169–171°, $[\alpha]^{25}\mathrm{D}$ +46° (dioxane)) in benzene. The yellow precipitate which formed overnight was dissolved in a minimum quantity of water. Addition of concd. aqueous potassium hydroxide precipitated an oil which solidified, m.p. 167–170° dec. The solid was dissolved in acetone and the mixture was filtered. The filtrate was evaporated to give product (0.10 g.), m.p. 168–169° dec., $[\alpha]^{25}{}_{546}$ −800°, $[\alpha]^{25}{}_{578}$ −637°, $[\alpha]^{28}\mathrm{D}$ −527° (*c* 1.0, ethanol).

*Anal.* Calcd. for $C_{19}H_{20}BrN_3O_4$: Br, 18.4; N, 9.7. Found: Br, 18.0; N, 9.0.

**(−)-2,7-Dihydro-4′,1″-dichloro-3,4,5,6-dibenzazepinium-1-spiropiperidinium bromide (X)** was prepared from (+)-6,6′-dichloro-2,2′-bis-(bromomethyl)-biphenyl[3] (0.16 g., m.p. 70–71°, $[\alpha]^{29}\mathrm{D}$ +77° (benzene)) and piperidine in the manner described for the synthesis of the 4′,1″-dinitro analog. Recrystallization from acetone afforded 0.08 g. of product, m.p. 297–298.5° dec., $[\alpha]^{27}{}_{546}$ −84°, $[\alpha]^{27}{}_{578}$ −84°, $[\alpha]^{27}\mathrm{D}$ −83° (*c* 1.2, ethanol).

*Anal.* Calcd. for $C_{19}H_{20}BrCl_2N$: Cl, 17.2; N, 3.4. Found: Cl, 16.7; N, 3.4.

**(−)-Methyl 6,6′-dichloro-2,2′-diphenate** was prepared by reaction of (−)-6,6′-dichloro-2,2′-diphenic acid[27] (m.p. 261–262.5°, $[\alpha]^{29}\mathrm{D}$ −7.2 (methanol)) with ethereal diazomethane in the usual manner. The product, after recrystallization from ethanol, had m.p. 104–105.5°, $[\alpha]^{27}\mathrm{D}$ −5.8 (*c* 1.0, methanol), $[\alpha]^{27}\mathrm{D}$ −11.5° (*c* 1.0, ethyl acetate).

*Anal.* Calcd. for $C_{16}H_{12}Cl_2O_4$: C, 56.7; H, 3.6. Found: C, 56.4; H, 3.5.

**(−)-Methyl 1,1′-binaphthalene-2,2′-dicarboxylate** was prepared by reaction of (−)-1,1′-binaphthalene-2,2′-dicarboxylic acid[16] (m.p. *ca.* 135° dec., $[\alpha]^{22}{}_{546}$ −123° (0.1 *N* NaOH)) with ethereal diazomethane in the usual manner. The product, after recrystallization from ethanol, had m.p. 154–155°, $[\alpha]^{29}\mathrm{D}$ −18° (*c* 1.2, methanol), $[\alpha]^{27}\mathrm{D}$ −27° (*c* 1.4, ethyl acetate).

*Anal.* Calcd. for $C_{24}H_{18}O_4$: C, 77.8; H, 4.9. Found: C, 77.9; H, 4.7.

**(+)-2,2′-Dimethyl-1,1′-binaphthyl.**—A mixture of 0.23 g. of (−)-2,2′-bis-(bromomethyl)-1,1′-binaphthyl[16] (m.p. 183.5–185.5°, $[\alpha]^{29}{}_{546}$ −200° (*c* 0.90, benzene)), 0.6 g. of lithium aluminum hydride and 45 ml. of ether was refluxed for one hour. The product, isolated in the usual way and recrystallized from a minimum quantity of ethanol, had m.p. 64–67°, $[\alpha]^{22}\mathrm{D}$ +19° (*c* 1.3, ethanol).

*Anal.* Calcd. for $C_{22}H_{18}$: C, 93.6; H, 6.4. Found: C, 93.2; H, 6.4.

**Acknowledgment.**—We wish to express our appreciation to Professor J. G. Kirkwood of Yale University for his helpful discussions and advice.

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[CONTRIBUTION FROM THE WM. H. NICHOLS CHEMICAL LABORATORY, NEW YORK UNIVERSITY]

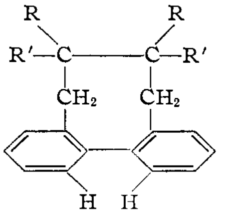
# Stereochemistry of the 1,2,3,4-Dibenz-1,3-cyclooöctadiene System[1]

BY LEO V. DVORKEN, R. BRUCE SMYTH AND KURT MISLOW[2]

RECEIVED JULY 1, 1957

The diastereomeric 1,2,3,4-dibenz-1,3-cyclooöctadiene-6,7-dicarboxylic acids (α- and β-forms) have been prepared, resolved and identified as *trans* and *cis* stereomers by the fact that the enantiomeric forms of the former mutarotate while those of the latter racemize. The conformation of the bridge system has features closely resembling those of cyclohexane, the racemization of the *cis* compound corresponding to an interconversion of *aa*- and *ee*-isomers, and the mutarotation to an interconversion of *aa*- and *ee*-isomers. Rate constants of racemization and mutarotation in neutral and basic solvents have been determined; the *cis* isomer racemizes with $\Delta F^{\ddagger}$ 23 kcal./mole.

In connection with our work on the absolute configuration of hindered biphenyls, with particular reference to some members of the series containing substituents bridging the 2,2′-positions (preceding papers),[1] we had occasion to enquire into the resolvability of 1,2,3,4-dibenz-1,3-cyclooöctadiene (Ia) or suitable derivatives.



I

Ia, R = R′ = H
b, R = R′ = $COOC_2H_5$
c, R = R′ = COOH
d, R = R′ = $COOCH_2C_6H_5$
e, R = H, R′ = COOH
f, R = H, R′ = $COOCH_3$

Optical resolutions have been reported for several biphenyls possessing 2,2′-bridges and no 6,6′-substituents other than hydrogen.[3] Judged[4] by the hypsochromic shift and attenuated extinction of the biphenyl maximum (K-band, configuration band) in Ia, Ib and If, the system of Ia and derivatives should be resolvable.[5]

Solution of the problem by optical activation of a suitable derivative of Ia not containing additional elements of dissymmetry resulted in failure: (a) no solid complex of Ib and TAPA[6] could be realized; (b) the 2′,3″-diamino derivative of Ib (IIb), prepared by the route IIIa → IIIb[7] → IIIc → IIa → IIb

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(1) Configurational Studies in the Biphenyl Series. V. Part IV, preceding paper.

(2) To whom correspondence regarding the article should be addressed.

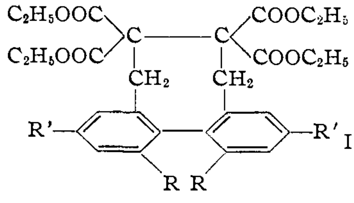
(3) (a) F. Bell, *J. Chem. Soc.*, 1527 (1952); (b) I. G. M. Campbell and R. C. Poller, *ibid.*, 1195 (1956), and preceding papers; (c) D. C. Iffland and H. Siegel, *J. Org. Chem.*, **21**, 1056 (1956); (d) W. E. Truce and D. D. Emrick, THIS JOURNAL, **78**, 6130 (1956); (e) F. McCullough, Jr., and J. C. Bailar, Jr., *ibid.*, **78**, 714 (1956).

