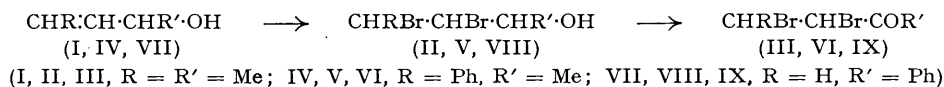


### 504. *The Addition of Bromine to (+)-1-Phenylallyl Alcohol and the Oxidation of the (+)-Dibromo-alcohol.*

By C. L. ARCUS and H. E. STRAUSS.

1-Phenylallyl alcohol, to which free bromine does not add satisfactorily, yields 2:3-dibromo-1-phenylpropanol on reaction with pyridine hydrobromide perbromide. (+)-1-Phenylallyl alcohol forms the (+)-dibromo-alcohol; the latter on oxidation with chromic anhydride-acetic acid yields ( $\pm$ )- $\alpha\beta$ -dibromopropiophenone. Similar reactions with (-)-1:3-dimethylallyl alcohol and (+)-1-methyl-3-phenylallyl alcohol are known to give optically active dibromo-ketones. It is concluded that  $\alpha\beta$ -dibromopropiophenone, which has an asymmetric centre only at C<sub>( $\alpha$ )</sub>, becomes racemised through the occurrence of enolisation during oxidation; the dibromo-ketones derived from the 1:3-disubstituted allyl alcohols are not racemised because they have at C<sub>( $\beta$ )</sub> an additional asymmetric centre, which is not subject to racemisation by enolisation.

KENYON and PARTRIDGE (*J.*, 1936, 1313) found that addition of bromine to (-)-1:3-dimethylallyl alcohol (I) yielded a (+)-2:3-dibromo-4-pentanol (II) which on oxidation with chromic anhydride in glacial acetic acid gave a (+)-2:3-dibromo-4-pentanone (III). These reactions constitute a partial asymmetric synthesis: the original centre of asymmetry has been rendered symmetrical by oxidation and the optical activity of the ketone is due to new centres of asymmetry having been formed with the possible configurations present in unequal amounts. Similar reactions with (+)-1-methyl-3-phenylallyl alcohol (IV) yielded (-)-3:4-dibromo-4-phenylbutan-2-ol (V) and (-)-3:4-dibromo-4-phenylbutan-2-one (VI). Four diastereoisomeric dibromo-alcohols may theoretically be formed from one optical isomer of (I) or (III), *e.g.*, from the *d*-allyl alcohol, the *dd'd''*, *dl'l''*, *dd'l''*, *dl'd''*-dibromo-alcohols; however, by fractionally crystallising a specimen of (V) prepared from fully active (IV), Kenyon and Partridge isolated only two diastereoisomeric forms. These diastereoisomers, which were obtained in unequal amounts, on oxidation separately gave enantiomeric (+)- and (-)-dibromo-ketones (VI).

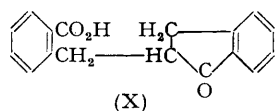


It was decided to attempt an asymmetric synthesis with 1-phenylallyl alcohol (VII), an apparently simpler case because the dibromo-ketone (IX) has only one asymmetric centre.

From the reaction of bromine with 1-phenylallyl alcohol Klages and Klenk (*Ber.*, 1906, **39**, 2553) and Moureu and Gallagher (*Bull. Soc. chim.*, 1921, **29**, 1010) isolated only 1:2:3-tribromo-1-phenylpropane. We have repeated the reaction in dry chloroform, carbon tetrachloride, and carbon disulphide; absorption of bromine virtually ceased when 60–70% of that required to form the dibromo-alcohol had been added, and 1:2:3-tribromo-1-phenylpropane crystallised and was isolated in 5–10% yield; none of the dibromo-alcohol (VIII) was isolated. In order to minimise the concentration of free bromine, the reagent pyridine hydrobromide perbromide (Djerassi and Scholtz, *J. Amer. Chem. Soc.*, 1948, **70**, 417) was then used; from its reaction with 1-phenylallyl alcohol in glacial acetic acid 2:3-dibromo-1-phenylpropanol (VIII) and 1:2:3-tribromo-1-phenylpropane were isolated in 47% and 6% yield respectively. Repetition of this reaction with (+)-1-phenylallyl alcohol yielded (+)-2:3-dibromo-1-phenylpropanol and optically inactive 1:2:3-tribromo-1-phenylpropane; oxidation of this (+)-dibromo-alcohol with chromic anhydride in glacial acetic acid gave optically inactive  $\alpha\beta$ -dibromopropiophenone (IX) in 25% yield.

