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STUDIES ON THE CONSTITUENTS OF UMBELLIFERAE PLANTS—XI

STEREOCHEMISTRY OF 3-BUTYLHYDROPHTHALIDES

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Abstract—The absolute configuration of cnidilide (I) and (−)-3-butylphthalide (II) has been determined by two independent methods.

IN THE previous paper,[1] we proposed the relative configurations of cnidilide (I) and neocnidilide (III). Although the absolute configuration of I may be ascertained by determining the absolute configuration of one of the three asymmetric carbons, in order to obtain further evidence on the relative configuration, the absolute configurations of two asymmetric centers, C-3 and C-7a, were determined independently.

Catalytic hydrogenation of I affords quantitatively β-dihydrosedanolide (IV).[2] Since the configuration probably does not change during hydrogenation, compound IV instead of I is discussed.

Compound IV was hydrolysed to the corresponding hydroxy acid (V) by alkaline treatment and V was oxidized to the oily keto acid (VI) with chromium trioxide–pyridine complex. Compound VI was epimerized to the isomeric keto acid (VII) by heating in an alkaline solution. Since VII was also oily, it was converted to the 2,4-dinitrophenylhydrazone (VIII), m.p. 165–168°, $[\alpha]_D$ −56°.

On the other hand (+)-*trans*-hexahydrophthalic acid (IX) was treated with acetyl chloride to give the anhydride (X),[3] which reacted with butyl-cadmium to yield an oily keto acid (XI) and the latter was converted to the crystalline 2,4-dinitrophenylhydrazone (XII); m.p. 165°, $[\alpha]_D$ +69°. Since VIII and XII show the same R_f-value as the racemic form in four systems of thin layer chromatography, which discriminates between the *cis*- and the *trans*-racemates, they are considered to be enantiomeric. The pathway of these conversions is shown below. It is concluded from the results that the absolute configuration of IV at C-7a is the reverse of (+)-*trans*-hexahydrophthalic acid (IX).

The absolute configuration of IX has been established,[4,5] and we came to the same conclusion independently by the route used by one of the investigators but in the enantiomeric series of compounds as shown below. The route had been established in racemates by Owen *et al.*[6] Hückel *et al.* converted (+)-cyclohexane-*trans*-1,2-diacetic acid (XIX) into (−)-*trans*-hydrindanone-(2) (XX),[7] the absolute configuration of which is known to be R from the study of optical rotatory dispersion by

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[1] U. Nagai and H. Mitsuhashi, *Tetrahedron* in print.

[2] H. Mitsuhashi and T. Muramatsu, *Tetrahedron* **20**, 1971 (1964).

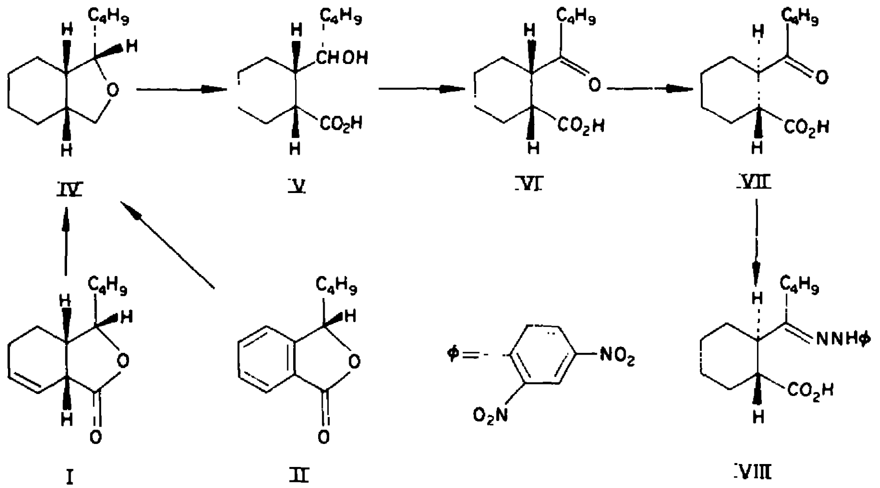
[3] A. Werner and H. E. Conrad, *Ber. Dtsch. Chem. Ges.* **32**, 3046 (1899).

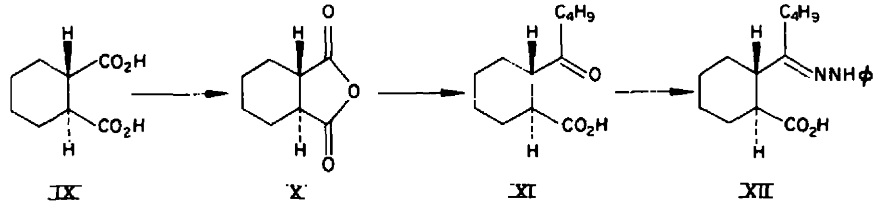
[4] D. E. Applequist and N. D. Werner, *J. Org. Chem.* **28**, 48 (1963).

[5] H. M. Walborsky, L. Barash and T. C. Davis, *Tetrahedron* **19**, 2333 (1963).