(4) For a summary of work relating absorption in the ultraviolet to hindered rotation, *cf.* E. A. Braude and E. S. Waight, in Klyne, "Progress in Stereochemistry," Academic Press, Inc., New York, N. Y., 1954, pp. 136 ff.; and ref. 3d.

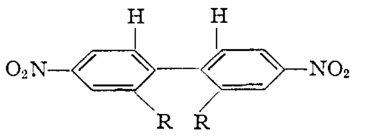
(5) (a) G. H. Beaven, G. R. Bird, D. M. Hall, E. A. Johnson, J. E. Ladbury, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.*, 2708 (1955); (b) A. C. Cope and R. D. Smith, THIS JOURNAL, **78**, 1012 (1956). An interplanar angle of 59° has been calculated (G. H. Beaven and D. M. Hall, *J. Chem. Soc.*, 4637 (1956)) for Ib and If; from the values given in (b) above and using the relationship $\cos^2\theta = \epsilon/\epsilon_0$ (E. A. Braude and W. F. Forbes, *J. Chem. Soc.*, 3776 (1955)), an interplanar angle of 44° is calculated for Ia. The average interplanar angle and the K-band shift might be considered measures, to a first approximation, of the free energy of racemization of simple bridged biphenyls.

(6) M. S. Newman and W. B. Lutz, THIS JOURNAL, **78**, 2469 (1956). A sample was kindly supplied us by Prof. Newman.

(7) This compound was prepared through the use of $CaCl_2$–$NaBH_4$ (J. Kollonitsch, P. Fuchs and V. Gábor, *Nature*, **173**, 125 (1954); **175**, 346 (1955)), which also proved a satisfactory reagent for the reduction of methyl 6,6′-dinitro-2,2′-diphenate to 6,6′-dinitro-2,2′-bis-(hydroxymethyl)-biphenyl, previously obtained by reduction with $LiAlH_4$–$AlCl_3$ (P. Newman, P. Rutkin and K. Mislow, THIS JOURNAL, **80**, 465 (1958)).



IIa, R = H, R' = $NO_2$
b, R = H, R' = $NH_2$
c, R = $NO_2$, R' = H



IIIa, R = $COOCH_3$
b, R = $CH_2OH$
c, R = $CH_2Br$

was obtained as a glass which could not be induced to crystallize and whose camphor-7-sulfonate did not exhibit mutarotation; (c) basic hydrolysis of Ib to give Ic under mild conditions was unsuccessful[8] and under vigorous conditions resulted in decarboxylation to Ie[9]; (d) an attempt to prepare Ic by hydrogenolysis of Id yielded a partly decarboxylated glass despite the mildness of the conditions employed, and (e) an attempt to prepare optically active IIb by reduction, followed by deamination, of IIc[10] foundered on our inability to prepare the latter compound by the method successfully employed in the preparation of the corresponding cycloheptadiene.[3c,8b]

Attention was next focused on the 6,7-dicarboxylic acid derivatives of Ia (Ie), of which two forms may be obtained[9]: vigorous alkaline hydrolysis of Ib yields α-Ie, m.p.[11] 219–220° dec., m.p. of derived α-If 127–128°; heating at 250° of α-Ie results in an anhydride, basic hydrolysis of which affords β-Ie, m.p. 196–197°, m.p. of derived β-If 139–140° (m.m.p. with α-If 110–124°).[12] The number of forms demanded by theory depends on the ease with which the biphenyl system can pass through a planar (or equivalent) conformation. Three alternatives are summarized in Fig. 1: (a) if the biphenyl system is rigidly locked ("restricted" rotation), six optically stable stereomers *i.e.*, three diastereomeric (±)-pairs are possible: (+)- and (−)-*cis*, (+)- and (−)-*trans A*, and (+)- and (−)-*trans B*; (b) if the biphenyl system exhibits "hindered" rotation about the pivotal bond, the six stereomers described for (a) are still predictably isolable, but (slow) enantiomeric interconversion (arrows, Fig. 1) should result in *racemization* of (+)- and (−)-*cis* and in *mutarotation* of (+)- and (−)-*trans A* (resp. (+)- and (−)-*trans B*); (c) if the biphenyl system exhibits "free" rotation about the central pivotal bond, the resulting rapid equilibration among the various species should lead to isolation of one non-resolvable *cis* (or *meso*) form, and one resolvable *trans* form.[13]

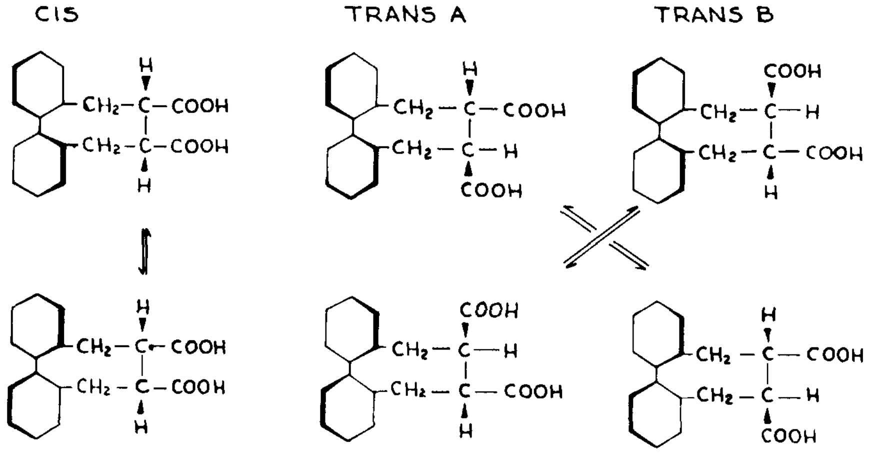


Fig. 1.—The six stereomers of 1,2,3,4-dibenz-1,3-cycloöctadiene-6,7-dicarboxylic acid and their interconversion. The structures in the bottom row are mirror images of those in the top row.

Resolution of α-Ie by fractional separation of brucine salts from acetone afforded (+)-α-Ie, $[\alpha]^{31.5}_D$ +159° (ethanol) (derived α-If $[\alpha]^{31.5}_D$ +178° (diglyme)) from the head fraction and (−)-α-Ie, $[\alpha]^{31.5}_D$ −158° (ethanol) (derived α-If, $[\alpha]^{31.5}_D$ −178° (diglyme)) from the tail fraction. The quoted rotations refer to equilibrium values, for it was observed that the optical activity of freshly prepared solutions of (+)- and (−)-α-Ie in ethanol and of (+)- and (−)-α-If in diglyme rapidly decayed on standing. Satisfactory straight-line plots of log $\alpha_D$ *vs.* *t*, obtained at 20.0 and 31.5°, gave calculated[14] first-order rate constants listed in Table I. Owing to the small half-lives and the small differences between initial[15]

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[8] This result was unexpected, for (a) ethyl 1,2,3,4-dibenz-1,3-cycloheptadiene-6,6-dicarboxylate readily affords the corresponding 6,6-dicarboxylic acid (J. Kenner, *J. Chem. Soc.*, 613 (1913); *cf.* Experimental Part); (b) ethyl 4',1''-dinitro-1,2,3,4-dibenz-1,3-cycloheptadiene-6,6-dicarboxylate can be converted easily to the corresponding 6,6-dicarboxylic acid under mild alkaline conditions (*cf.* Experimental Part); (c) 1,1,2,2-ethanetetracarboxylic acid has been prepared similarly by E. Buchner and H. Witter, *Ber.*, **25**, 1157 (1892).

