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DIELS–ALDER REACTION—IX*

THE REACTION OF 1,7-, 2,7-, 2,6-, AND 1,6-DIHYDROXYNAPHTHALENE AND 6-BROMO-2-NAPHTHOL WITH MALEIC ANHYDRIDE AND THE RESOLUTION OF SOME DERIVATIVES OF THE ADDUCTS

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Abstract—The Diels–Alder reaction of 1,7-, 2,7-, 2,6-, 1,6-dihydroxynaphthalene and 6-bromo-2-naphthol with maleic anhydride was investigated. All of these 2-naphthol derivatives gave *exo*- and *endo*-adducts (II and III) except for the bromo-naphthol, from which only *endo*-adduct was obtained. The assignment of *exo* or *endo* configuration was based on lactone formation on $NaBH_4$ reduction possible only from the *exo* isomer, comparison of NMR spectra and in some cases dipole moment measurements. The *exo*/*endo* ratios of the formed adducts vary over a wide range.

Resolution of methoxy-*trans*-dicarboxylic acid VIII and IX was accomplished via the cinchonidine salts. The absolute configratuion of the resolved active compounds was determined by applying the octant rule.

THE Diels-Alder reactions of 2-naphthol[1–4] and naphthalene[1,5,6] with maleic anhydride have been reported to give adducts with the benzobicyclo[2.2.2]octene system. 2-Naphthol gave a mixture of *endo*-(IIIf) and *exo*-adducts (IIf)† in 30·6% yield (*endo*/*exo* ratio, 90:10), while naphthalene afforded the isomeric adducts in 5·2% yield (*endo*/*exo* ratio, 57:43).[6] These facts suggest a strong effect of the substituent of the naphthalene ring on the reactivity and *endo*/*exo* ratio of the adducts formed. Consequently, it seemed interesting to investigate further substituent effects on the diene syntheses of naphthalenes and naphthols with additional functional groups.

In this paper, the reaction of maleic anhydride with four kinds of dihydroxynaphthalenes (1,7- 2,7-, 2,6-, and 1,6-dihydroxynaphthalene) and 6-bromo-2-naphthol Ia-e, all with an OH group in the β-position, is described. From another point of view, the anticipated adducts with almost rigid conformation of the benzobicyclo-[2.2.2]octenone system were interesting as suitable models for the study of the UV and CD spectra of the ketones homoconjugated with a benzene ring carrying hydroxy or alkoxy (or bromo) functions at different positions. For this purpose the resolution of the compounds was performed in some cases.

The four dihydroxynaphthalenes cited and 6-bromo-2-naphthol were reacted with maleic anhydride by heating the mixture at 190–220° without solvent in an N_2 atmosphere, similar to the case of 2-naphthol itself.[1,2] The adducts were separated by direct fractional crystallization or sometimes by column chromatography. In some

* Part VIII: see Ref. 7. Presented in part at the 19th Annual Meeting of the Japanese Pharmaceutical Society, Tokyo, April 1964, Abstracts, p. 242.

† The prefixes *exo* and *endo* are used in the sense that substituents on the same side of the bicyclo[2.2.2]-octene ring as the benzene ring are *endo*, those on the other side are *exo*.

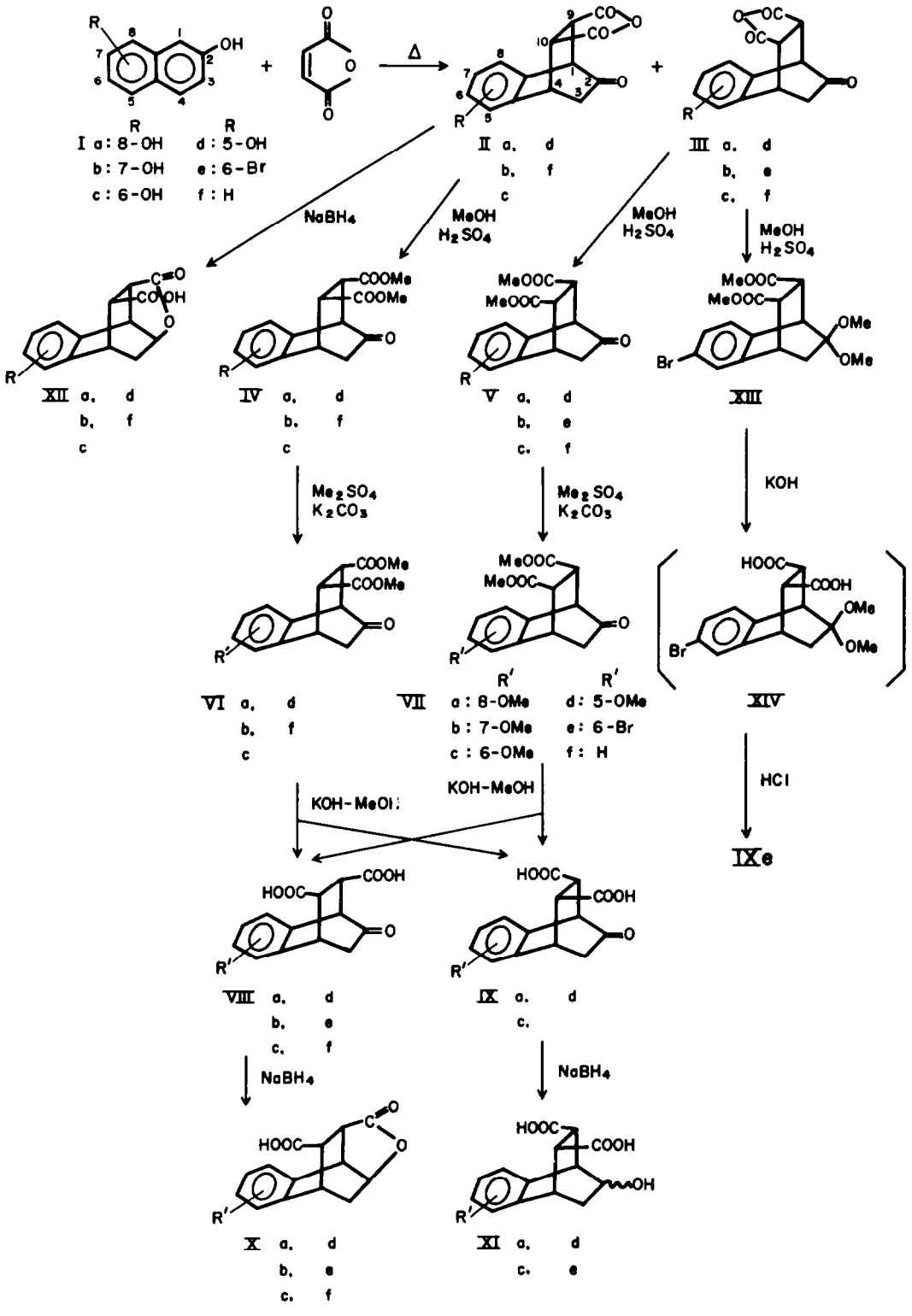

I a: 8-OH d: 5-OH
b: 7-OH e: 6-Br
c: 6-OH f: H
Δ
II a, d
b, f
c
III a, d
b, e
c, f
NaBH4
MeOH H2SO4
MeOH H2SO4
MeOH H2SO4
XII a, d
b, f
c
IV a, d
b, f
c
V a, d
b, e
c, f
XIII
Me2SO4 K2CO3
Me2SO4 K2CO3
KOH
VI a, d
b, f
c
VII a: 8-OMe d: 5-OMe
b: 7-OMe e: 6-Br
c: 6-OMe f: H
XIV
KOH-MeOH
KOH-MeOH
HCl
IXe
VIII a, d
b, e
c, f
IX a, d
c,
NaBH4
NaBH4
X a, d
b, e
c, f
XI a, d
c, e

TABLE 1. MALEIC ANHYDRIDE ADDUCTS FROM NAPHTHALENE DERIVATIVES AND NMR DATA (60 Mc) OF THEM OR THEIR DERIVATIVES (IN d_6-ACETONE)

