- and β-naphthol had already been investigated by Smith (7) and by Buu-Hoï and Jacquignon (8), but the *meta* compound had not been used in such condensations. A mixture of 10 g. of *m*-fluoroaniline and 18 g. of α-naphthol was gently refluxed for 12 hr. with 0.2 g. of iodine; after cooling, the product was taken up in benzene, the benzene solution washed with aqueous sodium hydroxide, then with water, and dried over sodium sulfate, the solvent was removed, and the residue vacuum-fractionated. The portion b.p. 235°/19 mm. was a thick yellow oil (9 g.), $n_D^{19.2}$ 1.6715.

Anal. Calcd. for $C_{16}H_{12}FN$: C, 81.0; H, 5.1; N, 5.9. Found: C, 81.0; H, 5.1; N, 6.1.

N-*m*-Fluorophenyl-β-naphthylamine.

This was similarly prepared with β-naphthol, but with better yield (15 g.) and crystallized from ethanol in shiny colorless prisms, m.p. 77°.

Anal. Calcd. for $C_{16}H_{12}FN$: C, 81.0; H, 5.1; N, 5.9. Found: C, 81.2; H, 5.1; N, 5.8.

N-*m*-Trifluoromethylphenyl-α-naphthylamine.

This *amine*, b.p. 209-210°/12 mm., was obtained as above, from *m*-trifluoromethylaniline and α-naphthol, in 40% yield, and crystallized from hexane in yellowish prisms, m.p. 69°. When heating was prolonged to 20 hr., the yield dropped to 15%, and became nil after 24 hr.

Anal. Calcd. for $C_{17}H_{12}F_3N$: C, 71.1; H, 4.2; N, 4.9. Found: C, 71.2; H, 4.1; N, 5.0.

Phenarsazine Syntheses.

A solution of the secondary amine (0.01 mole) and 1.8 g. (0.01 mole) of arsenic trichloride in 8 ml. of anhydrous *o*-dichlorobenzene was gently refluxed for 2 hr.; after cooling, the solid formed was collected and recrystallized from toluene or chlorobenzene. All the phenarsazines thus prepared in 65-95% yield, were shiny, bright yellow, sublimable prisms, which on heating gave off highly sternutatory vapors. Their solutions in sulfuric acid showed halochromisms ranging from orange-red to vermilion.

Physical determinations (infra-red spectra and nuclear magnetic resonance) on these compounds will be reported in detail in another paper.

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