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Macro Rings. I. Syntheses of a Novel Class of Compounds with a Chain of Alternating Benzene Rings and Methylene Groups[1]

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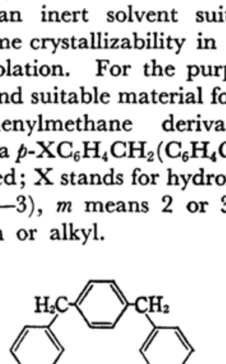
As starting materials for the synthesis of a macrocyclic compound, I, bridged diphenylmethane derivatives of the general formula p-$XC_6H_4CH_2(C_6H_4CH_2)_mC_6H_4X$-$p$ were synthesized; X is hydrogen or $(CH_2)_nCOOR$ (n=0—3), m=2 or 3, and R=hydrogen or alkyl.

Because of the possibility of forming clathrate compounds and other charge-transfer complex, a macrocyclic compound constructed of four or five benzene rings and intervening methylene bridges attached to their para positions is of particular interest.

In the hope of synthesizing a paracyclophane such as I carrying four or five benzene rings, the cyclization of a chain compound with the same number of benzene rings in its molecule has been attempted several times,[2,3] all these attempts have been unsuccessful. As a result of a preliminary experiment, it seemed necessary for a compound to be cyclized to have both an appreciable solubility in an inert solvent suitable for ring closure and some crystallizability in order to avoid difficulty of isolation. For the purpose of finding an accessible and suitable material for the synthesis, bridged diphenylmethane derivatives of the general formula p-$XC_6H_4CH_2(C_6H_4CH_2)_mC_6H_4X$-$p$ were synthesized; X stands for hydrogen or $(CH_2)_n\cdot COOR$ (n=0—3), m means 2 or 3, and R represents hydrogen or alkyl.



I

Fig. 1

Esters of dicarboxylic acids derived from p-bis(p-benzylbenzyl)benzene, Vb—f, were synthesized as shown in Fig. 2 by the Friedel-Crafts acylation of 4-substituted diphenylmethanes, II, with terephthaloyl chloride to terephthalophenone derivatives, III, and either by the Wolff-Kishner reduction of III and subsequent esterification or by the formation of thioketals, IV, and subsequent desulfurization with Raney nickel. Their characteristic infrared absorption bands over the 2000—1660 cm^{-1} range obviously showed that the Friedel-Crafts acylation products, III, and the reduction products, V and VI were para-substituted compounds.

Although the Friedel-Crafts acylation of p-dibenzylbenzene VIII with p-ethoxycarbonylbenzoyl chloride yielded, as is shown in Fig. 3, p-bis[p-(p-ethoxycarbonylbenzoyl)benzyl]benzene, IX, which might be reducible to Vb, this route seemed to be less general than that illustrated in Fig. 2.

The p-dibenzylbenzene, VIII, has been obtained by the Friedel-Crafts reaction of benzyl chloride and benzene, but it has also been reported that the product was accompanied by other isomers and that the separation was fairly difficult because of the similarity of boiling point, melting point and other characteristics between these isomers.⁽⁴⁾ The p-dibenzylbenzene, VIII, was prepared in a pure state either by the Friedel-Crafts alkylation of benzene with p-xylylene chloride, using sulfuric acid as a catalyst, or by the Grignard-coupling reaction of phenylmagnesium bromide with p-xylylene chloride.

Dimethyl bis(p-benzylphenyl)methanedipropionate, XII, was synthesized as shown in Fig. 4. The condensation of p-substituted diphenylmethane, IId, with chloral gave a DDT-type compound, X. The hydrolysis and decarboxylation of X according to the method of Bergmann⁽⁵⁾ led to XI, which was then esterified to XII.

Of all the reactions leading to cyclic compounds, the acyloin condensation of diester is one of the

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[1] Presented in part at the 17th Annual Meeting of the Chemical Society of Japan, Tokyo, April, 1964.
[2] J. J. Randall, *Dissertation Abstr.*, **20**, 2568 (1960).
[3] C. F. Koelsch and C. E. Bryan, *J. Am. Chem. Soc.*, **67**, 2041 (1945).
[4] T. Zinke, *Ber.*, **6**, 119 (1873).
[5] A. B. Galun, A. Kaluszyner and E. D. Bergmann, *J. Org. Chem.*, **27**, 1246 (1962).

