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A METHOD FOR THE DEMETHYLATION OF N^+-METHYL QUATERNARY AMMONIUM SALTS

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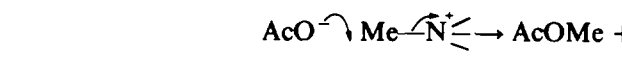
Abstract—It is shown that heating an N^+-Me quaternary acetate in an aprotic solvent, or solvent mixture, with a low dielectric constant is an efficient method for converting the salt to the demethylated amine.

SEVERAL methods exist for the demethylation of N^+-Me quaternary ammonium salts. Each of these can be useful in certain cases, though all suffer from disadvantages. This paper describes a further method which is to be seen as complimentary to those already available since it does not have several of the drawbacks of other methods but does have its own limitations.

Of the methods available for demethylation of quaternary salts, four are most frequently utilised. The classical method[1] involves pyrolysis of the chloride form of the salt when the base and methyl chloride are formed. High temperatures (often 200° or more) are necessary. An analagous process utilising iodide from lithium iodide is carried out in refluxing decanol[2] (230°). Hydride from LAH[3] and thiophenoxide[4] are nucleophiles which displace tertiary amine from an N^+-Me quaternary salt with the concomitant formation of methane and methyl phenyl sulphide respectively. Neither method can be used for salts containing ester substituents since both reagents react with such groups. The fourth widely used method[5] involves heating the quaternary salt in ethanolamine when transfer of the quaternary Me group to the ethanolamine occurs. Here again side reactions can complicate the reaction.

The process we have examined involves heating a quaternary salt in the form of its acetate at temperatures from 60° to 140°. The acetate ion acts as a nucleophile and methyl acetate is formed as a detectable biproduct. The process is essentially irreversible under the conditions employed. Methyl acetate does not react at all with the tertiary amines we have examined at reflux temperatures.



The reaction is conveniently carried out in a suitable solvent. Isolation of the product is usually simple since the final reaction mixture contains only solvent (including a trace of methyl acetate), product amine and any unchanged starting material.

The observation[6] which initiated this enquiry was of the demethylation of reserpine

methacetate in benzene solution. We have found subsequently that, not surprisingly, the solubility of this particular salt in a hydrocarbon solvent is exceptional. Usually a more polar co-solvent is required to take a methacetate into solution in a hydrocarbon. We have examined the effect of changing the solvent composition on the rate of demethylation and also the relative ease of demethylation of simple aliphatic and aromatic amine methacetates. Finally, to test the usefulness of the process for more complex molecules, we have demethylated some alkaloid methacetates by this method.

Aromatic amine methosalts (*runs* A *to* N *in Table*). The methacetate of N,N-dimethylaniline was easily demethylated, giving only N,N-dimethylaniline, in solution in mixtures of benzene and chloroform or even in suspension in benzene alone (run L) at temperatures of 60° to 80°. Kinetic analysis of the homogeneous reactions (runs A to D) showed that the greater the percentage of chloroform the slower the reaction, though all proceeded in one or two hours to yields in excess of 90%. Acetonitrile (run E) could also be used as a co-solvent. Even comparitively small amounts of methanol in benzene (runs F to I) slowed the demethylation down extensively. In the extreme, reflux in methanol alone gave only a 1% yield of amine after 20 hr.

The use of methylene chloride as co-solvent with benzene proved undesirable (runs J and K). Although demethylation occurred, during reflux, a salt, which proved to be the methochloride of N,N-dimethylaniline, separated from the solution thus reducing the overall yield. As will be seen later, a similar drawback was encountered in the demethylation of aliphatic amine methacetates using chloroform. For these reasons chlorinated solvents, though useful in other respects as co-solvents, are best avoided for the demethylation process.

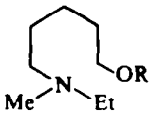
A comparison of the effect of solvent dielectric constant was obtained from runs in dimethylformamide and chloroform (runs M and A) at 60°. The rate of demethylation was slower in the solvent (DMF) of higher dielectric constant.

N,N-Dimethyl-*p*-toluidine methacetate demethylated at a slower rate than the corresponding aniline derivative (runs E and N).

Simple aliphatic amine methosalts (*runs* O *to* U *in Table*). The methosalts of aliphatic amines proved to be more difficult to demethylate than those of the less basic aromatic amines. N-Methylpiperidine methacetate was demethylated in 88% yield, giving only N-methylpiperidine, at 100° in solution in xylene-acetonitrile for 24 hr. Once again the greater the percentage of polar co-solvent the slower the rate of demethylation. No demethylation at all could be detected when only 1% of methanol was added to a benzene solution as co-solvent. The drawback discussed for the aromatic amines with methylene chloride occurred even with chloroform in the aliphatic series. N-Methylpiperidine methochloride crystallized out of a refluxing solution of the corresponding methacetate in benzene–chloroform.

