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The Methylation of 3-Picoline and *N*-(3-Picolyl)-pyrrolidine with Methyl-lithium

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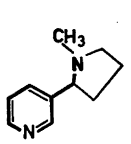
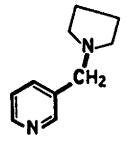
3-Picoline is methylated with methyl-lithium mainly in position 2, to a smaller extent in position 6 and not at all in position 4. Methylation of *N*-(3-picolyl)-pyrrolidine yields 2-, 6- as well as 4-methylated products. The effects of some variations in the reaction conditions have been studied. Some physiological properties of the three methylated *N*-(3-picolyl)-pyrrolidines are briefly reported.

In a previous paper [1] the reaction of nicotine with methyl-lithium was studied. 4-Methyl- and 6-methylnicotine were formed as well as trace amounts of 2-methylnicotine; the yields of the two main products were found to be highly dependent on the reaction conditions.

For comparative purposes we have investigated the methylation of 3-picoline and *N*-(3-picolyl)-pyrrolidine, which like nicotine contains a 3-picolylamine unit.



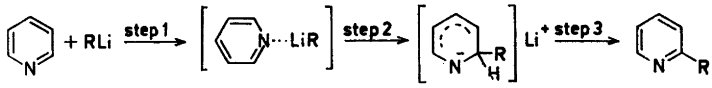
Nicotine



N-(3-Picolyl)-pyrrolidine

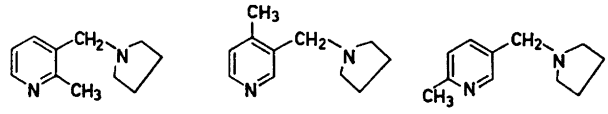
The 2-position of *N*-(3-picolyl)-pyrrolidine is less sterically hindered than the corresponding position in nicotine. Hence it would be expected that *N*-(3-picolyl)-pyrrolidine would be more easily methylated in this position than nicotine.

Two different procedures were employed: method A, in which step 1 (Scheme 1) was carried out in ether and steps 2 and 3 at elevated temperatures in a higher boiling solvent (toluene or decalin) and method B, in which the two first steps were carried out in tetrahydrofuran (THF) at room temperature. Step 3 was effected by oxidation with air at low temperature.



Scheme 1

Methylation of 3-picoline according to method A yielded 2,3-lutidine and 2,5-lutidine in a ratio of 50:1 (Table 1, expt. 1) and according to method B in a 10:1 ratio (Table 1, expt. 2). No 3,4-lutidine could be detected in either case. Abramovitch [2] phenylated 3-picoline with phenyl-lithium according to method A and obtained 3-methyl-2-phenyl- and 3-methyl-6-phenyl-pyridine as the only products in a 19:1 ratio.



I II III

N-(2-Methyl-3-picolyl)-pyrrolidine (I) as well as the 4- and 6-substituted isomers (II and III) were prepared in the following manner. The methyl esters of 2-, 4- and 6-methylnicotinic acid were reduced to the corresponding alcohols with lithium aluminium hydride. The alcohols were converted into the corresponding chlorides and finally treated with pyrrolidine.

Table 1. 3-Picoline and methyl-lithium.
(THF = tetrahydrofuran; eth. = ether; tol. = toluene; dec. = decalin).

Expt.	MeLi/picoline ratio	Reaction method	Solvent	Products % 2,3-	2,5-lutidine	Recovered start. mat.%
1	1	A	eth./tol.	47	1	18
2	1	B, 2 h	THF	30	3	9

Table 2. N-(3-Picolyl)-pyrrolidine ("Pic.") and methyl-lithium.

Expt.	MeLi/"Pic." ratio	Reaction method	Solvent	Products % I	II	III	I/III ratio	Recovered start. mat. %
3	1	A	eth./tol.	12	<1	7	1.7	50
4	2	A	eth./tol.	20	4	11	1.8	11
5	2	A	eth./dec.	25	<1	15	1.7	20
6	2	A,1 h,70° then B	eth./tol.	9	3	6	1.5	39
7	1	B, 4 h	THF	11	4	16	0.7	22
8	2	B, 4 h	THF	10	7	16	0.6	15

When methyl-lithium was allowed to react with *N*-(3-picolyl)-pyrrolidine a mixture of 2-, 4- and 6-methylated products (I, II, and III) resulted (Table 2). The 2- and 6-methylated isomers I and III were the major products in all experiments (expt. 3—8). The ratio (I:III) remained virtually constant and 2-substitution predominated when toluene or decalin were used as solvents (expt. 3—6). In experiment 6 the reaction was started according to method A, interrupted and step 3 (Scheme 1) carried out according to method B. The result of this experiment thus demonstrates the equivalence in the two procedures (method A and B) of carrying out step 3 (Scheme 1) of the methylation reaction.

Methylation in position 4 (product II) occurred only to a minor extent (expt. 3—8) and was strongly dependent both on the amount of methyl-lithium used as well as the solvent system.

