69. *Preparation of Certain Optically Active Semicarbazides and a Resolution of Benzoin.*

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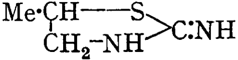
In this communication a resolution of benzoin by means of *d*- and *l*-δ-(α-phenylpropyl)semicarbazides, $NH_2{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}CHEtPh$, is described. α-Phenylpropylamine, required in these experiments, has been resolved by an improved method. A resolution of 2-imino-5-methylthiazolidine as hydrochloride has also been effected, but this amine proved unsuitable for the purposes in view. Unsuccessful attempts were made to resolve camphor and 3-methyl*cyclo*hexanone.

A resolution of *r*-benzoin by active semicarbazides has been reported by Hopper and Wilson (J., 1928, 2483), who used *d*- and *l*-δ-(α-phenylethyl)semicarbazides, and by Crawford and Wilson (J., 1934, 1122), who by means of *l*-menthylsemicarbazide isolated *l*-benzoin. In this paper a resolution by *d*- and *l*-δ-(α-phenylpropyl)semicarbazides is described.

The preparation of an optically active semicarbazide involves, as in previous cases, the use of an active amine which reacts with acetonesemicarbazone, $CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NH_2 + R{\cdot}NH_2 \xrightarrow{-NH_3} CMe_2{:}N{\cdot}NH{\cdot}CO{\cdot}NHR$, whence on hydrolysis with acid the hydrochloride of the active semicarbazide, $NH_2{\cdot}NH{\cdot}CO{\cdot}NHR$, is obtained. This with benzoin gives diastereoisomeric benzoinsemicarbazones, $CHPh(OH){\cdot}CPh{:}N{\cdot}NH{\cdot}CO{\cdot}NHR$, which on hydrolysis yield the active benzoins, $CHPh(OH){\cdot}CPh{:}O$. In this particular case it is worthy of note that the mother-liquors from which *d*-benzoin-*d*-δ-(α-phenylpropyl)semicarbazone had separated gave nearly optically pure *l*-benzoin on hydrolysis.

We experimented with α-phenylpropylamine, α-camphylamine, and 2-imino-5-methylthiazolidine as active bases. A resolution of *r*-α-phenylpropylamine by means of *d*-tartaric acid has been described by Billon (*Compt. rend.*, 1926, **182**, 1470; *Ann. Chim.*, 1927, **17**, 314), but by employing first *l*-malic acid and then *d*-tartaric acid we have succeeded in preparing active forms of this amine showing much higher rotations than those given by this author.

The resolution of *r*-2-imino-5-methylthiazolidine  $\begin{matrix}\mathrm{Me{\cdot}CH}\text{——}\mathrm{S}\\ \mathrm{CH_2\text{–}NH}\end{matrix}\!\!>\mathrm{C{:}NH}$ (Gabriel, *Ber.*, 1889, **22**, 2985), not accomplished hitherto, was effected by means of *d*- and *l*-camphor-10-sulphonic acids, the active forms of the base being obtained as hydrochlorides. This base, however, proved to be unsuitable owing to the ease with which it underwent thermal decomposition.

Unsuccessful attempts were made to resolve *r*-camphor as the active δ-(α-phenylethyl)-semicarbazones, the active δ-(α-phenylpropyl)semicarbazones, and the *d*-δ-α-camphyl-semicarbazone. 3-Methyl*cyclo*hexanone did not give a suitable product with δ-(α-phenylethyl)semicarbazide.

Experimental.

r-α-*Phenylpropylamine*.—This was prepared from propiophenoneoxime (Billon, *loc. cit.*), which was obtained in improved yield by modifying the method of Janny (*Ber.*, 1882, **15**, 2781) in that the acidity developed during the reaction was neutralised from time to time with potassium hydroxide.

