

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

New Antibacterial Agents. II. An Alternate Synthesis of DL-threo-2-Dichloroacetamido-1-(4-methylsulfonylphenyl)-1,3-propanediol¹

By C. M. SUTER, SAMUEL SCHALIT AND ROYAL A. CUTLER

RECEIVED MAY 15, 1953

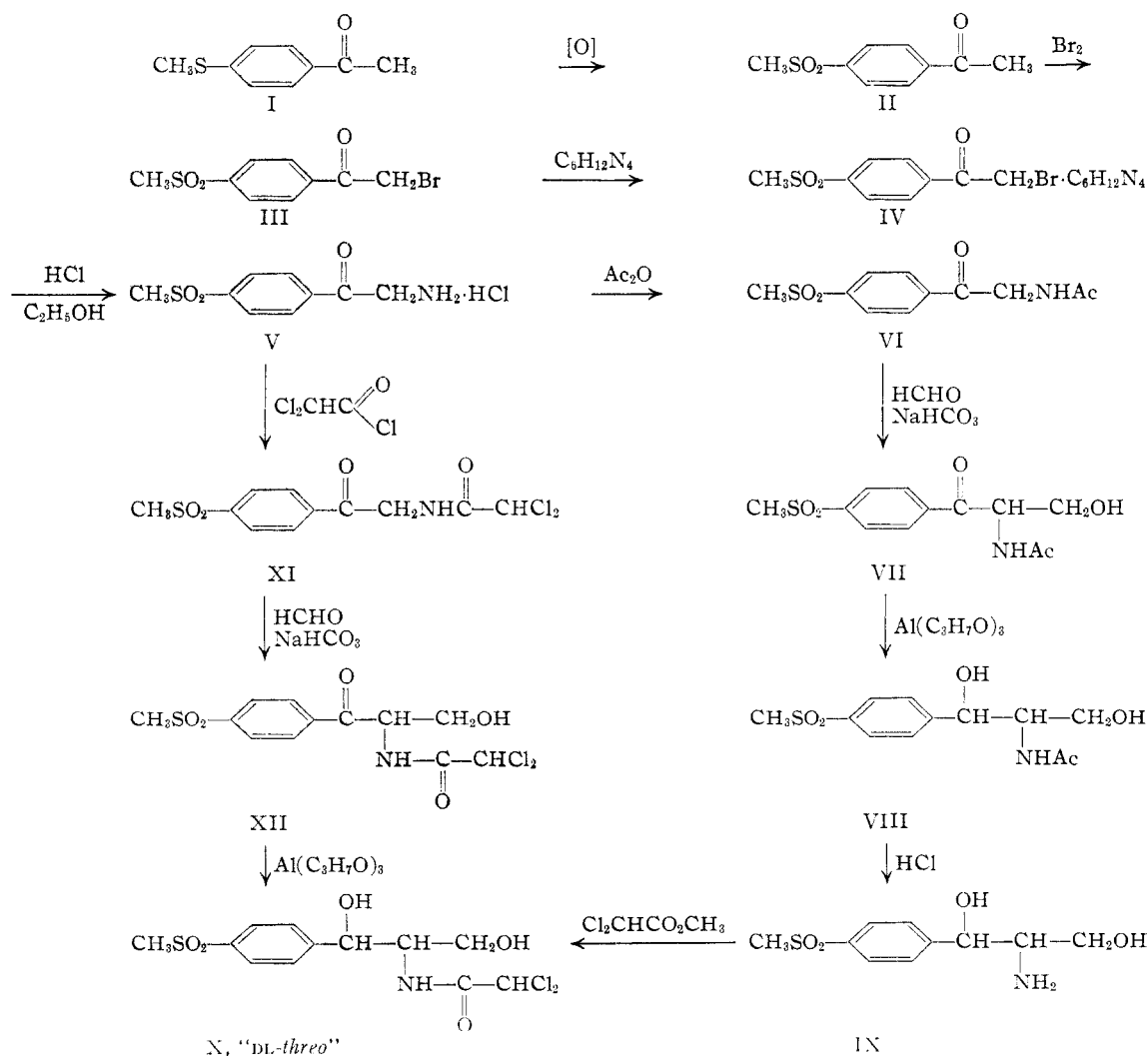
An alternate method for the preparation of DL-threo-2-dichloroacetamido-1-(4-methylsulfonylphenyl)-1,3-propanediol (X) is described. According to this method, 4-methylmercaptoacetophenone (I) was first converted to 4-methylsulfonylacetophenone (II) which was in turn converted to the desired product (X) by a series of reactions (see Chart I) paralleling those previously described for the preparation of DL-threo-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol.¹ In addition, a number of the sulfone intermediates in the present series were also synthesized directly from the corresponding sulfides¹ by oxidation with 40% peracetic acid (see Table I).

