62. *Molecular Dissymmetry due to Symmetrically Placed Hydrogen and Deuterium. Part III. The Attempted Resolution of 4 : 4′-Dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamine. A Method for the Determination of Deuterium in Organic Compounds.*

By G. R. Clemo and G. A. Swan.

Attempts to resolve 4 : 4′-dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamine have been unsuccessful. The Harteck method for the determination of deuterium has been developed for the estimation of the relative proportions of hydrogen and deuterium in organic compounds.

PREVIOUS work (Clemo, Gardner, and Raper, J., 1939, 1958) resulted in resolution of 4-chloro-, 4-bromo-, and 4-iodo-benzhydrylamines, but was unsuccessful in that of the 4-methyl compound. Failure to resolve α-pentadeuterophenylbenzylamine has been recorded by Adams and Tarbell (*J. Amer. Chem. Soc.*, 1938, **60**, 1260) and by Clemo and Swan (J., 1939, 1960). Nevertheless, we decided to prepare 4 : 4′-*dibromo*-2 : 3 : 5 : 6-*tetradeuterobenzhydrylamine*, and to attempt to resolve it, hoping that the presence of the symmetrically placed bromine atoms in the molecule, together with the dissymmetry due to the difference between hydrogen and deuterium, would render resolution practicable.

As a preliminary, the preparation of 4 : 4′-*dibromobenzhydrylamine* was investigated by the method used by Clemo, Gardner, and Raper for preparing 4-bromobenzhydrylamine, but the experimental conditions were modified so as to minimise the risk of exchange, when applied to the preparation of the " heavy " base : the time of heating with formamide was reduced, and the hydrolysis carried out by means of alkali instead of acid.

Resolution of the 4 : 4′-dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamine was attempted by crystallisation of the *d*-hydrogen tartrate and of the *d*-bromocamphorsulphonate from alcohol. No change in the specific rotation of the salt was observed, and the recovered base was optically inactive. This work was completed some time ago. We hope to attack the problem along a new line when opportunity occurs.

The relative proportions of hydrogen and deuterium in water can be conveniently estimated by a method making use of the considerable difference in thermal conductivity between the vapours of protium oxide and deuterium oxide, in equilibrium with the corresponding ice at a constant temperature. This method has several advantages over other methods : the effect on which it depends is very favourable because it is really the resultant of two effects which reinforce one another; deuterium oxide has a lower vapour pressure than protium oxide, so the amount of the former in the vapour phase is less than that of the latter, and, moreover, the thermal conductivity of duterium oxide vapour is lower than that of protium oxide vapour. Also the method requires only a very small quantity of water and it has a number of advantages over that of Farkas (*Proc. Roy. Soc.*, 1934, *A*, **144**, 467) which depends on thermal conductivity measurements on the purified hydrogen gas formed by decomposition of the water by passage over a hot tungsten wire. In the method we use, the latter processes and the pressure measurement are eliminated. It was suggested by Harteck (*Z. Elektrochem.*, 1938, **44**, 4), but a detailed description of the apparatus has not been published. We have employed this method for estimating the proportion of deuterium in the water formed by combusting "heavy" compounds in a current of oxygen, with platinum contacts. Although only 0·5 mg. of water was used in each determination, sufficient of the compound was usually combusted to give at least 4 mg. of water, so that several successive values could be obtained. When relatively large amounts of water were used, consistent results were readily obtained; but when only a very small amount (*e.g.*, 2 or 3 mg.) was available, each successive determination was slightly higher than the previous one, doubtless because protium oxide, being slightly more volatile than deuterium oxide, is enriched in the vapour, so that the residual liquid has a slightly higher deuterium content than the original water. Although this effect had been observed by Harteck and by Geib (*ibid.*, p. 7), they do not appear to have applied a correction for it; the following method was therefore adopted.

If C represents the ratio of protium atoms to deuterium atoms in the gas divided by this ratio in the liquid, it is given (Urey and Teal, *Rev. Mod. Physics*, 1935, **7**, 48) by

$$C = \frac{2AB + (ABkK)^{\frac{1}{2}}}{2 + (ABkK)^{\frac{1}{2}}} \cdot \frac{2 + (BK)^{\frac{1}{2}}}{2B + (BK)^{\frac{1}{2}}}$$

where A is the ratio of the vapour pressures of pure H_2O and D_2O and B is the ratio of their mole-fractions in the liquid; $k = p_{12}^2/p_{11}p_{22}$, where p_{12}, p_{11}, and p_{22} are the vapour pressures of the pure liquids HDO, H_2O, and D_2O respectively; and K is the equilibrium constant of the reaction $H_2O + D_2O \rightleftharpoons 2HDO$. For the gaseous reaction at 25°, Topley and Eyring (*J. Chem. Physics*, 1934, **2**, 217) have calculated K to be 3·26; this will also be the value for liquid water if $k = 1$, which is approximately the case. The value of A was taken as 1·149 (Lewis and Macdonald, *J. Amer. Chem. Soc.*, 1933, **55**, 3058). Then the value of C is approximately 1·075.

