Partial Reduction of Diazines

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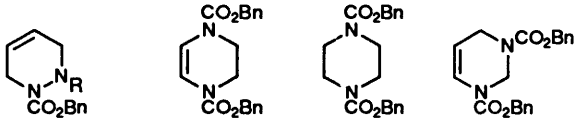
Pyridazine, pyrimidine, pyrazine, quinazoline, phthalazine and quinoxaline give tetra- or hexa-hydro-*N*-benzyloxycarbonyl derivatives on exposure to $NaB(CN)H_3$ in the presence of $PhCH_2OCOCl$.

An elegant method for the partial reduction of pyridines, which also allows isolation of otherwise unstable 1,2- or 1,4-dihydro derivatives in protected/stabilised form, was introduced by Fowler,[1] who found that treatment of pyridine with sodium borohydride in the presence of methyl chloroformate gave a mixture of methyl 1,2- and 1,4-dihydropyridine-1-carboxylates thus stabilised as urethanes; the process involves reductive trapping of the *N*-acylpyridinium cation generated *in situ*. Related work showed that other chloroformates could also be used to give alkoxycarbonylpyridinium ions which could be trapped by nucleophilic addition of Grignard and related reagents.[2] Of the diazines, only pyridazine has been subjected to comparable reductive treatment, methyl chloroformate and sodium borohydride generating a mixture of methyl 1,2- (main) and 1,4- (minor)-dihydropyridazine-1-carboxylates.[3] Pyrazine has been converted[4] into 1,4-dihydro-1,4-bistrimethylsilylpyrazine using a combination of Li and Me_3SiCl and this, by further reaction with carbon dioxide, was converted into an *O,O*-bistrimethylsilylurethane,[5] electrolytic reduction in the presence of acylating agents afforded 1,4-diacylated 1,4-dihydro derivatives.[6] Addition of 2,2,2-trichloroethoxycarbonyl (at nitrogen) and an enamine (at C-4) has been achieved with pyridazine,[7] however the sequential reaction of pyrimidine with trimethylsilyl triflate then silylenol ethers gave adducts in which hydrolysis of silylamine units during work-up led to further nucleophilic addition to the initial dihydropyrimidine.[8] Dimethyl 1,2,3,6-tetrahydro- and 1,2-dihydropyridazine-1,2-dicarboxylates are accessible *via* Diels–Alder additions of dimethyl azodicarboxylate to dienes.[9]

Attempts to trap electrolytically reduced quinoxaline with methyl chloroformate led to polymeric products, though 2-phenyl- and 2,3-diphenylquinoxalines gave methyl and dimethyl 1,4-dihydroquinoxalines-1,4-dicarboxylates; comparable treatment of phthalazine led to a 1,1′-dimer of methyl 1,2-dihydrophthalazine-2-carboxylate.[10] Reduction of quinoxaline with sodium produced a species which could be trapped as 1,4-dihydro-1,4-dimethyl- or 1,4-dihydro-1,4-bismethoxycarbonylquinoxaline.[11]

In connection with our work[12] towards the cofactor of the oxomolybdoenzymes, Moco,[13] and models thereof, we needed a reliable method for the controlled reduction of a 1,4-diazine ring, ultimately in pteridines, such that the normally easily oxidised forms would be stable enough to be useful during synthetic manipulations elsewhere in the molecule. The methodology introduced by Fowler (see above) seemed to be ideal and we report here our results (Table 1) with monocyclic diazines and benzene-fused derivatives.

Exposure of pyridazine to benzyl chloroformate and $NaB(CN)H_3$ in methanol at room temperature gave a mixture of tetrahydro derivatives, **1a** and **1b**; we observed no formation of dihydro derivatives (*cf.* ref. 3), perhaps because the protic solvent encouraged second quaternisation and reduction.



