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Synthetic Analogues of Nicotine. II *

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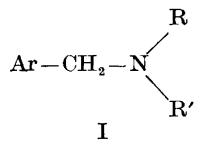
A number of N-substituted 3-picolylamines together with their benzyl-, thenyl-, furfuryl-, 2-pyrrolylmethyl- and 3-indolylmethyl-analogues have been prepared and some of their biological activities have been recorded and compared with those of nicotine.

In Part I[1] of this series we prepared a number of synthetic analogues of nicotine and examined their physiological activities, in particular their nicotine-like action. In a continuation of this work, we decided to search for a series of model compounds which would enable us to compare systematically changes in structure with changes in physiological activity. The need for a model series arises from the difficulty of synthesising 2-aryl-1-methylpyrrolidines of the same structural type as nicotine.

The low but definite nicotine-like activity exhibited by 3-(dimethylaminomethyl)-pyridine (I, Ar = 3-pyridyl: R = R′ = Me), prepared in Part I[1], suggested that compounds of this type might provide such a series. Analogues of type I are relatively easy to prepare and they contain the "essential" elements of the nicotine molecule, *i.e.* an aromatic nucleus substituted with a basic side chain unit.



I

As early as 1931, Craig and Hixon[2] prepared a compound of this type, 1-benzylpyrrolidine (I, Ar = phenyl: $-N\begin{matrix}R\\R'\end{matrix}$ = pyrrolidino), as part of a study on insecticides. Since then many compounds of this type have been prepared, but no interest was shown in their biological activities before Bach-

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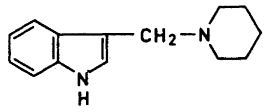
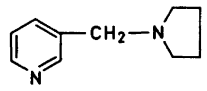
man and Heisey [3] prepared some pyrrole analogues (I, Ar = 2-pyrrolyl: $-N\begin{matrix}R\\R'\end{matrix}$ = piperidino or morpholino) for pharmacological testing.

During an investigation of synthetic analogues of the ergot alkaloids Akkerman, Jongh and Veldstra [4] prepared 3-piperidinomethylindole (II, comp. 23, Table 5) and showed that it had about 20 % of the activity of ergometrine when tested on the rabbit uterus *in situ*.

More recently, 1959, Sam, Minor and Perron [5] noted that 3-pyrrolidinomethylpyridine (III, comp. 3, Table 1), which is isomeric with nicotine, had pronounced nicotine-like activity.



II

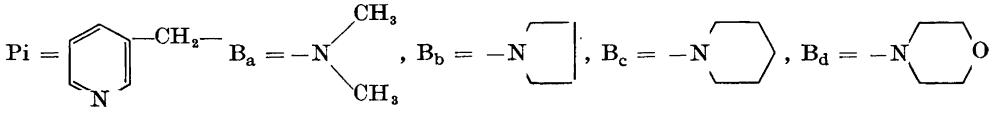


III

Compound III had been prepared independently by us at an early stage of our work, and its observed nicotine-like activity confirmed our belief that compounds of type I would provide a useful series for investigation.

In this paper six main series of compounds based on structure I are described. Each series is formed by using a different aromatic nucleus as the aromatic part of the molecule (Ar in I). The choice of aromatic nuclei has been dependent largely upon the ease of synthesis of the various compounds, and is as follows: 3-pyridyl, phenyl, 2-thienyl, 2-furyl, 2-pyrrolyl and 3-indolyl. The

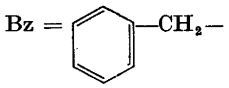
Table 1. Physiological activities of N-substituted 3-aminomethylpyridines tested as described in Part I. 0 signifies < 0.001 activity: *l*-nicotine = 1.0.



