

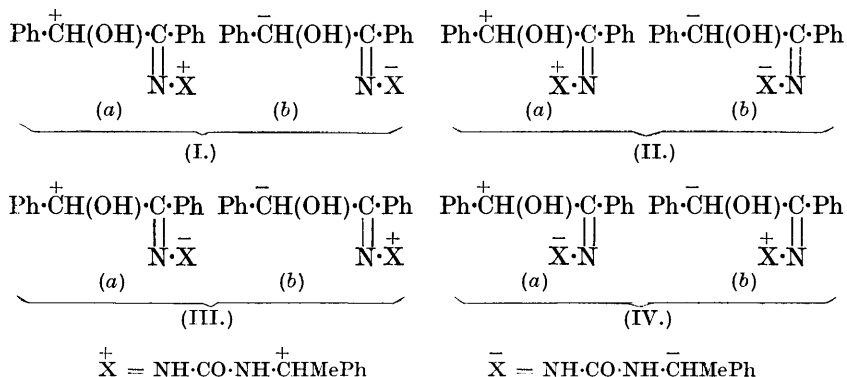
CCCXXIX.—*A Resolution of Benzoin.*

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IN a previous paper (J., 1922, **121**, 866) it was pointed out that *d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide,  $\text{NH}_2\cdot\text{NH}\cdot\text{CO}\cdot\text{NH}\cdot\text{CHMePh}$ , of which we prepared the hydrochloride, should prove of service in resolving racemic aldehydes and ketones. We have now prepared also the *hydrochloride* of the *l*-isomeride, and by means of these reagents have succeeded in isolating the *d*- and *l*-forms of benzoin.

In order to gain experience of the semicarbazones involved, we decided first to experiment with the racemic semicarbazide both in pyridine and alcoholic solution. Since with *r*-benzoin- $\delta$ -( $\alpha$ -phenyl-

ethyl)semicarbazone stereoisomerism of the Hantzsch-Werner type is possible, four racemic modifications should exist (+ = *d*, - = *l*):



The reaction between benzoïn and *r*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide hydrochloride took place smoothly in pyridine solution and three of the four possible *compounds* were obtained, the  $\alpha$ -modification melting at 174°, the  $\beta$ - at 154°, and the  $\gamma$ - (obtained in very small quantity) at 137°: each of these gave benzoïn on hydrolysis with acid. The reaction proceeded much less conveniently in alcoholic solution, the  $\alpha$ - and  $\beta$ -modifications in addition to some unaltered benzoïn being obtained—a result which was somewhat unexpected, since previous experiments (J., 1925, 127, 1282) had shown that as a rule only one modification of a benzoïn-semicarbazone was obtained when working in alcoholic solution. It was decided therefore to employ pyridine as solvent in attempting a resolution of benzoïn.

An optically active semicarbazide has not hitherto been successfully employed in a resolution: Forster and Fierz (J., 1905, 87, 722) prepared camphoryl- $\psi$ -semicarbazide, but do not appear to have used it for this purpose. Other active derivatives of hydrazine have, however, been employed for the resolution of *r*-arabinose (Neuberg, *Ber.*, 1903, 36, 1192) and of *r*-arabinose and *r*-galactose (Neuberg and Federer, *Ber.*, 1905, 38, 868). Benzoïn itself does not appear to have been previously resolved, although the two enantiomorphs have been synthesised (McKenzie and Wren, J., 1908, 93, 809; Wren, J., 1909, 95, 1583).

By combining *r*-benzoïn with *d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide four active modifications of the semicarbazone are possible, *viz.*, Ia, IIa, IIIb, and IVb. When combination was effected in pyridine solution, however, only one product was obtained in a crystalline condition, the others being oily and very soluble. This lævorotatory

substance, a *d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone of *d*-benzoin, agreed in rotation and m. p. with the product obtained by condensing the *d*-semicarbazide with *d*-benzoin (prepared according to McKenzie and Wren, *loc. cit.*). Hydrolysis of this semicarbazone in aqueous solution with oxalic acid liberated *d*-benzoin. In the same way, from the *l*-semicarbazide hydrochloride and *r*-benzoin, we isolated a dextrorotatory semicarbazone which yielded *l*-benzoin on hydrolysis.

