67. *The Resolution of Benzoin.*

By (the late) JOSEPH KENYON and R. L. PATEL.

By crystallisation of its (+)-quinidine salt, the hydrogen phthalate of (±)-benzoin is rapidly and quantitatively separated into its (+)- and (−)-isomerides; these, by hydrolysis with hot dilute ethanolic sulphuric acid, yield optically pure (+)- and (−)-benzoin, respectively.

THE direct resolution of benzoin was first recorded by Hopper and Wilson [1] who condensed it with (+)- and with (—)-4-(1-phenylethyl)semicarbazide ($NH_2 \cdot NH \cdot CO \cdot NH \cdot CHPh \cdot Me$) and subsequently hydrolysed the resulting semicarbazones with oxalic acid. Much earier, McKenzie and Wren [2] obtained (—)-benzoin by the action of phenylmagnesium bromide on (—)-mandelamide, and Wren [3] synthesised (+)-benzoin similarly from (+)-mandelamide. Both of these methods, which are laborious, gave optically pure benzoins, but only in low yields.

In the present work, benzoin readily combined with a molecular proportion of phthalic

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[1] I. V. Hopper and F. J. Wilson, *J.*, 1928, 2483.
[2] A. McKenzie and H. Wren, *J.*, 1908, **93**, 309.
[3] H. Wren, *J.*, 1909, **95**, 1583.

anhydride, in the presence of pyridine and triethylamine, to give an almost quantitative yield of the crystalline hydrogen phthalate ester of (±)-benzoin, which readily formed a salt with (+)-quinidine; the salt, after one crystallisation, was almost completely separated into its diastereoisomerides. Decomposition of the less soluble salt with acid yielded the (+)-acid ester, whilst the more soluble salt was so rich in the second diasteroisomeric salt that its decomposition yielded a (—)-acid ester which could be obtained optically pure by means of simple crystallisation.

EXPERIMENTAL

Hydrogen Phthalate of (±)-*Benzoin.*—A solution of phthalic anhydride (6 g.) in hot pyridine (4 ml.) was rapidly cooled to ensure that small crystals would be formed. (±)-Benzoin (8·4 g.) was then added and the mixture well stirred for 5 min., after which triethylamine (4·8 ml.) was added and the stirring continued. The mixture became warm and mobile at first but, after a few minutes, became a pasty mass which was then triturated with an equal volume of acetone, and the resulting solution diluted with water. Sufficient sodium hydrogen carbonate solution was then added, to dissolve the hydrogen phthalate formed, and the solution was filtered to remove traces of uncombined benzoin. The filtrate was added dropwise to the calculated amount of hydrochloric acid mixed with ice, and stirred. The precipitated acid ester, after thorough washing and drying, gave microscopic needles (from methylene chloride–light petroleum), (13·6 g.; 95·7%), m. p. 154—156° (Equiv., by titration with 0·1N-NaOH, 360. Calc. for $C_{21}H_{15}O_3{\cdot}CO_2H$: 360).

The hydrogen succinate of (±)-benzoin was obtained similarly, in quantitative yield, from succinic anhydride (4 g.) and benzoin (8·4 g.), as small needles (from carbon disulphide) (11·9 g.), m. p. 84—85° (Equiv., by titration, 311. Calc. for $C_{17}H_{15}O_3{\cdot}CO_2H$: 312).

(+)-*Hydrogen Phthalate of Benzoin.*—The hydrogen phthalate of (±)-benzoin (67·5 g.) was added to a warm suspension of (+)-quinidine (60·76 g.) in methanol (360 ml.). The initially formed clear solution rapidly deposited the crystalline quinidine salt of the (+)-hydrogen phthalate (64 g.); this crop, after recrystallisation from warm acetone (600 ml.) and methanol (5 ml.), yielded the optically pure salt as needles (63·4 g.), m. p. 132°.

This salt, suspended in twice its bulk of acetone, was decomposed by addition of a slight excess of ice-cold dilute hydrochloric acid, and the liberated (+)-hydrogen phthalate was precipitated by slow addition of water. After being washed and dried, it gave needles (from methylene chloride–light petroleum) (32·7 g.), m. p. 132—133° (Equiv., by titration, 359·8). Values for the rotatory power of the (+)-hydrogen phthalate are recorded in Table 1.