[9] While this work was in progress a similar observation was reported by G. H. Beaven, *et al.* (ref. 5a).

[10] For a similar but successful reaction sequence in the dibenzcycloheptadiene series *cf.* ref. 3c.

[11] Freshly recrystallized sample. On standing, the acid gradually changes in melting point; a value of *ca.* 235° dec. (that reported by G. H. Beaven, *et al.* (ref. 5a)) is thus obtained.

[12] The virtual identity of the ultraviolet spectra of α-If ($\lambda^{MeOH}_{max}$ 236 mμ, ε 12,000) and β-If ($\lambda^{MeOH}_{max}$ 236 mμ, ε 13,000) serves to eliminate the possibility of ring contraction during anhydride formation and hydrolysis.

[13] Taking $A = 10^{11}$ sec.$^{-1}$ as typical for biphenyl racemizations (G. B. Kistiakowsky and W. R. Smith, THIS JOURNAL, **58**, 1043 (1936)), representative values for $E_{act}$ corresponding to the three alternatives may be calculated: (a) restricted rotation ($t_{0.5}$ 50–500 hr. or more at 100°), $E_{act.}$ 29–31 kcal./mole (or more); (b) hindered rotation ($t_{0.5}$ 1–10 hr. at 25°), $E_{act}$, 21–22 kcal./mole; (c) free rotation ($t_{0.5}$ 1–30 sec. (or less) at 0°), $E_{act.}$ 14–16 kcal./mole (or less).

[14] $k_1 = (1/t) \ln (\alpha_0 - \alpha_\infty)/(\alpha_t - \alpha_\infty)$; $t_{0.5} = \ln 2/k$ (treating the reaction as an irreversible process). For racemization the same equations were employed, since (+) → (±); in the alternative treatment the reaction is considered reversible ((+) ⇄ (−)) with $k_1' = 0.5k_1$ and $t'_{0.5} = 2t_{0.5}$.

[15] $[\alpha_0]_D$ refers to the value found by linear extrapolation to $t_0$, the moment of solution (uncertainty ±5 sec.). The first polarimetric reading was obtained 6–30 min. following $t_0$.

TABLE I

MUTAROTATION OF (+)- AND (−)-α-1,2,3,4-DIBENZ-1,3-CYCLOÖCTADIENE-6,7-DICARBOXYLIC ACIDS (α-Ie) AND METHYL ESTERS (α-If)

| Compound | α-Ie (in ethanol) | | | α-If (in diglyme) | | | |
|---|---|---|---|---|---|---|---|
| Temp., °C. | 20.0 | | 31.5 | 20.0 | | 31.5 | |
| Enantiomer | (+) | (−) | (+)[a] | (+) | (−) | (+) | (−) |
| $[\alpha_0]\mathrm{D}$[b] | +159° | −164° | +177° | +212° | −198° | +201° | −201° |
| $[\alpha_{eq}]\mathrm{D}$ | +148° | −152° | +159° | +188° | −178° | +178° | −178° |
| $k_1 \times 10^4$, sec.$^{-1}$ | 3.8 | | 9.5 | 2.0 | | 12.3 | |
| $t_{0.5}$, min. | 30 | | 12 | 58 | | 10 | |

[a] $c$ 5.0, $l$ 2; $c$ 2.0, $l$ 2, for all other listed values. [b] By extrapolation to $t_0$, taken as the time of mixing (ref. 15).

TABLE II

RACEMIZATION OF (+)- AND (−)-β-1,2,3,4-DIBENZ-1,3-CYCLOÖCTADIENE-6,7-DICARBOXYLIC ACIDS (β-Ie)

| Solvent | Ethanol | | | | | 2.32 *N* NaOH | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Temp., °C. | 16.5 | 31.5 | | 40.0 | 50.0 | 16.5 | 31.5 | | 40.0 | 50.0 |
| Enantiomer | (−) | (+)[a] | (−) | (−) | (−) | (−) | (+)[a] | (−) | (−) | (−) |
| $[\alpha_0]\mathrm{D}$[b] | −103° | +176° | −103° | −103° | −140° | −123° | +107° | −141° | −171° | −298° |
| $k_1 \times 10^4$, sec.$^{-1}$ | 0.184 | 1.36 | | 3.78 | 11.4 | 0.19 | 2.27 | | 6.21 | 22.1 |
| $t_{0.5}$, min. | 630 | 85 | | 31 | 10 | 610 | 51 | | 19 | 5 |

[a] $c$ 5.0, $l$ 1; $c$ 1.6, $l$ 2, for all other values. [b] By extrapolation to $t_0$, taken as the time of mixing (ref. 15).

($[\alpha_0]_\mathrm{D}$) and final ($[\alpha_{eq}]_\mathrm{D}$) rotations, the effect, while real, requires some dispatch in observation so that it may be detected in the first place.

The fact that optically active α-Ie and α-If mutarotate proves that: (a) enantiomerism in the system Ia, exclusive of asymmetric centers, is demonstrable under ordinary conditions; (b) the biphenyl system exhibits hindered, rather than restricted, rotation; (c) α-Ie corresponds to one of the two possible diastereomeric *trans* forms; and (d) β-Ie must be either the other *trans* form or the *cis* modification.

The morphine salt of β-Ie, obtained in 62% yield by slow crystallization from acetone, exhibited mutarotation. Decomposition with ammonia at *ca.* 5° afforded (−)-β-Ie, $[\alpha]^{50}\mathrm{D}$ −78° (2.32 *N* NaOH) to $[\alpha]^{16.5}\mathrm{D}$ −121° (2.32 *N* NaOH) and $[\alpha]^{50}\mathrm{D}$ −89° (ethanol) to $[\alpha]^{16.5}\mathrm{D}$ −101° (ethanol), depending on the time required for liberation and collection, temperature of solution and time elapsed[15] between solution and polarimetric observation. The acid liberated from the residue obtained by removal of solvent from the mother liquors of the crystallization proved to be optically inactive.

The brucine salt of β-Ie was obtained in 47% yield by crystallization from acetone over a 24-hour period at room temperature. The salt, decomposed with ammonia at *ca.* 5°, afforded (+)-β-Ie, $[\alpha]^{31.5}\mathrm{D}$ +133° (ethanol)[16]; acid obtained by decomposition of the mother liquors from the crystallization was optically inactive.

Both enantiomeric forms of β-Ie racemized; satisfactory straight-line plots of log $\alpha\mathrm{D}$ *vs.* $t$, obtained at four temperatures, gave calculated[14] first-order rate constants listed in Table II.

The racemized product in each run was found to be optically inactive and identical with authentic (±)-β-Ie, as judged by comparison of the derived (±)-β-If. Further, in several cases the racemized product was again optically activated to give enantiomers having $k_1$ of racemization identical with the original sample. The racemization could not therefore have involved structural rearrangement. It thus has been established rigorously that the β-form corresponds to the *cis* stereomer.[17] This conclusion also serves to account for the following observations: (a) the (−)-β-Ie-morphine salt mutarotates; (b) only one enantiomer is obtained with morphine, (−), and brucine, (+)[18]; (c) rotations of liberated acids, and values of $[\alpha_0]\mathrm{D}$ obtained by extrapolation, show wide variation in magnitude, depending on temperature and time factors.

