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O-Substituted Pyridine-N-oxide Derivatives

1. N-Trimethylammoniumethoxy-Pyridinium Compounds, a New Type of Choline Derivatives

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The synthesis of a series of O-substituted pyridine-*N*-oxides containing an *N*-trimethylammoniumethoxy substituent is described. This new type of choline derivatives was obtained by a reaction between the *N*-oxide and bromocholine.

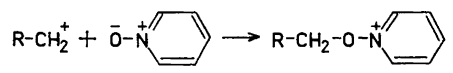
The reaction of amine oxides with alkyl halogenides to form C-alkyl compounds, known since the classical experiments of Meisenheimer in 1913 [1], has also been studied with pyridine-*N*-oxides [2,3]. Particular interest in the quaternary salts formed arose when it was demonstrated that these compounds are decomposed by alkali to tertiary amine and aldehyde [4]. This is a suitable method for preparing aromatic aldehydes and for deoxygenating pyridine-*N*-oxides under non-reducing conditions [3,5].

In the following report is described the synthesis of a series of O-substituted pyridine-*N*-oxides containing an *N*-trimethylammoniumethoxy substituent. This new type of choline derivatives was obtained by a reaction between the *N*-oxide and bromocholine. The biological properties of these compounds are under investigation.

In the cases of pyridine-*N*-oxide and its monomethyl derivatives, the *N*-oxide and bromocholine reacted readily when heated at about 120°C in the absence of any solvent. When the technique was applied to the dimethylpyridine-*N*-oxides, degradation of these compounds occurred, giving rise to a brownish mass of unknown composition. The reaction between these N-oxides and bromocholine was therefore carried out in a solvent, acetonitrile giving the best results except in the case of 2,6-lutidine-*N*-oxide.

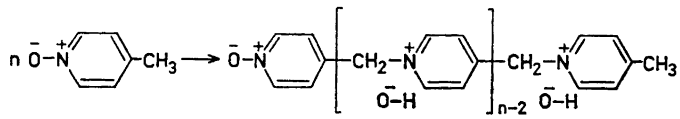
The reaction between the two components, being used in concentrated solutions, probably proceeds as a S_N1 reaction according to the following sequence of reactions:

$$R\text{-}CH_2\text{-}Br \longrightarrow R\text{-}CH_2^+ + Br^-$$



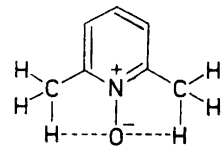
The more readily Br is split off as anion, the higher is the reaction velocity. This splitting is determined by the polarisation of the C—Br bond, being increased both by the inductive effect of the quaternary ammonium group in bromocholine and by the polar *N*-oxide present. The carbenium cation formed reacts with the electron-donating oxygen in the *N*-oxide. This reaction is obviously dependent also on the polarity of the N—O bond in the *N*-oxide, which in its turn is regulated by the inductive and hyperconjugation (Baker-Nathan) effects of the methyl groups in the ring.

With two exceptions the reaction proceeded without complications. In the case of 4-methylpyridine-*N*-oxide (4-picoline-*N*-oxide) a violent exothermic reaction started when it was melted with bromocholine. The boiling mass resulted in a viscous dark-brown product. Part of the original *N*-oxide was degraded to 4-picoline by the high temperature of the reaction mixture. The brown mass consisted of a polymerisation product, probably being formed according to the following reaction:



This process is analogous with the thermic polymerisation shown by 4-chloropyridine [6].

Bromocholine and 2,6-lutidine-*N*-oxide (in contradistinction to the other dimethyl derivatives used) reacted only in aqueous solution; no reaction occurred in acetonitrile or by melting the two compounds together. We suggest, as a possible explanation for this phenomenon, that weak H-bonds block the oxygen in the *N*-oxide (I), thus preventing it from reacting with the carbenium ion. A similar idea was proposed recently by Jerchel and Melloh[7] for 2-substituted



(I)

pyridine-*N*-oxides with active hydrogen atoms in the substituents (OH, NH_2, CH_3), for which hydrogenation (deoxygenation) proceeds at a much lower rate than for 3- and 4-substituted *N*-oxides. Steric hindrance may also partly be a determining factor for the lower reactivity of 2,6-dimethylpyridine-*N*-oxide. The fact that the reaction proceeds in aqueous solution, but not in acetonitrile, may be due to the much higher dielectric constant of water.