Starting compd.	*exo*/*endo* ratio	Total yield %	*exo*-Series Chemical shift (τ) CH_3(ester),	H^{3b}	Coupling constant (Hz)	*endo*-Series Chemical shift (τ) CH_3(ester)	H^{3b}	Coupling constant (Hz)
Naphthalene	43/57	5·2			*			
β-Naphthol	10/90	47·7		7·64[e]	$J_{3b,3a}$ = 19·5 $J_{3b,4}$ = 3·5 $J_{3b,10}$ = 2·5		7·72[e]	$J_{3b,3a}$ = 19·0 $J_{3b,4}$ = 3·2
1a	50/50	44·7	6·32 6·36[b]	7·95[b]	$J_{3b,3a}$ = 18·4 $J_{3b,4}$ = 3·5 $J_{3b,10}$ = 2·0		7·92[c]	$J_{3b,3a}$ = 18·5 $J_{3b,4}$ = 2·8
Ib	42/58[a]	28·5[a]	6·34 6·37[a]	7·93[a]	$J_{3b,3a}$ = 19·7 $J_{3b,4}$ = 3·8 $J_{3b,10}$ = 2·0	6·52 6·55[a]	7·91[a]	$J_{3b,3a}$ = 18·6 $J_{3b,4}$ = 3·1
1c	93/7	30·1	6·35 6·37[a]	7·95[a]	$J_{3b,3a}$ = 18·3 $J_{3b,4}$ = 3·5 $J_{3b,10}$ = 2·0			
1d	69/31[b]	3·3[b]	6·31 6·32[d]	7·87[d]	$J_{3b,3a}$ = 19·0 $J_{3b,4}$ = 3·0 $J_{3b,10}$ = 2·0	6·48 6·52[d]	7·85[d]	$J_{3b,3a}$ = 18·5 $J_{3b,4}$ = 2·3
1e	0/100	16·3				6·54[a]	7·86[a]	$J_{3b,3a}$ = 18·5 $J_{3b,4}$ = 2·5

[a] Diester (IV and V) [b] *cis*-Methoxy diester (VId and VIId) [c] *cis*-Diacid [d] *cis*-Methoxy diester (VId and VIId) in $CDCl_3$ [e] Adduct (II and III) in pyridine

* See Ref. 8.

cases, unseparable mixtures were converted to the corresponding diester or methyl ether followed by fractional crystallization. All these 2-naphthol derivatives gave the *exo*- and *endo*-adducts, although in a wide range of yields, except for 6-bromo-2-naphthol (only *endo*-adduct). Exclusive 1,4-addition to the benzene ring bearing the β-OH group becomes evident from elemental analyses, IR (indicating the presence of anhydride group and 6-membered ring ketone) and UV spectra (showing absorptions of phenol derivatives with one benzene ring). The *endo* and *exo* configuration of the anhydride group of the adducts was assigned chemically by the fact that only the *exo*-adduct formed the lactone-acid on $NaBH_4$ reduction of the adducts or their dimethyl esters. The assignment was further confirmed by comparison of the NMR spectra and/or dipole moments. The adducts and/or their derivatives are listed in Table 1.

The configuration of the two adducts from 1,7-dihydroxynaphthalene was established by measurement of the dipole moments. The adduct of higher m.p. (m.p. 280–281°) showed a moment value of 6·82D and the lower melting one (m.p. 242°) 2·89D. From the model inspection and referring to the reported results of the dipole moments of the *endo*- and *exo*-adducts from 2-naphthol and maleic anhydride,[2, 7] we concluded that the anhydride group of the adduct IIa with larger moment has the *exo* configuration and that of IIIa having smaller value is *endo* oriented.

Two adducts from 2,7-dihydroxynaphthalene could be separated by careful fractional crystallization of the reaction mixture or more satisfactorily column chromatography on silica gel of the mixture of the corresponding dimethyl ester. Comparison of the NMR spectra of these two esters (Figs 1 and 2) shows the proton of position 3b* of the adduct, m.p. 168–170°, as a doublet of doublets (J = 18·6, 3·1

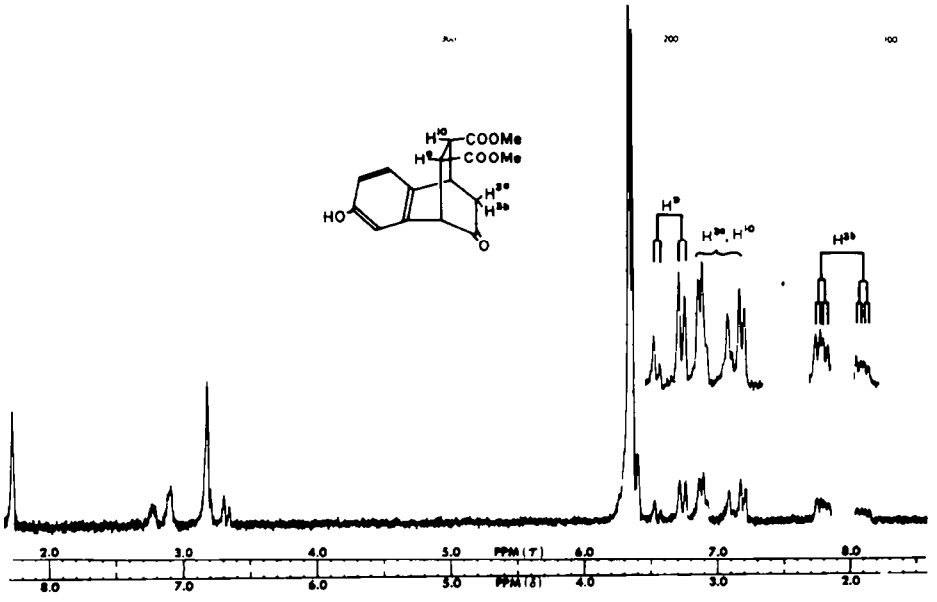


FIG. 1 NMR spectrum of *exo-cis*-dimethyl ester IVb

* The numbering of the benzobicyclo[2.2.2]octene system used in this paper is shown in formula II.

Hz) in d_6-acetone, while that of the other, m.p. 190–192°, exhibits an additional W-letter long-range coupling[8] with the proton of the position 10 (J = 19·7, 3·8, 2·0 Hz). We therefore decided that the former adduct has the *endo* configuration Vb and the latter the *exo* configuration IVb.

