On the Reactivity of N-Benzylpyrimidinium Salts with Nitrogen Nucleophiles (1,2)

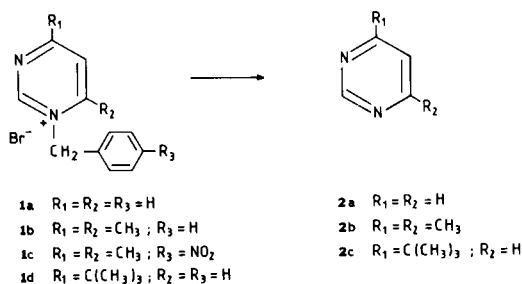A. Dlugosz, H. C. van der Plas* and A. van Veldhuizen

Laboratory of Organic Chemistry, Agricultural University,
Wageningen, The Netherlands
Received August 4, 1981

Treatment of the 1-benzyl salts of pyrimidine, 4,6-dimethylpyrimidine, and 4-t-butylpyrimidine with liquid ammonia leads to debenzylation. The ¹H-nmr spectroscopic evidence is presented that the initial step in the debenzylation of 1-benzyl-4,6-dimethylpyrimidinium bromide is the addition of the ammonia at C-2, while with 1-benzyl-4-t-butylpyrimidinium bromide the addition takes place at C-6. It is proved by ¹⁵N labelling that the debenzylation occurs according to the ANRORC mechanism. The above-mentioned 1-benzylpyrimidinium bromides give with hydrazine, pyrazole, 3,5-dimethylpyrazole and 3-t-butylpyrazole, respectively.

In continuation of our work on the occurrence of degenerate ring transformation reactions of N-methyl-pyrimidinium salts with liquid ammonia (3), amidines (4), isothiouronium salts (4) and cyanamide (4), we become interested in the reactivity of N-benzylpyrimidinium salts. Therefore, a number of N-benzylpyrimidinium salts *i.e.* N-benzyl- (**1a**), N-benzyl-4,6-dimethyl- (**1b**), N-(p-nitrophenyl)-4,6-dimethyl- (**1c**) and 1-benzyl-4-t-butylpyrimidinium bromide (**1d**) were prepared and their behavior towards liquid ammonia and hydrazine was investigated. The preparation of the pyrimidinium bromides was achieved by heating of the corresponding pyrimidine with benzyl-or p-nitrobenzyl-bromide in toluene. All attempts to prepare N-benzyl-4,6-di-t-butylpyrimidinium bromide by treatment of 4,6-di-t-butylpyrimidine with benzyl bromide failed; dealkylation occurs, **1d** being obtained.

Scheme 1

1a   R₁=R₂=R₃=H
1b   R₁=R₂=CH₃ ; R₃=H
1c   R₁=R₂=CH₃ ; R₃=NO₂
1d   R₁=C(CH₃)₃ ; R₂=R₃=H

2a   R₁=R₂=H
2b   R₁=R₂=CH₃
2c   R₁=C(CH₃)₃ ; R₂=H

When **1b** was stirred with liquid ammonia at -33° for 2 hours, 4,6-dimethylpyrimidine (**2b**) was isolated in a 65% yield using column chromatography. The debenzylation reaction also occurs on treatment of **1c** with liquid ammonia, **2b** and p-nitrobenzylamine being obtained (yields 65 and 37%). Analogously, from **1d**, 4-t-butylpyrimidine (**2c**) (94%, glc) was obtained. On reacting **1a** with liquid ammonia at -35° a mixture of non-identified (probably open-chain) products was formed; however, when carried out at room temperature (closed tube) pyrimidine **2a** was isolated. These results suggest that the N-benzylpyrimi-

dinium bromides **1a-1d** show a similar behaviour in liquid ammonia as the N-methylpyrimidinium salts, which are known to undergo *demethylation* under the same reaction conditions according to the ANRORC process. ¹⁵N Labelled 4,6-dimethylpyrimidine containing 5.8% of excess of nitrogen-15 was found when **1b** was debenzylated with liquid ammonia containing 6% of excess of nitrogen-15. This result shows that the debenzylation has occurred with ring opening and has not taken place by a direct nucleophilic attack of the nitrogen of ammonia on the methylene group. The data show that the benzylation occurs for 96% according to a so-called ANRORC mechanism, a mechanism that involves addition of the nucleophile as the first step, ring opening and ring closure (5). Proof for the formation of a 1:1 σ-adduct as intermediate in this ANRORC process was provided by measuring the ¹H nmr spectrum of a solution of **1b** in liquid ammonia at about -50°. It was found that in this solution the signals for the H-2 and H-5 protons are shifted considerably upfield, when they are compared with those observed in a solution of **1b** in chloroform (Table I). Furthermore the benzyl protons were found to appear as a pair of doublets at 4.75 and 4.49 ppm, indicating non-equivalence of both benzyl protons (diastereotopic), due to the formation of a chiral centre on addition of the ammonia (6). In order to distinguish which upfield shift belongs to H-2 and which to H-5, the 2-deutero analogue of **1b** was prepared (see experimental) and its ¹H-nmr spectrum in liquid ammonia at -60° was compared with that of **1b**. From these data it was concluded that the upfield shift of $\triangle\delta = 4.65$ ppm is caused by change of hybridization of the C-2 from sp² → sp³, leaving no doubt that the σ-adduct takes place at C-2. It is of interest that the demethylation of 1,4,6-trimethylpyrimidinium salt has been reported to take place *via* an initial adduct at C-6 (3). This interesting difference in the position of adduct formation between the N-methyl- and N-benzylpyrimidinium salt is probably due to the fact that the benzyl group can undergo deprotonation in liquid ammonia. It leads to an ylid, which has an addition pattern,

