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No. 97

THE CONFIGURATION OF TROPINE AND Ψ-TROPINE

AND

THE RESOLUTION OF ATROPINE

BY

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CCXVI.—*The Configuration of Tropine and ψ-Tropine, and the Resolution of Atropine.*

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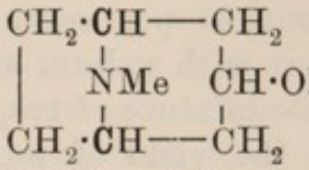
The base tropine, obtained by the hydrolysis of the alkaloids atropine and hyoscyamine, has been shown by Willstätter (*Ber.*, 1898, **31**, 1534) to possess the following constitutional formula:



Liebermann (*Ber.*, 1891, **24**, 2332) obtained from Java coca leaves an alkaloid, designated tropacocaine, which he proved to be the benzoyl derivative of a base isomeric with tropine. This base has been designated ψ-tropine, and Willstätter has shown (*Ber.*, 1896, **29**, 936) that it may readily be obtained from tropine by heating the latter with sodium amyloxide.

Tropine and ψ-tropine both possess the same structural formula, for, on oxidation, they each yield tropinone, whilst the latter, when reduced, gives a mixture of the two hydroxy-bases (Willstätter and Iglauer, *Ber.*, 1900, **33**, 1170). Willstätter concluded, therefore, that a *cis-trans*-isomerism, dependent on the relative positions in space of the hydroxyl and methyl groups, existed between tropine and ψ-tropine. Objection to this explanation might be made on the ground that no quite parallel case of isomerism seems to have been observed, and it therefore appeared to the present authors that it should not be accepted unreservedly so long as another explanation is possible.

The tropine molecule contains two similar asymmetric carbon atoms, and the base should therefore be capable of existing in a racemic and an internally compensated form. The possibility of these two optically inactive modifications being represented by tropine and ψ-tropine had been considered by Willstätter, but he rejected this explanation, as both bases, on oxidation, yielded the same ketone. It seemed to the present authors, however, that the possibility of the difference between tropine and ψ-tropine being dependent on the configuration of the two asymmetric carbon atoms was not entirely excluded, for each of these bases might undergo racemisation during the process of oxidation, thus yielding identical ketonic products. Tropinone would then be a mixture of the racemic and meso-ketonic bases, and this would account for its yielding both tropine and ψ-tropine on reduction. On the other

hand, if racemisation does not occur during the oxidation of tropine or ψ-tropine, it was thought possible that two compounds so nearly related as racemic and meso-tropinones might be so similar in properties that their individuality had been overlooked.

In view of the above considerations, therefore, it would appear that the formation of ψ-tropine by the action of sodium amyloxide on tropine might be a process of racemisation, and this seemed to be in harmony with the experimental facts, since the change in question is never complete. Thus, in our experiments on the preparation of ψ-tropine, about 35 per cent. of the basic product resulting from the treatment with sodium amyloxide was found to consist of an uncrystallisable mixture of tropine and ψ-tropine, and Willstätter mentions that the yield of pure ψ-base obtained by him did not exceed 50 to 55 per cent. of that theoretically possible. It appeared, therefore, that the action of sodium amyloxide on tropine resulted in the formation of an equilibrium mixture of this base and ψ-tropine, just as the action of alkali on pilocarpine or *iso*pilocarpine results in the production of an equilibrium mixture of these two stereoisomeric bases (Jowett, Trans., 1905, **87**, 794). This, however, is not the case, since the change is irreversible, no tropine being formed by the action of sodium amyloxide on ψ-tropine.

Apart from the question of the relation of tropine to ψ-tropine, the individual configuration of each of these bases requires to be established. This point was considered by Gadamer (*Arch. Pharm.*, 1901, **239**, 294), who drew the conclusion that tropine was internally compensated, since hyoscyamine yielded inactive tropine, even when hydrolysed only with water, and he did not consider it likely that a naturally occurring compound would be partially racemic. Much value should not, however, be attached to the grounds on which Gadamer based his conclusions, for partially racemic compounds do occur in nature, as an example of which prulaurasin may be quoted (Hérissey, *Compt. rend.*, 1905, **141**, 959). Moreover, as proved in the present investigation, hyoscyamine always suffers some racemisation when liberated from its salts, and this change might occur in the tropine part of the molecule. That is to say, that if free hyoscyamine were partially racemic, the base, when in the form of its naturally occurring salts, might, nevertheless, be a derivative of optically active tropine.

