(2:1), to give 0.35 g (72%) of a homogeneous foam. This was identified with compound **20** obtained above by nmr and uv spectroscopy.

Anal. Calcd for $C_{17}H_{18}N_2O_7S$: C, 51.78; H, 4.61; N, 7.10. Found: C, 51.77; H, 4.71; N, 6.78.

Registry No.—**1**, 6554-10-5; **2**, 37440-10-1; **3**, 14985-34-3; **4**, 362-43-6; **5**, 32464-90-7; **6**, 37440-11-2; **7**, 37440-12-3; **8**, 37440-13-4; **9**, 37440-14-5; **10**, 37445-38-8; **11**, 37567-14-9; **13**, 37445-39-9; **15**, 37445-43-5; **16**, 28734-85-2; **17**, 37445-44-6; **18**, 37445-40-2; **19**, 37445-41-3; **20**, 37445-42-4; **21**, 37445-45-7; uridine, 58-96-8.

Stobbe Condensations of Dimethyl 3,5-Bis(benzyloxy)homophthalate[1a]

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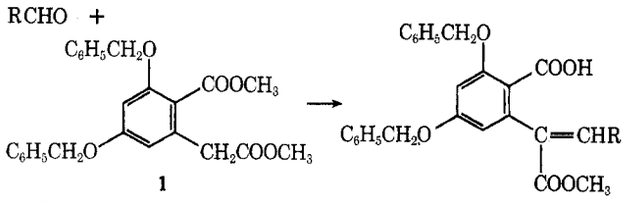
Dimethyl 3,5-bis(benzyloxy)homophthalate (**1**) reacts with aliphatic aldehydes under conditions of the Stobbe condensation to give preparative yields of Stobbe acid esters analogous to the Stobbe products of succinic esters. From butyraldehyde (**2**) and 4-benzyloxybutyraldehyde (**4**), respectively, are obtained 2,4-bis(benzyloxy)-6-(1-carbomethoxy-1-penten-1-yl)benzoic acid (**5**) and 6-(5-benzyloxy-1-carbomethoxy-1-penten-1-yl)-2,4-bis(benzyloxy)benzoic acid (**7**). In the case of 4-chlorobutyraldehyde (**3**), the Stobbe product (**6**) forms a cation (**9**) in the presence of base that undergoes intramolecular displacement of chlorine to give the cyclopropane derivative (**8**). In the condensation of **1** and **4** to give **7**, a second product (**12**) is concurrently formed that is analogous to the paraconic esters formed in the Stobbe condensations of succinic esters. 3,4-Dihydroisocourmarins such as **12** have not been observed previously in Stobbe condensations of homophthalic esters. Ester acid (**7**) was readily saponified to diacid **13** and reduced to the β-resorcyclic acid derivative **14**.

In the course of development of a synthetic route for (*R,S*)-zearalanone,[2] we have studied the reaction of dimethyl 3,5-bis(benzyloxy)homophthalate (**1**) with several aliphatic aldehydes under conditions of the Stobbe condensation.[3]

The original concept of the Stobbe reaction as a basic condensation of esters of succinic acid with aldehydes and ketones has been extended to homophthalic esters with a variety of aromatic aldehydes and ketones.[4] We find that this condensation proceeds smoothly with aliphatic aldehydes using sodium hydride as base,[5] to give preparative yields of the Stobbe half-esters. With butyraldehyde (**2**), for example, a quantitative yield of the Stobbe half-ester **5** was readily obtained.

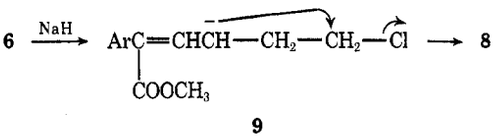


1

2, R = C_3H_7
3, R = $ClCH_2CH_2CH_2-$
4, R = $C_6H_5CH_2OCH_2CH_2CH_2-$

5, R = C_3H_7
6, R = $ClCH_2CH_2CH_2-$
7, R = $C_6H_5CH_2OCH_2CH_2CH_2-$
8, R = 

With 4-chlorobutyraldehyde (**3**), a secondary reaction also took place. In addition to normal Stobbe condensation (which would have given the half-ester **6**), cyclization occurred so that the only product isolated (in 63% yield) was the cyclopropane-containing half-ester **8**. The mechanism of formation of **8** probably involves the reaction of base with the first-formed Stobbe product **6** to give carbanion **9**, which



9

then cyclizes to **8** by intramolecular displacement of chlorine. Similar intermediates have been proposed before in the formation of cyclopropane derivatives, such as in the reaction of 4-chlorobutyronitrile and sodamide to give cyclopropanenitrile.[6] We believe that the formation of **8** represents the first observation of cyclization of a derivative of 6-halo-2-hexenoic acid to a cyclopropane.