No.	Compound	Rabbit jejunum	Guinea Pig ileum	Cat B.P.	Frog muscle
1[a]	Pi—B_a	0.11	0.10	0.08	0.02
2[a]	Pi—$N(C_2H_5)_2$	0.02	0	0.004	0
3	Pi—B_b	0.16	0.3	0.10	0.3
4	Pi—B_c	0.13	0.08	0.13	0.2
5	*l*-N-Methylanabasine	0.005	0		inhibit.
6	Pi—B_d	0	0		0

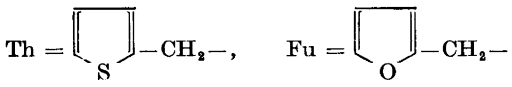
[a] Described in Part I [1].

Table 2. Physiological activities of N-substituted benzylamines.



No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
7	Bz–B_a	0.02	0.09	0
8	Bz–B_b	0.08	0.07	0.015
9	Bz–B_c	0.03	0.02	0.005
10	Bz–B_d	0	0	0

Table 3. Physiological activities of N-substituted thenyl- and furfurylamines.



No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
11	Th–B_b	0.03	0.03	0.02
12	Th–B_c	0.02	0.01	0.002
13	Fu–B_b	0.05	0.08	0.016
14	Fu–B_c	0.008	0.007	0.004
15	Fu–B_d	0	0	0

effect of the basic side chain grouping ( in I) has also been studied using, in the main, the following four bases: dimethylamine, pyrrolidine, piperidine and morpholine.

The preparation of the compounds described was undertaken by four different synthetic procedures:

The pyridine and thiophene analogues (Tables 1 and 3) were prepared by lithium aluminium hydride reduction of the corresponding amides.

The phenyl analogues (Table 2) were prepared by heating benzyl chloride with excess of the corresponding secondary amine.

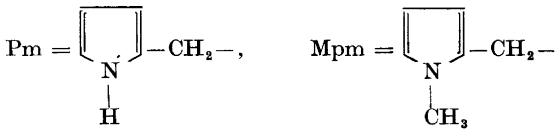
The furan derivatives (Table 3) were synthesised from furfural and the formyl derivative of the amine by means of a modified Leuckart [6] reaction.

The pyrrole and indole analogues (Tables 4 and 5) were synthesised using the Mannich reaction.

DISCUSSION OF THE PHYSIOLOGICAL ACTIVITIES

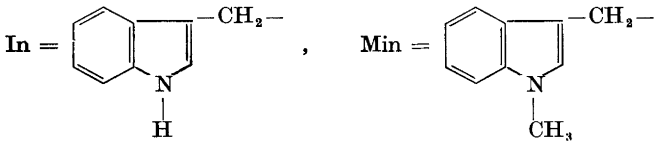
From an examination of Tables 1—5, it is seen that compounds of type I which contain the 3-pyridyl nucleus have the highest biological activity.

Table 4. Physiological activities of N-substituted 2-aminomethylpyrroles.



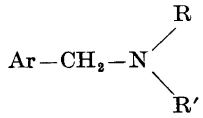
No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
16	Pm–B_a	0.002	0.007	0
17	Pm–B_b	0.02	0.01	0.002
18	Pm–B_c	0.002	0.004	0
19	Mpm–B_b	0.03	0	0
20	Mpm–B_c	0.01	0	0

Table 5. Physiological activities of N-substituted 3-aminomethylindoles.



No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
21	In–B_a	0.01	0.1	0
22	In–B_b	0.02	0.1	0
23	In–B_c	0.05	0.1	0
24	Min–B_a	0.004	0	0
25	Min–B_b	inhibit.	0.02	0
26	Min–B_c	inhibit.	0.05	0

This is true whatever the nature of the basic side chain grouping $-N\begin{matrix}R\\R'\end{matrix}$ may be.



I

The relative effect of the different aromatic nuclei on the physiological activity of compounds of type I is demonstrated in Table 6. In the case of the frog muscle test, the order is as follows:

3-pyridyl $\gg$ 2-thienyl = 2-furyl = phenyl $\gg$ 2-pyrrolyl = 3-indolyl
(30 %) (2 %) (1.6 %) (1.5 %) (0.2 %) (0 %)

Table 6. Comparison of the activities of pyrrolidinomethyl compounds of type I having different aromatic nuclei.

