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Synthetic Analogues of Nicotine. III *

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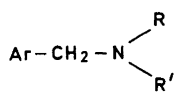
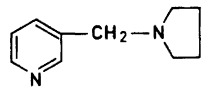
A number of N-substituted aminoalkylpyridines and phenylalkylamines have been prepared. Some of the biological activities of the compounds have been recorded and compared with those of nicotine.

In Part II [1] of this series, we prepared a number of model compounds of type I which enabled us to compare systematically changes in structure with changes in physiological activity. The structural changes which were studied in greatest detail were those resulting from varying the aromatic nucleus (Ar in I) and the basic group ($-N\begin{matrix}R\\R'\end{matrix}$ in I).



I



II

3-Pyrrolidinomethylpyridine, II (1, Table 1) and 3-piperidinomethylpyridine (4, Table 1) were the biologically most active compounds prepared in this model series. This suggested that isomers of II, in which the pyridine ring is substituted at different positions, should be examined. The relationship between the structure and activity of the corresponding isomers of nicotine has been investigated by earlier workers. Thus "α-nicotine" [2–4], 1-methyl-2-(2-pyridyl)-pyrrolidine, has been synthesised and was found to be less active than "β"- or natural nicotine. The third isomer, "γ-nicotine",[4,5] 1-methyl-2-(4-pyridyl)-pyrrolidine, has also been prepared, but no report has been found describing its biological action.

It is interesting to note that most of the compounds of type I have a stronger nicotine-like action than 1-methylpyrrolidine, which has 0.4 % of

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the activity of nicotine when tested on the frog's rectus muscle. In order to determine the importance of the aromatic ring for the physiological activity of a compound, several alicyclic analogues of type I were prepared.

By examining the physiological activities of two such compounds as 3-dimethylaminomethylpyridine (25, Table 5) and 3-dimethylaminomethyl-piperidine (26, Table 5), the relative importance of the pyridine and the piperidine ring can be compared.

Craig[6], in 1933, made a similar type of comparison between 1-methyl-2-alkyl- and 1-methyl-2-arylpyrrolidines and showed that, in almost all cases, those compounds containing an aromatic ring were the more toxic.

Further use was made of model compounds of type I to investigate the effect on biological activity of the following changes:

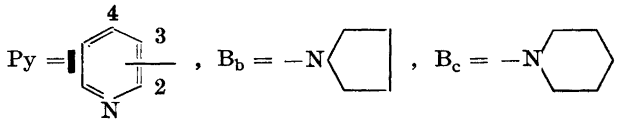
1. The effect of lengthening the side chain joining the aromatic nucleus and the basic group.

2. The effect of methylating the bridge methylene group in compounds of type I.

The synthetic methods used in preparing the compounds in Tables 1 to 5 were mainly of a standard type. Most compounds in Tables 1 to 3 were prepared *via* lithium aluminium hydride reduction of the corresponding amides, with exception of the 2- and 4-aminoethylpyridines in Table 2, which were obtained by amine addition to the vinylpyridines. The piperidine analogues in Table 5 were prepared from the parent pyridine compounds by reduction with sodium in absolute ethanol or by catalytic hydrogenation at low pressure. A modified method was applied in the preparation of 1-(α-phenylethyl)-pyrrolidine (21, Table 4): α-phenethylamine was alkylated with 1,4-dibromobutane in the presence of potassium carbonate.

The biological activities of the compounds were tested on the isolated rabbit's jejunum, the guinea-pig's ileum, and the isolated rectus abdominis muscle of the frog *Rana temporaria*.

Table 1. Physiological activities of aminomethylpyridines. 0 signifies < 0.001 activity: *l*-nicotine = 1.0.



No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
1[a]	3-Py−CH_2−B_b	0.16	0.3	0.3
2	2-Py−CH_2−B_b	0.04	0.03	0.001
3	4-Py−CH_2−B_b	0.01	0.01	0.007
4[a]	3-Py−CH_2−B_c	0.13		0.2
5	2-Py−CH_2−B_c	0.02	0.01	0
6	4-Py−CH_2−B_c	0.02	0	0

[a]) Described in Part II [1].

