

CVI.—*Studies of Dynamic Isomerism. Part IV.*
Stereoisomeric Halogen Derivatives of Camphor.

By THOMAS MARTIN LOWRY.

It has been shown (Lowry, *Trans.*, 1898, **73**, 569) that on brominating α -chlorocamphor and on chlorinating α -bromocamphor mixtures are formed of the isomorphous stereoisomerides represented by the formula

$\text{C}_8\text{H}_{14} \begin{smallmatrix} \text{C} \text{Cl Br} \\ \diagup \quad \diagdown \\ \text{CO} \end{smallmatrix}$, the isomerism depending on the asymmetry of the

α -carbon atom. Similar isomerides are also obtained by the action of halogens on nitrocamphor (*Trans.*, 1898, **73**, 986—991), but as these are not isomorphous, it is possible by repeated crystallisation to isolate each compound in a pure state.

Whilst the α -derivatives thus appear invariably to yield a mixture of isomerides (compare Forster, *Trans.*, 1902, **81**, 160), it is possible to obtain from camphor itself an almost theoretical amount of a single bromo-derivative, the well-known α -bromocamphor. Even in this case, however, it has long been supposed that two isomerides are formed initially, one of which undergoes isomeric change during the subsequent purification. Thus, Marsh, in 1891 (*Trans.*, **59**, 968), was able to separate from the initial product a fraction which differed widely from α -bromocamphor, its optical rotatory power being $[\alpha]_D + 29.4^\circ$ only, whilst that of the ordinary bromocamphor is $[\alpha]_D + 135^\circ$. Marsh found

that by distilling under atmospheric pressure the low-rotatory compound was largely converted into ordinary bromocamphor, and proposed to use this method in order to purify the crude product.

A far more effective method of purification had, however, been introduced by Armstrong in 1878 (*Chem. News*, 37, 4). This consisted in the use of alcoholic potash, and there could be no doubt that this agent served not only to remove hydrogen bromide and to reduce any dibromocamphor that might be present, but also to convert into the stable α -compound any isomeric bromocamphor which might be formed by the action of the halogen.

On account of the large proportion of α -bromocamphor obtained by Armstrong's method, it has been generally supposed that the conversion of the labile into the stable isomeride was complete and non-reversible. Kipping has, however, recently shown (*Proc.*, 1905, 21, 125) that there is in the alcoholic solution a marked reversal of the isomeric change. By working alternately in alkaline and in acid solution he was able to prepare from pure α -bromocamphor a product of low rotatory power, very similar to that described by Marsh. When alkali was added to a concentrated alcoholic solution of this substance, crystals of α -bromocamphor separated; in less concentrated solutions, the product remained dissolved and was found to have the same rotatory power, $[\alpha]_D + 122^\circ$, as that prepared directly by the action of alkali on α -bromocamphor.

The principle of the method by which solubility measurements may be applied to determine the equilibrium between dynamic isomerides has been described in two previous papers (*Trans.*, 1904, 85, 1541, 1551). In the case of the stereoisomeric bromocamphors, the application of the method is rendered exceptionally easy by the fact that isomeric change takes place only in presence of added alkali, and is therefore completely under control. The difficulty previously encountered in determining the initial solubility of the unchanged material is therefore absent, and after adding the alkali the final equilibrium is very quickly attained. The facility of the method proved to be such that the observations were extended, not only to chlorocamphor (the isomeric change of which had already been noted by Kipping), but also to several of the dihalogen derivatives of camphor; the further application of the method to the sulphonic derivatives of camphor is described in a subsequent paper.

It should be noted that whilst it is possible to determine by means of solubility measurements the approximate proportions in which the isomerides are in equilibrium in solution, and to estimate roughly the rotatory power of the α -compounds, physical methods of this kind can form no adequate substitute for the actual separation of these substances which has been undertaken by Kipping. The chief advantage of the physical methods is that they enable a rapid survey to be

made of the behaviour of a range of compounds far exceeding the number which could well be submitted to the tedious process of fractionation.