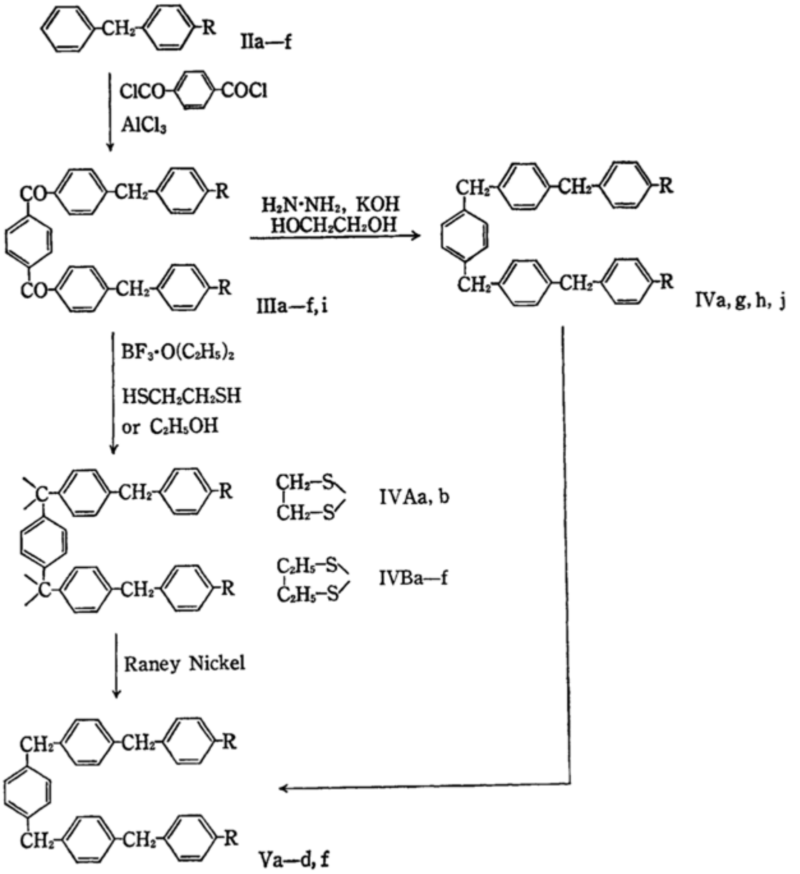

Fig. 2

R: a=H, b=$COOC_2H_5$, c=$CH_2COOC_2H_5$, d=$(CH_2)_2COOC_2H_5$, e=$CO(CH_2)_2COOCH_3$, f=$(CH_2)_3COOCH_3$, g=COOH, h=$(CH_2)_2COOH$, i=$CO(CH_2)_2COOH$, j=$(CH_2)_3COOH$.

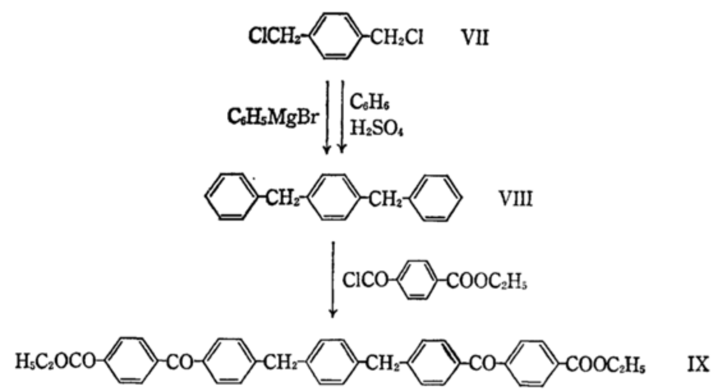

Fig. 3

most popular methods, especially when a satisfactory yield is needed. However, acyloin condensation is usually inapplicable to a compound with a carboxylate group or an acetate group attached to a benzene ring. The Blomquist cyclization method,[6] utilizing the intramolecular condensation of a bifunctional ketene derived from a dicarboxylic acid chloride, is also unsuitable for a compound with an chloroformyl group substituted in

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[6] A. T. Blomquist and R. D. Spencer, *J. Am. Chem. Soc.*, **70**, 30 (1948).