EXPERIMENTAL

2,5- and 3,5-Lutidine-*N*-oxides

The *N*-oxides used (with two exceptions) were either synthesised according to previously described methods (Table 1) or purified from commercial grade products. The synthesis of the 2,5- and 3,5-lutidine-*N*-oxides, not previously described in the literature, was performed according to a general method described by Thomas and Jerchel [8].

Table 1. *N*-Oxides of the pyridine-series used and references to methods for their synthesis.

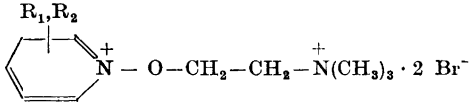
N-oxide	b.p. or m.p.*	Authors	Ref.
Pyridine-*N*-oxide	138–140/15	Ochiai 1953; see also Thomas and Jerchel 1958	4,8
2-Picoline-*N*-oxide	123–124/15	Boekelheide and Linn 1954	9
3-Picoline-*N*-oxide	146–149/15	*Idem*	9
4-Picoline-*N*-oxide	185–186 *	*Idem*	9
2,4-Lutidine-*N*-oxide	148/13	*Idem*	9
2,5-Lutidine-*N*-oxide	149/23	Present authors	
2,6-Lutidine-*N*-oxide	115–119/18	Boekelheide and Linn 1954	9
3,5-Lutidine-*N*-oxide	166–168/23	Present authors; picrate, see Shindo 1956	10

A mixture of lutidine (10 g, 93 mmoles), glacial acetic acid (25 ml) and 30 % hydrogen peroxide (12.5 ml) was refluxed for 8 h on a water bath at 80°C; an addition of another 9 ml H_2O_2 was made after 3 h. The mixture was left for 15 h at 35°C, evaporated under vacuum to half its volume and mixed with the same volume of water. After evaporation under vacuum in a boiling water bath to completely remove all water, an equal volume of chloroform and dry Na_2CO_3 was added until no more CO_2 was evolved. After 24 h at room temperature, the crystals formed were treated with three volumes of chloroform under stirring. Sodium acetate and Na_2CO_3 were filtered off, and the clear chloroform solution was evaporated under vacuum in a boiling water bath.

2,5-Lutidine-N-oxide and its picrate. The residue was fractionated under vacuum on an oil bath. The *N*-oxide (b.p. 149°C) was obtained as a colourless liquid in 62 % yield (7.15 g); 0.3 g (2.4 mmoles) was dissolved in 1 ml water, and 30 ml of a saturated aqueous solution of picric acid was added. The *N*-oxide picrate was precipitaed immediately, isolated by filtration after 3 h at room temperature and washed carefully with water. The pure product in the form of yellow blades, recrystallised three times from absolute ethanol, had m.p. 128–129°C. Yield 46.5 % (0.4 g). Because the m.p. found was close to that of picric acid (122–123°C), the mixed m.p. of the two compounds was measured and found to be 95–108°C; the m.p. of 2,5-lutidine picrate was 169°C. Analyses of 2,5-lutitine-*N*-oxide picrate, calc. for $C_{13}H_{12}O_8N_4$ (352.16): C 44.33; H 3.44; N 15.91. Found: C 44.62; H 3.47; N 15.94.

3,5-Lutidine-N-oxide and its picrate. The residue (from above), a hygroscopic almost colourless crystalline mass, was distilled by fractionation under vacuum over an open flame; steam was introduced into outer jacket of the condenser, since the *N*-oxide easily solidified there at lower temperature. The pure product, b.p. 166–168°C/23, was a colourless liquid which solidified immediately in the receiver and was very hygroscopic. It can, if desired, be recrystallised from a small amount of benzene and washed with benzene-petrol ether (1:1). The picrate was made in the same way as described for 2,5-lutidine-*N*-oxide picrate (see above) and was isolated as small yellow needles, m.p. 135–136°C. Yield 65.2 % (0.56 g). This picrate has been described previously by Shindo [9] who reported m.p. 138–139°C.