DISCUSSION OF THE PHYSIOLOGICAL ACTIVITIES

It is clear from an examination of Table 1, that aminomethylpyridines which contain the 3-pyridyl nucleus have the greatest physiological activity, while the 2- and 4-pyridyl derivatives are much less active both in the pyrrolidine and the piperidine series. A comparison of the relative effect of the isomers of the pyrrolidine series in the frog muscle test, leads to the following order of activity:

3-pyridyl	>>	4-pyridyl	>	2-pyridyl
(30 %)		(0.7 %)		(0.1 %)

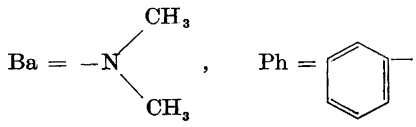
When the same comparison is made with the aminoethylpyridines, Table 2, it is seen that derivatives containing the 3-pyridyl nucleus are still the most active, but that the 2-pyridyl isomers have almost the same activity. The relative effect of the different isomers of the pyrrolidine derivatives in Table 2 in the frog muscle test is as follows:

3-pyridyl	=	2-pyridyl	>	4-pyridyl
(1.5 %)		(1.2 %)		(0.1 %)

Table 2. Physiological activities of aminoethylpyridines.

No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
7	3-Py$-(CH_2)_2-B_b$	0.08	0.13	0.015
8	2-Py$-(CH_2)_2-B_b$	0.15	0.07	0.012
9	4-Py$-(CH_2)_2-B_b$	0.04	0	0.001
10	3-Py$-(CH_2)_2-B_c$	0.2	0.4	0.01
11	2-Py$-(CH_2)_2-B_c$	0.2	0.02	Loss of sensitivity
12	4-Py$-(CH_2)_2-B_c$	0.02	0.02	0.005

Table 3. Comparison of physiological activity and chain length. Phenylalkylamines.



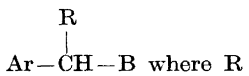
No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
13	Ph$-CH_2-B_a$	0.02	0.09	0
14	Ph$-(CH_2)_2-B_a$	0.12	0.05	0.002
15	Ph$-(CH_2)_3-B_a$	0.02	0	0
16	Ph$-(CH_2)_4-B_a$	0	0	0
17	Ph$-CH_2-B_b$	0.08	0.07	0.015
18	Ph$-(CH_2)_2-B_b$	0.3	0.09	0.021

A comparison of the activities of the compounds in Tables 1 and 2, shows that lengthening of the side chain joining the aromatic nucleus and the basic group from one to two carbon atoms causes a fall in activity in the 3- and 4-pyridyl analogues. The activity of the 2-pyridyl analogue, however, increases ten fold in the case of the frog muscle test.

These facts may be interpreted by assuming that within series of compounds of the same type, those derivatives in which the two nitrogen atoms are separated by a 3-carbon unit are normally among the most active biologically. Examples of such compounds are 3-pyrrolidinomethylpyridine (1, Table 1), 2-pyrrolidinoethylpyridine (8, Table 2) and nicotine (22, Table 5).

Further examples of the effect of chain length on the physiological activity of some phenylalkylamines are given in Table 3. Two basic groups, dimethyl-

Table 4. Physiological activities of compounds of the type III.



Ar—CH(R)—B where R = H or CH_3

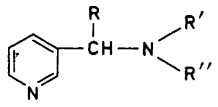
No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
1	3-Py—CH_2—B_b	0.16	0.3	0.3
19	3-Py—CH(CH_3)—B_b	0.02	0.01	0.008
13	Ph—CH_2—B_a	0.02	0.09	0
20	Ph—CH(CH_3)—B_a	0.02	0	0
17	Ph—CH_2—B_b	0.08	0.07	0.015
21	Ph—CH(CH_3)—B_b	0.01	0	0

Table 5. Showing the loss (fall) in physiological activity when an aromatic nucleus is replaced by an alicyclic ring.