The loss in rotatory power with time of a solution of the (+)-hydrogen phthalate in freshly distilled pyridine at 25—26° is recorded in Table 2. The plot of the logarithm of the specific rotatory power against time was linear. The optically inactive solution was not examined for the (±)-hydrogen phthalate.

(—)-*Hydrogen Phthalate of Benzoin.*—The combined filtrates from the quinidine salt of the

TABLE 1.

Specific rotatory power, $[\alpha]_\lambda$, of the (+)-hydrogen phthalate of benzoin at 25—26°.

Solvent	c (l 1)	$[\alpha]_{5893}$	$[\alpha]_{5461}$	$[\alpha]_{5086}$	$[\alpha]_{4358}$
Methylene chloride	2·50	+187°	+229·6°	+290°	+489·6°
Pyridine	2·00	+176·5	+213·5	+272	+460
Glacial acetic acid	2·365	+169	+206	+259	+439
Chloroform	2·50	+166	+204	+257	+436
Acetone	2·54	+140·2	+175	+216·6	+375
90% Ethanol	2·52	+140	+172·6	+215	+370

The (+)-hydrogen phthalate was too sparingly soluble in benzene and carbon disulphide for accurate polarimetric determinations to be made.

TABLE 2.

Loss in rotatory power, $[\alpha]_{5893}$, of a solution of (+)-benzoin hydrogen phthalate in freshly distilled pyridine at 25—26° (l 1, c 2·00).

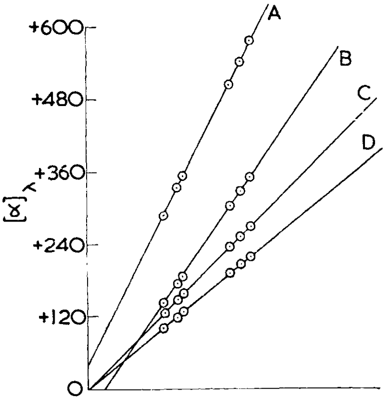
Time (hr.)	0	25	35	58	122	170	218
$[\alpha]_{5893}$	+176·5°	+152°	+136·5°	+107·5°	+64°	+46·5°	+36°
Time (hr.)	298	319	335	388	484	549	648
$[\alpha]_{5893}$	+27°	+24°	+22·5°	+19°	+17·5°	+16·5°	+15°

The solution was too yellow after 648 hr. for further accurate polarimetric readings to be made.

(+)-hydrogen phthalate were concentrated, and then decomposed with ice-cold dilute hydrochloric acid, and the (−)-hydrogen phthalate was precipitated by addition of water. The washed and dried material was more readily soluble in cold methylene chloride than was the (±)-acid ester, and hence the (−)-acid ester was obtained optically pure after two crystallisations from methylene chloride–light petroleum, as needles (33 g.), m. p. 132—133°, $[\alpha]_{5893}^{25}$ −140·0 (*l* 1, *c* 2·50 in acetone) (Equiv., by titration, 359·3).

A solution containing equal weights of (+)- and (−)-hydrogen phthalate (each of m. p. 132—133°) in methylene chloride–petroleum deposited needles of the (±)-hydrogen phthalate, m. p. 155—156°.

(+)-*Benzoin.*—Sulphuric acid (1N, 40 ml.) was added to a solution of the (+)-hydrogen phthalate (7·2 g.) in ethanol (95%, 200 ml.), and the mixture heated for 24 hr. Water (40 ml. was added and the heating was continued for a further 100 hr.; then, after adding water (160 ml.), most of the ethanol was distilled off. The cooled solution was mixed with ice and set aside. The next day, the precipitated material was removed and triturated with an equal volume of ethanol; sodium hydrogen carbonate solution (5%) was then added until the mixture was slightly alkaline to Methyl Orange, in order to dissolve a small amount of unhydrolysed (+)-hydrogen phthalate. The mixture was stirred, diluted with water, filtered after 2 hr., and washed with water. The (+)-benzoin thus obtained gave needles (from ethanol) (2·2 g.; 52%), m. p. 132—133°, $[\alpha]_{5893}^{25}$ +118·4° (1, *c* 2·50 in acetone) {lit.,[3] $[\alpha]_D^{11\cdot5}$ +120·5° (*l* 4, *c* 0·4128 in acetone), m. p. 131—132·5°; lit.,[1] $[\alpha]_D^{11}$ +118·3° (*l* 4, *c* 1·258 in acetone), m. p. 133—134°}.



