CCXXIX.—*The Resolution of Externally Compensated Pavine and α -Bromocamphor- π -sulphonic Acid.*

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PYMAN has recently demonstrated the probability (Trans., 1909, **95**, 1610) that the "tetrahydropapaverine" described by Goldschmiedt (*Monatsh.*, 1886, **7**, 485; 1898, **19**, 324) is the 1:2-dihydropapaverine; some little uncertainty still remains as to the constitution of Goldschmiedt's base, and Pyman and Reynolds (this vol., p. 1320) consequently prefer to call the substance pavine. The presence of an asymmetric carbon atom in the molecule of "tetrahydropapaverine," or pavine, was demonstrated by the resolution of the base into its optically active components (Pope and Peachey, Trans., 1898, **73**, 893), but in view of the interest which now attaches to pavine it seemed desirable to apply to its resolution the methods which have been developed since that date.

Preparation of Externally Compensated Pavine.

The method of reducing papaverine described by Pyman yields the true tetrahydropapaverine as the chief product; the following process furnishes good yields of pavine. Papaverine (35 grams), hydrochloric acid (480 c.c.), and water (800 c.c.) are heated together under reflux, powdered tin (95 grams) being added in small portions; the tin becomes completely dissolved after about twenty hours' boiling, and, on cooling, a white, crystalline double salt separates. The latter is crystallised once from boiling water, and freed from tin by precipitation with hydrogen sulphide in boiling aqueous solution; the filtered solution, on evaporation, yields pavine hydrochloride, which is purified by crystallisation from hot water. About one-quarter of the papaverine used is thus obtained as pavine, whilst the mother liquors contain both the latter base and tetrahydropapaverine. This considerable yield of pavine is of interest in connexion with the suggestion, made and rejected by Pyman and Reynolds (*loc. cit.*), that this base is formed from some impurity present in the papaverine used.

Resolution of Externally Compensated Pavine.

The resolution of pavine into its optically active components, by crystallising the externally compensated base with one equivalent of α -bromocamphor- π -sulphonic acid, as described by Pope and Peachey, proceeds slowly, because the sparingly soluble crystalline salt of the lævo-component and the resinous salt of the dextro-

component separate together; the former salt is with difficulty purified from the latter by crystallisation. The following application of Pope and Peachey's method (Trans., 1899, **75**, 1066) leads to a more satisfactory resolution of the base into its optically active components.

Externally compensated pavine hydrochloride is treated with one-half an equivalent proportion of ammonium *d*- α -bromocamphor- π -sulphonate in hot aqueous solution; on cooling, *l*-pavine *d*- α -bromocamphor- π -sulphonate separates in long needles not contaminated by the resinous salt of the *d*-base. That the salt *lBdA* thus obtained contained none of the salt *dBdA* was shown by treating it, without recrystallisation, with ammonia, and determining the specific rotatory power of the liberated base; in an 8 per cent. chloroform solution the value $[\alpha]_D -152.0^\circ$ was obtained, which agrees well with the more accurately determined constant given below. It is clear that the resolution proceeds in accordance with the first type distinguished by Pope and Read (this vol., p. 989).

Although the separation of a pure *l*-pavine salt is rendered easy by the above method, yet the yield is not large, because on working in concentrated solutions, or on concentrating the mother liquors, hydrochloride of the base crystallises together with the salt *lBdA*; the following modification of the original process, which is applicable in other cases, was therefore adopted. The salts formed by pavine with inorganic acids are in general sparingly soluble in water, but Pope and Peachey found that the *d*-camphor- β -sulphonates of the base are readily soluble in water (Trans., 1898, **73**, 902); the externally compensated pavine was therefore dissolved in one equivalent proportion of *d*-camphor- β -sulphonic acid, and to the solution was added half an equivalent of ammonium *d*- α -bromocamphor- π -sulphonate, water being used as the solvent, and the solution being kept as concentrated as conveniently possible. Of the number of salts which might be formed in the mixed solution, *l*-pavine *d*- α -bromocamphor- π -sulphonate is the least soluble, and, as only sufficient ammonium salt was added to allow of the formation of this salt, it was to be expected that practically the whole of the *l*-pavine would separate as the pure salt. In accordance with this anticipation, the solution, prepared as described above, deposited almost all of the *l*-pavine as the sparingly soluble *d*- α -bromocamphor- π -sulphonate, and the deposited salt, after once recrystallising from boiling aqueous alcohol, has the properties previously ascribed to it.

After the *l*-pavine *d*- α -bromocamphor- π -sulphonate has been obtained in a pure state, the residual base—consisting almost entirely of *d*-pavine—is precipitated from the mother liquors by addition of

ammonia, and its actual content of *d*-pavine determined from its rotatory power in chloroform solution; the base is then dissolved in the requisite amount of *d*-camphor- β -sulphonic acid solution, and ammonium *l*- α -bromocamphor- π -sulphonate added in just sufficient quantity to precipitate all the *d*-pavine as the salt *d*B α A, which, being enantiomorphously related to the crystalline salt *l*B α A dealt with above, exhibits ordinary physical properties identical with those of the latter.

d-Pavine *l*- α -Bromocamphor- π -sulphonate,
 $C_{20}H_{23}O_4N, C_{10}H_{14}OBr \cdot SO_3H$.