[6] G. A. Haggis and L. N. Owen, *J. Chem. Soc.* 389 (1953).
Md. Erfan Alli and L. N. Owen, *J. Chem. Soc.* 2111 (1958).

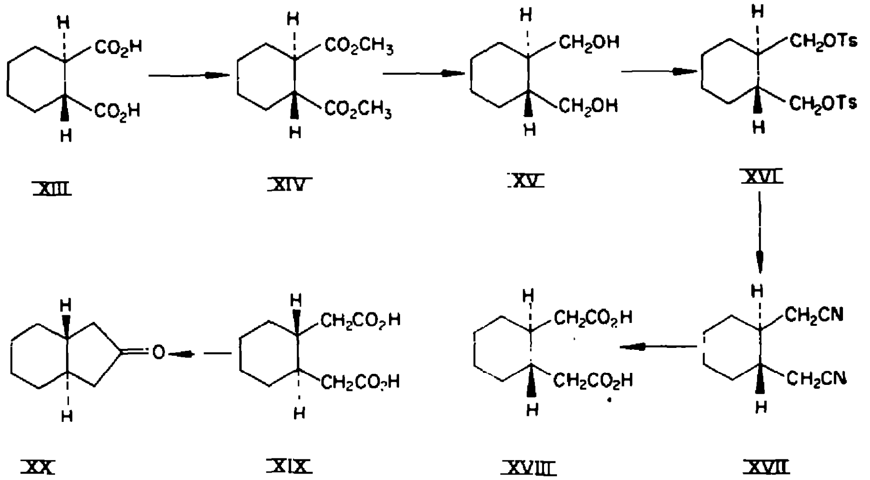
[7] W. Hückel, M. Sachs, L. Yantschulewitsch and F. Nerdel, *Liebigs Ann.* **518**, 183 (1935).





Bourn and Klyne.[8] By tracing back the above routes of correlation, the absolute configuration of IV at C-7a has been established as R. If the relative stereochemistry of IV is correctly assigned, it may be described as 3(S), 3a(S), 7a(R)-3-butylhexahydrophthalide.

In order to confirm this conclusion, the absolute configuration at C-3 was determined by another method. Since Barton and de Vries[9] obtained IV by catalytic



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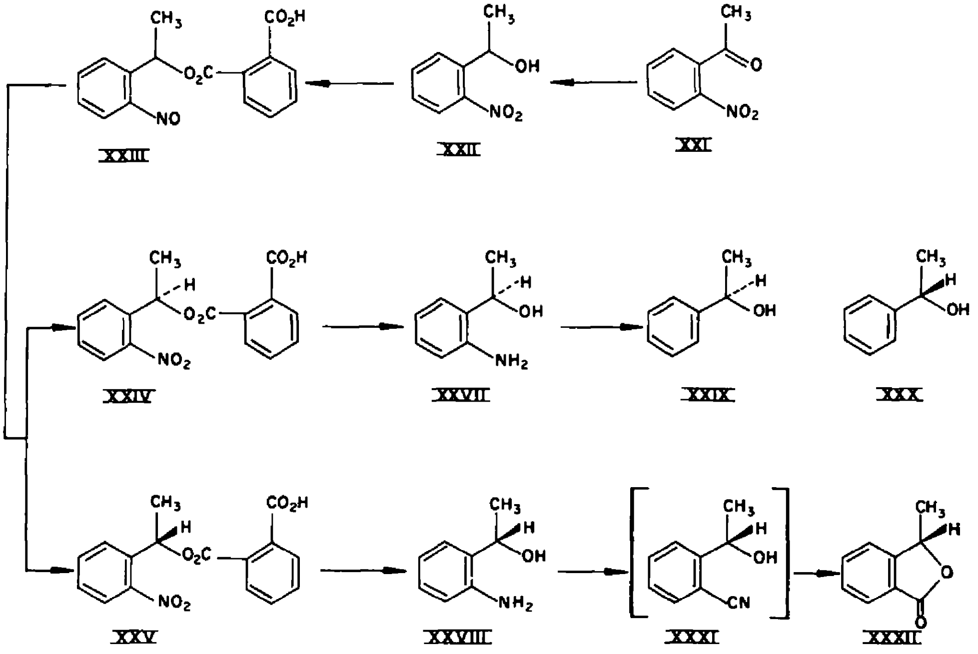
[8] P. M. Bourn and W. Klyne, *J. Chem. Soc.* 2045 (1960).

[9] D. H. R. Barton and J. X. de Vries, *J. Chem. Soc.* 1916 (1963).

hydrogenation of (−)-3-butylphthalide (II), the absolute configuration of which is identical with that of IV at C-3, compound II is discussed.

