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Synthetic Analogues of Nicotine. I *

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All the possible isomers obtained, when the pyrrolidine ring of the nicotine molecule is opened in different positions, have been synthesised together with some substituted 3-picolylamines. Some of their biological activities have been recorded and compared with those of nicotine.

In view of the large amount of work devoted to the physiological and insecticidal action of nicotine, it is surprising that so little systematic work has been done on studying synthetic analogues of nicotine. Several earlier groups of research workers investigated various synthetic analogues to determine "whether the toxicity of nicotine is specific for the whole molecule or whether this effect is due to some special grouping of its component parts [1]". In their efforts to answer this question these workers often prepared several analogues of a series, but in no case was a complete, systematic series of analogues synthesised. The incompleteness of the early work may be explained by the difficulties attendent on preparing the required nicotine analogues when the chemistry of pyridine compounds was at a rather early stage. The aspects of the problem which they attempted to investigate are the following:

(*a*) The importance of the configuration of the nicotine molecule.

(*b*) The effect of substituting the pyridine nucleus in different positions.

(*c*) The effect of introducing an amino group into the pyridine nucleus.

(*d*) The effect of substituting other nuclei in the place of pyridine in the nicotine molecule.

(*e*) The importance of the N-methylpyrrolidine unit in synthetic nicotine analogues.

As early as 1904, Pictet [2] compared the activities of *d*-, *l*- and *dl*-nicotine and showed that *d*-nicotine and *dl*-nicotine were less toxic than the natural

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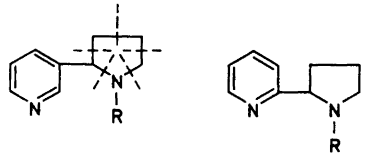
alkaloid. These results were later confirmed by Macht[3], who demonstrated the relationship between the pharmacodynamic action of the nicotine molecule and its configuration.

Several workers[3–5] have shown that derivatives in which the pyridine nucleus is substituted in the α-position are much less active than the corresponding derivatives in the β-series. Thus "α-nicotine"[4,6] (II: R = Me) is less toxic than nicotine (I: R = Me) and "α-nornicotine" (II: R = H) has only half the toxicity of the naturally occurring nornicotine (I: R = H).

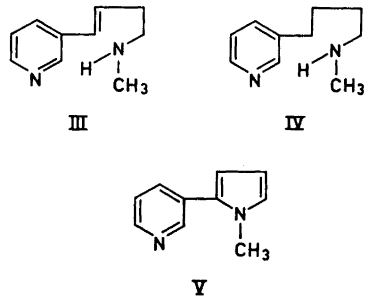


I II

The introduction of an amino group into the pyridine ring of the nicotine molecule[7,8] furnishes derivatives which are much less active than nicotine. This has been demonstrated with 2-aminonicotine and 6-aminonicotine which are, respectively, 2000 and 1000 times less active than nicotine itself. This effect is in contrast to that in the phenylethylamine series where the introduction of the amino group in the *para*-position to the ethylamine group considerably reinforces the physiological activity[9].

The effect of replacing the pyridine nucleus in nicotine with different aliphatic and aromatic nuclei has been studied by three main groups. In 1928, La Forge[1] prepared 2-methyl- and 2-phenylpyrrolidine together with their N-methyl derivatives and found that they did not approach nicotine in toxicity. Later, Craig[10] and Craig and Hixon[11] examined the variation of toxicity with different aliphatic and aromatic substituents in the 2-position in an effort to establish the "toxifore" grouping as the pyrrolidine nucleus with suitable groups situated in the 2-position. They concluded that those compounds containing the most electronegative 2-substituents were the most toxic. The most recent work done on this problem was carried out by Burckhalter and Short[12] in 1958, when they synthesised a number of 2-substituted pyrrolidines and N-methylpyrrolidines as possible antihypertensive agents.

The question of whether the pyrrolidine group is essential to the specific toxic effect of nicotine was first investigated by La Forge[13]. He prepared



III IV

V

several analogues in which the pyrrolidine ring of nicotine was opened and compared their activities with those of nicotyrine (V) and nicotine. Of these "metanicotine" (III) and "dihydrometanicotine" (IV) showed the highest toxicity which, however, did not exceed that of nicotine.