#### EXPERIMENTAL.

*Benzoin and r*- $\delta$ -( $\alpha$ -Phenylethyl)semicarbazide Hydrochloride.—  
 (a) *In pyridine solution.* Solutions of 8 g. of benzoin (1 mol.) in 80 c.c. of pyridine and 8.1 g. (1 mol.) of the hydrochloride in 100 c.c. of water were mixed in the cold, kept for 6 days, and poured into a large volume of cold water; the sticky product, which would not solidify, was collected, dissolved in ether, the ethereal solution shaken with water to remove pyridine, decolorised with animal charcoal, and filtered hot. In a few hours a product (Crop I) began to separate, and was collected after 2 days. Whilst it was difficult to obtain further solid matter from the filtrate, gradual addition of light petroleum during 2 days precipitated a coloured product, which was filtered and washed with ether until colourless (Crop II). Further gradual addition of light petroleum during a few weeks deposited a small crop (Crop III) which was collected and washed as before. Crop I was recrystallised successively from ether, benzene, and alcohol (the solubility increasing in this order of solvents), from which long, colourless needles (4 g., m. p. 154°) of *benzoin*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone ( $\beta$ -modification) were deposited (Found : N, 11.19.  $C_{23}H_{23}O_2N_3$  requires N, 11.26%). Crop II, which was less soluble in the usual organic solvents, dissolved completely on prolonged boiling with benzene, and a fine, amorphous product separated on cooling. This crystallised from alcohol in prisms (3 g., m. p. 174°) of the  $\alpha$ -modification of the semicarbazone (Found : N, 11.26%). These two stereoisomerides, a mixture of which melted at 140–145°, both gave benzoin on hydrolysis with either hydrochloric or oxalic acid. Crop III was separated by ether into a less soluble ( $\beta$ -modification) and a more soluble fraction. The latter on recrystallisation from a mixture of ether and light petroleum gave long, woolly needles (0.4 g., m. p. 187°) of the  $\gamma$ -modification (Found : N, 11.37%) which gave benzoin on hydrolysis with hydrochloric acid. The colouring matters produced in the reaction had a marked effect on the solubilities of the substances.

(b) *In alcoholic solution.* 4 G. of benzoin in 300 c.c. of alcohol were mixed in the cold with 4 g. of the semicarbazide hydrochloride in a little water. After standing for 6 days, dilution with much

cold water gave a soft, but filterable, precipitate which was collected and dissolved in the minimum of boiling alcohol. The crystals deposited on cooling were fractionally recrystallised from ether; a little benzoïn separated first and was removed, then a mixture of needles and prisms appeared. On reheating the mixture in the mother-liquor, the needles redissolved so much more quickly that it was possible to effect a fairly complete separation of the prisms by filtering the hot solution at the appropriate moment. The prisms on recrystallisation from alcohol proved to be the  $\alpha$ -isomeride, m. p. 174°. The ethereal mother-liquor on standing gave needles, mixed with a small quantity of prisms which were separated by reheating and filtering. The warm filtrate diluted with two volumes of light petroleum deposited crystals which, after purification from alcohol, proved to be the  $\beta$ -isomeride, m. p. 154°.

1- $\delta$ -( $\alpha$ -Phenylethyl)semicarbazide Hydrochloride.—26.3 G. of *l*- $\alpha$ -phenylethylamine ( $[\alpha]_D^{25} - 41.48^\circ$ , prepared by a combination of the methods of Lovén and Betti; see Hopper and Ritchie, *J. Roy. Tech. Coll.*, 1926, **3**, 65) and 25 g. of acetonesemicarbazone were heated in a bath at 135—138° for 30 minutes under reflux, and then for a further 30 minutes without the condenser. The product, poured into 200 c.c. of ice-water, solidified on standing for a short time. The acetone-*l*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone was collected and hydrolysed by heating with 5% hydrochloric acid (1 mol., calculated on acetonesemicarbazone used) for 2.5 hours on a boiling water-bath, acetone being thus expelled. On cooling, an amorphous solid—probably a derivative of carbamide—was removed, the filtrate was concentrated under reduced pressure (which increases the yield), and the 1- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide hydrochloride allowed to crystallise out in a number of crops so that the heating of very concentrated solutions was avoided. On recrystallisation from boiling absolute alcohol, 36.5 g. (79% yield) of the hydrochloride were obtained; m. p. 188°;  $\alpha_D^{25} - 4.00^\circ$ ,  $[\alpha]_D^{25} - 66.06^\circ$  ( $c = 3.027$  in water;  $l = 2$ ).