Examination of the products of heating the methacetate of N-ethylpiperidine in benzene-acetonitrile showed that a minimum yield of 84% of mixture of N-ethylpiperidine and N-methylpiperidine (2·6:1) was formed. There was an indication in the mass spectrum of the total crude basic product of the alcohol (1, R = H) formed during work up from the acetate (1, R = Ac), the product of the alternative nucleophilic attack at ring carbon.

Alkaloid methosalts (*runs* V *to* X *in Table*). The methacetates of isoreserpine (**2**), yohimbine (**3**) and strychnine (**4**) were successfully demethylated in high yields.



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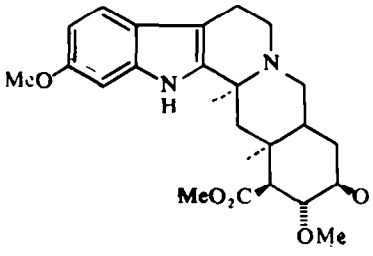

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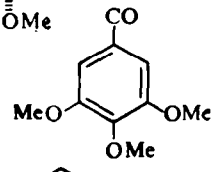

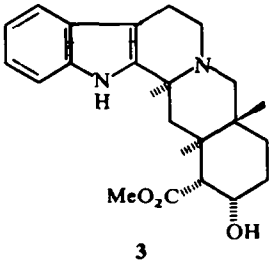

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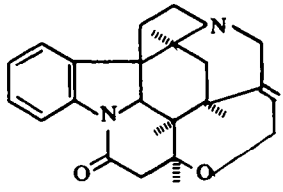

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CONCLUSIONS

The optimum conditions for the demethylation of a methacetate vary with the structure of the base. Weaker aromatic bases require temperatures of the order of 80° whilst aliphatic amine methacetates require heating at 110° to 140°. Reaction proceeds best for aromatic and aliphatic amine salts in non-polar aprotic solvents. The reaction is faster the lower the overall dielectric constant of the solution. An aromatic hydrocarbon and the minimum of acetonitrile is a good combination. Though only a small percentage of a protic solvent such as methanol is necessary to take a methacetate into solution, the consequent extreme deactivation of the demethylation process far outweighs this advantage and methanol is consequently not a useful co-solvent for this process. The superiority of non-polar aprotic solvents presumably reflects their poor solvation of the ionic starting materials relative to a less ionic transition state for demethylation.

EXPERIMENTAL

Preparation of methacetates from methiodides. A column of Amberlite I.R.A. 400 (chloride form) was washed with aq NaOAc (20%) until the eluate was free from Cl^-. The resin was then washed with H_2O and finally with MeOH till eluates, in each case, left no residue on evaporation.

A soln of the methiodide in MeOH was passed slowly through the column. The eluate was evaporated and last traces of solvent removed at 10^{-1} mm Hg. The simple methacetates were all crystalline but highly hygroscopic.

Kinetic and yield analysis of aromatic amine methacetate demethylations. These reactions were followed by removing aliquots at various times and assessing the product base concentration by quantitative UV spectroscopy (the maximum at ca 300 mμ is not present in the spectra of the salts). The products were all homogeneous by TLC.