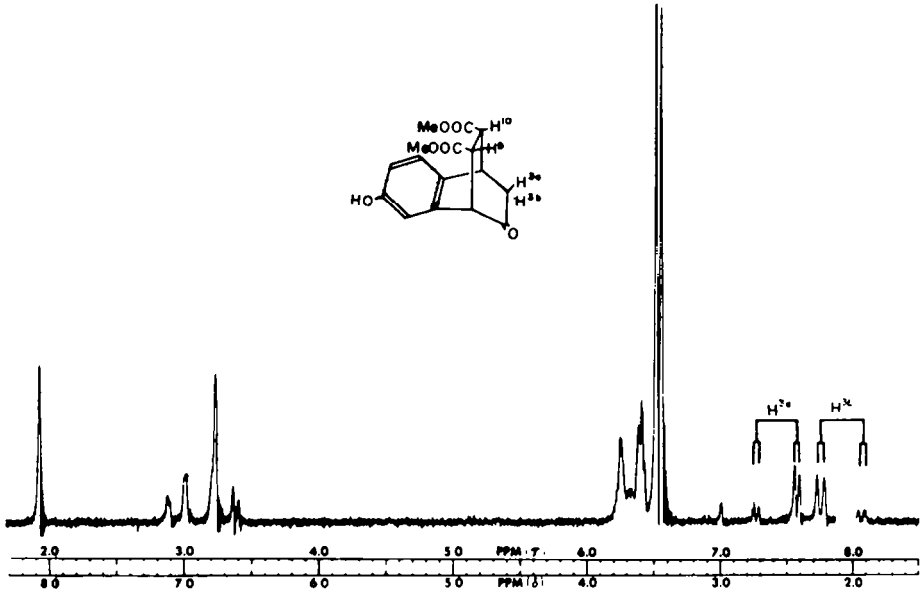


FIG. 2 NMR spectrum of *endo-cis*-dimethyl ester Vb

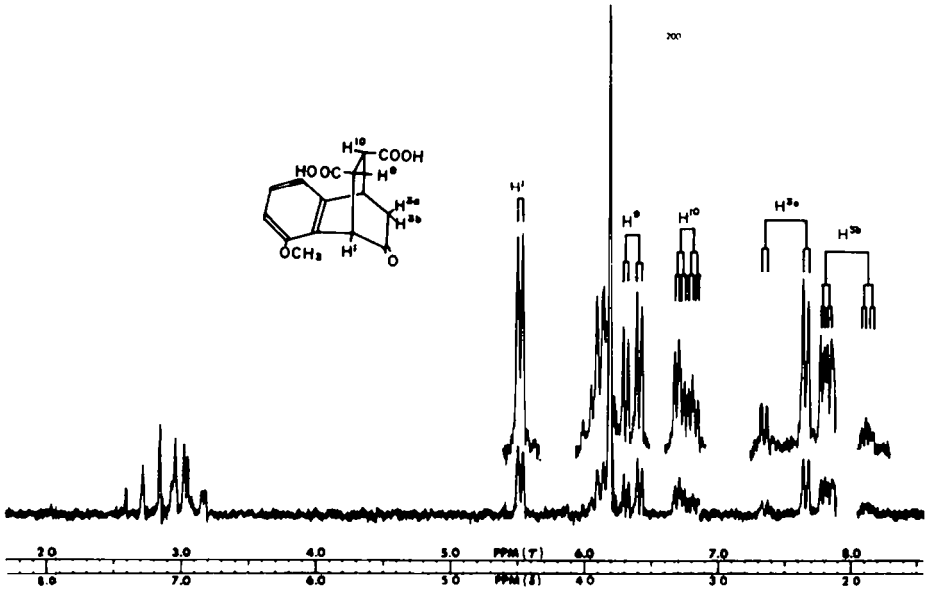


FIG. 3 NMR spectrum of *trans*-diacid IXa

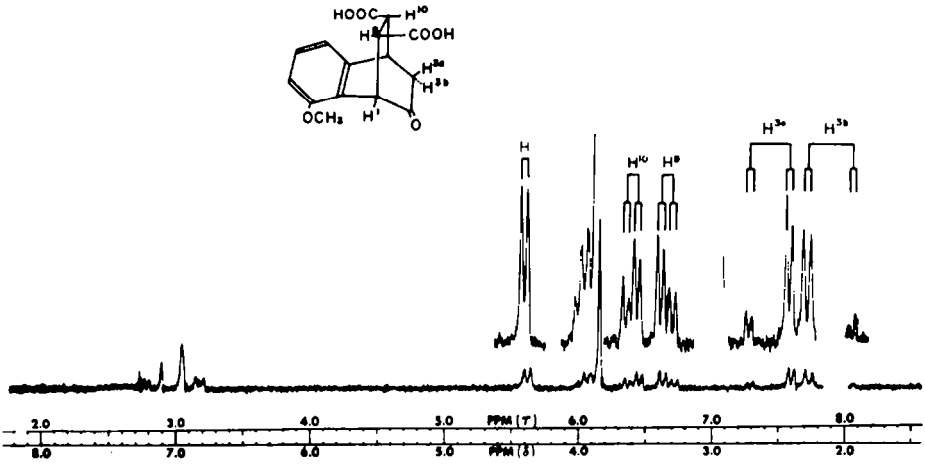


FIG. 4 NMR spectrum of *trans*-diacid VIIIa

Only a small amount of the *exo*-adduct IId of 1,6-dihydroxynaphthalene was isolated by fractional crystallization, but in another experiment separation of two isomers was achieved as dimethyl ester or methoxy diester on chromatography of the mixture. The configuration of each isomer was determined similarly as above by way of the analysis of the NMR spectra in $CDCl_3$: H^{3b} of the *endo*-isomer VIId, J = 18·5, 2·3 Hz; H^{3b} of the *exo*-isomer VId, J = 19·0, 3·0, 2·0 Hz (long-range coupling).

Adducts from 2,6-dihydroxynaphthalene were separated by fractional crystallization; one isomer being obtained in a fair yield, the other one in small amounts only. The NMR spectra of the dimethyl ester from the main adduct showed peaks with W-letter long-range coupling ascribed to a proton at position 3b. Hence this adduct is *exo*-IVc and the other one the *endo*-isomer Vc.*

Reaction of 6-bromo-2-naphthol with maleic anhydride gave only one adduct IIIe. The dipole moment of the compound is 3·30D. Calculated value for an *exo*-adduct is 5·23D and that for an *endo*-adduct 2·75D. Consequently, the obtained adduct was assigned *endo* configuration. The NMR spectra of the adduct and its diester have a doublet of doublets pattern for the proton at position 3b, supporting the above assignment.

From the results so far obtained for the present Diels-Alder reaction, the following aspects can be pointed out. (i) One mole of maleic anhydride adds to the 1,4-position of the benzene ring having a β-OH group. Addition of the reagent to the other benzene ring was not observed in any case; although such an attack can not be excluded, retrogression of the adduct formed should occur under our reaction conditions,[1] in contrast to stabilization of the obtained adducts due to ketonization of the β-OH function. (ii) The total yields of the adducts from 1,7-, 2,7-, and 2,6-dihydroxynaphthalene are comparable with that of 2-naphthol, whereas the yield of the adducts from 1,6-dihydroxynaphthalene was very poor and that from 6-bromo-2-naphthol was

* In this connection, reaction of 2,3-dihydroxynaphthalene with maleic anhydride was examined, but a 1,4-adduct was not obtained.

between the two. (iii) The obtained *exo/endo* ratios of the adducts vary over a wide range depending upon the starting naphthalene derivatives. This fact may be noteworthy, but it is difficult to rationalize these differences at present.

To obtain suitable compounds for optical resolution, *trans*-diacid derivatives of the adducts were prepared as follows:

From the dimethyl esters (IV and V) of the adducts, methoxy-*cis*-dimethyl esters VI and VII were prepared by the usual manner. The corresponding methoxy-*trans*-diacids type VIII and IX were obtained on treatment of *cis*-diester with MeOH-KOH. Two isomeric *trans*-acids VIII and IX were formed from *exo*-5-, 6-, and 8-methoxy-dimethyl ester (VId, VIc and VIa), but only one *trans*-acid VIII was produced from *endo*- and *exo*-7-methoxy diester (VIIb and VIb) and *endo*-6-bromo-diester VIIe. Heating of the *endo*-2-naphthol-maleic anhydride adduct IIIf in 10% KOH aq at 100 gave exclusively VIIIf. The isomer ratios of the two kinds of *trans*-diacids, IX/VIII, are listed in Table 2, including NMR data, and the configurations of the *trans*-acids were determined as follows.