The familiar, accepted mechanism for the Stobbe reaction proposed an intermediate paraconic ester.[3] In the use of succinic esters in the Stobbe reaction, paraconic esters have been identified and isolated on several occasions. A similar mechanism for the reaction of an aldehyde with methyl homophthalate would involve the steps shown in Scheme I. The 3,4-dihydroisocoumarin **10** is analogous to the paraconic esters formed during the Stobbe condensation of succinic esters, but until now **10** has not been isolated under Stobbe conditions. Instead, **11** is the isolated product. Under acidic conditions, however, **11** may be isomerized to **10**.[4b]

In the present work it was demonstrated that an analog of **10** was obtainable by reaction of **1** with 4-benzyloxybutyraldehyde (**4**) under Stobbe conditions. Two products were isolated, one of which is the expected half-ester **7**, and the other of which is the 3,4-dihydroisocoumarin **12**. The latter product was converted quantitatively into **7** by treatment with sodium

(1) (a) Part of this work was presented as a paper at the 157th National Meeting of the American Chemical Society, Minneapolis, Minn., April 1969, MEDI 28. (b) G. D. Searle International Co., P. O. Box 5486, Chicago, Ill. 60680.

(2) R. N. Hurd and D. H. Shah, *J. Med. Chem.*, in press.

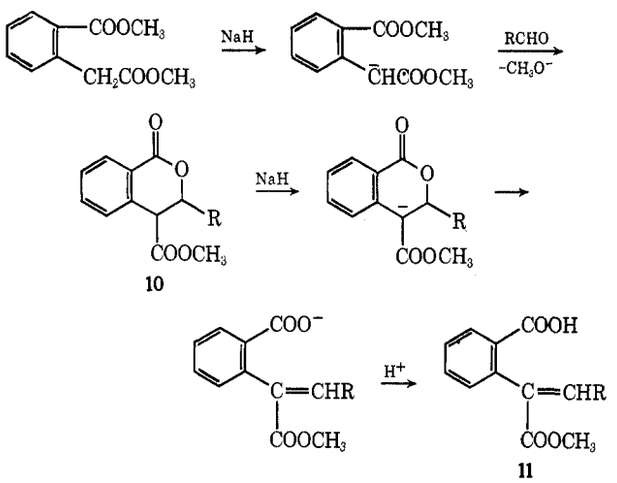
(3) W. S. Johnson and G. H. Daub, *Org. React.*, **6**, 1 (1951).

(4) (a) W. Dieckmann, *Chem. Ber.*, **47**, 1432 (1914); (b) H. J. E. Loewenthal and R. Pappo, *J. Chem. Soc.*, 4799 (1952); (c) J. B. Jones and A. R. Pinder, *ibid.*, 2612 (1958); (d) J. N. Chatterjea and H. Mukherjee, *J. Indian Chem. Soc.*, **37**, 379 (1960); (e) J. H. Chatterjea, K. D. Banerji, and H. Mukherjee, *ibid.*, **40**, 45 (1963).

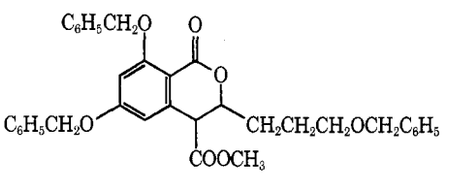
(5) G. H. Daub and W. S. Johnson, *J. Amer. Chem. Soc.*, **72**, 501 (1950).

(6) J. B. Cloke, R. J. Anderson, J. Lachmann, and G. E. Smith, *ibid.*, **53**, 2791 (1931).

SCHEME I



methoxide in absolute methanol. Products **7** and **12** were separated chromatographically.