*Synthesis of d-Benzoin-d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone.—*d*-Benzoin was synthesised from *d*-mandelic acid by Wren's method (*loc. cit.*) with certain modifications suggested to us by Professor McKenzie and Dr. Roger, to both of whom we are much indebted for advice in this connexion. The *d*-mandelamide was prepared from methyl *d*-mandelate by the method of McKenzie and Smith (*J.*, 1922, **121**, 1358). In this and in subsequent preparations and recrystallisations, quartz vessels were employed and solvents were distilled in quartz before use. It was found more convenient to recrystallise *d*-benzoïn from a mixture of alcohol and light petroleum than from alcohol alone. The *d*-benzoïn melted at 133—134°;  $\alpha_D^{25} + 4.47^\circ$ ,

$[\alpha]_D^{25} + 118.5^\circ$  ( $c = 0.9433$  in acetone;  $l = 4$ ); a solution in freshly distilled pyridine showed no alteration in specific rotation ( $[\alpha]_D^{25} + 92.8^\circ$ ;  $c = 1.040$ ;  $l = 1$ ) on standing for a week in a quartz apparatus. *d*-Benzoïn is therefore not racemised by pyridine under these conditions.

A mixture of 1.1 g. of *d*-benzoïn, dissolved in 67 c.c. of pyridine, with 1.3 g. of *d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide hydrochloride, dissolved in 2.5 c.c. of water, deposited crystals of the *d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone of *d*-benzoïn when left for 6 days. These were collected, and the filtrate, when worked up as described for the reaction product obtained in the resolution (below) yielded some more; two recrystallisations from absolute alcohol gave needles (0.5 g.), m. p. 181—182°,  $\alpha_D^{25} - 2.405^\circ$ ,  $[\alpha]_D^{25} - 140.7^\circ$  ( $c = 0.4274$  in absolute alcohol;  $l = 4$ ) (Found: N, 11.30.  $C_{23}H_{23}O_2N_3$  requires N, 11.26%). Further recrystallisation failed to alter the specific rotation.

*Resolution of Benzoïn.*—(1) *By means of d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide hydrochloride. 9 G. of the semicarbazide hydrochloride, dissolved in 18 c.c. of water, were added to a solution of 8 g. of benzoïn in 70 c.c. of pyridine at 18°, and the mixture after standing for 7 days was poured into 1000 c.c. of cold water. In about 80 minutes the opalescent liquor was decanted from the thick, sticky oil, and the latter was agitated three times with almost boiling water, with cooling and decanting each time. The hard, glassy solid thus obtained (and the beaker containing it) were exposed for 72 hours in an evacuated desiccator over sulphuric acid to remove the last traces of pyridine and water. A solution of the product in about 50 c.c. of pure dry ether deposited a crop of crystals on standing a few hours or on addition of light petroleum. (The ethereal mother-liquor, after various attempts to recover material from it, gave only a gummy product.) The crystals were collected, washed with ether, and recrystallised twice from boiling absolute alcohol, in which the compound was sparingly soluble when cold. The *d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone of *d*-benzoïn thus obtained was optically pure (repeated recrystallisation from alcohol failing to raise its specific rotation) and consisted of needles, m. p. 181—182°; yield 1.8 g. (Found: N, 11.29%);  $\alpha_D^{25} - 2.415^\circ$ ,  $[\alpha]_D^{25} - 141.5^\circ$  ( $c = 0.4268$  in absolute alcohol;  $l = 4$ ). It showed no lowering of m. p. on admixture with the product (m. p. 181—182°) obtained from synthetic *d*-benzoïn; the appearance of both was identical under the microscope, and the specific rotations ( $-140.7^\circ$  and  $-141.5^\circ$ ) are identical within the limits of experimental error.