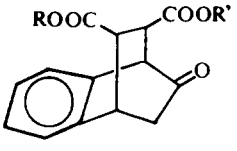
TABLE 2. *trans*-DIACIDS VIII AND IX FROM VI, VII AND XIII AND THEIR NMR DATA (60 Mc) IN d_6-ACETONE

Starting Compd.	IX/VII ratio	Chemical shift of H^{3b} of IX (τ)	Coupling constant (Hz)	Chemical shift of H^{3b} of VIII (τ)	Coupling constant (Hz)
VIa	22/75	7·96	$J_{3b,3a} = 18·3$ $J_{3b,4} = 3·4$ $J_{3b,10} = 2·0$	7·87	$J_{3b,3a} = 18·0$ $J_{3b,4} = 3·4$
VIIIb	0/100			7·84[a]	$J_{3b,3a} = 18·0$ $J_{3b,4} = 3·5$
VIb	0/100			7·84	$J_{3b,3a} = 18·0$ $J_{3b,4} = 3·5$
VIc	29/71			7·85	$J_{3b,3a} = 18·6$ $J_{3b,4} = 3·3$
VId	48/52	7·98	$J_{3b,3a} = 18·5$ $J_{3b,4} = 3·2$ $J_{3b,10} = 2·0$	7·87[b]	$J_{3b,3a} = 19·0$ $J_{3b,4} = 3·3$
VIIe	0/100			7·82	$J_{3b,3a} = 18·5$ $J_{3b,4} = 3·3$
XIII	100/0	7·87	$J_{3b,3a} = 18·7$ $J_{3b,4} = 2·5$ $J_{3b,10} = 1·8$		
VIIf	0/100			7·85[c]	$J_{3b,3a} = 19·0$ $J_{3b,4} = 3·2$

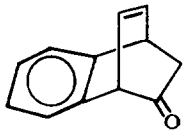
[a] Dimethyl ester in $CDCl_3$. [b] in D_2O–K_2CO_3. [c] in $CDCl_3$.

When the *trans*-diacids of the type VIII were reduced with $NaBH_4$, followed by acidification, lactone-acids X were produced, while from the *trans*-diacids of the type IX hydroxy-diacids XI were obtained. From this fact we can assign *endo* and *exo* configurations of the carboxylic functions in the keto acids VIII and IX. Also comparison of the signals of the proton at position 3b in the NMR spectra supports these configurations. (Figs 3 and 4, and Table 2).

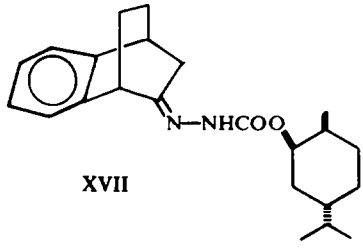
The results shown in Table 2 indicate that steric effects may decide which of the two *trans*-dicarboxylic acids is formed preferentially. In the series a, b, c and e, isomer VIII predominates over IX in the equilibrium mixture mainly because the repulsion between the C-10 carbomethoxyl group and the C-3 methylene group is greater than that between the carbomethoxyl and the aromatic OMe group.[9] A similar reason can be applied for the formation of *trans*-acid VIIIf. On the other hand, the observation that isomers VIIId and IXd are formed in nearly equal amounts suggests that the repulsion between the C-10 carbomethoxyl group and the C-5 OMe group is almost the same as that between the carbomethoxy group and the C-3 methylene group. Another but even more apparent repulsion was exerted in the case of XIII. Contrary to the result obtained from the base treatment of VIIe (only VIIIe was obtained), XIII was transferred to IXe because the repulsion between the C-9 carbomethoxyl group and the ketal moiety is greater than that between the carbomethoxyl group and a bromo-benzene group. From steric factors one would expect relatively less formation of VIII isomer from 8-OMe than from 7-OMe. As the contrary was found to be the case, another factor may be involved.



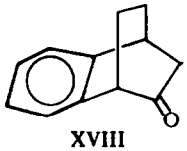
XVa: R = R' = Me
b: R = Me, R' = H



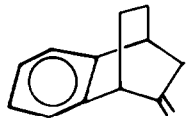
XVI



XVII



XVIII



XIX

Some of these *trans*-diacids were successfully resolved with cinchonidine. In one case both optical antipodes were obtained (VIIIc and antipode). The specific rotations of the pure active salts and the optical properties of the corresponding free acids are listed in Table 3. The active diester (+)-XVa was obtained from the active mono-ester XVb, which was prepared by resolution via the cinchonidine salt from racemic XVb. The monoester XVb* could be obtained by C-9 epimerization and partial hydrolysis of *endo*, *cis*-diester Vf with K_2CO_3. From the unsaturated and saturated ketones, XVI and XVIII,[10] one of active isomers was isolated according to the method of Woodward *et al.*[11] by recrystallization of their menthydrazones and regeneration of the active ketones by acid treatment of the pure hydrazones. Methylene compound XIX were also prepared from ketone XVIII using the Wittig reaction.[12, 13] Optical data of these active compounds (+)-XVI, (−)-XVIII and (−)-XIX are also given in Table 3.

* The structure of XVb was based on the formation of a lactone-ester (methylester of Xf), which will be reported elsewhere.

TABLE 3. OPTICAL ROTATION OF CINCHONIDINE SALTS OF TRANS-ACIDS AND OPTICAL PROPERTIES OF OPTICALLY ACTIVE COMPOUNDS

	$[\alpha]_D$ (MeOH)		UV (MeOH) λ_{max}^{max} (ε)			CD (MeOH) λ_{max}^{max} (θ)		
	Salt	Free compd.						
E* XVIII		+ 356·2[d]	313 (140)	306 (250)	295·5 (278)	318 (+ 19,700)	306 (+ 36,000)	296 (+ 36,300)
			270 (235)	263 (404)	224 (4680)[e]	262 (− 3850)	224 (− 48,000)[e]	
XVa	+ 50·3[b]	+ 208·1[c]	295 (432)	272 (395)	264 (400)	296·5 (+ 37,400)	263 (− 932)	226 (− 50,000)
VIIId	+ 31·0	+ 209·5	295 (440)	281 (2120)	275 (2080)	294 (+ 42,400)		227 (− 31,100)
IXc	+ 44·6	+ 249·8	297 (1140)	284 (2190)	279 (2440)	297 (+ 52,700)		239 (− 77,600)
			237·5 (7290)					
IXe	+ 52·0	+ 192·3	294 (725)	278 (764)	271 (686)	294 (+ 43,600)		235 (− 76,900)
	(− 176·0)†	(− 193·3)†	235 (10,100)	231 (10,600)				
VIIIb	+ 24·5	+ 152·7[a]	282·5 (2040)[a]			295 (+ 63,000)	274 (− 22,400)	236 (− 10,600)[a]
IXa	+ 19·1	+ 207·0	295 (860)	282 (2710)	225[s] (7150)	295 (+ 40,400)	231 (− 35,800)	220 (− 18,500)
E* XIX		+ 140·4[d]	269·5 (740)	262 (730)		268 (+ 680)	221 (+ 63,900)	
XVI		+ 12·4[e]	305 (365)	266 (436)	215 (11,900)[e]	304 (− 7880)	265 (+ 11,170)	238 (− 14,400)
						219 (+ 121,100)[e]		

s: shoulder [a] sodium salt [b] in EtOH [c] methyl ester [d] in $CHCl_3$ [e] in *iso*-octane

* The letter E is used to indicate "enantiomer of."

† The value for (−)-IXe.

The absolute configurations of these active compounds were determined by the CD (Table 3). Very high rotational strength of the Cotton effect associated with the $n \rightarrow \pi^*$ transition in the region 294–307 mμ of these compounds is characteristic of dissymmetric β,γ-unsaturated ketones.[14] The study of the β,γ-unsaturated ketones has already been done, and the chirality of the composite β,γ-benzo ketone chromophore[15] has been related to the sign of the Cotton effect by the octant rule.[16] It is concluded therefore that the absolute configuration of the compounds, (+)-VIIIb, d and (+)-XVa in Table 3, is 1*R*, 4*S*, 9*S*, 10*S*, while that of (+)-IXa, c, e is 1*R*, 4*S*, 9*R*, 10*R*. The active keto compound (−)-XVIII are similarly determined to have 1*S*, 4*S* configuration and the 2-methylene compound (−)-XIX derived from (−)-XVIII has therefore 1*R*, 4*S* configuration. Since catalytic hydrogenation of (+)-XVI gave (−)-XVIII, (+)-XVI has 1*S*, 4*S* configuration.