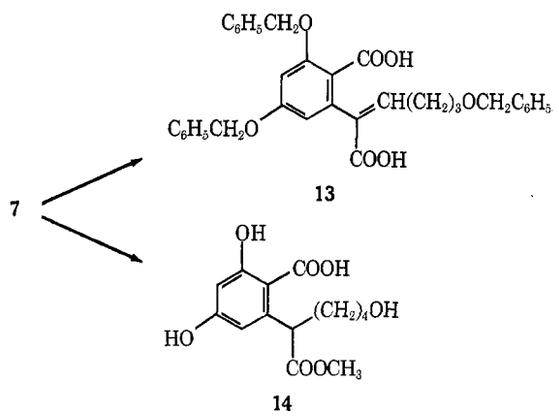
The infrared spectra of half-esters **5**, **7**, and **8** showed intense sharp bands at 1707 cm^{-1} from carbonyl absorptions of the α,β-unsaturated ester functions. The 3,4-dihydroisocoumarin **12** exhibited an equally intense sharp band at 1720 cm^{-1} for the lactone carbonyl, a value in good agreement with the values previously reported[4b] for other 3,4-dihydroisocoumarins prepared from Stobbe products. Crystalline half-esters **5** and **8** showed intense sharp bands at 1680 and 1688 cm^{-1}, respectively, for carboxyl carbonyl absorptions. Half-ester **7**, which was noncrystalline although analytically pure, showed only a poorly defined shoulder on the ester carbonyl band to indicate carboxyl.

Daub and Johnson, who developed the use of sodium hydride as a superior basic reagent for Stobbe condensations, reported that, although this reaction proceeded at a suitable rate to give a high yield of product from diethyl succinate, acetophenone, and this base, no appreciable reaction occurred comparably with benzophenone until a few drops of alcohol were added.[7] The reaction then proceeded suitably. As a general procedure, they recommended use of 0.25 mol of alcohol/mol of ketone (or aldehyde).[5] With respect to Stobbe condensations of homophthalic esters using sodium hydride, the literature is not consistent: Loewenthal and Pappo[4b] did not report use of alcohol in any of their successful Stobbe condensations, including one with benzophenone. Chatterjea, *et al.*,[4e] reported use of a catalytic amount of alcohol in one out of seven successful Stobbe condensations.

In our hands, using equimolar amounts of **1**, aldehyde, and sodium hydride in dry benzene at 25°, the Stobbe condensation proceeded satisfactorily to preparative yields *only* when alcohol was added. With **1** and **2**, for example, a quantitative yield of **5** was obtained if a 0.25 molar equiv of absolute ethanol was added initially; reduction to half this amount of alcohol gave only a 40% yield of Stobbe product **5**, accompanied by a 40% yield of a methyl hydrogen 3,5-bis(benzyloxy)homophthalate.

Similarly, condensation of **1** and **4** gave a quantitative total yield of **7** and **12** with use of 0.25 molar equiv of alcohol in a reaction time of 1 hr. Half this amount of alcohol, in the same time, gave only a 70% yield of Stobbe product together with a 30% recovery of **1**. When no alcohol was used, the yield fell to 66% in 1 hr of reaction time, and unchanged **1** was detected after 4 days.

Ester acid **7** was readily saponified to diacid **13**. Low pressure hydrogenolysis, catalyzed by palladium on charcoal, readily removed the three benzyl groups of **7** and reduced the ethylenic double bond, to give **14**.



Experimental Section

Infrared spectra were obtained with a Perkin-Elmer 21 spectrophotometer. Nuclear magnetic resonance spectra were obtained on a Varian A-60A spectrometer. Melting points were taken in a Thomas-Hoover capillary melting point apparatus and are uncorrected.

Dimethyl 3,5-Bis(benzyloxy)homophthalate (1).—Dimethyl 3,5-dihydroxyhomophthalate[8] (1.2 g, 0.005 mol), benzyl chloride (2.35 ml, 0.02 mol), and anhydrous potassium carbonate[9] (2.0 g, 0.0146 mol) were mixed with 25 ml of dry methyl ethyl ketone. The mixture was refluxed for 72 hr, and then the solvent was removed under reduced pressure. The residue was treated with water, and the aqueous mixture was extracted with ether. From evaporation of the dried ether extract was obtained an oil that crystallized on trituration with methanol to yield 0.65 g (33%) of pure **1**, mp 85–86°.

Anal. Calcd for $C_{25}H_{24}O_6$: C, 71.33; H, 5.71. Found: C, 70.94; H, 5.96.