No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
22	Nicotine	1	1	1
23	1-Methyl-2-(3-piperidyl)-pyrrolidine	0.005		0
1	3-Py—CH_2—B_b	0.16	0.3	0.3
24	3-(N-Methylpiperidyl)-—CH_2—B_b	0.008	relaxing	0.004
25	3-Py—CH_2—B_a	0.11	0.10	0.02
26	3-Piperidyl-CH_2—B_a	0.002	0.003	0
13	Ph—CH_2—B_a	0.02	0.09	0
27	Cyclohexyl-CH_2—B_a	0.008	0.002	0

amino and pyrrolidino, were used in this series and in the former case the maximum activity was obtained at a chain length of two methylene groups.

In Part I of this series, it was shown that the presence of an alkyl group on the carbon atom between the pyridine ring and the N-dialkyl group in compounds of type III causes a decrease in the physiological activity of the compound.



III

The results given in Table 4 provide further support for this conclusion and show that it can be extended to include compounds of type I which have a benzene ring as the aromatic part of the molecule.

Finally, Table 5 shows the remarkable loss of activity that takes place when the aromatic nucleus of a compound such as nicotine (22) or 3-pyrrolidinomethylpyridine (1) is replaced by the corresponding alicyclic ring. This suggests that the aromatic nucleus plays an important role in the nicotine-like activity of these compounds. Even in the case of N,N-dimethylbenzylamine (13), the physiological activity falls when the benzene ring is replaced by the cyclohexane ring (compound 27).

EXPERIMENTAL

All meltingpoints are uncorrected.

1-Picolinoylpyrrolidine. Picolinoyl chloride (7.5 g) prepared from picolinic acid by the general method of Grigorovskiĭ and Kimen,[7] was added slowly to a stirred solution of pyrrolidine (12.5 g) in water (5 ml) at 0°. The reaction mixture was worked up as described for 1-nicotinoylpyrrolidine[1]. The crude product was distilled to give pure *1-picolinoylpyrrolidine* (3.8 g), b.p. 164–165°/7 mm. (Found: N 15.95. $C_{10}H_{12}N_2O$ requires N 15.9). By the same general method were prepared (40–70 %) yield): *1-Isonicotinoylpyrrolidine*, b.p. 165–167°/7 mm. (Found: N 16.0. Calc. for $C_{10}H_{12}N_2O$: N 15.9). *1-Picolinoylpiperidine*,[8] *1-isonicotinoylpiperidine*,[9] *β-phenylpropionic acid dimethylamide*[10] and *γ-phenylbutyric acid dimethylamide*[11].

1-(3-Pyridylaceto)-pyrrolidine. Ethyl 3-pyridylacetate (16.5 g) was refluxed for 48 h with pyrrolidine (30 g). Fractional distillation of the resulting mixture gave the *amide* (18 g), b.p. 170–172°/0,8 mm, which solidified on cooling to a crystalline mass (ethanol), m.p. 50–51°. (Found: N 14.6. $C_{11}H_{14}N_2O$ requires N 14.7).

1-(3-Pyridylaceto)-piperidine (19 g), b.p. 177–179°/1.5 mm, was prepared in the same way from ethyl 3-pyridylacetate (16.5 g) and piperidine (34 g). (Found: N 13.65. $C_{12}H_{16}N_2O$ requires N 13.7).

No. 2. *2-Pyrrolidinomethylpyridine.* 1-Picolinoylpyrrolidine (10 g) in dry ether (100 ml) was added to a stirred suspension of lithium aluminium hydride (1.6 g) in dry ether (100 ml). The mixture was refluxed for 2 h, decomposed and worked up in the usual way. The crude product was distilled to give *2-pyrrolidinomethylpyridine.*

No. 8. *2-Pyrrolidinoethylpyridine*[13]. This compound was prepared from 2-vinylpyridine (5.3 g) and pyrrolidine (7.4 g) by the general method of Doering and Weil[14]. Fractional distillation of the resulting mixture gave *2-pyrrolidinoethylpyridine* (7.0 g). By the same general method were obtained (75–85 % yield): No. 9, *4-pyrrolidinoethylpyridine*,[15] No. 11, *2-piperidinoethylpyridine*[14] and No. 12, *4-piperidinoethylpyridine*[15].