With the object, therefore, of definitely establishing the configuration of tropine and of ψ-tropine, we have conducted experiments on the resolution of these bases, and some of their derivatives, by fractionally crystallising their salts with certain optically active acids. It may at once be stated that the results of these experi-

ments point to the conclusion that both the bases in question are internally compensated compounds. The relation between them must, therefore, be of the nature of a *cis-trans*-isomerism, as concluded by Willstätter (*loc. cit.*). Attempts were made to racemise tropine by heating the latter at high temperatures with hydrochloric acid, but these were unsuccessful.

ψ-Tropine d-*camphorsulphonate* (m. p. 224—226°) and d-*bromocamphorsulphonate* (m. p. 180°) were prepared and fractionally crystallised, but no evidence of resolution could be obtained. The *normal* and *hydrogen* d-*tartrates* were also prepared, but these salts could not be crystallised. The d-*camphorsulphonate* (m. p. 176—177°) and d-*bromocamphorsulphonate* (m. p. 190°) of benzoyl-ψ-tropeine were then prepared; these salts crystallised well, and were submitted to a prolonged fractionation, but no separation could be effected in either case.

Tropine d-*camphorsulphonate* (m. p. 236°) and *benzoyltropeine* d-*camphorsulphonate* (m. p. 240°) were next investigated, and were found, like the preceding salts, to be incapable of resolution. Finally, tropinone was prepared, both from tropine and from ψ-tropine, and the base obtained from each source was converted into its *d*-camphorsulphonate. The two preparations of *tropinone* d-*camphorsulphonate* (m. p. 216°) thus obtained were found to be incapable of resolution, and were in all respects identical.

Further and conclusive proof that tropine is an internally compensated compound was obtained by a study of the resolution of atropine. This base is, of course, the tropine ester of *dl*-tropic acid, the latter containing one asymmetric carbon atom. Now, if atropine is a derivative of internally compensated tropine, it would, on resolution, yield only two bases, but if it is derived from racemic tropine, it should be capable of resolution into four stereoisomeric bases, or, at all events, in the latter case, it would be possible to obtain proof of the existence of more than two isomerides. *Atropine* d-*camphorsulphonate* was therefore prepared, and submitted to fractional crystallisation. It was then found that resolution was readily effected, but the operation yielded only two salts, namely, d- and l-*hyoscyamine* d-*camphorsulphonates*. Atropine must therefore contain only one racemic asymmetric carbon atom, namely, that contained in the tropic acid molecule.

l-Hyoscyamine *d*-camphorsulphonate melts at 159°, and the specific rotation of the base contained in it, calculated from that of the salt, is $[\alpha]_D - 32{\cdot}1°$. This figure is considerably higher than any value previously obtained for the rotation of hyoscyamine, the pure base being usually stated to have about $[\alpha]_D - 21{\cdot}0°$. It was, however, found impossible directly to obtain from the camphor-

sulphonate a base of higher rotatory power than about $[\alpha]_D - 20{\cdot}0°$. That this decrease in optical activity was due to the fact that racemisation had occurred was proved by reconverting the base into the camphorsulphonate, when a rather impure product was obtained, from which, by fractional crystallisation, it was possible to separate the salt of a dextrorotatory base. A preparation of *l*-hyoscyamine having $[\alpha]_D - 25{\cdot}8°$ was, however, obtained by fractionally crystallising, from an anhydrous solvent, a quantity of the base having $[\alpha]_D - 20{\cdot}0°$. The ease with which hyoscyamine undergoes racemisation in presence of water is shown by the fact that the rotation diminishes on allowing the base to remain dissolved in moist chloroform. These observations render it evident that no optically pure hyoscyamine has yet been obtained, and that, in all probability, the only salts of this base which have been prepared in a state of purity are those described in the present communication.