2,4-Bis(benzyloxy)-6-(1-carbomethoxy-1-penten-1-yl)benzoic Acid (5).—A solution of **1** (6.72 g, 0.016 mol), 53.3% sodium hydride (0.720 g, 0.016 mol), and anhydrous ethanol (12 drops) in 20 ml of dry benzene under nitrogen was added dropwise in 10 min to a solution of **2** (1.152 g, 0.016 mol) in 10 ml of dry benzene. After stirring overnight at room temperature, 50 ml of water was added. The aqueous phase was separated, washed with ether, and then acidified (dilute HCl) to precipitate a quantitative yield (7.5 g) of **5**, mp 130–132°.

Anal. Calcd for $C_{28}H_{28}O_6$: C, 73.02; H, 6.12. Found: C, 72.77; H, 6.47.

2,4-Bis(benzyloxy)-6-(1-carbomethoxy-2-cyclopropylvinyl)benzoic Acid (8).—Under conditions identical with those given for the preparation of **5**, except for the substitution of 1.70 g

(7) G. H. Daub and W. S. Johnson, *J. Amer. Chem. Soc.*, **70**, 418 (1948).

(8) D. S. Jerdan, *J. Chem. Soc.*, 808 (1899); H. Nogami, *J. Pharm. Soc. Jap.*, **61**, 24 (1941); A. Kamal, A. Robertson, and E. Tittensor, *J. Chem. Soc.*, 3375 (1950); W. R. Allison and G. T. Newbold, *ibid.*, 2512 (1960).

(9) With use of potassium carbonate sequihydrate, only dimethyl 4-benzyloxy-2-hydroxyhomophthalate can be obtained from this reaction.

(0.016 mol) of 3[10] for 2, 5.00 g (63%) of white 8, mp 178–179°, was obtained: nmr (DMSO-d_6) δ 0.5–1.0 (broad m, 5.5, cyclopropyl H's), 3.58 (s, 3, OCH_3), 5.15 (s, 4, 2 $OCH_2C_6H_5$), 6.24 (broad s, 1, >C=CH—), 6.45 (d, J = 2 cps, 1, aromatic H), 6.85 (d, J = 2 cps, 1, aromatic H), 7.45 (s, 10, 2 $OCH_2H_6H_5$).

Anal. Calcd for $C_{28}H_{26}O_6$: C, 73.35; H, 5.71. Found: C, 73.21; H, 5.80.

6-(5-Benzyloxy-1-carbomethoxy-1-penten-1-yl)-2,4-bis(benzyloxy)benzoic Acid (7) and 3-(3-Benzyloxypropyl)-4-carbomethoxy-6,8-bis(benzyloxy)-3,4-dihydroisocoumarin (12).—Under conditions identical with those given for the preparation of 5, except for the substitution of 2.85 g (0.016 mol) of 4[11] for 2, 9.00 g (quantitative yield) of a paste was obtained. This paste was a mixture of 7 and 12.

When 7 was desired, the paste was dissolved in 60 ml of anhydrous methanol, 0.865 g (0.016 mol) of sodium methoxide was added, and the resulting mixture was refluxed overnight. After cooling, it was acidified (dil HCl). Methanol was removed under reduced pressure, and the paste that remained was extracted with ether. The extract was dried ($MgSO_4$), and removal of ether gave 8.36 g (92.2%) of 7 as a paste: nmr ($CDCl_3$) δ 1.5–2.2 (broad m, 4, $-CHCH_2CH_2CH_2OCH_2C_6H_5$), 3.2–3.92 (m, 5, $-OCH_2$ and $-OCH_3$), 4.40 (s, 2, $-OCH_2C_6H_5$, aliphatic), 5.00–5.10 (d, 4, 2 $OCH_2C_6H_5$, aromatic), 6.40 (d, J = 2 cps, 1, aromatic H), 6.8–6.95 (m, 1, >C=CH—), 7.20–7.35 (d, 15, 3 $OCH_2C_6H_5$), 9.83 (broad s, 1, –COOH).

Anal. Calcd for $C_{35}H_{34}O_7$: C, 74.20; H, 6.00. Found: C, 73.97; H, 6.36.