Methyl *o*-nitrophenyl carbinol (XXII) was prepared by Meerwein–Pondorf–Verley reduction of *o*-nitroacetophenone (XXI),[10] and resolved by recrystallization of the brucine-salt of its hydrogenphthalate (XXIII). The optically active methyl *o*-nitrophenyl carbinyl hydrogenphthalates, (XXIV and XXV) were reduced with sodium sulphide to yield *o*-aminophenyl methyl carbinols, XXVII and XXVIII, respectively. (+)-*o*-Aminophenyl methyl carbinol (XXVII) obtained from (−)-hydrogenphthalate (XXIV), was diazotized and reduced with hypophosphorous acid to afford (+)-methyl phenyl carbinol (XXIX). The optical rotatory power of XXIX had to be measured in solution because of the poor yield. But, since no reliable data measured in solution could be found in the literature, authentic (−)-methyl phenyl carbinol (XXX) was prepared by the method of Downer and Kenyon[11] and its rotatory power measured both without dilution and in solution with the same solvent used for XXIX. No change in sign was observed. The 3,5-dinitrobenzoates of XXIX and XXX were prepared and comparison of their rotatory powers confirmed the above result. (−)-*o*-Aminophenyl methyl carbinol (XXVIII) was diazotized, treated with cuprous cyanide by the procedure of Sandmeyer cyanation, and afforded (−)-3-methylphthalide (XXXII). By tracing the correlation routes shown below, it is concluded that XXXII has the S configuration on the basis of the known absolute configuration of methyl phenyl carbinol.[12]



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[10] Prepared by the method on *Organic Synthesis* **30**, p. 70.

[11] E. Downer and J. Kenyon, *J. Chem. Soc.* **1156** (1939).

[12] P. A. Levene and S. A. Harris, *J. Biol. Chem.* **113**, 55 (1936).
P. A. Levene and P. G. Stevens, *J. Biol. Chem.* **87**, 375; **89**, 471 (1930).
K. Freudenberg, J. Todd and R. Seidler, *Liebigs Ann.* **501**, 199 (1933).

Rotatory dispersions were measured for II, XXVIII, XXX and XXXII. (Fig. 1). Both II and XXXII show negative plain curves, and are considered to have the same absolute configuration. Therefore, II, IV and I are also considered to have the S configuration at C-3 as expected, and their relative configurations are likewise supported. It is interesting to note the opposite sign of rotatory dispersion curves of XXVIII and XXX despite their identical absolute configurations.

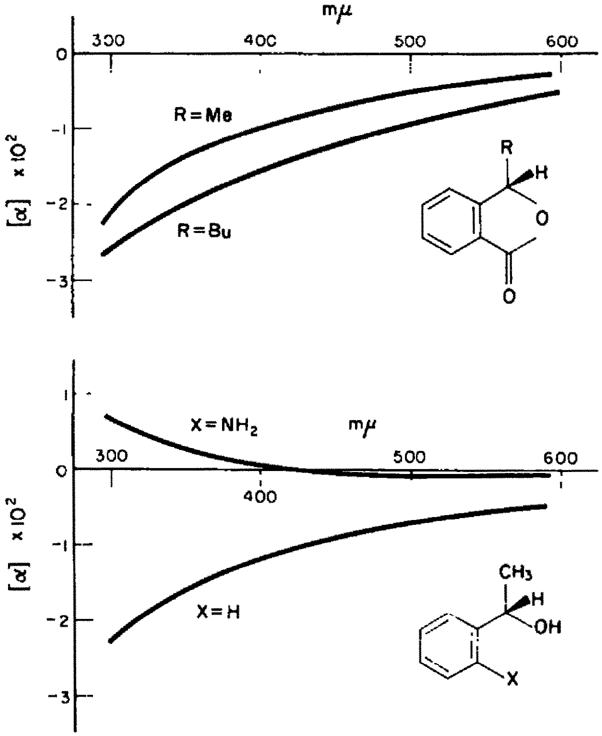
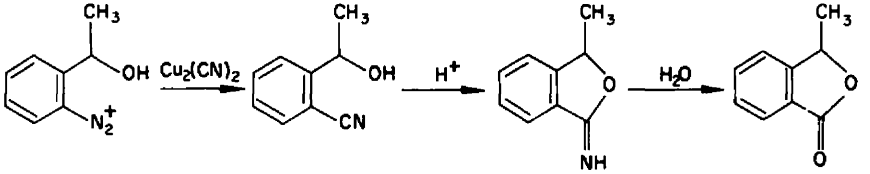


FIG. 1. ORD curves in methanol.

The direct formation of XXXII by Sandmeyer cyanation can be considered as follows. *o*-Cyanophenyl methyl carbinol (XXXI) would be first formed, and the cyano group under the influence of the acidic medium would then react with the neighbouring γ-hydroxyl group to form an intramolecular imino-ether which would then be hydrolysed to XXXII.

Usually, imino-ether formation is carried out in absolute alcohol and the product decomposed with water to form an ester. In this case, the presence of an hydroxyl group in the sterically favoured position excludes the influence of water in the formation of a cyclic imino-ether, which then reacts spontaneously with water to form a lactone. In the preliminary experiments with racemates, *o*-cyanophenyl methyl carbinol was detected by a band at 2200 cm^{-1} in addition to a band at 1770 cm^{-1} due to γ-lactone in the IR spectrum of the crude products with a mild reaction procedure of Sandmeyer cyanation.

From a biogenetic point of view, III is considered to have the same absolute configuration at C-3, though no chemical evidence has been obtained.



