[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkylations at the α-Carbon of Phenylacetic and Diphenylacetic Acids with Benzyl Chloride and Related Halides by Alkali Amides

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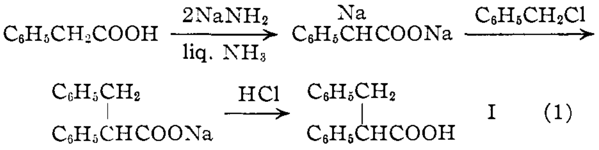
A method was developed for alkylation at the α-carbon of phenylacetic and diphenylacetic acids with benzyl, α-phenylethyl and benzhydryl halides to form the corresponding α-alkylphenylacetic and α-alkyldiphenylacetic acids. The method involves the use of two molecular equivalents of sodium amide or potassium amide in liquid ammonia and one equivalent of the halide. The α-phenylethylation of phenylacetic acid produced one of the two possible diastereomeric pairs. The benzhydrylations were accompanied by self-alkylation of some of the benzhydryl halide to form tetraphenylethylene. The present method is superior to other known methods.

The alkylation of phenylacetic or diphenylacetic acid at the α-carbon appears not to have been realized previously in good yield. Cohen and Wright[2] reported only a 12% yield of α-benzylphenylacetic acid on benzylating phenylacetic acid through the Ivanov reagent,[3] $C_6H_5\overset{MgCl}{C}HCOOMgCl$ which was prepared by means of excess isopropylmagnesium chloride. Birch[4] effected the dimethylation of phenylacetic acid to form α,α-dimethylphenylacetic acid by means of potassium amide, but the yield was not given. Apparently no alkylation of diphenylacetic acid has previously been described.

In the present investigation certain alkylations at the α-carbon of phenylacetic and diphenylacetic acids were achieved satisfactorily by means of sodium amide or potassium amide.

Alkylations of Phenylacetic Acid.—These alkylations were carried out by adding phenylacetic acid to a suspension of two molecular equivalents of sodium amide in liquid ammonia, followed by one equivalent of the alkyl halide in some ether. The reaction may be illustrated by the benzylation of this acid to form α-benzylphenylacetic acid (I) which was obtained in 88% yield (equation 1).



$$C_6H_5CH_2COOH \xrightarrow[\text{liq. NH}_3]{2NaNH_2} C_6H_5\overset{Na}{C}HCOONa \xrightarrow{C_6H_5CH_2Cl}$$

$$\begin{array}{c} C_6H_5CH_2 \\ | \\ C_6H_5CHCOONa \end{array} \xrightarrow{HCl} \begin{array}{c} C_6H_5CH_2 \\ | \\ C_6H_5CHCOOH \end{array} \quad \text{I} \quad (1)$$

The excess amide ion evidently effected immediate ionization of the α-hydrogen of sodium phenylacetate (which presumably was first formed) to give a green solution of the disodium salt. Moreover, benzylation at the α-carbon of this salt appeared to be complete as soon as the equivalent of the halide had been added, since the color was then discharged. No ester formation, which could have involved the carboxylate anion of the intermediate disodium salt or that of the product salt, was observed under the conditions employed. Neither did possible further alkylation of the product to form α,α-dibenzylphenylacetic acid take place. The latter type of dibenzylation has been shown to accompany monobenzylation of phenylacetonitrile under similar conditions.[5]

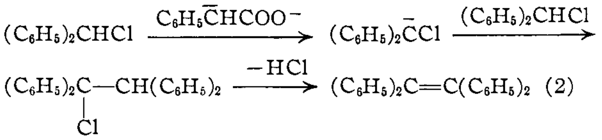
The α-phenylethylation and benzhydrylation of phenylacetic acid were effected similarly to form acids II and III in yields of 74 and 51%, respectively. These alkylations also appeared to be complete as soon as the halide had been added.

$$\begin{array}{c} C_6H_5CHCH_3 \\ | \\ C_6H_5CHCOOH \end{array} \qquad \begin{array}{c} (C_6H_5)_2CH \\ | \\ C_6H_5CHCOOH \end{array}$$

II III

The α-phenylethylation is of particular interest since diastereomers of II are possible. Actually only one racemic modification, the higher melting one, was obtained. This racemic modification has been shown to have the erythro configuration.[6]