1. The substances investigated were :

α - and β -bromocamphor and α -chlorocamphor.

$\alpha\beta$ - and $\alpha\pi$ -dibromocamphor.

$\alpha\beta$ - and $\alpha\pi$ -chlorobromocamphor.

$\alpha\alpha'$ -Dibromocamphor could not be used, as its alcoholic solutions soon decomposed, becoming yellow on exposure to the air. Measurements were made, however, of a trisubstituted compound, a $\pi\alpha\alpha'$ -chlorobromonitrocaphor, $C_8H_{10}Cl\begin{smallmatrix} CBrNO_2 \\ | \\ CO \end{smallmatrix}$, obtained by the action of nitric

acid on crude $\pi\alpha$ -chlorobromocamphor. The solvent used in the majority of cases was absolute alcohol of 99.5 per cent. concentration, but observations were also made of the solubility of α -bromocamphor and α -chlorocamphor in ethyl alcohol of lower concentration and in commercial methyl alcohol. The alkali was made by dissolving sodium in the alcohol, and was added in such proportions as to give solutions of approximately known strength, usually $N/100$, $N/500$, or $N/1000$.

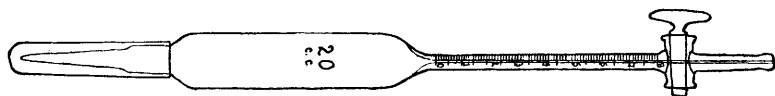
2. The saturated solutions were prepared by stirring the solid with the solvent in a large test-tube supported in a water-bath. The bath was stirred mechanically and was kept at a constant temperature by means of an automatic gas-regulator. The majority of the measurements were made within one- or two-hundredths of 20° as determined by a thermometer graduated to 0.01° , which had recently been standardised at the Reichsanstalt.* As no isomeric change took place until alkali was added, it was not necessary to secure saturation rapidly. The solid was therefore added in coarse crystals and, after stirring during one or two hours, was allowed to settle. Samples of the saturated solution were then withdrawn by means of a warm pipette and could be used immediately; as filtration was unnecessary, the chief risk of change in concentration taking place was thus avoided.

3. The solubilities were determined by evaporating weighed quantities of the saturated solutions in weighing bottles. In the case of the monohalogen compounds, considerable care was needed to avoid loss by sublimation; the solutions were gently heated on the top of an air-oven and the temperature was adjusted, so that from twelve to thirty-six hours were required for the evaporation of 10 c.c. of the alcoholic solution. In the case of the dihalogen compounds, no such trouble was experienced, but some of the sulphonic compounds referred to in the

* By using one of the spiral regulators recently described (Trans., 1905, 87, 1030), the temperature of one of the baths was maintained without readjustment between 20.00° and 20.02° whenever the bath was in use throughout the six months from September, 1905, to March, 1906.

following paper formed compact crystals, and it was necessary to heat these more strongly in order to expel the last traces of the solvent.

4. The densities were determined by means of a special form of graduated pipette (Fig. 1), the ordinary Meyerhoffer-Saunders pipette not being suited to the conditions of experiment. The pipette was heated to 20° in the thermostat and quickly lowered into the tube containing the saturated solution. The solution was drawn up into the narrow graduated stem, the tap closed, and the position of the meniscus noted. The capillary point was then wiped and covered with a glass cap to prevent evaporation during the weighing. The earlier experiments were made with a pipette of 42 c.c. capacity, provided with a thermometer: this had been designed and calibrated by Mr. W. R. Bousfield, to whom I am indebted for the loan of the instrument.



Graduated pipette for determining the density of saturated solutions.

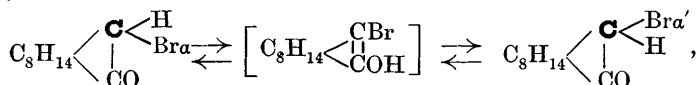
FIG. 1.

