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Synthetic Analogues of Nicotine. IV

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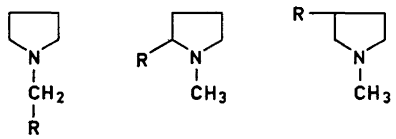
A number of 2- and 3-substituted 1-methylpyrrolidines together with some N-substituted pyrrolidines have been synthesised. Some of their biological activities have been recorded and compared with those of nicotine.

In Parts II [1] and III [2] of this series a number of compounds of type I were prepared and their physiological activities examined. The results obtained indicated that the activities of those compounds varied considerably depending on the nature of the group R.



I II III

The 2-substituted 1-methylpyrrolidines (II) form a group of compounds which are isomeric with substances of type I. Nicotine (II, R = 3-pyridyl) belongs to this group. A third isomeric group is the 3-substituted 1-methylpyrrolidines (III). In this paper derivatives of all three types have been synthesised in an attempt to assess the effect of the nature and position of the group R on the physiological activity of the 1-methylpyrrolidine nucleus.

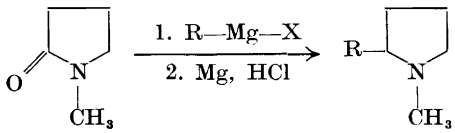
Several earlier groups of research workers have synthesised and tested compounds of type I; this work is reviewed in Part II [1] of this series.

A large number of 2-alkyl- and 2-aryl-1-methylpyrrolidines (II, R = alkyl or aryl) have been described in the literature. However, compounds of this type having an aromatic heterocyclic nucleus in the 2-position are relatively rare. Apart from pyridine, which is present in nicotine (14), thiophene and quinoline are the only other two heteroaromatic ring systems incorporated in this type of compound. In 1940, Nandi prepared the *dl*-form of 1-methyl-2-(3-quinolyl)-pyrrolidine and it was shown to be one third as active as *l*-nicotine [3]. The thiophene analogue of type II, 1-methyl-2-(2-thienyl)-pyrrolidine

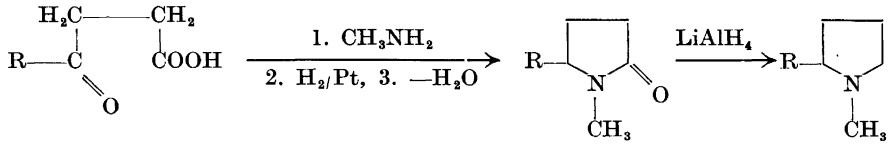
(17), was prepared by Burckhalter and Short [4] in 1958 and was found to be inactive. Bergel and coworkers,[5] in a study of synthetic analgesics, prepared 1-methyl-3-phenylpyrrolidine (18) and some of its derivatives, but otherwise 3-substituted 1-methylpyrrolidines of type III are little known in the literature.

The synthesis of the analogues of type I (see Table 1) was accomplished by using standard alkylating procedures.

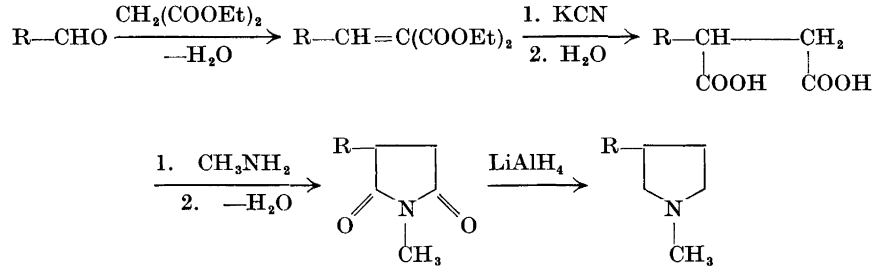
Two main synthetic methods were used to prepare the 2-substituted 1-methylpyrrolidines (II). The first method involved the action of a Grignard reagent on 1-methylpyrrolidone to give a hydroxypyrrolidine (or the corresponding pyrroline) which was reduced to the desired 1-methylpyrrolidine:



