The Optically Active Hexahydrohomophthalic Acids and their Anhydrides

ENDRE BERNER and OTTO STEFFENSEN

Universitetets Kjemiske Institutt, Blindern, Oslo, Norway

The two stereoisomeric hexahydrohomophthalic acids, *trans* m.p. 161° and *cis* m.p. 147°, which were prepared by catalytic hydrogenation of homophthalic acid as described by Windaus, Hückel and Reverey [1], have now been resolved into optically active components by fractional crystallization of the brucine salts. The components of the *trans*-acid had m.p. 116° and a specific rotation of ± 40.0°, while those of the *cis*-acid had m.p. 82° and a rotation of ± 12.5°. By treatment with acetic anhydride the active acids were easily transformed into the corresponding anhydrides without any racemization taking place. The sign of the rotation changed, however, during this process, a dextrorotatory acid giving a levorotatory anhydride and vice versa. The active anhydrides of the *trans*-acid had m.p. 111° and a specific rotation of ± 71.5°, and those of the *cis*-acid m.p. 88° and a rotation of about ± 30°.

Stereochemically the anhydrides of the hexahydrohomophthalic acids can be compared with the isomeric decalins. It should, however, be kept in mind that the six-membered anhydride ring contains two carbonyl groups and one oxygen atom instead of methylene groups as in a cyclohexane ring, and consequently the valency angles at these points will deviate somewhat from the tetrahedral angle. This will obviously result in a certain flattening of the heterocyclic ring, but as a whole it should be justifiable to assume that the molecules of the anhydrides and those of the decalins are similar in shape. In the following some simplified models will demonstrate the possible steric forms of the hexahydrohomophthalic acids and their anhydrides. Only one of the active components is considered in each case. In the models of the acids a small circle indicates a carboxyl group and a greater circle the group $CH_2 \cdot COOH$.

Hassel [2] has shown that the cyclohexane itself and its derivatives generally exist in the centrosymmetrical, so-called "staircase", model. Using his notations ε and $\varkappa$ for the two types of bonds at the ring carbon atoms the substituents in the case of *trans*-hexahydrohomophthalic acid will be either $\varepsilon\varepsilon$ or $\varkappa\varkappa$ as shown in the models T_1 and T_2 in Fig. 1. The one model may be converted into the other in this way that the three ring carbon atoms in the upper plane

move downwards and the three in the lower plane move upwards. The two models are not enanthiomorphic and no racemization would therefore follow an interconversion.
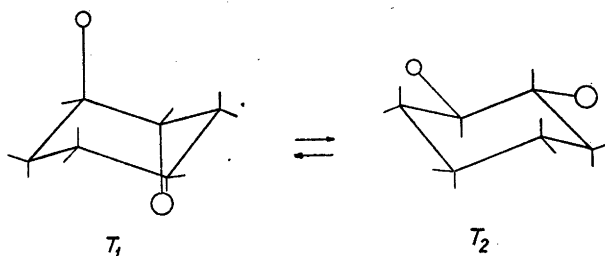

Fig. 1. Models of trans-hexahydrohomophthalic acid

No investigation has as yet been carried out in order to show if any of the two models is predominating. Neither can theoretical considerations give any certain indication of the one model being more stable than the other. Actually the distance between the two substituents in T_1 (about 3.9 Å) is 1.3 times as great as that in T_2 and for that reason T_1 might be more stable than T_2. (The figure given refers to the distance between the carbon atoms bound directly to the ring.) On the other hand the substituents in T_1 will be relatively near (2.5 Å) to two ε-hydrogen atoms, while the substituents in T_2 will have only one of the ring carbon atoms at the same short distance. The van der Waals forces arising at such a distance will certainly cause some deformation of the molecule, but it would not be safe to predict their influence on the interconversion of the two models. The only conclusion we can draw at the present time is that trans-hexahydrohomophthalic acid probably consists of an equilibrium between the models T_1 and T_2.