Duplicate determinations (compare β -bromocamphor) usually differed by only a few units in the fourth place of decimals; the densities shown in brackets were not measured, but were calculated with sufficient exactness by assuming that each 1 per cent. of solute increased the density of the alcohol by 0.004. The experiments described in the subsequent paper were made with pipettes of the pattern figured and had capacities of 10 and 20 c.c. only.

5. The rotatory powers of the solutions were determined by means of a polarimeter graduated to read to 0.001° by means of a vernier. This instrument, which was made to the design of the late Mr. J. W. Rodger, is provided with exceptionally large optical parts, the triple field being divided horizontally. For the loan of this I am indebted to the Board of Education, and desire to express my indebtedness to Prof. Tilden, through whom permission was obtained to use the instrument. The polariser and analyser are mounted on separate bases, an important point when jacketed tubes are used, and are supported on a teak base provided with V-grooves. The temperature of the 2-dcm. tubes is maintained at 20° by enclosing them in a hollow copper jacket through which water is circulated from a large thermostat. The circulation is maintained by an eccentric pump driven by an electromotor, the speed of which can be varied by lamp resistances.

Solute.	Solvent.	Alkali.	Density of saturated solutions.	Concentration of saturated solutions.						Rotatory power of saturated solutions.								
				Grams per 100 grams of solvent.			Grams per 100 c.c. of solution.			α_D (2-dcm. tube).			$[\alpha]_D$.					
				α .	$\alpha \rightleftharpoons \alpha'$.	Ratio.	α .	$\alpha \rightleftharpoons \alpha'$.	Ratio.	α .	$\alpha \rightleftharpoons \alpha'$.	Ratio.	α .	$\alpha \rightleftharpoons \alpha'$.	Ratio.	α .	$\alpha \rightleftharpoons \alpha'$.	Ratio.
Per cent.																		
α -Bromocamphor	EtOH	N/1000	0.8536	0.8618	21.1	23.7	0.89	14.9	16.5	0.90	41.0	41.6	+138	+126	< +18			
"	EtOH	N/100	0.854	0.863	20.5	23.3	0.88	14.5	16.3	0.89	40.5	40.8	+139	+125	< +9			
"	EtOH	N/1000			20.2	23.1	0.87	—	—	—	—	—	—	—	—			
"	EtOH	N/1000	0.855	0.862	18.8	21.5	0.88	—	—	—	—	—	—	—	—			
"	MeOH (comm.)	N/100	0.860	0.868	23.2	25.9	0.89	16.2	17.8	0.91	42.7	43.1	+132	+121	< +12			
β -Bromocamphor	EtOH	N/1000	0.8506	0.8503	19.5	19.3	1.01	13.8	—	—	5.30	5.32	+19	—	—			
α -Chlorocamphor	EtOH	N/100	0.825	0.830	15.9	18.2	0.87	11.3	12.8	0.885	22.65	23.6	+100	+92	< +34			
"	EtOH	N/100	0.830	0.835	17.5	20.1	0.87	12.3	13.9	0.884	23.9	24.75	+97	+89	< +27			
"	MeOH (comm.)	N/1000	0.805	0.807	3.18	3.58	0.89	2.48	2.79	0.89	4.92	4.54	+99	+81	-61			
$\alpha\beta$ -Dibromocamphor	EtOH	N/1000	—	—	3.26	3.64	0.90	2.54	2.83	0.90	4.93	4.59	+97	+81	-58			
"	EtOH	N/1000	—	—	4.00	4.42	0.90	3.22	3.57	0.90	4.22	3.98	+65	+55	-34			
$\alpha\beta$ -Chlorobromocamphor	EtOH	N/500	0.805	0.807	4.00	4.42	0.90	3.22	3.57	0.90	4.22	3.98	+65	+55	-34			
$\alpha\pi$ -Dibromocamphor	EtOH	N/1000	[0.799]	[0.800]	2.09	2.35	0.89	1.64	1.83	0.89	3.22	3.62	+98	+99	+105			
$\alpha\pi$ -Chlorobromocamphor	EtOH	N/1000	[0.804]	[0.806]	3.20	3.65	0.88	2.49	2.84	0.88	4.24	5.10	+85	+90	+123			
$\pi\alpha\alpha'$ -Chlorobromonitro-camphor	EtOH	N/1000	0.801	0.801	2.61	2.61	1.00	2.04	2.04	1.00	5.00	5.01	+121	—	—			

