Alkylations of Phenylacetic Esters with Halides by Means of Sodium Amide in Liquid Ammonia. Comparisons with Alkylations of Phenylacetic Acid[1a]

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Ethyl phenylacetate was alkylated with alkyl and aralkyl halides through the sodio ester, which was prepared by means of sodium amide in liquid ammonia. The methyl, *n*-butyl, benzyl, and the α- and β-phenylethyl derivatives were obtained in high yields but the α,β-diphenylethyl derivative was produced in only fair yield along with stilbene. Similarly, *t*-butyl phenylacetate was alkylated with representative halides through the sodio ester. The α-phenylethylation of both the ethyl and *t*-butyl phenylacetates afforded largely the corresponding *erythro* isomers. Evidence was obtained that the latter alkylation is stereospecific. The alkylated ethyl and *t*-butyl phenylacetates were hydrolyzed by alkali and acid, respectively. The present method of alkylation appears preferable to earlier methods for the synthesis of alkylated phenylacetic esters and, also, for the preparation of certain of the corresponding carboxylic acids. Alkylations of the sodio esters are compared with those of disodiophenylacetate, which has a greater tendency to effect side reactions with certain of the halides. In contrast to sodio ethyl phenylacetate, disodiophenylacetate reacted with β-phenylethyl bromide to give mainly styrene.

A number of alkylations of ethyl phenylacetate have previously been effected with alkyl halides by means of basic reagents, but the yields generally have not been very satisfactory.[2] Three of the best yields have been 35% with ethyl bromide by potassium in ether,[2] 38% with benzyl chloride by potassium hydroxide in certain acetals or ethers,[2] and 45% with *n*-butyl bromide by sodium in ether and toluene.[3]

In the present investigation alkylations of this ester were accomplished in much better yields by means of sodium amide in liquid ammonia (equation 1).

$$C_6H_5CH_2COOC_2H_5 \xrightarrow[\text{liq. } NH_3]{NaNH_2} \underset{\text{I}}{C_6H_5\overset{Na}{C}HCOOC_2H_5} \xrightarrow{RX} C_6H_5\overset{R}{C}HCOOC_2H_5 \quad (1)$$
$$\text{II}$$

As indicated, ethyl phenylacetate was converted to its sodio derivative I with a molecular equivalent each of the reagent and of the halide.

The results are summarized in Table I. Alkylations with the first six halides listed in this table afforded the corresponding monoalkylation products II in good to excellent yields (69–91%). The liquid products were shown by v.p.c. to be essentially pure, though that from methyl iodide evidently contained a trace of the corresponding dimethylation derivative. The alkylation products II generally afforded good to excellent yields on saponification (see Experimental).

The α-phenylethylation was of particular interest since the formation of diasteroisomers of II (R = α-phenylethyl) was possible. Actually only one isomer was isolated, its yield being 70%. On the basis of the corresponding results with *t*-butyl phenylacetate described later, this isomer may be assumed to have the *erythro* configuration. Saponification of this isomer evidently brought about some epimerization, since both the *erythro* and *threo* acids were obtained.

Although the alkylation of sodio ester I with β-phenylethyl bromide was unaccompanied by appreciable β-elimination (see Table I), that of I with α,β-diphenylethyl chloride was accompanied by considerable β-elimination to form stilbene (Scheme A).

SCHEME A

$$\underset{\text{liq. alkylation}}{C_6H_5\overset{Na}{C}HCOOC_2H_5 + C_6H_5CH_2\overset{C_6H_5}{C}HCl} \xrightarrow[\beta\text{-elimination}]{NH_3}$$

II (R = α,β-diphenylethyl) $\quad C_6H_5CH{=}CHC_6H_5$

This experiment afforded the *erythro* isomer of II and stilbene in yields of 32 and 39%, respectively. Also, an oil was obtained that appeared to consist of alkylation product (15%). Saponification of the pure *erythro* isomer, as well as that of the oil, yielded a mixture of the *erythro* and *threo* acids.

Similarly *t*-butyl phenylacetate was alkylated through its sodio intermediate III to form IV in yields of 72–93% (Table II). Acid-catalyzed hydrolysis of the alkylation products IV afforded good to excellent yields of the corresponding carboxylic acids (see Experimental).

$$\underset{\text{III}}{C_6H_5\overset{Na}{C}HCOOC(CH_3)_3} \qquad \underset{\text{IV}}{C_6H_5\overset{R}{C}HCOOC(CH_3)_3} \quad (2)$$

Like the sodio ethyl ester I, the sodio *t*-butyl ester III underwent α-phenylethylation to form largely (72–73%) one of the two possible diastereoisomers which, in this case, was shown to have the *erythro* configuration. This was accomplished by acid-catalyzed hydrolysis, which occurred without epimerization to form the corresponding *erythro* carboxylic acid (equation 3).

$$\underset{\text{erythro}}{C_6H_5\overset{C_6H_5CHCH_3}{C}HCOOC(CH_3)_3} \xrightarrow[\text{dioxane}]{HCl} \underset{\text{erythro}}{C_6H_5\overset{C_6H_5CHCH_3}{C}HCOOH} \quad (3)$$

Actually the yield of the *erythro* alkylated ester IV (R = α-phenylethyl) must have been at least 80%, since treatment of the crude product[4] with *p*-toluene-

(1) (a) Supported in part by the National Science Foundation; (b) Union Carbide and Carbon Chemicals Co. Fellow, 1961–1963.