d-Hyoscyamine *d*-camphorsulphonate was obtained pure only with considerable difficulty. It melts at 135°, and yields a base possessing properties similar to those of its optical antipode. *d*-Hyoscyamine has not been observed to occur in nature, but it has been obtained synthetically, although only in an impure state. Ladenburg and Hundt (*Ber.*, 1889, **22**, 2590) prepared a base by combining *d*-tropic acid with tropine. This product they called "*d*-atropine," but more recent work has rendered it evident that, in reality, it was impure *d*-hyoscyamine. Amenomiya (*Arch. Pharm.*, 1902, **240**, 498), employing a method similar to that used by Ladenburg and Hundt, prepared a *d*-hyoscyamine of greater purity. This preparation had $[\alpha]_D + 23{\cdot}0°$ when in the form of its hydrochloride, the latter having been obtained from the aurichloride without liberation of the base. Amenomiya, however, did not determine the rotation of the free base obtained from the salt which he had thus prepared.

Particular interest is attached to the resolution of atropine, inasmuch as it is known that the two stereoisomeric hyoscyamines differ greatly in their respective physiological activities. Thus, Cushny (*J. Physiol.*, 1904, **30**, 176) has shown that *l*-hyoscyamine ($[\alpha]_D^{\circ} - 21{\cdot}0°$) has about fourteen times the activity of the *d*-hyoscyamine prepared by Amenomiya. The material employed by Cushny was, however, not only partially racemised, but was also, in the case of the *d*-base, extremely limited in amount. A more complete comparison of the physiological actions of the two isomerides has therefore been made by Dr. P. P. Laidlaw, at the Wellcome Physiological Research Laboratories, with the employment of the optically pure *d*-camphorsulphonates obtained

by the resolution of atropine. It has thus been rendered evident that the two optical antipodes have, qualitatively, essentially the same physiological action, and differ only in the intensity of their effects. The ratio of activity of the *l*- to the *d*-isomeride has been found, however, when employing the pure salts, to be much greater than was indicated by Cushny. Thus, the mydriatic action of the former base was found to be about one hundred times that of the latter, whilst the paralysis of the vagus induced by them was in the ratio of 25 : 1, or possibly rather greater.

Experimental.

Tropine.

Tropine d-*camphorsulphonate.*—This salt is very readily soluble in water or alcohol. It crystallises well, however, from a mixture of alcohol and ethyl acetate, or from chloroform, giving large, tabular crystals, melting at 236°:

0·1138 gave 0·2408 CO_2 and 0·0871 H_2O. C = 57·7; H = 8·5.

$C_8H_{15}ON,C_{10}H_{16}O_4S$ requires C = 57·9; H = 8·3 per cent.

The salt was fractionally crystallised under various conditions, but no appreciable difference could be detected between any of the resulting fractions:

0·3761, made up to 25 c.c. with chloroform, gave $\alpha_D + 0° 58'$ in a 2-dcm. tube, whence $[\alpha]_D + 32·1°$.

0·4123, made up to 25 c.c. with water, gave $\alpha_D + 0° 27'$ in a 2-dcm. tube, whence $[\alpha]_D + 13·6°$ and $M_D + 50·6°$.

Benzoyltropeine d-*camphorsulphonate.*—Benzoyltropeine was prepared by Ladenburg (*Annalen*, 1883, **217**, 82) by the interaction of tropine and benzoic acid. An improved method of preparation has recently been described by Jowett and Pyman (this vol., p. 1028), who heated tropine hydrochloride with benzoyl chloride, thereby obtaining 77 per cent. of the theoretical yield of benzoyltropeine hydrochloride. The present authors, however, found that a practically theoretical yield of the latter salt could be obtained in a few minutes by employing free tropine instead of its hydrochloride. The base was added to an excess of benzoyl chloride, and the mixture heated to the boiling point of the latter. An additive compound of the base and the acid chloride, analogous to the corresponding compound obtained from pyridine, appeared first to be formed, but, when the temperature was raised, this soon redissolved, whereupon the hydrochloride of the benzoylated base rapidly separated. The cooled mixture was then diluted with ether, and the hydrochloride collected. After being once crystallised from alcohol, it melted and decomposed at 267° (uncorr.).

Benzoyltropeine d-*camphorsulphonate* crystallises readily from a mixture of ethyl acetate and alcohol, forming small, flattened needles, which melt at 240°:

0·1131 gave 0·2600 CO_2 and 0·0773 H_2O. C = 62·7; H = 7·6.

