in 20 min., after which time hydrogenation practically ceased.

Compound *B* was also ozonized by the above procedure to produce acetone 2,4-dinitrophenylhydrazone, m.p. 110–116° (crude), and an oil, b.p. 121–125°, (0.5 mm.), which gave a deep red color with ferric chloride solution; its infrared spectrum was identical with the sample of XI obtained from compound *A*.

Ozonolysis of $C_{18}H_{28}O_2$, (compounds A and B) Procedure B. A 2.76-g. sample of compound *A* dissolved in chloroform was ozonized as described above. The ozonide was decomposed, after removal of the chloroform, by refluxing with 250 ml. of water and 2 ml. of 30% hydrogen peroxide for 5 hr., while a stream of nitrogen was passed through the solution. The exit gases were passed first through Johnson's 2,4-dinitrophenylhydrazine reagent followed by *Anhydrone* and *Ascarite* packed tubes. The *Ascarite* tube absorbed 0.33 g. (0.75 mole-equiv.) of carbon dioxide. Acetone 2,4-dinitrophenylhydrazone was isolated from the Johnson's reagent as in procedure A.

The residue remaining after refluxing was extracted with ether and washed with sodium bicarbonate solution. The neutral material, a yellow oil, was recovered from the ether and distilled; 0.25 g., b.p. 112–113° (0.3 mm.). It gave no color with ferric chloride solution; carbonyl absorption bands were observed at 1760, 1720, and 1680 cm.$^{-1}$ Acidification of the sodium bicarbonate extracts with hydrochloric acid, followed by ether extraction, led to 1.17 g. of material, b.p. 122–124° (0.15 mm.), n_D^{25} 1.4706; infrared bands: 2500–3500 cm.$^{-1}$ (OH stretching), 1725 (shoulder) and 1690 cm.$^{-1}$ (C=O stretching); found: C, 65.12; H, 9.96; neut. equiv., 192, 194. A 2,4-dinitrophenylhydrazone was prepared and crystallized (slowly) from methanol, m.p. 131–133°; found: C, 55.04; H, 5.44; N, 15.02. Ozonolysis of compound *B* by the same procedure also gave the above acidic material (infrared spectrum identical). The acid revealed significant differences in the infrared spectrum in the 7–9 μ region, when compared with the spectrum of 4-cyclopropyl-2-isopropyl-4-ketobutanoic acid (preparation described below).

The above aqueous part remaining after extracting with methylene chloride was made alkaline (*p*H 11) with sodium hydroxide and distilled to remove neutral impurities. The residue was diluted with water and made acidic (*p*H 1) with sulfuric acid and distilled. The distillate (1 l.) was neutralized with sodium hydroxide solution (0.011 mole-equiv. required) and concentrated to near dryness. The residue was acidified with sulfuric acid (*p*H 1) and extracted continuously with ether for 3 hr. Removal of the ether from the extract and distillation of the residue gave 0.27 g. of cyclopropanecarboxylic acid, b.p. 177° (699 mm.), m.p. 14–15°, neut. equiv. 85.6 (calcd. for $C_4H_6O_2$, 86). When mixed with an authentic sample of cyclopropanecarboxylic acid, m.p. 15–16°, the melting point was not depressed (reported,[14] 18.1°, b.p. 181.8–182°, 766 mm.). The infrared spectrum of the above acid was found to be identical with that of authentic cyclopropanecarboxylic acid.

4-Cyclopropyl-2-isopropyl-4-ketobutanoic acid. A solution of 2.0 g. of 1-cyclopropyl-4-methyl-2-penten-1-one (V), 6 ml. of ethanol, 2 ml. of water, and 1.1 g. of potassium cyanide was refluxed for 21 hr. Potassium hydroxide (3.0 g., 85% assay) was added and refluxing continued for 8 hr., during which time ammonia was continuously evolved. After cooling and diluting with water the mixture was extracted with ether. The aqueous part was acidified with hydrochloric acid and extracted with ether. The ether solution was extracted with sodium bicarbonate solution, and the aqueous part extracted once with ether before acidifying with dilute hydrochloric acid. After extraction with ether, the ether solution was dried and the ether removed to yield 1.80 g. of the crude acid. Distillation gave 1.4 g. (52% yield), b.p. 126–128° (0.4 mm.), n_D^{25} 1.4714; viscous liquid having a faint pleasant odor; infrared bands, neat, cm.$^{-1}$: 2500–3500, broad OH stretching; 1690 (ketone) and 1725, shoulder (carboxyl), C=O stretching.