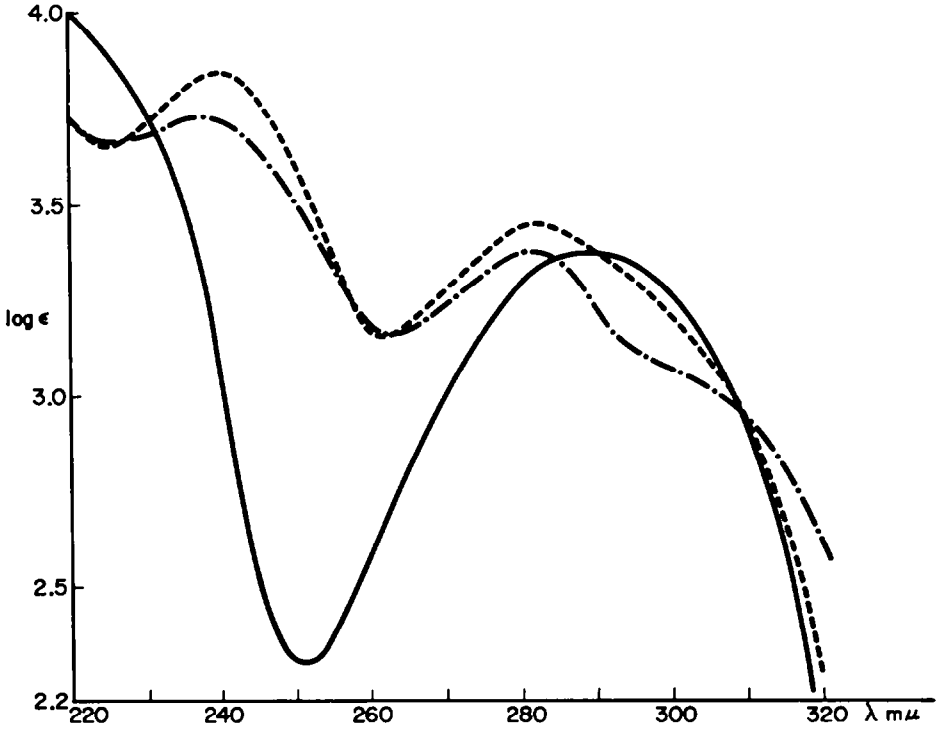


FIG. 5 UV spectra of the adduct IIb (——), IIc (- - - -) and IIIc (–·–) in 95% EtOH

The UV spectra of the adducts IIc and IIIc from 2,6-dihydroxynaphthalene or their derivatives VIIIc and IXc show characteristic strong absorption bands at about 240 mμ (B_{1u}-band) as shown in Fig. 5 and Table 3, which enabled us to distinguish these adducts from those of the other dihydroxynaphthalenes.[17] The CD spectra of the *trans*-acids in Table 3 show characteristic patterns depending upon the relative situation of the CO group and the OMe substituent in the different positions of the benzene ring. For example, the homo-*para* substituted ketones IXc and IXe exhibit a strong negative Cotton effect associated with the B_{1u} transition

(~235 mμ), as well as a strong positive one due to the CO n → π* transition, while the negative Cotton effect associated with B_{2u} transition (~280 mμ) is observed for the homo-*meta* substituted ketone VIIIb.

It can be seen from the comparison between the CD data of XVIII and XVa in Table 3, that the *trans*-dicarboxyl group has no influence on the optical rotatory powers associated with the benzenoid transitions above 220 mμ. Therefore, the great influence of an OMe substituent on the rotatory powers associated with the benzenoid transitions is attributable to the interaction between the benzenoid and the carbonyl states. The compounds XVIII and XIX are structurally similar and have corresponding absolute configurations, yet their optical rotatory properties provide some interesting contrasts, as reported by Mislow *et al.*[15, 18] in benzobicyclo[2.2.1]heptane system; while the Cotton effects associated with the B_{2u} (ca. 265 mμ) and B_{1u} (ca. 220 mμ) benzenoid transitions of XVIII are of negative sign ($[\theta]_{262}$ − 3850 and $[\theta]_{224}$ − 48,000), XIX exhibits the two positive Cotton effects ($[\theta]_{268}$ + 680 and $[\theta]_{221}$ + 63,900). These contrasts are attributed to the manner in which the benzenoid transitions interact with the ethylenic π → π* transition in XIX, whereas in XVIII they interact mainly with the carbonyl n → π* transition through the mixing of the charge transfer transitions. We may, therefore, reasonably conclude that the influence of an OMe substituent on the CD spectra of benzobicyclo[2.2.2] octen-2-one system is attributable to the mixing of the carbonyl n → π* transition with the benzenoid transitions through the charge transfer state. Detailed study of the spectra will be described in the subsequent paper.

EXPERIMENTAL

The IR spectra were measured on a Koken Model D.S. 301 double-monochromatic spectrophotometer and the UV spectra were run on a Hitachi Model E.P.S.-2 UV spectrometer. The NMR spectra were taken at 60 Mc with a Varian A-60 spectrometer using TMS as internal standard. $[\alpha]_D$ were measured with a Perkin Elmer polarimeter Model 141, and CD and ORD spectra were taken with JASCO Model ORD/UV-6. Woelm silica gel (grade II) was used for column chromatograph and Merck silica gel G for TLC, unless otherwise noted.

Preparation of dihydroxynaphthalene- and 6-bromo-2-naphthol-MA adduct*

General procedure. A mixture of dihydroxynaphthalene and an excess of MA (5 molar equiv) was heated at 190–210° (bath temp) in N_2 atmosphere for 1·5–3 hr. In some experiments the remaining MA was distilled off *in vacuo* at 150°. The procedure was also applied for IIIe.

1,7-*Dihydroxynaphthalene adduct* IIa *and* IIIa. 1,7-Dihydroxynaphthalene (2·0 g) and MA (6·5 g) were used. The red brown oily residue was dissolved in acetone and kept overnight. Yellow crystals (0·062 g) precipitated, which were recrystallized from acetone to give yellow needles, m.p. 327°. The residue (4·8 g) of the filtrate of the crystals was chromatographed on silica gel (90 g). The fraction (1·44 g, 44·7%) eluted with $CHCl_3$ and AcOEt (2:1) was recrystallized 4 times from acetone to give IIa as prisms (0·145 g, 4·5%), m.p. 280–281° (dec); IR ν_{max}^{KBr} (cm^{-1}) 1866, 1722 (anhydride), 1723 (carbonyl); dipole moment: μ = 6·82D (in dioxan at 25°); UV λ_{max}^{dioxan} 279 mμ (ε = 2,372), 284 mμ (ε = 2,507). (Found: C, 65·30; H, 4·01. Calc. for $C_{14}H_{10}O_5$: C, 65·12; H, 3·90%).

From the mother liquor another product was obtained by fractional recrystallizations repeated 5 times from acetone-$CHCl_3$; IIIa, prisms (0·150 g, 4·5%), m.p. 242°; IR ν_{max}^{KBr} (cm^{-1}) 1878, 1789, 1732; dipole moment: μ = 2·89D (in dioxan at 25°). (Found: C, 64·95; H, 4·09. Calc. for $C_{14}H_{10}O_5$: C, 65·12; H, 3·90%).

2,7-*Dihydroxynaphthalene adduct* IIb *and* IIIb. 2,7-Dihydroxynaphthalene (2·0 g) and MA (6·1 g) were used. The reddish brown reaction mixture was extracted several times with ether (650 ml). The residue from the ether extract was separated by fractional recrystallizations from AcOEt into the following two products. Sandy crystals of IIb (5·84 g, 18·1%), m.p. 277–278°; IR ν_{max}^{Nujol} (cm^{-1}) 1880, 1860, 1780, 1710;

* MA will be used as abbreviation for maleic anhydride.

UV λ_{max}^{dioxan} 286 mμ (ε = 1,723), 310 mμ (ε = 555), 322 mμ (ε = 260). (Found: C, 64·85; H, 4·10. Calc. for $C_{14}H_{10}O_5$: C, 65·12; H, 3·90%); cubic crystals of IIIc (0·85 g, 2·6%), m.p. 211–212°; IR ν_{max}^{Nujol} (cm^{-1}) 1867, 1844, 1777, 1737; UV λ_{max}^{dioxan} 285 mμ (ε = 2312), 301 mμ (ε = 596), 319 mμ (ε = 269). (Found: C, 65·24; H, 3·96. Calc. for $C_{14}H_{10}O_5$: C, 65·12; H, 3·90%).