An earlier publication¹ described the synthesis of DL-threo-2-dichloroacetamido-1-(4-methylsulfonylphenyl)-1,3-propanediol (X) by a method which started with 4-methylmercaptoacetophenone (I) and led, after a suitable series of steps, to DL-threo-2-dichloroacetamido-1-(4-methylmercaptophenyl)-1,3-propanediol. Oxidation of the latter with 40% peracetic acid gave the desired sulfone X in excellent yield.

In the present method the conversion of the methylmercapto group to methylsulfonyl was achieved in the initial step by the oxidation of 4-methylmercaptoacetophenone (I) to 4-methylsulfonylacetophenone² (II). Subsequent steps in the synthesis followed the scheme outlined in Chart I.

It will be noted that from the amine hydrochloride V two alternate routes were employed.

CHART I



(1) For the first paper in this series see R. A. Cutler, R. J. Stenger and C. M. Suter, *THIS JOURNAL*, **74**, 5475 (1952).

(2) (a) A. T. Fuller, I. M. Tonkin and J. Walker, *J. Chem. Soc.*, 633 (1945); (b) H. Burton and P. F. Hu, *ibid.*, 601 (1948).

The first (V \rightarrow VI \rightarrow VII \rightarrow VIII \rightarrow IX \rightarrow X) followed the general sequence of reactions used by Long and Troutman³ in their synthesis of DL-threo-2-dichloroacetamido-1-(4-nitrophenyl)-1,3-propanediol, while the second (V \rightarrow XI \rightarrow XII \rightarrow X) utilized the shorter modification introduced by Sörm and co-workers.⁴

Inasmuch as the properties of the sulfones differed considerably, in some cases, from those of the corresponding sulfides¹ it was necessary to modify the experimental details in several of the steps. For example, the adduct IV proved to be much less stable than the corresponding sulfide.¹ This instability⁵ was especially apparent when chloroform was used as the solvent in its preparation. The product separated therefrom as an orange, gummy solid from which only a low yield of pure adduct could be obtained. On the other hand, the use of acetonitrile as the reaction medium resulted in an 80% yield of white product IV in analytically pure condition.

As would be expected, the presence of the sulfone group increased considerably the water solubility of a number of the intermediates. This was especially true of V¹¹ and IX, both of which were very water soluble and, as a consequence, were difficult to isolate in good yield.

The sulfones, with the exception of IV, VIII and IX, melted higher than the corresponding sulfides¹ and were, in most cases, much less soluble in organic solvents. Thus, in the preparation of some of these compounds, it was necessary to use an extremely large volume of solvent (XI) or to extend the reaction times (VII, XII).

As an alternate method of synthesizing a number of the sulfone intermediates, the oxidation of the corresponding sulfides¹ was undertaken. In this connection the conversion of α -dichloroacetamido-4-methylmercaptoacetophenone¹ to the sulfone XI was studied in some detail. The use of potassium permanganate, 30% hydrogen peroxide or 90% hydrogen peroxide all gave little or none of the desired product. On the other hand, the oxidation was readily achieved with 40% peracetic acid resulting in a practically quantitative yield of the pure sulfone XI.⁶ Application of this method to the synthesis of the remaining sulfones listed in Table I gave good yields in each case.⁷

An additional compound prepared by the above method was the ethylsulfonyl analog of XII, namely, racemic α -dichloroacetamido- β -hydroxy-4-ethylsulfonylpropionophenone (XIII) (see Experi-

mental). This compound as well as the methyl analog XII showed significant antifungal activity against several species.⁸ In this respect the methyl compound XII is from one and one-half to two times as active as the ethyl analog.⁹

Experimental¹⁰

4-Methylsulfonylacetophenone (II).²—In the present work this ketone was prepared in excellent yields by the oxidation of 4-methylmercaptoacetophenone (I) with potassium permanganate in aqueous acetic acid solution or with hydrogen peroxide.^{2b} After recrystallization from alcohol, the white needles melted at 129.0–130.4°.