This new salt separates immediately in long, colourless needles when the above operation is performed; after cooling, the salt is collected and recrystallised from boiling aqueous alcohol. The substance decomposes at 290–300°, and gave the following results on analysis:

0.0933 gave 0.1888 CO₂ and 0.0482 H₂O. C=55.19; H=5.78.

C₃₀H₃₈O₈NBrS requires C=55.19; H=5.87 per cent.

d- and *l*-Pavine.

These substances separate on cooling a hot dilute alcoholic solution of the corresponding bromocamphorsulphonates after addition of ammonia; after recrystallisation from benzene, the bases melted at 224°. The following determinations of rotatory power were made with the recrystallised substances after drying at 110°:

<i>l</i> -Pavine.			<i>d</i> -Pavine.		
0.1983 gram, made up to 20 c.c. with chloroform, in a 2-dcm. tube at 23°:			0.1970 gram, made up to 20 c.c. with chloroform, in a 2-dcm. tube at 23°:		
Na(<i>D</i> line).	Hg(yellow).	Hg(green).	Na(<i>D</i> line).	Hg(yellow).	Hg(green).
α - 2.990°	- 3.119°	- 3.500°	α + 2.960°	+ 3.093°	+ 3.470°
$[\alpha]$ - 150.8	- 157.3	- 176.5	$[\alpha]$ + 150.3	+ 157.0	+ 176.1
0.7316 gram, made up to 20 c.c. with chloroform, in a 1-dcm. tube at 22°:			0.7033 gram, made up to 20 c.c. with chloroform, in a 1-dcm. tube at 22°:		
α - 5.445°	- 5.730°	- 6.500°	α + 5.241°	+ 5.520°	+ 6.250°
$[\alpha]$ - 148.8	- 156.6	- 177.7	$[\alpha]$ + 149.0	+ 157.0	+ 177.7

The values obtained under similar conditions for the two enantiomorphously related bases are in good agreement, and are slightly higher than those previously recorded; the specific rotatory power diminishes slowly with increasing concentration, and the numbers afford some indication that the rotatory dispersion is dependent on the concentration of the solution.

dl-Pavine dl- α -Bromocamphor- π -sulphonate,
 $2C_{20}H_{28}O_4N, 2C_{10}H_{14}OBr \cdot SO_3H, H_2O.$

In view of the sparing solubility of the two crystalline salts dealt with above, namely, *lBdA* and *dBlA*, and of the fact that the salts *dBdA* and *lBlA* are resinous and also sparingly soluble, it seemed desirable to examine the salt formed by externally compensated pavine with the externally compensated α -bromocamphor- π -sulphonic acid. This substance was easily prepared by dissolving *dl*-pavine in an aqueous solution of the requisite amount of *dl- α -bromocamphor- π -sulphonic acid*, and evaporating to a gummy consistency; the residue crystallises on keeping, and after several recrystallisations from strong alcohol the salt is obtained in radiate clusters of soft, white, silky needles. The salt is optically inactive in aqueous solution, and the following analyses were made on the air-dried material:

0.1111 gave 0.2204 CO_2 and 0.0595 H_2O . $C=54.11$; $H=5.97$.

0.3233, heated at 110° for three hours, lost 0.0044. $H_2O=1.36$.

$C_{60}H_{76}O_{16}N_2Br_2S_2 \cdot H_2O$ requires $C=54.44$; $H=5.94$;
 $H_2O=1.36$ per cent.

This fully racemic salt thus differs from the active ones previously described, which crystallise without water, in containing water of crystallisation; it is also very soluble in water, and melts without blackening at $248-250^\circ$, whilst the active salts are sparingly soluble and decompose at $290-300^\circ$.

The Resolution of Externally Compensated α -Bromocamphor- π -sulphonic Acid.

The ease with which the resolution of externally compensated pavine can be effected with the aid of *d*- and *l- α -bromocamphor- π -sulphonic acid* suggests that the optically active bases could be used in effecting the resolution of the externally compensated acid in accordance with the method of Pope and Peachey.

With this object, an aqueous solution was prepared containing *d*-pavine (one equivalent), ammonia (one equivalent), and *dl- α -bromocamphor- π -sulphonic acid*; a clear solution is obtained on boiling with addition of a little alcohol, and, on cooling, the greater part of the alkaloid separates as the crystalline *d*-pavine *l- α -bromocamphor- π -sulphonate*. After recrystallisation from water, the latter salt was treated with ammonia, and the resulting ammonium *l- α -bromocamphor- π -sulphonate* separated by crystallisation; 0.1080 gram of this ammonium salt, made up to 20 c.c. with water, gave $\alpha_D - 0.915^\circ$ in a 2-dcm. tube at 22° , whence $[\alpha]_D - 84.7^\circ$. The latter

value is identical with that observed with ammonium *l*- α -bromocamphor- π -sulphonate prepared from *l*-camphor, so that the resolution of the externally compensated acid has been effected.

The mother liquors from which the *d*-pavine salt had been separated were next treated with ammonia, filtered, and evaporated until crystallisation occurred; on recrystallising the residue from aqueous alcohol, pure ammonium *d*- α -bromocamphor- π -sulphonate was obtained. 0.1082 gram, made up to 20 c.c. with water, gave $\alpha_D + 0.915^\circ$ in a 2-dcm. tube at 22° , whence $[\alpha]_D + 84.6^\circ$, which is the value ordinarily assigned to pure ammonium *d*- α -bromocamphor- π -sulphonate.

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