In another experiment the two adducts were separated as dimethyl ester as follows. After removing MA, the residue was esterified with MeOH-H_2SO_4. After usual treatment the ether extract was concentrated and the residual oil dissolved in $CHCl_3$ and filtered through silica gel (200 g). The obtained ester mixture was recrystallized twice from AcOEt to give needles of IVb (12·0%), m.p. 190–192°; IR ν_{max}^{Nujol} (cm^{-1}) 1714, 1610; NMR: see Fig. 1. (Found: C, 63·24; H, 5·35. Calc. for $C_{16}H_{16}O_6$: C, 63·15; H, 5·30%).

2,6-*Dihydroxynaphthalene adduct* IIc *and* IIIc. 2,6-Dihydroxynaphthalene (30·0 g) and MA (92·0 g) were used. While the reaction mixture was still warm, ether was added. A slightly brown powder was filtered off and recrystallized from acetone-AcOEt to give crystals of IIc (14·56 g, 30·1%), m.p. 295°; IR ν_{max}^{Nujol} (cm^{-1}) 1848, 1768, 1732, 1597, 1622; UV λ_{max}^{EtOH} 282 mμ (ε = 2,770), 240 mμ (ε = 6,970). (Found: C, 65·25; H, 3·79. Calc. for $C_{14}H_{10}O_5$: C, 65·12; H, 3·90%). Evaporation of the ether filtrate and recrystallizations from acetone-AcOEt afforded IIIc as (3·08 g, 6·46%), m.p. 234–236°; IR ν_{max}^{Nujol} (cm^{-1}) 1852, 1765, 1740, 1618; UV λ_{max}^{EtOH} 281 mμ (ε = 2,390), 237 mμ (ε = 5,340).

1,6-*Didhydroxynaphthalene adduct* IId *and* IIId, *and their ester* IVd *and* Vd. 1,6-Dihydroxynaphthalene (Id, 15 g) and MA (12·2 g) were used. From the ether extract of the deep red reaction mixture, crude crystals (206 mg) were obtained, which were recrystallized from AcOEt to give IId as prisms (73·1 mg, 1·1%), m.p. 257–258°; IR ν_{max}^{Nujol} (cm^{-1}) 3451, 1862, 1764, 1725. (Found: C, 65·34; H, 4·02. Calc. for $C_{14}H_{10}O_5$: C, 65·12; H, 3·90%). The adduct IIId itself was not isolated.

In another run where Id (30·0 g) and MA (90·0 g) were used, the remaining MA was distilled off from the reaction mixture and the brown residue was esterified with MeOH-H_2SO_4. After usual treatment the ether extract was condensed, and the separated crystals of IVd (2·0 g, m.p. 225°) were collected. The residue (ca. 26 g) of the filtrate was chromatographed on silica gel (1 kg) and the fraction eluted with $CHCl_3$-AcOEt (95:5) was recrystallized from acetone to give an additional crop of IVd (5·71 g), m.p. 225–226°. Total yield of IVd was 7·71 g (13·5%); IR ν_{max}^{Nujol} (cm^{-1}) 1735, 1713. (Found: C, 63·27; H, 5·57. Calc. for $C_{16}H_{16}O_6$: C, 63·15; H, 5·30%).

The crystals from the mother liquor and the fractions of the chromatography eluted with $CHCl_3$–AcOEt (90:10–0:100) were combined (19·6 g) and again chromatographed on silica gel (700 g). Recrystallization of the fraction eluted with $CHCl_3$-AcOEt (98:2) from benzene gave crystals (6·18 g) found to be a mixture of

TABLE 4

cos-Diester	m.p., °C (Solvent)	IR (Nujol) cm^{-1}	Anal.,[a] C	Found, % H	Br
IVa	187–189 (MeOH-H_2O)	1752, 1725	62·67	5·38	
Va	95–96 (C_6H_6-$CHCl_3$)	1730	62·85	5·39	
IVb	190–192 (AcOEt)	1710	63·24	5·35	
Vb	171·5–173 (C_6H_6-CCl_4)	1706	63·02	5·28	
IVc	181–182 (MeOH-H_2O)	1760, 1738	63·07	5·33	
Ve	100–100·5 (MeOH)	1730	52·22	4·17	21·99[b]
XIII	126–127 (MeOH)	1745	52·42	5·22	19·58[c]
	* Calc. for $C_{16}H_{16}O_6$:		63·15	5·30	
	$C_{16}H_{15}O_5Br$:		52·33	4·12	21·76
	$C_{18}H_{21}O_6Br$:		52·42	5·12	19·34

IVd and Vd. Pure Vd was obtained by further chromatography of the mixture on silica gel and seeding a pure specimen of Vd (isolated by TLC) to the early benzene eluate. Prisms from benzene-acetone, m.p. 145–145·5°; IR ν_{max}^{Nujol} (cm^{-1}) 1724, 1744. (Found: C, 62·60; H, 5·28. Calc. for $C_{16}H_{16}O_6$: C, 63·15; H, 5·30%).

6-Bromo-2-naphthol adduct IIIe. Ie (5·0 g) and MA (10·0 g) were used. After the remaining MA in the reaction mixture was removed, the residue was dissolved in benzene. After benzene insoluble part (83 mg) was filtered off the filtrate was evaporated and crystallization from acetone gave needles of IIIe (1·17 g, 16·3%), m.p. 234°; IR ν_{max}^{Nujol} (cm^{-1}) 1856, 1835, 1770, 1728; dipole moment: μ = 3·30 D (in dioxan at 25°). (Found: C, 52·39; H, 2·81; Br, 24·69. Calc. for $C_{14}H_9BrO_4$: C, 52·36; H, 2·82; Br, 24·89%). Formation of adduct IIe was not detected.

Esterification of the adduct

General procedure. A soln of the adduct II or III (5 g) in MeOH-H_2SO_4 (5%, 100 ml) was heated under reflux for 2 hr. After cooling, the soln was poured into ice water (500 ml), and extracted with ether. After treating as usual, evaporation of the soln gave the ester IV or V quantitatively.

The dimethyl esters IV and V obtained are summarized in Table 4 (the ester IVd and Vd were already described above). The ketal-diester XIII was obtained from IIIe according to the general procedure. Treatment of XIII with HCl in acetone gave the diester Ve.

$NaBH_4$ *Reduction of the adduct* IIa–d

General procedure. Adduct II (380 mg) was dissolved in 2% NaOH aq (7 ml) with gentle warming. $NaBH_4$ (153 mg, 10 molar equiv) was added to the cold soln and kept at room temp for 2 hr. The soln was acidified with 10% HCl aq and concentrated. The precipitated crystals were collected and recrystallized to give lactone-acid XII.

The data of the obtained lactone-acids XII (and their methyl ester) are summarized in Table 5.

TABLE 5

Lactone-acid	m.p., °C (Solvent)	IR (Nujol) cm^{-1} (lactone)	Anal.,[a] C	Found, % H
XIIa	222–226 (MeOH)	1775	64·78	4·89
XIIb	278–280 (MeOH)	1760	64·55	4·83
Me-ester of XIIb	205–207 (acetone)	1755	65·86	5·25[b]
XIIc	262–264 (MeOH-H_2O)	1769	64·74	4·68
Me-ester of XIId	201–204 (acetone)	1767	64·74	5·33[b]
	[a] Calc. for $C_{14}H_{12}O_5$:		64·61	4·65
	[b] Calc. for $C_{15}H_{14}O_5$:		65·69	5·15

Methoxy-cis-dimethylester VI *and* VII

General procedure. K_2CO_3 (10 g) was suspended in a soln of IV or V (5 g) in acetone (120 ml). Under vigorous stirring, Me_2SO_4 (5 g) was added dropwise, and the mixture was heated under reflux for 5 hr. After dilution with water under cooling, the product was extracted with ether.

The data of the OMe compounds thus obtained are summarized in Table 6.

