

The resolution of benzoyloscine / by Frank Tutin.

Contributors

Tutin, Frank.
Wellcome Chemical Research Laboratories.

Publication/Creation

London : Wellcome Chemical Research Laboratories, [1910?]

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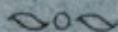
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THE RESOLUTION
OF
BENZOYLOSCINE

BY

FRANK TUTIN

(From the Transactions of the Chemical Society, Vol. 97, 1910)



THE WELLCOME CHEMICAL RESEARCH LABORATORIES
FREDERICK B. POWER, PH.D., LL.D., *Director*
6, King Street, Snow Hill
LONDON, E.C.



CXCII.—*The Resolution of Benzoyloscine.*

By FRANK TUTIN.

THE base oscine (scopoline), $C_8H_{13}O_2N$, formed by the hydrolysis of the alkaloid hyoscine (scopolamine), is generally acknowledged to be closely related structurally to tropine, $C_8H_{15}ON$, although its constitution is not known. Tropine, which contains two similar asymmetric carbon atoms, has recently been examined from a stereochemical point of view by M. Barrowcliff and the present author (Trans., 1909, **95**, 1966), and found to be an internally compensated compound. It was therefore considered of interest to investigate oscine in the same direction, particularly as the evidence so obtained might be of service in assigning a constitutional formula to this compound.

Oscine was prepared from *l*-hyoscine, and examined polarimetrically, when it was found to be optically inactive. As the amount of material prepared was not large, the base was converted into its benzoyl derivative before attempting its resolution, thereby increasing the size of the molecule. Moreover, the salts of benzoyloscine crystallise more readily than those of the original base.

Benzoyloscine d-camphorsulphonate (m. p. 167—168°) was first prepared, but, although this salt was submitted to a prolonged fractional crystallisation, no evidence of resolution could be obtained. When, however, *benzoyloscine d-bromocamphorsulphonate* was fractionally crystallised, it was at once seen that a separation was being effected, and, after three fractionations, *benzoyl-d-oschine d-bromocamphorsulphonate* (m. p. 246°) was obtained in a state of purity. This salt had $[\alpha]_D +51.9^\circ$ in aqueous solution, from which it is calculated that the basic ion has $[\alpha]_D +10.0^\circ$. The *base* obtained from this salt, when examined in 50 per cent. alcohol, had

$[\alpha]_D + 3.5^\circ$. In order further to characterise this optically active base, several salts were prepared from it, each of which was found to melt at a higher temperature than the corresponding salt of the inactive base, as will be seen from the following table:

Name of salt	M. p. of salt of <i>dl</i> -base.	M. p. of salt of <i>d</i> -base.
Hydrochloride	266°	283—284°
Nitrate	195	200°
Picrate.....	185	211—212
Aurichloride	183—194	189—190

d-Oscine could not be obtained from benzoyl-*d*-oscine by hydrolysis with an alkali, since racemisation rapidly occurred under these conditions. Recourse was therefore had to acid hydrolysis, the liberated benzoic acid being removed by means of steam. A solution containing *d*-oscine hydrochloride was thus obtained, by means of which an approximate determination of the optical rotatory power of *d*-oscine was made, when the value $[\alpha]_D + 77.7^\circ$ was found.

Attempts to obtain benzoyl-*l*-oscine *d*-bromocamphorsulphonate in a state of purity were unsuccessful.

It is evident from the results given in this paper that oscine is capable of resolution into two stereoisomerides, and no evidence of the existence of more than two such compounds was obtained. Any structural formula which may be assigned to this base must therefore contain either one or two asymmetric carbon atoms, but, if the latter be the case, both the asymmetric groupings must be similar.

EXPERIMENTAL.