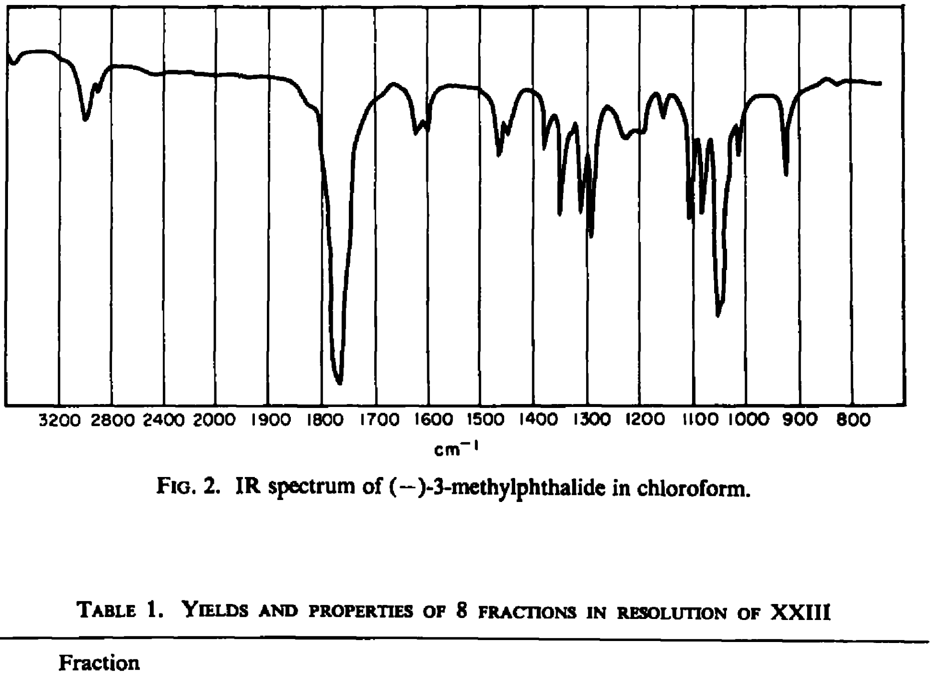


FIG. 2. IR spectrum of (−)-3-methylphthalide in chloroform.

TABLE 1. YIELDS AND PROPERTIES OF 8 FRACTIONS IN RESOLUTION OF XXIII

	Fraction no.	1	2	3	4	5	6	7	8
	Wt (g)	1·3	4·8	5·4	2·7	0·9	2·7	1·9	2·8
Brucine salt	M.p. (dec)	110°–115°	110°–115°	155°	110°–115°	110°	168°–185°	194°	190°–194°
	[α]D	−30·4°	−3·58°	−88·0°	−10·8°	−114°	+40·7°	+120°	+129°
Free acid	Wt-A* (g)	0·4	1·9	2·0	1·0	0·3	1·0	0·6	1·1
	Wt-B* (g)	0·15	1·25	1·2	0·7	0·1	0·5	0·15	0·7
	M.p.	135°–137°	135°–139°	127°–133°	134°–135°	131°–135°	131°–137°	131°–137°	135°–137°
	[α]D	−7·78°	0·00°	−227°	0·00°	−288°	+78·7°	+236°	+320°

* Wt-A and -B indicates the weight before and after recrystallization, respectively.

EXPERIMENTAL

M.ps are uncorrected. Rotatory dispersions were measured in MeOH with the recording spectropolarimeter, ORD/UV-5 Model of JASCO Ltd. Na_2SO_4 was used as drying agent, unless otherwise stated.

Hydrolysis of β-dihydrosedanolide (IV)

Compound IV (70 mg) was dissolved in a small amount of EtOH and heated with 20% KOHaq (0·3 ml) for ½ hr on a boiling water-bath.

The reaction mixture was diluted with water, acidified under cooling, and extracted with cold ether. The ethereal solution was dried ($CaCl_2$) in a refrigerator for 1 hr, and evaporated under red. press. The residue was recrystallized from methylene chloride–hexane and afforded crystals, m.p. 86–90° (30 mg). Crystalline plates, m.p. 93–94° were obtained by recrystallization, $[\alpha]_D^8 = -25·5°$ ($c = 1·55$, $CHCl_3$).

Oxidation of the hydroxy-acid (V)

Epimerization and formation of 2,4-*dinitrophenylhydrazone* (VIII). Chromic acid–pyridine complex was prepared from CrO_3 (50 mg) and pyridine (0·5 ml). Compound V (15 mg) in pyridine (0·15 ml) was added to the complex. More pyridine (0·4 ml) was added to the mixture until homogeneous, and the solution left overnight at room temp. The reaction mixture was diluted with water, acidified and extracted with ether. The ethereal solution was washed with water, dried and evaporated.

The residue (9 mg) was dissolved in 5% KOHaq. The solution (alkaline to Cresol Red) was heated on a boiling water-bath for 1 hr. When cool, the solution was made acidic to Bromphenol Blue and extracted with ether. The ethereal solution was washed with water, dried and evaporated. The residue was dissolved in EtOH, reacted with a solution of 2,4-dinitrophenylhydrazine in alcoholic H_3PO_4 by heating for 5 min on a boiling water-bath and left at room temp for several hr. The precipitate formed was recrystallized from EtOH as needles, m.p. 150–167°. Recrystallization from EtOH yielded plates (2·3 mg); m.p. 165–167° (sint. at 161°), $[\alpha]_D^{11} = -55·6°$ ($c = 0·55$, EtOH).