Table I

Chemical Shifts of the Aromatic Protons of the Compounds
1b-d in Deuteriochloroform, Perdeuteriomethanol,
and Liquid Ammonia

Compound	solvent	2H	5H	6H
1b	deuteriochloroform	9.88	8.05 (s)	
		$\triangle$ = 4.65	$\triangle$ = 3.12	
	liquid ammonia	5.23 (s)	4.93 (s)	
1c	perdeuteriomethanol	9.62 (s)	8.05 (s)	
		$\triangle$ = 4.37	$\triangle$ = 3.06	
	liquid ammonia	5.25 (s)	4.99 (s)	
1d	deuteriochloroform	9.60 (br. s)	8.08 (d)	9.30 (dd)
	perdeuteriomethanol	$\triangle$ = 2.35	$\triangle$ = 3.27	$\triangle$ = 4.85
	liquid ammonia	7.25 (s)	4.81 (d)	4.45 (d)

being characteristically different from that of a non-deprotonated species. That in a ylid the addition pattern is indeed different from that of the non-deprotonated species has already been shown with the behavior of N-amino-4,6-dimethylpyrimidinium salt (3) that in reaction with liquid ammonia is converted into dimer 5 and 3,5-dimethylpyrazole (6) (7).

The structure of the dimer suggests the formation of the

Scheme 2

N-ylid (4), that dimerizes via a 1,3-dipolar cyclization into 5. The formation of 6 takes place by addition of ammonia to C-2, probably in the N-ylid (4).

In the reaction of 1b with liquid ammonia we could not find any trace of a dimer. This result cannot be considered as some evidence for the non-existence of an intermediary ylid, since it is likely that in case the ylid should have been formed, the formation of the dimer is very difficult, partly due to the presence of the two bulky phenyl groups and partly due to the low electron density on the carbon of the -CH-C₆H₄pX (X = H) group, caused by mesomerism with the phenyl group. The mechanism of the debenzylation can be described as given in Scheme 3. From the 2-amino-

Scheme 3
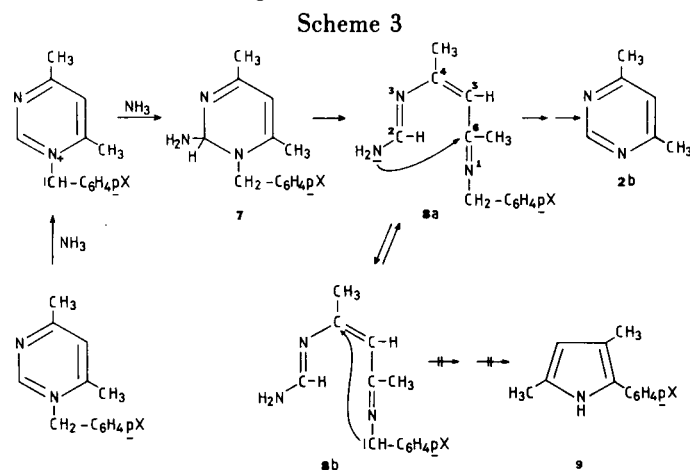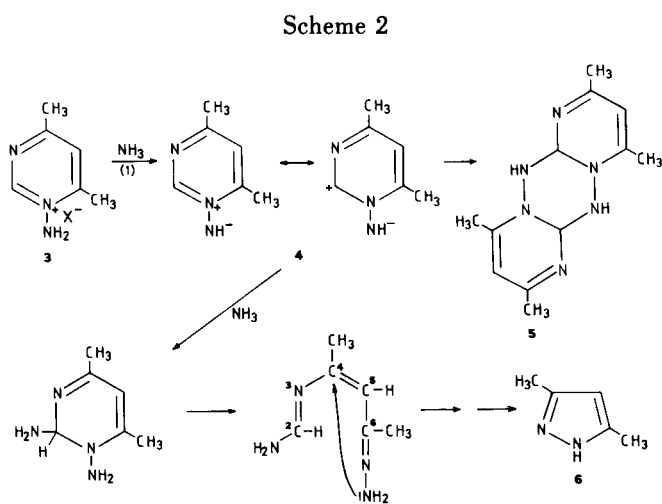
1-benzyl-4,6-dimethyl-1,2-dihydropyrimidine (7, X = H) the open-chain intermediate 8a was obtained, which undergoes ring closure into 2b. The isolation of p-nitrobenzylamine from the reaction of 1c with liquid ammonia is in accordance with this mechanism. Indications for a ring closure occurring by nucleophilic attack of the -CH-C₆H₄pX (X = H) group in 8b to the C(4)-C(5) bond has not been found, since in that case the pyrrole derivative 9 (X = H) should have been formed; this compound has not been detected however.