Table 2. Melting points, analytical data and yield of the compounds synthesised



Derivative	Code	Mol. formulae	Mol. wt.	m.p. °C	% C		% H		% N		% Br		Yield	
					calc.	found	calc.	found	calc.	found	calc.	found	g	% of theor.
Pyridinium (R_1, R_2 = H)	AH 7	$C_{10}H_{18}ON_2Br_2$	342.09	198	35.11	35.07	5.34	5.44	8.19	8.00	46.7	46.9	1.04	75
Picolinium (R_1= CH_3, R_2= H):														
2–	AH 6	$C_{11}H_{20}ON_2Br_2$	356.12	196	37.10	37.11	5.66	5.63	7.87	7.65	44.9	44.8	0.45	51
3–	AH 8	$C_{11}H_{20}ON_2Br_2$	356.12	175	37.10	37.42	5.66	5.75	7.87	7.57	44.9	44.5	0.20	14
4–	AH 18	$C_{11}H_{20}ON_2Br_2$	356.12	190 *	37.10	36.82	5.66	6.06	7.87	8.03	44.9	44.5	0.25	50
Lutidinium (R_1, R_2= CH_3):														
2,4–	AH 21	$C_{12}H_{22}ON_2Br_2 \cdot H_2O$	388.16	195–195.5	37.13	36.50	6.23	6.43	7.22	7.21	41.2	40.9	0.31	67
2,5–	AH 22	$C_{12}H_{22}ON_2Br_2 \cdot H_2O$	388.16	191	37.13	37.59	6.23	6.47	7.22	7.17	41.2	40.9	0.23	49
2,6–	AH 24	$C_{12}H_{22}ON_2Br_2 \cdot 2H_2O$	406.18	175–175.5	35.48	35.37	6.45	6.19	6.90	6.86	39.4	40.4	0.16	9.5
3.5–	AH 20	$C_{12}H_{22}ON_2Br_2$	370.14	196.5–197	38.94	38.52	5.99	6.15	7.57	7.66	43.2	42.0	0.45	100

* See text for comments on this melting point.

N-Trimethylammoniumethoxy-pyridinium aibromides

General techniques used in preparing the choline derivatives. A mixture of the *N*-oxide and finely powdered bromocholine bromide (BrCh) was heated for various periods of time. After completion of the reaction, the product was isolated in crystalline form and recrystallised. All compounds synthesised were readily soluble in water and methanol, and decomposed on melting. Table 2 summarises melting points (uncorrected), analytical data and yield.

N-Trimethylammoniumethoxy-pyridinium dibromide (AH 7). A mixture of 1.0 g (4.1 mmoles) of BrCh and 3.0 g (31.6 mmoles) of pyridine-*N*-oxide was heated on a paraffin bath at 140°C for 5 min. After 1 min, the BrCh had dissolved and the reaction product had begun to crystallise out; some *N*-oxide was decomposed during the reaction (smell of pyridine). After cooling, 50 ml of benzene was added to the reaction mixture; the insoluble crystals were isolated by filtration and recrystallised from methanol-acetone. The product was obtained as colourless prisms which were soluble in hot methanol and slightly soluble in acetone. This synthesis was also carried out with acetonitrile as solvent, the constituents being boiled for 6 h, which gave the same yield.

N-Trimethylammoniumethoxy-2-picolinium dibromide (AH 6). BrCh (0.61 g, 2.5 mmoles) was suspended in 1.2 g (11 mmoles) of 2-picoline-*N*-oxide and heated on a paraffin bath at 140°C until all BrCh had dissolved (about 5 min). After cooling the reaction product crystallised as small needles. The crystalline mass was treated with benzene, filtered off and washed with the same solvent. The colourless needles were readily soluble in glacial acetic acid and slightly soluble in acetone and benzene.

N-Trimethylammoniumethoxy-3-picolinium dibromide (AH 8). 3-Picoline-*N*-oxide (1.1 g, 10 mmoles) and BrCh (1.0 g, 4 mmoles) were heated with stirring on a paraffin bath at 130°C, giving after 5 min a homogeneous dark-brown mass. After heating for another 2 min and cooling, ethanol (3 ml) was added followed by acetone until crystallization began. The reaction product was extremely hygroscopic, and special precautions were therefore undertaken during filtration. The crystalline mass was transferred to a glass filter (No. 3); during sucking care was taken to keep the mass moist with solvent. Washing was performed with acetonitrile in the same way, and the crystalline mass, still wet with acetonitrile, was rapidly transferred to a test tube and dissolved in as small an amount of methanol as possible. Three volumes of acetonitrile were added, and the brown solution treated with active carbon and filtered. Methanol was evaporated by heating the colourless filtrate on a water bath, when the product crystallised. After complete crystallisation in a closed bottle, the colourless needles were filtered off and washed with acetonitrile in the way described. The final product in the glass filter was transferred to a desiccator, which was evacuated; the product was slightly soluble in acetone and acetonitrile.