The second method depended upon the reductive amination of γ-substituted γ-oxobutyric acids with methylamine by hydrogenation of an aqueous methylamine solution of the acid over a platinum oxide catalyst at 6—7 atm. Distillation of the reaction product furnished the pyrrolidone, which was reduced with lithium aluminium hydride to the 1-methylpyrrolidine:



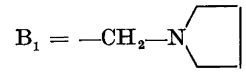
The 3-substituted 1-methylpyrrolidines of type III were prepared using a novel method of building up the pyrrolidine ring system *via* aryl substituted succinic acids:



Good yields were obtained for all stages of this synthesis. Only in the case of lithium aluminium hydride reduction of the 2-chloro- and 4-chlorophenyl succinimide analogues was a low yield recorded.

The physiological 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 compounds of type I. 0 signifies < 0.001 activity: *l*-nicotine = 1.0.



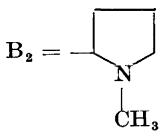
No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
1	H—B_1	0.025	0.006	0.004
2[a]	Phenyl-B_1	0.07	0.08	0.015
3	4-Methylphenyl-B_1	0.25		0
4	4-Chlorophenyl-B_1	0.13	0.04	0
5	4-Dimethylamino-phenyl-B_1	0	inhibit.	inhibit.
6[a]	3-Pyridyl-B_1	0.16	0.3	0.3

a) Described in Part II [1].

DISCUSSION OF PHYSIOLOGICAL ACTIVITIES

A comparison of the activities of the compounds described in this paper has been made more difficult, since several of the substances desensitize the test organs used. The nature of this desensitizing action has not been analyzed at present, but may itself be of interest in later investigations.

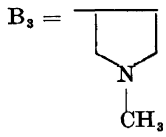
Table 2. Physiological activities of compounds of type II.



No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
1	H—B_2	0.025	0.006	0.004
7	Phenyl-B_2	0.006	0.016	0.005
8	4-Methylphenyl-B_2	loss of sensitivity of test organs		
9	2-Methylphenyl-B_2	loss of sensitivity of test organs		
10	Benzyl-B_2	0.03	0.02	0
11	2,4-Dimethylphenyl-B_2	0.02		0.002
12	2,4,6-Trimethylphenyl-B_2	inhibit.		0.004
13	4-Chlorophenyl-B_2	0.25		0.003
14	Nicotine	1	1	1
15[b]	3-Piperidyl-B_2	0.005		0
16	3-(1-Methylindolyl)-B_2	relaxing effect	relaxing effect	0
17	2-Thienyl-B_2	0.013	0.03	0

b) Described in Part III [2].

Table 3. Physiological activities of compounds of type III.



No.	Compound	Rabbit jejunum	Guinea Pig ileum	Frog muscle
1	H—B_3	0.025	0.006	0.004
18	Phenyl-B_3	0.02	0.015	0
19	4-Methylphenyl-B_3	0.03	0.013	0.003
20	4-Chlorophenyl-B_3	0.03	relaxing effect	loss of sensitivity
21	2-Chlorophenyl-B_3	0.04		loss of sensitivity
22	4-Dimethylamino-phenyl-B_3	0.03	0	0

In the N-benzyl series, Nos. 2—6 (Table 1), the low but measurable nicotine-like activity of the unsubstituted phenyl analogue, 2 (Table 1) falls and even disappears when the phenyl nucleus is substituted in the 4-position. However, compounds 3 and 4 have got a quite high stimulating action on the rabbit jejunum preparation.

1-(4-Dimethylaminobenzyl)-pyrrolidine, 5 (Table 1) is of particular interest as it inhibits the effect of nicotine on the frog muscle at concentrations as low as 0.1 μg/ml. During this work, several of the substances prepared were found to inhibit the action of nicotine. Those compounds will be studied in more detail in future experiments.