The results of the experiments 3—6 agree well with those obtained with nicotine.[1]

During preliminary experiments (see Exptl. part) the observation was made that when ether-toluene or ether-decalin were used as solvents, the main alkylation reaction (step 2, Scheme 1) took place at an elevated temperature after the ether had evaporated. Gilman [3] and others have found that the use of THF as solvent greatly increases the rate of reaction of the organo-lithium reagents. An investigation by Settle and coworkers [4] indicates that this effect is mainly due to the low steric requirements of THF.

In experiments 2 (Table 1), 7, and 8 (Table 2) THF was used as solvent according to reaction method B. This resulted in an increase in 6-substitution and a decrease in 2-substitution for both 3-picoline (*cf.* expt. 1 with 2) and *N*-(3-picolyl)-pyrrolidine (*cf.* expts. 3—6 with 7, 8). When ether-toluene was used as solvent an increased amount of methyl-lithium gave increased yields of 2- and 6-methylated products (*cf.* expt. 3 with 4). A corresponding result was not noted when THF was used as solvent (*cf.* expt. 7 with 8). The course of experiments 7 and 8 were followed by GLC analysis. It was found that the reaction had proceeded to near completion within the first two hours. The only effect of increasing the amount of methyl-lithium was to increase the yield of the 4-substituted product. A contributive reason for these results might be the instability of methyl-lithium in THF solutions.[3]

The pharmacological investigation, kindly carried out at the Department of Physiology (Prof. U. S. von Euler), Karolinska Institutet, Stockholm, showed that the 2- and 4-methyl substituted *N*-(3-picolyl)-pyrrolidines (I and II) exerted very low biological activity while *N*-(6-methyl-3-picolyl)-pyrrolidine, III, behaved in a way similar to that of the starting material, *N*-(3-picolyl)-pyrrolidine (*cf.* Ref. 5). The stimulating effect of III on the isolated rabbit's jejunum was more than three times stronger than that of *N*-(3-picolyl)-pyrrolidine while the "nicotine-like" action observed in the frog muscle test [5] was only 30 % of that of the starting material.

EXPERIMENTAL

Melting points were taken on a Kofler micro hot stage and are uncorrected. For analytical gas-liquid chromatography (GLC) a Pye argon chromatograph (column length 1.2 m, inner diameter 4 mm) and for preparative GLC and Aerograph A-700 "Autoprep" instrument (column length 10′, outer diameter 3/8″) were used.

The alkylation reaction. Method A. To a stirred solution of the pyridine derivative (10 mmole) in ether (25 ml) in an atmosphere of nitrogen an ethereal solution of methyl-lithium (10 mmole ~ 11.5 ml) was added dropwise over a period of 15 min. At the end of the addition ether was distilled off and simultaneously replaced with dry, higher boiling solvent (toluene or decalin, 50 ml). This period of solvent exchange was set to 1 h in which time the oil bath temperature was increased to 110°. This temperature was maintained for 7 h. The mixture was then cooled in an ice bath and treated with water. The aqueous layer was separated, the organic layer was extracted repeatedly with dilute hydrochloric acid, the aqueous fractions were combined, washed with ether, made alkaline and thoroughly extracted with ether. The extract was dried over potassium carbonate and evaporated. The residue was distilled and analysed by GLC.

Method B. The required amount of ethereal methyl-lithium solution was added to a stirred equal volume of dry THF at 0°. The ether was removed under reduced pressure and the pyridine compound (10 mmole) in THF (25 ml) was added. During the addition the reaction vessel was cooled by means of a dry ice bath. The flask with the reaction mixture was then placed in a large water bath of room temperature (22°). The reaction was interrupted by cooling in a dry ice bath and dry, carbon dioxide-free air was sucked through the dark solution, the temperature of which was allowed to rise to but not exceed 0° until its colour suddenly turned into pale yellow. The aeration was continued for a few more minutes, then the bulk of the solvent was evaporated under reduced pressure at room temperature. The resulting light syrup was covered with ether and shaken with water while cooled in an ice bath. The aqueous layer was separated, basified with potassium hydroxide and extracted with ether. The combined ethereal extracts were dried (potassium carbonate) and evaporated. The residue was distilled and submitted to GLC.

Preliminary experiments. An ethereal methyl-lithium solution (10 mmole ~ 11.5 ml) was added to 3-picoline (1.94 ml, 20 mmole) in dry ether (25 ml). A white heavy precipitate formed immediately. When the precipitate had settled, a sample was taken from the supernatant ether solution and another sample from the suspended solid. The samples were tested for methyl-lithium using the colour reaction with benzylamine according to Gilman.[6] The colour given by the supernatant ether solution was very faint while the precipitate rapidly developed a strong colour. After stirring for 2 h at room temperature the reaction was interrupted according to method B yielding starting material contaminated with traces of lutidines (about 1 %).

The experiment described above was repeated with methyl-lithium (20 mmole) and 3-picoline (20 mmole) in ether (25 ml). The mixture was stirred and heated to reflux for 2 h and the reaction was interrupted according to method B. During the period of heating most of the precipitate dissolved. A somewhat higher yield of lutidines was obtained in this experiment (about 10 %).