The table shows the numerical values obtained. It will be noticed that in the case of all compounds containing the group $-\text{CHBr}\cdot\text{CO}-$ or $-\text{CHCl}\cdot\text{CO}-$ the addition of a mere trace of alkali is followed by a marked increase in the density and concentration of the saturated solutions, the ratio of the initial to the final solubility remaining almost constant at 0.88 to 0.90 throughout the series. No change of solubility occurred in the case of β -bromocamphor, $\text{C}_8\text{H}_{13}\text{Br} \begin{smallmatrix} \text{CH}_2 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{CO} \end{smallmatrix}$, in which both α -positions are occupied by hydrogen, nor in the case of $\pi\alpha\alpha'$ -chlorobromonitrocamphor, $\text{C}_8\text{H}_{13}\text{Cl} \begin{smallmatrix} \text{CBr}\cdot\text{NO}_2 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{CO} \end{smallmatrix}$, in which both these hydrogen atoms have been displaced. It is thus evident that, although isomeric change probably takes place through an intermediate enolic form,



the increase of solubility must be attributed mainly to the interchange of the radicles occupying the α and α' positions. The case is somewhat analogous to that of glucose, mannose, and fructose studied by Lobry de Bruyn (*Rec. trav. chim.*, 1895, 14, 201); in each case the isomerides have a common enolic form, but the proportion of this in the neutral solutions is so small that no isomeric change takes place until alkali is added.

Proportions in which the Isomerides are in Equilibrium in Solution.—In order to deduce from the solubility measurements the proportions of the isomerides in the alkaline solutions, it was necessary to ascertain whether the α' -form would be likely to influence the solubility of the α -isomeride. Direct experiments were not practicable, but the following observations were made to test this point.

1. The solubility of $\alpha\beta$ -dibromocamphor was determined (*a*) in alcohol, (*b*) in alcohol containing 0.50 gram of $\alpha\pi$ -dibromocamphor per 100 grams of alcohol. The total amount of solid per 100 grams of alcohol in the two saturated solutions was found to be :

(a) 3.24	3.27		Mean, 3.26 per cent.
(b) 3.76	3.75	3.76	Mean, 3.76 „

Difference 0.50 per cent.

The solubility of $\alpha\beta$ -dibromocamphor is thus not affected by the addition of 0.5 per cent. of the $\alpha\pi$ -isomeride, and it is probable that the presence of 0.4 per cent. of the $\alpha'\beta$ -isomeride would have equally little effect. In the case of the sparingly soluble dihalogen compounds

the solubility measurements can therefore be directly applied to determine the proportions of the isomerides in the solutions. These are practically uniform throughout the series, the amount of the α -form being 89 per cent. of the total matter in solution, and the ratio $\alpha : \alpha' = 8 : 1$ approximately.

2. The solubility of α -bromocamphor was determined (*a*) in alcohol, (*b*) in alcohol in which 2 per cent. of the β -isomeride had been dissolved. The total amounts of dissolved solid per 100 grams of alcohol were found to be :

(<i>a</i>)	21.18	21.09	21.15	Mean, 21.14 per cent.
(<i>b</i>)	24.21	24.19	24.25	Mean, 24.22 „

Ratio = 0.873. Difference = 3.08 per cent.