" Characteristic diagram " for (+)-benzoin. A, $[\alpha]_{4358}$. B, $[\alpha]_{5086}$. C, $[\alpha]_{5461}$. D, $[\alpha]_{5893}$. For the significance of the abscissae, see the text.

Values for the rotatory power of (+)-benzoin are recorded in Table 3; the present work is an extension of that report by Roger and McGregor.[4] It is known [5] that (+)-benzoin undergoes very slow racemisation in glacial acetic acid at room temperature.

TABLE 3.

Specific rotatory power, $[\alpha]_\lambda$, of (+)-benzoin at 25—26°.

Solvent	*c* (*l* 1)	$[\alpha]_{5893}$	$[\alpha]_{5461}$	$[\alpha]_{5086}$	$[\alpha]_{4358}$
Glacial acetic acid	2·50	+216°	+267°	+352°	+576°
Methylene chloride	1·88	+205	+251·6	+328	+539
Chloroform	2·21	+191	+234	+304	+504
99% Ethanol	2·50	+124	+157·6	+184	+352
Acetone	2·50	+118·4	+146	+172	+336
Pyridine	2·00	+99·5	+123	+139·5	+288

The solution of (+)-benzoin in freshly distilled pyridine showed no loss in specific rotatory power after 7 days at room temperature. A similar observation was made by Hopper and Wilson,[1] who used a quartz apparatus.

(−)-*Benzoin.*—The (−)-hydrogen phthalate (3·6 g.) was hydrolysed by using exactly the same procedure as for the (+)-hydrogen phthalate; the liberated (−)-benzoin gave fine needles (from ethanol) (1·06 g.; 50%), m. p. 132—133°, $[\alpha]_D^{25}$ −118·3° (*l* 1, *c* 2·40 in acetone) {lit.,[2] $[\alpha]_D^{10\cdot5}$ −118·6° (*l* 4, *c* 0·923 in acetone), m. p. 131—132·5°; lit.,[1] $[\alpha]_D^{11}$ −118·5 (*l* 4, *c* 1·1467 in acetone),

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[4] R. Roger and A. McGregor, *J.*, 1934, 1545.

[5] R. Roger, K. C. Reid, and R. Wood, *J.*, 1954, 3453.

m. p. 133—134°}. A solution containing equal weights of (+)- and (−)-benzoin (each of m. p. 132—133°) in ethanol gave, after evaporation, needles of (±)-benzoin, m. p. 133—134°.

A " characteristic diagram " for (+)-benzoin has been constructed according to the method of Armstrong and Walker [6] (see the Figure). A reference line with slope of unity was drawn, and on it were plotted the values of $[\alpha]_{5461}$ for different solvents. The values for the specific rotatory power at other wavelengths, $[\alpha]_\lambda$, were then plotted against the abscissae of the points of the reference line (each abscissa representing a given solvent). Each set of $[\alpha]_\lambda$ values was found to lie on a straight line, the slope of which was larger the smaller the value of λ.

Benzil from (+)- and (−)-Benzoin.—Benzil (optically inactive), m. p. 94—95°, yellow needles from carbon tetrachloride, was obtained in 75% yield from both (+)- and (−)-benzoin by oxidation with copper sulphate and pyridine.[7]

It may be pointed out that many reference books state that benzoin has m. p. 137°. This is surprising since, over fifty years ago, McKenzie and Wren [2] recorded that they were unable to raise the m. p. of a specimen of Kahlbaum's benzoin above 132·5—133°, even after six crystallisations from methanol. The benzoin used in the present experiments was a commercial sample of m. p. 133—134° (uncorrected). The m. p. was unchanged after crystallisation from ethanol.

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[6] H. E. Armstrong and E. E. Walker, *Proc. Roy. Soc.*, 1913, *A*, **88**, 388.

[7] H. T. Clark and E. E. Dreger, *Org. Synth.*, 1926, **6**, 6.