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Preparation and Structures of Unsubstituted and Monofluorinated 2*H*(or 4*H*)-1,3,4-Benzoxadiazines

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Synopsis. Azo-coupling of diazomethane with benzenediazonium-2-oxide yielded 2*H*-1,3,4-benzoxadiazine while coupling of the same reagent with the monofluoro-substituted benzenediazonium-2-oxide derivatives gave the corresponding 4*H*-1,3,4-benzoxadiazines.

The preparation of 6,7,8-trifluoro-5-methoxycarbonyl-4*H*-1,3,4-benzoxadiazine by the reaction of 3,4,5-trifluoro-6-methoxycarbonylbenzenediazonium-2-oxide with diazomethane was previously reported.[1] An analogous reaction between a diazo-oxide and a substituted diazomethane was studied by Huisgen and Fleischman,[2] who observed the formation of 5,6,7,8-tetrachloro-2-phenyl-4*H*-1,3,4-benzoxadiazine from 3,4,5,6-tetrachlorobenzenediazonium-2-oxide and phenyldiazomethane.

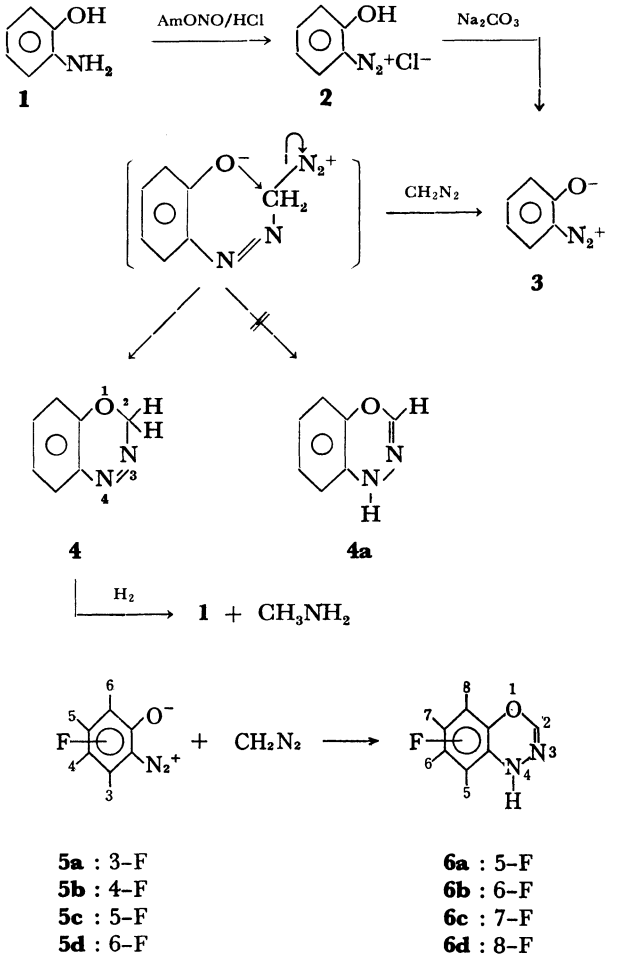
No other report seems to have appeared on the heterocyclic system. We undertook to prepare unsubstituted 2*H*(or 4*H*)-1,3,4-benzoxadiazine and to confirm the effect of the electronegative halogen atoms of the benzene ring upon the stability of this heterocyclic compound.

For the purpose of preparing unsubstituted 2*H*(or 4*H*)-1,3,4-benzoxadiazine (**4** or **4a**), *o*-aminophenol (**1**) was reacted with *iso*-amyl nitrite to give 2-hydroxybenzenediazonium chloride (**2**),[3] from which elimination of a molecule of hydrochloric acid was effected with sodium carbonate.[4] On reaction with diazomethane, benzenediazonium-2-oxide (**3**) then afforded an oxadiazine compound, the result of diazo coupling followed by loss of nitrogen prior to ring cyclization.

The product, a fairly unstable yellow liquid, was assigned the structure 2*H*-1,3,4-benzoxadiazine (**4**), from infrared and nuclear magnetic resonance spectra. Thus, the IR absorptions at 2890 cm^{-1} and 2885 cm^{-1} were assigned to the methylene group, and those at 1360 cm^{-1} and 1250 cm^{-1} to C–N stretching vibrations and an ether linkage, respectively. The NMR spectrum, besides showing a complex multiplet at τ 2.27—3.35 due to the four aromatic protons, also revealed a singlet at τ 4.74, assigned to the methylene protons.[5]

On reacting with hydrogen over palladium catalyst, **4** afforded *o*-aminophenol (**1**) and methylamine, supporting the assignment of structure **4** for 2*H*-1,3,4-benzoxadiazine but not for 4*H*-compound (**4a**), since formation of these products is a consequence of hydrogenolysis during the course of reaction.

Introduction of a negative group such as fluorine atom in the benzene ring seemed to stabilize the 4*H*-1,3,4-benzoxadiazine compound rather than the 2*H*-compound, and we therefore attempted to prepare



5a : 3-F
5b : 4-F
5c : 5-F
5d : 6-F

6a : 5-F
6b : 6-F
6c : 7-F
6d : 8-F

all species of hydro-1,3,4-benzoxadiazines which carry fluorine substituent in their benzene rings.