Table 6. The following amines of type $Ar-CH_2-NH_2$ were prepared as described for No. 2, p. 1739.

No.	Ar	$-NR_2$	b.p.	Picrate m.p.	C found	C calc.	H found	H calc.	N found	N calc.	Yield %
2	2-Pyridyl	pyrrolidino	106–108°/9 mm		73.7	74.0	8.9	8.7			37
	Dipicrate	$C_{22}H_{20}N_8O_{14}$		191–192°	42.6	42.6	3.4	3.2	18.4	18.1	
3	4-Pyridyl	pyrrolidino	114–116°/9 mm		73.8	74.0	9.1	8.7			55
	Dipicrate	$C_{22}H_{20}N_8O_{14}$		211–212°	42.6	42.6	3.5	3.2	18.1	18.1	
5	2-Pyridyl [8]	piperidino	110–112°/7 mm								48
	Dipicrate	$C_{23}H_{22}N_8O_{14}$		180–181°	43.8	43.5	4.0	3.5	17.7	17.7	
6	4-Pyridyl	piperidino	122–124°/7 mm		74.4	74.95	9.3	9.15	16.3	15.9	60
	Dipicrate	$C_{23}H_{22}N_8O_{14}$		193–194°	44.0	43.5	3.8	3.5	18.0	17.7	
7	3-Pyridyl-methyl	pyrrolidino	101–102°/1 mm		74.85	74.95	9.4	9.15			65
	Dipicrate	$C_{23}H_{22}N_8O_{14}$		199–200°	43.7	43.5	3.75	3.5	17.5	17.7	
10	3-Pyridyl-methyl	piperidino	102–103°/0.8 mm		75.5	75.7	9.7	9.5			74
	Dipicrate	$C_{24}H_{24}N_8O_{14}$			44.9	44.45	4.1	3.7	17.1	17.3	
15	β-Phenyl-ethyl [12]	dimethyl-amino	88– 90°/8 mm								70
	Picrate [12]			98– 99°							
16	γ-Phenyl-propyl	dimethyl-amino	110–112°/11 mm		81.1	81.3	10.8	10.8			72
	Picrate	$C_{18}H_{22}N_4O_7$		132–133°	52.9	53.2	5.35	5.5	14.0	13.8	

No. 18. *1-Phenethylpyrrolidine* [16] was prepared from β-phenethylbromide and pyrrolidine by standard methods in 43 % yield. B.p. 115–116°/8 mm.

No. 19. *α-(3-Pyridyl)-ethylpyrrolidine.* 3-Acetylpyridine (16 g) (Raschig Chemische Fabrik) was reduced with potassium borohydride (1.0 g) in methanol (50 ml) at room temperature to give *3-pyridylmethylcarbinol* [17] (13 g), b.p. 120–122°/4 mm. *Picrate* (ethanol), m.p. 133–134°. (Found: C 44.2; H 3.1; N 16.1. $C_{13}H_{12}N_4O_8$ requires C 44.3; H 3.4; N 15.9).

The carbinol (12.3 g) was dissolved in benzene (40 ml) and treated with excess thionyl chloride in the cold. The mixture was refluxed for 2 h and the thionyl chloride was then removed by azeotropic distillation with benzene. The residue was slowly added, with stirring and ice cooling, to excess pyrrolidine and the whole slowly heated to reflux. After refluxing for 10 min, the reaction mixture was cooled, diluted with water and the solution made strongly alkaline with solid potassium hydroxide. The oily layer was extracted with chloroform and the chloroform extract dried ($MgSO_4$). Removal of the solvent gave an oil which was distilled to yield *α-(3-pyridyl)-ethylpyrrolidine* (8.8 g), b.p. 139–141°/7 mm. (Found: C 74.6; H 9.2. $C_{11}H_{16}N_2$ requires C 74.95; H 9.15). *Dipicrate* (acetic acid), m.p. 206–207°. (Found: C 43.6; H 3.7; N 17.4. $C_{23}H_{22}N_8O_{14}$ requires C 43.5; H 3.5; N 17.7).

