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ISO AMYGDALIN

AND THE RESOLUTION OF ITS

HEPTA-ACETYL DERIVATIVE

BY

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LXXX.—iso*Amygdalin and the Resolution of its Hepta-acetyl Derivative.*

By Frank Tutin.

It was shown by J. W. Walker (Trans., 1903, **83**, 472) that, under certain conditions, amygdalin yields inactive mandelic acid on hydrolysis, instead of the lævo-isomeride. If, for example, amygdalin be directly hydrolysed with concentrated hydrochloric acid, *l*-mandelic acid is formed, but if it be first hydrolysed to amygdalinic acid and the latter subsequently treated with hydrochloric acid, the resulting mandelic acid is optically inactive. Walker also demonstrated that the racemisation of the mandelic part of the molecule does not occur during hydrolysis, but that this takes place whenever amygdalin is dissolved in dilute solutions of an alkali. He concluded, therefore, that amygdalinic acid is partially racemic, but did not ascertain definitely the nature of the product formed by the action of dilute alkalis on amygdalin.

The subject in question was studied more fully by H. D. Dakin (Trans., 1904, **85**, 1512), who showed that amygdalin, when treated with dilute aqueous alkalis, is converted into an optically isomeric product, which was designated *iso*amygdalin. He confirmed the observation of Walker that amygdalinic acid, on hydrolysis, yields inactive mandelic acid, but found that the mandelic acid prepared by the acid hydrolysis of *iso*amygdalin always had a small dextro-rotation. These facts have also been confirmed by the present author.

Dakin, however, considered it highly improbable that the preponderance of *d*-mandelic acid yielded by *iso*amygdalin was due to the latter being "a mixture of *i*-mandelonitrile maltoside and *d*-mandelonitrile maltoside." He, therefore, offered the explanation that it was due to the occurrence of both racemisation and hydrolysis, the derivative of the *d*-mandelonitrile undergoing the latter change more rapidly than that of the *l*-nitrile. During the course of hydrolysis, therefore, the unchanged part of the material would contain a preponderance of the latter derivative, and this, he considers, would undergo some racemisation, the final result being the production of more *d*-mandelic acid than of its optical antipode.

It appears to the present author, that of these two explanations, the one preferred by Dakin is not the correct one. When an optically active compound is completely racemised, the resulting optical antipodes are, of course, formed in equal proportions, but when one asymmetric carbon atom suffers racemisation in a molecule containing

other asymmetric groups, which are stable, the latter may influence the relative proportions of the constituents of the resulting mixture. Thus it was shown by Barrowcliff (Trans., 1907, **91**, 875) that the "dextro-menthone" of Beckmann, formed from *l*-menthone by the racemisation of one of its asymmetric carbon atoms, contains 60 per cent. of *l*-menthone and 40 per cent. of *d-iso*menthone (compare Beckmann, *Ber.*, 1909, **42**, 846).

It therefore appeared probable to the present author that Dakin's *iso*amygdalin contains a slight preponderance of the bioside of *d*-mandelonitrile. Moreover, since it possessed such poor powers of crystallisation, and melted indefinitely at relatively so low a temperature (125—140°), it was concluded that it did not consist chiefly of a definite, partially racemic compound, but was merely a mixture of isomerides. It was considered probable, therefore, that *iso*amygdalin would be capable of separation into its components, namely, amygdalin and the corresponding derivative of *d*-mandelonitrile—which is unknown—provided that it could be fractionally crystallised.

As, however, *iso*amygdalin itself cannot be fractionally crystallised in a satisfactory manner, its acetyl derivative has been selected as being a compound more suitable for effecting this resolution.

*iso*Amygdalin was therefore acetylated, and from the resulting product there have been separated, without much difficulty, hepta-acetylamygdalin and the hepta-acetyl derivative of the unknown isomeride of amygdalin. It is proposed to designate the latter *neo-amygdalin*. *Hepta-acetyl*neo*amygdalin* has $[\alpha]_D$ $-65{\cdot}6°$ in chloroform, and forms long needles, melting at 174°. On hydrolysis with concentrated hydrochloric acid it yields *d*-mandelic acid. All three varieties of mandelic acid may therefore be obtained from amygdalin.