The low nicotine-like action of the compounds in Table 2 indicates that the presence of a phenyl or substituted phenyl group in the 2-position of 1-methylpyrrolidine generally decreases the physiological activity of the molecule. Similarly when the pyridine nucleus in nicotine, 14 (Table 2), is replaced by the thiophene or N-methylindole nucleus, the nicotine-like activity disappears.

The stimulating action of the 3-substituted 1-methylpyrrolidines (Table 3) on the rabbit jejunum is weak but remarkably constant throughout the series and closely resembles that of 1-methylpyrrolidine, 1 (Table 3). This suggests that the substitution of a phenyl or substituted phenyl group in the 3-position of the 1-methylpyrrolidine molecule has little effect on the physiological activity of the compound.

It may be noted that even the chlorine substituted analogues, compounds 20 and 21 (Table 3), fit into this pattern contradictory to their analogues of type I and II, compounds 4 (Table 1) and 13 (Table 2) which both deviate from the rest in their stimulating effect on the rabbit intestine.

EXPERIMENTAL

All meltingpoints are uncorrected.

No. 3. *1-(4-Methylbenzyl)-pyrrolidine* was obtained in 65 % yield by lithium aluminium hydride reduction of 4-methylbenzoylpyrrolidine prepared from 4-methylbenzoic acid chloride and pyrrolidine by the same general route as described in part II of this work [1]. B.p. 107—108°/7 mm. (Found: C 82.1; H 9.2. Calc. for $C_{12}H_{17}N$: C 82.2; H 9.8). *Picrate* (ethanol), m.p. 130—131°. (Found: C 53.5; H 5.1; N 14.2. Calc. for $C_{18}H_{20}N_4O_7$: C 53.5; H 5.0; N 13.9).

No. 4. *1-(4-Chlorobenzyl)-pyrrolidine* was obtained in 38 % yield when pyrrolidine (0.2 mole) was alkylated with 4-chlorobenzylchloride (0.1 mole) by the general method. B.p. 98—100°/1.5 mm. (Found: Cl 17.9. Calc. for $C_{11}H_{14}NCl$: Cl 18.1). *Picrate* (ethanol), m.p. 129—130°. (Found: C 48.3; H 4.4; N 13.2. $C_{17}H_{17}N_4O_7Cl$ requires C 48.1; H 4.0; N 13.2).

No. 5. *1-(4-Dimethylaminobenzyl)-pyrrolidine.* 4-Dimethylaminobenzaldehyde (17.5 g) was dissolved in ethanol (75 ml) and pyrrolidine (20 ml) was added. The mixture was then hydrogenated at atmospheric pressure and room temperature in the presence of Adam's catalyst. When the theoretical amount of hydrogen had been taken up (2 h), the catalyst was filtered off and the resulting solution fractionally distilled to give *1-(4-dimethylaminobenzyl)-pyrrolidine* (12.2 g). B.p. 107—108°/0.5 mm. (Found: C 76.1; H 10.0; N 13.7. $C_{13}H_{20}N_2$ requires C 76.4; H 9.9; N 13.7). *Picrate* (acetic acid), m.p. 166—167°. (Found: C 53.0; H 5.65; N 16.2. $C_{19}H_{23}N_5O_7$ requires C 52.65; H 5.35; N 16.2).

No. 8. *1-Methyl-2-(4-tolyl)-pyrrolidine.* 1-Methyl-2-pyrrolidone (9.9 g, 0.1 mole) was added slowly to a vigorously stirred ether solution of 4-tolyl magnesium bromide prepared from 4-bromotoluene (34.2 g, 0.2 mole) and magnesium (4.85 g) in dry ether (500 ml). In the event of a heavy oily precipitate forming during the addition of the pyrrolidone, the mixture is stirred and refluxed vigorously until the precipitate dissolves; the addition is then continued. After the addition was complete, the reaction mixture was stirred and refluxed overnight. During the overnight stirring, the stirrer should not extend further than half way into the solution in case a precipitate formed during this period should stop the stirrer.