(2) See A. C. Cope, H. L. Holmes, and H. O. House, *Org. Reactions*, **9**, 284 (1957).

(3) A. L. Mndzhoyan, O. L. Mndzhoyan, E. R. Bagdasaryan, and V. A. Mnatsakanyan, *Dokl. Akad. Nauk Arm. SSR*, **30**, 97 (1960); *Chem. Abstr.*, **55**, 3508*h* (1961).

(4) An attempted analysis of the crude ester product by v.p.c. was unsuccessful, since pure *erythro* ester, as well as the pure *threo* ester, underwent epimerization under these conditions.

TABLE I

ALKYLATIONS OF ETHYL PHENYLACETATE WITH HALIDES BY SODIUM AMIDE IN LIQUID AMMONIA TO FORM ESTERS II (SEE EQUATION 1)

Halide	Moles of each reactant	Time, hr	Ethyl esters II	Yield, %	B.p. (mm) or m.p., °C. Found	B.p. (mm) or m.p., °C. Literature
Methyl iodide	0.1[a]	0.5	2-Phenylpropanoate	69[b]	115–118 (19)	229–230 (atm.)[c]
n-Butyl bromide	0.2	1	2-Phenylhexanoate	91	76–77 (0.1)	114–119 (4)[d]
Benzyl chloride	0.1	1	2,3-Diphenylpropanoate	85	115–116.5 (0.13)	325 (atm.)[e]
Benzhydryl chloride	0.1	6	2,3,3-Diphenylpropanoate	76[f]	122–123	120[g]
α-Phenylethyl chloride	0.05	2	2,3-Diphenylbutanoate	70[h]	88–89.5	91–92[i]
β-Phenylethyl bromide	0.05	10	2,4-Diphenylbutanoate	87[j]	113–114 (0.05)	
α,β-Diphenylethyl chloride	0.05	12	2,3,4-Triphenylbutanoate	32[k]	90–92	91.5–92.5[l]

[a] A 10% excess (0.11 mole) of sodium amide was used. [b] Purity (v.p.c.) 97% (see Experimental). [c] W. Wislicenus and R. v. Schrötter, *Ann.*, **424**, 215 (1921). [d] Ref. 3. [e] A. Meyer, *Ber.*, **21**, 1306 (1888). [f] A 50% yield was obtained in 2 hr. [g] E. P. Kohler and G. Heritage, *Am. Chem. J.*, **33**, 153 (1905). [h] Presumably the *erythro* isomer. [i] W. R. Brasen and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 395 (1957). [j] A low yield was obtained when the chloride was used (see Experimental). [k] *erythro* isomer. Stilbene (39%) was also obtained (see Experimental). [l] Ref. 20.

TABLE II

ALKYLATIONS OF *t*-BUTYL PHENYLACETATE WITH HALIDES BY SODIUM AMIDE IN LIQUID AMMONIA TO FORM ESTERS IV (SEE EQUATION 2)

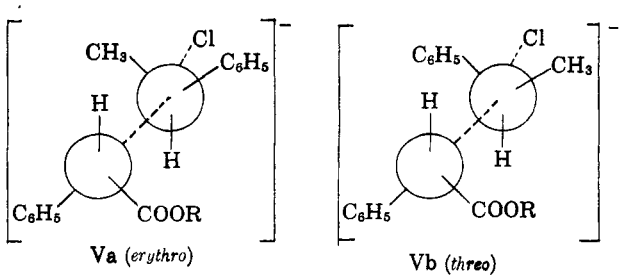
Halide	Moles of each reactant	Time, hr.	*t*-Butyl Esters IV[a] Yield, %	B.p. (mm.) or m.p., °C.	Formula	C Calcd.	C Found	H Calcd.	H Found
n-Butyl bromide	0.1	1	86	93 (1.0)	$C_{16}H_{24}O_2$	77.37	77.15	9.74	9.72
Benzyl chloride	0.1	1	93	38.5 (−40)[b]	$C_{19}H_{22}O_2$	80.81	81.13	7.86	7.80
Benzhydryl chloride	0.05	6	78[c]	127–128[d]	$C_{25}H_{26}O_2$	83.76	83.97	7.31	7.34
α-Phenylethyl chloride	0.08	0.25	72–73[e]	136–136.5[f]	$C_{20}H_{24}O_2$	81.04	81.29	8.16	8.28

[a] See Table I for names of the acid portions of the esters. [b] Recrystallized from methanol–water. [c] A 52% yield was obtained in 2 hr. [d] Recrystallized from 95% ethanol. [e] *erythro* isomer. [f] Recrystallized from methanol.

sulfonic acid in refluxing toluene afforded the *erythro* acid in this yield based on the starting ester or halide. Also there was obtained a mixture of the *erythro* and *threo* acids (11%) and the pure *threo* acid (1%).