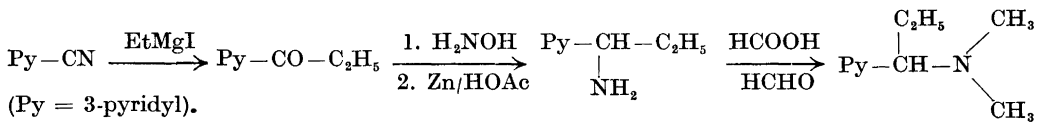
In a later series of three papers, Craig and Hixon described the synthesis of a series of N-substituted pyrrolidines [11,14,15]. They showed that these compounds were weak insecticides and concluded that the presence of a pyrrolidine group in a molecule did not necessarily confer "nicotine-like" activity on the compound.

With a view to studying relationships between structure and pharmacological action more systematically it was decided to synthesise series of nicotine analogues in which, as far as possible, only one part of the nicotine molecule at a time is changed. In this paper two main series are described: series *a* (Table 1), in which the pyrrolidine ring of nicotine (I: R=Me) is broken in the various possible ways, and series *b* (Table 2), in which the hydrogen on the nitrogen atom of the pyrrolidine ring of nornicotine (I: R = H) is replaced by alkyl groups of different size.

Finally some model compounds are described which contain only a simple side chain representing a part of the pyrrolidine ring unit present in nicotine.

Series *a* (Table 1) is made up of seven compounds. Five of these come from breaking the pyrrolidine ring of nicotine as shown in formula I (R = Me), giving three ditertiary bases and two bases containing a tertiary and a secondary nitrogen atom (where the C—N bonds of the pyrrolidine ring are broken). Methylation of the two last named bases furnishes two more ditertiary bases (Nos. 2 and 4).

The preparation of the compounds in series *a* was undertaken by several different synthetic procedures. "Dihydrometanicotine", 1 (Table 1), was obtained by hydrogenating an aqueous solution of nicotine over a Pd/charcoal catalyst at 50°. Methylation of the product with aqueous formaldehyde and formic acid gave the ditertiary base, 2 (Table 1). The method of synthesis used for preparing compounds 3, 4, 5, and 6 (Table 1) was essentially that of La Forge [13], and is exemplified by the synthesis of compound 5 (Table 1):



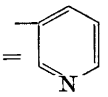
(Py = 3-pyridyl).

Finally compound 7 (Table 1) was prepared by reacting nicotinic acid chloride with methylpropylamine and reducing the resulting amide with lithium aluminium hydride.

Series *b* contains four compounds, nicotine, nornicotine, N-ethylnornicotine and N-propylnornicotine. The nornicotine is series *b* was obtained by extracting a tobacco, Geudertheimer III, according to the method described in Manske's "The Alkaloids" [16]. This type of tobacco has a low nicotine content but is relatively rich in nornicotine *. N-Ethylnornicotine was prepared by

* The authors thank the Swedish Tobacco Company for a gift of this tobacco.

Table 1. The physiological activities of compounds having open chain units corresponding to a broken pyrrolidine ring. (Series *a*). 0 signifies < 0.001 activity; *l*-nicotine = 1.0.