By analogy with the syntheses reported by Kenyon and Partridge an optically active ketone was to be expected. The substantial differences between (IX) and the two ketones (III) and (VI) are: (a) the presence in (III) and (VI) of a second asymmetric centre, not

adjacent to the carbonyl group, and (b) the fact that the double bond in the enol of (IX) is conjugated with a phenyl group, tending to stabilise the enol. Ingold and Wilson (*J.*, 1934, 773) found (+)-2-*o*-carboxybenzylindan-1-one (X) to be stable in glacial acetic acid solution, but to become half-racemised in 4 minutes at 20° when hydrogen bromide is present in 0.002M-concentration. (+)-*sec*-Butyl phenyl ketone in acetic acid containing nitric acid (1.19N) becomes half-racemised in 23 minutes at 36.75° (Bartlett and Stauffer, *J. Amer. Chem. Soc.*, 1935, 57, 2580). The reaction mechanisms discussed by these authors require as an intermediate either the enol



—C(OH)=C— or its mesomeric anion —C(O<sup>-</sup>)=C— ↔ —C(O)=C—, both of which imply a planar configuration for the α-carbon atom. Since oxidation of (VIII) to (IX) was by chromic anhydride in glacial acetic acid, the medium was probably sufficiently acid to catalyse the racemisation of the ketone.

Retention of asymmetry during the similar oxidation of (II) to (III) and (V) to (VI) is considered to be due to the immunity of the β-carbon atom to racemisation by enolisation. Two enols CHRBr·CBr·C(OH)·CH<sub>3</sub> and CHRBr·CHBr·C(OH)·CH<sub>2</sub> are possible; in the latter the asymmetric centres are not involved; when the former resumes the keto-form the configuration of the asymmetric centre at the β-carbon atom appears to permit one configuration of the >C<sup>α</sup>HBr group to be formed much more readily than the other, yielding as product a single diastereoisomer of the dibromo-ketone.

#### EXPERIMENTAL

Ligroin refers to petroleum of b. p. 100—120°.

1-Phenylallyl alcohol was prepared and resolved by Duveen and Kenyon's method (*J.*, 1939, 1697). Seven recrystallisations of the quinidine salt of 1-phenylallyl hydrogen phthalate from methyl acetate were necessary to yield the optically pure quinidine salt of the (+)-hydrogen phthalate. The (+)-1-phenylallyl hydrogen phthalate obtained from this salt had m. p. 57.5—60°, [α]<sub>5893</sub><sup>22</sup> +51.0°, [α]<sub>5461</sub><sup>22</sup> +61.8° in carbon disulphide (*l*, 2.0; *c*, 5.03) (Found: equiv., 284. Calc. for C<sub>17</sub>H<sub>14</sub>O<sub>4</sub>: equiv., 282). These rotatory powers are 20% higher than those recorded by Duveen and Kenyon for their hydrogen phthalate, which was an oil. The methyl acetate mother-liquors from the resolution yielded the quinidine salt of the (−)-hydrogen phthalate; it was recrystallised from acetone and gave on decomposition (−)-1-phenylallyl hydrogen phthalate, m. p. 58—60°, [α]<sub>5893</sub><sup>20</sup> −50.8°, [α]<sub>5461</sub><sup>20</sup> −61.7° (*l*, 2.0; *c*, 5.01 in carbon disulphide). The (+)-1-phenylallyl alcohol obtained from this ester by saponification had b. p. 79—82°/3 mm., *n*<sub>D</sub><sup>25</sup> 1.5372, *d*<sub>4</sub><sup>16</sup> 1.027, α<sub>5893</sub><sup>17</sup> +5.10°, α<sub>5461</sub><sup>17</sup> +6.59° (*l*, 0.5), the rotatory powers being only 1% greater than those recorded by Duveen and Kenyon. Saponification of the (+)-hydrogen phthalate yielded (−)-1-phenylallyl alcohol having α<sub>5893</sub><sup>17</sup> −5.12°, α<sub>5461</sub><sup>17</sup> −6.61° (*l*, 0.5).