Interestingly, the α-phenylethylation of sodio *t*-butyl phenylacetate (III), and presumably also that of sodio ethyl phenylacetate (I), appears to be stereospecific. Thus, blank experiments involving treatment of the *threo* isomer of IV (R = α-phenylethyl) with the starting sodio ester III or sodium amide failed to afford an isolable amount of the *erythro* isomer (see Experimental). The *threo* isomer of IV employed in these blank experiments was obtained by treating the *erythro* isomer with a catalytic amount of potassium amide in ether, and then separating the resulting mixture of the *erythro* and *threo* isomers.

A possible explanation of the predominant formation of the *erythro* isomer is that the α-phenylethylation, which presumably involves the SN2 type of mechanism, has a more favorable transition state leading to this isomer than that leading to the *threo* isomer. The transition states may be assumed to have configurations similar to those of the alkylation products as represented by Va and Vb for the *erythro* and *threo* isomers, respectively (R = C_2H_5, $C(CH_3)_3$).



Va (*erythro*) Vb (*threo*)

The present method of alkylation of phenylacetic esters by means of sodium amide in liquid ammonia appears superior to earlier methods. Thus, our yields of *n*-butylation and benzylation products of ethyl phenylacetate (see Table I) were twice the best of those reported previously (see introduction).

Incidentally, *t*-butyl acetate[5] and triethylcarbinyl diethylacetate[6] previously have been alkylated satisfactorily with halides in liquid ammonia by means of lithium amide and potassium amide, respectively.

Comparison with Alkylations of Phenylacetic Acid.—The alkylations of phenylacetic esters described above compliment earlier alkylations of phenylacetic acid by means of two molecular equivalents of sodium amide in liquid ammonia (equation 4).[7-9]

$$C_6H_5CH_2COOH \xrightarrow[\text{liq. } NH_3]{2NaNH_2} \underset{\text{VI}}{C_6H_5\overset{Na}{C}HCOONa} \xrightarrow[\text{2. acid}]{\text{1. RX}} \underset{\text{VII}}{C_6H_5\overset{R}{C}HCOOH} \quad (4)$$

Alkylations of disodio salt VI with *n*-butyl bromide, and benzyl and α-phenylethyl chlorides have afforded VII in yields of 65–88%, which are comparable to those (70–93%) of II and IV obtained in corresponding alkylations of sodio esters I and III (see Tables I and II). Moreover, like the α-phenylethylation of sodio ester III, that of disodio acid VI is evidently stereospecific to form largely the corresponding *erythro* isomer of VII[8]; in fact, the yield of this isomer is about the same (80%) as that obtained in the α-phenylethylation of the sodio ester III followed by hydrolysis (see preceeding section).

However, alkylations of disodio salt VI with benzhydryl, β-phenylethyl, and α,β-diphenylethyl halides

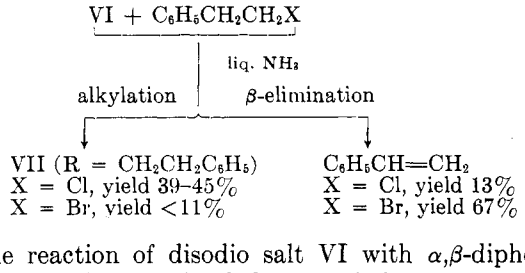
(5) K. Sisido, Y. Kazama, H. Kodama, and H. Nozaki, *J. Am. Chem. Soc.*, **81**, 5817 (1959).
(6) C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 3837 (1956).
(7) C. R. Hauser and W. J. Chambers, *ibid.*, **78**, 4942 (1956).
(8) C. R. Hauser, D. Lednicer, and W. R. Brasen, *ibid.*, **80**, 4345 (1958).
(9) R. B. Meyer and C. R. Hauser, *J. Org. Chem.*, **26**, 3696 (1961).

have not been as satisfactory as those of sodio ester I or III with these halides. This is because the dianion VI, which is presumably a stronger base than the monoanion of I or III, effects side reactions involving the α-hydrogen of the first halide and the β-hydrogen of the second and third halides as described subsequently.