$C_{15}H_{19}O_2N,C_{10}H_{16}O_4S$ requires C = 62·9; H = 7·3 per cent.

0·4012, made up to 20 c.c. with water, gave α_D + 0° 26′ in a 2-dcm. tube, whence $[\alpha]_D$ + 10·8° and M_D + 51·5°.

The salt was submitted to a very thorough fractionation, but no resolution could be effected.

ψ-Tropine.

ψ-Tropine was prepared according to the method described by Willstätter (*Ber.*, 1896, **29**, 936). The base was purified by distillation, followed by crystallisation from a mixture of benzene and light petroleum. The mother liquors from the first crystallisation contained a quantity of oily material, amounting to about 35 per cent. of the total product. As this could not be crystallised, it was benzoylated by heating with benzoyl chloride, and the resulting hydrochloride of the benzoylated product crystallised from alcohol. The material thus obtained formed colourless needles, melting at 241°, and appeared to be quite homogeneous; it yielded a picrate melting at 216—217°. The product, however, was found to be a mixture of the hydrochlorides of benzoyltropeine and benzoyl-ψ-tropeine, apparently in equal proportions, since, by the addition of successive portions of picric acid solution, it first yielded benzoyltropeine picrate (m. p. 249—250°), and finally benzoyl-ψ-tropeine picrate (m. p. 238—239°).

ψ-Tropine d-*camphorsulphonate*.—This salt crystallised readily from a mixture of alcohol and ethyl acetate, forming flat prisms, which were anhydrous, and melted at 224—226°:

0·1101 gave 0·2337 CO_2 and 0·0842 H_2O. C = 57·8; H = 8·5.

$C_8H_{15}ON,C_{10}H_{16}O_4S$ requires C = 75·9; H = 8·3 per cent.

ψ-Tropine *d*-camphorsulphonate is very readily soluble in water, ethyl, methyl, and amyl alcohols, and in chloroform, but only very sparingly soluble in ethyl acetate, acetone, benzene, or toluene. It was fractionally crystallised from both cold and boiling solvents, but no evidence of resolution could be obtained:

0·4682, made up to 25 c.c. with alcohol (98 per cent.), gave α_D + 0° 59′ in a 2-dcm. tube, whence $[\alpha]_D$ + 26·3°.

0·4119, made up to 25 c.c. with water, gave α_D + 0° 27′ in a 2-dcm. tube, whence $[\alpha]_D$ + 13·7° and M_D + 51·2°.

ψ-Tropine d-*bromocamphorsulphonate*.—The solubilities of this salt are similar to those of the corresponding *d*-camphorsulphonate.

It is deposited from cool, saturated solutions in large prisms, but separates from a boiling mixture of ethyl acetate and alcohol in fine needles. When anhydrous it melts at 180°, but it separates from moist solvents in needles, which contain one molecule of water of crystallisation, and melt at 112°:

0·9388 of hydrated salt, on heating at 100°, lost 0·0344 H_2O. $H_2O = 3·7$.

0·1269 of anhydrous salt gave 0·2229 CO_2 and 0·0788 H_2O. $C = 47·9$; $H = 6·9$.

$C_8H_{15}ON,C_{10}H_{15}O_4BrS,H_2O$ requires $H_2O = 3·8$ per cent.

$C_8H_{15}ON,C_{10}H_{15}O_4BrS$ requires $C = 47·8$; $H = 6·6$ per cent.

0·4457 of anhydrous salt, made up to 25 c.c. with chloroform, gave $\alpha_D + 2°\ 28'$ in a 2-dcm. tube, whence $[\alpha]_D + 69·1°$.

0·5030 of anhydrous salt, made up to 25 c.c. with water, gave $\alpha_D + 2°\ 26'$ in a 2-dcm. tube, whence $[\alpha]_D + 60·5°$ and $M_D + 273·3°$.

Prolonged fractional crystallisation of this salt gave no evidence of resolution.

Benzoyl-ψ-tropeine d-*camphorsulphonate*. — Benzoyl-ψ-tropeine (tropacocaine) was prepared in a manner similar to that employed for the preparation of benzoyltropeine; the yield was practically quantitative. The hydrochloride of the base was found to melt at 283° (uncorr.), a temperature 12° higher than that recorded by Liebermann (*loc. cit.*) and by Willstätter (*loc. cit.*) for the melting point of benzoyl-ψ-tropeine (tropacocaine) hydrochloride. The aurichloride melted at 208°, and was analysed:

0·1391 gave 0·0468 Au. $Au = 33·6$.