Resolution of the amine. To a solution of 65 g. of *l*-malic acid in 400 c.c. of alcohol, 65 g. of the amine were added in a thin stream with stirring. After standing overnight and being stirred, the d-*amine* l-*hydrogen malate* separated; when recrystallised to constant rotation from alcohol (four times), it had $\alpha_D^{13\cdot5°}$ −3·18° (*c* = 6·8024 in water, *l* = 4), $[\alpha]_D^{13\cdot5°}$ −11·68°, and formed needles, m. p. 169° (Found : N, 5·4, 5·4. $C_9H_{13}N,C_4H_6O_5$ requires N, 5·2%). The *d*-amine, liberated from this salt with 50% potassium hydroxide solution, was separated, dried over solid potassium hydroxide, and distilled in hydrogen, the fraction, b. p. 204—206°, being collected; $[\alpha]_D^{17°}$ +20·15° (Billon, *loc. cit.*, gives $[\alpha]_D$ +9·5°). The solution from which the malate had separated was evaporated to small bulk, concentrated potassium hydroxide solution added, and the crude *l*-amine separated and distilled. It was added (55 g.) slowly with stirring to 60 g. (1 mol.) of *d*-tartaric acid in 1 l. of absolute alcohol, whereupon the l-*amine* d-*hydrogen tartrate* separated. After five recrystallisations from absolute alcohol it gave a constant rotation, $\alpha_D^{14°}$ +2·195° (*c* = 4·8464 in water, *l* = 2), $[\alpha]_D^{14°}$ +22·65°; it formed needles, m. p. 179° (Found : N, 5·1, 5·1. $C_9H_{13}N,C_4H_6O_6$ requires N, 4·9%). From this salt the *l*-amine was liberated and distilled as in the case of the enantiomorph; $[\alpha]_D^{17°}$ −19·85° (Billon gives $[\alpha]_D$ −10·5°).

d-δ-(α-*Phenylpropyl*)*semicarbazide Hydrochloride*, $NH_2{\cdot}NH{\cdot}CO{\cdot}NH{\cdot}CHEtPh,HCl$.—8 G. of *d*-α-phenylpropylamine and 6 g. of acetonesemicarbazone in 30 c.c. of xylene were heated for ¾ hr., ammonia being evolved. The syrup remaining after removal of the solvent under reduced pressure solidified on keeping in a vacuum overnight; the *acetone*-d-δ-(α-*phenylpropyl*)*semicarbazone* after recrystallisation from alcohol (m. p. 92°. Found : N, 18·1, 18·2. $C_{13}H_{19}ON_3$ requires N, 18·0%) was hydrolysed by heating with twelve times its weight of *N*-hydrochloric acid for ½ hr. The *hydrochloride* obtained by evaporation of the solution under reduced pressure crystallised from alcohol in pearly crystals, m. p. 165°, $\alpha_D^{13°}$ +4·89° (*c* = 3·621 in water, *l* = 2), $[\alpha]_D^{13°}$ +67·5° (Found : N, 18·4. $C_{10}H_{15}ON_3,HCl$ requires N, 18·3%).

l-δ-(α-*Phenylpropyl*)*semicarbazide hydrochloride*, similarly prepared from the *l*-amine, had m. p. 165°, $\alpha_D^{13°}$ −4·89° (*c* = 3·6348 in water, *l* = 2), $[\alpha]_D^{13°}$ −67·3° (Found : N, 18·4%). The intermediate *acetone*-l-δ-(α-*phenylpropyl*)*semicarbazone* melted at 92° (Found : N, 18·0%).

The following compounds were obtained by use of the *r*-amine : *acetone*-r-δ-(α-*phenylpropyl*)-*semicarbazone*, which crystallised from alcohol and melted at 110° (Found : N, 17·8%), and r-δ-(α-*phenylpropyl*)*semicarbazide hydrochloride*, which crystallised from alcohol containing a little ether and melted at 135° (Found : N, 18·4, 18·5%).

Resolution of r-*Benzoin*.—d-*Benzoin*. *d*-δ-(α-Phenylpropyl)semicarbazide hydrochloride (9 g.) was added to *r*-benzoin (7 g.) in 75 c.c. of pyridine, and the solution kept for a week at room temperature. When it was poured into 1 l. of water with stirring, a resinous precipitate separated after some time. The supernatant liquor was decanted, and the resin washed several times with boiling water to remove pyridine, and then dried in a vacuum over sulphuric acid. The now hard resin was dissolved in alcohol, and water added dropwise to incipient precipitation. After standing for a few days the d-*benzoin*-d-δ-(α-*phenylpropyl*)*semicarbazone* was collected; it crystallised from alcohol in fine needles, m. p. 166° (Found : N, 10·9, 11·0. $C_{24}H_{25}O_2N_3$ requires N, 10·9%), $\alpha_D^{12\cdot5°}$ −2·51°, $[\alpha]_D^{12\cdot5°}$ −126·0° (*c* = 0·498 in alcohol, *l* = 4). The substance was hydrolysed by heating in alcoholic solution with 0·3N-sulphuric acid on a boiling water-bath for 10 minutes, and the cold solution poured into ice water; the precipitate was dissolved in boiling light petroleum (b. p. 40—60°), and on cooling, some unhydrolysed material separated, followed by crops of *d*-benzoin, further amounts of which were obtained by extracting the aqueous alcoholic acid liquors with carbon tetrachloride. The several crops of *d*-benzoin were recrystallised from alcohol; the pure substance had m. p. 133—134° (Found : C, 79·2; H, 5·7. Calc. for $C_{14}H_{12}O_2$: C, 79·2; H, 5·7%), $\alpha_D^{10°}$ +3·04° (*c* = 1·286 in acetone, *l* = 2), $[\alpha]_D^{10°}$ +118·1°. In all, 1·2 g. of the semicarbazone were hydrolysed, yielding 0·4 g. of pure *d*-benzoin.

