Biochemical Studies on Pityrol, V. Basic Constituents of Pityrol

By

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Although the basic fraction is composed of the smallest part of the pityrol, the odour of the drug is principally due to its presence.

It was separated from the commercial pityrol by means of dilute sulphuric acid from neutral and acidic fractions, and was a dark brown viscous liquid of a peculiar odour somewhat reminiscent of the pyridine bases.

For purification, it was subjected to steam distillation, and the basic compounds separated as an oily substance in the distillate amounted to 460 grm., and 190 grm. of the soluble bases were extracted from the distillate with ether after the insoluble oil had been separated.

Both the soluble and insoluble bases ascertained by chemical reactions

Table I

	Soluble bases.		Insoluble bases.	
B. p.	(46°–150°) 15 mm.		(41°–160°) 14 mm.	
Yield	110 grm.		390 grm.	
Density	0.9750		0.9248	
n_D^{25}	1.491		1.494	
C	66.6	84.7	77.2	95.4
H	8.7		9.6	
N	9.4		8.6	

Primary amine		
aliphatic	−	−
aromatic	+	+
Secondary amine	+	+
Tertiary amine	+	+
Pyrrol	−	−

to be composed of primary, secondary and tertiary amines, and it is of interest to note that the basic fractions especially of the latter bases, but contain not a single trace of pyrrol.

Two fractions were treated with picric acid in order to isolate only the tertiary bases as picrate, and 77 grm. and 120 grm. of the picrates were obtained from the soluble and insoluble bases respectively and the picrate which were then treated with hydrochloric acid to convert the hydrochlorides. From the hydrochlorides free bases were isolated by means of caustic soda.

The yield of free bases from both fractions is shown in Table II with their physical constants.

Table II

	Fraction	Yield	d_4^{25}	n_D^{25}
Soluble bases	100°—170°	14.5 grm.	0.9184	1.502
	above 170°	3.6 „	−	1.504
Insoluble bases	140°—200°	26.0	0.9129	1.503
	above 200°	8.4	−	1.552

The basic compouud is a colourless light oil of pyridine-like odour, and on being left exposed to the air becomes dark yellowish due to oxidation by the air.

Each low boiling fraction was carefuly distilled under ordinary pressure, and the high boiling one distilled under reduced pressure many times and the physical constants of the fractions were studied with the following results:

To isolate the basic compounds which occurring in the distillates in a pure state, the hydrochlorides of each fraction were treated with mercuric chlorides to convert them into the double salt. By repeated crystallisation

Table III
Soluble Bases

		Fraction	Yield	n_D^{25}	d_4^{25}	Double salt of $HgCl_2$	
						Yield	M. p.
Lower	1	to 130°	1.6 grm.	1.453	0.9127	0.9 grm.	(151°)
	2	130 –140°	2.0 „	1.478	0.9155	0.5 „	147°
	3	140°–150°	2.8 „	1.483	0.9222	0.2 „	147°
	4	150°–160°	3.5 „	1.486	0.9507	1.5 0.4	127° 131°
	5	Residue	0.6 „	—	—		
Higher	1	to 70° 13mm.	1.1 grm.	1.492	0.9285	No definite double salt of $HgCl_2$ and picric acid.	
	2	70°–80°	0.8	1.498	0.9393		
	3	80°–90°	1.1	1.500	0.9530		
	4	Residue	0.31	—	—		