Turning now to the anhydride of trans-hexahydrohomophthalic acid it is evident that it stereochemically must be derived from model T_2 as shown in Fig. 2. Consequently, if any part of the acid is present as model T_1 it must pass over to T_2 before it can form the anhydride. As in the case of trans-decalin the model in Fig. 2 is locked and no conversion can take place.
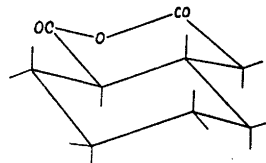

Fig. 2. Model of trans-hexahydrohomophthalic anhydride

In cis-hexahydrohomophthalic acid one substituent will be ε and the other $\varkappa$ and accordingly there will be the two interconvertible models C_1 and C_2 as shown in Fig. 3. The models are again not enanthiomorphic and no racemization would accompany a conversion. The distance between the substituents is

the same in both models as are also the other main intramolecular distances. The acid is therefore probably a mixture of approximately equal parts of the models C_1 and C_2.
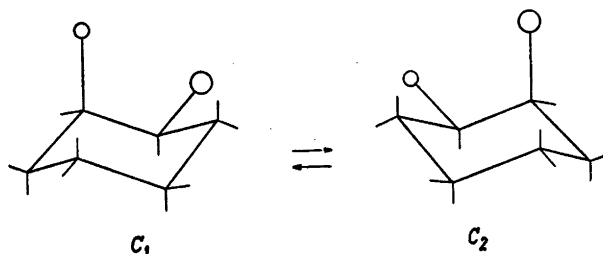

Fig. 3. Models of cis-hexahydrohomophthalic acid

The model of the anhydride of the *cis*-acid may be derived either from C_1 or C_2 giving thus the interconvertible models A_1 and A_2 respectively (Fig. 4). In A_2 one of the hydrogen atoms of the methylene group in the heterocyclic ring (marked with a cross) will come very near to the two ε-hydrogen atoms in the cyclohexane ring, also marked with a cross. This will not be the case in A_1 in which both hydrogen atoms of the methylene group in question are pointing away from the cyclohexane ring. Model A_1 is therefore most probably the dominating form of the *cis*-anhydride molecule.
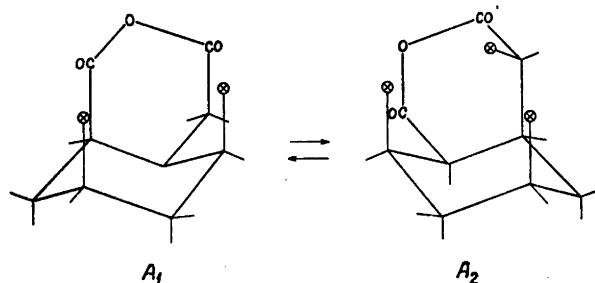

Fig. 4. Models of cis-hexahydrohomophthalic anhydride

EXPERIMENTAL PART

Preparation of the hexahydrohomophthalic acids

By the hydrogenation of homophthalic acid according to Windaus, Hückel and Reverey [1] a mixture of *cis*- and *trans*-hexahydrohomophthalic acids was obtained. After decoloration by boiling an aqueous solution with charcoal the acid-mixture melted from 120° to 140°. The separation of the two acids by fractional crystallization from water is a tedious process as there is only a small difference in the solubility of the isomers. For the isolation of the *cis*-acid it was found advantageous to proceed in the following way. The finely powdered acid mixture was heated 4—5 times with warm carbon tetrachloride stirring vigorously and filtering the still warm solution after each treatment. In this way most of the *trans*-acid dissolved and a *cis*-acid with m.p. 145° remained undissolved. For

further purification the acid was recrystallized twice from water when the m.p. rose to 147°. A renewed crystallization did not change the m.p. and on evaporation of the mother liquor an acid with the same m.p. resulted

$C_9H_{14}O_4$ (186.2)   Calc.   C 58.05   H 7.58
                                 Found   » 58.17   » 8.00

The isolation of the *trans*-acid was carried out as described by the authors mentioned above, *viz.* after most of the *cis*-acid in the mixture had been converted into the *trans*-acid by heating with concentrated hydrochloric acid. After recrystallization several times from water the *trans*-acid melted at 161° and did not change its m.p. on a renewed crystallization. Windaus, Hückel and Reverey found m.p. 146° and 157° for the *cis*- and the *trans*-acid respectively.