(2) *By means of l*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide hydrochloride. Using 13.2 g. of the *l*-semicarbazide hydrochloride in 26 c.c. of water, and 12.5 g. of benzoïn in 95 c.c. of pyridine, and working up the

product as in the last preparation, we obtained 1.8 g. of pure *l*-benzoin-*l*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone, m. p. 181—182° (Found: N, 11.32%). The product was optically pure after two recrystallisations from absolute alcohol, in which  $\alpha_D^{25} = +4.40^\circ$ ,  $[\alpha]_D^{25} +140.9^\circ$  ( $c = 0.7808$ ;  $l = 4$ ).

*Liberation of d- and of l-Benzoin*—(1) *d-Benzoin*. Boiling solutions of 1.4 g. of *d*-benzoin-*d*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone in 50 c.c. of absolute alcohol and of 15 g. of oxalic acid in 12 c.c. of water were mixed and boiling was continued for 1 minute. (Longer boiling causes oxidation to benzil derivatives; see J., 1925, **127**, 1282.) The solution, cooled immediately and diluted with 250 c.c. of water, gave a precipitate of *d*-benzoin which was collected after a few hours. Boiling for some time with 200 c.c. of light petroleum (b. p. 60—80°) dissolved the active benzoin but left undissolved the traces of unhydrolysed semicarbazone and other impurities. After cooling and standing, the petroleum extract was filtered and concentrated to half its volume; the *d*-benzoin which crystallised was optically pure after one recrystallisation from absolute alcohol; yield 0.7 g.; m. p. 133—134°; mixed m. p. with synthetic *d*-benzoin (with which it is identical in appearance) 133—134°;  $\alpha_D^{25} + 5.954$ ,  $[\alpha]_D^{25} + 118.3^\circ$  ( $c = 1.2581$  in acetone;  $l = 4$ ).

(2) *l-Benzoin*. 1.6 G. of *l*-benzoin-*l*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone were hydrolysed in an exactly similar fashion. The liberated *l*-benzoin was recrystallised once from light petroleum and once from alcohol, and was then optically pure; yield 0.8 g.; m. p. 133—134°;  $\alpha_D^{25} - 5.435^\circ$ ,  $[\alpha]_D^{25} - 118.5^\circ$  ( $c = 1.1467$  in acetone;  $l = 4$ ). Oxidation of both the active benzoin with nitric acid yielded benzil.

The gummy product referred to on p. 2487 was dissolved in boiling alcohol, then mixed with a hot, concentrated, aqueous solution of oxalic acid, and boiled for 5 minutes. The mixture of solid and semi-solid, obtained after dilution with water and standing, was separated by ether into sparingly soluble (m. p. above 200°), soluble (m. p. 129—132°), and very soluble (a gum) fractions. The first fraction on recrystallisation from alcohol proved to be *benzildi*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazone, long, fine needles, m. p. 233° (Found: N, 15.86.  $C_{32}H_{32}O_2N_6$  requires N, 15.79%);  $\alpha_D^{25} + 3.08^\circ$ ,  $[\alpha]_D^{25} 178.2^\circ$  ( $c = 0.4320$  in glacial acetic acid;  $l = 4$ ). By boiling in alcohol with concentrated hydrochloric acid—but not with oxalic acid—it was hydrolysed to benzil. The second fraction on fractional recrystallisation from ether gave chiefly inactive benzoin, which separated first, followed by a crop of benzoin showing *l*avorotation, m. p. 132—133°;  $\alpha_D^{25} - 0.46^\circ$ ,  $[\alpha]_D^{25} - 25.7^\circ$  ( $c = 0.8974$  in absolute alcohol;  $l = 2$ ). The corresponding gummy product

obtained in the condensation of benzoin and *l*- $\delta$ -( $\alpha$ -phenylethyl)semicarbazide hydrochloride gave, on hydrolysis with oxalic acid, a sparingly soluble product (m. p. 238°), *r*-benzoin (m. p. 134°), and benzoin (m. p. 131—133°) showing dextrorotation.

We propose to extend our investigations to the resolution of other racemic ketones and aldehydes by means of active semicarbazides.

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