Table IV
Insoluble Bases

		Fraction	Yield	n_D^{25}	d_4^{25}	Double salt of $HgCl_2$	
						Yield	M. p.
Lower	1	115°–130°	0.8 grm.	1.466	0.9703	0.3 grm.	151°
	2	130°–145°	2.1 „	1.483	0.9297	0.6 „ 0.5 „	154° 116°
	3	150°–157°	3.7 „	1.483	0.9689		
	4	157°–164°	3.4 „	1.485	0.9343	1.6 0.07 0.5 0.4 0.1 0.8	116° 163° 166° 127° 131° 188°
	5	164°–166°	1.0 „	1.485	0.9434	—	—
	6	166°–176°	2.6 „	1.488	0.9343	0.5 0.1	163° 127°
	7	Residue	8.4 „	—	—	—	—
Higher	1	70°–80° (13 mm.)	1.2 „	1.495	0.9962	0.1	162°*
	2	80°–90°	0.3 „	1.500	0.9974	0.05	162°*
	3	90°–100°	0.7 „	1.517	0.9986	0.3	200°*
	4	100°–117°	2.1 „	1.549	1.0428	0.4	200°*
	5	Residue	—	—	—	—	picrate

from the aqueous solution, pure salts were isolated which show a definite melting point, and the results are shown in the table. The basic compounds which are difficult to isolate in a pure state by the aid of the double salt of mercuric chloride, in forming an oily salt, were accordingly converted into a picrate in an alcoholic solution after the free base was isolated from the hydrochlorides. We, however, noticed that some of the basic compounds occurring in the pityrol were difficult to isolate in a crystalline form either by means of the double salt of mercuric chloride or by means of a picrate.

The basic compounds which occur in the soluble basic fraction and form no crystalline picrates, were separated from crystals and set in a free state by means of caustic soda.

The yield of the free base was 21 grm., & it boils at 140°–230°, and shows the constants

$$n_D^{25} = 1.4989\,; \quad d_4^{25} = 0.9403$$

It was fractionated 3 times:

Table V

	Fraction	Yield	n_D^{25}	d_4^{25}
1	to 155°	1.8 grm.	1.5050	0.9031
2	155°–165°	2.6 „	1.5053	0.9158
3	165°–175°	2.9 „	1.5060	0.9256
4	175°–190°	2.0 „	1.5070	0.9419
5	190°–200°	2.4 „	1.5120	0.9550
6	Residue	1.7 „	—	—

The fraction was again treated to convert it into the double salt of mercuric chloride, and the salts isolated in a pure state by repeated crystallization were as follows:

Table VI

	Fraction	Double salt of $HgCl_2$	
		Yield	M.p.
1	to 155°	1.4	167°
2	155°–165°	8.0	157°
3	165°–175°	9.6	154°

By repeated crystallisation of these salts from their aqueous solution, they were found to be composed of the same substance which melts at 188°, and thus 2 : 6-dimethyl pyridine was confirmed to be composed mostly of these fractions.

The basic compounds which occur in the insoluble fraction to form an oily compound with picric acid, were regenerated into the free base by the usual method and distilled.

The fraction has a B.p. of 150°–270°, and its constants showed $d_4^{25}=0.9452$; $n_D^{25}=1.5170$, and it weighed 107 grm.

It contains much of the tertiary bases and some quantity of the secondary & primary bases, and accordingly it was fractionated under ordinary pressure 5 times with the following results.

Table VII

	Fraction	Yield	n_D^{25}	$d_4^{25°}$
1	145°–160°	8.1 grm.	1.4890	0.9245
2	160°–165°	4.8 „	1.4891	0.9263
3	165°–170°	5.0 „	1.4893	0.9275
4	170°–175°	5.8 „	1.4914	0.9307
5	175°–180°	7.9 „	1.4925	0.9410
6	180°–190°	5.6 „	1.4943	0.9551
7	192°–200°	7.7 „	1.5010	0.9532
8	200°–210°	6.5 „	1.5085	0.9661
9	210°–220°	5.3 „	1.5200	0.9909
10	220°–230°	1.6 „	1.5400	1.0059
11	230°–255°	5.9 „	1.5520	1.0251

To isolate the basic compounds in a pure state, the fractions were treated in their hydrochlorides with mercuric chloride, and the double salt of mercuric chloride separated in a solid form was purified by recrystallisation from the aqueous solution and the following pure salts were obtained as shown in Table VIII from the corresponding fraction.