The two experiments described were then repeated using methyl-lithium (20 mmole) and *N*-(3-picolyl)-pyrrolidine [5] (1.62 g, 10 mmole) in ether (25 ml). No precipitate was formed in these experiments. The yields obtained corresponded to those from the experiments done with 3-picoline above.

N-*(2,4- and 6-Methyl-3-picolyl)-pyrrolidine.* These reference compounds were prepared by alkylation of pyrrolidine with the corresponding methyl-3-pyridylmethanol [9,8,10] which was treated for 12 h with excess thionyl chloride in chloroform at room temperature. The crude picolyl chloride hydrochloride remaining after evaporation of solvent and excess thionyl chloride, was dissolved in absolute ethanol and treated with a three-fold excess of pyrrolidine. The resulting mixture was heated to reflux for 2 h and taken to dryness in vacuum. The residue was dissolved in water, basified with 40 % aqueous potassium hydroxide and extracted with ether. The extract was dried over potassium carbonate, concentrated to a small volume and distilled yielding the compounds shown in Table 3.

Table 3. *N*-(Methyl-3-picolyl)-pyrrolidines.

Methyl in position	b.p. °/mm	Dipicrate	Analysis C found	C calc. for $C_{23}H_{22}N_8O_{14}$	H found	H calc.
2	126—127/10	206—208	43.5	43.5	3.6	3.5
4	127—129/10	191—193	43.5	43.5	3.5	3.5
6	124—125/8	202—204	43.4	43.5	3.5	3.5

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

Identification and separation by GLC. For the analytical GLC a stationary phase consisting of 25 % silicone SE 30 on Gas-Chrom P (60—80 mesh) was used. 3-Picoline had the retention time 6.6 min (temp. 80°, gas flow 86 ml/min).

Table 4. Relative retention times for 3-picoline and some lutidines.

Compound	Relative retention time
3-Picoline	1.00
2,5-Lutidine	1.62
2,3-Lutidine	1.79
3,4-Lutidine	2.52

The reaction mixture from experiment 1 (Table 1) was oxidized with permanganate (5 h), esterified and analysed by GLC as described in the previous paper.[1] The major component in the mixture was found to be quinolinic acid dimethyl ester together with smaller amounts of nicotinic acid methyl ester and isocinchomeronic acid dimethyl ester. No cinchomeronic acid dimethyl ester was detected.

For analytical GLC of the picolyl-pyrrolidines the stationary phase described above was used. *N*-(3-Picolyl)-pyrrolidine had a retention time of 12.1 min (temp. 145°, gas flow 86 ml/min).

For the preparative GLC a stationary phase of 10 % silicone SE 30 on Gas-Chrom P (100—120 mesh) was used. *N*-(3-Picolyl)-pyrrolidine had the retention time 10.0 min (temp. 160°, gas flow 200 ml/min).

Table 5. Relative retention times for the *N*-(picolyl)-pyrrolidines.

Compound	Relative retention time Analytical GLC	Preparative GLC
3-Picolylpyrrolidine	1.00	1.00
2-Methyl- »	1.27	1.22
6-Methyl- »	1.35	1.31
4-Methyl- »	1.51	1.42

The products were isolated by preparative GLC and compared with the reference compounds (IR and mixed m.p. of picrates). The estimation of the product ratio was

performed exactly as described in the previous paper.[1] The average error in the ratio determination was of the same magnitude (± 5%) estimated by analysis of standard mixtures. The figures given in Tables 1 and 2 are mean-values of repeated experiments.

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REFERENCES

1. Haglid, F. *Acta Chem. Scand.* **21** (1967) 329.
2. Abramovitch, R. A., Giam, C. S. and Notation, A. D. *Can. J. Chem.* **38** (1960) 761.
3. Gilman, H. and Gaj, B. J. *J. Org. Chem.* **22** (1957) 1165.
4. Settle, F. A., Haggerty, M. and Eastham, J. F. *J. Am. Chem. Soc.* **86** (1964) 2076.
5. Haglid, F. and Wellings, I. *Acta Chem. Scand.* **17** (1963) 1727.
6. Gilman, H. and Woods, L. A. *J. Am. Chem. Soc.* **65** (1943) 33.
7. Tsuda, K., Satoh, Y., Ikekawa, N. and Mishima, H. *J. Org. Chem.* **21** (1956) 800.
8. Bobbitt, J. M. and Scola, D. A. *J. Org. Chem.* **25** (1960) 560.
9. Bohlmann, F. and Rahtz, D. *Abhandl. Braunschweig. Wiss. Ges.* **9** (1957) 170; (*cf. Chem. Abstr.* **52** (1958) 11056 i).
10. Yoshida, M. and Kumagae, H. *Nippon Kagaku Zasshi* **81** (1960) 345. (*cf. Chem. Abstr.* **55** (1961) 6477 g).

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