About five grams of *l*-hyoscine (scopolamine) were heated for several hours on a water-bath with a large excess of alcoholic potassium hydroxide. Water was then added, and the resulting oscine (scopoline) extracted with chloroform, after which it was purified by distillation, when it passed over at 240—245°. The solid so obtained, which was optically inactive, was treated with a large excess of benzoyl chloride, when an additive compound of the base and the acid chloride was first formed. On heating the mixture, however, this substance dissolved, and then the liquid darkened somewhat, after which benzoyloscine hydrochloride separated in almost quantitative yield, the mixture becoming solid. After allowing the reaction mixture to cool, it was crushed in a mortar and mixed with ether, the solid being collected, and washed with this solvent. On recrystallisation from alcohol, the benzoyloscine hydrochloride was obtained in tufts of colourless needles, which melted and evolved gas at 266°. This melting point is higher than that previously given for the salt in question, namely, 249—250° (*Beilstein's Handbuch, Ergänzungsband, III, p. 619*),

and in order, therefore, to confirm the identity of the product, it was converted into the aurichloride. This salt crystallised in small tufts of yellow needles and melted at 183—184°:

0.0864 gave 0.0284 Au. Au = 32.9.

$C_{15}H_{17}O_3N, HAuCl_4$ requires Au = 33.0 per cent.

Benzoyloscine nitrate, prepared from the above-described hydrochloride, was very sparingly soluble in water, from which it crystallised in long, colourless needles. It melted and violently evolved gas at 195°. The corresponding picrate crystallised well in flattened needles, and melted at 185° without decomposing.

Benzoyloscine (benzoylscopoline) has previously been prepared by the repeated evaporation of oscine benzoate with dilute hydrochloric acid (D.R.-P. 79864), but the above-described method is far more expeditious, and gives much better yields.

Benzoyloscine d-Camphorsulphonate.

The benzoyloscine obtained from the above-described hydrochloride was converted into its *d-camphorsulphonate*. This salt was dissolved in ethyl acetate containing a little alcohol, when, after some time, it separated in the form of a white powder. When examined under the microscope, this was seen to consist of minute, diamond-shaped crystals.

Benzoyloscine d-camphorsulphonate melted at 167—168°, but, although it was submitted to a prolonged fractional crystallisation, no evidence of resolution could be obtained:

0.1476 gave 0.3312 CO_2 and 0.0918 H_2O . C = 61.2; H = 6.9.

$C_{15}H_{17}O_3N, C_{10}H_{16}O_4S$ requires C = 61.1; H = 6.7 per cent.

0.4226, made up to 20 c.c. with water, gave $\alpha_D + 0.26'$ in a 2-dcm. tube, whence $[\alpha]_D + 10.3^\circ$; $[M]_D + 50.6^\circ$.

Resolution of Benzoyloscine d-Bromocamphorsulphonate.

The base was recovered from the previously-described *d-camphorsulphonate*, and neutralised with *d-bromocamphorsulphonic acid*. The salt so obtained crystallised fairly readily from water, but much more easily from a mixture of ethyl acetate and alcohol, forming colourless needles. After one recrystallisation, it had somewhat the appearance of a mixture, and melted at 234—239°, previously softening at 211°.

0.4068, made up to 20 c.c. with water, gave $\alpha_D + 2.2'$ in a 2-dcm. tube, whence $[\alpha]_D + 50.0^\circ$; $[M]_D + 285.0^\circ$.

Since *d-bromocamphorsulphonic acid* has $[M]_D + 271^\circ$, it appeared that the benzoyloscine *d-bromocamphorsulphonate* was resolving.

It was again crystallised as before, when it seemed much less soluble, and melted at 238—244°.

0.3982, made up to 20 c.c. with water, gave $\alpha_D + 2^{\circ}4'$ in a 2-dcm. tube, whence $[\alpha]_D + 51.9^{\circ}$; $[M]_D + 295.8^{\circ}$.

When recrystallised a third time, this salt yielded handsome, glistening needles, which melted sharply at 246—246.5°.

0.4092, made up to 20 c.c. with water, gave $\alpha_D + 2^{\circ}8'$ in a 2-dcm. tube, whence $[\alpha]_D + 52.1^{\circ}$; $[M]_D + 297.0^{\circ}$.