Table II

Yields and Physical Data of N-Benzylpyrimidinium Bromides

Compound	mp °C	Crystallized from	Yield %		Microanalyses		¹H-NMR Spectra (a)
					Calcd.	Found	
1a	192	Ethanol (absolute)	64	52.61	5.26	52.51 5.12	10.0 (H₂, s), 9.4, 8.3 (H₅, t), 7.6 (C₆H₅, m) 5.9 (CH₂, s) (b)
1b	201	Chloroform	62	55.92	5.42	55.97 5.63	9.88 (H₂, s), 8.05 (H₅, s), 7.33 (C₆H₅, s), 2.73 (CH₃, s) (c)
1c	182	Chloroform Acetone	66	48.16	4.35	48.44 4.61	9.62 (H₂, s), 8.05 (H₅, s), 8.25, 7.59 (C₆H₄, d), 6.04 (CH₂, s), 2.82 (CH₃, s), 2.75 (CH₃, s) (d)
1d	185	Acetone	56	58.65	6.23	58.43 6.14	9.60 (H₂, s), 9.30 (H₆, dd), 8.08 (H₅, d), 7.20-7.60 (C₆H₅, m), 5.9 (CH₂, s), 1.42 (C(CH₃)₃, s) (e)

(a) Solvents: (b) DMSO: (c) Deuteriochloroform: (d) Perdeuteriomethanol: (e) Deuteriochloroform/Perdeuteriomethanol.

Also the ^{1}H-nmr spectrum of **1c** in liquid ammonia (Table I) showed that in the solvent, formation of the 2-amino-1,2-dihydro-1-(*p*-nitrobenzyl)-4,6-dimethylpyrimidine (7, X = NO$_2$) takes place. Thus the debenzylation occurs *via* the C-2 adduct. Surprisingly when the ^{1}H-nmr spectrum of **1d** was measured in liquid ammonia, good evidence was obtained that the adduct formation takes place at C-6. From the two doublets appearing at high field (4.81 and 4.45 ppm) it could be established - by measuring the ^{1}H-nmr spectrum of the 6-deutero analogue of **1d** (see for its preparation the experimental)-that the doublet at 4.45 has to be ascribed to H-6. The upfield shift of $\triangle\delta$ = 4.85 ppm for H-6, when changing the solvent from deuteriochloroform(perdeuteriomethanol) to ammonia, strongly suggests that the addition takes place at C-6. These results and those obtained from previous studies indicate that generally in *N*-benzylpyrimidinium salts position 6 is the most favored for addition, however, addtion at position 2 is favored when position 6 is blocked and the *N*-methylene group is deprotonated. Treatment of the benzylpyrimidinium bromides **1a-1d** with hydrazine at room temperature gives pyrazole, 3,5-dimethylpyrazole and 3-*t*-butylpyrazole, respectively, in reasonable yields (~ 70%). This behavior towards hydrazine is identical to that found with *N*-methylpyrimidinium salts (8). Thus, there is no difference in reactivity between the *N*-benzyl- and *N*-methylpyrimidinium salts towards hydrazine. This similarity in reactivity suggests that hydrazine, being a weaker base than ammonia, is less able to deprotonate the *N*-benzyl group.

EXPERIMENTAL

The ^{1}H-nmr spectra were obtained with a Hitachi Perkin-Elmer R-24B, a Varian XL 100-15 and a Varian EM-390 spectrometer. TMS (δ = 0.00) was used as internal standard. In liquid ammonia the solvent peak was used as standard. The spectra were converted to the TMS scale by addition of 0.95 ppm.

The following pyrimidines were prepared by procedures described in the literature: pyrimidine (4), 4,6-dimethylpyrimidine (8,9), 4-*t*-butylpyrimidine (10) and 4,6-di-*t*-butylpyrimidine (11).

Preparation of 2-Deutero-4,6-dimethylpyrimidine.