Table 1

Run	Salt	Solvent(s)	% composition by volume	Time (min) for 50% yield	Yield after x hr t°			conc (g/l)
A	$PhN^+Me_3\ OAc^-$	$CHCl_3$	100	36	82	7	61	10·4
B	$PhN^+Me_3\ OAc^-$	$CHCl_3$–PhH	75–25	20	95	7	65	11·5
C	$PhN^+Me_3\ OAc^-$	$CHCl_3$–PhH	50–50	10	97	7	70	10·1
D	$PhN^+Me_3\ OAc^-$	$CHCl_3$–PhH	17–83	3	99	7	77	7·6
E	$PhN^+Me_3\ OAc^-$	MeCN–PhH	25–75	9	94	7	74	11·1
F	$PhN^+Me_3\ OAc^-$	MeOH	100	—	1	20	65	4·9
G	$PhN^+Me_3\ OAc^-$	MeOH	100	—	2	5	80[a]	50
H	$PhN^+Me_3\ OAc^-$	MeOH–PhH	4·7–95·3	—	33	7	66	10·9
I	$PhN^+Me_3\ OAc^-$	MeOH–PhH	1–99	12	94	7	77	10·4
J	$PhN^+Me_3\ OAc^-$	CH_2Cl_2	100	—	27[b]	7	40	11·7
K	$PhN^+Me_3\ OAc^-$	CH_2Cl_2–PhH	50–50	56	61[b]	7	52	10·2
L	$PhN^+Me_3\ OAc^-$	PhH[c]	100	59	100	7	80	10·1
M	$PhN^+Me_3\ OAc^-$	DMF	100	102	83	7	60	10·8
N	$pMeC_6H_4$–$N^+Me_3\ OAc^-$	MeCN–PhH	25–75	22	100	7	73	9·2
O	N-methylpiperidine methacetate	MeCN	100	[d]	0	24	80	20·9
P	N-methylpiperidine methacetate	MeCN	100	[d]	9·5	24	112[a]	32·1
Q	N-methylpiperidine methacetate	MeCN–xylene	29–71	[d]	19	24	96	36·8
R	N-methylpiperidine methacetate	MeCN–PhH	17–83	[d]	13	24	78	4·1
S	N-methylpiperidine methacetate	MeCN–PhMe	17–83	[d]	64	24	91	4·3
T	N-methylpiperidine methacetate	MeCN–xylene	13–87	[d]	88	24	101	4·5
U	N-ethylpiperidine methacetate	MeCN–xylene	15–85	[d]	84[e]	24	102	4·4
V	isoreserpine methacetate	PhMe	100	[d]	81	8·5	111	1·9
W	yohimbine methacetate	MeCN–xylene	50–50	[d]	80	14	140[a]	2·9
X	strychnine methacetate	MeCN–PHMe	50–50	[d]	90	12	112[a]	3·5

[a] In an evacuated sealed tube.
[b] Low yield due to irreversible separation of insoluble methochloride.
[c] Suspension.
[d] Not determined.
[e] Mixture (2·6:1) of N-ethylpiperidine and N-methylpiperidine.

Product and yield analysis of aliphatic amine methacetate demethylations. These reactions were analysed by passing the total reaction solution down a column of Al_2O_3, 'H'. The eluate together with Et_2O washings of the column was divided into two portions. The first portion was reacted with MeI, evaporated and the residual methiodide derived thereby from product base, weighed. The second portion was treated with conc HCl and all solvents removed under vacuo. The resultant hydrochloride (or hydrochloride mixture) was basified with NaOH and extracted into a small volume of Et_2O. The Et_2O solution was used directly for GLC analysis using a 4 ft silanised glass column packed with 20% Carbowax 15–20 M on 2% KOH washed M and B Embacel.

Representative demethylation procedures

(a) N,N-Dimethylaniline methacetate (667 mg) was refluxed in PhH–MeCN (45 ml–15 ml) at 74° for 1 hr. The solvents were evaporated and the residue partitioned between H_2O and Et_2O. The organic phase was dried and evaporated to give N,N-dimethylaniline (379 mg, 90%).

(b) N-Methylpiperidine methacetate (520 mg) was refluxed in xylene–MeCN (100 ml–15 ml) at 101° for 24 hr. The soln was cooled and passed through Al_2O_3 'H' washing with Et_2O. The total eluate was treated with conc HCl and the solvents evaporated to give N-methylpiperidine hydrochloride (358 mg, 88%).

(c) Yohimbine methacetate (m.p. 210–215° dec, Found: C, 62·9; H, 7·4; N, 5·7; $C_{24}H_{32}N_2O_5 \cdot 2H_2O$ requires: C, 62·1; H, 7·4; N, 5·7%) (29 mg), xylene (5 ml) and MeCN (5 ml) were heated in a sealed tube at 140° for 14 hr. The reaction mixture was evaporated and the residue partitioned between H_2O and $CHCl_3$. The organic layer was dried and evaporated to give crude yohimbine (20 mg, 80%) identified after crystallization by the usual means.

(d) Strychnine methacetate (m.p. 213–217° dec, Found: C, 70·3; H, 7·2; N, 6·7; $C_{24}H_{28}N_2O_4$ requires: C, 70·6; H, 6·9; N, 6·9%) (42 mg), PhMe (6 ml) and MeCN (6 ml) were heated in a sealed tube at 112° for 12 hr. The solvents were evaporated and the residue partitioned between H_2O and $CHCl_3$. The organic phase was dried and evaporated to give crude strychnine (32 mg, 90%) identified after crystallization by the usual means.

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