The reaction of disodio salt VI with benzhydryl chloride has been shown to form not only the corresponding alkylation product VII (51%) but also tetraphenylethylene (39%).[7] The latter product arose through self-alkylation of the halide, followed by β-elimination.[10] None of this side reaction was observed in the alkylation of sodio ester I or III with benzhydryl chloride, in which the corresponding alkylation product II or IV was obtained in yields of 76–78% (see Tables I and II).[11]

The reaction of disodio salt VI with β-phenylethyl chloride has afforded the corresponding alkylation product VII in only 45% yield,[9] compared to the 87% yield of alkylation product II from sodio ester I and β-phenylethyl bromide[12] (see Table I). We have observed that alkylation of disodio salt VI with β-phenylethyl chloride is accompanied by β-elimination to form styrene, and that relatively more β-elimination occurs with the bromide (Scheme B).

SCHEME B



The reaction of disodio salt VI with α,β-diphenylethyl chloride has afforded none of the corresponding alkylation product VII; instead β-elimination occurred to form stilbene (75%).[13] Even sodio ester I undergoes considerable β-elimination with this halide, though the corresponding alkylation product II was obtained in fair yield (see Table I).

It should be pointed out that benzhydrylation and β-phenylethylation of sodio ester I or III, followed by hydrolysis, has afforded better over-all yields of the corresponding phenylacetic acid derivatives VII than the direct alkylation of disodio salt VI.

Although the alkyl derivatives of phenylacetic acid VII would generally be prepared by direct alkylation of disodiophenylacetate VI or through the sodio ester I or III (see preceeding section), the method of choice for acid VII where R is α,β-diphenylethyl involves the alkylation of sodiophenylacetonitrile with α,β-diphenylethyl chloride, followed by hydrolysis.[14] Actually, hydrolysis of the alkylated nitrile with acid and alkali have afforded the *erythro* and *threo* isomers of the acid in over-all yields of 71 and 72%, respectively.[14]

Experimental[15]

Alkylations of Ethyl Phenylacetate (Table I).—To a stirred suspension of 0.05–0.2 mole of sodium amide[16] in 250–500 ml. of commercial, anhydrous liquid ammonia was added a molecular equivalent of ethyl phenylacetate in 25–50 ml. of dry ether, followed after 10–15 min. by a molecular equivalent of the appropriate halide in 25–50 ml. of dry ether. After stirring for the appropriate length of time, using a Dry Ice–acetone condenser for longer periods, a slight excess of a molecular equivalent of ammonium chloride was added, and the ammonia was evaporated on the steam bath as an equal volume of ether was added. The resulting ethereal suspension was cooled, acidified with 100 ml. of 3 *N* hydrochloric acid, and stirred for 15 min., followed by separation of the two layers. The ethereal layer was washed with saturated sodium bicarbonate solution, followed by saturated sodium chloride solution, and then combined with two ethereal washings of the original aqueous solution. The ethereal solution of the product was dried over anhydrous magnesium sulfate, and the solvent was removed. The residue was distilled *in vacuo* or recrystallized. Data and results are summarized in Table I or as described later.

In the experiment with methyl iodide employing the slight excess of sodium amide (see Table I), the ethereal solution of the reaction product was washed with saturated sodum bisulfite solution to remove the brown color (iodine) before drying. After drying, the solvent was removed and the residue was distilled *in vacuo*. A vapor phase chromatogram (5-ft. Apiezon L column) of a sample of the distillate showed that it consisted of 97% of ethyl 2-phenylpropanoate, 3% of ethyl 2-methyl-2-phenylpropanoate, and no ethyl phenylacetate. When the methylation was effected without the slight excess of reagent (3-hr. reaction period), the product (58% yield) was shown by v.p.c. to consist of 93% of ethyl 2-phenylpropanoate, 2% of ethyl 2-methyl-2-phenylpropanoate, and 5% of ethyl phenylacetate.

In the experiments with *n*-butyl bromide and benzyl chloride the residues were distilled *in vacuo* to give ethyl 2-phenylhexanoate and ethyl 2,3-diphenylpropanoate, respectively. Vapor phase chromatograms of samples of each of these products showed only a single peak, indicating that each was essentially pure.

In the experiments with benzhydryl and α-phenylethyl chlorides, the residues were recrystallized from methanol–water and 95% ethanol, respectively, to yield ethyl 2,3,3-triphenylpropanoate and ethyl *erythro*-2,3-diphenylbutanoate, each product being obtained in two crops.

In the experiment with β-phenylethyl bromide, a few crystals of hydroquinone were added to the dried ether solution of the product and the solvent was then removed. A vapor phase chromatogram of the crude residue showed a large peak corresponding to the monoalkylation product II (R = β-phenylethyl), small peaks for ethyl phenylacetate and β-phenylethyl bromide, but no noticeable peak for styrene. Distillation of the crude residue afforded the pure alkylation product (87%), b.p. 113–116° (0.06 mm.). A vapor phase chromatogram of the distillate showed only one peak. The boiling point of an analytical sample was 113–114° (0.05 mm.).