Py = 

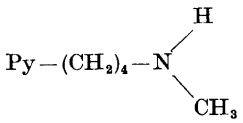
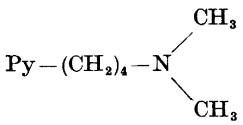
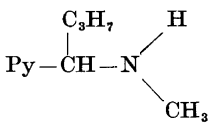
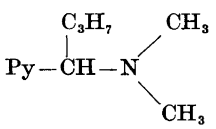
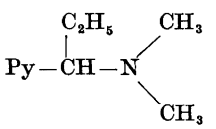
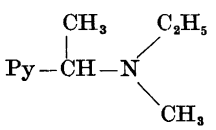
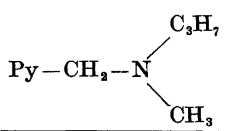
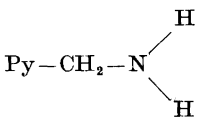
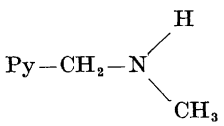
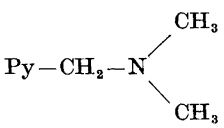
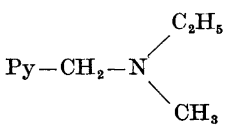
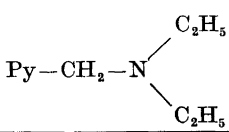
No.	Compound	Rabbit jejunum	Guinea Pig ileum	Cat B.P.	Frog muscle
1		0.02	0.08	0.05	0.08
2		0.13	0.07	0.10	0.20
3		0.11	0.05	0.01	0.01
4		0	0		0
5		0	0		0
6		0.003	0.002		0
7		0.001	0.003		0

Table 2. The physiological activities of nornicotine and N-alkyl substituted nornicotines. (Series *b*).

No.	Compound	Rabbit jejunum	Guinea Pig ileum	Cat B.P.	Frog muscle
8	Nornicotine	0.08	0.4		0.5
9	Nicotine	1	1	1	1
10	N-Ethylnornicotine	0.33	0.33	0.06	0.07
11	N-Propylnornicotine	0.02	0.02	0.006	0.015

Table 3. The physiological activities of model compounds.

No.	Compound	Rabbit jejunum	Guinea Pig ileum	Cat B.P.	Frog muscle
12 *		0.004	0.001		0
13 *		0	0		0
14		0.11	0.10	0.08	0.02
15		0.06	0.02		0.03
16		0.002	0	0.004	0

* Obtained from Raschig Chemische Fabrik, Ludwigshafen, Germany.

acetylation of nornicotine followed by lithium aluminium hydride reduction of the resulting amide. In the same way N-propylnornicotine was synthesised starting with nornicotine and a mixture of propionic acid and its anhydride. Table 2 shows the variation in biological activity with the nature of the substituent on the nitrogen atom of the pyrrolidine ring.

In spite of their "apparent" structural similarity to nicotine, several of the compounds in series *a* showed almost no specific "nicotine-like" action in the frog muscle test. It was decided, therefore, to prepare a series of simple model substances in which only a part of the pyrrolidine unit of nicotine is present. These model substances (12—16 in Table 3) were prepared by standard literature methods (see Experimental Part).

TEST METHODS

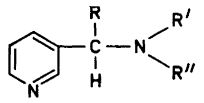
The biological activities of the different compounds mentioned in Tables 1—3 have been tested on the isolated rabbit's jejunum, the guinea-pig's ileum, the cat's blood pressure, and the isolated rectus abdominis muscle of the frog *Rana temporaria*. The effect on the isolated intestines was tested in Tyrode solution at 37°, the frog muscle in frog's Ringer solution at 20—22°, and the cat's blood pressure in Nembutal anesthesia. All compounds were tested against *l*-nicotine tartrate as standard and the effects given in relation to nicotine base as 1.0. Hence a value of 0.1 indicates that a ten times higher concentration (by weight) of the relevant compound was needed to cause an effect equivalent to that of nicotine.

In several instances repeated tests have been made on different biological preparations of the same kind. The results have generally shown a good agreement and the figures are given as means of the different tests.

As seen in the tables there is a varying degree of agreement between the different test organs, indicating that the effects are not solely nicotinic in nature. Usually, however, a compound giving a high figure in the frog muscle test also has a stronger effect on the other test preparations than those compounds which only show a weak action.

DISCUSSION OF THE PHYSIOLOGICAL ACTIVITIES

The rather unexpected discovery that two of the model compounds prepared (Nos. 14 and 15 in Table 3) had quite a measurable nicotinic action in the frog muscle test suggested that there may exist certain relationships between structure and physiological activity within the series investigated here.