The benzyhydrylation was accompanied by a side reaction involving the self-alkylation of the benzhydryl chloride, followed by dehydrochlorination to form tetraphenylethylene (39%).[7] This side reaction, which has been effected in high yield by the amide ion,[8] was evidently brought about by the carbanion portion of the dianion of phenylacetic acid, the phenylacetate anion being formed as by-product (equation 2).[9]



$$(C_6H_5)_2CHCl \xrightarrow{C_6H_5\bar{C}HCOO^-} (C_6H_5)_2\bar{C}Cl \xrightarrow{(C_6H_5)_2CHCl}$$

$$(C_6H_5)_2\underset{\begin{array}{c}|\\Cl\end{array}}{C}—CH(C_6H_5)_2 \xrightarrow{-HCl} (C_6H_5)_2C{=}C(C_6H_5)_2 \quad (2)$$

The present direct method of alkylation of phenylacetic acid appears preferable for the synthesis of acids I, II and III to the alkylation and hydrolysis of phenylacetonitrile[5] or phenylacetic acid esters[10] and to the alkylation, hydrolysis and decarboxylation of phenylmalonic ester.[11] Although the α-

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[1] E. I. du Pont de Nemours & Co. Fellow, 1955–1956.

[2] H. L. Cohen and G. F. Wright, *J. Org. Chem.*, **18**, 432 (1953).

[3] This reagent has been carbonated to form phenylmalonic acid in 65% yield; D. Ivanov and A. Spassov, *Bull. soc. chim. France*, [4] **49**, 19 (1931). The Ivanov reagent has also been condensed satisfactorily with certain carbonyl compounds; see F. F. Blicke and H. Zinnes, THIS JOURNAL, **77**, 4849, 5168 (1955).

[4] A. J. Birch, *J. Chem. Soc.*, 1551 (1950).

[5] C. R. Hauser and W. R. Brasen, THIS JOURNAL, **78**, 494 (1956).

[6] Unpublished result of W. R. Brasen and C. R. Hauser. A study of the possible interconversion of one racemic modification to the other is being made.

[7] When benzhydryl bromide was substituted for the chloride, a side reaction producing tetraphenylethane was observed. This is being further investigated.

[8] C. R. Hauser, W. R. Brasen, P. S. Skell, S. W. Kantor and A. E. Brodhag, THIS JOURNAL, **78**, 1653 (1956).

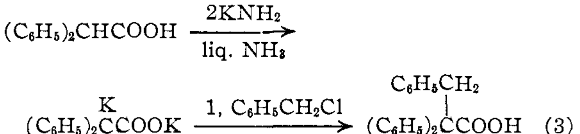
[9] It is of interest that this side reaction was not observed in the corresponding benzhydrylation of phenylacetonitrile (reference 5) the carbanion of which is presumably a weaker base.

[10] P. Ramart and A. Haller (*Compt. rend.*, **178**, 1583 (1924)) reported the benzylation of benzyl phenylacetate, but the yield was not given, and the ester was not hydrolyzed.

[11] W. Wislicenus and K. Goldstein (*Ber.*, **28**, 815 (1895)) effected the benzylation of phenylmalonic ester in 55% yield and hydrolyzed and decarboxylated the alkylated product to form acid I in unreported yield.

phenylethylated and benzhydrylated phenylacetonitriles have been obtained in almost quantitative yields, they have been difficult to hydrolyze to the corresponding acids, II and III, respectively.[5] Also the present method seems superior to at least certain indirect methods.[12]

Alkylations of Diphenylacetic Acid.—These alkylations were effected by adding diphenylacetic acid to two molecular equivalents of potassium amide[13] in liquid ammonia, followed by one equivalent of the halide in some ether. The reaction may be illustrated by the benzylation of this acid to form α-benzyldiphenylacetic acid (IV) which was obtained in 85% yield (equation 3).

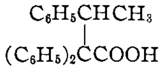


IV

$$(C_6H_5)_2CHCOOH \xrightarrow[\text{liq. } NH_3]{2KNH_2} (C_6H_5)_2\overset{K}{C}COOK \xrightarrow[2,\ HCl]{1,\ C_6H_5CH_2Cl} (C_6H_5)_2\overset{C_6H_5CH_2}{\overset{|}{C}}COOH \quad (3)$$

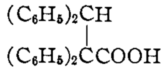
The ionization of the α-hydrogen of potassium diphenylacetate evidently occurred within a few minutes to produce a greenish-yellow suspension of the dipotassium salt. However, benzylation at the α-carbon required several hours.