The mixture was hydrolysed by adding ice and excess dilute hydrochloric acid. The two phases were separated and the ether phase was extracted with dilute hydrochloric acid. The combined acidic phase was washed with benzene and magnesium (10 g) was added.

Concentrated hydrochloric acid was then added slowly with stirring until all the magnesium had dissolved, care being taken to keep the temperature below 35° by external

Table 4. Compounds of type II prepared as described for No. 8 above.

No.	R	Halide used in the Grignard reaction	b.p.	m.p.	C found	C calc.	H found	H calc.	N found	N calc.	Yield %
8	4-Tolyl	bromide	100—102°/7 mm		82.4	82.2	9.6	9.8			76
	Picrate	$C_{18}H_{20}N_4O_7$		139—140°	53.6	53.5	5.0	5.0	13.6	13.9	
9	2-Tolyl	bromide	102—103°/9 mm		81.9	82.2	9.5	9.8			43
	Picrate	$C_{18}H_{20}N_4O_7$		157—159°	53.5	53.5	5.1	5.0	13.8	13.9	
10	Benzyl [a]	chloride	87— 89°/1 mm								30
	Picrate [b]			145—146°							
13	4-Chlorophenyl [c]	bromide	113—115°/7 mm								44
	Picrate [d]			173—174°							
17	2-Thienyl [e]	iodide	88— 90°/2 mm								17
	Picrate [f]			124—125°							

Literature values: *a*) B p 69—70°/0.3 mm[4], *b*) m.p. 144—145° [4], *c*) b.p. 118°/9 mm[6], *d*) m.p. 173°[6], *e*) b.p. 47—48°/0.3 mm[4], *f*) m.p. 123—124° [4].

ice-cooling. After stirring for a further 10 min, the solution was made strongly alkaline with 50 % potassium hydroxide solution and steam distilled.

The distillate 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 gave *1-methyl-2-(4-tolyl)-pyrrolidine* (13.2 g), b.p. 100—102°/7 mm.

γ-Mesityl-γ-oxobutyric acid. Finely powdered aluminium chloride (60 g) was slowly added to a mixture of succinic anhydride (20 g), mesitylene (26.5 g) and tetrachloroethane (80 ml). The reaction proceeded smoothly with low heat formation and was complete after 3—4 h. The reaction mixture was worked up in the normal manner for a Friedel Crafts reaction to give *γ-mesityl-γ-oxobutyric acid* (33 g), m.p. 106° (benzene/light petroleum). Meyer [7] reports m.p. 109°.

γ-(2,4-Dimethylphenyl)-γ-oxobutyric acid, m.p. 113°, was prepared in 82 % yield by the same method. Barnett [8] reports m.p. 114°.

γ-3-(N-Methylindolyl)-γ-oxobutyric acid, m.p. 115—116° (from benzene/light petroleum), was prepared in 32 % yield according to the method of Ballantine *et al.*[9]

No. 7. *1-Methyl-2-phenylpyrrolidine.* γ-Phenyl-γ-oxobutyric acid (20 g) was dissolved in excess 33 % aqueous methylamine solution (100 ml) and hydrogenated over a platinum oxide catalyst at 6—7 atm. pressure. The hydrogenation was stopped after 20—25 h by which time about 0.8 mole of hydrogen had been taken up. The catalyst was removed by filtration and the filtrate evaporated *in vacuo* to give a residue. The residue was then heated at 170—200° under a stream of nitrogen gas until no more water was given off. The product was distilled giving a main fraction of *1-methyl-2-phenyl-5-pyrrolidone* (13.5 g), b.p. 162—164°/10 mm. Lukeš and Večeřa [10] report b.p. 171—173°/14 mm.