Some of the fractions which hardly yielded to the crystalline double salt of mercuric chloride, were tried with picric acid to convert picrate as indicated in Table VIII.

From the first to the fourth fraction, their hydrochlorides form a

Table VIII

	Fraction	Double salt of $HgCl_2$	
		Yield	M.p.
1	145°–160°	8 grm. 3 „ 0.4 0.2 0.4	127° 154° 147° 110° 151°
2	160°–165°	3 grm. 0.2 „ 0.1 0.5	116° 191° 110° 112°
3	165°–170°	0.3 0.5	127° 112°
4	170°–175°	0.3 1.2	154° 106°*
5	175°–180°	0.2 0.1	157° 106°*
6	180°–190°	0.6	130 ⊕
7	192°–200°	—	—
8	200°–210°	—	—
9	210°–220°	0.2	200°*
10	220°–230°	0.3	200°*
11	230°–255°	0.5	200°*

definite double salt with mercuric chloride, and others which do not yield a definite compound in this manner, were transformed into their picrate in an alcohol solution.

The sixth fraction which seems from its physical constants to be composed of aniline, was identified to be so by transforming it into benzene azo-β-naphthol.

2-Methyl Pyridine

A basic substance which occurs in the low boiling fraction with a B.p. of 150°–160°, yields its double salt of mercuric chloride with a M.p. of 151° or 154°, shown in Tables III, IV, & VIII.

The double salt was analysed and the results for carbon, hydrogen & nitrogen all agree with the theoretical values for 2-methyl pyridine.

* Picrate.

⊖ benzene azo-β-naphthol.

Salt, m.p. 154°	CO_2	H_2O	Found		Calc for $C_6H_7NHCl_22HgCl_2$	
			C.	H.	C.	H.
12.755 mg	5.005 mg	1.419 mg	10.70	1.24	10.71	1.05
Salt, m.p. 151°						
15.048 mg	6.004 „	1.490 „	10.88	1.10	10.71	1.05
14.002 „	5.580 „	1.488 „	10.87	1.18	11	„

Salt, m.p. 154°	N (c.c.)	Found N.	Calc N.
19.605 mg.	0.37 (20°, 758 mm,)	2.09	2.08
24.747 „	0.46 (19°, 758 „)	2.08	—
Salt, m.p. 151°			
13.694 mg	0.25 (18°, 766 mm.)	2.07	—
14.243 „	0.25 (17°, 766.5 „)	2.00	

3-Methyl Pyridine

The double salt of the base with mercuric chloride, showing a m.p. of 147°–146°, in Tables III, an l VIII was analysed with the following results :

Salt	N (c.c)	t.	p.	Calc for $C_6H_7NHCl_2HgCl_2$			Found		
				C	H	N	C	H	N
15.118 mg	0.30	25.5	757	10.71	1.05	2.08	10.31	1.17	2.14
16.238 „	0.32	23	758	—	—	—	—	—	2.16
13.162 „	4.976 mg CO_2 1.386 mg H_2O								

2 : 6-Dimethyl Pyridine

The double salt formed from a base with mercuric chloride, which occurs in the fractions having B.p. of 157°–164° in Table IV, and B.p. of 160°–165° in Table VIII, was found to melt at 188° & 191° respectively. The two salts were noticed to be the same substance because there was no indication of any lowering of the m.p. of the mixed salts also by analysis.