Anal. Calcd. for $C_{18}H_{20}O_2$: C, 80.56; H, 7.51. Found: C, 80.38; H, 7.75.

In the experiment with α,β-diphenylethyl chloride, the residue was distilled *in vacuo* to recover 1.93 g. (24%) of ethyl phenylacetate, b.p. 115–118° (20 mm.) [lit.[17] b.p. 132–138° (32 mm.)], and give 3.54 g. (39%) of *trans*-stilbene,[18] b.p. 97–100° (1 mm.)

(10) See C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor, and A. E. Brodhag, *J. Am. Chem. Soc.*, **78**, 1653 (1956).

(11) Sodio ester I underwent alkylation with benzhydryl bromide in about the same yield as with the chloride under similar conditions (2 hr., footnote *f*, Table I). Neither tetraphenylethylene nor tetraphenylethane was detected by v.p.c. The latter hydrocarbon (39%) has been obtained along with the alkylation product (21%) in the reaction of disodio salt VI with benzhydryl bromide; ref. 7, footnote 7.

(12) β-Phenylethyl chloride afforded, under similar conditions (see Table I), only a 48% yield of alkylation product as determined by v.p.c. A trace of styrene was also detected.

(13) C. R. Hauser, C. F. Hauser, and P. J. Hamrick, Jr., *J. Org. Chem.*, **23**, 1713 (1958).

(14) D. Lednicer and C. R. Hauser, *J. Am. Chem. Soc.*, **80**, 3409 (1958).

(15) Analyses are by Dr. Ing. Schoeller, Kronach, West Germany, and Galbraith Microanalytical Laboratories, Knoxville, Tennessee. Melting points and boiling points are uncorrected. An F & M Model 500 programmed temperature gas chromatograph, using a 2-ft. silicone gum rubber column except where noted, was used to produce the vapor phase chromatograms. The carrier gas was helium.

(16) See C. R. Hauser, F. W. Swamer, and J. T. Adams, *Org. Reactions*, **8**, 122 (1954).

(17) I. Heilbron, "Dictionary of Organic Compounds," Vol. IV, Oxford University Press, New York, N. Y., 1953, p. 96.

(18) This stilbene evidently arose from the reaction of sodio ester I with the α,β-diphenylethyl chloride, and not from the possible thermal elimination, since this halide has been distilled without apparent decomposition at 127–129° (0.5 mm.); see C. R. Hauser, S. W. Kantor, and W. R. Brasen *J. Am. Chem. Soc.*, **75**, 2660 (1953).

TABLE III

SAPONIFICATIONS OF ALKYLATION PRODUCTS II TO FORM CARBOXYLIC ACIDS

Ester II, R	Carboxylic acid	Yield, %	B.p. (mm.) or m.p., °C. Found	Literature
Methyl[a]	2-Phenylpropanoic	20 (91)[b]	153–155 (21)	155 (21)[c]
n-Butyl	2-Phenylhexanoic	57 (92)[b]	170–178 (19)	180–183 (20)[d]
Benzyl	2,3-Diphenylpropanoic	97	84–85[e]	82[f]
Benzhydryl	2,3,3-Triphenylpropanoic	94	221.5–222[g]	221.5–222[f]
α-Phenylethyl	2,3-Diphenylbutanoic	(96)[b,h]	130–170	187–187.5,[i] 135[j]
β-Phenylethyl	2,4-Diphenylbutanoic	67 (99)[b]	70.5–72[k]	72–73[l]
α,β-Diphenylethyl[m,n]	2,3,4-Triphenylbutanoic	85 (95)[b]	145–150	131–135,[o] 159–160[p]

[a] 0.02 mole of potassium hydroxide used. [b] Crude yield. [c] S. P. Bakshi and E. E. Turner, *J. Chem. Soc.*, 171 (1961). [d] Ref. 3. [e] Recrystallized from ether–hexane. [f] Ref. 7. [g] Recrystallized from methanol. [h] Fractionally recrystallized from ethanol–water to yield *erythro* isomer (52%, m.p. 184–186°) and *threo* isomer (33%, m.p. 125–128°). [i] *erythro* isomer, ref. 8. [j] *threo* isomer, ref. 8. [k] Recrystallized from hexane. [l] Ref. 9. [m] 0.005 mole of ester and 0.02 mole of potassium hydroxide used in each case. [n] Data refer to the crystalline ester (m.p. 90–92°). The same quantities of oil (see Experimental) and base gave an 84 (94)% yield of acids, m.p. 145–147°. [o] *erythro* isomer, ref. 14. [p] *threo* isomer, ref. 14.