No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
3	Pi–B_b	0.16	0.3	0.3
8	Bz–B_b	0.08	0.07	0.015
11	Th–B_b	0.03	0.03	0.02
13	Fu–B_b	0.05	0.08	0.016
17	Pm–B_b	0.02	0.01	0.002
19	Mpm–B_b	0.03	0	0
22	In–B_b	0.02	0.1	0
25	Min–B_b	inhibit.	0.02	0

This is also the order of the stimulating effect on the rabbit's jejunum and the guinea-pig's ileum.

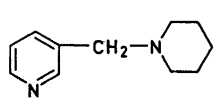
In each of the series considered in Tables 1–5 those compounds containing the pyrrolidine ring have the highest physiological activity. In Table 1 a comparison of the nicotine-like activity with the basic side chain grouping present leads to the following order of importance:

pyrrolidino (30 %) > piperidino (20 %) >> dimethylamino (2 %)

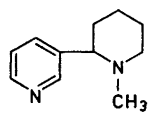
The morpholino derivatives show complete lack of "nicotine-like" activity.

In Part I of this series,[1] it was established that the intact pyrrolidine ring is a definite contributing factor to the biological activity of nicotine. A comparison of compounds 2 and 3 (Table 1) shows that this conclusion also applies to compounds of type I. The nicotine-like activity of compound 3 (Table 1), which has an intact pyrrolidine ring, is 30 % of that of nicotine. However, compound 2 (Table 1), which has an open chain unit corresponding to a pyrrolidine ring broken at the 3–4 bond, has an activity of less than 0.1 % of that of nicotine.

The fact that 3-pyrrolidinomethylpyridine, compound 3 (Table 1), has the highest nicotine-like activity of the compounds examined may not appear surprising in view of its structural similarity to nicotine itself. Thus both are ditertiary bases containing a 3-pyridyl group and a pyrrolidine ring which is alkylated on its nitrogen atom. However, an analogous structural relationship exists between 3-piperidinomethylpyridine, IV (compound 4, Table 1), and N-methylanabasine, V (compound 5, Table 1). But here the former compound possesses a rather high nicotine-like activity while the latter is almost inactive.



IV



V

Table 7. Amines of the type $Ar-CH_2-N(R)_2$ prepared as described for No. 3 below.

No.	Ar	$-N(R)_2$	b.p.	m.p.	C found	C calc.	H found	H calc.	N found	N calc.	Yield %
3	3-Pyridyl [a]	pyrrolidino	122–124°/12 mm								56
	Dipicrate	$C_{22}H_{20}N_8O_{14}$		191–192°	42.6	42.6	3.6	3.2	17.8	18.1	
4	3-Pyridyl	piperidino	134–136°/12 mm		74.85	74.95	9.45	9.15			52
	Dipicrate	$C_{23}H_{22}N_8O_{14}$		178–179°	43.6	43.5	3.9	3.5	17.7	17.7	
6	3-Pyridyl	morpholino	136–138°/9 mm		67.4	67.4	7.7	7.9			62
	Dipicrate	$C_{22}H_{20}N_8O_{15}$		232–233°	41.7	41.5	3.2	3.2	17.6	17.6	
11	2-Thienyl	pyrrolidino	110–111°/10 mm		64.4	64.6	7.6	7.8			68
	Picrate	$C_{15}H_{16}N_4O_7S$		106–107°	45.8	45.45	4.1	4.1	14.1	14.1	
12	2-Thienyl [b]	piperidino	117–119°/8 mm								77
	Picrate			148–149°							

[a] Ref.[5] [b] Ref.[9], b.p. 139.5°/29 mm, picrate m.p. 147–148°.

EXPERIMENTAL

All melting points are uncorrected.

1-Nicotinoylpyrrolidine. Nicotinoyl chloride (15 g) (prepared according to the method of Grigorovskiĭ and Kimen [7]) was slowly added to a stirred solution of pyrrolidine (25 g) in water (10 ml) at 0°. After the addition, the reaction mixture was allowed to warm up to room temperature and left for 2 h. Water (40 ml) was added and the solution made strongly alkaline with solid sodium hydroxide. The oil which separated was extracted with chloroform and the extract dried ($MgSO_4$). Removal of the solvent gave an oil which was fractionally distilled to give *1-nicotinoylpyrrolidine* [5] (12 g).