TABLE 6

Methoxy-*cis*-diester	Yield %	m.p., °C (Solvent)	IR (Nujol) cm^{-1}	Anal.,[a] C	Found, % H
VIa	83·0	157·5–159 (C_6H_6-pet. ether)	1760 1740	64·75	5·84
VIb	79·8	111–113 (MeOH)	1735	64·27	5·74
VIIb	69·5	126–128 (MeOH)	1753 1735	64·01	5·76
VIc	82·6	127·0–128·5 (MeOH)	1730	64·12	5·77
VId	82·5 2·3[b]	143–145 (AcOEt-n-Hexane)	1737	64·20	5·74
VIIId	1·2[b]	126–127 (MeOH)	1730	63·90	5·72
	[a] Calc. for $C_{17}H_{18}O_6$:			64·14	5·70

[b] Yield isolated by fractional crystallization of the esterified reaction mixture from Id.

Preparation of methoxy-trans-*dicarboxylic acid* VIII *and* IX *from methoxy*-cis-*diester* VI *or* VII

General procedure. The *cis*-dimethyl ester VI or VII (3 g) in MeOH-KOH (10%, 60 ml) was heated under reflux for 3 hr. The soln was condensed *in vacuo*, acidified with 6N-HCl, and extracted with ether.

8-*Methoxy*-2-*oxo*-1,2,3,4-*tetrahydro*-1,4-*ethanonaphthalene*-9(*exo*), 10(*endo*)-*dicarboxylic acid* (VIIIa) *and* 9(*endo*), 10(*exo*)-*dicarboxylic acid isomer* (IXa) *from* VIa. The acid mixture from VIa was recrystallized 5 times from AcOEt to give IXa. The NMR spectrum is shown in Fig. 3 and Table 2. Crystals from the mother liquor were recrystallized twice from AcOEt-benzene and then from MeOH-H_2O to give VIIIa.

trans-*Diacid* VIIIb *from* VIb *or* VIIb. The crude acid both from VIb and VIIb showed only one spot on TLC (10% AcOH in $CHCl_3$). After chromatography on silica gel (100 g), the fraction eluted with $CHCl_3$-AcOEt (1:1) was recrystallized from MeOH-H_2O to give VIIIb.

trans-*Diacid* VIIIc *and* IXc *from* VIc. The crude acid mixture from VIc was chromatographed over silica gel (70 g, Woelm, grade II) in AcOEt-$CHCl_3$ (1:2). The first fraction gave IXc (0·31 g) on recrystallization from $CHCl_3$. The second fraction gave VIIIc (0·75 g) on recrystallization from AcOEt-$CHCl_3$.

trans-*Diacid* VIIId *and* IXd *from* VId. The acid mixture from VId (3·0 g) was chromatographed over silica gel (100 g) in AcOEt-$CHCl_3$ (1:4). The first fraction (0·64 g) was recrystallized from MeOH-H_2O to give IXd. The second fraction (0·69 g) was recrystallized from MeOH-H_2O to give VIIId.

trans-*Diacid* VIIIe *from* VIIe. The crude *trans*-acid from VIIe showed only one spot on TLC (10% AcOH in $CHCl_3$). Recrystallization from MeOH-H_2O gave VIIIe in quantitative yield.

trans-*Diacid* IXe *from the ketal* XIII. The crude *trans*-acid from XIII prepared by the general procedure showed only one spot on TLC (10% AcOH in $CHCl_3$). Crystallization from AcOEt gave IXe.

The data of the obtained *trans*-diacid VIII and IX are listed in Table 2, including the VIII/IX ratio and the NMR data. The m.p. and elemental analyses of *trans*-diacids are summarized in Table 7.

trans-*Diacid* VIIIf *and its diester* XVa *from* IIIf. *endo*-2-Naphthol-MA adduct IIIf (62·51 g) was heated in 10% KOH aq (870 ml) at 97–100° (bath temp) for 11 hr. The soln was acidified with conc HCl, extracted with ether and dried. Evaporation and recrystallization from acetone-benzene gave VIIIf as plates (58·31 g, 86·7%), m.p. 189·5–192°; IR ν_{max}^{Nujol} (cm^{-1}) 1710, 1734. (Found: C, 64·69; H, 4·70. Calc. for $C_{14}H_{12}O_5$: C, 64·61; H, 4·65%). The compound was also obtained from *cis,endo*-diester V (R = H).

Dimethyl ester XVa. Prepared by general procedure for esterification. Plates (from AcOEt), m.p. 99–100°. IR ν_{max}^{Nujol} (cm^{-1}) 1227, 1740. (Found: C, 66·72; H, 5·73. Calc. for $C_{16}H_{16}O_5$: C, 66·60; H, 5·59%).

$NaBH_4$ *Reduction of the* trans-*diacid* VIII *and* IX

General procedure. The *trans*-diacid (100 mg) was dissolved in 2% NaOH aq (4 ml). $NaBH_4$ (50 mg) was added, and the soln was kept at room temp for 2 hr. After acidification with dil HCl the crystalline product was collected and recrystallized. In some runs the product was extracted with ether.

TABLE 7

trans-Diacid	m.p., °C	IR (Nujol) cm^{-1}	Anal. Found, % C	H	Br
VIIIa ($1/2H_2O$)	228–229	1700, 1723	60·35	4·98[a]	
IXa	251–253·5	1690, 1735	61·64	4·91	
VIII ($1/2H_2O$)	200·5–202	1715	60·75	5·03[a]	
VIIIc	216–217	1720, 1695	62·10	4·80	
IXc	220–221	1725, 1700	62·03	4·97	
VIIId	240·5–241	1740, 1710	61·70	5·22	
IXd	248·5–249·5	1735, 1700	62·13	4·88	
VIIIe ($1/2H_2O$)	261–262	1700	47·68	3·59	23·14[b]
IXe	165–166	1735, 1700	49·13	3·25	23·66[c]
	Calc. for $C_{15}H_{14}O_6$:		62·07	4·86	
	[a] Calc. for $C_{15}H_{16}O_6 \cdot 1/2H_2O$:		60·21	5·05	
	[b] Calc. for $C_{16}H_{15}BrO_5 \cdot 1/2H_2O$:		48·29	3·48	22·95
	[c] Calc. for $C_{16}H_{15}BrO_5$:		49·58	3·27	23·56

TABLE 8

X or XI	m.p., °C (Solvent)	IR (Nujol) cm^{-1} (lactone)	Formula	Anal. Found, % C	H	Calc. % Br
Xa	241–243	1742	$C_{15}H_{14}O_5 \cdot H_2O$	61·18	5·47	
	($MeOH-H_2O$)			61·64	5·52	
XIa	268·5–270		$C_{15}H_{16}O_6$	61·49	5·57	
	($MeOH-H_2O$)			61·64	5·52	
Xb	197·5–198·5	1742	$C_{15}H_{14}O_5$	65·57	4·91	
	($AcOEt-C_6H_6$)			65·69	5·15	
Xc	232–234	1758	$C_{15}H_{14}O_5$	65·91	5·26	
	($MeOH-H_2O$)			65·69	5·15	
XIc	219–220		$C_{15}H_{16}O_5 \cdot 1/2H_2O$	59·18	5·52	
	($MeOH-H_2O$)			59·79	5·69	
Xe	238–241	1773	$C_{14}H_{11}BrO_4$	52·11	3·46	24·93
	(MeOH)			52·03	3·43	24·73
XIe	239–240		$C_{14}H_{13}BrO_5 \cdot 1/2H_2O$	48·28	4·06	23·17
	($MeOH-H_2O$)			48·02	4·03	22·82

The data of the lactone-acid X or hydroxy-*trans*-diacid XI thus obtained are summarized in Table 8.

Optical resolution of trans-*diacid* VIIIa, b, d, IX c, e, *and* XVb *with cinchonidine*

General procedure. A soln of *trans*-diacid (0·5 g) and cinchonidine (0·5 g) in EtOH (15 ml) was heated under reflux for 1 hr. The soln was evaporated and the residue was dissolved in AcOEt. After standing overnight the precipitated salt was recrystallized from MeOH until the optical rotation ($[\alpha]_D$) of the salt became constant. The purified salt (molecular ratio, 1:1, as shown by elemental analyses) was suspended in ether and decomposed by shaking with dil HCl. The free active acid was purified by recrystallization.