The volume of the "pipette" (the space bounded by taps 10, 11, 12, 13, and 17; see Fig. 1), by means of which an approximately equal amount of water vapour was measured for each determination, was about 35 c.c., so that approximately 0·5 mg. of water was used. The volume of the tube (14, 15, or 16) in which the liquid water was contained was about half this amount. Consider a sample of water containing a g.-atoms of protium and b g.-atoms of deuterium. Suppose that the vapour produced (in the tube itself and in the "pipette") contains $3x$ g.-atoms of protium and $3y$ g.-atoms of deuterium. Of this, $\frac{2}{3}$ will be used in the determination (and pumped out afterwards) and the remaining $\frac{1}{3}$ will be left in the tube. Thus $(x/y)/[(a - 3x)/(b - 3y)] = 1{\cdot}075$ and the ratio of protium to deuterium in the residual liquid water will be $(a - 3x)/(b - 3y)$, whereas that in the original water was a/b; $2(x + y)$ represents the amount of water used in each determination (*i.e.*, 0·5 mg.) and $(a + b)$ represents the total amount of water available. Then

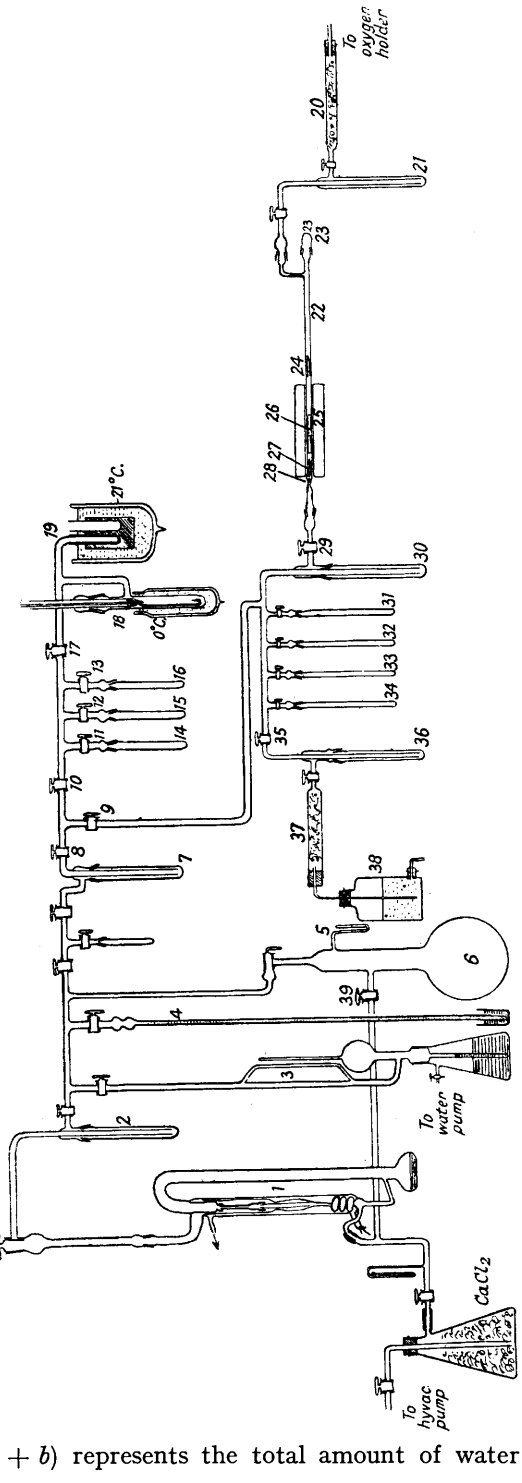


FIG. 1.