$C_{15}H_{19}O_2N,HAuCl_4$ requires $Au = 33·7$ per cent.

Benzoyl-ψ-tropeine d-*camphorsulphonate* crystallises very readily from a mixture of ethyl acetate and alcohol, forming large prisms, melting at 176—177°:

0·1236 gave 0·2846 CO_2 and 0·0823 H_2O. $C = 62·8$; $H = 7·4$.

$C_{15}H_{19}O_2N,C_{10}H_{16}O_4S$ requires $C = 62·9$; $H = 7·3$ per cent.

0·5412, made up to 20 c.c. with water, gave $\alpha_D + 0°\ 36'$ in a 2-dcm. tube, whence $[\alpha]_D + 11·1°$ and $M_D + 51·8°$.

The salt was separated into a large number of fractions, but no evidence of resolution could be obtained.

Benzoyl-ψ-tropeine d-*bromocamphorsulphonate*.—This salt differs from the sulphonates above described, inasmuch as it forms a hydrate which is only sparingly soluble in cold water. This compound forms slender needles, which melt at 73°:

0·5420, on drying at 123°, lost 0·0464 H_2O. $H_2O = 8·6$.

$C_{15}H_{19}O_2N,C_{10}H_{15}O_4BrS,3H_2O$ requires $H_2O = 8·8$ per cent.

The anhydrous salt crystallises readily from a mixture of ethyl acetate and alcohol, and forms thin prisms, which melt at 190°:

0·1401 gave 0·2779 CO_2 and 0·0794 H_2O. C = 54·1; H = 6·3.

$C_{15}H_{19}O_2N,C_{10}H_{15}O_4BrS$ requires C = 54·0; H = 6·1 per cent.

0·4827, made up to 20 c.c. with water, gave α_D + 2° 17′ in a 2-dcm. tube, whence $[\alpha]_D$ + 47·3° and M_D + 262·9°.

This result for the molecular rotatory power is rather lower than would have been expected for the bromocamphorsulphonate of an inactive base. Nevertheless, the base was devoid of optical activity, and the discrepancy can only be ascribed to the fact that the solutions examined were highly supersaturated. The salt was separated by crystallisation into a number of fractions, but all of these had the same rotatory power and melting point.

Tropinone.

Tropine and ψ-tropine were each separately oxidised to tropinone, according to the method described by Willstätter (*Ber.*, 1896, **29**, 393), and the resulting base purified by means of the picrate. Willstätter states that this salt melts at 220°, but the present authors find that the temperature of fusion is dependent on the rate of heating, and may lie at any point from 210—250°. Each preparation of the base was converted into the d-*camphorsulphonate*, when the resulting salts were found to be in all respects identical.

Tropinone *d*-camphorsulphonate is fairly readily soluble in dry ethyl acetate, from which it crystallises in moss-like growths, apparently composed of needles; it melts and decomposes at 216°:

0·1130 gave 0·2421 CO_2 and 0·0830 H_2O. C = 58·4; H = 8·1.

$C_8H_{13}ON,C_{10}H_{16}O_4S$ requires C = 58·2; H = 7·9 per cent.

The salt is much less soluble in ethyl acetate which has not been specially dried, and crystallises from this solvent in tufts of leaflets, which, when rapidly heated, suddenly lose water of crystallisation at 140°, but without completely melting:

2·0429, on heating at 123°, lost 0·0939 H_2O. H_2O = 4·6.

$C_8H_{13}ON,C_{10}H_{16}O_4S,H_2O$ requires H_2O = 4·6 per cent.

The hydrated salt appears to be dimorphous, since, at low temperatures, it crystallises from a mixture of ethyl acetate and dilute alcohol in long, slender prisms.

No resolution of tropinone *d*-camphorsulphonate could be effected by fractional crystallisation.

The Resolution of Atropine.

Forty grams of atropine were neutralised with *d*-camphorsulphonic acid, and the resulting salt was fractionally crystallised from ethyl acetate containing some alcohol. The first crop of crystals consisted of prismatic needles, and melted at 136—140°. This was recrystallised several times until no further change occurred; it then melted at 159°.