Salt, m.p. 188°	N (c.c)	Found	Theory for $C_7H_9NHClHgCl_2H_2O$.
13.801 mg	0.41 (21°, 758 mm.)	3.36	3.24
12.103 „	0.36 (22° 758, „)	3.34	„

CO_2		H_2O	C		H	
			found	theory	found	theory
11.803 mg	8.558 mg	2.704 mg	19.77	19.44	2.54	2.10
13.273 „	9.632 „	2.880 „	19.79	„	2.41	„

Salt, m.p. 191°	CO_2	H_2O	C	H
13.526 mg	9.515 mg	2.889 mg	19.18	2.37
12.303 „	8.906 „	2.448 „	19.74	2.25

	N (c.c)	Found	Theory for $C_7H_9NHClHgCl_2H_2O$
11.384	0.34, (22°, 757 mm)	3.28	3.24
11.295	0.33, (21°, 758 mm)	3.22	„

2 : 4 Dimethyl Pyridine

The base which occurs in the fractions having B.p. of 150°–160° in Table III, and B.p. of 157°–164° in Table IV; B.p. 145°–160°, and B.p. of 165°–170° in Table VIII, yields equally the double salt of mercuric chloride which shows the m.p. of 127°, was confirmed to be the salt of 2 : 4 dimethyl pyridine.

Salt		Found			Calc. for $C_7H_9NHCl_2HgCl_2$		
		C	H	N	C	H	N
16.657 mg	0.31 c.c.N (20°, 758 mm.)	12.00	1.54	2.07	12.23	1.32	2.04
20.452 „	0.39 „ (22°, 758 „)	—	—	2.10			
12.272 „	5.415 mg CO_2, 1.699 mg H_2O						

2 : 4 : 6-Trimethyl Pyridine

The fractions with B.p. of 155°–175 in Table VI, B.p. of 170°–180°

in Table VIII, contain a base which yields the double salt with the mercuric chloride having a m.p. of 157° & 154°, and this was found by analysis to be the same salt derived from 2 : 4 : 6 trimethyl pyridine :

Salt, m.p. 154°	CO_2	H_2O	Found		Theory for $C_8H_{11}NHCl_2HgCl_2$	
			C	H	C	H
13.051 mg	6.700 mg	1.910 mg	14.00	1.63	13.68	1.58
12.104 „	6.205 „	1.809 „	13.98	1.66	—	—
Salt, m.p. 157°						
12.505 mg	6.197 mg	1.840 mg	13.52	1.63	13.68	1.58
13.211 „	6.584 „	1.953 „	13.59	1.64	—	—

Salt, m.p. 154°	N (c.c.)	N	
		Found	Calc. for $C_8H_{11}NHCl_2HgCl_2$
17.969 mg	0.29 (18 , 766 mm).	1.83	2.00
17.265 „	0.30 (18°, 762 „)	1.95	„

Salt, m.p. 157°		Found	Calc. for $C_8H_{11}NHCl_2HgCl_2\frac{1}{2}H_2O$
24.114 mg	0.40 (22°, 752.5)	1.81	1.97
27.864 „	0.45, (23°, 752.5)	1.79	

Aniline

This was isolated from the fraction B.p. 180°–190° shown in Table VIII in the form of phenyl azo-β-naphthol, m.p. 130°, and was confirmed to be so by analysis :

Sample		N					
		Found			Calc. for $C_6H_5N_2C_{10}H_7OH$		
		C	H	N	C	H	N
2.502 mg	0 26 c.c.N (25°, 763 mm)	76.88	4.63	11.34	77.38	4.88	11.28
4.0075 „	0.40 „ (17°, 758 „)			11.24			
4.057 „	11.437 mg CO_2, 1.691 mg H_2O						

Quinoline

The occurrence of the base in the fraction. B.p. 240°–255°, in Table VIII, and also in the high fraction with a B.p. above 117°, 13 mm. in Table IV, was confirmed by isolating it as a salt of picrate, m.p. 200°.

Salt		N					
		Found			Calc. for $C_{15}H_{10}N_4O_7$		
		C	H	N	C	H	N
2.735 mg	0.40 c.c.N (21°, 749 mm)	50.10	3.14	16.0	50.26	2.81	15.64
3.458 „	0.59 „ (20°, 752 „)			15.93			
2.298 „	4.302 mg CO_2, 0.650 mg H_2O						

Dimethyl Pyridine (2.5 ?)

