CLXXX.—*Racemisation Phenomena observed in the
Study of l-Benzoin and its Derivatives.*

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IN a recent paper entitled "Studien über katalytische Razemisierung," Winther (*Zeitsch. physikal. Chem.*, 1906, **56**, 465) has divided the known cases of racemisation—which is defined as the transformation of an optically active substance into an *isomeric* inactive substance—into four classes : (1) autoracemisation, (2) racemisation by heat, (3) racemisation due to the catalytic action of water or bases, and (4) racemisation due to other catalysts, for instance, hydrochloric acid, sulphuric acid, and aluminium chloride. In close connexion with this phenomenon are those cases in which optical activity is wholly or partly lost during the conversion of an optically active substance into one of its derivatives.

During a study of the derivatives of *l*-benzoin, frequent instances of racemisation have been encountered. *l*-Benzoin ethyl ether is partly, and carbanilido-*l*-benzoin completely, racemised under the action of heat. *l*-Benzoin and its methyl ether are completely and rapidly racemised by the action of alcoholic potash or sodium ethoxide. Further, methyl *l*-mandelate undergoes partial racemisation during conversion into *l*-mandelamide by the action of cold ethyl-alcoholic ammonia, whilst under the action of benzoyl chloride at a rather high temperature, of aniline at 100°, and of a saturated solution of hydrogen chloride in

ethyl alcohol at a temperature not exceeding 40°, *l*-benzoin is converted into derivatives of inactive benzoin. Lastly, *l*-benzoin- α -oxime undergoes partial racemisation when acetylated by means of acetic anhydride.

The racemisation of *l*-benzoin and of its methyl ether by alkali is of special interest, since it is probably attributable to keto-enolic change. Such a possibility in the case of *r*-benzoin has been indicated by several investigators. Thus Graebe (*Ber.*, 1898, **31**, 2975) showed that benzoin, under the influence of sulphuric acid, condenses with gallic acid to form benzoin-yellow. The assumption is made that benzoin is first converted into ω -dihydroxystilbene, thus :

which then reacts in accordance with the equation :

Similarly, Haworth (*Trans.*, 1909, **95**, 486) has shown that benzoin condenses with the sodium derivative of ethyl cyanoacetate, forming $\alpha\delta$ -dicyano- $\beta\gamma$ -diphenyl- Δ^{β} -butene- $\alpha\delta$ -dicarboxylic acid, a reaction which is explicable on the assumption that benzoin is first converted into ω -dihydroxystilbene, and that this substance then condenses with the sodiocyano-ester according to the following scheme :

The reverse transformation, that of ω -dihydroxystilbene into benzoin, occurs, according to Thiele (*Annalen*, 1899, **306**, 142), when benzil is reduced to benzoin, the course of the reaction being indicated by the scheme :

Although ω -dihydroxystilbene itself could not be isolated, derivatives of it were obtained by Thiele. Thus, when a solution of benzil in acetic anhydride, to which a little sulphuric acid had been added, was reduced by zinc dust, two stereoisomeric forms of ω -diacetoxystilbene were obtained, each of which yielded benzoin when hydrolysed with alcoholic potash. Similarly, Nef (*Annalen*, 1899, **308**, 289) showed that the addition of acetic anhydride to the product of the action of sodium on a dry ethereal solution of benzil resulted in the formation of ω -diacetoxystilbene, a product identical with one of the modifications previously obtained by Thiele.

A similar transformation is to be expected with *l*-benzoin, the active

benzoin passing into inactive ω -dihydroxystilbene, from which inactive benzoin would be regenerated :

l-Benzoin might thus be expected to undergo autoracemisation. In ordinary circumstances, however, the velocity of transformation of *l*-benzoin into ω -dihydroxystilbene is so slow that the substance behaves as a stable active compound. Thus a solution of *l*-benzoin in acetone was found to retain its activity unchanged during eight days, whilst a crystalline specimen showed no change in activity during three months.

The presence of a trace of alkali has been repeatedly shown to favour the enolic form in the case of keto-enolic desmotropy. In the case of *l*-benzoin, the presence of potassium hydroxide or of a trace of sodium ethoxide so increases the velocity of the reaction *l*-benzoin $\rightarrow$ ω -dihydroxystilbene that, in the course of a few hours, the active benzoin is completely converted into the inactive form. In neither of the above cases was direct polarimetric observation possible, since the addition of alkali causes alcoholic solutions of benzoin to acquire a purple coloration. This disadvantage is not encountered when *l*-benzoin methyl ether is used. It could then be shown that a solution of the latter in cold alcoholic potash (0.113*N*) became completely inactive within five minutes, whilst, under the action of sodium ethoxide, an alcoholic solution of the same substance showed no activity after three and a-half hours.