The information thus obtained now allows us to rule out the possibility that the observed mutarotation corresponded in actuality to racemization of small amounts of β-Ie (or β-If) contaminating optically stable α-Ie (or α-If): (a) $t_{0.5}{}^{31.5}$ of (+)-β-Ie and of (+)-α-Ie (in ethanol) differ widely (85 and 12 min., resp.); (b) a sample of α-Ie was refluxed for four hours in glacial acetic acid and the material which crystallized on cooling had $k_1$ of mutarotation identical with the original α-Ie. It is also possible now to state that the presence of the third diastereomer predicted by theory is proven by indirection. Evidently one of the *trans* diastereomers crystallizes preferentially, so that the diastereomeric mixture of the corresponding Ie (or If) is converted in this process, by a second-order asymmetric transformation, into a single form. On dissolution, the mixture is formed again, as proved by the mutarotation.

The assignment of configuration to the stereomeric forms of Ie may be refined in the following manner. Inspection of molecular models of Ia reveals that the hydrogens on the 6,7-positions of the

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[16] A sample having $[\alpha]^{31.5}\mathrm{D}$ +178° (ethanol) was obtained in a similar preparation. Other batches had lower rotations.

[17] In analogy with cyclohexane chemistry, the *cis*-anhydride may be obtained by heating the *trans*-1,2-dicarboxylic acid (A. Baeyer, *Ann.*, **258**, 145 (1890)). In contrast to the obtention of *trans*-Ie by saponification–decarboxylation of Ib, however, it has been reported (K. Alder and H. F. Rickert, *Ber.*, **72**, 1983 (1939)) that ethyl 1,1,2,2-cyclohexanetetracarboxylate undergoes alkaline hydrolysis to give *cis*-1,2-cyclohexanedicarboxylic acid.

[18] The enantiomeric forms of β-Ie were therefore not obtained by resolution, but by second-order asymmetric transformation (*cf.* E. E. Turner, *Quart. Revs.*, **1**, 299 (1947)).

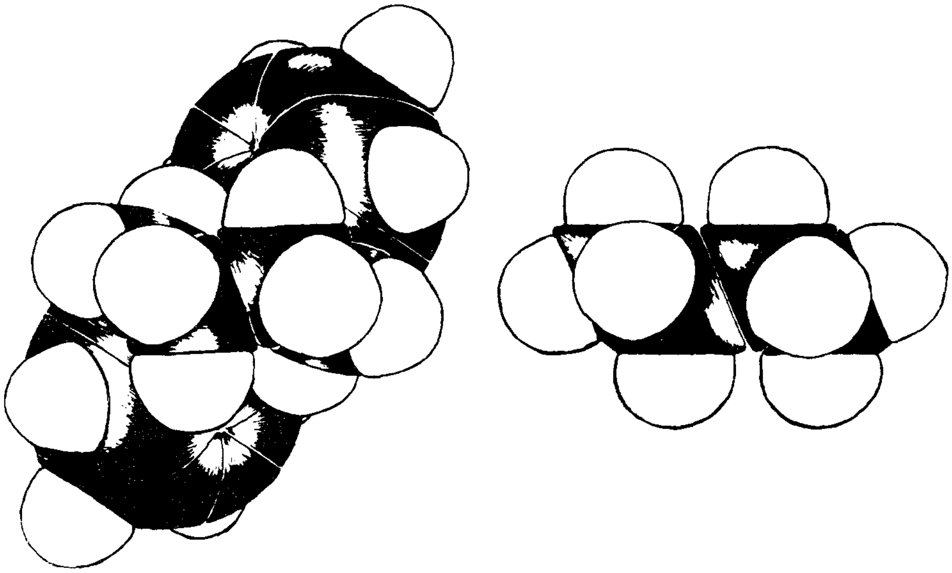

Fig. 2.—Models showing the conformational similarity between chair-cyclohexane (right) and the bridge (chair conformation) of 1,2,3,4-dibenz-1,3-cycloöctadiene.

bridge are disposed *axially* and *equatorially* in close analogy to the chair form of cyclohexane (Fig. 2).[17,19] Racemization of β-Ie may then be viewed as a process involving interconversion of *ae*- and *ea*-6,7-dicarboxylic acid groupings with concomitant twisting of the biphenyl moiety (Fig. 3A), while mutarotation of α-Ie involves interconversion of *aa*- and *ee*-6,7-dicarboxylic acids accompanied by biphenyl twisting (Fig. 3B). The diastereomeric *trans*-acids (A and B, Fig. 1) would thus correspond to *aa*- and *ee*-conformers; it is impossible to say from our data which of these corresponds to α-Ie.

*Optical activation of β-Ie may therefore be regarded as a separation of conformational enantiomers.*[20] The energy of activation for the racemization process, 23 kcal./mole, is of the order of magnitude expected for a hindered biphenyl.[13] Interestingly, while $\Delta F^{\neq}$ for racemization of β-Ie is the same in ethanol and in aqueous sodium hydroxide (Table III), enthalpies and entropies of activation in the two media show marked differences. The enthalpy of activation in sodium hydroxide is *ca.* 3 kcal./mole higher than $\Delta H^{\neq}$ in ethanol. Since, in the course of racemization, the two carboxyl groups must at some time slide past one another (*ae* ⇄ *ea*, Fig. 3A),[21] it is tempting to suggest that the higher enthalpy is associated with passage of two charged *carboxylate* groups: coulombic interaction in the transition state would effectively raise the potential energy of the molecule and slow the process of racemization. This simple rationalization is beclouded by the fact that the entropy of the reaction is positive in base, negative in ethanol. As a result there is a crossover point in the Arrhenius plot (−4° by extrapolation), and the rate of racemization in base is actually larger than that in ethanol above that temperature. No doubt solvation effects enter which are not considered in the simple interpretation.[22]

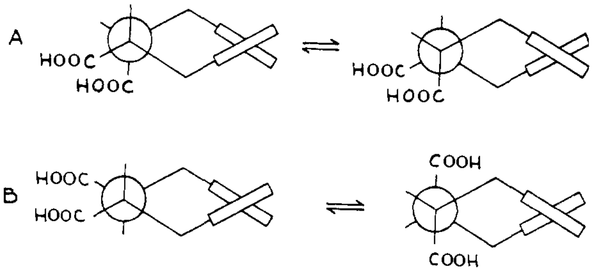

Fig. 3.—A. Racemization of *cis*-1,2,3,4-dibenz-1,3-cycloöctadiene-6,7-dicarboxylic acid. B. Mutarotation of *trans*-1,2,3,4-dibenz-1,3-cycloöctadiene-6,7-dicarboxylic acids.

Optical activation of β-Ie represents the first resolution of a *cis* or *meso* diastereomer. Since in 2.32 *N* NaOH, $t_{0.5}^{100}$ of β-Ie is 1 sec., the compound may be regarded as unresolvable at that temperature and in that solvent. Aside from considerations of conformational isomerism[20] this result bears directly on the problem of "internal compensation," as discussed in a previous communication.[23]

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[19] A second conformation, akin to boat-cyclohexane, is also possible. Hydrogens on the 6- and 7-positions are now eclipsed with those on the 5- and 8-positions, respectively, but staggered with respect to each other. We recognize that the ultraviolet spectrum of Ib ($\lambda_{max}^{EtOH}$ 239 mμ, ε 13,000) in conjunction with those of If (ref. 12) allows estimation (ref. 5) of an interplanar angle of 34°, considerably less than that of *ca.* 60° indicated by models. The representation in Fig. 2 must therefore be regarded as somewhat idealized.