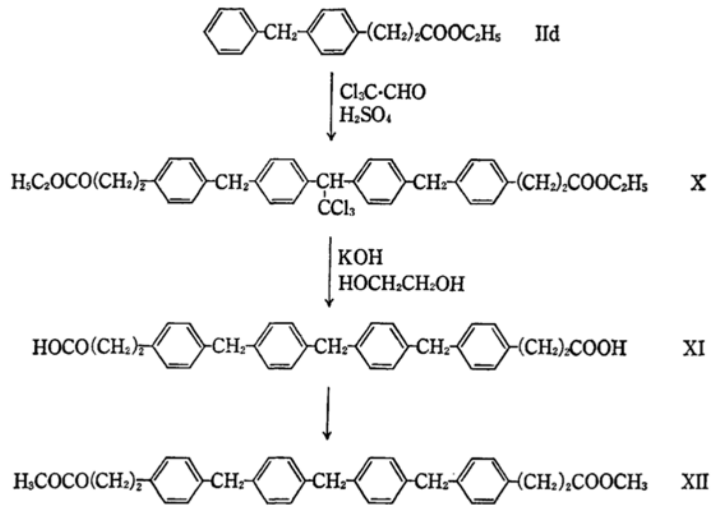

Fig. 4

a benzene ring. For the purpose of obtaining a compound adaptable to cyclization by acyloin or a like reaction, the synthesis of the diphenylmethane derivative, XX, carrying three benzene rings and two cyclohexane rings was carried out as shown in Fig. 5 in a way analogous to that outlined in Fig. 2.

4-Benzylcyclohexanecarboxylic acid, XV, obtained by the reduction of diphenylmethane-4-carboxylic acid, XIV, with sodium and isoamyl alcohol, was confirmed to be identical with the *trans*-4-benzylcyclohexanecarboxylic acid derived from *trans*-hexahydroterephthalic acid, by a comparison of the melting points, infrared spectra, and thin-layer chromatograms of the two anilides.[7]

As a result of the present work, some synthetic procedures for obtaining a compound to be cyclized have been found to be disadvantageous because of either a poor over-all yield or a tedious separation of an intermediate difficult to crystallize or of an end product.

Experimental

All melting points are uncorrected. The physical properties and analytical data of the products are summarized in Table 1.

4-Substituted Diphenylmethanes (IIb—f). *The Ester IIb.* A haloform-reaction product of 4-acetyldiphenylmethane was esterified with ethanol and sulfuric acid.

The Ester IIc was prepared by the hydrolysis[8] and esterification of the 4-cyanomethyldiphenylmethane derived from 4-chloromethyl diphenylmethane.

The Ester IId was prepared by the hydrolysis, decarboxylation, and esterification of the condensation product of 4-chloromethyldiphenylmethane and diethyl sodiomalonate.[8,9] The ester IId was also obtained by the hydrolysis and esterification of a thiomorphoride which had been derived, by a modified Willgerodt reaction, from 4-propionyldiphenylmethane.[10]

The Ester IIe was prepared by the Friedel-Crafts acylation of diphenylmethane with β-methoxycarbonylpropionyl chloride.[11]

The Ester IIf was prepared by the reesterification of the Wolff-Kishner reduction product of IIe.

Terephthalophenone Derivatives (IIIb). To a stirred mixture of 9.2 g of terephthaloyl chloride[3] and 27.5 g of anhydrous aluminum chloride in 100 m*l* of carbon disulfide, there was added slowly, at room temperature, 21.0 g of ethyl 4-diphenylmethanecarboxylate. After the addition, the mixture was stirred for 5 hr at room temperature, left to stand overnight, and refluxed with stirring for 5 hr. After the distillation of the carbon disulfide, the residue was poured onto crushed ice and water. The white solid which deposited was collected by filtration and washed with water, dilute hydrochloric acid, and again with water. Recrystallization from ethanol gave 23.2 g of colorless crystals, mp 162—164°C. An analytical sample was recrystallized from a benzene-ethanol mixture to give colorless needles.

The Thioketal (IVAb). To a mixture of 10.0 g of the keto ester, IIIb, and 4 m*l* of ethanedithiol in 150 m*l* of benzene, 4 m*l* of boron trifluoride etherate were added, after which the mixture was refluxed for 2 hr. After it had then stood for 3 hr at room temperature, 50 m*l* of methanol were added. The removal of the solvent gave 12.0 g of a pale yellow, crystalline powder, which was then washed with acetone and ethanol. An analytical sample was recrystallized from benzene-ethanol mixture.

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7) T. Inazu and T. Yoshino, unpublished data.

8) C. Maquin and H. Gault, *Compt. rend.*, **234**, 629 (1952).

9) C. Maquin and H. Gault, *J. recherches centre natl. recherche sci., Labs. Bellevue*, **No. 34**, 57 (1956) (*Chem. Abstr.*, **51**, 2667e (1957)).