0·5072, made up to 25 c.c. with water, gave α_D −0° 19·5′ in a 2-dcm. tube, whence $[\alpha]_D$ −8·0° and M_D −41·7°.

Since the molecular rotation of *d*-camphorsulphonic acid is +51°, it is evident that the basic ion of the above salt has M_D −92·7°, which corresponds with a specific rotatory power of −32·1°. It is seen, therefore, that resolution had been effected, and that the salt melting at 159° was l-*hyoscyamine* d-*camphorsulphonate*:

0·1302 gave 0·2974 CO_2 and 0·0902 H_2O. C = 62·3; H = 7·7.

$C_{17}H_{23}O_3N,C_{10}H_{16}O_4S$ requires C = 62·4; H = 7·5 per cent.

For the purpose of comparison a quantity of natural *l*-hyoscyamine was converted into the *d*-camphorsulphonate. The salt so obtained melted at 149—150°, and was somewhat impure; after recrystallisation, however, it melted at 159°, and was identical with the salt obtained from atropine. *l*-Hyoscyamine *d*-camphorsulphonate is extremely readily soluble in water, alcohol, or chloroform, and very sparingly soluble in ethyl acetate, benzene, or xylene. The material contained in the mother liquors obtained during the separation of the *l*-hyoscyamine *d*-camphorsulphonate from the original atropine salt, which would contain the salt of *d*-hyoscyamine, was submitted to a very elaborate process of fractional crystallisation, whereby it was shown conclusively that the salts of only two bases were present. The product did not crystallise readily, and exhibited a considerable tendency to separate as an oil. After a large number of crystallisations, however, the salt of the *d*-base was obtained in a state of purity.

d-*Hyoscyamine* d-*camphorsulphonate* forms small needles, which melt at 135°. Its solubilities are similar to, but rather greater than, those of the corresponding lævo-salt:

0·1212 gave 0·2793 CO_2 and 0·0840 H_2O. C = 62·1; H = 7·7.

$C_{17}H_{23}O_3N,C_{10}H_{16}O_4S$ requires C = 62·4; H = 7·5 per cent.

0·5229, made up to 20 c.c. with water, gave α_D +1° 25·5′ in a 2-dcm. tube, whence $[\alpha]_D$ +27·25° and M_D +143·7°.

From this result it is calculated that the basic ion has M_D +92·7° and $[\alpha]_D$ +32·1°, figures which are in exact agreement with the corresponding values obtained for the *l*-base.

It would appear, therefore, that the respective bases contained in the above-described pure *d*-camphorsulphonates have a specific rotation of $[\alpha]_D \pm 32{\cdot}1°$, a value considerably higher than that usually given for hyoscyamine (about $-21{\cdot}0°$). It was, however, found impossible to obtain directly from either of the camphorsulphonates in question a base of higher specific rotatory power than about $[\alpha]_D \pm 20{\cdot}0°$, even when the greatest care was taken to avoid racemisation. That this change, nevertheless, had occurred to some extent was shown by reconverting a quantity of the base having $[\alpha]_D - 20{\cdot}0°$ into the *d*-camphorsulphonate, when a somewhat impure salt was obtained, from which the derivative of a dextro-base was separated. A considerable quantity of the lævo-base, having $[\alpha]_D - 20{\cdot}2°$, was fractionally crystallised from petroleum (b. p. 90—120°), when a fraction was eventually obtained which melted at 107—108°, and had the following rotatory power:

0·4331, made up to 20 c.c. with 50 per cent. alcohol, gave $\alpha_D - 1° 7'$ in a 2-dcm. tube, whence $[\alpha]_D - 25{\cdot}8°$.

This is a higher value than has heretofore been observed for the rotation of hyoscyamine.

d-Hyoscyamine, obtained from its *d*-camphorsulphonate, was in all respects analogous to its optical antipode.

As it appears probable from the above results that optically pure hyoscyamines have never been obtained in a free state, several salts of these bases were prepared by double decomposition from the pure *d*-camphorsulphonates. Corresponding salts of atropine have also been made for the purpose of comparison.