[20] O. Hassel, *Quart. Revs.*, **7**, 221 (1953), has pointed out that *cis*-cyclohexane-1,2-dicarboxylic acid is separable in principle into the enantiomeric *ae*- and *ea*-forms; the low energy barrier to interconversion (probably of the order of 10 kcal./mole) is expected to make realization of this prediction a formidable task. Recently, the separation of certain, related, conformational diastereomers has been accomplished (G. Wittig, G. Koenig and K. Clauss, *Ann.*, **593**, 127 (1955)).

[21] By contrast, mutarotation does not involve passage of the 6,7-substituents (*aa* ⇄ *ee*, Fig. 3B).

[22] Activation parameters could not be calculated for the process of mutarotation, since of the two possible *trans* forms only one (α-Ie) was ever isolated.

[23] K. Mislow, *Trans. N. Y. Acad. Sci.*, [2] **19**, 298 (1957).

TABLE III

ACTIVATION PARAMETERS FOR THE RACEMIZATION OF $\beta$-1,2,3,4-DIBENZ-1,3-CYCLOÖCTADIENE-6,7-DICARBOXYLIC ACID

| | Arrhenius parameters[a] | | Thermodynamic constants[b] | | |
|---|---|---|---|---|---|
| Solvent | $E_{act}$, kcal./mole | $A$, sec.$^{-1}$ | $\Delta H^{\ddagger}$, kcal./mole | $\Delta S^{\ddagger}$, e.u. | $\Delta F^{\ddagger}$, kcal./mole |
| Abs. ethanol | 22.8 | $3.16 \times 10^{12}$ | 22.2 | −3.4 | 23.3 |
| 2.32 $N$ NaOH | 25.4 | $3.98 \times 10^{14}$ | 24.8 | 6.3 | 22.9 |

[a] Calculated from the straight-line plot of the data in Table II (four temperatures). [b] From the Arrhenius plot (S. Glasstone, K. J. Laidler and H. Eyring, "The Theory of Rate Processes," McGraw-Hill Book Co., Inc., New York, N. Y., 1941, pp. 195–199). Values refer to 31.5°.

Finally, it may be anticipated in the light of our results that apogalanthamine, a natural product derivative[24] related to Ia (N-methyl 7-aza-3′,4′-dihydroxy Ia), is resolvable and optically unstable, as independently reflected by the position and the intensity of the reported[24] K-band.

## Experimental Part[25]

**Ethyl 1,2,3,4-Dibenz-1,3-cycloheptadiene-6,6-dicarboxylate.**—This compound, prepared from 2,2′-bis-(bromomethyl)-biphenyl[26] and sodiomalonic ester according to the directions of Kenner,[8a] was obtained as an oil which, after elution on neutral alumina with petroleum ether, gave white blocky crystals in 52% yield, m.p. 48–49°. Kenner[8a] reports m.p. 64°.

*Anal.* Calcd. for $C_{21}H_{22}O_4$: C, 74.5; H, 6.6. Found: C, 74.6; H, 7.0.

A solution of 0.64 g. of the ester and 1.0 g. of potassium hydroxide in 33 ml. of 10:1 ethanol–water was refluxed for 30 minutes; the mixture, worked up in the conventional manner, yielded 0.41 g. (77%) of **1,2,3,4-dibenz-1,3-cycloheptadiene-6,6-dicarboxylic acid**, m.p. 200–203° dec. (lit.[8a] 205° dec.). A sample of the dicarboxylic acid, heated at 210° for 15 minutes, yielded **1,2,3,4-dibenz-1,3-cycloheptadiene-6-carboxylic acid**, m.p. 160–162° (lit.[8a] m.p. 158°, lit.[5a] m.p. 161–162°).

**Ethyl 4′,1″-Dinitro-1,2,3,4-dibenz-1,3-cycloheptadiene-6,6-dicarboxylate.**[27,28]—A hot solution of 13.3 g. of 6,6′-dinitro-2,2′-bis-(bromomethyl)-biphenyl[7] in 25 ml. of dioxane was added to a refluxing mixture prepared by addition of a solution of 5 g. of ethyl malonate in 30 ml. of dioxane to a solution of 1.4 g. of sodium in 28 ml. of abs. ethanol. An instantaneous precipitation of sodium bromide was observed. Refluxing was continued for 15 minutes, the mixture was filtered and the filtrate freed of solvent. The residue, after one recrystallization from ethanol, had m.p. 150–156° (4.1 g., 64%). Four recrystallizations gave product with m.p. 159.5–160.5°.

*Anal.* Calcd. for $C_{21}H_{20}N_2O_8$: C, 58.9; H, 4.7; N, 6.5. Found: C, 58.3; H, 4.5; N, 6.9.

A solution of the ester (0.99 g.) and potassium hydroxide (0.52 g., 87% KOH) in 33 ml. of 95% ethanol was refluxed for 0.5 hr., and filtered. The residual potassium salt was washed with ice-cold ethanol, dissolved in water and the solution made acid to congo red with hydrochloric acid. The precipitate was washed with water and dried to give 0.59 g. (67%) of **4′,1″-dinitro-1,2,3,4-dibenz-1,3-cycloheptadiene-6,6-dicarboxylic acid**,[28] m.p. *ca.* 244° dec. Recrystallization from aqueous ethanol gave pure acid, m.p. 247–249° dec.

*Anal.* Calcd. for $C_{17}H_{12}N_2O_8$: C, 54.8; H, 3.3; N, 7.5. Found: C, 55.0; H, 3.2; N, 7.4.

**Ethyl 1,2,3,4-Dibenz-1,3-cycloöctadiene-6,6,7,7-tetracarboxylate (Ib).**—The procedure of Kenner[8a] gave uncertain results, in that almost all of the product was an intractable liquid. Use of the method employed by Bachér[29] in the preparation of ethyl 1,2-dibenzoyl-1,1,2,2-ethanetetracarboxylate proved far more satisfactory. A mixture of 31.8 g. of ethyl 1,1,2,2-ethanetetracarboxylate,[30] 7.8 g. of potassium and 300 ml. of anhydrous toluene was stirred under reflux for six hours. To the resulting, slightly murky suspension was added 30.0 g. of 2,2′-bis-(bromomethyl)-biphenyl[26] in one portion and stirring under reflux was continued for 40 hours. Water was added, the organic layer separated and freed of solvent. The residual oil crystallized on standing to give, after trituration with petroleum ether, 34.0 g. (77%) of product, m.p. 108–109°. Recrystallization from 1:10 benzene–petroleum ether (30–60°) afforded large parallelepipeds,[31] m.p. 110–111° (lit.[8a] 108.5°, lit.[5a] 108–109.5°), $\lambda_{max}^{EtOH}$ 239 m$\mu$ ($\epsilon$ 13,000) (lit.[5a] $\lambda_{max}^{EtOH}$ 239.5 m$\mu$ ($\epsilon$ 13,100)).