10) D. J. Cram and M. F. Antar, *J. Am. Chem. Soc.*, **80**, 3103 (1958).

11) J. Cason, "Organic Syntheses," Coll. Vol. III, p. 169 (1955).

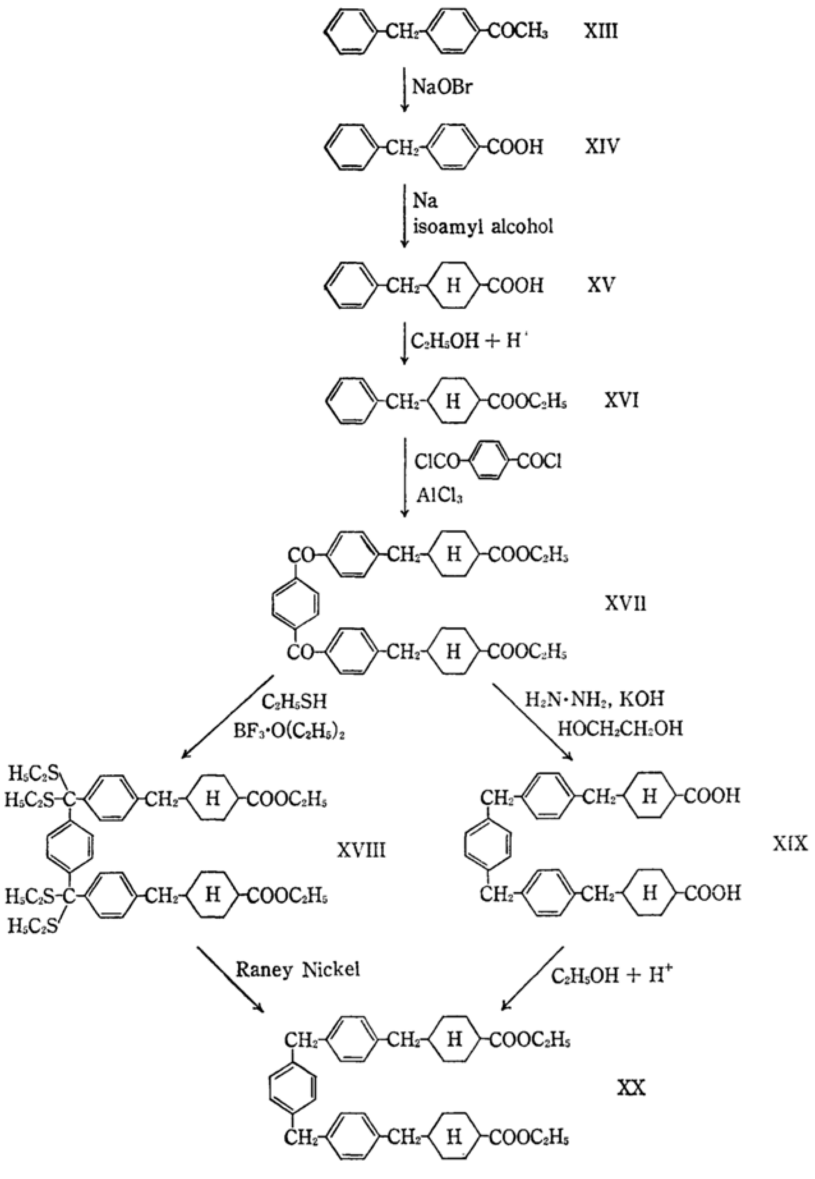

Fig. 5

The Ester (Vb). The thioketal, IVBb, obtained from 1.0 g of the keto ester, IIIb, was refluxed for 16 hr with an excess of Raney nickel in a benzene-ethanol mixture, after which the catalyst was filtered off. The concentration of the filtrate gave 500 mg of colorless crystals, which were recrystallized from a benzene-ethanol mixture, mp 140—141°C.

Carboxylic Acid (VIj). A mixture of 40 m*l* of 90% hydrazine hydrate, 40 g of potassium hydroxide, 250 m*l* of ethylene glycol, and 10 g of keto acid, IIIi, was refluxed for 12.5 hr. After cooling, the deposit, consisting of 5 g of the potassium salt of VIj, was recrystallized from acetic acid to give needles of free acid, mp 225—229.5°C. The potassium salt was converted to free acid during the recrystallization.

The Ester (Vf). Carboxylic acid, VIj (14.5 g, dissolved in benzene), was esterified with methanol and sulfuric acid, and then recrystallized from a benzene-ethanol mixture to give 13.7 g of colorless crystals, mp 133.5—135°C.