The Aurichlorides.—*l*-Hyoscyamine aurichloride has previously been described as forming leaflets, melting at 162° (Will, *Ber.*, 1888, **21**, 1717). The pure salt forms golden-yellow, hexagonal plates, which melt at 165°, and are anhydrous:

0·1244 gave 0·0391 Au. Au = 31·35.

$C_{17}H_{23}O_3N,HAuCl_4$ requires Au = 31·35 per cent.

l-Hyoscyamine aurichloride is much more soluble in alcohol than in water, but can readily be crystallised from the former solvent.

Somewhat impure *d*-hyoscyamine aurichloride was prepared by Amenomiya (*loc. cit.*). The pure salt crystallises similarly to its optical antipode, melts at 165°, and is anhydrous:

0·1198 gave 0·0374 Au. Au = 31·22.

$C_{17}H_{23}O_3N,HAuCl_4$ requires Au = 31·35 per cent.

Atropine aurichloride showed some tendency to separate as an oil, but crystallised fairly readily. It formed tufts of very small, anhydrous leaflets, which melted at 134—139°:

0·0926 gave 0·0292 Au. Au = 31·5.

$C_{17}H_{23}O_3N,HAuCl_4$ requires Au = 31·35 per cent.

The Auribromides.—*l*-Hyoscyamine auribromide was first prepared by Jowett (Trans., 1897, **71**, 679), who stated that it melts at 115—120°, and regarded it as being anhydrous. The present authors find that the pure salt separates from water with one molecule of water of crystallisation, and, when dried in the air, melts at about 123—130°. The anhydrous salt, on heating, sinters slightly at 155°, after which it fuses sharply at 160°, without decomposition. The salt is even more sparingly soluble in water than the corresponding aurichloride, and crystallises in very long, highly lustrous, flattened needles, possessing a deep red colour. It dissolves much more readily in absolute alcohol than in water, and crystallises from the former solvent with one molecule of alcohol:

0·0350, crystallised from water, on heating at 110°, lost 0·0418 H_2O. $H_2O = 2·1$.

0·3029, crystallised from alcohol, on heating at 110°, lost 0·0158 EtOH. EtOH = 5·2.

0·1210 of anhydrous salt gave 0·0294 Au. Au = 24·3.

$C_{17}H_{23}O_3N,HAuBr_4,H_2O$ requires $H_2O = 2·2$ per cent.
$C_{17}H_{23}O_3N,HAuBr_4,EtOH$,, EtOH = 5·4 ,,
$C_{17}H_{23}O_3N,HAuBr_4$,, Au = 24·3 ,,

d-*Hyoscyamine auribromide* has not previously been obtained. It agrees in all respects with the description of the corresponding lævo-salt given above:

0·2197 of hydrated salt, on heating at 110°, lost 0·0044 H_2O. $H_2O = 2·0$.

0·0966 of anhydrous salt gave 0·0235 Au. Au = 24·3.

$C_{17}H_{23}O_3N,HAuBr_4,H_2O$ requires $H_2O = 2·2$ per cent.
$C_{17}H_{23}O_3N,HAuBr_4$,, Au = 24·3 ,,

Atropine auribromide was described by Jowett (*loc. cit.*), who considered it to be anhydrous, and stated that it crystallised in chocolate-coloured prisms melting at 120°. The salt, as prepared by the present authors, does not crystallise nearly so readily as the corresponding derivatives of the hyoscyamines. It forms very small tufts of dark red needles, which contain one molecule of water of crystallisation, and, when air dried, forms a crystalline powder, melting at 110°. The anhydrous salt fuses at 120°:

0·1225, on heating at 100°, lost 0·0027 H_2O. $H_2O = 2·2$.

0·1082 of anhydrous salt gave 0·0263 Au. Au = 24·3.

$C_{17}H_{23}O_3N,HAuBr_4,H_2O$ requires $H_2O = 2·2$ per cent.
$C_{17}H_{23}O_3N,HAuBr_4$,, Au = 24·3 ,,

The Picrates.—The picrates of *l*-hyoscyamine and atropine are mentioned in the literature, but their melting points have not been recorded. d-*Hyoscyamine picrate* has not previously been prepared.

Both *d*- and *l*-hyoscyamine picrates crystallise fairly readily, forming needles, which melt at 163°, without decomposition. Atropine picrate crystallises much more readily than the corresponding salts of either of the active bases, and forms rectangular plates, which melt at 173—174°.

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