In a few cases, racemisation has previously been attributed to keto-enolic change. Kipping (Proc., 1902, 18, 34; compare Salway and Kipping, this vol., 167) ascribes the ready racemisation of *d*- β -methylhydrindone by alkali to isodynamic change according to the scheme :

whilst the transformation of *d*-camphoric acid into *l*-isocamphoric acid when heated with water is probably also due to the same cause (compare Lowry, Brit. Assoc. Report, 1904, 211).

EXPERIMENTAL.

Interaction of Methyl l-Mandelate and Alcoholic Ammonia.

The conversion of methyl *l*-mandelate into *l*-mandelamide has been described by McKenzie and Wren (Trans., 1908, 93, 312). A more extended study of this reaction has shown that this change is apt to

be accompanied by a certain amount of racemisation. In order to obtain the maximum yield of *l*-mandelamide, the experimental conditions have been slightly altered. The following experiment may be considered as typical :

A solution of methyl *l*-mandelate (74 grams, $[\alpha]_D - 236^\circ$ for $c = 3.6335$ in carbon disulphide solution*) in ethyl alcohol (74 c.c.) was cooled in ice and treated with a brisk current of dry ammonia during thirty minutes. Subsequently, the ice was replaced by a freezing mixture of ice and salt, and the passage of ammonia continued for a further period of forty-five minutes. The flask was tightly corked, when, after a few hours, a copious precipitate of *l*-mandelamide separated. The next day the mixture was cooled in a freezing mixture and the precipitate collected, ground with ether, and again filtered. The yield of *l*-mandelamide was 44 grams. Its specific rotation was determined in acetone solution :

$$l = 2, c = 1.685, \alpha_D - 2.42^\circ, [\alpha]_D - 71.8^\circ.$$

The pure amide (*loc. cit.*), dissolved in acetone, has $[\alpha]_D - 73.1^\circ$ ($c = 1.6416$).

The alcoholic-ammoniacal filtrate obtained above was evaporated in a vacuum at the ordinary temperature. The semi-solid mass which remained was triturated with ether and filtered, whereby a further crop (4.5 grams) was isolated, which, when dissolved in acetone, had $[\alpha]_D - 62.4^\circ$, and thus contained some of the *r*-amide :

$$l = 2, c = 2.235, \alpha_D - 2.79^\circ, [\alpha]_D - 62.4^\circ.$$

The conversion of the ester into amide is never complete. The unattacked ester was recovered by washing the ethereal solutions, obtained during the purification of the crude amide, successively with water, dilute sulphuric acid, and finally with water. After drying the solution over anhydrous sodium sulphate and removal of ether, the residue was distilled under diminished pressure. The ester so recovered from different experiments possessed specific rotations varying between -198° and -227° when dissolved in carbon disulphide.

l-Mandelamide itself does not appear to suffer racemisation when its solution in cold alcoholic ammonia is allowed to remain at the ordinary temperature for some time. Thus a partly racemised specimen of the amide, which possessed $[\alpha]_D - 62.8^\circ$ in acetone solution, was dissolved in alcohol and the solution saturated with ammonia. The solution was kept for six days at 10° , after which the alcohol and ammonia were removed under diminished pressure at the ordinary

* Walden (*Zeitsch. physikal. Chem.*, 1895, **17**, 706) gives the values $[\alpha]_D - 214.1^\circ$ for $c = 3.33$ and $[\alpha]_D - 217.0^\circ$ for $c = 1.67$ for the specific rotation of methyl *l*-mandelate in carbon disulphide. The examination of several specimens of the ester has shown that this value is rather low.

temperature. The residual amide had $[\alpha]_D - 62.3^\circ$ in acetone solution :

$$l = 2, c = 3.306, \alpha_D - 4.12^\circ, [\alpha]_D - 62.3^\circ.$$

Partly racemised *l*-mandelamide cannot be economically purified by recrystallisation if its specific rotation falls below about -65° . In one case, a sample of amide (7 grams), possessing $[\alpha]_D - 60^\circ$ in acetone solution, was purified by recrystallisation from a mixture of acetone (1 vol.) and benzene (4 vols.). The crop weighed 5.6 grams, and gave the following value for the specific rotation in acetone :

$$l = 2, c = 2.10, \alpha_D - 2.61^\circ, [\alpha]_D - 62.1^\circ.$$

After two more recrystallisations from the same mixture of solvents, this value had only increased to -62.8° :

$$l = 2, c = 3.05, \alpha_D - 3.83^\circ, [\alpha]_D - 62.8^\circ.$$

Possibly *r*-mandelamide and *l*-mandelamide have the tendency to form mixed crystals.