The α-phenylethylation and benzylhydrylation of diphenylacetic acid were effected similarly to form acids V and VI in yields of 89 and 42%, respectively. These alkylations also proceeded rather slowly.



V

$$(C_6H_5)_2\overset{C_6H_5CHCH_3}{\overset{|}{C}}COOH$$



VI

$$(C_6H_5)_2\overset{(C_6H_5)_2CH}{\overset{|}{C}}COOH$$

The benzhydrylation to form acid VI was accompanied by the same self-alkylation and dehydrohalogenation of the benzhydryl halide to produce tetraphenylethylene (49%). This side reaction was presumably brought about by the carbanion portion of the dipotassium salt of diphenylacetic acid similar to that represented by equation 2. In contrast to the other alkylated acids, acid VI failed to dissolve appreciably in hot sodium bicarbonate solution or even in hot dilute sodium hydroxide.

The present method of synthesis of acids IV, V and VI appears to be superior to other known methods. Although diphenylacetonitrile[14] and diphenylacetic acid esters[15] may be alkylated in satisfactory yields, the alkylated products are generally difficult to hydrolyze to the corresponding acids. In fact acids V and VI apparently have not previously been described.

Experimental[16]

Benzylation of Phenylacetic Acid to Form I.—To a stirred suspension of 0.204 mole of sodium amide[17] in 500 ml. of liquid ammonia was added carefully 14.2 g. (0.104 mole) of solid phenylacetic acid. The resulting dark green solution was stirred for 15 min. and 12.7 g. (0.1 mole) of benzyl chloride in 25 ml. of anhydrous ether then added rapidly. The green color was discharged immediately. The stirring was continued for 15 min. and the liquid ammonia then allowed to evaporate on the steam-bath while 200 ml. of ether was being added. The resulting suspension was refluxed for 15 min. and 200 ml. of water added. The ether was removed by distillation and the resulting mixture stirred with Norite. After filtration, the aqueous solution was acidified to precipitate the alkylated acid which was collected on a funnel and washed with water. The crude acid was dissolved in ether and most of the ether then removed by distillation. Approximately 80 ml. of 35–40° petroleum ether was added to precipitate, on standing, 19.9 g. (88%) of α-benzylphenylacetic acid (I), m.p. 92–93.5°. One recrystallization from a mixture of ether and petroleum ether gave 18.9 g. (84%) of I, m.p. 95.5–96.5°. This compound has been reported[18] to exist in three crystalline forms, melting at 82°, 88–89° and 95–96°. Recently this compound, prepared by the benzylation of phenylacetonitrile followed by hydrolysis, melted at 88–89° on recrystallization from acetic acid and water.[5] A sample of this product has now been recrystallized from a mixture of ether and petroleum ether to give crystals melting at 95.5–96.5°. The melting point was the same when this product was mixed with a sample of I prepared in the present investigation.

α,β-Diphenylbutyric Acid (II).—This acid, m.p. 183–184.5°, was obtained in a 74% yield (after one recrystallization from methanol) by the alkylation of phenylacetic acid with α-phenylethyl chloride essentially as described for the benzylation. A second recrystallization from methanol gave 17.1 g. (71%) of II, m.p. 187–187.5°, which was not depressed on admixture with a sample of II prepared by the α-phenylethylation of phenylacetonitrile followed by hydrolysis.[5]

α,β,β-Triphenylpropionic Acid (III).—This acid was prepared by the alkylation of phenylacetic acid with benzhydryl chloride essentially as described above for the benzylation. The crude acid was recrystallized from methanol to give 15.4 g. (51%) of III, m.p. 220–221°. A second recrystallization from methanol gave 15.2 g. (50%) of the acid, m.p. 221.5–222°, reported m.p. 217–218°,[19] 211°.[20] The amide melted at 209.5–210° after recrystallization from methanol, reported m.p. 208–209°.[21]

Anal. Calcd. for $C_{21}H_{19}ON$: C, 83.69; H, 6.35; N, 4.65. Found: C, 83.92; H, 6.49; N, 4.63.