[lit.[19] b.p. 166–167° (12 mm.)]. After crystallization from methanol–chloroform the stilbene melted at 122–124°, m.m.p. 121–124° (lit.[13] m.p. 126–127°). Crystallization of the pot residue from methanol–water afforded 5.42 g. (32%) of ethyl *erythro*-2,3,4-triphenylbutanoate, m.p. 88–89° and 90–92° after recrystallization from ethanol. Evaporation of the mother liquor left 4.08 g. (15%) of an oil, which presumably consisted at least partly of the pure *threo* isomer, since it has been reported as an oil.[20]

Saponification of Alkylation Products II (Table III).—Solutions of 0.01 mole of esters II and 5.6 g. (0.1 mole) of potassium hydroxide in 25 ml. of 95% ethanol were refluxed for 24 hr. The ethanol was removed by distillation, and the residue dissolved in water. After the aqueous solution was extracted once with ether to remove any unchanged ester, it was chilled and acidified with concentrated hydrochloric acid. Three ether extracts of the aqueous solution were washed with saturated sodium chloride solution, combined, and dried over anhydrous magnesium sulfate. The solvent was removed and the residue distilled *in vacuo* or recrystallized from an appropriate solvent (see Table III).

The residue from the saponification of ethyl *erythro*-2,3-diphenylbutanoate was fractionally crystallized from ethanol–water to give 1.24 g. (52%) of *erythro*-2,3-diphenylbutanoic acid, m.p. 184–186°, and 0.79 g. (33%) of *threo*-2,3-diphenylbutanoic acid, m.p. 125–128°.

The residue from the saponification of ethyl *erythro*-2,3,4-triphenylbutanoate was recrystallized from 95% ethanol to give 1.28 g. (85%) of acid, m.p. 145–150°, which was apparently a mixture of the *erythro* and *threo* acids, m.p. 131–135° and 159–160°,[14] respectively. Similarly, saponification of the oil (footnote *o*, Table III) gave 1.23 g. (84%) of a mixture of the acids, m.p. 145–147°.

***t*-Butyl Phenylacetate.**—This ester was prepared by an adaption of the method described previously for *t*-butyl acetate.[21]

A solution of 45 g. of *t*-butyl alcohol and 75 g. of dimethylaniline in 200 ml. of dry ether was treated with 93 g. of phenylacetyl chloride. After refluxing 1 hr., the reaction mixture was cooled and treated with water. The ethereal layer was washed with 3 *N* hydrochloric acid, 10% sodium bicarbonate solution, and water, and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled to give *t*-butyl phenylacetate (44%), b.p. 108–110° (15 mm.) [lit.[22] b.p. 110° (15 mm.)].

Alkylations of *t*-Butyl Phenylacetate (Table II).—These alkylations were effected and worked up essentially as described earlier for the corresponding alkylations of ethyl phenylacetate.

In the experiment with *n*-butyl bromide, the residue was distilled *in vacuo* and the distillate was shown to be pure by v.p.c.

In the experiments with benzyl, benzhydryl, and α-phenylethyl chlorides, the residues were recrystallized from appropriate solvents (see Table II).

Acid-Catalyzed Hydrolysis of Alkylation Products IV (Table IV).—Solutions of 0.005–0.01 mole of esters IV in 25 ml. of dioxane and 5 ml. of concentrated hydrochloric acid were refluxed for 2 hr. After cooling, the reaction mixture was diluted with ether and the resulting solution was extracted with cold 5% sodium hydroxide solution. The aqueous alkaline extract was washed with ether, chilled, and acidified with concentrated hydrochloric acid. The resulting mixture was extracted three times with ether, and the combined ethereal extract was dried over anhydrous magnesium sulfate. After removal of the solvent, the residue was distilled *in vacuo* or recrystallized from an appropriate solvent (see Table IV).

TABLE IV

ACID-CATALYZED HYDROLYSIS OF ALKYLATION PRODUCTS IV TO FORM CARBOXYLIC ACIDS

Ester IV R	Carboxylic acid	Yield, %	B.p. (mm.) or m.p., °C. Found	Literature[a]
n-Butyl	2-Phenylhexanoic	78	173–178 (19)	180–183 (20)
Benzyl	2,3-Diphenylpropanoic	62	93–96	95.5–96.5
Benzhydryl	2,3,3-Triphenylpropanoic	99	221.5–222.5	221.5–222
α-Phenylethyl	2,3-Diphenylbutanoic	75 (88)[b,c]	188–189[c]	187–187.5[c]

[a] See Table III for references and recrystallization solvents. [b] Crude yield. [c] *erythro* isomer.