Reaction of (−)-trans-*hexahydrophthalic anhydride* (X) *with butylcadmium*

Formation of the 2,4-*dinitrophenylhydrazone* (XII). An ethereal solution of BuMgBr was prepared from metallic Mg (0·28 g) and butyl bromide (2·1 g), and converted into butylcadmium by refluxing with $CdCl_2$ (0·78 g) for 40 min until a negative Gilman's test for Grignard reagent was observed. The solvent was replaced with benzene. Finely powdered (−)-*trans*-hexahydrophthalic anhydride (0·6 g) was added to the cold benzene solution of butylcadmium with vigorous stirring. The reaction mixture was refluxed for 3 hr, cooled and stirred with 10% H_2SO_4. The aqueous layer was separated and extracted with ether.

The ethereal solution was combined with the benzene layer, dried and evaporated, yielding 0·79 g of an oily residue. A small portion of the residue was converted to the 2,4-dinitrophenylhydrazone (XII) by the same procedure as above. Recrystallization of XII from EtOH gave plates or needles; m.p. 164–168°, $[\alpha]_D^7 = +69·3°$ ($c = 0·92$, EtOH). (Found: C, 55·32; H, 6·23. $C_{18}H_{24}O_6N_4$ requires: C, 55·09; H, 6·17%).

On admixture with VIII the m.p. was depressed to 135–140°. VIII, XII and their racemate[1] showed the same R_f-value in 4 systems of T.L.C. (MeOH: C_6H_6 = 1:3 and *n*-BuOH saturated with water on alumina G, Merck; MeOH:C_6H_6 = 3:97 and MeOH:$CHCl_3$ = 1:99 on Toshin–Layer G).

Dimethyl trans-*hexahydrophthalate* (XIV)

An ethereal solution of diazomethane was added to the cold solution of (−)-*trans*-hexahydrophthalic acid (700 mg) in ether until the yellowish colour due to diazomethane remained, and kept in a refrigerator overnight. Acetic acid was added dropwise to decompose excess diazomethane. Evaporation of the solvent afforded an oil (XIV; 600 mg).

(+)-trans-1,2-*Bishydroxymethylcyclohexane* (XV)

Compound XIV (600 mg) was dissolved in absolute ether and added to the ethereal solution of LAH (600 mg) under stirring. After 1 hr stirring, the reaction mixture was treated with wet ether to decompose excess of the reagent, then with dil. H_2SO_4 and filtered.

The filtrate was separated. The aqueous layer was extracted with ether continuously for 9 hr. The ethereal solution was dried (K_2CO_3) and evaporated. The residue contained some ester (by IR measurement) and was reduced again with LAH (500 mg). A similar work-up gave an oil (400 mg) with an IR pattern of the expected diol (XV). Crystallized from benzene–hexane, XV showed m.p. 60–63° and $[\alpha]^{17}_{D} = +22{\cdot}2°$ ($c = 3{\cdot}89$, benzene). (lit.[4,6]: m.p. 63–64°, $[\alpha]_D = -20{\cdot}2°$; m.p. 61–62°, $[\alpha]_D = +21{\cdot}4°$.)

(−)-*Ditoluene*-p-*sulphonate* (XVI)

Compound XV (200 mg) was dissolved in pyridine (1 ml) and added drop by drop to the cold solution of toluene-*p*-sulphonyl chloride (800 mg) in pyridine (1·5 ml) under vigorous stirring. Stirring was continued for 2 hr. The reaction mixture was poured into ice-water. The precipitate formed was filtered and recrystallized from MeOH yielding yellowish needles (100 mg), m.p. 105–108° $[\alpha]^{9}_{D} = -17{\cdot}2°$ ($c = 3{\cdot}31$, benzene). (lit.[4,6]: m.p. 109–109·7°, $[\alpha]_D = +25{\cdot}0°$; m.p. 109–110°, $[\alpha]_D = -24{\cdot}8°$.) The filtrate was extracted with ether continuously and the ethereal solution dried, evaporated, yielding crystals of XV.

(−)-trans-1,2-*Biscyanomethylcyclohexane* (XVII)

Compound XVI (100 mg), KCN (42 mg), EtOH (0·6 ml) and water (0·06 ml) were sealed in a test-tube and heated on a boiling water-bath for 60 hr. The solvents were evaporated under red. press, water added to the residue and extracted with ether 7 times. The combined ethereal solution was dried, evaporated yielding an oil (20 mg). The oil was distilled *in vacuo* and the fraction b.p.$_3$ 185–190° (16 mg) collected, (lit.[6]: b.p.$_{0\cdot4}$ 143–144° for the racemate). This crystallized after cooling and showed m.p. 72–73° (sint. at 60°), $[\alpha]^{18}_{D} = -52{\cdot}2°$ (in $CHCl_3$). (lit.[4]: m.p. 62–63°, $[\alpha]_D = -64{\cdot}7°$ in benzene.)