Conversion of l-Mandelamide into l-Benzoin.

The preparation of *l*-benzoin by the action of magnesium phenyl bromide on *l*-mandelamide has been described by McKenzie and Wren (*loc. cit.*). Further experience has shown that it is not necessary to heat the mixture of amide and Grignard reagent for more than six hours instead of eight, as previously described. The crude reaction product, isolated as in previous experiments, possesses, after one recrystallisation from methyl alcohol, a specific rotation of approximately -110° in acetone solution, and is sufficiently pure to serve as the starting point for the preparation of derivatives of *l*-benzoin. Pure *l*-benzoin has $[\alpha]_D - 118.6^\circ$ in acetone. As the mean of many experiments, 10 grams of *l*-mandelamide have been found to yield 2.5 grams of *l*-benzoin.

Partly racemised *l*-benzoin cannot be purified by recrystallisation if its specific rotation falls below about -100° . An impure specimen having $[\alpha]_D - 82.9^\circ$, after one recrystallisation from methyl alcohol, had $[\alpha]_D - 87.8^\circ$, but after two further recrystallisations from the same solvent, this value had only increased to -88.8° .

In consequence of the partial racemisation which occurs when methyl *l*-mandelate is converted into *l*-mandelamide, and of the difficulty of purifying partly racemised specimens of *l*-mandelamide and *l*-benzoin, it is necessary to take special precautions that the methyl *l*-mandelate used as a starting point for the preparation of pure *l*-benzoin is as pure as possible. In one series of experiments, a specimen of methyl *l*-mandelate having $[\alpha]_D - 212.6^\circ$ ($c = 2.2715$) in carbon disulphide solution was employed. Successive preparations of

amide possessed $[\alpha]_D -64.7^\circ$ and -65.1° respectively when dissolved in acetone. These were converted into *l*-benzoin, which, after two recrystallisations from methyl alcohol, had $[\alpha]_D -101.8^\circ$, this value being increased to only -104.8° after another recrystallisation from the same solvent.

Racemisation of l-Benzoin.

Although *l*-benzoin is readily racemised by alkali, it does not appear to undergo autoracemisation. Thus *l*-benzoin (0.3599 gram) was dissolved in acetone, and the solution made up to 20 c.c. A portion of this solution, when examined in a 2-dcm. tube, had $\alpha_D -4.17^\circ$. The remainder was kept for a week. When brought into a 2-dcm. tube, its rotation was found to be identical with that of the first portion. Also a crystalline specimen of *l*-benzoin showed no change in activity during three months, the values for the specific rotation at the beginning and end of that period being respectively -115.9° and -116.3° .

The action of alkali on *l*-benzoin was studied in the following manner. *l*-Benzoin (1 gram) was boiled for thirty minutes with 50 c.c. of alcoholic potash (1 c.c. = 0.0065 gram KOH). The purple solution was poured into water (200 c.c.). After some time, the precipitated benzoin was collected and dried in a vacuum over sulphuric acid. Its solution in acetone was optically inactive. The crude product was recrystallised from methyl alcohol, after which it melted at $132.5-134^\circ$. In acetone solution it was optically inactive.

To a solution of *l*-benzoin (0.22 gram) in ethyl alcohol (20 c.c.), two drops of sodium ethoxide solution were added, after which it remained at the laboratory temperature during twenty-one hours. The solution was then poured into water, and the precipitated benzoin isolated as above. The latter was optically inactive when dissolved in acetone.

Racemisation of l-Benzoin Methyl Ether.

l-Benzoin methyl ether (0.2364 gram) was dissolved in cold alcoholic potash (0.113*N*) and the solution made up to 20 c.c. After an interval of five minutes, no optical activity could be detected ($l=4$). Similarly a few drops of dilute sodium ethoxide solution were added to a solution of *l*-benzoin methyl ether in absolute ethyl alcohol. Five minutes after addition, the activity of the solution had diminished to two-thirds of its original value; after thirty minutes to rather less than a-half, whilst at the end of three and a-half hours no activity was observable.

Ethylation of l-Benzoin.

An attempt was made to prepare *l*-benzoin ethyl ether by Fischer's hydrochloric acid method, since Irvine and McNicoll (Trans., 1908, 93,

1601) have shown that *r*-benzoin can be ethylated in this manner without the formation of by-products, such as were encountered when *r*-benzoin was methylated. It was found, however, that complete racemisation had occurred under the following conditions.