Caldwell and Courtauld (Trans., 1907, **91**, 675) obtained from *iso*-amygdalin a product which they regarded as hepta-acetyl*iso*amygdalin, although stating that its rotation differed but little from that of hepta-acetylamygdalin. Now, since amygdalin and *iso*amygdalin differ only stereochemically, and the biose radicle, which alone undergoes acetylation, is identical in both compounds, it follows that, if such a definite compound as hepta-acetyl*iso*amygdalin existed, its rotation would bear approximately the same relation to that of *iso*amygdalin as the rotation of hepta-acetylamygdalin does to that of amygdalin. This conclusion is substantiated by the results recorded in the present paper. It is evident, therefore, that Caldwell and Courtauld's "hepta-acetyl*iso*amygdalin" was only somewhat impure hepta-acetylamygdalin, and, by obtaining it, they afforded proof that the resolution of hepta-acetyl*iso*amygdalin was possible.

It does not appear feasible to regenerate *neo*amygdalin from its acetyl derivative, for, when treated with alkalis the lat er is

racemised, and when the acetyl groups are removed by mineral acids dextrose is also liberated.

Experimental.

The amygdalin employed was obtained from Kahlbaum. After drying for a short time at 120°, it melted at about 220°, when heated somewhat rapidly. The temperature at which fusion occurs, however, depends entirely on the rate of heating:

0·4054, made up to 20 c.c. with water, gave α_D −1°32′ in a 2-dcm. tube, whence $[\alpha]_D$ −37·8°.

The material was twice recrystallised from dilute alcohol, and then dried for two hours at 120°, when the weight was constant, no appreciable change in colour occurring:

0·4247, made up to 20 c.c. with water, gave α_D −1°37′ in a 2-dcm. tube, whence $[\alpha]_D$ −38·0°.

The rotation of *iso*amygdalin was determined by dissolving 0·4597 of anhydrous amygdalin in 20 c.c. of water containing a little ammonia. After standing overnight this solution gave α_D −2°25′ in a 2-dcm. tube, whence $[\alpha]_D$ −52·6°. These values for the specific rotations of amygdalin and *iso*amygdalin, −38·0° and −52·6° respectively, are somewhat higher than those given by Caldwell and Courtauld (*loc. cit.*) for these substances (−35·5° and −47·6° respectively), but the latter figures probably refer to the hydrated material.

Before conducting experiments with hepta-acetyl*iso*amygdalin, a quantity of amygdalin was acetylated for the purpose of comparison. It is stated by the above-mentioned authors that hydrated amygdalin may be completely acetylated by boiling it for two hours with ten times its weight of acetic anhydride. The following method of preparing hepta-acetylamygdalin is, however, much more rapid and convenient.

Amygdalin was heated with an excess of acetic anhydride, and a trace of *d*-camphorsulphonic acid added (A. Reychler, *Bull. Soc. chim. Belg.*, 1907, **21**, 428). A vigorous reaction then takes place and the mixture boils spontaneously, acetylation being complete in about one minute. The greater part of the anhydride was then removed by distillation, and the residue diluted with about five times its volume of ether. Pure hepta-acetylamygdalin separates immediately, and the yield is almost quantitative. The product thus obtained melted at 166—167°, and, when recrystallised from alcohol, formed long, glistening needles:

0·4074, make up to 20 c.c. with chloroform, gave α_D −1°32′ in a 2-dcm. tube, whence $[\alpha]_D$ −37·6°.

0·4065, made up to 20 c.c. with ethyl acetate, gave α_D −1°23′ in a 2-dcm. tube, whence $[\alpha]_D$ −34·0°.

Acetylation of iso*Amygdalin. Separation of Hepta-acetylamygdalin.*

A few grams of amygdalin were dissolved in water, a little ammonia added, and the mixture allowed to stand overnight. The solution was then evaporated on the water-bath to a syrup, and the residue boiled for a short time with a large excess of acetic anhydride, a trace of *d*-camphorsulphonic acid having been added. After concentrating the solution to a small bulk, it was diluted with ether and cooled. As crystallisation did not begin quickly, this was initiated by means of a trace of hepta-acetylamygdalin. After about three hours the crystals were collected and washed with ether, when they melted at 159—160°. The yield was about 20 per cent. of that theoretically possible:

0·3400, made up to 20 c.c. with chloroform, gave α_D −1°24′ in a 2-dcm. tube, whence $[\alpha]_D$ −41·2°.

After three crystallisations from alcohol the material melted at 166—167°, and was evidently pure hepta-acetylamygdalin, since the melting point was not lowered on mixing with an authentic specimen of the latter. A determination of the specific rotatory power gave the the following result:

0·4030, made up to 20 c.c. with chloroform, gave α_D −1°31′ in a 2-dcm. tube, whence $[\alpha]_D$ −37·6°.