α-Phenylethylation of *t*-Butyl Phenylacetate and Hydrolysis of Crude Product.—This alkylation was carried out on the 0.05-mole scale as indicated above to give a 96% yield of solid crude product. A portion (2.96 g., 0.01 mole) of the crude product was dissolved in 50 ml. of dry toluene containing 0.5 g. (0.0026 mole) of *p*-toluenesulfonic acid monohydrate. The solution was refluxed, until the evolution of isobutylene had ceased. After cooling, the reaction mixture was diluted with an equal volume of ether and washed with water to remove the acid catalyst. The organic layer was extracted with two portions of 10% sodium hydroxide solution which were combined, chilled, and acidified with concentrated hydrochloric acid. The acidified aqueous solution was extracted three times with ether, the combined extract dried over anhydrous magnesium sulfate, and the solvent removed to leave 2.17 g. (91%) of crude 2,3-diphenylbutanoic acids, m.p. 175–185°. A portion (2.13 g.) of this residue was crystallized from ethanol–water to yield 1.70 g. (80%) of *erythro*-2,3-diphenylbutanoic acid, m.p. 184–186°. There was also obtained a second crop (0.24 g., 11%), m.p. 120–145°; and a third crop (0.03 g., 1%) m.p. 123–128°, which showed no depression upon admixture with an authentic sample of *threo*-2,3-diphenylbutanoic acid (see Table III for lit. melting points).

***threo*-*t*-Butyl 2,3-Diphenylbutanoate.**—The *threo* isomer was prepared by refluxing 8.9 g. (0.03 mole) of *erythro*-*t*-butyl 2,3-diphenylbutanoate in 300 ml. of dry ether containing a suspension of 0.006 mole of potassium amide for 2 hr. essentially as described previously for *erythro*- and *threo*-2,3-diphenylbutyronitrile.[8] Removal of the solvent from the dried ethereal solution of the product gave a residue which was fractionally crystallized from methanol to afford the *erythro* (55%) and the *threo* (14%) isomers.

(19) See ref. 17, p. 375.

(20) H. M. Crawford, J. C. Davidson, and M. A. Plunkett, *J. Am. Chem. Soc.*, **66**, 2010 (1944).

(21) C. R. Hauser, B. E. Hudson, B. Abramovitch, and J. C. Shivers, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., p. 142.

(22) D. L. Yabroff and C. W. Porter, *J. Am. Chem. Soc.*, **54**, 2453 (1932).

The *threo-t*-butyl 2,3-diphenylbutanoate (white cubes) melted at 99–100.5°.

Anal. Calcd. for $C_{20}H_{24}O_2$: C, 81.04; H, 8.16. Found: C, 80.92; H, 8.02.

A mixture of the *threo* isomer and the *erythro* isomer (m.p. 136–136.5°) melted at 88–104°. Hydrolysis of 0.2 g. of *threo-t*-butyl 2,3-diphenylbutanoate by the dioxane–hydrochloric acid method (see preceding section) yielded *threo*-2,3-diphenylbutanoic acid (94%), m.p. 134–136° (see Table IV for literature melting point and reference).

Failure of *threo-t*-Butyl 2,3-Diphenylbutanoate to Undergo Epimerization in Liquid Ammonia. (A) With Sodio *t*-Butyl Phenylacetate.—To a stirred suspension of 0.01 mole of sodium amide in 100 ml. of liquid ammonia was added 1.41 g. (0.01 mole) of *t*-butyl phenylacetate in 10 ml. of dry ether, followed, after 15 min., by 0.053 g. (1.79 mmoles) of finely powdered *threo-t*-butyl 2,3-diphenylbutanoate (washed in with 5 ml. of dry ether). After stirring for 2 hr., the reaction mixture was neutralized with ammonium chloride, and the ammonia was replaced with ether. The resulting ethereal suspension was worked up as described before for the alkylations of ethyl and *t*-butyl phenylacetates. The residue left after removal of the solvent from the dried ethereal solution was distilled *in vacuo* to remove the *t*-butyl phenylacetate. Recrystallization of the pot residue from methanol–water yielded *threo-t*-butyl 2,3-diphenylbutanoate, m.p. 91–94°. Upon admixture with an authentic sample (m.p. 96–98°) it melted 94–97°. None of the *erythro* isomer (m.p. 136–136.5°) was found.[23]

(B) With Sodium Amide.—To a stirred suspension of 0.609 mmole of sodium amide in 100 ml. of liquid ammonia was added 0.1504 g. (0.501 mmole) of *threo-t*-butyl 2,3-diphenylbutanoate in 10 ml. of dry ether. After stirring for 2 hr., the reaction mixture was worked up as described before for the alkylation of ethyl and *t*-butyl phenylacetates. Removal of the solvent from the dried ethereal solution of the product gave a residue which was crystallized from methanol–water to yield 0.0726 g. (48%) of recovered *threo-t*-butyl 2,3-diphenylbutanoate, m.p. 92–96°. Upon admixture with an authentic sample (m.p. 96–98°) it had m.p. 94–97°. None of the *erythro* isomer (m.p. 136–136.5°) was found.[23]