*Anal.*[32] Calcd. for $C_{28}H_{32}O_8$: C, 67.7; H, 6.5; mol. wt., 497. Found: C, 67.6; H, 7.0; mol. wt., 503.

Under conditions, *i.e.*, refluxing with aqueous ethanolic potassium hydroxide, which served to hydrolyze both unsubstituted and 4′,1″-dinitro-substituted ethyl 1,2,3,4-dibenz-1,3-cycloheptadiene-6,6-dicarboxylates (see above), Ib remained unsaponified and could be recovered in 97% yield. Fifty hours of refluxing gave a 28% yield of solid acid, m.p. 210–218° dec. ($\alpha$-Ie, see below), and a 64% recovery of Ib. A solution of Ib (10.0 g.) in a mixture of 200 ml. of ethanol and 240 ml. of 12 $N$ hydrochloric acid, refluxed for eight hours, gave a 95% recovery of unreacted Ib.

Solutions of Ib and TAPA[6] in benzene and benzene–ethanol gave no complexes either on standing or on slow evaporation of solvent.

**Preparation and Hydrogenation of Benzyl 1,1,2,2-Ethanetetracarboxylate.**—A mixture of 80.0 g. of ethyl malonate, 11.5 g. of sodium and 400 ml. of dry benzene was refluxed for four hours. Benzyl alcohol (119 g.) was added and the resulting mixture was fractionated to remove the benzene–ethanol azeotrope (150 ml., b.p. 68°). Iodine (63.5 g.) in anhydrous ether was added to the residual solution with stirring, water was added and the water layer was extracted with ether. The combined organic layers were washed with 5% sodium carbonate, 5% sodium thiosulfate and water. After drying, the solvent was removed; the residual oil gradually deposited crystals (30 g.), m.p. 85–90° after trituration with petroleum ether. Recrystallization from 1:10 benzene–petroleum ether afforded 27.3 g. (19%) of needles, m.p. 92–93°.

*Anal.* Calcd. for $C_{34}H_{30}O_8$: C, 72.1; H, 5.3. Found: C, 71.7; H, 5.7.

The same compound could be prepared by self-condensation of benzyl malonate (obtained[33] in 53% yield by reaction of silver malonate[34] with benzyl chloride) as the sodio derivative through the agency of iodine, following the similar preparation of ethyl 1,1,2,2-ethanetetracarboxylate by Bischoff and Rach.[30] The yield was 87%.

Hydrogenolysis of the tetraester (5% palladinized charcoal, ethanol solvent) at 1 atm. and room temperature resulted in uptake of 95% of the theoretical volume of gas in two hours. The product, **1,1,2,2-ethanetetracarboxylic acid**, had m.p. 163–165° dec. (lit.[35] m.p. 167–169° dec.).

**Preparation and Hydrogenation of Benzyl 1,2,3,4-Dibenz-1,3-cycloöctadiene-6,6,7,7-tetracarboxylate (Id).**—A mixture of 100.0 g. of benzyl 1,1,2,2-ethanetetracarboxylate, 13.8 g. of potassium metal and 500 ml. of toluene was stirred under reflux for three hours. 2,2′-Bis-(bromomethyl)-biphenyl[26] (60.0 g.) was added and stirring under reflux was continued for 24 hours. The product, worked

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[24] S. Kobayashi and S. Uyeo, *J. Chem. Soc.*, 638 (1957).

[25] Microanalyses by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y.

[26] D. M. Hall, M. S. Lesslie and E. E. Turner, *J. Chem. Soc.*, 711 (1950). Large (5 mm.) blocky crystals may be grown from acetone, m.p. 92–93°. Triclinic system; $\alpha = 81.2° \pm 0.5°$, $\beta = 98.0° \pm 0.5°$ and $\gamma = 99.5° \pm 0.5°$.

[27] Independently prepared by Iffland and Siegel (ref. 3c); Dr. D. C. Iffland, private communication.

[28] Prepared by Mr. P. Newman.

[29] F. Bachér, *J. prakt. Chem.*, [2] **120**, 301 (1929).

[30] C. A. Bischoff and C. Rach, *Ber.*, **17**, 2781 (1884).

[31] Crystals as large as 1 cm. to the side can be grown readily from this solvent mixture; monoclinic system, $\beta = 100.6° \pm 0.5°$.

[32] Molecular weight in acetone by the isopiestic method of R. Signer (*Ann.*, **478**, 246 (1930)) as modified by E. P. Clark (*Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941)). Kenner has reported[8a] mol. wt. 364, 387; Beaven, *et al.*,[5a] found mol. wt. 502 by the ebullioscopic method in benzene.

[33] C. A. Bischoff and A. v. Hedenström, *Ber.*, **35**, 3452 (1902).

[34] B. Finkelstein, *Ann.*, **133**, 338 (1865).

[35] C. Mannich and E. Ganz, *Ber.*, **55**, 3509 (1922).

up and recrystallized as described for Ib (above), was obtained as 65.0 g. (50%) of chunky crystals, m.p. 172–173°.

*Anal.* Calcd. for $C_{48}H_{40}O_8$: C, 77.1; H, 5.4. Found: C, 77.4; H, 5.4.

Hydrogenolysis of Id in ethanol at 1 atm. and 27° in the presence of 5% palladinized charcoal resulted in uptake of 96% of the theoretical volume of gas in two hours. The product, obtained after filtration and removal of solvent at room temperature, consisted of a white. opaque, tacky gum, entirely soluble in cold 10% sodium carbonate, which gradually changed into a porous, friable, non-crystalline glass, m.p. 130–245° dec. with evolution of gas throughout this interval.

*Anal.* Calcd. for $C_{20}H_{16}O_8$: C, 62.5; H, 4.2. Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 71.7; H, 5.7.

The analytical evidence points to a mixture of acids in various stages of decarboxylation. In substantiation of this inference, a paste of the product and glycerol evolved a gas at 75°, suggesting the presence of tetracarboxylic acid, and reaction of the product with diazoethane[36] at 0–5° gave a product, m.p. 91–92° after recrystallization from petroleum ether, which did not depress the m.p. of β-Ie ethyl ester (see below), thus proving the presence of decarboxylated material.

**4,4′-Dinitro-2,2′-bis-(hydroxymethyl)-biphenyl (IIIb).**—2,7-Dinitro-9,10-phenanthraquinone[37] was oxidized[38] to 4,4′-dinitro-2,2′-diphenic acid, m.p. 258–259°, esterification of which with methanol yielded the dimethyl ester,[39] m.p. 175–176°. A mixture of methyl 4,4′-dinitro-2,2′-diphenate (63.0 g.) (IIIa), pulverized anhydrous calcium chloride (38.8 g.), sodium borohydride (26.6 g.) and 500 ml. of anhydrous tetrahydrofuran was stirred for five hours at room temperature. Water (300 ml.) was added, the mixture was made acid to congo red, and the resulting upper layer was separated and distilled down. The residual oil, triturated with ethyl acetate, crystallized on standing overnight in the refrigerator. The solid was collected and the remaining oil was extracted several times with boiling water. The water extracts gave further quantities of crystals on cooling. The combined solids were recrystallized from 1:4 ethyl acetate–ethanol to give 26.8 g. (51%) of product, m.p. 159–161°.

*Anal.* Calcd. for $C_{14}H_{12}N_2O_6$: C, 55.3; H, 4.0; N, 9.2. Found: C, 55.5; H, 4.0; N, 9.0.