By the same general procedure were obtained in around 60 % yield: *1-Nicotinoylpiperidine* [8], *4-nicotinoylmorpholine* [5], *1-(2-thenoyl)-pyrrolidine* (b.p. 181–183°/8 mm, m.p. 72–73°) and *1-(2-thenoyl)-piperidine* (b.p. 187–189°/8 mm). (The thenoyl compounds were prepared as intermediates and were not analysed).

No. 3. *3-Pyrrolidinomethylpyridine.* 1-Nicotinoylpyrrolidine (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). After addition of the amide, the reaction mixture was refluxed for 2 h and then decomposed and worked up in the usual manner. Distillation of the crude product yielded *3-pyrrolidinomethylpyridine* [5] (5.2 g).

1-Benzylamines. The following amines were prepared in around 40 % yield from benzyl chloride and the corresponding amine by the method of Craig and Hixon [2]: No. 7, *N,N-dimethylbenzylamine*[10,11], No 8, *1-benzylpyrrolidine*[2,12], No. 9, *1-benzylpiperidine* [13] and No. 10, *4-benzylmorpholine* [14].

No. 13. *1-Furfurylpyrrolidine.* Pyrrolidine (24 g) was added slowly with stirring and cooling to formic acid (16 g, 98–100 %, *d* 1.22). The mixture was then distilled up to a temperature of 140°, leaving a residue of N-formylpyrrolidine. The N-formylpyrrolidine was cooled and freshly distilled furfural (6.5 g) was added over a period of 20 min. The resulting mixture was heated at 150–170° for 4 h and then allowed to cool to room temperature. Water (100 ml) was added and the solution made strongly alkaline with solid potassium hydroxide. The oil which precipitated out was extracted with ether, the ether extract washed with water and then extracted with 2 N hydrochloric acid. The acid extract was immediately neutralised, made strongly alkaline with solid potassium hydroxide and extracted with ether. The ether extract was dried ($MgSO_4$) and the solvent removed, leaving an oil which on fractional distillation gave *1-furfurylpyrrolidine* (6.3 g), b.p.

82—84°/8 mm. (Found: C 71.4; H 8.7. Calc. for $C_9H_{13}NO$: C 71.5; H 8.7). *Picrate* (ethanol), m.p. 135—136°. (Found: C 47.4; H 4.3; N 14.7. Calc. for $C_{15}H_{16}N_4O_8$: C 47.4; H 4.2; N 14.7).

By the same general method were prepared: No 14, *1-furfurylpiperidine*,[15] b.p. 91—93°/8 mm, *picrate* (ethanol), m.p. 107—108°. (Ref.[15]: B.p. 93—94°/11 mm, picrate m.p. 107—108°). No. 15, *4-furfurylmorpholine*, b.p. 96—98°/8 mm. (Found: C 65.1; H 7.8. Calc. for $C_9H_{13}NO_2$: C 64.65; H 7.8). *Picrate* (ethanol), m.p. 97—98°. (Found: C 45.7; H 4.2; N 14.3. Calc. for $C_{15}H_{16}N_4O_9$: C 45.5; H 4.1; N 14.1).

No. 17. *2-Pyrrolidinomethylpyrrole*. A solution of pyrrolidine hydrochloride (11.3 g) in 37 % aqueous formaldehyde solution (8.5 g) was added slowly with stirring and cooling to pyrrole (6.7 g), at such a rate that the temperature did not rise above 60°. Stirring was continued for 2 h after the addition was complete and the mixture was allowed to stand overnight. It was then poured into 25 % sodium hydroxide solution (50 ml) and extracted with ether. The ether extract was washed with water, dried ($MgSO_4$) and the solvent removed to give a crude oil. Fractional distillation of the oil furnished *2-pyrrolidinomethylpyrrole* (10.7 g), b.p. 107—110°/11 mm. (Found: C 71.9; H 9.5; N 18.3. $C_9H_{14}N_2$ requires C 71.95; H 9.4; N 18.65). *Picrate* (ethanol), m.p. 102—103°. (Found: C 47.8; H 4.7; N 18.6. $C_{15}H_{17}N_5O_7$ requires C 47.5; H 4.5; N 18.5).