This salt was evidently that of the dextrorotatory component of the racemic base, and since, as shown below, it yielded *d*-oscine on hydrolysis, it must be designated *benzoyl-d*-oscine *d*-bromocamphor-sulphonate. Repeated crystallisation caused no further change in its melting point or rotatory power:

0.1437 gave 0.2767 CO₂ and 0.0800 H₂O. C = 52.5; H = 6.2.

C₁₅H₁₇O₃N, C₁₀H₁₅O₄BrS requires C = 52.6; H = 5.7 per cent.

The molecular rotation of *benzoyl-d*-oscine, calculated from that of its *d*-bromocamphorsulphonate, is $[M]_D + 26.0^{\circ}$, whence the basic ion has $[\alpha]_D + 10.0^{\circ}$.

A small quantity of the above-described salt of *benzoyl-d*-oscine was treated with sodium carbonate, the base extracted with chloroform, and examined polarimetrically, when a reading of $+0^{\circ}25'$ was obtained. It was evident, therefore, that the base could be obtained in the free state without suffering complete racemisation. A larger quantity of the salt was then decomposed, and the resulting base dissolved in 20 c.c. of 50 per cent. alcohol, when it had $\alpha_D + 0^{\circ}49'$ in a 2-dcm. tube. Ten c.c. of the solution were subsequently found, on titration, to contain 0.1172 of base, whence $[\alpha]_D + 3.5^{\circ}$; $[M]_D + 9.75^{\circ}$. The fact that the value thus obtained for the rotation of *benzoyl-d*-oscine is lower than that previously calculated for the basic ion of *benzoyl-d*-oscine *d*-bromocamphor-sulphonate ($[\alpha]_D + 10.0^{\circ}$) may be due, in part, to racemisation, but it is probably largely owing to the fact that the free base is incompletely ionised when dissolved in 50 per cent. alcohol (compare Carr and Reynolds, this vol., p. 1328).

Attempts were made to isolate *benzoyl-l*-oscine *d*-bromocamphor-sulphonate, but without success. A fraction of salt, melting at 219—227°, was, however, obtained, the basic ion of which had $[M]_D - 4.7^{\circ}$.

Benzoyl-d-oscine hydrochloride was prepared from the corresponding *d*-bromocamphorsulphonate by double decomposition. It formed colourless needles, melting at 283—284°.

Benzoyl-d-oscine nitrate was similarly prepared. It was very sparingly soluble in water, and crystallised in irregular prisms,

which decomposed violently at 200° , and differed considerably in appearance from the long needles of the corresponding salt of the inactive base.


Benzoyl-d-oscine picrate crystallised very readily in handsome, yellow needles, which melted at 211 — 212° without undergoing any decomposition, a behaviour very remarkable in a picrate melting at so high a temperature.

Benzoyl-d-oscine aurichloride crystallised much more readily than the corresponding salt of the inactive base. It formed yellow needles, melting at 189 — 190° .

Hydrolysis of Benzoyl-d-oscine. Formation of d-Oscine.

The quantity of base which was employed, as above described, for determining the rotatory power of benzoyl-*d*-oscine in 50 per cent. alcohol was hydrolysed by means of hydrochloric acid, steam being passed through the mixture for the removal of the benzoic acid formed. To ensure that this was thoroughly accomplished, the operation was continued for three days. The liquid was maintained at a practically constant volume, and examined polarimetrically from time to time, when it was observed that the optical rotation increased appreciably as the hydrolysis proceeded. When the change was complete, the mixture was made alkaline, and the resulting *d*-oscine rapidly extracted with chloroform. The chloroformic liquids were then concentrated somewhat, and extracted with hydrochloric acid, after which the acid liquid, which measured 23 c.c., had $\alpha_D + 1^{\circ}35'$ in a 2-dcm. tube, whence the specific rotation of *d*-oscine is calculated at $[\alpha]_D + 77.7^{\circ}$. This result must, however, be regarded as only approximate.

THE WELLCOME CHEMICAL RESEARCH LABORATORIES,
LONDON, E.C.



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