1 R
a CO_2Bn
b H

2a **2b** **3**

Pyrazine, too, produced a mixture of tetrahydro- and hexahydro products, **2a** and **2b**, in both cases, however, doubly

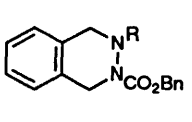
Table 1

	Yield[a] (%)	m.p. (°C)	Key ^1H NMR values (δ, in $CDCl_3$)	Formula	Found	Required
1a	12	gum[b]	3.83 (2 H, br s), 4.46 (2 H, br s), 5.14 (4 H, br s), 5.79 (2 H, br s)	$C_{20}H_{20}N_2O_4$	MH^+, 353.1501	353.1501
1b	28	gum[b]	3.49 (2 H, br s), 4.08 (2 H, br s), 5.21 (2 H, s), 5.90 (2 H, m)	$C_{12}H_{14}N_2O_2$	MH^+, 219.1134	291.1134
2a	11	60–62 (hexane)	3.75 (4 H, br s), 5.19 (4 H, s), 6.35 (2 H)	$C_{20}H_{20}N_2O_4$	C, 68.5; H, 6.0; N, 8.2%	C, 68.2; H, 5.7; N, 8.0%
2b	50	89–90 (hexane)	3.51 (8 H, s), 5.27 (4 H, s)	$C_{20}H_{22}N_2O_4$	C, 66.1; H, 6.2; N, 7.8%	For hemihydrate, C, 66.1; H, 6.3; N, 7.7%
3	37	gum[b]	4.05 (2 H, s), 5.18 (1 H, m), 5.20 (6 H, br s), 6.83 (1 H, m)	$C_{20}H_{20}N_2O_4$	MH^+, 353.1501	353.1501
4a	42	61–63 (MeOH)	4.45 (2 H, br s), 5.14 (6 H, br s)	$C_{24}H_{22}N_2O_4$	C, 71.8; H, 5.8; N, 6.8%	C, 71.6; H, 5.5; N, 7.0%
4b	58	92–94 (MeOH)	4.13 (2 H, s), 4.76 (2 H, s), 5.23 (2 H, s)	$C_{16}H_{16}N_2O_2$	C, 71.6; H, 6.3; N, 10.4%	C, 71.6; H, 6.0; N, 10.4%
5	37	81–82 (MeOH)	4.71 (2 H, s), 5.19 (4 H, br s), 5.32 (2 H, s)	$C_{24}H_{22}N_2O_4$	C, 71.5; H, 5.7; N, 6.9%	C, 71.6; H, 5.5; N, 7.0%
6	52	105–107 (MeOH)	3.92 (4 H, s), 5.26 (4 H, 3)	$C_{24}H_{22}N_2O_4$	C, 71.5; H, 5.5; N, 6.9%	C, 71.6; H, 5.5; N, 7.0%

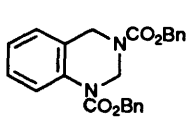
[a] Yields are for purified material. [b] Purity of non-crystalline products was determined by TLC and NMR criteria.

protected. Even when the reductive acylation was conducted at −78 °C and with 1 mol equiv. of reductant, production of **2b** could not be prevented. Pyrimidine gave the cleanest result, producing only one product, **3**, from a room temperature reaction.

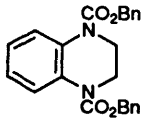
As in the monocyclic series, reaction of a benzene-fused isomer with adjacent nitrogen atoms, phthalazine, produced a mixture of tetrahydro-, doubly and singly protected products, **4a** and **4b**. Quinazoline and quinoxaline were reduced cleanly to afford doubly protected tetrahydro derivatives, **5** and **6**.



4 R
a CO_2Bn
b H



5



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Experimental

Typical Reduction Procedure.—Benzyl chloroformate (1.66 ml, 12.60 mmol) followed by $NaB(CN)H_3$ (850 mg, 13.26 mmol) were added to a solution of pyrimidine (266 mg, 3.32 mmol) in methanol (20 ml) under nitrogen and the whole was stirred for 16 h at room temperature. Removal of solvent and addition of acetone (3 × 20 ml) to the residue, followed by evaporation of the filtered acetone extracts and column chromatography of the residue (2.13 g) produced product (977 mg) which was purified by precipitation from Et_2O–hexane at −20 °C to give pure (TLC and ^1H NMR) **3** as a colourless gum (430 mg, 37%).

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