$$1/\left(1 + \frac{a - 3x}{b - 3y}\right) - 1/\left(1 + \frac{a}{b}\right) = \frac{\Delta}{100}$$

where Δ is the excess of the observed over the true percentage of deuterium. The value of Δ is a maximum when the proportion of deuterium is in the region of 50 atoms %; in the region of 0% or 100%, the value is very small. The value of Δ also increases as the weight of water available decreases; *e.g.*, for a 1 : 1 mixture, the value is 0·6 when only 2 mg. water are available, and about 0·35 for 4·5 mg. water. When several successive measurements are made from the same sample of water, the correction for the final measurement is obtained by summation of the separate Δ values (gradually increasing, on account of the amount of water diminishing); *e.g.*, if 4 mg. of water of deuterium content 50 atoms % are used, then the correction for the fourth measurement would be approximately (0·4 + 0·45 + 0·5 + 0·55), *i.e.*, 1·9%. In the calibration, a relatively enormous amount of water is used, so no appreciable error arises on account of fractionation.

EXPERIMENTAL.

Formo-4 : 4′-dibromobenzhydrylamide.—4 : 4′-Dibromobenzophenone (Hoffmann, *Annalen*, 1891, **264**, 163) (2 g.) was heated with formamide (6 c.c.) for 6 hours at 175°, and the mixture poured into water; the product was filtered off, washed with water, dried, and recrystallised from methanol, forming colourless prisms (1·8 g.), m. p. 159° (Found : C, 45·3; H, 3·3; N, 4·0. $C_{14}H_{11}ONBr_2$ requires C, 45·5; H, 3·0; N, 3·8%).

4 : 4′-*Dibromobenzhydrylamine.*—The above formyl derivative (1 g.) was heated with potassium hydroxide (1·5 g.) in methanol (8 c.c.) for 6 hours on the water-bath. After distillation of most of the methanol and pouring the residue into water, the base was taken up in ether, the extract dried with potassium carbonate, the ether removed, and the product recrystallised from light petroleum (b. p. 60—80°), forming colourless prisms, m. p. 76° (Found : C, 45·9; H, 2·8; N, 4·4. $C_{13}H_{11}NBr_2$ requires C, 45·7; H, 3·2; N, 4·1%). The *hydrochloride* formed colourless needles (Found : C, 41·7; H, 3·7. $C_{13}H_{12}NClBr_2$ requires C, 41·4; H, 3·2%). The *d*-hydrogen tartrate has m. p. 210—211°, $[\alpha]_D^{18°}$ +9·5° (l = 2, c = 2, in methanol); the *d*-bromocamphorsulphonate has m. p. 260—262°, $[\alpha]_D^{18°}$ +46·4° (l = 2, c = 2, in methanol).

4 : 4′-*Dibromo*-2 : 3 : 5 : 6-*tetradeuterobenzophenone.*—Bromopentadeuterobenzene (0·40 g.), *p*-bromobenzoyl chloride (0·55 g.), freshly sublimed aluminium chloride (0·38 g.), and dry carbon disulphide (0·3 c.c.) were mixed in a small flask fitted with a ground-in condenser, leading to a trap containing potassium hydroxide (to remove the evolved deuterium chloride from the sphere of chemical reaction and hence minimise the chance of exchange occurring). After being heated for 22 hours on the water-bath, the mixture was cooled, decomposed by addition of ice and dilute hydrochloric acid, and warmed on the water-bath for 10 minutes to hydrolyse excess of *p*-bromobenzoyl chloride. The ketone was taken up in chloroform, the extract washed with water and with sodium hydroxide solution, dried with sodium sulphate, the chloroform removed, and the product recrystallised from ethanol, forming colourless leaflets (0·55 g.), m. p. 172—173° (Found : C, 45·2; water, 22·1. $C_{13}H_4D_4OBr_2$ requires C, 45·3; water, 22·1%. Isotopic analysis. Found : 47 atoms % D. $C_{13}H_4D_4OBr_2$ requires 50 atoms % D).

Formo-4 : 4′-dibromo-2 : 3 : 5 : 6-tetradeuterobenzhydrylamide.—The above ketone (0·55 g.) was heated with formamide (1·7 c.c.) for 6 hours at 175°. After being poured into water, the product was filtered off, washed with water, dried, and recrystallised from methanol, affording colourless prisms (0·50 g.), m. p. 158—159° (Found : C, 44·7; water, 29·5. $C_{14}H_7D_4ONBr_2$ requires C, 45·0; water, 27·6%. Isotopic analysis. Found : 36·8 atoms % D. $C_{14}H_7D_4ONBr_2$ requires 36·4 atoms % D).