Resolution of *cis*-hexahydrohomophthalic acid

To a solution of the *cis*-acid (9 g) in warm water (200 ml) 45 g of brucine (2 mole alkaloid to 1 mole acid) were added in portions. It was necessary to keep the solution warm and to stir continuously in order to dissolve the alkaloid. One should, however, be careful not to heat too long as the solution then would darken and the subsequent crystallization of the salt be impeded. Generally the crystallization of the brucine salt took place over night especially on keeping the solution at a cool place. The salt was recrystallized 3—4 times from water, the purified salt dissolved in hydrochloric acid and the *cis*-acid extracted with ether. From the dried ethereal solution a residue was obtained which partly crystallized and obviously consisted of a mixture of active and racemic acid. Great difficulties were encountered in obtaining the active acid in the crystalline state. After decolorizing the crude acid with charcoal crystallizations from water gave fractions of practically inactive acid, the active acid being enriched in the mother liquor. From the latter the active acid was obtained as a thick syrup the crystallization of which in the end was achieved in the following way. The syrup was placed at the bottom of a low glass dish and covered with a layer of water. Placing the dish at zero degree for several days big clear crystals of the pure dextrorotatory *cis*-acid separated which after washing and drying had m.p. 82°.

$C_9H_{14}O_4$ (186.2)   Calc.   C 58.05   H 7.58
                                 Found   » 57.76   » 7.53

The levorotatory *cis*-acid was isolated from the easily soluble brucine salt in the same way as described for the dextrorotatory acid, even greater difficulties being met with, however, in obtaining the pure (—)-acid which also had m.p. 82°.

The specific rotations of the optical components at various concentrations in dioxan are given in Table 1. The concentration c is g acid in 100 ml solution; all measurements taken in a 1 dm tube. The specific gravity at various concentrations was determined on solutions of the racemic acid and could be expressed sufficient accurately by means of the linear equation.

$$d_4^{20} = 1.035 + c \cdot 0.00168.$$

Table 1. *Specific rotations of the cis-acids in dioxan.*

	(+)-*cis*-acid				(—)-*cis*-acid		
c	d_4^{20}	a_D^{20}	$[a]_D^{20}$	c	d_4^{20}	a_D^{20}	$[a]_D^{20}$
4.80	1.043	+0.60°	+12.0°	3.42	1.041	—0.39°	—11.0
9.49	1.051	1.25	12.5	5.48	1.044	0.67	11.6
12.33	1.056	1.62	12.5	10.29	1.052	1.31	12.1
14.35	1.059	1.95	12.8	14.57	1.059	1.93	12.5
19.89	1.068	2.65	12.5	23.41	1.074	3.28	13.0
26.70	1.080	3.84	13.3				

The melting point curve obtained for mixtures of the inactive *cis*-acid with its levorotatory component (see Fig. 5) shows that the inactive acid is a true racemic form.
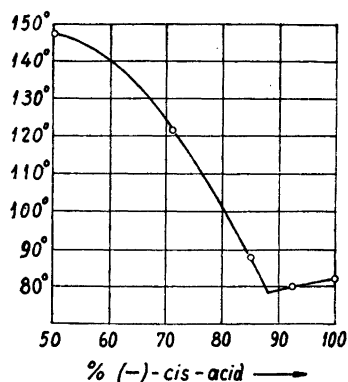
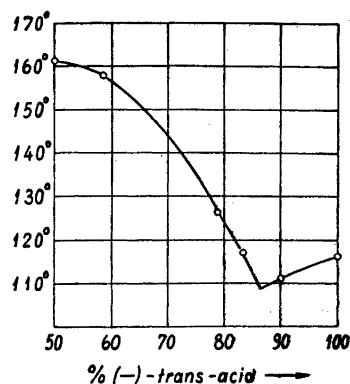Fig. 5. Mixtures of inactive and leverota-
tory cis-acids

Fig. 6. Mixtures of inactive and levorota-
tory trans-acids.