The pyrrolidone (10 g) in dry ether (100 ml) was reduced with lithium aluminium hydride (1.5 g) in dry ether (200 ml). The reaction mixture was decomposed and worked up in the normal way to yield *1-methyl-2-phenylpyrrolidine* (6.3 g), b.p. 69—70°/2 mm.

Diethyl 4-dimethylaminobenzylidenemalonate. 4-Dimethylaminobenzaldehyde (52 g), diethyl malonate (50 g), benzoic acid (1.0 g), piperidine (1.2 ml) and benzene (100 ml) were placed in a 500 ml flask fitted with a reflux condenser and a unit for removing water. The mixture was refluxed vigorously on an oil bath at 130—140° until no more water was collected (12—18 h). After cooling the yellow crystalline mass was filtered off and recrystallised giving *diethyl 4-dimethylaminobenzylidenemalonate* (82 g), m.p. 109—110° (from ethanol). Cohan and Wayne [12] report m.p. 110°.

The following procedure was used when the product was an oil: After the reaction mixture had cooled, benzene was added and the solution washed first with water, then with 1 N hydrochloric acid and finally with saturated sodium bicarbonate solution. The aqueous wash solutions were shaken with benzene and the benzene extract added to the main benzene solution. After drying ($MgSO_4$), the benzene was removed under reduced pressure and the residue distilled to give the product.

In the same way were prepared (75—90 % yield): *Diethyl benzylidenemalonate*,[13] *diethyl 4-methylbenzylidenemalonate*,[14] *diethyl 4-chlorobenzylidenemalonate* [15] and *diethyl 2-chlorobenzylidenemalonate* [16].

Table 5. Compounds of type II prepared as described for No. 7 above.

No.	R	b.p.	m.p.	C found	C calc.	H found	H calc.	N found	N calc.	Yield %
7	Phenyl [a]	69— 71°/2 mm								47
	Picrate [b]		146—147°							
11	2,4-Dimethylphenyl	111—113°/7 mm		82.3	82.5	9.7	10.1			35
	Picrate	$C_{19}H_{22}N_4O_7$	139—140°	54.6	54.5	5.3	5.3	13.4	13.4	
12	Mesityl	92— 94°/1 mm		82.9	82.7	10.3	10.4			17
	Picrate	$C_{20}H_{24}N_4O_7$	132—133°	55.9	55.55	5.7	5.6	12.9	13.0	
16	3-(1-Methylindolyl)	136—138°/1 mm								24
	Picrate	$C_{20}H_{24}N_5O_7$	197—198°	54.4	54.2	4.8	4.8	15.7	15.8	

Literature values: *a*) B.p. 88°/7 mm [11], *b*) m.p. 148° [11].

4-Dimethylaminophenylsuccinic acid. A suspension of diethyl 4-dimethylaminobenzylidenemalonate (58.5 g) in absolute ethanol (500 ml) was placed in a 2 l flask fitted with a stirrer, a dropping funnel and a reflux condenser. The stirrer was started and the temperature of the oil bath was raised to 65—75° and maintained there until a clear solution was obtained. A solution of potassium cyanide (14 g) in water (25 ml) was added rapidly from the dropping funnel and the oil bath was then held at 65—75° for 18 h.

The reaction mixture was cooled to 15°, and the precipitated potassium bicarbonate removed by filtration and washed with ethanol (40 ml). The combined filtrate and wash liquor was made slightly acid with dilute hydrochloric acid and then neutralised with dilute ammonium hydroxide. The solution was then concentrated under reduced pressure to a semi-solid residue. The residue was shaken with a mixture of water (100 ml) and ether (300 ml). The ether layer was separated and the aqueous layer shaken with a further quantity of ether (50 ml). The combined ether solutions were dried ($MgSO_4$) and the ether was removed to give crude *ethyl β-(4-dimethylaminophenyl)-β-cyanopropionate* (38 g).