(−)-*Cyclohexane*-trans-1,2-*diacetic acid* (XVIII)

Compound XVII (17 mg) and 50% H_2SO_4 (0·3 ml) were sealed in a tube and heated in an oil-bath at 160° for 8 hr. On cooling the reaction mixture, the crystals which formed were filtered off and recrystallized from aqueous MeOH, m.p. 152–153°, $[\alpha]_D = -18{\cdot}9°$ ($c = 0{\cdot}54$, abs. EtOH). (lit.[4,7,13]: m.p. 149–150°, $[\alpha]_D = +49{\cdot}4°$; m.p. 148–150°, $[\alpha]_D = -48{\cdot}28°$.) The $[\alpha]_D$-value obtained may be inaccurate because the observed rotation was as small as the possible experimental error, but the sign of rotation was definite.

Meerwein–Pondorf–Verley reduction of o-*nitroacetophenone* (XXI)

Cut Al foil (commercial cooking foil was cut and washed with ether; 9·5 g) was dissolved in absolute isopropanol (200 ml) by adding a catalytic amount of $HgCl_2$ (0·5 g) and CCl_4 (2 ml). Heating under reflux for 5 hr was required to dissolve all the Al. Compound XXI (19·0 g) in absolute isopropanol (200 ml) was added to the black solution of aluminium isopropoxide. A check was made with a solution of 2,4-dinitrophenylhydrazine. A negative acetone-test was only observed after 3 days, but the total reaction time was ca. 24 hr, since the heating was interrupted during night. Isopropanol was removed under slightly red. press. and the residue treated with dil. HCl while still hot. After cooling, the reaction mixture was extracted with ether. The ethereal solution was washed with water, dried and evaporated. The residue was distilled *in vacuo* and the fraction b.p.$_5$ 129–133° (13·3 g) collected. Compound XXII showed $\nu^{\text{liq.}}_{\text{max}}$ 3600–3200 (broad, O—H), 1600, 1570 (aromatic C═C), 1520, 1340 (nitro N═O) cm^{-1} in IR spectrum. (lit.[14]: b.p.$_3$ 131–132°.)

Preparation of methyl o-*nitrophenyl carbinyl hydrogenphthalate* (XXIII)

(a) A mixture of XXII (11·0 g), phthalic anhydride (9·8 g) and pyridine (12·0 g) was heated in an oil-bath at 120 ± 10° for 3 hr. The reaction mixture was poured onto a mixture of ice, conc. HCl (12 ml) and water (20 ml). Benzene was added and the solution stirred slowly for ½ hr. The crystals formed between two layers were filtered off and washed with $CHCl_3$. Recrystallization from 90% acetic acid afforded crystals (11 g), m.p. 133–135°.

(b) A mixture of XXII (22 g), phthalic anhydride (20 g) and pyridine (25 ml) was heated in an oil-bath at 120 ± 10° for 3·5 hr. The reaction mixture after pouring onto cold dil. HCl, on which

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[13] W. Hückel and H. Friedrich, *Liebigs Ann.* **451**, 150 (1927).

[14] A. H. Ford-Moore and H. N. Rydon, *J. Chem. Soc.* 679 (1946).

several ml of benzene were floated, was left at room temp overnight. A crystalline precipitate formed and was filtered off. The filtrate was extracted with benzene and the benzene extracted with 10% Na_2CO_3aq. The aqueous layer was separated and used to dissolve the above precipitate. The alkaline solution was washed with benzene, acidified under cooling and gave a sticky precipitate. Benzene (ca. 50 ml) was added to the mixture and left overnight at room temp. The sticky precipitate turned to a crystalline powder during the night. Filtration and recrystallization from 90% acetic acid (100 ml) gave crystals (21 g), m.p. 135–137°.

The mother liquor gave the second crop (4 g) on concentration. (Found: C, 61·16; H, 4·50; N, 4·43. $C_{16}H_{13}O_6N$ requires: C, 60·95; H, 4·16; N, 4·44%).

Resolution of methyl o-*nitrophenyl carbinyl hydrogenphthalate* (XXIII)

(a) Compound XXIII (10·3 g) was dissolved in acetone (35 ml) and finely powdered brucine (12·8 g) added to the hot acetone solution. The precipitate which formed on cooling was filtered off and dissolved in a small volume of MeOH and an equal volume of acetone was added to the solution. The precipitate which formed was dissolved again by heating and the solution kept in a refrigerator overnight. The resulting crystals were filtered off and recrystallized 5 times from MeOH–acetone (1:1). After a few days the crystals formed in some of the mother liquors and were filtered off. The remaining mother liquors were evaporated and the oily residue crystallized by adding a small amount of acetone. In all, the brucine-salt was divided into 8 crystalline fractions, and numbered in order of decreasing solubility. Each fraction was freed from brucine by pouring a hot conc. methanolic solution of the brucine-salt into a flask containing dil. HCl and ether under stirring. The aqueous layer was separated and extracted with ether. The combined ethereal solutions were washed with water, dried, evaporated and recrystallized from 90% acetic acid. The properties of each fraction are listed in Table 1. The analytical data for the fraction 8 was as follows: (Found: C, 60·84; H, 4·26; N, 4·23. $C_{16}H_{13}O_6N$ requires: C, 60·95; H, 4·16; N, 4·44%).