***p*-Dibenzylbenzene (VIII).** *Method A*: A mixture of 10 g of *p*-xylylene chloride,[12] 5 m*l* of sulfuric acid, and 100 g of benzene was refluxed for a few days. After the removal of the acid, the mixture was distilled to remove the benzene, and then fractionated under diminished pressure. The first fraction removed, boiling at 125°C/5 mmHg, was an unchanged chloride amounting to 2.5 g; the successive fraction, boiling at 185°C/5 mmHg, was collected to give 3.4 g of colorless crystals, which were recrystallized from ethanol to give VIII, mp 85—86.5°C (reported mp 86°C).[4]

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[12] T. Azumi and M. Hayashi, *Kōgyō Kagaku Zassi* (*J. Chem. Soc. Japan, Ind. Chem. Sect.*), **55**, 476 (1952).

TABLE 1.

Compd.	mp or bp	Cryst. solv.	Cryst. form	Formula	Analyses, %				Yield %
					Found		Calcd		
					C	H	C	H	
IIb	161.5—163°C (3 mmHg)		liq						82
IIc	179—181.5°C (4 mmHg)		liq						88
IId	170—178°C (3 mmHg)		liq						
IIe	213.5—216°C (3 mmHg)		liq						49
IIf	190—194.5°C (5.5 mmHg)		liq						31a)
IIg	159—161°C	W-E	w.n.						97b)
IIIa	107—111.5°C	E	w.c.	$C_{34}H_{26}O_2$	87.53	5.55	87.53	5.62	16
IIIb	162—164°C	E-B	w.n.	$C_{40}H_{34}O_6$	78.77	5.67	78.67	5.61	81
IIIc	101—103°C	E	w.n.	$C_{42}H_{36}O_6$	78.76	5.93	78.97	6.00	35
IIId	99—101°C	E	w.c.	$C_{44}H_{42}O_6$	79.39	6.32	79.25	6.35	33
IIIe	102—103°C	E-B	w.n.	$C_{44}H_{38}O_8$	75.99	5.65	76.06	5.51	40
IIIf	128.5—129°C	M	w.c.	$C_{44}H_{42}O_6$	79.19	6.54	79.25	6.35	
IIIi	231—232°C (decomp.)	AcOH	w.n.	$C_{42}H_{34}O_8$p)	75.03	5.32	74.65	5.22	55
IVAa	148°Cc)	E-B	py.p	$C_{38}H_{34}S_4$	73.83	5.52	73.74	5.54	98
IVAb	144—146°C	E-B	w.c.	$C_{44}H_{42}O_4S_4$	69.13	5.68	69.26	5.55	96—99
IVBa	121—123°C	E-PB	py.c.	$C_{42}H_{46}S_4$	74.39	7.12	74.31	6.83	76
IVBb—fd)									
Vae)	127—128.5°C	E	w.c.						
Vaf)	123.5—125.5°C	E	w.c.	$C_{34}H_{30}$	92.81	7.23	93.11	6.89	47
Vbg)	140—141.5°C	E-B	w.c.	$C_{40}H_{38}O_4$	82.45	6.62	82.44	6.57	58
Vc	133—134.5°C	E-B	w.c.	$C_{42}H_{42}O_4$	82.57	7.15	82.59	6.93	31
Vd	127.5—129°C	E	w.p.	$C_{44}H_{46}O_4$	82.74	7.13	82.72	7.26	29
Vf	133.5—135°C	E-B	w.c.	$C_{44}H_{46}O_4$	82.73	7.28	82.72	7.26	14
Vfh)		E-B	w.c.						91
VIg	>290°C	AcOH	w.p.	$C_{36}H_{30}O_4$q)	81.51	5.82	81.41	5.80	100
VIh		AcOH	w.c.	$C_{40}H_{38}O_4$	79.67	6.49	79.01	6.63	38
VIj	225—229.5°C	AcOH	w.n.	$C_{42}H_{42}O_4$	82.23	7.12	82.59	6.93	96
VIIi)	100°C	E	w.n.						
VIIIj)	85—86.5°C	E	w.pr.	$C_{20}H_{18}$	92.81	7.03	92.81	6.98	23
VIIIk)	85.5—87°C	E	w.pr.						68
IX	121—126.5°C	E	w.n.	$C_{40}H_{34}O_6$	78.52	5.84	78.67	5.61	26
Xd)									
XIl)	212—213°C	E	w.p.	$C_{33}H_{32}O_4$p)	79.12	6.56	79.01	6.63	7
XII	122—122.5°C	M	w.n.	$C_{35}H_{36}O_4$	80.93	6.82	80.74	6.97	95
XIII	161—167°C (3 mmHg)		liq						60
XV	80°C	M-W	w.n.	$C_{14}H_{18}O_2$	77.01	8.23	77.03	8.31	70
XVI	148°C (2.5 mmHg)		liq	$C_{16}H_{22}O_2$	77.75	8.78	78.01	9.00	80
XVII	162°C	Ac-PB	w.p.	$C_{40}H_{46}O_6$	76.99	7.39	77.14	7.45	16
XVIIId)									57
XIX	219.5°Cm)	Ac-W	w.p.	$C_{36}H_{42}O_4$q)	79.20	7.94	78.94	7.91	31
XXn)	107.5—110°C	E	w.c.	$C_{40}H_{50}O_4$	80.45	8.68	80.77	8.47	63
XXo)	107.5—110°C	E	w.c.						57

