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The Methylation of Nicotine with Methyl-lithium

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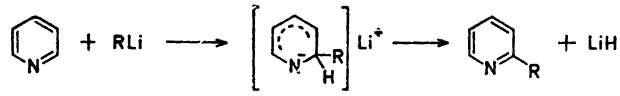
The alkylation of nicotine with methyl-lithium gives as the main product 6-methylnicotine together with 4-methylnicotine. 2-Methylnicotine is possibly also formed in trace amounts. Some physiological properties of 4-methyl- and 6-methylnicotine are briefly reported.

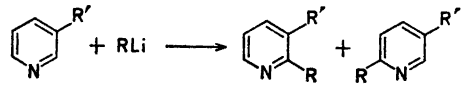
During an investigation regarding the relations between structure and biological activity of nicotine-like compounds,[1–3] nicotine homologues with alkyl groups in the pyridine ring were required.

Ziegler and Zeiser's [4] method of alkylating and arylating pyridine with organo-lithium compounds involves the formation of an intermediate which on heating eliminates lithium hydride to give the 2-substituted pyridine:



The formation of a 4-substituted pyridine has not been reported in this reaction but is known to occur in the arylation of acridine (in the 9-position) with lithium aryls.[5] 4-Substituted pyridines may, however, result when organo-magnesium compounds are used.[6,7]

The addition of an organo-lithium reagent to a 3-substituted pyridine may give two isomers.



Abramovitch and coworkers [8a,8b] found that the reaction of phenyllithium with 3-substituted pyridines (methyl, ethyl, isopropyl) gave preferentially 2-substitution. If the 3-substituent was sufficiently bulky (tert. butyl, phenyl) substitution occurred largely in the 6-position. Phenylation of nicotine [8a] yielded equal amounts of 2- and 6-substituted products.

When nicotine was treated with an equimolar amount of methyl-lithium according to the traditional method (see Exptl. part), the product mixture was found by gas-liquid chromatography (GLC) to consist mainly of starting material and two products A and B, one of them, B, in trace amounts (Table 1, expt. 1). With two equivalents of methyl-lithium the amount of unchanged starting material was decreased while the yield of minor product B increased (Table 1, expt. 2).

Table 1. Nicotine and methyl-lithium.

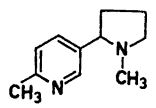
Expt. No.	MeLi/nicotine ratio	Solvent	Products % A	B	Recovered start. mat. %
1	1	ether, toluene	22	<1	46
2	2	» »	20	4	11
3	2	» decalin	37	1	18

In the last experiment (Table 1, expt. 3) decalin was substituted for toluene. The yield of product A increased while that of B decreased.

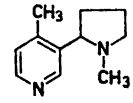
The reaction products were isolated by preparative GLC and investigated.

The major reaction product A afforded 6-methylnicotinic acid and isocinchomeronic acid on permanganate oxidation. The minor product B gave 4-methylnicotinic acid and cinchomeronic acid (identified as methyl esters by GLC and IR).

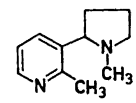
The NMR-spectra (Table 4) agreed with the structures indicated by the oxidative degradations and so did the elementary analyses of the picrates. Thus product A is 6-methylnicotine and product B 4-methylnicotine.



A



B



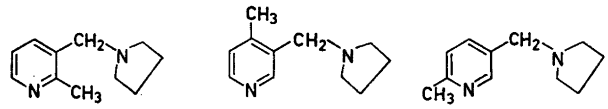
C

The signals given by the two methyl groups of 4-methylnicotine appeared at 2.19 and 2.33 ppm, while those of 6-methylnicotine appeared at 2.10 and 2.46 ppm. It is likely that the signals from the nuclear methyl groups in both products are those with the largest δ-values as the shifts of the remaining methyl groups closely resemble that of the *N*-methyl group of nicotine (2.12 ppm).

The third possible product C, 2-methylnicotine, could not be isolated. However when the entire product mixture from experiment 2 (Table 1) was oxidized with permanganate and esterified, the presence of trace amounts of 2-methylnicotinic acid methyl ester and quinolinic acid dimethyl ester was indicated by means of GLC-analysis. It must be considered very likely that 2-methylnicotine is also formed during the methylation reaction.

Abramovitch [8c] has observed useful empirical correlations for disubstituted pyridines in the 1500—1600 cm^{-1} infrared region. The disubstituted pyridines

can thus be divided into two groups. The 2,3- and 2,6-substituted pyridines exhibit a band in the range 1578—1588 cm^{-1} while 2,4-, 3,4- and 2,5-substituted pyridines show a band in the 1599—1605 cm^{-1} region. A second band (Band II, Table 2) at a somewhat lower wave number was generally observed in both groups but was considered to be less characteristic.