l-*Benzoin*. After removal of the *d*-benzoinsemicarbazone as above, the mother-liquor was heated for ½ hr. with 15 c.c. of 5N-hydrochloric acid on the water-bath in order to hydrolyse the *l*-benzoin-*d*-δ-(α-phenylpropyl)semicarbazone present. The solution was poured into water, filtered from *r*-benzoin, and the filtrate (which contained the more soluble *l*-benzoin) extracted with carbon tetrachloride. The extract was evaporated, and the residual crude *l*-benzoin after two recrystallisations from alcohol was almost optically pure; m. p. 133—134°, $\alpha_D^{11°}$ −1·81° (*c* = 0·388 in acetone, *l* = 4), $[\alpha]_D^{11°}$ −116·6°. To obtain pure *l*-benzoin, 5·5 g. of *r*-benzoin, including that recovered as above, were treated with 7 g. of *l*-δ-(α-phenylpropyl)semicarbazide hydrochloride in pyridine and the reaction mixture worked up as in the previous case. The l-*benzoin*-l-δ-(α-*phenylpropyl*)*semicarbazone*, obtained pure after two recrystallisations from alcohol, melted at 166° and gave $\alpha_D^{12\cdot5°}$ +2·64° (*c* = 0·519 in alcohol, *l* = 4), $[\alpha]_D^{12\cdot5°}$ +127·1° (Found : N, 10·9. $C_{24}H_{25}O_2N_3$ requires N, 10·9%). This semicarbazone was hydrolysed as before and gave *l*-benzoin, m. p. alone or admixed with an authentic specimen 133—134°

(Found : C, 78·8; H, 5·7%), $\alpha_D^{10^\circ}$ −4·21° (*c* = 0·891 in acetone, *l* = 4), $[\alpha]_D^{10^\circ}$ −118·1°. Hopper and Wilson found $[\alpha]_D^{11^\circ}$ −118·5° (*c* = 1·1467 in acetone), Crawford and Wilson $[\alpha]_D^{13 \cdot 5^\circ}$ −118·3° (*c* = 1·069 in acetone), Wren (J., 1909, **95**, 1584), $[\alpha]_D^{10 \cdot 5^\circ}$ −118·6° (*c* = 0·9232 in acetone).

These resolution experiments were carried out in quartz apparatus. The following compounds were obtained in unsuccessful attempts to resolve *r*-camphor. The first four were obtained from camphor and the appropriate δ-(α-phenylpropyl)semicarbazide hydrochloride in pyridine solution, the reaction mixture being worked up as usual.

r-*Camphor*-r-δ(α-*phenylpropyl*)*semicarbazone* crystallised from alcohol in needles, m. p. 137° (Found : N, 12·9. $C_{20}H_{29}ON_3$ requires N, 12·8%). r-*Camphor*-l-δ(α-*phenylpropyl*)*semicarbazone* was obtained as a sticky resin which solidified after keeping for a month in a vacuum; it was then cautiously recrystallised from aqueous alcohol (nucleation), from which it separated in fine needles, m. p. 104° (Found : N, 12·8%), $\alpha_D^{14^\circ}$ +1·53° (*c* = 1·253 in alcohol, *l* = 2), $[\alpha]_D^{14^\circ}$ +61·1°. d-*Camphor*-d-δ-(α-*phenylpropyl*)*semicarbazone*, rhomboids from aqueous alcohol, melted at 118° (Found : N, 12·9%) and gave $\alpha_D^{14^\circ}$ −1·55° (*c* = 0·828 in alcohol, *l* = 2), $[\alpha]_D^{14^\circ}$ −93·6°. l-*Camphor*-d-δ-(α-*phenylpropyl*)*semicarbazone*, rhomboids from aqueous alcohol, melted at 120° (Found : N, 13·0%) and gave $\alpha_D^{14 \cdot 5^\circ}$ −1·72° (*c* = 1·1088 in alcohol, *l* = 4), $[\alpha]_D^{14 \cdot 5^\circ}$ − 38·8°.