Resolution of *trans*-hexahydrohomophthalic acid

The resolution of the *trans*-acid met with no difficulties especially because the active components crystallized very easily. The neutral brucine salt was used also in this case. After recrystallizing the first fraction of the brucine salt 3—4 times from water a crude dextrorotatory *trans*-acid was isolated in the usual way. Although the active acid was more soluble than the inactive it was easily obtained in a pure state by repeated crystallizations from water. It formed big clear crystals with m.p. 116°. The leverotatory *trans*-acid, isolated in a similar way from the easily soluble brucine salt, formed the same kind of clear crystals with n.p. 116°. The rotation of the two components will be found in Table 2.

Table 2. Specific rotations of the trans-acids in dioxan.

	(+)-*trans*-acid				(−)-*trans*-acid		
c	d_4^{20}	a_D^{20}	$[a]_D^{20}$	c	d_4^{20}	a_D^{20}	$[a]_D^{20}$
5.11	1.044	+2.14°	+40.2°	4.95	1.044	−2.07°	−40.1°
9.42	1.051	3.98	40.2	9.50	1.051	4.02	40.1
14.86	1.060	6.22	40.0	18.42	1.066	7.84	39.9
31.85	1.092	13.86	39.9	30.14	1.086	13.14	40.2

The melting point curve for mixtures of active and inactive *trans*-acids again shows that the inactive acid is a true racemic form; see Fig. 6.

Anhydrides of the active *cis*-hexahydro-homophthalic acids

On boiling a solution of an active component of the *cis*-acid in acetic anhydride the acid was transformed into the corresponding acid anhydride. For isolation of the anhydride the solution was simply evaporated at room temperature when the anhydride

crystallized. Both the active anhydrides had m.p. 88°. The anhydride prepared from the levorotatory acid was dextrorotatory.

$C_9H_{12}O_3$ (168.2)   Calc.   C 64.27   H 7.19
                       Found   » 63.96, 64.12   » 7.16, 7.22

The optical rotation of the two *cis*-anhydrides will be found in Table 3.

Table 3. Specific rotations of the cis-anhydrides in dioxan.

	(+)-*cis*-anhydride				(−)-*cis*-anhydride		
c	d_4^{20}	a_D^{20}	$[a]_D^{20}$	c	d_4^{20}	a_D^{20}	$[a]_D^{90}$
10.50	1.051	+3.35°	+30.3°	9.40	1.051	−2.98°	−30.2°
15.10	1.060	4.90	30.6	18.60	1.066	6.06	30.5

The active *cis*-anhydrides could be distilled in a vacuum without any racemization taking place, the specific rotation being the same after as before the distillation. When (+)-*cis*-anhydride was boiled with water it was transformed into the same levorotatory acid from which it had been prepared, the specific rotation of the recovered acid being −12.5° ($c = 11.4$ in dioxan) and the m.p. 82°.

Anhydrides of the active *trans*-hexahydro-homophthalic acids

Both the active components of the *trans*-acid were transformed into the corresponding anhydrides in the same way as described for the *cis*-acids. Also in this case the sign of the rotation changed on formation of an anhydride. The *trans*-anhydrides were crystalline with m.p. 111°. Their optical rotations are given in Table 4.

Table 4. Specific rotations of the trans-anhydrides in dioxan.

	(+)-*trans*-anhydride				(−)-*trans*-anhydride		
c	d_4^{20}	a_D^{20}	$[a]_D^{20}$	c	d_4^{20}	a_D^{20}	$[a]_D^{20}$
4.56	1.043	+3.40°	+71.5°	10.93	1.053	−8.30°	−72.1°
10.54	1.053	7.90	71.5				

As in the case of the *cis*-anhydrides distillation in a vacuum did not cause any racemization. On boiling (−)-*trans*-anhydride with water an acid was obtained which had the specific rotation +40.2° ($c = 11.3$ in dioxan) and the m.p. 116°.

SUMMARY

The *cis*- and *trans*-forms of hexahydrohomophthalic acid were resolved into optically active components by means of brucine. The active acids could easily be transformed into the corresponding active anhydrides by treatment

with acetic anhydride. By this process the sign of the rotation changed as well in the case of the *cis*-acid as in that of the *trans*-acid but no racemization took place. Both the inactive hexahydrohomophthalic acids were found to be true racemic forms.

REFERENCES

1. Windaus, A., Hückel, W., and Reverey, G. *Ber.* **56** (1923) 92.
2. Hassel, O. *Research* **3** (1950) 504.