The absorption in this infrared region (1500—1600 cm^{-1}) of the isomeric *N*-(2-, 4- and 6-methyl-3-picolyl)-pyrrolidines [9] were compared with those of products A and B.

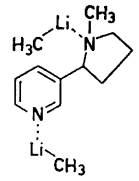
Table 2. IR-absorptions of some disubstituted pyridines.
(s = strong, m = medium, w = weak and sh = shoulder).

Substituent R-	*N*-(R-3-picolyl)-pyrrolidine Band I	Band II	R-nicotine I	II in cm^{-1}
6-Me-	1603 (s)	1574 (m)	1603 (s)	1575 (m)
4-Me-	1599 (s)	1566 (w)	1600 (s)	1565 (w)
2-Me-	1588 (m,sh)	1579 (s)		

Table 2 shows good agreement of the band wave numbers of the 4- and 6-substituted products, which belong to the same group of disubstituted pyridines outlined above.

The optical rotations (Table 5) of the recovered nicotine and the products A and B from experiment 2 (Table 1) were measured. The specific rotation obtained for the recovered nicotine was about 30 % of the value obtained from (—)-nicotine, which corresponds to a racemisation of 70 % during the reaction.

The formation of the 4-substituted product B can be interpreted in the following way. It is known that methyl-lithium can form complexes with tertiary amines.[10] Nicotine contains two tertiary amino functions both able of complex formation with the lithium reagent.



In a complex formed between methyl-lithium and the pyrrolidine nitrogen of nicotine, the methyl group of the methyl-lithium may be oriented in such a way that nucleophilic attack at the 4-position of nicotine is facilitated.

The attack would be further assisted, if the pyridine nitrogen of nicotine were also involved in a complex formation, as this would increase the susceptibility of the pyridine ring to nucleophilic attack in the 4-position, as well as in the 2- and 6-position. The formation of lithium complexes with both nitrogen atoms in nicotine would account for the particular dependence on the yield of the 4-substituted product B on the amount of methyl-lithium used (*cf.* Table 1, expts. 1 and 2).

As the inertness of toluene in these reactions is doubtful (*cf.* Ref. 10) a less reactive and less polar solvent, decalin, (Table 1, expt. 3) was used for comparison. The yield of 6-substituted product increased (*cf.* expt. 2) but, probably due to the lower polarity of decalin, the formation of 4-substituted product decreased.

The pharmacological investigation, kindly carried out at the Department of Physiology (Prof. U.S. von Euler), Karolinska Institutet, Stockholm, showed that 4-methylnicotine exerted a very low pharmacological activity in all the tests used[1] while that of 6-methylnicotine was fairly strong but dependent on the nature of the biological preparation. The stimulating effect of 6-methylnicotine on the isolated guinea-pig's ileum was 25 % stronger than that of natural nicotine.[1]

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer No. 237 grating instrument (sample as liquid film or for solids in KBr unless otherwise stated, wave numbers in relation to the 1603 cm^{-1} band of polystyrene film), and nuclear magnetic resonance (NMR) spectra on a Varian A 60 instrument operating at 60 Mc/s (solvent carbon tetrachloride, as internal standard tetramethylsilane). For analytical gas-liquid chromatography (GLC) a Pye argon chromatograph [column: length 1.2 m, inner diameter 4 mm, stationary phase: 25 % silicone SE-30 on Gas-Chrom P (60–80 mesh)] and for preparative GLC an Aerograph A-700 "Autoprep" instrument [column: length 10′, outer diameter 3/8″, stationary phase: 10 % silicone SE-30 on Gas-Chrom P (100–120 mesh)] were used.

Methyl-lithium. Ethereal solutions of methyl-lithium were prepared by the standard method,[11] filtered and stored in a burette. The content of methyl-lithium was determined before each run by titration with 0.1 M hydrochloric acid using methyl orange as indicator.

Alkylation reactions. An ether solution containing the calculated amount of methyl-lithium (10 mmole ~ 11.5 ml) was slowly (15 min) added to nicotine (1.62 g, 10 mmole) dissolved in ether (25 ml). The reaction mixture was heated on an oil bath, ether was allowed to distil off and simultaneously replaced by a higher boiling solvent (toluene or decalin, 50 ml). The temperature of the oil bath was increased to 110° over a period of 1 h and then kept constant for 7 h. The reaction mixture was cooled in an ice bath and water carefully added. The aqueous layer was separated and the organic phase repeatedly extracted with 2 M hydrochloric acid. The aqueous fractions were combined, washed with ether, made alkaline and extracted with ether. Concentration of the combined ethereal extracts yielded the crude product which was distilled and the fraction distilling below 150°/0.1 mm investigated by means of GLC.