(±)-1-Phenylallyl alcohol was conveniently purified by conversion into the hydrogen phthalate, and recrystallisation and hydrolysis of the latter; the alcohol so prepared had b. p. 75—78°/1 mm., *n*<sub>D</sub><sup>25</sup> 1.5373.

*Bromine-addition and Oxidation.*—(a) *With (±)-1-phenylallyl alcohol.* Bromine (1.2 g.) in chloroform (16 ml.) was added dropwise to (±)-1-phenylallyl alcohol (1.0 g.); the solvent and excess of bromine were removed by drawing dry air through the flask. The residual oil partly crystallised; the solid was filtered off and recrystallised from ethyl alcohol, needles (0.2 g.), m. p. 121—122°, being obtained which, after repeated recrystallisation, yielded 1 : 2 : 3-tribromo-1-phenylpropane, m. p. 124—125° (Found: C, 30.7; H, 2.2; Br, 67.0. Calc. for C<sub>9</sub>H<sub>9</sub>Br<sub>3</sub>: C, 30.3; H, 2.5; Br, 67.2%). Grimaux (*Bull. Soc. chim.*, 1873, 20, 121) records m. p. 124°. Carbon tetrachloride and carbon disulphide were also used as solvents; the solution of bromine was added from a burette and absorption almost ceased when 0.60—0.70 mol. of bromine had been added. 1 : 2 : 3-Tribromo-1-phenylpropane was isolated in yields of 5—10%.

Pyridine hydrobromide perbromide, red needles, m. p. 135—138° (decomp.), was prepared according to Djerassi and Scholtz (*loc. cit.*) (these authors record m. p. 134°) except that one additional equivalent of hydrobromic acid was employed. When one equivalent only of hydrobromic acid was used the product, after three recrystallisations, had m. p. 120—125°.

(±)-1-Phenylallyl alcohol (3.0 g.) was allowed to react with pyridine hydrobromide perbromide (7.2 g.) by the method described below for the (+)-alcohol; after the separation of 1 : 2 : 3-tribromo-1-phenylpropane (0.44 g.), m. p. 124—125°, the product was twice distilled and yielded (±)-2 : 3-dibromo-1-phenylpropanol (3.1 g.), an almost colourless viscous oil, b. p. 145.5—147.5°/3 mm. (Found : C, 36.8; H, 3.4; Br, 54.9.  $C_9H_{10}OBr_2$  requires C, 37.3; H, 3.6; Br, 54.5%). Crystals slowly appeared in the liquid; they were filtered off and, after being washed with ligroin-acetic acid and recrystallised from hot ligroin, had m. p. 124—125° alone or mixed with authentic 1 : 2 : 3-tribromo-1-phenylpropane.