VI

1. When a comparison is made between model compound 14 (Table 3) and compounds 4 and 5 of series *a* (Table 1), it is seen that they may all be represented by the general formula VI. Thus in each of these compounds

R′ = R″= Me and the variable factor is the group R. When R = H, compound 14 (Table 3), the activity is about 2 % of that of nicotine; when R = an alkyl group, however, the activity falls to a very low value, less than 0.1 % of that of nicotine (compounds 4 and 5 of series *a*, Table 1).

The same factor can account for the difference in activity between compounds 15 (Table 3, 3 % nicotinic action) and 6 (Table 1, less than 0.1 % nicotinic action). These compounds are also represented by VI, where R′= Me and R″= Et. *Thus, the presence of an alkyl group on the C-atom between the pyridine ring and the N-dialkyl group in compounds of type VI causes a decrease in the physiological activity of the compound.*

2. Compound 15 (Table 3) has the highest activity of the model substances examined (3 % nicotinic action) and is represented by structure VI, where R = H, R′= Me and R″= Et. When the ethyl group of this compound is replaced by a larger alkyl group, as in compound 7 (Table 1) where R″ = propyl, the activity falls to a low value (0.1 %). A similar decrease in activity is observed when the methyl group of compound 15 (Table 3) is replaced by an ethyl group to give compound 16 (Table 3) having less than 0.1 % of the activity of nicotine.

Thus for maximum activity in compounds of type VI: *(a) One of the groups R′ or R″ should be a methyl group; (b) The other alkyl group should not be larger than an ethyl group.*

These conclusions are further supported by considering the series of compounds in Table 2. Thus nicotine, which is the only compound in Table 2 having a methyl group on the pyrrolidine nitrogen, has the greatest activity. When the size of the alkyl group is increased, as in compounds 10 and 11 (Table 2), the activity again falls rapidly.

3. The importance of the intact pyrrolidine ring is clearly established by comparing the highly active nornicotine and nicotine with the compounds of series *a* in Table 1. In nearly all cases these synthetic analogues, which have open chain units corresponding to a broken pyrrolidine ring, exhibit a much lower activity, *i.e. the intact pyrrolidine ring is a definite contributing factor to the biological activity of nicotine.*

EXPERIMENTAL

All melting points are uncorrected.

No. 1. *3-(δ-Methylaminobutyl)-pyridine. ("Dihydrometanicotine").* Nicotine (10 g) in water (200 ml) was hydrogenated at 54° over a saturated 10 % palladium/charcoal catalyst (2 g) as described by Hromatka [17]. After the uptake of 1 mole of hydrogen, the catalyst was removed by filtration and the product isolated as the oxalate. Decomposition of the oxalate furnished the free base which was distilled giving pure *3-(δ-methylaminobutyl)-pyridine* (6.4 g), b.p. 135–137°/12 mm. *Dipicrate* (acetic acid), m.p. 165–167°. (Lit.[17]: B.p. 147°/20 mm. Dipicrate, m.p. 167–168°).

No. 2. *3-(δ-Dimethylaminobutyl)-pyridine.* 3-(δ-Methylaminobutyl)-pyridine (8.2 g) was methylated by heating with 90 % formic acid (12.5 g) and 37 % aqueous formaldehyde solution (6 ml) for 8 h on a steambath. The reaction mixture was then treated with 2 N hydrochloric acid (50 ml) and the whole evaporated under reduced pressure to a syrup. Water (20 ml) was added and the resulting solution made strongly alkaline with 50 % potassium hydroxide solution. The oil which separated was extracted with ether, the ether extract dried ($MgSO_4$) and concentrated to give the crude product. Fractional distillation afforded *3-(δ-dimethylaminobutyl)-pyridine* (7.6 g) b.p. 127–129°/12 mm.

Dipicrolonate (acetic acid), m.p. 209—210°. (Lit.[18]; B.p. 93—94°/1 mm. Dipicrolonate, m.p. 208—210°).

Propyl 3-pyridyl ketone. This ketone was prepared as described by La Forge [13]. 3-Cyanopyridine (25.5 g) in dry ether (500 ml) was added to an ether solution of propyl magnesium bromide (from magnesium (9.6 g) and propyl bromide (47.5 g) in dry ether (250 ml)). On working up the reaction mixture the *propyl ketone* (19 g), b.p. 117—120°/8 mm, was obtained. By the same general method were prepared (40—50 % yield): *Ethyl 3-pyridyl ketone* [19] and *methyl 3-pyridyl ketone* [13].