Separations and product ratio determinations by GLC. In the analytical GLC nicotine had the retention time 9.3 min (temp. 145°, gas flow 86 ml/min) and in the preparative GLC the retention time 8.1 min (temp. 160°, gas flow 200 ml/min).

A direct gravimetric determination of the product ratio was not possible by preparative GLC. Pure samples of the reaction products and the starting material were obtained together with fairly large intermediate fractions. The ratio of the products had thus to be estimated by analytical GLC. A number of mixtures with known composition were made from the isolated products and analysed by GLC. The average error in these

Table 3. Relative retention times of products A (6-methylnicotine) and B (4-methylnicotine).

Compound	Relative retention time Analytical GLC	Preparative GLC
Nicotine	1.00	1.00
A	1.33	1.16
B	1.77	1.44

estimations was found to be ± 5 %. The figures in Table 1 are mean-values of repeated experiments.

Analyses. The picrates were prepared in and recrystallized from mixtures of absolute ethanol and glacial acetic acid.

Dipicrate of 4-methylnicotine, m.p. 193—195°. Found: C 43.9; H 3.8; N 17.5. Dipicrate of 6-methylnicotine, m.p. 202—205°. Found: C 43.4; H 3.6. $C_{23}H_{22}N_8O_{14}$ requires C 43.5; H 3.5; N 17.7.

Table 4. NMR-spectra of nicotine, 4-methyl- and 6-methylnicotine (aromatic region).

Compound	Proton in position	Signal at δ ppm	Coupling constants J c/s (to proton in pos.)		
Nicotine	2	8.59	2 (4)		
	4	7.72	2 (2/6)		8 (5)
	5	7.22		5 (6)	8 (4)
	6	8.50	2 (4)	5 (5)	
4-Methylnicotine	2	8.59			
	5	6.93		5 (6)	
	6	8.26		5 (5)	
6-Methylnicotine	2	8.34	2 (4)		
	4	7.53	2 (2)		8 (5)
	5	7.03			8 (4)

Optical rotations. The rotations of the products and the recovered nicotine from experiment 2 (Table 1) were measured in chloroform (Table 5).

Table 5. Optical rotations of nicotine, 4-methyl- and 6-methylnicotine.

Compound	c	$[\alpha]_D^{22}$
Nicotine	1.0	−56.3°
4-Methylnicotine	1.0	−103.5°
6-Methylnicotine	1.1	−58.1°

The rotation for the pure original nicotine was found to be −168.9° (c 1.2). The recovered nicotine had thus suffered racemisation to a degree of 67 %.

Oxidative degradations. The isolated methylation products (50 mg) were mixed with water (50 ml) and heated on a water bath with stirring. Potassium permanganate was added in small portions and after about 20 min the rapid consumption of permanganate

ceased. A further portion of permanganate was added and heating continued for 10 min, when methanol was added and the hot mixture was filtered with the aid of celite. After washing with hot water the resulting filtrate was acidified with concentrated hydrochloric acid and taken to dryness. The solid residue was triturated with a small amount of methanol, triethylamine was added and the mixture treated with diazomethane in ether and then worked up in the usual manner. The resulting 4- and 6-methylnicotinic acid methyl esters (obtained in 50–60 % yield) were compared by means of IR and GLC with authentic samples.

Prolonged oxidation (5 h) with excess of permanganate gave, after methylation, the pyridinedicarboxylic acid dimethyl esters in somewhat lower yields, which were also compared with the relevant authentic acid esters by IR and GLC.

The identification of disubstituted pyridines *via* the melting points of the free dicarboxylic acids seemed less satisfactory. The isocinchomeronic acid had m.p. and mixed m.p. 262–265° (decomp.). Literature values range from 236 to 258°. Cinchomeronic acid showed m.p. and mixed m.p. 265–268° (decomp.); literature values: 249 to 268°.

In the analytical GLC nicotinic acid methyl ester had a rentention time of 7.9 min (temp. 110°, gas flow 115 ml/min) and cinchomeronic acid dimethyl ester a retention time of 11.0 min (temp. 150°, gas flow 90 ml/min).

Table 6. Relative retention times of the esterified oxidation products.

Methyl esters	Rel. ret. time	Dimethyl esters	Rel. ret. time
Nicotinic acid	1.00	Cinchomeronic acid	1.00
2-Methyl » »	1.47	Quinolinic »	1.21
6-Methyl » »	1.68	Isocinchomeronic »	1.54
4-Methyl » »	1.89		

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