Anal. Calcd. for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75; mol. wt., 184. Found: C, 65.45; H, 9.22; neut. equiv., 186 (by direct titration with 0.1*N* sodium hydroxide).

A *2,4-dinitrophenylhydrazone* was readily prepared, needles from ethanol, m.p. 183–184°; infrared (potassium bromide disk) cm.$^{-1}$: broad OH stretching, 2500–3500; C=O, 1690.

Anal. Calcd. for $C_{16}H_{20}N_4O_6$: C, 52.74; H, 5.53; N, 15.38; mol. wt., 364.3. Found: C, 52.41; H, 5.02; N, 15.24; neut. equiv., 364 (by direct titration with 0.1*N* sodium hydroxide).

CHINA LAKE, CALIF.

(14) P. Bruylants and A. Stassens, *Bull. acad. roy. Belg.*, 702 (1921); *Chem. Abstr.*, **17**, 2872 (1923).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

Alkylations at the α-Carbon of Phenylacetamide and Phenylacetic Acid Through Their Disodio Salts[1]

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Disodiophenylacetamide, prepared from phenylacetamide and two molecular equivalents of sodium amide in liquid ammonia, was alkylated with alkyl and benzyl halides to give α-alkylphenylacetamides in good yields. α-Phenylethylation produced mainly *erythro*-2,3-diphenylbutyramide. Benzhydrylation was accompanied by self-alkylation of the halide to form tetraphenylethylene. The alkylations of disodio phenylacetate with *n*-butyl bromide and β-phenylethyl chloride are also reported.

Disodio phenylacetate has previously[2] been alkylated with benzyl, benzhydryl, and α-phenylethyl chlorides to form the corresponding α-substituted phenylacetic acids I (Equation 1).

$$C_6H_5CH_2COOH \xrightarrow[\text{liq. } NH_3]{2\ NaNH_2} C_6H_5\overset{Na}{C}HCOONa \xrightarrow[2.\ NH_4Cl]{1.\ RX} \underset{I}{C_6H_5\overset{R}{C}HCOOH} \quad (1)$$

This method has now been extended to include alkylations with *n*-butyl bromide and β-phenyl-

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(2) C. R. Hauser and W. J. Chambers, *J. Am. Chem. Soc.*, **78**, 4942 (1956).

ethyl chloride, and disodiophenylacetamide has been alkylated similarly with all five of the halides to give the corresponding α-substituted phenylacetamides II (Equation 2).

$$C_6H_5CH_2CONH_2 \xrightarrow[\text{liq. } NH_3]{2\ NaNH_2} C_6H_5\overset{Na}{C}HCONHNa \xrightarrow[2.\ NH_4Cl]{1.\ RX} \underset{II}{C_6H_5\overset{R}{C}HCONH_2} \quad (2)$$

These reactions were effected by adding phenylacetic acid or phenylacetamide to two molecular equivalents of sodium amide in liquid ammonia, followed by one molecular equivalent of the halide in a little ether. The reaction appeared to be complete as soon as the halide was added since the green color of the intermediate disodio phenylacetate or disodiophenylacetamide was then discharged. The yields of the alkylation products of types I and II are summarized in Table I, those of type I reported earlier being included for comparison. The products from the new alkylations were identified by standard procedures (see Experimental).

TABLE I

YIELDS OF ALKYLATION PRODUCTS OF TYPES I AND II IN EQUATIONS 1 AND 2

Alkyl Chloride	Type I, %	Type II, %
n-Butyl[a]	65	86
β-Phenylethyl	45	52
Benzyl	88[b]	65
α-Phenylethyl	84[c]	64[d]
Benzhydryl	51[b,e]	19[f]

[a] *n*-Butyl bromide was used. [b] Ref. 2. [c] *erythro* Isomer; an 8% yield of the *threo* isomer was also isolated (ref. 4). [d] *erythro* Isomer; none of the *threo* isomer was isolated. [e] Tetraphenylethylene was obtained in 39% yield (ref. 2). [f] Tetraphenylethylene was obtained in 50% yield.