No. 20. *α-Phenylethyldimethylamine.* α-Phenylethylamine (6 g) was methylated by heating with 90 % formic acid (25 g) and 37 % aqueous formaldehyde solution (12 ml) for 8 h on a steam-bath. The reaction mixture was worked up as described in the preparation of β-phenylethyldimethylamine by Icke *et al.*[18] *α-Phenylethyldimethylamine* [19] (5.0 g), b.p. 60–62°/7 mm, was obtained after distillation of the crude product.

No. 21. *α-Phenylethylpyrrolidine.* α-Phenylethylamine (12 g) was dissolved in absolute ethanol (100 ml) and dried, finely powdered potassium carbonate (27.5 g) was added. 1,4-Dibromobutane (21.5 g) was slowly run into the above suspension with vigorous stirring. The reaction mixture was refluxed for 6 h with continuous stirring. After cooling and filtering, the filtrate was acidified with concentrated hydrochloric acid and the solution evaporated to dryness *in vacuo*. The residue was dissolved in water and the resulting solution made alkaline with solid potassium hydroxide until 3 layers were formed. This 3-phase system was shaken with ether and the ether extract dried ($MgSO_4$). Removal

of the ether yielded an oil which was fractionally distilled to give *α-phenylethylpyrrolidine* (8.9 g), b.p. 96–98°/7 mm. *Picrate* (ethanol), m.p. 128–129°. (Lit.[20]: B.p. 111°/13 mm. Picrate, m.p. 127–129°).

No. 23. "*Hexahydronicotine*". Sodium (22.5 g) was added to nicotine (13 g) in absolute ethanol (200 ml) during the course of 20–30 min. The sodium was added in as large pieces as possible. Absolute ethanol (100 ml) was run in and the mixture heated for 2–3 h on an oil bath until the sodium disappeared. Without allowing the reaction mixture to cool, the alcohol was distilled off. During this procedure water (100 ml) was added, slowly at first and then as rapidly as possible. The distillation was continued until practically all the alcohol had distilled. The residue in the flask was discarded.

The distillate was acidified with concentrated hydrochloric acid (20 ml) and the alcohol removed by distillation on the water-bath. The residual volume (30–35 ml) was made strongly alkaline with solid potassium hydroxide and the oil which separated was extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent removed to give an oil which, after two fractional distillations, yielded pure "*hexahydronicotine*" (2.4 g), b.p. 243–245°/760 mm. Blau [21] reports b.p. 244–245°. *Dipicrate* (ethanol), m.p. 201–202°. Harlan and Hixon [22] report m.p. 202°.

No. 24. *1-Methyl-3-pyrrolidinomethylpiperidine.* 1-Nicotinoylpyrrolidine (10 g) was refluxed for 24 h with methyl iodide (9 g) in acetonitrile to give the quaternary methiodide [23] (17.3 g), m.p. 214–215°.

The methiodide (10 g) was hydrogenated in ethanol (100 ml) over a platinum oxide catalyst (0.1 g). The hydrogenation was carried out at 6 atm. for 18 h. When the reduction was complete, the solution was filtered to remove the catalyst and the ethanol removed *in vacuo*. The residue was dissolved in water, the solution made strongly alkaline with 50 % sodium hydroxide solution and extracted with ether. The ether extract was dried ($MgSO_4$) and evaporated to give an oil. Distillation of the oil furnished *1-(1-methylnipecotoyl)-pyrrolidine* [23] (6.0 g), b.p. 122–124°/1 mm.

Reduction of the amide (5 g) with lithium aluminium hydride (0.7 g) in the normal fashion yielded *1-methyl-3-pyrrolidinomethylpiperidine* [23] (4.1 g), b.p. 111–113°/12 mm. *Dipicrate* (acetic acid), m.p. 165,5–167°. (Found: C 43.1; H 4.9; N 17.5. $C_{23}H_{28}N_8O_{14}$ requires C 43.1; H 4.4; N 17.5).