Reduction of methyl 6,6′-dinitro-2,2′-diphenate under similar conditions gave a 53% yield of **6,6′-dinitro-2,2′-bis-(hydroxymethyl)-biphenyl**, m.p. 142–144°, undepressed by admixture of authentic[7] material.

**4,4′-Dinitro-2,2′-bis-(bromomethyl)-biphenyl (IIIc).**—A mixture of 4,4′-dinitro-2,2′-bis-(hydroxymethyl)-biphenyl (13.5 g.) and 48% hydrobromic acid (300 ml.) was refluxed with stirring for two hours, while a stream of hydrogen bromide gas was continuously introduced. The mixture was poured onto ice and the solid, which had formed on standing, was collected and recrystallized from ethyl acetate and then twice from 1:4 ethyl acetate–benzene to give 13.4 g. (70%) of product, m.p. 152–153°.

*Anal.* Calcd. for $C_{14}H_{10}Br_2N_2O_4$: C, 39.1; H, 2.3; N, 6.5. Found: C, 39.2; H, 2.4; N, 6.4.

**Preparation and Hydrogenation of Ethyl 2′,3′′-Dinitro-1,2,3,4-dibenz-1,3-cycloöctadiene-6,6,7,7-tetracarboxylate (IIa).**—Sodium (2.78 g.), then ethyl 1,1,2,2-ethanetetracarboxylate[30] (19.2 g.), was dissolved in 95 ml. of abs. ethanol. To the warm solution was added a solution of 26.0 g. of 4,4′-dinitro-2,2′-bis-(bromomethyl)-biphenyl in 280 ml. of dioxane (purified by distillation from sodium) and the resulting mixture was stirred under reflux for three hours. The suspension was poured into 600 ml. of ice-water, the crude solid collected by filtration, triturated with ethanol, and recrystallized from 1:4 ethyl acetate–benzene. There was thus obtained 14.5 g. (41%) of light yellow solid, m.p. 169–171°.

*Anal.* Calcd. for $C_{28}H_{30}N_2O_{12}$: C, 57.3; H, 5.2; N, 4.8. Found: C, 57.3; H, 5.2; N, 4.6.

Attempts to prepare IIc from 6,6′-dinitro-2,2′-bis-(bromomethyl)-biphenyl and ethyl 1,1,2,2-ethanetetracarboxylate, either by the procedure described above for the preparation of IIa, or by that employed in the preparation of Ib, only resulted in the formation of red, intractable liquids.

Hydrogenation of IIa in ethanol over 5% palladinized charcoal at 30° and 1 atm. for 24 hours resulted in uptake of gas corresponding to 97% of theory. The product, isolated after filtration and removal of solvent, consisted of 1.47 g. (100%) of a glass which could not be induced to crystallize. Elution on silica gel (Davison, grade 1) with 1:10 methanol–benzene gave 1.42 g. (97%) of impure **ethyl 2′,3′′-diamino-1,2,3,4-dibenz-1,3-cycloöctadiene-6,6,-7,7-tetracarboxylate** (IIb), a light yellow glass which resisted all attempts at crystallization and which melted indefinitely at 60–80°.

*Anal.* Calcd. for $C_{28}H_{34}N_2O_8$: C, 63.9; H, 6.5; N, 5.3. Found: C, 65.6; H, 6.2; N, 5.2.

**The (+)-camphor-7-sulfonate**, which precipitated as a pale yellow solid upon mixing solutions of IIb and (+)-camphor-7-sulfonic acid in acetone, had m.p. 222–226°, $[\alpha]^{31.5}D$ +25° (*c* 5.0, chloroform). The rotation showed no change with time. The solid was not obtained analytically pure.

*Anal.* Calcd. for $C_{38}H_{50}N_2O_{12}S$: C, 60.1; H, 6.6. Found: C, 58.8; H, 6.3.

**Preparation and Resolution of α-1,2,3,4-Dibenz-1,3-cycloöctadiene-6,7-dicarboxylic Acid (α-Ie).**—A mixture of ethyl 1,2,3,4-dibenz-1,3-cycloöctadiene-6,6,7,7-tetracarboxylate (Ib, 4.0 g.), potassium hydroxide (15.0 g.) and ethylene glycol (100 ml.) was refluxed for two hours. The solution was poured into 400 ml. of water; acidification with 6 *N* hydrochloric acid yielded the desired product, 1.95 g. (82%), m.p. 216–218° dec. Several recrystallizations from acetic acid yielded microcrystalline aggregates of α-Ie, m.p.[11] 219–220° dec.

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4; neut. equiv., 148. Found: C, 73.1, 72.6; H, 5.2, 5.5; neut. equiv., 144.

Difficulties were experienced in preparing the derived **methyl ester (α-If)** by the usual route (with methanol/HCl). Treatment of α-Ie with diazomethane in ether at 5° gave a 99% yield of the desired product, m.p. 127–128° after recrystallization from benzene–petroleum ether or ethanol; $\lambda_{\max}^{\mathrm{MeOH}}$ 236 mμ (ε, 12,000).

*Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2. Found: C, 74.1, 74.0; H, 6.4, 6.1.

A solution of 30.0 g. of α-Ie in 500 ml. of acetone was added to a solution of 44.4 g. of anhydrous brucine in 600 ml. of acetone. The mixture was concentrated to 500 ml. and left to crystallize in the refrigerator for 48 hours. The precipitated solid (59.4 g.) was refluxed with 200 ml. of acetone for two hours and the mixture was filtered hot. The residue (47.8 g.) was similarly leached, in succession, with 100 ml. of acetone for one hour, 100 ml. of acetone for two hours, and 300 ml. of acetone for three hours. The residual **brucine salt** (18.8 g.) had m.p. 227–229° dec., $[\alpha]^{31}D$ +71.5° (*c* 1.3, chloroform). No mutarotation could be observed.

*Anal.* Calcd. for $C_{41}H_{42}N_2O_8$: C, 71.3; H, 6.1. Found: C, 71.4; H, 5.9.

The (+)-α-Ie was liberated by treating 0.5 g. of brucine salt with concd. aqueous ammonia. The resulting suspension was filtered and the filtrate made acid with 6 *N* hydrochloric acid. The precipitate was collected and recrystallized from acetic acid to give product, m.p. 221–222° dec., $[\alpha]^{31.5}D$ +159° (*c* 5.0, ethanol; equil. value).

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 73.0; H, 5.3.

Further leachings of the brucine salt with acetone did not increase the rotation of liberated α-Ie.

The combined mother liquors and leachings from the resolution were reduced to a volume of 30 ml. The solid thus obtained (24.7 g., m.p. 190–225° dec.) was decomposed with concd. aqueous ammonia to give acid, 8.2 g., which was recrystallized from acetic acid. The (−)-α-Ie (3.4 g.) which crystallized had m.p. 223–225° dec., $[\alpha]^{31.5}D$ −158° (*c* 5.9, ethanol; equil. value).

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(36) A. L. Wilds and A. L. Meader, *J. Org. Chem.*, **13**, 763 (1948).

(37) J. Schmidt and A. Kämpf, *Ber.*, **36**, 3738 (1903).

(38) H. W. Underwood, Jr., and E. L. Kochmann, This Journal, **46**, 2069 (1924).

(39) G. Schultz, *Ann.*, **203**, 95 (1880).

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 72.7; H, 5.5.