The *ketoximes* were prepared from the ketones above by standard procedures (60—80 % yield): *Propyl 3-pyridyl ketoxime*, m.p. 79—80°, (from petroleum ether). (Found: N 16.8. $C_9H_{12}N_2O$ requires N 17.1). La Forge [13] reports that the could not obtain the ketoxime in a crystalline form. Engler [20] reports a crystalline oxime, but no melting point is given. *Ethyl 3-pyridyl ketoxime*, m.p. 117—118° (from benzene). (Lit.[20]: M.p. 115°). *Methyl 3-pyridyl ketoxime*, m.p. 116—117°, (from ethanol). (Lit.[13]: M.p. 113°).

3-(α-Aminobutyl)-pyridine. Propyl 3-pyridyl ketoxime (10 g) in ethanol (100 ml) was reduced with zink dust (75 g) and glacial acetic acid (100 ml). The solution was gently warmed on the steam-bath and continuously stirred during the addition of the reactants. The mixture was then worked up as described by La Forge [13] and fractionally distilled to give *3-(α-aminobutyl)-pyridine* (7 g), b.p. 109—111°/12 mm. (Found: N 18.4. Calc. for $C_9H_{14}N_2$: N 18.65). *Dipicrate* (acetic acid), m.p. 237—238° (decomp.). (Found: C 41.7; H 3.6; N 18.1. $C_{21}H_{20}N_8O_{14}$ requires C 41.45; H 3.3; N 18.4).

By the same method were prepared (70—80 % yield): *3-(α-Aminopropyl)-pyridine*, b.p. 105—108°/12 mm. (Found: N 20.3. $C_8H_{12}N_2$ requires N 20.6). With phenylisothiocyanate in ethanol it gave the *phenylthiourea*, m.p. 164—165°. (Found: C 66.5; H 6.7; N 15.2. $C_{15}H_{17}N_3S$ requires C 66.4; H 6.3; N 15.5).

3-(α-Aminoethyl)-pyridine, b.p. 100—102°/12 mm. *Dipicrate* (acetic acid), m.p. 204—205°. (Lit.[13]: M.p. 186—187°, lit.[21]: M.p. 204—205°).

No. 3. *3-(α-Methylaminobutyl)-pyridine*. 3-(α-Aminobutyl)-pyridine (10 g) was dissolved in water (30 ml) and treated with dimethyl sulphate (9 g) at 0°, as described by La Forge [13]. Fractional distillation of the crude product afforded *3-(α-methylaminobutyl)-pyridine* (5.5 g), b.p. 112°/10 mm. (Found: N 16.9. Calc. for $C_{10}H_{16}N_2$: N 17.1). La Forge [13] reports b.p. 244—247°/760 mm. *Dipicrate* (ethanol), m.p. 234—235°. (Found: C 42.5; H 3.4; N 18.4. $C_{22}H_{22}N_8O_{14}$ requires C 42.45; H 3.6; N 18.0).

No. 4. *3-(α-Dimethylaminobutyl)-pyridine*. 3-(α-Aminobutyl)-pyridine (15 g) was methylated by heating with 90 % formic acid (25 g) and 37 % aqueous formaldehyde solution (24 ml) for 8 h on a steam-bath. The reaction mixture was worked up as described for No. 2 above, giving *3-(α-dimethylaminobutyl)-pyridine* (11 g), b.p. 76—78°/1 mm. (Found: N 15.7. $C_{11}H_{18}N_2$ requires N 15.7). *Dipicrate* (ethanol), m.p. 204—205°. (Found: C 43.7; H 3.9; N 17.8. $C_{23}H_{24}N_8O_{14}$ requires C 43.4; H 3.8; N 17.6).