In this experiment, a solid product was obtained mixed with the Norite caught on the funnel (see above procedure for the benzylation). The mixture was refluxed with methanol and the Norite removed by filtration. The methanolic solution was concentrated and cooled to precipitate 5.4 g. (39%) of tetraphenylethylene, m.p. and mixed m.p. 221–222°. This melting point was lowered to 200–208° on admixture with a sample of acid III.

Benzylation of Diphenylacetic Acid to Form IV.—To a stirred solution of 0.204 mole of potassium amide[22] in 600 ml. of liquid ammonia was added 22.1 g. (0.104 mole) of solid diphenylacetic acid. The resulting greenish-yellow suspension was stirred for 20 min. and 12.7 g. (0.1 mole) of benzyl chloride in 40 ml. of anhydrous ether added. The

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[12] W. Miller and G. Rohde *Ber.*, **25**, 2017 (1892)) reduced α-phenylcinnamic acid to form acid I, while E. P. Kohler and G. Heritage (*Am. Chem. J.*, **33**, 153 (1905)) added phenylmagnesium bromide to methyl α-phenylcinnamate and saponified the product to give acid III. The yields of these acids were not reported.

[13] A preliminary experiment employing sodium amide was unsatisfactory. The disodium salt of diphenylacetic acid was so insoluble in liquid ammonia that stirring was difficult.

[14] Diphenylacetonitrile has been benzylated, α-phenylethylated and benzhydrylated in yields of 89–99%, but the products resisted attempts at hydrolysis; C. R. Hauser and W. R. Brasen, THIS JOURNAL, **78**, 82 (1956).

[15] P. Ramart (*Compt. rend.*, **178**, 93 (1924)) benzylated benzyl diphenylacetate by means of sodium amide and hydrolyzed the product to form acid IV, but the yield was not reported. W. Schlenk, H. Hillemann and I. Rodloff (*Ann.*, **487**, 135 (1931)) benzylated and benzhydrylated methyl diphenylacetate by means of sodium triphenylmethide, but the yields were not given, and the esters were not hydrolyzed.

[16] Melting points are uncorrected. Analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

[17] C. R. Hauser, F. W. Swamer and J. T. Adams, "Organic Reactions," Vol. VIII, John Wiley and Sons, Inc., New York, N. Y. 1954, p. 122.

[18] See Miller and Rohde, reference 12.

[19] J. Wegmann and H. Dahn, *Helv. Chim. Acta*, **29**, 415 (1946).

[20] See Kohler and Heritage, reference 12.

[21] R. L. Shriner and G. B. Brown, *J. Org. Chem.*, **2**, 560 (1938).

[22] See R. S. Yost and C. R. Hauser, THIS JOURNAL, **69**, 2325 (1947).

reaction mixture was stirred for 4.5 hr. under a Dry Ice–acetone condenser. The liquid ammonia was then allowed to evaporate on the steam-bath while 300 ml. of ether was being added. The resulting ether suspension was refluxed for 15 min., and 300 ml. of water was added. The two layers were separated. The aqueous layer (to which was added a 5% sodium hydroxide extract of the ether layer) was made strongly acidic and the resulting mixture extracted with methylene chloride. The methylene chloride layer was dried over Drierite and the solvent removed. The residue was dissolved in ether and the solution concentrated. Approximately 80 ml. of hexane was added and the solution cooled to precipitate 25.8 g. (85%) of α,α,β-triphenylpropionic acid (IV), m.p. 128–130°. One recrystallization from a mixture of ether and hexane gave 25.2 g. (83%) of IV, m.p. 130–131.5°; reported m.p. 130–132°,[19] 125–127°.[23]

α,α,β-Triphenylbutyric Acid (V).—This acid, m.p. 146–147°, was obtained in an 89% yield by the alkylation of diphenylacetic acid with α-phenylethyl chloride essentially as described for the benzylation. One recrystallization from methanol containing a small amount of water gave 27.5 g. (87%) of V, m.p. 148–148.5°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.51; H, 6.37. Found: C, 83.47; H, 6.26.

Admixture of this acid with diphenylacetic acid (m.p. 147.5–148°) lowered the melting point to 118–123°.

A sample of this acid was converted to the acid chloride by means of thionyl chloride. To the crude acid chloride was carefully added excess liquid ammonia[24] (vigorous reaction) and the liquid ammonia allowed to evaporate. After washing with water, the solid was collected on a funnel and recrystallized from methanol to give α,α,β-triphenylbutyramide, m.p. 147–147.5°.