(b) Compound XXIII (21 g) was dissolved in acetone (70 ml), and mixed with a solution of brucine (26·5 g) in MeOH (70 ml). The mixture was left overnight in a refrigerator, but no crystals formed. After scratching the wall of the flask, the solution became turbid and after leaving in a refrigerator for 5 hr 8·6 g crystals were deposited. These were recrystallized from MeOH–acetone (25 ml:25 ml) and yielded 6·0 g, m.p. 190–191°, $[\alpha]_D^{21} = +141°$ ($c = 1·13$, MeOH). A hot conc. solution of the brucine-salt in MeOH was poured into dil. HCl under stirring, and extracted with ether. The ethereal solution was washed with water, dried and evaporated.

The crude hydrogenphthalate (XXV; 2·2 g) was recrystallized from 90% acetic acid and yielded 1·4 g, m.p. 135–138°, $[\alpha]_D^{20} = +318°$ ($c = 0·54$, MeOH). (Found: C, 59·80; H, 3·89; N, 4·46. $C_{16}H_{13}O_6N$ requires: C, 60·95; H, 4·16; N, 4·44%). Crystals (0·35 g), m.p. 134–136° $[\alpha]_D^{20} = +295°$, were obtained from the mother liquor.

Reduction of methyl o-*nitrophenyl carbinyl hydrogenphthalates*, XXIII, XXIV *and* XXV, *with sodium sulphide*

(a) Compound XXIII (5·5 g) was dissolved in a solution of $Na_2S·9H_2O$ (12·5 g) in water (80 ml). The clear orange solution which became turbid after 10 min, was shaken mechanically for 3 hr and then heated for ½ hr on a boiling water-bath. The reaction mixture was extracted with dil. H_2SO_4, made alkaline with 5% NaOHaq and extracted with ether. The ethereal solution was washed with water, dried and evaporated. The residual basic fraction (1·7 g) crystallized, m.p. 57°. Crystals (0·2 g), m.p. 54° were also obtained from the neutral fraction. IR ν_{max}^{Nujol} 3400 (O—H), 3300, 3180 (N—H), 1630 (shoulder, N—H), 1610, 1590 (aromatic C═C) cm^{-1}.

(b) A solution was prepared from XXIV (830 mg; m.p. 129–132°, $[\alpha]_D^{11} = -216°$), $Na_2S·9H_2O$ (1·85 g), MeOH (7 ml) and water (5 ml), and left for 2 days at room temp. The reaction mixture was diluted with water, freed from MeOH by evaporating under red. press, and extracted with ether. The ethereal solution was extracted with 5% H_2SO_4, made alkaline with NaOHaq and extracted with ether. The ethereal solution was washed with water, dried and evaporated. The residue was recrystallized from benzene–hexane and gave needles (160 mg); m.p. 49–54° (Kofler), $[\alpha]_D^{18} = +4·53°$ ($c = 16·2$, MeOH), b.p.$_3$ 96–98°, and IR ν_{max}^{Nujol} 3390 (O—H), 3200 (N—H), 1620 (shoulder, N—H), 1610, 1585 (aromatic C═C) cm^{-1}. (Found: C, 70·24; H, 8·23; N, 10·30. $C_8H_{11}ON$ requires: C, 70·04; H, 8·08; N, 10·21%).

(c) Compound XXV (1·4 g; m.p. 135–138°, $[\alpha]_D = +318°$) dissolved in MeOH (10 ml) and $Na_2S·9H_2O$ (7·0 g) dissolved in water (10 ml), were mixed together in a stoppered flask, left for 2 days at room temp and then refluxed for $\frac{1}{2}$ hr. The reaction mixture was freed from MeOH by evaporating under red. press. and the resulting aqueous solution extracted with ether. The ethereal solution was extracted with dil. H_2SO_4. The aqueous layer was made alkaline with NaOHaq and extracted with ether, washed with water, dried and evaporated. The residue (370 mg) was distilled *in vacuo* (b.p.$_2$ 80–100°) and gave crystalline needles (320 mg); m.p. 54–59°, $[\alpha]_D^{16} = -4{\cdot}10°$ (c = 13·6, MeOH) and IR ν_{max}^{Nujol} 3380 (O—H), 3180 (N—H), 1605, 1582 (aromatic C=C) cm^{-1}. (Found: N, 10·12. $C_8H_{11}NO$ requires: N, 10·21%) ORD: $[\alpha]_{400} = +4{\cdot}27°$, $[\alpha]_{350} = +33{\cdot}2°$, $[\alpha]_{300} = +66{\cdot}3°$ (c = 0·94, MeOH).

Deamination of (+)-o-*aminophenyl methyl carbinol* (XXVII).