The densities at $20^{\circ}/4^{\circ}$ were 0.8536 and 0.8616 and the volume concentrations 14.89 and 16.78 grams per 100 c.c.; ratio, 0.888. The actual proportion of the α -compound in the artificial mixture, 0.917, is higher than either of the above ratios, the solubility being increased by the presence of the isomeride. In the case of the mixture formed by the action of alkali on α -bromocamphor the percentage by weight increases in the ratio 0.88 : 1, the percentage by volume in the ratio 0.90 : 1; the proportion of the α -compound is therefore probably 0.93, and the ratio $\alpha : \alpha' = 13 : 1$ approximately.

No direct measurements were made with reference to the influence of an isomeride on the solubility of α -chlorocamphor, but the solubility-ratios, 0.87 by weight and 0.89 by volume, probably correspond to about 91 per cent. of the α -compound in the solution.

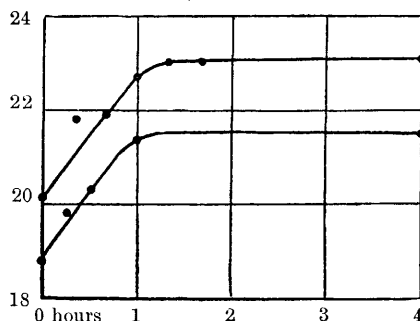
Whilst these values are probably correct within 1—2 per cent., the high solubility of α -bromocamphor and α -chlorocamphor places them beyond the limits within which it was originally proposed to apply the solubility method to determine the proportions of dynamic isomerides in solution.

Rotatory Power of the Isomerides.—On referring to the table, it will be seen that the increased concentration which follows the addition of alkali is usually accompanied by an increase in the rotatory power, α_D , of the saturated solution. In the case of $\alpha\beta$ -dibromocamphor and $\alpha\beta$ -chlorobromocamphor, the rotatory power decreases and the products of change are evidently levorotatory. In other cases the products, although dextrorotatory, must as a rule be less active than the original material, since the specific rotatory power, $[\alpha]_D$, of the $\alpha \rightleftharpoons \alpha'$ mixture is less than that of the α -compound. Exceptions are found in the case of $\alpha\pi$ -dibromocamphor and $\alpha\pi$ -chlorobromocamphor, which show a slight increase of specific rotatory power on the addition of alkali.

These exceptions afford an illustration of the fallacy underlying the

"Principle of Optical Superposition," to which attention has been directed by Rosanoff (*J. Amer. Chem. Soc.*, 1906, 28, 525). If this principle were valid, the change of rotatory power following from a reversal of the asymmetry of the α -carbon atom should be independent of the configuration of the rest of the molecule, and could not possibly be opposite in sign in compounds so closely related as the β - and π -bromocamphors. Such irregularities can, however, be understood if it be recognised that a change in the balancing of a single carbon atom may, and indeed must, disturb the balance of the whole molecule and affect every centre of asymmetry. Until much more information is available, it will evidently not be possible to make any important generalisation as to the rotatory power of compounds containing

FIG. 2.—Solubility of α -bromocamphor in alcohol with N/1000 sodium ethoxide.



several centres of asymmetry, especially when these are connected together in a complex ring system as in the case of camphor and the cyclic terpenes.

Whilst the rotatory powers of the solutions give a rough idea of the optical properties of the α' -compounds, accurate values cannot be deduced on account of the small concentrations of these compounds and the presence of a large excess of the α -isomerides. In the case of the monohalogen derivatives, it must further be recognised that the increased concentration which follows the addition of alkali is not wholly due to the formation of the α' -compound, since an additional quantity of the α -compound also passes into solution. If a correction be made for this, it appears probable that α' -bromocamphor is laevorotatory and α' -chlorocamphor only feebly dextro-rotatory; the uncorrected figures given in the table are maximum values only.

Velocity of Isomeric Change.

Two experiments in which alkali was added to the extent of $N/100$ showed that equilibrium was already attained in an alcoholic solution of bromocamphor at the end of 0.6 and 0.7 hour. When the quantity of alkali was reduced to $N/1000$, regular curves were obtained which showed a gradual increase of solubility during the first hour, after which the solubility remained constant. The curves shown represent two series of experiments with alcohol of 98.7 and 97 per cent. concentration, and indicate that the rate of change is not increased by doubling the proportion of water in the alcohol. When the quantity of alkali was further reduced to $N/10,000$, the change became exceedingly slow, and it is probable that the alkali becomes used up either in reducing the bromocamphor or in neutralising traces of acid formed in the solution.