Table I shows that most of the alkylation products of type I and II were obtained in good to excellent yields. Actually these yields may not be the maximum obtainable since most of the alkylations were performed only once. These alkylations furnish convenient methods for the synthesis of various α-substituted phenylacetic acids and phenylacetamides.

The benzhydrylation of disodiophenylacetamide was realized in only 19% yield. The main reaction involved self-alkylation of the benzhydryl chloride leading to the formation of tetraphenylethylene (50%). This reaction was presumably initiated by sodium-hydrogen exchange between the disodiophenylacetamide and the halide.[3] Such a self-alkylation of this halide has been observed[2] to the extent of 39% along with the benzhydrylation of disodio phenylacetate, but the yield of the alkylation product of type I was still good (51%).

The alkylation with α-phenylethyl chloride is of particular interest since diastereoisomers of the product are possible. α-Phenylethylation of disodio phenylacetate has previously[4] been shown to occur stereoselectively to produce the *erythro* and *threo* isomers of I(R = $C_6H_5CHCH_3$) in yields of 84 and 8% respectively. Somewhat similarly the present α-phenylethylation of disodiophenylacetamide produced mainly (64%) the *erythro* isomer of II (R = $C_6H_5CHCH_3$). The structure of this isomer was established by hydrolysis to *erythro*-2,3-diphenylbutyric acid, whose configuration has been established.[5] None of the *threo* isomer was isolated. However, the indicated stereospecificity of the reaction is not considered established since an appreciable amount of starting material was unaccounted for. Moreover, the *threo* isomer might have been formed and then epimerized, though such an epimerization has been shown not to occur in the corresponding α-phenylethylation of disodiophenylacetate.[4] Incidently the *erythro* isomer of II (R = $C_6H_5CHCH_3$) was shown not to undergo epimerization under the reaction conditions.

EXPERIMENTAL[6]

Butylation of disodio phenylacetate. To a stirred suspension of 0.10 mole of sodium amide in 300 ml. of liquid ammonia[7] was added 6.8 g. (0.050 mole) of solid phenylacetic acid. The green solution was stirred for 15 min., and a solution of 6.8 g. (0.050 mole) of *n*-butyl bromide in 10 ml. of anhydrous ether was added during 1.5 min. The color faded and a dark gray precipitate formed. After stirring for 15 min., the suspension was neutralized by the addition of 6.0 g. of solid ammonia chloride and the ammonia was evaporated as an equal volume of ether was added. The ethereal suspension was poured into 50 ml. of 3*N* hydrochloric acid, and the layers were separated. The ethereal solution was combined with two ethereal washings of the aqueous solution, dried over Drierite, filtered, and the solvent was distilled under reduced pressure. Distillation of the residual oil afforded 6.3 g. (65%) of 2-phenylhexanoic acid (I. R = $n-C_4H_9$), b.p. 170–178° at 19 mm. (lit.[8] 182–183° at 20 mm.).

The 2-phenylhexanoic acid (6.3 g.) and 4.0 g. of thionyl chloride in 15 ml. of benzene was refluxed for 1 hr. After cooling, the solution was saturated with ammonia and diluted with 50 ml. of benzene. The resulting suspension was boiled and filtered while hot. The addition of hexane to the cooled filtrate precipitated 2-phenylhexanamide (4.1 g., 66%), m.p. 89–90°. Two crystallizations from hexane, followed by one recrystallization from dilute methanol

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

(4) C. R. Hauser, D. Lednicer, and W. R. Brasen, *J. Am. Chem. Soc.*, **80**, 4345 (1958).

(5) W. R. Brasen and C. R. Hauser, *J. Am. Chem. Soc.*, **79**, 395 (1957).