Anal. Calcd. for $C_{22}H_{21}ON$: C, 83.77; H, 6.71; N, 4.44. Found: C, 84.05; H, 6.88; N, 4.28.

α,α,β,β-Tetraphenylpropionic Acid (VI).—This acid, m.p. 189–192°, was obtained in a 42% yield by the alkylation of 0.051 mole of diphenylacetic acid with 0.05 mole of benzhydryl bromide in 600 ml. of liquid ammonia essentially as described for the benzylation. One recrystallization from glacial acetic acid gave 7.8 g. (41%) of VI, m.p. 192–193.5° dec.

Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.68; H, 5.86. Found: C, 85.53; H, 6.03.

There was also obtained 4.1 g. (49%) of tetraphenylethylene, m.p. and mixed m.p. 221–222°. This product was isolated by removing the solvent from the ethereal layer. The crude product was recrystallized from methanol.

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[23] See Schlenk and co-workers, reference 15.

[24] A preliminary attempt to prepare the amide from the acid chloride and concentrated ammonium hydroxide in the usual manner gave a product that was difficult to purify.

DURHAM, NORTH CAROLINA

[CONTRIBUTION FROM ROHM AND HAAS CO., REDSTONE ARSENAL RESEARCH DIVISION]

Oxygen Alkylation of Negatively Substituted Esters[1]

BY CHARLES O. PARKER

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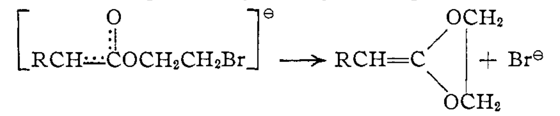
The anions of the mono-β-bromoethyl esters of cyanoacetic, malonic, acetoacetic and *p*-nitrophenylacetic acids undergo intramolecular displacement of bromide ion to yield substituted ketene ethylene acetals. From the β-bromoethyl esters of acetic, isobutyric, phenylacetic and diphenylacetic acids under the same conditions, no evidence of intramolecular alkylation could be found. The latter group of esters gave a mixture of products apparently derived from intermolecular interaction.

In connection with other work, reactions of certain negatively substituted β-bromoethyl esters were observed wherein intramolecular displacement of halide ion was apparently performed by the ester enolate ion to give oxygen alkylation products as



Identification of the products as substituted ketene ethylene acetals rests upon agreement between analytical data, infrared and ultraviolet absorption spectra. These data are presented in Table I.

Esters which have been studied in this investigation fall into two groups. Those bearing an α-substituent contributing to a resonance-stabilized anion underwent intramolecular oxygen alkylation as described. Bromoethyl cyanoacetate (I), (mono)-malonate (II), *p*-nitrophenylacetate (III) and acetoacetate (IV) comprise this group. Choice of base necessary to promote reaction of these esters was not critical. Cyanoketene-ethylene acetal could be isolated from I by reaction with alcoholic potassium hydroxide, with sodium methoxide or with potassium carbonate in water. These experiments confirmed the previously reported[2] relative resistance to attack by base of negatively substituted ketene acetals besides illustrating that oxygen alkylation occurred even in hydroxylic media. In order to avoid accompanying direct displacement of halide ion by base, reactions generally were performed using sodium hydride suspended in tetrahydrofuran. Under these conditions reaction was rapid, exothermic and its completeness measurable by observing hydrogen evolution. Isolation of product was accomplished simply by evaporating the filtrate from the precipitated sodium bromide. The yields of crude, solid products were greater than 90% from all esters except III. However, the fact that the products as initially isolated were not completely pure and required considerable purification (especially the *p*-nitrophenylketene ethylene acetal) suggests that other products were formed in the reaction in varying amounts. The possibility that *p*-nitrophenylketene ethylene acetal was being lost in gross amounts due to decomposition by adventitious moisture or by solubility in recrystallization solvents was checked and rejected. It proved to be stable toward water and hot alcohol and to be sparingly soluble in most solvents in the cold.

The second group of esters examined included bromoethyl acetate (V), isobutyrate (VI), phenylacetate (VII) and diphenylacetate (VIII). None of these gave products which appeared to include a ketene ethylene acetal structure. Neither was

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[1] This research was carried out under Army Ordnance Contract W-01-021-ORD-334.

[2] S. M. McElvain and J. P. Schroeder, THIS JOURNAL, **71**, 47 (1949).