A solution of *l*-benzoin (2 grams) in dry ethyl alcohol (30 grams) was saturated with dry hydrogen chloride, first at 30—40° and subsequently at the temperature of the laboratory. After five days, the solution, which showed only feeble reducing action towards boiling Fehling's solution, was poured into water and the emulsion extracted with ether. The solid, obtained from the ethereal extract, was purified by crystallisation from boiling light petroleum, when 1·3 grams of substance were obtained, which, after a second crystallisation, melted at 60·5—61·5°. This product when dissolved in benzene yielded an optically inactive solution. The melting point of *r*-benzoin ethyl ether is given by Irvine and McNicoll (*loc. cit.*) as 62—63°, whereas Fischer (*Ber.*, 1893, 26, 2415) gives 62° and Lander (*Trans.*, 1900, 77, 733) 58—58·5°. On analysis :

0·1562 gave 0·4597 CO₂ and 0·0974 H₂O. C = 80·3 ; H = 7·0.

C₁₆H₁₆O₂ requires C = 80·0 ; H = 6·7 per cent.

Racemisation was shown to be complete by evaporating to dryness the mother liquor from the first recrystallisation and polarimetrically examining the solution of the residue in acetone.

It thus appears that *l*-benzoin and alcoholic hydrogen chloride interact to form *r*-benzoin ethyl ether.

The silver oxide method was next employed for the ethylation of *l*-benzoin. To a solution of *l*-benzoin (4 grams = 1 mol.) and ethyl iodide (26·5 grams = 9 mols.) in acetone (60 c.c.), dry silver oxide (13·1 grams = 3 mols.) was added. The mixture was cautiously heated to its boiling point and maintained at this temperature during two and a-half hours. After filtration from silver oxide and iodide and removal of acetone, an oil remained which had the odour of ethyl benzoate. Since it was possible that complete alkylation had not taken place, the product was dissolved in acetone (30 c.c.) and re-alkylated by treatment with half the above quantities of ethyl iodide and silver oxide. After removal of silver oxide, silver iodide, and acetone as before, an oil was obtained which could not be caused to crystallise. As it was conceivable that the oily nature of the product was due to the presence of ethyl benzoate, the latter was removed by steam distillation, but the residue could be obtained in no form other than an oil. It was accordingly distilled under diminished pressure. Under 6 mm. pressure a viscous, yellow oil of indefinite boiling point (up to 175°) was obtained, which slowly solidifies when placed in a freezing mixture. The solid was recrystallised from a small quantity

of boiling light petroleum. The whole filtrate, from which the crystals had been removed, when examined in a 1-dcm. tube had $\alpha_D + 8.08^\circ$. The crystals, which melted indefinitely at $54\text{--}61^\circ$, were polarimetrically examined in chloroform solution:

$$l = 2, c = 1.913, \alpha_D - 0.22^\circ, [\alpha]_D - 5.7^\circ.$$

The chloroform solution was evaporated to dryness, and the residue examined in heptane solution:

$$l = 2, c = 1.615, \alpha_D + 1.21^\circ, [\alpha]_D + 37.4^\circ.$$

The amount of substance was insufficient for further purification. It appears, therefore, that the product obtained was partly racemised *l*-benzoin ethyl ether, the optical properties of which are analogous to those of the methyl ether (see preceding paper). Racemisation is presumably due to the high temperature necessary for distillation, since it is improbable that the mechanism of methylation and ethylation by the silver oxide method differ, and in the former case a fully active product was readily isolated.

Racemisation of Carbanilido-l-benzoin.

It has been pointed out in the previous paper that carbanilido-*l*-benzoin melts at 121.5° , but solidifies again when heated slightly above this temperature, ultimately re-melting at 163.5° . The coincidence of this latter melting point with that of carbanilido-*r*-benzoin suggested that racemisation had taken place. To test this point, carbanilido-*l*-benzoin was heated in a soft glass tube for ten minutes at 130° and then for eight minutes at 150° . The product, which had solidified at the sides of the tube but not throughout the mass, was cooled and polarimetrically examined in acetone solution, when it proved to be but slightly racemised:

$$l = 2, c = 0.8065, \alpha_D - 3.35^\circ, [\alpha]_D - 207.7^\circ.$$

Pure carbanilido-*l*-benzoin has $[\alpha]_D^{21} - 214.8^\circ$ for $c = 0.6528$ in acetone.

The substance was therefore further heated during three and a-half hours at 140° , after which its solution in acetone was found to be optically inactive. It melted at about 163° .

In the above experiment, as also in the determination of the melting point, it was observed that the portions in contact with the glass were invariably the first to solidify, namely, to racemise. It would thus appear that racemisation is not conditioned solely by heat, but also by specific contact action of the glass.