One g of 2-hydrazino-4,6-dimethylpyrimidine (12) was suspended in deuterium oxide (10 ml), 5 g of silver acetate was added in portions and the mixture was stirred at room temperature for 24 hours. The product was isolated by the procedure as described for 5-nitropyrimidine from 4,6-dihydrazino-5-nitropyrimidine (13).

Preparation of 6-Deutero-4-*t*-butylpyrimidine.

To a solution of 10 g of 6-chloro-4-*t*-butylpyrimidine (14) in 110 ml of absolute ethanol, a solution of 1.92 g of anhydrous hydrazine in 15 ml of absolute ethanol was added dropwise at room temperature. The mixture was refluxed with stirring for 4 hours and after cooling the precipitate obtained was filtered off. The precipitate was treated with silver acetate in deuterium oxide according to the procedure given above. Also the isolation was carried out analogously (13).

General Procedure for the Preparation of the *N*-Benzylpyrimidinium Salts (**1a-1d**).

A solution of 1 g of the appropriate pyrimidine (pyrimidine, 4,6-dimethylpyrimidine, 4-*t*-butylpyrimidine) in 6 ml of toluene was heated with 1.1 molar equivalents of benzyl bromide or *p*-nitrobenzyl bromide at 100° for 1-3 hours. The white precipitate was filtered off, washed with ether and crystallized. The yields and physical data of the *N*-benzylpyrimidinium bromides are summarized in Table II.

General Procedure for the Reaction of *N*-Benzylpyrimidinium Bromide Derivatives with Liquid Ammonia.

One g of the pyrimidinium salts in 20 ml of freshly destilled liquid ammonia was allowed to react at -33° for 2 hours, after which the ammonia was evaporated. The residue obtained was separated by column chromatography using silica gel and chloroform-acetone (1:1) as eluent. By addition of methanol, **2b** could be separated from **1b** and *p*-nitrobenzylamine from **1c**. All compounds were identified by their mp (or in case of a liquid by the mp of their picrate) and by their ^{1}H-nmr data.

General Procedure for the Reaction of *N*-Benzylpyrimidinium Salts with hydrazine Hydrate.

A mixture of 1 g of the compounds **1a-d** and a threefold molar amount of hydrazine hydrate was stirred at room temperature for 4 hours, 10 ml of a 30% aqueous solution of potassium hydroxide was added and the basified solution was extracted with chloroform. After drying the extracts over magnesium sulphate, the solvent was evaporated and the residue was put on a column with silica gel and eluted with ether.

The pyrazoles obtained were known compounds and could easily be identified by their mp (or the mp of their picrates) and by their ^{1}H-nmr spectra.

REFERENCES AND NOTES

(1) Part **85** Pyrimidines from this laboratory. For part **84** see N. J. Kos and H. C. van der Plas, *J. Org. Chem.*, **46**, 5000 (1981).

(2) Part **31** on nmr-studies of σ-adducts. For part **30** see A. Counotte-Potman, H. C. van der Plas, A. van Veldhuizen and C. A. Landheer, *J. Org. Chem.*, (1981) submitted. Part **23** in the series of "Ring Transformations of Heterocyclic Compounds with Weak Nucleophiles", for Part **22** see C. Gönczi, Z. Swistun and H. C. van der Plas, *J. Org. Chem.*, **46**, 608 (1981).

(3) E. A. Oostveen, H. C. van der Plas, H. Jongejan, *Rec. Trav. Chim.*, **93**, 114 (1974).

(4) E. A. Oostveen, H. C. van der Plas, H. Jongejan, *ibid.*, **95**, 209 (1976).

(5) For a recent review on this subject see H. C. van der Plas, *Acc. Chem. Res.*, **11**, 462 (1978).

(6) J. A. Zoltewicz and J. K. O'Halloran, *J. Am. Chem Soc.*, **97**, 5531 (1975).

(7) F. Roeterdink and H. C. van der Plas, *Rec. Trav. Chim.*, **95**, 282 (1976).

(8) H. C. van der Plas, H. Jongejan, *ibid.*, **87**, 1065 (1968).

(9) H. Bredereck, R. Gompper and G. Morlock, *Chem. Ber.*, **90**, 942 (1957).

(10) H. Bredereck, R. Gompper and B. Geiger, *ibid.*, **93**, 1402 (1960).

(11) H. C. van der Plas, A. Koudijs, *Rec. Trav. Chim.*, **97**, 159 (1978).

(12) M. P. V. Boarland, J. F. W. McOmie, *J. Chem. Soc.*, 4961 (1952).

(13) H. C. van der Plas, H. Jongejan, A. Koudijs, *J. Heterocyclic Chem.*, **15**, 485 (1978).

(14) B. Capon, N. B. Chapman, *J. Chem. Soc.*, 600 (1957).