The crude ester (38 g) was refluxed with concentrated hydrochloric acid (250 ml) for 18 h. The reaction mixture was filtered, made slightly alkaline with 50 % sodium hydroxide solution and finally acidified with glacial acetic acid. The resulting solution was concentrated until precipitation began. On cooling, *4-dimethylaminophenylsuccinic acid* (35 g) was obtained (from acetic acid), m.p. 235—236° (decomp.). (Found: C 60.5; H 6.4; N 6.3. $C_{12}H_{15}NO_4$ requires C 60.7; H 6.4; N 5.9).

In the same way were obtained (70—75 % yield): *Phenylsuccinic acid*,[17] *4-tolylsuccinic acid*,[18] *4-chlorophenylsuccinic acid* [19] and *2-chlorophenylsuccinic acid* [20].

N-Methyl-4-dimethylaminophenylsuccinimide. 4-Dimethylaminophenylsuccinic acid (20 g) was dissolved in 33 % aqueous methylamine solution (80 ml) and the resulting solution refluxed for 2 h. The reaction mixture was evaporated to dryness and the solid mass heated above its melting point until effervescence ceased. The product was recrystallised to give *N-methyl-4-dimethylaminophenylsuccinimide* (17 g), m.p. 153—154° (from dimethylformamide). (Found: C 67.0; H 7.1; N 12.1. $C_{13}H_{16}N_2O_2$ requires C 67.2; H 6.9; N 12.1).

In the same way were prepared (75—85 % yield): *N-Methylphenylsuccinimide*,[21] *N-methyl-4-tolylsuccinimide*, m.p. 103—104°. (Found: C 70.8; H 6.4; N 6.85. $C_{12}H_{13}NO_2$ requires C 70.9; H 6.45; N 6.9). *N-Methyl-4-chlorophenylsuccinimide* [22] and *N-methyl-2-chlorophenylsuccinimide* [23].

No. 22. *1-Methyl-3-(4-dimethylaminophenyl)-pyrrolidine.* The N-methyl-4-dimethylaminophenylsuccinimide (10 g) in dry tetrahydrofuran (50 ml) was added to a stirred suspension of lithium aluminium hydride (3.0 g) in dry tetrahydrofuran (150 ml) at such a rate as to produce mild refluxing. After the addition was complete, the mixture was stirred and refluxed vigorously for 5 h. The reaction mixture was decomposed and worked up in the normal manner to give an oil which was fractionally distilled yielding *1-methyl-3-(4-dimethylaminophenyl)-pyrrolidine* (6.5 g), b.p. 160—162°/9 mm.

Table 6. Compounds of type III prepared as described for No. 22 above.

o.	R	b.p.	m.p.	C found	C calc.	H found	H calc.	N found	N calc.	Yield %
3	Phenyl [a]	104—106°/9 mm								72
	Picrate [b]		158—159°							
)	4-Tolyl	120—122°/9 mm		82.5	82.2	9.9	9.8			66
	Picrate	$C_{18}H_{20}N_4O_7$	163—164°	53.6	53.5	5.1	5.0	13.9	13.9	
)	4-Chlorophenyl	125—127°/9 mm		67.2	67.5	7.4	7.2			47
	Picrate	$C_{17}H_{17}ClN_4O_7$	165—166°	48.3	48.1	4.1	4.0	12.9	13.2	
l	2-Chlorophenyl	124—125°/9 mm		67.8	67.5	7.4	7.2			40
	Picrate	$C_{17}H_{17}ClN_4O_7$	160—161°	48.5	48.1	4.0	4.0	13.0	13.2	
2	4-Dimethylaminophenyl	160—162°/9 mm		76.5	76.4	9.8	9.9			62
	Distyphnate	$C_{25}H_{26}N_8O_{16}$	191° (decomp.)	43.4	43.2	3.9	3.8	15.9	16.1	

Literature values: *a*) B.p. 105—110°/11 mm[5], *b*) m.p. 155—158° [5].

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

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