4 : 4′-*Dibromo*-2 : 3 : 5 : 6-*tetradeuterobenzhydrylamine.*—The above formyl derivative (0·50 g.) was heated with potassium hydroxide (0·7 g.) in methanol (4 c.c.) for 3½ hours on the water-bath. After isolation as for the undeuterated compound (see above), the *base* crystallised from light petroleum (b. p. 60—80°) as colourless prisms (0·37 g.), m. p. 75—76° (Found : C, 45·5; water, 30·0. $C_{13}H_7D_4NBr_2$ requires C, 45·2; water, 29·9%. Isotopic analysis. Found : 36 atoms % D. $C_{13}H_7D_4NBr_2$ requires 36·4 atoms % D). The *d*-hydrogen tartrate has m. p. 210—212°, $[\alpha]_D^{18°}$ +9·3° (l = 2, c = 2·5, in methanol), $[\alpha]_{5461}^{18°}$ +10·5°, $[\alpha]_{4358}^{18°}$ +15·3° (l =2, c = 2, in methanol). The *d*-bromocamphorsulphonate has m. p. 260—262°, $[\alpha]_D^{18°}$ +45·9° (l = 2, c = 2, in methanol).

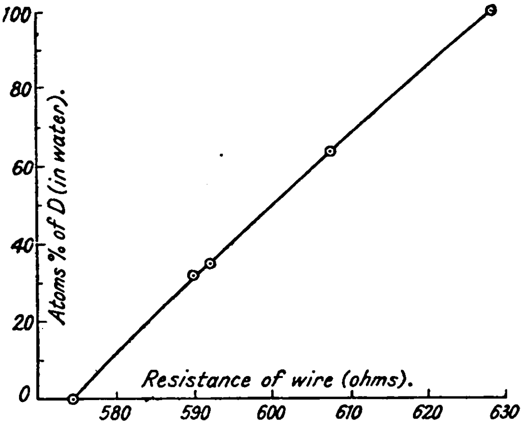
Attempted resolution. 0·57 G. of the *d*-hydrogen tartrate was recrystallised 4 times from 95% ethanol, 0·10 g. remaining. The specific rotation $[\alpha]_{4358}^{18°}$ remained constant within the limits of experimental error at +15·3° (*e.g.*, successive values, 15·1°, 15·0°, 15·7°), as did the m. p. The recrystallised tartrate (0·10 g.) was shaken with dilute sodium hydroxide solution, the base extracted with ether, the extract dried with potassium carbonate, the ether removed, and the residue recrystallised from light petroleum (b. p. 60—80°), giving 60 mg. of base, m. p. 75—76°. When examined in the micropolarimeter tube, this gave $\alpha_D^{18°}$ 0·00° ± 0·01° (l = 0·5, c = 8·6, in ethanol). The tartrate recovered after many recrystallisations was analysed isotopically (Found : 23·3 atoms % D, $C_{17}H_{13}D_4O_6NBr_2$ requires 23·5 atoms % D).

0·67 G. of the *d*-bromocamphorsulphonate was recrystallised 8 times from 90% ethanol, after which 0·10 g. remained. The base (recovered as described above) had m. p. 76°, and gave $\alpha_D^{18°}$ 0·00° ± 0·02° (l = 0·5; c = 9·8, in ethanol). This salt was also recrystallised 4 times from 10% ethanol, the specific rotation $[\alpha]_D^{18°}$ remaining vitually constant (*e.g.*, successive values, 45·9°, 45·8°, 45·9°). The recovered base had m. p. 75—76°, $\alpha_D^{18°}$ 0·00° ± 0·01° (l = 0·5, c = 6·8, in ethanol). The lower limit of any specific rotation which could have been detected with certainty on the recovered base is estimated at about 0·5°.

Isotopic Analysis.—The apparatus used is shown diagramatically in Fig. 1. The " heavy " compounds were combusted, by a micro-method, in a stream of pure oxygen (rate of flow 3·5 c.c./min.) from which the last traces of moisture had been removed by passage through a trap (21) cooled in liquid air. The combustion tube (22) was of Jena glass, 60 cm. long and 10 mm. in diameter; it contained two platinum contacts, each made from a piece of foil 5 × 5 cm., which were heated to 600° by an electric furnace, followed by a roll of silver wool, 6 cm. long, to remove halogens. The water formed was collected in a trap (30) cooled in solid carbon dioxide–alcohol; entry of moisture from the end of the train through which the oxygen escaped was prevented by drying-tubes and a second liquid-air trap (36). This water was purified by repeated pumping-out, while cooled with solid carbon dioxide, and redistillation until free from dissolved gases (about four distillations). A three-stage mercury diffusion pump was used, and all taps and ground joints lubricated with apiezon L grease. Whenever possible, sufficient of the compound was used to give 4 mg. of water on combustion; but measurements could be carried out with smaller quantities, although the results so obtained were not quite so accurate.