(6) Melting points and boiling points are uncorrected. Melting points were taken on a Fisher-Johns melting point apparatus. Microanalyses were by Spang Microanalytical Laboratory, Ann Arbor, Mich.

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

(8) R. Dolique, *Ann. chim.* [10], **15**, 468 (1931).

raised the melting point to 98–98.5° (lit., [9,10] m.p. 96° and 95–97°).

β-Phenylethylation of disodio phenylacetate. To a stirred solution of 0.050 mole of disodio phenylacetate, prepared as described above, there was added during 2 min. 7.0 g. (0.050 mole) of β-phenylethyl chloride in 10 ml. of anhydrous ether. After stirring for 30 min., the ammonia was replaced by ether, and 100 ml. of water was added. The layers were separated, and the ethereal solution was extracted with two 50-ml. portions of 10% sodium hydroxide solution. The alkaline solutions were combined, filtered to remove a small amount of tar, and acidified with 125 ml. of 3*N* hydrochloric acid. The acidified aqueous suspension was extracted three times with ether. The combined ethereal solutions were dried over Drierite, filtered, and the solvent was distilled under reduced pressure. The residual oil was distilled to remove unchanged phenylacetic acid (2.3 g., 33%), b.p. 100–110° at 5 mm., m.p. 76.5–77.5° after crystallization from ligroin (b.p. 60–90°). The melting point was not depressed on admixture with an authentic sample of phenylacetic acid.

Crystallization of the pot residue from ligroin (b.p. 60–90°) afforded 5.4 g. (45%) of 2,4-diphenylbutyric acid (I, R = $C_6H_5CH_2CH_2$), m.p. 73.5–74°. Recrystallization from hexane raised the m.p. to 74.5–75° (lit.,[11] m.p. 72–73°). On admixture with phenylacetic acid the melting point was depressed to 45–65°.

Butylation of disodiophenylacetamide. To a stirred suspension of 0.10 mole of sodium amide in 300 ml. of commercial anhydrous liquid ammonia[7] was added 6.8 g. (0.050 mole) of solid phenylacetamide. The green solution was stirred for 15 min. and a solution of 6.8 g. (0.050 mole) of *n*-butyl bromide in 15 ml. of anhydrous ether was added during 1.5 min. The color faded and a black gum formed. After stirring for 15 min., the suspension was neutralized by the addition of 6.0 g. of solid ammonium chloride, and the ammonia was replaced by ether. The ethereal suspension was poured into 50 ml. of 3*N* hydrochloric acid and 100 ml. of ethyl acetate was added. The layers were separated and the aqueous solution was washed with three portions of ethyl acetate. The organic solutions were combined, dried over Drierite, filtered, and the solvent was distilled under reduced pressure. Crystallization of the residual oil from benzene-hexane afforded 8.2 g. (86%) of 2-phenylhexanamide (II. R = $n-C_4H_9$), m.p. 89–92°. Two recrystallizations from benzene-hexane, followed by one recrystallization from dilute methanol raised the m.p. to 97.5–98.5°. No depression in melting point was observed on admixture with a sample of the amide prepared as described above.

2,3-Diphenylpropionamide (II. R = $C_6H_5CH_2$). This amide, m.p. 127–131°, was obtained in 66% yield by the alkylation of phenylacetamide with benzyl chloride essentially as described above for the butylation. Recrystallization of the crude amide from dilute ethanol gave 65% of this amide, m.p. 133–133.5° (lit.,[12] m.p. 133–134°).

Hydrolysis of a sample of this amide gave 2,3-diphenylpropionic acid, m.p. 82–82.5° after crystallization from petroleum ether (b.p. 30–60°). This acid has been reported[13] to exist in three crystalline forms melting at 82°, 88–89°, and 95–96°.

2,4-Diphenylbutyramide (II. R = $C_6H_5CH_2CH_2$). This amide, m.p. 88–91°, was obtained in 52% yield by the alkylation of phenylacetamide with β-phenylethyl chloride essentially as described above for the butylation. Several recrystallizations from benzene-hexane raised the m.p. to 98.5–90° (lit.,[14,15] m.p. 87 and 96).