No. 5. *3-(α-Dimethylaminopropyl)-pyridine*. 3-(α-Aminopropyl)-pyridine (13.5 g) was methylated by heating with 37 % aqueous formaldehyde solution (24 ml) and 90 % formic acid (25 g) for 8 h on a steam-bath. The reaction mixture was worked up as described above (No. 2). The crude product was fractionally distilled to give *3-(α-dimethylaminopropyl)-pyridine* (9 g), b.p. 80°/2 mm. (Found: N 17.0. $C_{10}H_{16}N_2$ requires N 17.1). *Dipicrate* (ethanol), m.p. 182—183°. (Found: C 42.1; H 3.6; N 18.0. $C_{22}H_{22}N_8O_{14}$ requires C 42.45; H 3.6; N 18.0).

3-(α-Ethylaminoethyl)-pyridine. 3-(α-Aminoethyl)-pyridine (10 g) was treated with ethyl iodide (12 g) in absolute ethanol (25 ml) as described by La Forge [13]. Fractional distillation of the crude product gave *3-(α-ethylaminoethyl)-pyridine* (5.5 g), b.p. 97—99°/8 mm. (Found: N 18.7. Calc. for $C_9H_{14}N_2$: N 18.65). *Dipicrate* (ethanol), m.p. 129—130°. (Found: C 41.1; H 3.5; N 18.65. $C_{21}H_{20}N_8O_{14}$ requires C 41.45; H 3.3; N 18.4).

No. 6. *3-(α-Ethylmethylaminoethyl)-pyridine*. 3-(α-Ethylaminoethyl)-pyridine (15 g) was methylated by heating with 90 % formic acid (25 ml) and 37 % aqueous formaldehyde solution (12 ml) for 8 h on a steam-bath. The reaction mixture was worked up in the same manner as described for No. 2 above to give *3-(α-ethylmethylaminoethyl)-pyridine* (9.5 g), b.p. 94—95°/8 mm. (Found: N 16.8. $C_{10}H_{16}N_2$ requires N 17.1.) *Dipicrate* (acetic acid), m.p. 186—187°. (Found: C 42.3; H 3.6; N 17.9. $C_{22}H_{22}N_8O_{14}$ requires C 42.45; H 3.6; N 18.0).

N-Methyl-N-propylnicotinamide. Nicotinoyl chloride (15 g) (prepared according to the method of Grigorovskiĭ and Kimen [22]) was added slowly to a stirred solution of methyl-

propylamine (35 g) and water (15 ml) at 0°. After the addition, the reaction mixture was allowed to warm up to room temperature and left for 2 h. Water (50 ml) was added to the resulting mixture followed by sufficient 50 % potassium hydroxide solution to render the solution strongly alkaline. The crude amide which precipitated was extracted with benzene, the benzene extract dried ($MgSO_4$) and concentrated to yield an oil. Distillation of the oil gave *N-methyl-N-propylnicotinamide* (12.5 g), b.p. 158–160°/8 mm. (Lit.[23]: B.p. 174°/16 mm).

No. 7. *3-(Methylpropylaminomethyl)-pyridine.* N-methyl-N-propylnicotinamide (6 g) in dry ether (100 ml) was added slowly to a stirred suspension of lithium aluminium hydride (1.4 g) in dry ether (150 ml). The reaction mixture was stirred and refluxed for 4 h. The resulting mixture was cooled to 0° and decomposed by the successive addition of water (1.4 ml), 2 N sodium hydroxide solution (1.4 ml) and water (4.2 ml). After stirring vigorously for 20 min, the mixture was filtered and the inorganic residue extracted 3 times with 25 ml portions of warm ether. The combined ether solution was dried ($MgSO_4$) and concentrated to give an oil. Fractional distillation of the oil yielded *3-(methylpropylaminomethyl)-pyridine* (3.8 g), b.p. 97–99°/8 mm. (Found: N 16.9. $C_{10}H_{16}N_2$ requires N 17.1). *Dipicrate* (acetic acid), m.p. 170–171°. (Found: C 42.25; H 3.5; N 17.7. $C_{22}H_{22}N_8O_{14}$ requires C 42.45; H 3.6; N 18.0.)