Coupling of the various monofluoro-substituted diazo-oxides (**5a**—**5d**) obtained from their respective fluoro-aminophenols by diazotization with aqueous sodium nitrite, gave fluorinated 4*H*-benzoxadiazines.

The compounds were obtained as stable crystals. The evidence for structures **6a**—**6d** for the fluorinated 4*H*-1,3,4-benzoxadiazines was readily deduced from their IR and NMR spectra. In line with the proposed structures, all the IR spectra showed absorptions which could be assigned to NH and C–N (Table 1). The NMR spectrum of **6d**, for example, also supported the structure, since the signal at τ 3.80, which was exchanged for deuterium oxide, could be assigned to a secondary amine, while the methine proton resonated as a singlet at τ 3.65.

In the azo-coupling of the fluoro-substituted diazo-oxide derivatives, preferable formation of the

Table 1. Preparation and properties of 4 and 6a—d

Compd. No.	Yield %	Mp °C (Bp °C/mmHg)	F Anal %		IR (cm^{-1})			
			Found	Calcd	CH_2	C-N	N-H	C=N
4	86	(58—59/2)	—	—	2885 2890	1360	—	—
6a	79	72.5—73.5	12.4	12.5	—	—	3420	1615
6b	94	73.5—74.5	12.5	12.5	—	—	3405	1630
6c	99	59	12.9	12.5	—	—	3410	1630
6d	99	83—83.5	12.6	12.5	—	—	3275	1645

4*H*-benzoxadiazines is expected, since the negative inductive effect of the fluorine atom is expected to make the oxadiazole ring somewhat acidic. The resulting intermolecular hydrogen bonding which combines N–H···N or N–H···O seems to stabilize the 4*H*-form and make the substances rather stable crystals.

Experimental

2H-1,3,4-Benzoxadiazine (4). Benzenediazonium-2-oxide (**3**) (3.90 g), prepared from *o*-aminophenol (**1**) by the reaction with isoamyl nitrite in hydrogen chloride saturated methanol and subsequent treatment of the resulting 2-hydroxybenzenediazonium chloride (**2**) with anhydrous sodium carbonate, was reacted with an excess of ethereal diazomethane at room temperature for 4 hr. The solvent was then evaporated. The crude product (4.23 g) was filtered through silica gel (20 g) in hexane. Evaporation of the solvent and subsequent distillation of the partially purified product gave pure benzoxadiazine **4** (3.80 g, 86%), bp 58—59 °C/2 mmHg. The yellow liquid, which turned reddish-brown when exposed to light, gradually decomposed at room temperature. Found: C, 60.8; H, 4.3; N, 20.3%. Calcd for $C_7H_6N_2O$: C, 62.7; H, 4.5; N, 20.9%. Mass spectrum: M^+ 134 (Calcd: 134).

Hydrogenolysis of 4. Benzoxadiazine **4** (1.32 g, 9.85 mmol) and 5% Pd/C catalyst (0.30 g) in ethanol (50 ml) were shaken in an atmosphere of hydrogen at room temperature and pressure. When the uptake of hydrogen had ceased (29.6 mmol), the catalyst was removed by filtration. The filtrate was heated to boiling in a water bath and the methylamine evolved was absorbed in ethanol (5 ml) maintained at about −5 °C. The filtrate was then evaporated and the resulting solid (0.86 g) was purified by sublimation *in vacuo* to give colorless crystals, mp 170—174 °C, which was undepressed on admixture with authentic *o*-aminophenol (**1**).

To the methylamine solution was added saturated ethanolic picric acid (5 ml), and the mixture was left at room temperature for 30 min, then heated in a water bath (5 min) and left to cool. The orange crystals deposited were purified by recrystallization from ethanol and confirmed to be methylamine picrate by IR and mixed mp.

Fluoro-4H-1,3,4-benzoxadiazine (6a—6d). The fluorobenzene diazonium oxides **5a—5d** were synthesized from the respective fluoro aminophenols, which in turn were prepared[6] from their corresponding nitro-derivatives by reduction with hydrogen gas over palladium catalyst. The diazo-oxides **5a—5d** thus obtained were then reacted with ethereal diazomethane in a similar manner.

As an example, 3-fluoro-2-aminophenol (1.50 g, 11.8 mmol), dissolved in water (32 ml) containing concentrated hydrochloric acid (5.5 ml), was converted into 6-fluorobenzenediazonium-2-oxide (1.51 g, 93%) with 5% aqueous sodium nitrite solution (18 ml, 13.0 mmol). This crude gummy product was treated with an excess of ethereal diazomethane and left at room temperature for 16 hr. The reaction mixture was filtered and the solvent evaporated to give a gum (1.5 g). This was extracted with boiling hexane, which was then evaporated leaving the benzoxadiazine **6a** (1.32 g, 79%) as yellow plates, mp 72.5—73.5 °C after crystallization from hexane followed by sublimation *in vacuo*. Found: C, 54.5; H, 3.4; N, 18.4; F, 12.4%. Calcd for $C_7H_5FN_2O$: C, 55.3; H, 3.3; N, 18.4; F, 12.5%. Mass spectrum: M^+ 152 (Calcd: 152).

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