(±)-2 : 3-Dibromo-1-phenylpropanol (0.2 g.) and phenyl isocyanate (0.09 g.) were heated on a steam-bath for 3 hours. Benzene, and then ligroin, were added to the product; the solution was filtered and set aside overnight; the urethane then separated. After recrystallisation from ether-light petroleum (b. p. 40—60°), (±)-2 : 3-dibromo-1-phenylpropyl phenylcarbamate (0.08 g.) was obtained as colourless rectangular crystals, m. p. 148—149° (Found : C, 46.6; H, 3.8; N, 3.5; Br, 38.8.  $C_{16}H_{15}O_2NBr_2$  requires C, 46.5; H, 3.6; N, 3.4; Br, 38.7%). An exactly similar preparation with 4-diphenyl isocyanate gave (±)-2 : 3-dibromo-1-phenylpropyl 4-diphenylcarbamate, m. p. 115—117° (Found : C, 54.6; H, 4.0; N, 2.6.  $C_{22}H_{19}O_2NBr_2$  requires C, 54.0; H, 3.9; N, 2.9%).

Oxidation of (±)-2 : 3-dibromo-1-phenylpropanol (4.5 g.) by the method described below for the (+)-alcohol yielded  $\alpha\beta$ -dibromopropiophenone (1 g.), long colourless rhombs, m. p. 51—53° (Found : C, 37.5; H, 2.7; Br, 54.4. Calc. for  $C_9H_8OBr_2$  : C, 37.0; H, 2.7; Br, 54.8%). Beaufour (*Bull. Soc. chim.*, 1913, 13, 356) records m. p. 56°.

(b) *With (+)-1-phenylallyl alcohol.* (+)-1-Phenylallyl alcohol (14.1 g.;  $\alpha_{D_{589}}^{20} + 4.13^\circ$ , *l*, 0.5) was dissolved in glacial acetic acid (140 ml.). To the mechanically stirred solution, pyridine hydrobromide perbromide (33.8 g.) was added in portions; the reaction mixture was kept at 12—15°, some crystals of acetic acid being present throughout. After 45 minutes the solution was poured into water (1 l.), and the whole extracted four times with ether. The combined ethereal extracts were repeatedly washed with dilute hydrochloric acid, with aqueous sodium hydrogen carbonate and with water, and dried ( $MgSO_4$ ). The ether was distilled and the oil which remained was dissolved in hot cyclohexane. On cooling, needles separated which were filtered off and, after thrice recrystallising from hot ethyl alcohol, gave 1 : 2 : 3-tribromo-1-phenylpropane (1.3 g.), m. p. 125—127°, optically inactive in chloroform. Evaporation of the cyclohexane filtrate at 20 mm. yielded (+)-2 : 3-dibromo-1-phenylpropanol having  $[\alpha]_{D_{589}}^{17} + 10.6^\circ$  (*l*, 2.0; *c*, 5.00 in chloroform). This specimen of the dibromo-alcohol (undistilled, 25.7 g.) was dissolved in glacial acetic acid (260 ml.). To the solution, at 60°, chromic anhydride (9 g.) was added in portions during 1 hour. The solution was poured into water (1.5 l.) and thrice extracted with ether; the combined ethereal extracts were repeatedly washed with aqueous sodium hydrogen carbonate, and with water, and dried ( $Na_2SO_4$ ). The oil remaining after evaporation of the ether was seeded with a crystal of  $\alpha\beta$ -dibromopropiophenone and kept for 2 days, whereupon it crystallised. After being collected and washed with a small quantity of ligroin, the solid (13.2 g.) was recrystallised from light petroleum (b. p. 40—60°) and yielded  $\alpha\beta$ -dibromopropiophenone (4.5 g.), m. p. 51—53°, optically inactive in chloroform and in carbon disulphide. A further quantity (1.8 g.) of (±)- $\alpha\beta$ -dibromopropiophenone, and also (±)-1 : 2 : 3-tribromo-1-phenylpropane (0.3 g.), were isolated from the filtrates. On evaporation of the latter, a lachrymatory oil (5.7 g.) remained; it had  $[\alpha]_{D_{589}}^{21} - 28.7^\circ$  (*c*, 4.81 in chloroform) and on distillation gave a fraction, b. p. 108—114°/0.3 mm., from which (±)- $\alpha\beta$ -dibromopropiophenone was isolated.

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