No. 10. *N-Ethylnornicotine.* Nornicotine (5 g) was refluxed gently for 30 min with acetic acid (5 ml) and acetic anhydride (5 ml). The reaction mixture was cooled, poured into water (100 ml) and the resulting solution made strongly alkaline with 50 % potassium hydroxide solution. The oil which precipitated out was extracted with ether, the ether extract dried ($MgSO_4$) and evaporated to give crude *N-acetylnornicotine* (4 g). The crude N-acetylnornicotine (4 g) was dissolved in dry ether (50 ml) and reduced with lithium aluminium hydride (0.6 g) in dry ether (100 ml). The reaction mixture was worked up in the normal manner to give *N-ethylnornicotine* (2.8 g), b.p. 128–130°/13 mm. *Dipicrate* (acetic acid), m.p. 175–176°. (Lit.[24]: B.p. 127–128°/12 mm. Dipicrate m.p. 174–176°).

No. 11. *N-Propylnornicotine.* Nornicotine (5 g) was refluxed gently for 1 h with propionic acid (5 ml) and propionic anhydride (6 ml). The reaction was worked up as in the above experiment (No. 10) to give crude *N-propionylnornicotine* (4 g). Reduction of the crude amide (4 g) with lithium aluminium hydride (0.6 g) in dry ether furnished *N-propylnornicotine* (3 g), b.p. 134–135°/13 mm. (Found: N 14.5. $C_{12}H_{18}N_2$ requires N 14.7). *Dipicrate* (acetic acid), m.p. 107–108°. (Found: C 44.3; H 4.1; N 17.1. $C_{24}H_{24}N_8O_{14}$ requires C 44.45; H 3.7; N 17.3).

No. 14. *3-(Dimethylaminomethyl)-pyridine.* 3-(Aminomethyl)-pyridine (10.8 g) was methylated by heating with 90 % formic acid (25 g) and 37 % aqueous formaldehyde solution (24 ml) for 8 h on a steam-bath. The product was worked up in the usual fashion to give *3-(dimethylaminomethyl)-pyridine* (8.4 g), b.p. 74–75°/7 mm. (Found: N 20.3. Calc. for $C_8H_{12}N_2$: N 20.6). *Hydrochloride,* m.p. 179–180°. (Lit.[25]: M.p. 178–179°).

3-(N-Acetyl-methylaminomethyl)-pyridine. 3-(Methylaminomethyl)-pyridine (12 g) (Raschig Chemische Fabrik) in acetic anhydride (15 ml) was heated on the steam-bath for 30 min. The reaction mixture was cooled and poured into water (100 ml) and the solution made strongly alkaline with solid sodium hydroxide. The oil which separated was extracted with chloroform and the chloroform extract dried ($MgSO_4$). The residue obtained after removal of the solvent was distilled to give the *amide* (12 g), b.p. 175–177°/12 mm. (Found: N 16.9. $C_9H_{12}N_2O$ requires N 17.1).

No. 15. *3-(Methylethylaminomethyl)-pyridine.* 3-(N-Acetyl-methylaminomethyl)-pyridine (8 g) in dry ether (100 ml) was added slowly to a stirred suspension of lithium aluminium hydride (1.4 g) in dry ether (100 ml). After addition of the amide, the reaction mixture was refluxed for 2 h and then worked up in the normal way. Distillation of the crude product gave pure *3-(methylethylaminomethyl)-pyridine* (5 g), b.p. 96–98°/12 mm. (Found: C 71.7; H 9.1; N 19.0. $C_9H_{14}N_2$ requires C 71.95; H 9.4; N 18.65). *Dipicrate* (acetic acid), m.p. 172–173°. (Found: C 41.1; H 3.3; N 18.6. $C_{21}H_{20}N_8O_{14}$ requires C 41.45; H 3.3; N 18.4).

No. 16. *3-(Diethylaminomethyl)-pyridine.* N,N-Diethylnicotinamide (8.9 g) in dry ether (100 ml) was reduced with lithium aluminium hydride (1.25 g) in dry ether (100 ml). The reaction product was worked up in the usual way to yield *3-(diethylaminomethyl)-pyridine*[26] (6 g), b.p. 106–108°/12 mm.

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