$\pi\alpha\alpha'$ -Chlorobromonitrocamphor.—This compound, prepared by the action of nitric acid on the crude chlorobromocamphor produced by heating α -bromocamphor- π -sulphochloride, is, like the chlorobromocamphor itself, contaminated with a certain amount of the isomorphous dibromocamphor (0.2352 gave 0.2565 AgCl + AgBr; Cl + Br = 38.0. $C_{10}H_{13}O_3NClBr$ requires Cl + Br = 37.2 per cent.). The mixture behaved in almost every respect like a pure substance, melted sharply at 138° , showed a constant solubility in alcohol, and crystallised magnificently.

Measurable crystals were obtained from a solution in acetone which was allowed to cool slowly to the atmospheric temperature. They belonged to the orthorhombic system and gave the following constants:

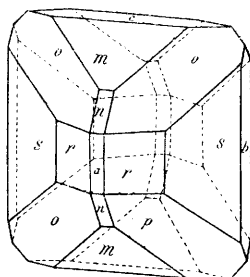


FIG. 3.

Forms present : $a\{100\}$, $b\{010\}$, $c\{001\}$, $o\{111\}$,
 $n\{101\}$, $m\{102\}$, $r\{110\}$, $s\{120\}$;

n , b , and c were only occasionally observed.

Axial ratios : $a:b:c = 0.889:1:1.049$.

Angles measured :

<i>ar</i> 100 : 110	(27)	41°39'	—	<i>nm</i> 101 : 102	(4)	19°20'	(19°11')
<i>rs</i> 110 : 120	(30)	18°57'	(19°0')	<i>ro</i> 110 : 111	(36)	32°21'	—
<i>ss</i> 120 : 120	(15)	58°48'	(58°42')	<i>co</i> 001 : 111	(20)	57°40'	(57°39')
<i>am</i> 100 : 102	(13)	59°34'	(59°28')	<i>mo</i> 102 : 111	(6)	38°40'	(38°35')
<i>cm</i> 001 : 102	(11)	30°27'	(30°32')	<i>os</i> 111 : 120	(6)	36°53'	(36°59')
<i>an</i> 100 : 101	(3)	40°13'	(40°17')	<i>sm</i> 120 : 102	(6)	104°15'	(104°25')

Summary.—(1) The method previously employed in the case of nitrocamphor and the sugars to determine the proportions in which the dynamic isomerides are in equilibrium in solution has been applied to the halogen derivatives of camphor, which have been shown by Kipping to undergo reversible isomeric change in presence of alkalis.

(2) In the case of each compound containing the group $-\text{CHBr}\cdot\text{CO}-$ or $-\text{CHCl}\cdot\text{CO}-$, the addition of alkali is followed by an increase in the concentration of the saturated solution in the ratio 0.89 : 1 approximately.

(3) The proportion of the α' -form is probably about 7 per cent. in the case of bromocamphor, 9 per cent. in the case of chlorocamphor, and 11 per cent. in the case of the $\alpha\beta$ - and $\alpha\pi$ -dihalogen compounds.

(4) No increase of solubility is observed in the case of β -bromocamphor or of the $\alpha\alpha'$ -derivatives.

(5) Approximate values are given for the rotatory powers of the α' -compounds. α' -Bromocamphor is probably levorotatory, and α' -chlorocamphor only feebly dextrorotatory.

A part of the expense incurred in the inquiry described in this and the following paper was defrayed by grants from the Research Fund of the Chemical Society and from the British Association. The author wishes to take this opportunity of expressing his indebtedness for the help thus afforded.

WESTMINSTER TRAINING COLLEGE,
LONDON, S.W.