The fractions with B.p. 150°–164°, B.p. 166°–176°, in Table IV, and B.p. to 155°, in Table VI, were to supposed to contain dimethyl pyridine (2.5 ?) as a constituent from the analysis and melting-point determination of its double salt of mercuric chloride.

Salt, m.p. 163°–4°	CO_2	H_2O	Found			Theory for $C_7H_9NHCl_2HgCl_2$		
			C	H	N	C	H	N
15.159 mg	6.882 mg	1.818 mg	12.38	1.33	2.04	12.33	1.32	2.04
12.643 „	5.639 „	1.525 „	12.16	1.34	—			
22.561 „	0.42 c.c.N (24°, 762 mm)				2.04			
Salt, m.p. 167°								
12.477 mg	5.665 mg	1.478 mg	12.38	1.32	2.08 „	..	„	
11.032 „	4.892 „	1.026 „	12.09	1.03	—			
23.105 „	0.43 c.c.N (24°, 762 mm)							

Dimlethy Pyridine

A base which yielded the double salt of mercuric chloride with a m.p. of 110°, and gave the analytical results of a dimethyl pyridine derivative, was found to occur in the fractions. B.p. 100°–117° at 13 mm.

in Table IV, B.p. 145°–160°, 160°–165° in Table VIII.

Salt	CO_2	H_2O	Found			Calc. for $C_5H_5NHCl\ 2HgCl_2$		
			C	H	N	C	H	N
12.632 mg	5.598 mg	1.592 mg	12.09	1.40	2.06	12.23	1.32	2.04
15.050 „	6.600 „	1.946 „	11.96	1.44	—			
12.681 „	0.24 c.c.N (23°, 756 mm)							

Dimethyl Pyridine

The double salt of a base occurs in the fraction with B.p. of 165°–170° in Table VIII, melts at 112° agrees in analytical results with these of dimethyl pyridine. Although the crystalline form of the salt is similer to that of the 2 : 5 dimethyl pyridine mentioned above, a mixture of two crystals above a lowering in the melting-point.

Salt	CO_2	H_2O	Found		
			C	H	N
12.243 mg	5.652 mg	1.856 mg	12.59	1.68	2.06
13.241 „	6.020 „	1.713 „	12.40	1.50	—
13.512 „	0.25 c.c.N (23°, 756 mm)				

A Pyridine Derivative

The fractions having B.p. of 130°–145° in Table IV, and B.p. of 160°–165° in Table VIII, contain a base which forms a double salt of mercuric chloride of m.p. 116°, and gave the following analytical results of the salt, which agree fairly well with those of the pyridine salt, $C_5H_5NHCl.\ 2HgCl_2$.

Salt	CO_2	H_2O	C	H	N
12.888 mg	4.422 mg	1.173 mg	9.35	1.01	2.21
13.653 „	4.730 „	1.278 „	9.45	1.04	2.10
17.942 „	0.35 c.c.N (20°, 756.5 mm)				
22.238 „	0.41 „ (19°, 758 „)				

Tetramethyl Pyridine (?)

The fraction B.p. 170°–175°, B.p. 175°–180° in Table VIII, contains a base which gave a picrate of m.p. 106°. The analytical results of the picrate were as follows:

Salt	CO_2	H_2O	C	H
4.987 mg	7.232 mg	1.603 mg	39.55	3.57
4.402 „	6.410 „	1.320 „	39.71	3.33

A Base

The mother liquor separated from the crystals of quinoline picrate, yielded on standing for a while in a dark cold place fine crystals with a m.p. of 180° with decomposition, which on analysis gave the following results:

Sample	CO_2	H_2O	C	H
3.445 mg	5.920 mg	1.113 mg	46.87	3.59
3.212 „	5.553 „	1.120 „	47.14	3.49

The chemical nature of the base is awaiting further research which could not be attempted at this present owing to the scantiness of the sample.