The mother liquors from the acetic acid crystallization after removal of solvent yielded 3.1 g. of acid, $[\alpha]^{31.5}\text{D}$ $-0.3°$ ($c$ 5.0, ethanol). This procedure thus leads to clean-cut separation of optically pure and racemic fractions of α-Ie from optically impure samples.

**The methyl esters** were prepared from the respective acids by reaction with diazomethane. (+)-α-Ie afforded (+)-α-If, m.p. 159–160° after four recrystallizations from ethanol, $[\alpha]^{31.5}\text{D}$ $+178°$ ($c$ 2.0 diglyme; equil. value).

*Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2. Found: C, 74.2; H, 6.3.

Similarly, (−)-α-Ie gave (−)-α-If, m.p. 159–160°, $[\alpha]^{31.5}\text{D}$ $-178°$ ($c$ 2.0, diglyme; equil. value).

*Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2. Found: C, 74.2; H, 6.5.

**β-1,2,3,4-Dibenz-1,3-cycloöctadiene-6,7-carboxylic Anhydride.**—α-1,2,3,4-Dibenz-1,3-cycloöctadiene-6,7-dicarboxylic acid (129 g.) was heated under a stream of nitrogen at 250° until the material had completely melted, and then at 235° for one hour. The glassy solid obtained on cooling was pulverized and dissolved in 1:10 benzene–petroleum ether. The solution, after standing in the refrigerator for 24 hours, deposited white crystals (94.4 g., 78%), m.p. 171–174° after further recrystallization from benzene–petroleum ether.

*Anal.* Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.1. Found: C, 77.1; H, 5.0.

In another preparation, a material, m.p. 306–307°, was similarly obtained.

*Anal.* Calcd. for $C_{18}H_{14}O_3$: C, 77.7; H, 5.1. Found: C, 78.0; H, 5.2.

Since both compounds gave the same acid (β-Ie, see below), on saponification, stereoisomerism is ruled out. Although this point was not further investigated, it is likely that the two forms are either polymorphous or polymeric modifications of the same anhydride.

**Synthesis and Optical Activation of β-1,2,3,4-Dibenz-1,3-cycloöctadiene-6,7-dicarboxylic Acid (β-Ie).**—A solution of the anhydride (10.0 g.) and potassium hydroxide (8 g.) in 90 ml. of 50% aqueous ethanol was refluxed for one hour (or allowed to stand for several days at room temperature). The solution was diluted to one liter with water and made acid. The resulting product (9.2 g., 82%) after recrystallization from acetic acid had m.p. 196–198° dec. (variable, depending on rate of heating).

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 72.5; H, 5.6.

The corresponding **methyl ester** (β-If), prepared from the acid by reaction with diazomethane, had m.p. 139–140° after recrystallization from methanol or benzene–petroleum ether; $\lambda_{\max}^{\text{MeOH}}$ 236 mμ (ε 13,000). A mixture of α-If and β-If melted at 110–124°.

*Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2. Found: C, 74.0, 74.2; H, 6.3, 6.3.

The **ethyl ester**, prepared from the acid by reaction with diazoethane,[38] had m.p. 91–92° after recrystallization from petroleum ether (lit.[5a] m.p. 77–79°).

*Anal.* Calcd. for $C_{22}H_{24}O_4$: C, 75.0; H, 6.9. Found: C, 74.9; H, 7.0.

A solution of β-Ie (4.8 g.) in 50 ml. of acetone was added to a solution of morphine (4.9 g.) in 750 ml. of acetone. The mixture was placed in the refrigerator and allowed to stand for three weeks. The resulting precipitate of **morphine salt** (6.0 g.) was collected, washed with cold acetone and air-dried, m.p. 195–203° dec., $[\alpha]^{27}\text{D}$ $-11.3°$ ($c$ 2.5, ethylene glycol monomethyl ether; equil. value), mutarotation with $k_1^{27}$ $1.2 \times 10^{-4}$ sec.$^{-1}$. The sample was not obtained in a state of analytical purity.

*Anal.* Calcd. for $C_{35}H_{35}NO_7$: C, 72.3; H, 6.1. Found: C, 71.2; H, 6.4.

The (−)-β-Ie, liberated from the morphine salt by addition of concd. aqueous ammonia in the cold (*ca.* 5°), filtration, acidification of filtrate in the cold, and collection of resulting precipitate, was dried *in vacuo* over sulfuric acid. The product (2.3 g.) had m.p. 189–210° and variable specific rotation (see text).

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 72.8; H, 5.6.

The derived **methyl ester** ((−)-β-If) was prepared by addition of ethereal diazomethane at −10° over a period of one min. to (−)-β-Ie slurried with ether at −10°. The solution was dried under vacuum; no attempt was made to purify the residue, m.p. 125–135°, $[\alpha]^{31.5}\text{D}$ $-77.2°$ ($c$ 1.6, diglyme; initial value), owing to its rapid racemization in solution ($k_1 \times 10^4$ sec.$^{-1}$ = 0.31 (16.5°), 2.40 (31.5°), 19.3 (50.0°); $k = 6.31 \times 10^{12}$, $\exp(-22.8/RT)$). The analysis indicated gross impurities.

*Anal.* Calcd. for $C_{20}H_{20}O_4$: C, 74.0; H, 6.2. Found: C, 67.8; H, 6.0.

A solution of β-Ie (4.0 g.) in 50 ml. of acetone was added to a solution of brucine (5.32 g.) in 100 ml. of acetone. The mixture was concentrated to 75 ml. and allowed to stand at room temperature for 24 hours. The precipitated **brucine salt** (4.2 g., m.p. 160–164°) was not obtained in a state of analytical purity.

*Anal.* Calcd. for $C_{41}H_{42}N_2O_8$: C, 71.3; H, 6.1. Found: C, 68.9; H, 6.4.

The (+)-β-Ie, liberated as described for the morphine salt, had variable specific rotation (see text), m.p. 185–200°.

*Anal.* Calcd. for $C_{18}H_{16}O_4$: C, 73.0; H, 5.4. Found: C, 72.5; H, 5.6.

In five similar optical activations, only three attempts led to optically active β-Ie. Slow precipitation of the salt seems to be an essential requirement.

**Kinetic Measurements.**—Rotations were measured with a Schmidt and Haensch polarimeter adapted with a Rudolph photoelectric attachment.[40] The time of the first set of "swings" was taken as $t$ in the rate expression (error ± *ca.* 10 sec.); four sets immediately subsequent to the first served as checks on the precision of the measurement. In most runs a 2-dm. semimicro jacketed polarimeter tube was used. Constant temperature (±0.02°) was maintained by rapid passage through the polarimeter tube jacket of water circulated through a Lux "Ultra Thermostat Circulating Bath" which gave most satisfactory service in this connection.

The sample of optically active material[41] was dissolved[15] in the appropriate solvent which had been prewarmed or precooled to the temperature of the bath. Polarimetric readings were plotted graphically (log α *vs.* $t$) and the slope of the best straight line was used in the calculation[14] of $k_1$ and $t_{0.5}$.

In all racemization runs, the racemized product was compared to authentic (±)-β-Ie and If. No difference in properties was noted (m.m.p. of esters).

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[40] H. Rudolph, *J. Opt. Soc. Amer.*, **45**, 50 (1955).

[41] The optically active *solid* samples of α- and β-Ie and If can apparently be stored indefinitely without change in optical purity.