Equal quantities of the last two semicarbazones were recrystallised together from aqueous alcohol. A compound resembling *r*-camphor-*l*-δ-(α-phenylpropyl)semicarbazone in every respect except sign of rotation was obtained; it formed needles melting sharply at 104° (mixed m. p. 104°) and gave $\alpha_D^{15^\circ}$ −1·29° (c = 1·0484 in alcohol, *l* = 2), $[\alpha]_D^{15^\circ}$ −61·6°.

The following camphor-δ-(α-phenylethyl)semicarbazones were prepared in unsuccessful attempts to resolve camphor by heating its semicarbazone with α-phenylethylamine at 180° for 1 hr., followed by recrystallisation of the gummy product.

r-*Camphor*-r-δ-(α-*phenylethyl*)*semicarbazone*, from *r*-camphorsemicarbazone and the *r*-amine, crystallised from alcohol in prisms, m. p. 144° (Found : N, 13·5. $C_{19}H_{27}ON_3$ requires N, 13·4%). d-*Camphor*-l-δ-(α-*phenylethyl*)*semicarbazone*, from *d*-camphorsemicarbazone and the *l*-amine, crystallised from aqueous alcohol on slow evaporation in prisms, m. p. 112° (Found : N, 13·5%), $[\alpha]_D^{15^\circ}$ +41·3° (*c* = 4·00 in alcohol). l-*Camphor*-l-δ-(α-*phenylethyl*)*semicarbazone* crystallised from alcohol in prisms, m. p. 112° (Found : N, 13·5%), $[\alpha]_D^{14^\circ}$ +102·4° (*c* = 4·004 in alcohol). r-*Camphor*-l-δ-(α-*phenylethyl*)*semicarbazone* crystallised from aqueous alcohol on slow evaporation in prisms, m. p. 122—123° (Found : N, 13·4%), $[\alpha]_D^{15^\circ}$ +68·9° (*c* = 4·004 in alcohol). This same compound was also obtained when equal quantities of the two preceding compounds were mixed and crystallised from aqueous alcohol. It is to be noted that the m. p. of the mixed compound is higher than that of either constituent.

Resolution of 2-*Imino*-5-*methylthiazolidine*.—18 G. of this *r*-base were added to 30 g. of *d*-camphor-10-sulphonic acid in 70 c.c. of absolute alcohol. The *d*-camphorsulphonate of the *l*-base separated on standing overnight and was optically pure after two recrystallisations from small quantities of absolute alcohol; concentration of the reaction mother-liquors yielded further quantities. It melted at 182—184° and gave $[\alpha]_D^{15^\circ}$ −19·63° (*c* = 4·000 in water). To 15 g. of this salt in 70 c.c. of water, excess of 50% potassium hydroxide solution was added, and the hot solution (to prevent separation of potassium camphorsulphonate) was extracted six times with benzene. The united extracts were evaporated under reduced pressure, and the syrupy *l*-base so obtained was dissolved in dilute hydrochloric acid. Evaporation of this solution yielded l-2-*imino*-5-*methylthiazolidine hydrochloride* (5 g.), which crystallised from alcohol–ether in flat needles, m. p. 175° (Found : N, 18·1, 18·2. $C_4H_8N_2S,HCl$ requires N, 18·3%), $[\alpha]_D^{14 \cdot 5^\circ}$ −76·5° (*c* = 4·000 in water). The mother-liquors from which the *l*-base *d*-camphorsulphonate had separated were evaporated to small bulk, and the syrup treated with 50% potassium hydroxide solution. Extraction six times with benzene and evaporation of the extracts yielded the crude *d*-base (9·5 g.), which was added to 19 g. of *l*-camphor-10-sulphonic acid in 40 c.c. of absolute alcohol. On standing overnight, the *d*-base *l*-camphorsulphonate separated, and was pure after two recrystallisations from alcohol; m. p. 182—184°, $[\alpha]_D^{15^\circ}$ +20·1° (*c* = 4·000 in water). From this salt, d-2-*imino*-5-*methylthiazolidine hydrochloride* (4 g.) was prepared exactly as described above; it crystallised from alcohol–ether in flat needles, m. p. 172—173° (Found : N, 18·3%), $[\alpha]_D^{14 \cdot 5^\circ}$ +77·5° (*c* = 4·000 in water).

We wish to thank Imperial Chemical Industries, Ltd., for grants and also for the award of the " Nobel " Bursary to one of us (A. J. L.).

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[*Received, January* 23*rd*, 1940.]