N-Trimethylammoniumethoxy-4-picolinium dibromide (AH 18). A mixture of 0.35 g (1.4 mmoles) BrCh and 0.35 g (3.2 mmoles) 4-picoline-*N*-oxide was refluxed with 1 ml acetonitrile in a boiling water bath for 10 h. BrCh was slowly dissolved with simultaneous crystallisation of the reaction product as brownish grey prisms. After completions of the reaction and the addition of 4 ml of acetonitrile, the crystals were filtered off and washed with acetonitrile and acetone. The crude product melted at 182—184°C (decomp.) Recrystallisation from *n*-butanol gave the pure compound as light brown prisms which were slightly soluble in acetone, *iso*propanol and ethyl acetate. Depending on the rapidity of heating, the compound melted at 182—190°C (melting occurred within one degree in this region). The brownish colour could not be removed with active carbon.

N-Trimethylammoniumethoxy-2,4-lutidinium dibromide (AH 21). BrCh (0.3 g, 1.2 mmoles), 2,4-lutidine-*N*-oxide (0.3 g, 2.4 mmoles) and 1 ml acetonitrile were refluxed for 18 h on a boiling water bath. The crystals formed were filtered off and washed with acetonitrile and acetone. The crude product (brown prisms, m.p. 193—194°C, decomp.) was dissolved in 1 ml methanol and 1.5 ml *n*-butanol, the solution treated with active carbon and filtered. Methanol was evaporated by gently heating on a boiling water bath. On cooling, small colourless prisms crystallised out and the product, readily soluble in ethanol and slightly soluble in aceton, *iso*propanol and ethyl acetate, was shown to be chromatographically pure.

N-Trimethylammoniumethoxy-2,5-lutidinium dibromide (AH 22). The synthesis was carried out in the same way as described for AH 21. The compound formed crystallised from *n*-butanol as rhombic crystals which were hygroscopic and had the same solubilities in various solvents as was reported for AH 21.

N-Trimethylammoniumethoxy-2,6-lutidinium dibromide (AH 24). BrCh (1.0 g, 4.1 mmoles), 2,6-lutidine-N-oxide (1.0 g, 8.1 mmoles) and 2 ml water were heated in a bomb tube at 100°C for 18 h. Part of the *N*-oxide was decomposed during the reaction, and some BrCh was left unchanged, as could be demonstrated by a paper chromatographic analysis. Because the reaction product and BrCh showed similar solubility in various organic solvents, and consequently, recrystallisation of the reaction mixture resulted in an appreciable loss of the *N*-substituted lutidinium derivative, the mixture was treated in the following way. The remaining BrCh was forced to react by pouring out the reaction mixture in a petri dish kept on a boiling water bath until all water had evaporated. The same volume of water was then added and evaporated in the same way. The brownish crystalline mass was shown chromatographically to be free of BrCh. The lutidine formed was removed by two extractions with 50 ml chloroform. The remaining product was treated with absolute ethanol, filtered off, washed carefully with the same solvent, and dried in a desiccator over KOH under vacuum. The crude product (260 mg) melted at 170—172°C (decomp.). The greyish crystalline powder was dissolved in as small an amount of boiling ethanol as possible, was treated with active carbon, and the solution filtered. On cooling the pure compound crystallised as hygroscopic colourless prisms, soluble in ethanol and slightly soluble in chloroform and acetone.

N-Trimethylammoniumethoxy-3,5-lutidinium dibromide (AH 20). The synthesis was carried out in the same way as was described for AH 21, except that the reaction was completed after 8 h. Acetonitrile (2 ml) was added to the reaction mixture, the crystals were filtered off and washed with acetonitrile and acetone. Recrystallisation from *n*-butanol gave the pure product as colourless blades, which were somewhat hygroscopic, and showed solubility properties similar to those of the other compounds in this series.

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