When 12 was desired, the pasty mixture of 7 and 12 (9.00 g) was subjected to dry column chromatography on silica gel HF 254 using 2:3 acetone–cyclohexane mixture as the solvent. There was obtained 1.13 g (12.5%) of 12 which, after recrystallization from methanol, melted at 128–130°: nmr ($CDCl_3$) δ 1.7–2.00 (m, 4, $-CH_2CH_2CH_2O-$), 3.65 (s, 3, OCH_3), 3.40–3.80 (m, 3, C-4 H and $-CH_2CH_2CH_2O-$), 4.38 (broad s, 3, $-OCH_2-C_6H_5$ aliphatic and C-3 H), 5.02–5.18 (d, 4, 2 $OCH_2C_6H_5$ aromatic), 6.40 (d, J = 2 cps, 1, aromatic H), 6.60 (d, J = 2 cps, 1, aromatic H), 7.29–7.39 (d, 15, 3 $OCH_2C_6H_5$).

Anal. Calcd for $C_{35}H_{34}O_7$: C, 74.20; H, 6.00. Found: C, 74.54; H, 6.64.

The 3,4-dihydroisocoumarin (12) was converted into 7 in good yield by the method given above for the pasty mixture of 7 and 12.

α-(4-Benzyloxybutylidene)-3,5-bis(benzyloxy)homophthalic Acid (13).—Half-ester 7 was hydrolyzed by boiling in 10% alkali for 2 hr to give 10 as a paste in quantitative yield. This paste contained about 0.7 g-atom of sodium/mol of 13. To free the acid from its salt, the paste was dissolved in a minimal amount of ethanol, excess concentrated HCl was added, and the resulting solution was stirred overnight at 25°. Ethanol was removed under reduced pressure and water was added to the mixture. The product was extracted with ether. The ethereal extract was dried ($MgSO_4$), and ether was removed to give 13 as a paste. Final purification was accomplished by column chromatograph on Florisil (100–200 mesh) with chloroform: nmr ($CDCl_3$) δ 1.35–2.25 (broad m, 4, $=CHCH_2CH_2CH_2O-$), 3.25 (m, 2, $-CH_2OCH_2C_6H_5$), 4.25 (s, 2, $-OCH_2C_6H_5$, aliphatic), 4.80 (broad d, 4, 2 $OCH_2C_6H_5$, aromatic), 6.25 (broad s, 1, aromatic H), 6.35 (broad s, 1, aromatic H), 6.80 (m, 1, >C=CH—), 7.02 (s, 5, $-OCH_2C_6H_5$), 7.10 (s, 10, 2 $OCH_2C_6H_5$), 10.7 (broad s, 2, –COOH).

Anal. Calcd for $C_{34}H_{32}O_7$: neut equiv, 552. Found: neut equiv, 549.

6-(1-Carbomethoxy-5-hydroxypentyl)-β-resorcyclic Acid (14).—Half-ester 7 (6.00 g, 1.01 mol) was dissolved in 100 ml of absolute ethanol and hydrogenated (60 psi) over 5.0 g of 5% Pd/C catalyst for 6 hr. After removal of solvent and catalyst, 3.0 g (94%) of 14 was obtained as a paste.

Anal. Calcd for $C_{14}H_{18}O_7$: C, 56.37; H, 6.04. Found: C, 55.80; H, 6.32.

Registry No.—1, 37172-97-7; 5, 37172-98-8; 7, 37172-99-9; 8, 37172-00-5; 12, 37172-01-6; 13, 37172-02-7; 14, 37172-03-8.

Acknowledgment.—The authors express their appreciation to Mr. Carl Wassink for combustion analyses and infrared spectra.

(10) 4-Chlorobutyraldehyde (3) was prepared both by the three-step procedure of R. Paul, *Bull. Soc. Chim. Fr.*, **8**, 911 (1941), from tetrahydrofurfuryl alcohol, and by a two-step process involving the conversion of butyric acid into 4-chlorobutyryl chloride followed by Rosenmund reduction of the latter to 3: R. B. Loftfield, *J. Amer. Chem. Soc.*, **73**, 1365 (1951). In our hands, the latter process was the more convenient for laboratory-scale preparations.

(11) 4-Benzyloxybutyraldehyde was readily prepared from tetrahydrofurfuryl alcohol by its conversion into 1,2,5-pentanediol, acetalization of the vicinal hydroxyl groups, benzylation of the 5-hydroxy function, hydrolysis of the acetal, and oxidative cleavage with lead tetraacetate: see C. L. Wilson, *J. Chem. Soc.*, 48 (1945), and R. Paul and S. Tchelitcheff, *Bull. Soc. Chim. Fr.*, **15**, 197 (1948).