In the measuring section of the apparatus, a constant temperature of about −21° was obtained by using an aluminium block in which was drilled a cylindrical cavity, into which the condensation-tube (19) just fitted; the block was dipped into liquid air and then immersed in a saturated sodium chloride solution at −20°, contained in a large Dewar vessel. A layer of cryohydrate thus formed around the block, which then acted as a thermostat. We, however, found this arrangement (originally suggested by Harteck) inconvenient, so we subsequently employed a block in which two cylindrical cavities were drilled, one to fit the condensation-tube, and the other considerably wider. This block was not dipped into liquid air, but was simply immersed in a previously cooled saturated solution of " AnalaR " sodium chloride in distilled water, contained in a well-lagged, silvered Dewar vessel 22 cm. deep and 11 cm. in diameter, and then liquid air was poured into the wider cavity until a sufficiently thick layer of cryohydrate had been formed. When so much of the cryohydrate had melted that the temperature was no longer constant, it was only necessary to pour in some more liquid air to restore the cryohydrate. After liquid air had been poured in, the block was allowed to stand for ½—1 hour to regain temperature equilibrium, before any measurements were carried out.

FIG. 2.



The measuring wire was of platinum, 5μ in diameter and 6 cm. long; it was kept taut by a spiral about 15 mm. long, made of platinum wire 0·05 mm. in diameter. A Sullivan rotary-switch Wheatstone Bridge was used; the rheostat arm consisted of four dials (having a range of 1—11,110 ohms), and the four pairs of ratio arm coils had resistances of 10, 100, 1,000, and 10,000 ohms respectively. A Sullivan Universal Galvanometer of resistance 132·2 ohms (20°) was employed in conjunction with a shunt of 10,000 ohms. The battery, of 4 volts, consisted of Fuller " block " type accumulators insulated so as to keep their temperature (and hence their E.M.F.) constant. Immediately after the water had been admitted to the condensation-tube, the accumulator switch was closed; 2 mins. later the bridge reading was taken, and measurements were repeated at intervals of 1 min. until the reading had reached a constant value (this usually occurred after the second reading). The ice was then pumped out from the condensation-tube, at least 5 mins. being allowed. Another sample of the same specimen of water was then introduced, and the measurements repeated; three or four sets of measurements were usually carried out on each specimen of water, the last one (with correction for fractionation) being taken for the final result. Before a new sample of water was introduced at least 15 mins. were allowed for pumping out. A current must never be passed through the measuring wire when the space surrounding it is completely evacuated, otherwise the wire becomes overheated, the nature of its surface changes, and hence the calibration is vitiated. The calibration was carried out by using mixtures of deuterium oxide and protium oxide of known composition. The graph of deuterium concentration (0—100%) plotted against resistance was almost linear (Fig. 2).

Before carrying out an isotopic analysis on a " heavy " compound (some of which contained halogen and nitrogen), the corresponding " light " compound was combusted, and measurements were carried out on the resulting " light " water, to ensure that the result on the " heavy " compound would not be inaccurate on account of impurities in the water. The results obtained on the compounds investigated here, as well as those concerned in a following paper, agreed fairly well with those given by pure " light " water.

The accompanying table gives a typical series of results :

Substance.	Weight (mg.). Substance.	Weight (mg.). Water formed.	Resistance (ohms).	% of D.
H_2O	—	—	575·9	—
$C_{14}H_{11}ONBr_2$	15	4	575·4, 575·5	—
D_2O	—	—	—, 628·7, 629·2	—
$C_{14}H_7D_4ONBr_2$	15	4	595·2, 593·6, 593·7	38·0 − 1·2 = 36·8
H_2O	—	—	—, —, 575·9	—
$C_{13}H_8D_5N,C_4H_6O_6$	9	4	587·5, 588·1, 588·0	27·5 − 1·0 = 26·5
$C_{13}H_7D_4NBr_2,C_4H_6O_6$	15	4·5	586·0, 586·3, 586·3	23·9 − 0·65 = 23·25
H_2O	—	—	—, 575·8, 575·9	—

A full description of the apparatus and of its use is to be found in a Ph.D. Thesis by one of us (G. A. S.) in our Library.

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