A solution of XXVII (90 mg) in conc. HCl (2·0 ml) and water (1·0 ml) was cooled and kept in an ice-salt bath between 0–5°. A solution of $NaNO_2$ (50 mg) in water (0·1 ml) was added drop by drop during 15 min under cooling at −5–0°. Hypophosphorous acid (1 ml, 50%) was added dropwise during 15 min and the solution kept in a refrigerator overnight. The reaction mixture was extracted with ether. The ethereal solution was washed with 10% NaOHaq and water, dried and evaporated. By distillation of the residual oil (44 mg) *in vacuo*, a yellow oil (20 mg), b.p.$_{16-18}$ 80–110°, $[\alpha]_D^{13} = -32{\cdot}6°$ (c = 1·99, CH_2Cl_2) was obtained. Its 3,5-dinitrobenzoate was prepared in the usual way, m.p. 90–120° (Kofler),* $[\alpha]_D^{16} = -33{\cdot}0°$ (c = 1·53, CH_2Cl_2). (Found: C, 57·05; H, 3·98; N, 8·84. Calc. for $C_{15}H_{12}O_6N_2$: C, 56·96; H, 3·82; N, 8·86%).

Authentic (−)-methyl phenyl carbinol was prepared and showed $[\alpha]_D^{22} = -43{\cdot}5°$ (without dilution), $[\alpha]_D^{22} = -52{\cdot}5°$ (c = 2·27, CH_2Cl_2), and ORD: $[\alpha]_{590} = -47{\cdot}4°$, $[\alpha]_{550} = -58{\cdot}0°$, $[\alpha]_{500} = -73{\cdot}8°$, $[\alpha]_{400} = -105{\cdot}0°$, $[\alpha]_{350} = -152{\cdot}5°$, $[\alpha]_{300} = -221°$ (c = 0·76, MeOH), and gave the 3,5-dinitrobenzoate; m.p. 120–122°, $[\alpha]_D^{22} = +36{\cdot}0°$ (c = 1·92, CH_2Cl_2).

Sandmeyer cyanation of o-*aminophenyl methyl carbinols*, XXVI *and* XXVIII

(a) Crystalline $CuSO_4{\cdot}5H_2O$ (5 g) was dissolved in water (20 ml) by heating and a solution of KCN (5·5 g) in water (10 ml) was added slowly to the hot solution keeping the temp between 60–70° during and after the addition. Meanwhile, XXVI (1·6 g) was dissolved in hot 30% H_2SO_4 (20 ml), and the solution immersed into an ice-bath under vigorous stirring in order to obtain a fine suspension of the amine-sulfate. A solution of $NaNO_2$ (1·6 g) in water (10 ml) was added to the suspension of the amine-sulfate under cooling at −5–0°. The diazonium solution was added to the warm solution of $Cu_2(CN)_2$ under stirring during 10 min and heated gently for 15 min on a water-bath under reflux with a vertical air-cooler. The reaction mixture was filtered, and the precipitate dissolved in ether. The ethereal solution was washed with 10% NaOHaq, 10% HCl and water, dried and evaporated. The residue showed a band at 2250 cm^{-1} due to a cyano group in addition to a band at 1770 cm^{-1} due to a γ-lactone in its IR spectrum.

(b) Crystalline $CuSO_4{\cdot}5H_2O$ (600 mg) was dissolved in hot water (2·4 ml) and a solution of KCN (670 mg) in water (1·2 ml) was added slowly keeping the temp between 60–70°. The diazonium solution, prepared from XXVIII (280 mg) as above, was added to the warm solution of $Cu_2(CN)_2$ under stirring during 10 min. The reaction mixture was heated on a boiling water-bath under reflux for 1·5 hr and after cooling extracted with ether. The ethereal solution was washed with dil. HCl, water, dil. NaOHaq and water, dried and evaporated. The residue (88 mg) was distilled *in vacuo*, and the fraction of b.p.$_2$ 60–96° (65 mg) was chromatographed on a column of silicic acid (Mallinckrodt 100 mesh) with $CHCl_3$ elution. An oily substance (29·6 mg) was obtained. UV λ_{max}^{EtOH} 227 mμ (log ε 3·96), 273 mμ (log ε 3·25), 280 mμ (log ε 3·23), IR ν_{max}^{CHCl} 1770 (γ-lactone C=O), 1620, 1600 (aromatic C=C) cm^{-1}. (Fig. 2),** ORD: $[\alpha]_{590} = -30{\cdot}7°$, $[\alpha]_{500} = -36{\cdot}8°$, $[\alpha]_{400} = -92{\cdot}5°$, $[\alpha]_{300} = -214°$ (c = 0·326, MeOH). TLC showed a single spot in 2 solvent systems (MeOH: C_6H_6 = 5:95 and 3:97) on WAKO Aluminium Oxide B-5. ORD data of (−)-3-butylphthalide: $[\alpha]_{590} = -60{\cdot}0°$, $[\alpha]_{500} = -86{\cdot}6°$, $[\alpha]_{400} = -155{\cdot}8°$, $[\alpha]_{300} = -259{\cdot}5°$.

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* The broad range would be due to the racemate, m.p. 91–94°.

** It is identical with that of the authentic (±)-3-methylphthalide sent from Professor P. R. Jones (University of New Hampshire), whom we wish to thank for his kindness.