Interaction of l-Benzoin and Aniline.

With the object of investigating the optical behaviour and action towards alkali of *l*-benzoinanilide, *l*-benzoin was condensed with aniline.

A mixture of *l*-benzoin (2.7 grams) with aniline (1.5 grams) was heated at 100° for four and a-half hours. The product melted at 97.5—99°, and was quite inactive. This melting point was practically unaltered by admixture with an approximately equal quantity of *r*-benzoinanilide (m. p. 98—99°) which had been prepared from *r*-benzoin and aniline. The product of the reaction was therefore *r*-benzoinanilide.

Interaction of l-Benzoin and Benzoyl Chloride.

The preparation of benzoyl-*r*-benzoin by heating together *r*-benzoin and benzoyl chloride has been described by Zinin (*Annalen*, 1857, 104, 116). An attempt was made to benzoylate *l*-benzoin in the same manner.

l-Benzoin (1.2 grams) was gently heated with re-distilled benzoyl chloride (2 grams). Evolution of hydrogen chloride started at 75°. After solution of the benzoin was complete at 100°, heating was continued in an oil-bath. Brisk evolution of hydrogen chloride occurred at 150°. The temperature was finally gradually raised to 195°, at which point gas evolution ceased. The cooled mixture was vigorously agitated with 75 per cent. alcohol (20 c.c.), whereupon it solidified. After three crystallisations from 80 per cent. alcohol, a well-crystallised product was obtained, which melted at 124—125° and was optically inactive in chloroform solution. Benzoyl-*r*-benzoin, according to Zinin, melts at 125°:

0.1779 gave 0.5199 CO₂ and 0.0777 H₂O. C=79.7; H=4.9.

C₂₁H₁₆O₃ requires C=79.7; H=5.1 per cent.

The substance obtained was therefore benzoyl-*r*-benzoin.

Acetylation of l-Benzoin- α -oxime.

l-Benzoin- α -oxime (1.6 grams) was covered with redistilled acetic anhydride (4 grams). With considerable development of heat, the oxime rapidly passed into solution, from which, on cooling, crystals separated. These were recrystallised from light petroleum (b. p. 60—80°), when colourless needles were obtained which melted at 86.5—87°. Their specific rotation was determined in benzene solution:

$$l = 4, c = 0.648, \alpha_D^{15} = -0.66^\circ, [\alpha]_D^{15} = -25.5^\circ.$$

In the light of the following observations, it is doubtful, however, if this product was optically pure.

In the hope of obtaining a better yield of the acetyl derivative, the experimental conditions were slightly altered in a second attempt. *l*-Benzoin- α -oxime (0.8 gram) was covered with acetic anhydride (2 grams). Solution of the oxime readily took place. After standing for thirty minutes, the mixture was placed in a vacuum desiccator over soda-lime in order to remove excess of acetic anhydride and acetic acid. The solid which remained was recrystallised from light petroleum. The colourless needles so obtained melted at $87.5-88^\circ$, and were polarimetrically examined in benzene solution :

$$l = 4, c = 0.974, \alpha_D^{16} = 0.85^\circ, [\alpha]_D^{16} = 21.8^\circ.$$

The observed angle did not change during twenty-one hours. After a second recrystallisation, the specific rotation was again determined in benzene solution :

$$l = 4, c = 0.7952, \alpha_D^{15} = 0.75^\circ, [\alpha]_D^{15} = 23.6^\circ.$$

Although the relative quantities of oxime and acetic anhydride were the same in both experiments, it will be observed that the product obtained in the second case was less active than in the first. This slight difference must be attributed to prolonged contact of the oxime, or more probably of its acetyl derivative, with acetic anhydride. A third experiment was made, in which the amount of the latter reagent was greatly reduced. A partly racemised product again resulted.

l-Benzoin- α -oxime (1.3 grams) was allowed to stand with acetic anhydride (1.1 grams) during fifteen minutes. The semi-solid reaction product was then brought into water, and the precipitated acetyl-*l*-benzoin- α -oxime collected, dried, and twice crystallised from boiling light petroleum. The colourless needles so obtained melted indefinitely at $89-96^\circ$. Their specific rotation was determined in benzene solution :

$$l = 4, c = 1.8452, \alpha_D^{17.2} = 1.15^\circ, [\alpha]_D^{17.2} = 15.6^\circ.$$

In this last experiment, owing to the reduction in the amount of acetic anhydride, the temperature attained by the reaction mixture was considerably higher than in the former cases. The extensive racemisation may be ascribed largely to this factor.

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