By the same general method were prepared (in 50—70 % yield): No. 16, *2-dimethylaminomethylpyrrole* [16] and No. 18, *2-piperidinomethylpyrrole* [16].

No. 19. *2-Pyrrolidinomethyl-1-methylpyrrole*. The sodium salt of 2-pyrrolidinomethylpyrrole, No. 17 (3 g), was formed with sodium amide (from 0.5 g sodium) in liquid ammonia by the general procedure of Potts and Saxton [17]. A solution of methyl iodide (3.12 g) in ether (10 ml) was added dropwise to the stirred solution of the pyrrole salt in liquid ammonia. Stirring was continued for 15 min, after which the ammonia was allowed to evaporate and water (10 ml) was added followed by ether (20 ml). The ether layer was separated, the aqueous phase extracted with an additional portion of ether (10 ml) and the combined ether extracts were washed with water (5 ml) and dried ($MgSO_4$). The ether was removed and the crude oil obtained was distilled to give *2-pyrrolidinomethyl-1-methylpyrrole* (2.5 g), b.p. 92—94°/7 mm. (Found: N 17.3. $C_{10}H_{16}N_2$ requires N 17.1). *Picrate* (ethanol), m.p. 121—122°. (Found: C 49.0; H 4.8; N 17.5. Calc. for $C_{16}H_{19}N_5O_7$: C 48.85; H 4.9; N 17.8).

By the same method was prepared (85 % yield): No. 20, *2-piperidinomethyl-1-methylpyrrole*[18], b.p. 107—109°/10 mm, *picrate* (ethanol), m.p. 159—160° (decomp.). (Ref.[18]: B.p. 97°/5 mm, picrate, m.p. 160° (decomp.).

No. 25. *3-Pyrrolidinomethyl-1-methylindole*. A solution of pyrrolidine (1.45 g) in glacial acetic acid (4 ml) was cooled to 5° and 37 % aqueous formaldehyde solution (1.65 ml) was added. The resulting mixture was cooled to 5° and added in one lot to 1-methylindole (2.62 g). The reaction mixture was shaken until it became homogeneous. During the process of shaking a spontaneous rise in temperature took place. The solution was allowed to stand overnight and was then poured into 10 % sodium hydroxide solution (40 ml). The oil which separated was extracted with ether, the ether extract dried ($MgSO_4$) and concentrated. The oily residue was distilled to give *3-pyrrolidinomethyl-1-methylindole* (3.05 g), b.p. 142—144°/1 mm. (Found: C 78.2; H 7.8; N 13.1. $C_{14}H_{18}N_2$ requires C 78.5; H 8.5; N 13.1). *Picrate* (ethanol), m.p. 146—147°. (Found: C 54.4; H 5.0; N 15.8. $C_{20}H_{21}N_5O_7$ requires C 54.2; H 4.8; N 15.8).

By the same general method were prepared (70—80 % yield): No. 22, *3-pyrrolidinomethylindole*, m.p. 127—128° (methanol-water). (Found: C 78.1; H 7.8; N 13.9. $C_{13}H_{16}N_2$ requires C 78.0; H 8.05; N 14.0). *Picrate* (ethanol), m.p. 158—159°. (Found: C 53.4; H 4.5; N 16.4. $C_{19}H_{19}N_5O_7$ requires C 53.1; H 4.5; N 16.3). No. 23, *3-piperidinomethylindole*[19], m.p. 160—161°. *Picrate* (ethanol), m.p. 172—173°. (Found: C 54.3; H 4.9; N 15.6. $C_{20}H_{21}N_5O_7$ requires C 54.2; H 4.8; N 15.8). No. 24, *3-dimethylaminomethyl-1-methylindole* [20] and No. 26, *3-piperidinomethyl-1-methylindole* [21].

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

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