No. 26. *3-Dimethylaminomethylpiperidine.* 3-Dimethylaminomethylpyridine (13.5 g) was hydrogenated in glacial acetic acid (50 ml) over a platinum oxide catalyst (0.2 g) for 4 h at 4 atm. The catalyst was removed by filtration and the filtrate diluted with water (50 ml). The resulting solution was made strongly alkaline with solid potassium hydroxide and extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent removed to give an oil. Fractional distillation of the oil yielded *3-dimethylaminomethylpiperidine* (10 g), b.p. 79–80°/12 mm. (Found: N 19.3. Calc. for $C_8H_{18}N_2$: N 19.7). *Dipicrate* (acetic acid), m.p. 232–233°. (Found: C 40.6; H 4.2; N 18.8. Calc. for $C_{20}H_{24}N_8O_{14}$: C 40.0; H 4.0; N 18.7).

No. 27. *N,N-Dimethylcyclohexanmethylamine* was prepared in about 60 % yield by lithium aluminium hydride reduction of N,N-dimethylcyclohexancarboxamide as described by Mousseron et al.[24]

The biological tests were made at Fysiologiska Institutionen, (Prof. U. S. v. Euler), Karolinska Institutet, Stockholm.

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REFERENCES

1. Haglid, F. and Wellings, I. *Acta Chem. Scand.* **17** (1963) 1727.
2. Oosterhuis, A. G. and Wibaut, J. P. *Rec. Trav. Chim.* **55** (1936) 729.
3. Craig, L. C. *J. Am. Chem. Soc.* **56** (1934) 1144.
4. Korte, F. and Schulze-Steinen, H.-J. *Ber.* **95** (1962) 2444.
5. Sugasawa, S., Tatsuno, T. and Kamiya, T. *Pharm. Bull. (Japan)* **2** (1954) 37.
6. Craig, L. C. *J. Am. Chem. Soc.* **55** (1933) 2543.

7. Grigorovskiĭ, A. M. and Kimen, Z. M. *J. Gen. Chem. USSR* **18** (1948) 171; (*cf. Chem. Abstr.* **42** (1948) 7296).
8. Sommers, A. H. *et al. J. Am. Chem. Soc.* **75** (1953) 57.
9. Büchi, J., Labhart, P. and Ragaz, L. *Helv. Chim. Acta* **30** (1947) 507.
10. Taverne, H. J. *Rec. Trav. Chim.* **16** (1897) 42; (*cf.* Beilstein, IX, 512).
11. Payot, P. H., Dauben, W. G. and Replogle, L. *J. Am. Chem. Soc.* **79** (1957) 4136.
12. von Braun, J. and Aust, E. *Ber.* **49** (1916) 501.
13. Reich, H. E. and Levine, R. *J. Am. Chem. Soc.* **77** (1955) 4913.
14. Doering, W. E. and Weil, R. A. N. *Ibid* **69** (1947) 2461.
15. Magnus, G. and Levine, R. *Ibid.* **78** (1956) 4127.
16. von Braun, J. and Cahn, R. S. *Ann.* **436** (1924) 262.
17. Strong, F. M. and Mc Elvain, S. M. *J. Am. Chem. Soc.* **55** (1933) 816.
18. Icke, N. *et al. Org. Syn. Coll. Vol.* **III** (1955) 723.
19. Cope, A. C., Foster, T. T. and Towle, P. H. *J. Am. Chem. Soc.* **71** (1949) 3929.
20. Shapiro, S. L., Soloway, H. and Freedman, L. *Ibid.* **80** (1958) 6060.
21. Blau, F. *Ber.* **26** (1893) 1029.
22. Harlan, W. R. and Hixon, R. M. *J. Am. Chem. Soc.* **52** (1930) 3385.
23. Sam, J., Minor, W. F. and Perron, Y. G. *Ibid.* **81** (1959) 710.
24. Mousseron, M. *et al. Bull. Soc. Chim. France* **1952** 1042.

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