Alkylation of Phenylacetic Acid. (A) With β-Phenylethyl Chloride.—To a green stirred suspension of 0.05 mole of disodiophenylacetate (VI), prepared from 0.1 mole of sodium amide and 6.81 g. (0.05 mole) of solid phenylacetic acid in 250 ml. of liquid ammonia, was added 7.03 g. (0.05 mole) of β-phenylethyl chloride in 25 ml. of dry ether. After 1 hr., the reaction mixture was neutralized with ammonium chloride and the ammonia replaced with ether. The resulting ether suspension was extracted twice with 5% sodium hydroxide solution and after addition of a few crystals of hydroquinone, the ethereal solution was dried over anhydrous magnesium sulfate. A portion of the solvent was removed and the solution was chilled, followed by the addition of a slight excess of 10% bromine–carbon tetrachloride solution. The excess bromine was decomposed with 10% sodium bisulfite solution and the layers were separated. The organic layer was washed with 10% sodium bisulfite solution and water and dried over anhydrous magnesium sulfate. The solvent was removed under reduced pressure and the residue recrystallized from ethanol–water to yield 2.36 g. (13%) of styrene dibromide, m.p. 71–72° (lit.[24] m.p. 72–73°).

The alkaline extract of the reaction product mentioned before was worked up as described previously to give recovered phenylacetic acid (33%) and 2,4-diphenylbutanoic acid (39%).[9]

(B) With β-Phenylethyl Bromide.—The alkylation was performed as described above, except that 9.26 g. (0.05 mole) of β-phenylethyl bromide was used. The ethereal layer was worked up to yield 12.24 g. (67%) of styrene dibromide, m.p. 72–73.5°, after crystallization from ethanol–water. The yield of 2,4-diphenylbutanoic acid was less than 11%.

(23) Since the *erythro* isomer is less soluble than the *threo* isomer in the solvent system employed, any *erythro* isomer present should have precipitated as the first crop.

(24) C. R. Hauser, J. C. Shivers, and P. S. Skell, *J. Am. Chem. Soc.*, **67**, 409 (1945).

Ethylenediketene Dimer

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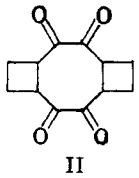
The ethylenediketene dimer obtained from the dehydrochlorination of adipyl dichloride has been reinvestigated and assigned the structure IV. Products derived from this dimer by hydrolysis and oxidation have been identified. The pertinence of this structural information to modes of reaction of alkylketenes is discussed.

In 1912, Staudinger announced Wedekind's discovery that adipyl dichloride reacts with triethylamine to give a $C_{12}H_{12}O_4$ compound, corresponding to a dimer of ethylenediketene (I).[1] Thirteen years later, Wedekind and co-workers published the details of this reaction and of their attempts to determine the structure of the

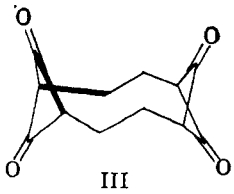
$$O{=}C{=}CH{-}CH_2CH_2{-}CH{=}C{=}O$$
I

dimer.[2] The $C_{12}H_{12}O_4$ compound, m.p. 141–142°, reacted with phenylhydrazine to give a bisphenylhydrazone, with alkaline peroxide to give both a diacid of m.p. 170–171° ($C_{10}H_{14}O_4$) and an acidic substance of m.p. 81–82° ($C_6H_{10}O_5$)[3], and with aqueous acid to give adipic acid.

Two structures for the dimer (II and III) were suggested for consideration; the biscyclobutanedione III was favored. No attempt was made to assign structures to the diacid of m.p. 170–171° or the acidic substance of m.p. 81–82°.



II



III

Assigning structures to the three compounds, $C_{12}H_{12}O_4$, $C_{10}H_{14}O_4$, and $C_6H_{10}O_5$, appeared difficult. An experimental reinvestigation of these compounds provided new analytical, chemical, and spectral data which were sufficient to resolve the problem.

Results and Discussion

The ethylenediketene dimer was prepared and found to have m.p. 142–144° and the molecular formula C_{12}-

(1) H. Staudinger, "Die Ketene," Ferdinand Enke, Stuttgart, 1912, p. 19.

(2) E. Wedekind, M. Miller, and C. Weinard, *J. prakt. Chem.*, [2] **109**, 161 (1925).

(3) There are two apparent misprints in the analytical data reported for the compound of m.p. 81–82° (ref. 2, p. 171); the first sample for combustion is evidently 0.1023 g. rather than 0.1203 g., and the calculated carbon and hydrogen percentages correspond to $C_6H_{10}O_5$, rather than to $C_6H_{10}O_3$ as printed.