The above experiments were repeated several times, and were always attended with a similar result.

*Separation of Hepta-acetyl*neo*amygdalin.*

Twenty grams of amygdalin were converted into *iso*amygdalin by means of ammonia, and the product acetylated as described above. After removing the greater part of the anhydride by distillation, some alcohol was added, and the mixture largely diluted with ether. The solution was then brought into a separator and washed with water, when, as the alcohol was removed, a quantity of heavy, oily material was deposited from the ether, and was separated with the water. This oil became solid on standing, but the greater part of it could not be crystallised; some hepta-acetylamygdalin was, however, separated from it. On keeping the ethereal solution overnight, a quantity (about 9 grams) of crystalline material separated. This was recrystallised from alcohol, after which it melted at 168—172°, but when mixed with hepta-acetylamygdalin fusion occurred at 155—158°. The substance was evidently fully acetylated, for it was not changed by prolonged treatment with acetic anhydride:

0·4027, made up to 20 c.c. with chloroform, gave α_D −2°34′ in a 2-dcm. tube, whence $[\alpha]_D$ −63·7°.

By successive crystallisations from alcohol the melting point and rotation of this preparation were at first slowly raised, but after the fifth crystallisation no further change was effected. The compound then melted sharply at 174°, but when mixed with hepta-acetylamygdalin fusion occurred at 155—157° :

0·1897 gave 0·3750 CO_2 and 0·0975 H_2O. C = 53·9 ; H = 5·7.

$C_{34}H_{41}O_{18}N$ requires C = 54·3 ; H = 5·5 per cent.

0·4422, made up to 20 c.c. with chloroform, gave α_D −2°54′ in a 2-dcm. tube, whence $[\alpha]_D$ −65·6°.

0·4436, made up to 20 c.c. with ethyl acetate, gave α_D −2°32′ in a 2-dcm. tube, whence $[\alpha]_D$ −57·1°.

*Hepta-acetyl*neo*amygdalin* crystallised in long, colourless needles, which are more slender than those yielded by hepta-acetylamygdalin. It is readily soluble in chloroform or ethyl acetate, but somewhat sparingly so in alcohol.

*Hydrolysis of Hepta-acetyl*neo*amygdalin. Formation of* d-*Mandelic Acid.*

As the change from amygdalin to *iso*amygdalin involves the racemisation of the mandelonitrile part of the molecule, *neo*amygdalin should yield *d*-mandelic acid on hydrolysis with concentrated hydrochloric acid, just as amygdalin yields the lævo-isomeride. A quantity of hepta-acetyl*neo*amygdalin was, therefore, boiled for three hours with a mixture of concentrated hydrochloric acid and alcohol. At the end of this time the solution, which had become very dark in colour, was treated with animal charcoal, after which it was extracted many times with ether. The residue obtained on removing the ether was crystallised from benzene, when highly lustrous leaflets were obtained which melted at 132—133° :

0·1038, made up to 20 c.c. with water, gave α_D +1°34′ in a 2-dcm. tube, whence $[\alpha]_D$ +151·1°.

The above substance was evidently nearly pure *d*-mandelic acid. When mixed with *l*-mandelic acid prepared from amygdalin, *i*-mandelic acid (m. p. 118°) was obtained.

*iso*Amygdalin and amygdalinic acid respectively consist of mixtures of stereoisomerides, but, for reasons stated in the introductory portion of this paper, it was concluded that the latter would not necessarily occur in equal proportions. In order to ascertain whether this was the case, each of the two compounds in question was hydrolysed by means of hydrochloric acid. It was then found, in agreement with the observations of Dakin (*loc. cit.*), that whilst the mandelic acid yielded

by amygdalinic acid was inactive, that obtained from *iso*amygdalin in variably possessed a slight dextro-rotation. It appears, therefore, that amygdalinic acid consists of a mixture of equal proportions of the biosides of *d*- and *l*-mandelic acids respectively, whilst *iso*amygdalin is a mixture of amygdalin and *neo*amygdalin, the latter slightly predominating. The specific rotation of *iso*amygdalin ($-52{\cdot}6°$) must therefore be greater than the mean of the corresponding values for amygdalin and *neo*amygdalin, and consequently the latter compound, when anhydrous, will have a specific rotation somewhat less than $-67{\cdot}0°$.

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