Anal. Calcd. for $C_{16}H_{17}NO$: C, 80.30; H, 7.16; N, 5.85. Found: C, 80.16; H, 7.23; N, 6.05.

Hydrolysis of a sample of this amide gave 2,4-diphenylbutyric acid, m.p. 75° after crystallization from hexane. No depression in melting point was observed on admixture with a sample of the acid prepared as described above.

2,3,3-Triphenylpropionamide [II. R = $(C_6H_5)_2CH$]. This amide was prepared (half scale) by the alkylation of phenylacetamide with benzhydryl chloride essentially as described above for the butylation. An orange precipitate formed immediately upon the addition of the halide. The color disappeared after about 2 min. Fractional crystallization of the residue alternately from ethanol and methanol afforded the following compounds: tetraphenylethylene (2.1 g., 51%), m.p. 223–224°, which was not depressed on admixture with authentic tetraphenylethylene (lit.,[16] m.p. 223–224°); phenylacetamide (8%), m.p. 155–158°, which was not depressed on admixture with an authentic sample; and 2,3,3-triphenylpropionamide [II. R = $(C_6H_5)_2CH$] (1.5 g., 19%), m.p. 208–210° after crystallization from methanol. Recrystallization of the amide from methanol raised the melting point to 209–209.5° (lit.,[2] m.p. 209–210°). On admixture with tetraphenylethylene the melting point was depressed to 200–202°.

A sample of the amide was hydrolyzed to give 2,3,3-triphenylpropionic acid, m.p. 221.5–222° after crystallization from methanol (lit.,[2] m.p. 221.5–222°).

erythro-2,3-Diphenylbutyramide (II. R = $C_6H_5CHCH_3$). This amide, m.p. 200–201°, was obtained in 64% yield by the alkylation of phenylacetamide with α-phenylethyl chloride essentially as described above for the butylation. The 64% represents several crops obtained by crystallization from ethanol. Each crop melted at 200–201° (lit.[4] m.p. 193°). The *threo* isomer is reported[17] to melt at 173–174°. On admixture with an authentic sample of the *erythro* isomer the melting point was not depressed.

A sample (1.0 g.) of this amide was hydrolyzed by refluxing for 3 days with 15 ml. of glacial acetic acid and 5 ml. of 50% sulfuric acid to give *erythro*-2,3-diphenylbutyric acid (70%), m.p. 189°. On admixture with an authentic sample of the *erythro* acid the melting point was not depressed (lit., *erythro*[2] m.p. 187–187.5°; *threo*[17] m.p. 135°).

Attempted epimerization of erythro amide II. R = $C_6H_5CHCH_3$. To a stirred suspension of 0.020 mole of sodium amide in 150 ml. of liquid ammonia[7] was added 2.4 g. (0.010 mole) of the *erythro* amide. After stirring for 30 min., the gray suspension was neutralized by the addition of 1.5 g. of solid ammonium chloride, and the ammonia was evaporated. The residue was stirred with 50 ml. of 3*N* hydrochloric acid and filtered to give 2.3 g. (96% recovery) of the *erythro* amide, m.p. 200–201°, which was not depressed on admixture with the starting amide.

DURHAM, N. C.

(9) J. Levy and P. Jullien, *Bull. soc. chim. France* [4], **45**, 941 (1929).

(10) K. Petterson and G. Willdeck, *Arkiv. Kemi*, **9**, 333 (1956).

(11) M. S. Newman, *J. Am. Chem. Soc.*, **60**, 2947 (1938).

(12) A. Meyer, *Ber.*, **21**, 1306 (1888).

(13) W. Miller and G. Rhode, *Ber.*, **25**, 2017 (1892).

(14) F. Salmon-Legegneur, *Bull. soc., sci. Bretange*, **26**, 9 (1951); *Chem. Abstr.*, **48**, 9985 (1954).

(15) M. S. Ziegler and R. M. Herbst, *J. Org. Chem.*, **16**, 920 (1951).

(16) J. Schmidlin, *Ber.*, **39**, 4203 (1907).

(17) A. A. Hentl and M. T. Bogert, *J. Am. Chem. Soc.*, **63**, 989 (1941).