a) from diphenylmethane. b) by haloform reaction, lit. mp 158°C. c) sintered at 140°C.
d) not isolated in pure state. e) by the Wolff-Kishner reaction of IIIa.
f) *via* thioketal IVBa. g) from ketone IIIb. h) from VIj. i) footnote 12.
j) by the Friedel-Crafts reaction. k) by the Grignard reaction. l) from ester IId.
m) sintered at 207°C. n) from XIX. o) from ketone XVII *via* XVIII.
p) as a hydrate with a half molecule of water. q) as a hydrate with one fourth molecule of water.
Ac=acetone, AcOH=acetic acid, B=benzene, c=crystals, E=ethanol, liq=liquid, M=methanol, n=needles, PB=petroleum benzin, p=powder, pr=prisms, py=pale yellow, w=white, W=water.

Method B: A solution of 10 g of *p*-xylylene chloride in 80 m*l* of benzene was added to a solution of phenylmagnesium bromide in 60 m*l* of ether. The mixture was refluxed and then distilled to remove the ether. After the solution had been left standing overnight, crushed ice and dilute hydrochloric acid were added. An oily substance which separated from the organic layer was distilled at 140—185°C/4 mmHg to give 7.6 g of colorless crystals, which were recrystallized to give colorless plates, mp 85.5—87°C.

No melting-point depression was observed when this substance was admixed with a sample prepared by the method A.

Keto Ester (IX). To a stirred mixture of 25.5 g of powdered anhydrous aluminum chloride and 15 g of *p*-ethoxycarbonylbenzoyl chloride[13] in 50 m*l* of carbon disulfide, there was added a solution of 10 g of *p*-dibenzylbenzene VIII in 80 m*l* of carbon disulfide. After additional stirring for 2 hr at room temperature, the mixture was refluxed for 21 hr, and decomposed with dilute hydrochloric acid and crushed ice after the removal of the carbon disulfide by distillation. The deposit was extracted with benzene to yield 5.6 g of colorless crystals. An analytical sample was recrystallized from ethanol to give colorless crystals, mp 121—126.5°C.

Carboxylic Acid (XI). To a stirred mixture of 2.75 g of freshly-prepared anhydrous chloral and 10.0 g of the ester IId, 25 m*l* of concentrated sulfuric acid were added, drop by drop, under cooling. After additional stirring for 3.5 hr, the mixture was poured onto crushed ice. The pale pink, gummy deposit was refluxed with a solution of potassium hydroxide in 100 m*l* of ethylene glycol for 14 hr, and then poured onto crushed ice and acidified with dilute hydrochloric acid. The deposit afforded XI as a pale brown powder (600 mg); this powder was crystallized from ethanol to give a crystalline powder with a mp 212—213°C.

***trans*-4-Benzylcyclohexanecarboxylic Acid (XV).** Into a solution of 60 g of 4-benzylbenzoic acid, XIV, obtained from 4-acetyldiphenylmethane, XIII, by haloform reaction and dissolved in 1250 m*l* of isoamyl alcohol, there were stirred, portion by portion, 148.9 g of sliced sodium. The mixture was refluxed with stirring for 3 hr, and then cooling water was added. After the removal of the isoamyl alcohol by steam distillation, the solution was neutralized and extracted with ether. The usual treatment gave 42 g of colorless needles, mp 79—80°C. An analytical sample was recrystallized from a methanol-water mixture.

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13) J. B. Cohen and H. S. de Pennington, *J. Chem. Soc.*, **113**, 63 (1918).