M.ps and solvents for recrystallization of the active acids were as follows: (+)-VIIIa·$1/2H_2O$, 168–169° ($MeOH-H_2O$); (+)-IXc·$1/2H_2O$, 112–114° ($MeOH-H_2O$); (+)-VIIId, 230–231° ($AcOEt-CHCl_3$); (+)-IXe, 166–167·5° ($AcOEt-C_6H_6$); (−)-IXe, 166–167·5° ($AcOEt-C_6H_6$). Satisfactory elemental analyses were obtained for these active acids. Attempted crystallizations of the active acid VIIIb and its dimethyl ester were unsuccessful. However, when the diacid was chromatographed on silica gel (Merck, 0·2–0·5 mm) and developed with MeOH-AcOEt (1:19), crystals of the Na salt-dihydrate were accidentally obtained;

IR ν_{max}^{KBr} (cm^{-1}) 3390, 1720, 1615, 1575. (Found: C, 48·37; H, 4·36. Calc. for $C_{15}H_{12}Na_2O_6 \cdot 2H_2O$: C, 48·65; H, 4·62%); $[\alpha]_D$ of the pure salts and active acids thus obtained are shown in Table 3.

Preparation and resolution of trans-*diacid-monoester* XVb

trans-*Diacid-monoester* XVb. To a soln of *cis* Vf (6·552 g) in MeOH (150 ml), K_2CO_3 (3·284 g) dissolved in water (30 ml) was added. The resulting soln was heated at 60–63° (bath temp) for 3 hr. The bulk of the MeOH was removed under reduced press, and the residue was acidified with 10% HCl aq, extracted with ether, washed with water, dried and evaporated. The residue (shown to be a mixture of VIIIf and XVb) was crystallized from AcOEt to give impure crystals, m.p. 141–151·5° (3·097 g), a soln of which was chromatographed on silica gel (62 g). The fraction (2·796 g) eluted with AcOEt-benzene (10:90–50:50) was recrystallized from AcOEt to give XVb as plates, m.p. 154–155° (2·444 g, 39·2%), IR ν_{max}^{Nujol} (cm^{-1}) 1754, 1732, 1710. (Found: C, 65·93; H, 5·12. Calc. for $C_{15}H_{14}O_5$: C, 65·69, H, 5·15%).

Resolution of XVb *and preparation of* (+)-XVa. A soln of XVb (10·045 g) and cinchonidine (5·412 g, 0·5 molar equiv) in abs MeOH (200 ml) was refluxed for 1 hr. After evaporation, the crystalline residue was recrystallized several times from acetone and then from $CHCl_3$-ether. Finally, recrystallization from MeOH was repeated until the $[\alpha]_D$ became constant; needles (0·682 g), m.p. 208–209° (dec), $[\alpha]_D^{24·5}$ + 50·3° (±0·7) (EtOH, c = 1·067). (Found: C, 71·55; H, 6·50; N, 5·04. Calc. for $C_{34}H_{36}N_2O_6$: C, 71·81; H, 6·38; N, 4·93%). The pure salt (370 mg) in CH_2Cl_2 (15 ml) was shaken with cold 5% $NaHCO_3$ aq, and aqueous layer was washed with ether, acidified with 5% H_2SO_4 and extracted with ether. Evaporation of the ether gave an oil (159 mg, active XVb). The dimethyl ester obtained by methylation of the active XVa was also an oily substance and purified by preparative TLC to give (+)-XVa. The IR in CCl_4 was identical with that of racemic XVa; $[\alpha]_D^{24}$ +208·1° (±4·6) (MeOH, c = 0·571). (Found: C, 66·49; H, 5·82. Calc. for $C_{16}H_{16}O_5$: C, 66·66; H, 5·59%).

Resolution of the unsaturated ketone XVI *through the menthydrazone* XVII[10]. A soln of XVII[10] (3·0 g) and 1-menthydrazide[11] (3·78 g, equivalent mole) in 95% EtOH (45 ml) containing $AcONa \cdot 3H_2O$ (0·9 g) and AcOH (0·45 ml) was refluxed for 48 hr. After cooling and dilution with water, the precipitated crystals were collected, washed with water and recrystallized from MeOH until the $[\alpha]_D$ became constant. Purified XVII was obtained as needles (190 mg), m.p. 225–226°, $[\alpha]_D^{22}$ +47·3° (±0·8) ($CHCl_3$, c = 1·001). (Found: C, 75·36; H, 8·22; N, 7·61. Calc. for $C_{23}H_{30}N_2O_2$: C, 75·37; H, 8·25; N, 7·64%).

The above hydrazone XVII (250 mg) was hydrolized by refluxing in 50% H_2SO_4 aq (14 ml) for 2 hr. Dilution with water and extraction with ether gave an oil (106 mg), which was distilled *in vacuo* and further purified by TLC on silica gel using benzene-AcOEt (10:1). The crystals (39 mg) obtained were recrystallized from ether–n–hexane to give (+)-XVI as rods (24 mg), m.p. 68–69°, $[\alpha]_D^{22}$ +87·5° (±1·2) ($CHCl_3$, c = 1·038).

Resolution of the saturated ketone XVIII *through the menthydrazone.* Menthydrazone of XVIII[10] was prepared similarly to the above. The mixture of the diasteoisomeric hydrazones was recrystallized from 95% EtOH until the $[\alpha]_D$ became constant to give needles, m.p. 223–225°, $[\alpha]_D^{22}$ −81·3° (±1·1) ($CHCl_3$, c = 0·983). (Found: C, 75·13; H, 8·75; N, 7·78. Calc. for $C_{23}H_{32}N_2O_2$: C, 74·96; H, 8·75; N, 7·60%). The hydrazone was hydrolysed similarly as above, and the oil obtained was purified by distillation *in vacuo* followed by crystallization from n-hexane to give (−)-XVIII as prisms, m.p. 52–53°, $[\alpha]_D^{22}$ −356·2° (±4) ($CHCl_3$, c = 0·957). The IR in $CHCl_3$ was identical with that of racemic XVIII. (Found: C, 83·63; H, 7·06. Calc. for $C_{12}H_{12}O$: C, 83·69; H, 7·02%). Catalytic hydrogenation of (+)-XVI with Pd-C in EtOH also gave (−)-XVIII with $[\alpha]_D^{22}$ −331·5° ($CHCl_3$, c = 1·047, somewhat lower value than the above).

Preparation of active and racemic XIX

(a) *Compound* (−)-XIX. Methylenetriphenylphosphorane was generated in DMSO (5 ml) according to Corey *et al.*[13] using NaH (87 mg) and methyltriphenylphosphonium bromide[12] (1·29 g). To a stirred solution of the phosphorane, (−)-XVIII (300 mg) in DMSO (0·5 ml) was added in an N_2 atmosphere at room temp. The mixture was stirred for 1 hr. After cooling and dilution with water, the product was extracted with ether, washed with water, dried and evaporated to give an oil (650 mg). This was chromatographed on silica gel (12 g, Merck) with benzene–n-hexane (2:1). Fractions eluted with the same solvent gave 200 mg of an oil. Vacuum distillation afforded pure (−)-XIX (oil, 167 mg, 57%), $[\alpha]_D^{22}$ −140·4° (±1·7) ($CHCl_3$, c = 1·178); IR $\nu_{max}^{CHCl_3}$ (cm^{-1}) 883 (>C=CH$_2$). (Found: C, 91·95; H, 8·42. Calc. for $C_{13}H_{14}$: C, 91·71; H, 8·29%).

(b) *Racemic* XIX. This compound was prepared similarly from racemic ketone XVIII as an oil. The IR in $CHCl_3$ was identical with that of (−)-XIX. (Found: C, 91·43; H, 8·32%).

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