α -Bromo-4-methylsulfonylacetophenone (III).—To 10 g. (0.051 mole) of 4-methylsulfonylacetophenone (II) suspended in 50 ml. of glacial acetic acid was added 8.1 g. of bromine. The reaction mixture was stirred and warmed gently to 70° whereupon all went into solution as the bromine color disappeared. The reaction mixture was poured immediately into cold water and the separated product collected on a filter; yield, 12.5 g. (90%), m.p. 120–122° (uncor.). Recrystallization from benzene gave dense, small white crystals, m.p., 127.0–128.4°.

Anal. Calcd. for C₉H₉BrO₃S: Br, 28.83. Found: Br, 29.42.

This compound was also prepared by the oxidation of α -bromo-4-methylmercaptoacetophenone¹ with potassium permanganate in aqueous acetic acid or with 40% peracetic acid in acetone.

Hexamethylenetetramine Salt of α -Bromo-4-methylsulfonylacetophenone (IV).—To a stirred solution of 15 g. (0.054 mole) of the α -bromoketone III dissolved in 150 ml. of acetonitrile was added 7.6 g. (0.054 mole) of hexamethylenetetramine. The temperature of the reaction mixture rose from 20 to 30°, whereupon cooling was instituted and the temperature maintained at 10–20° for two hours. The product was then collected on a suction filter and washed with cold acetonitrile to give 18 g. (0.043 mole) (80%) of white solid,⁶ m.p. 137.6–140.1° dec.

Anal. Calcd. for C₁₅H₂₁BrN₄O₃S: N, 13.43. Found: N, 13.57.

α -Amino-4-methylsulfonylacetophenone Hydrochloride (V).—To a solution of 320 ml. of concd. hydrochloric acid in 650 ml. of ethanol at room temperature was added 243 g. (0.58 mole) of the adduct IV, and the resulting mixture stirred overnight. After cooling to 10°, the separated solids were collected on a suction filter and washed with fresh ethanol. To remove the ammonium chloride present, the partially dried filter cake was dissolved at 70° in 400 ml. of water which contained 15 ml. of concd. hydrochloric acid, the hot solution was filtered free from a small amount of suspended solid and the filtrate cooled to 10°. The crystalline product was removed by filtration, washed with a small portion of ice-water¹¹ and dried to give 55 g. (0.22 mole) (38%) of V. An additional recrystallization from 2 volumes of acidulated water gave tiny white, dense platelets, m.p. > 300°.

Anal. Calcd. for C₉H₁₁ClNO₃S: Cl, 14.20; N, 5.61; S, 12.84. Found: Cl_(ion), 14.06; N, 5.55; S, 12.84.

α -Acetamido-4-methylsulfonylacetophenone (VI).—To five grams (0.02 mole) of the amine hydrochloride V,

(8) This parallels the findings of Dr. A. B. Hillegas on racemic α -dichloroacetamido- β -hydroxy-4-nitropropionophenone (L. M. Long and H. D. Troutman, *THIS JOURNAL*, **73**, 481 (1951)).

(9) The antifungal screening was done by Dr. J. H. Bailey and staff of these laboratories.

(10) The analyses and melting points were performed by M. E. Auerbach and K. D. Fleischer of these laboratories. All melting points, unless otherwise specified, are corrected and were determined with an electrically heated, mechanically stirred, Thiele type apparatus. Thermometers used were calibrated Anschütz internal thermometers. Samples were placed in 1-mm. capillary tubing and the latter immersed when the temperature of the melting point bath was about 20° below the approximate melting point of the sample and the rate of temperature rise of the bath was approximately 3° per minute. Nitrogen, unless otherwise specified, was determined by a modified Kjeldahl procedure. Chlorine and sulfur, exceptions noted, were determined by the Parr bomb method.

(11) The amine hydrochloride V is soluble in 3–4 parts of water at room temperature.

(3) (a) L. M. Long and H. D. Troutman, *THIS JOURNAL*, **71**, 2469 (1949); (b) *ibid.*, 2473.

(4) F. Sörm, J. Gut, M. Suchý and D. Reichl, *Collection Czechoslov. Chem. Commun.*, **15**, 501 (1950).

(5) The pure hexamethylenetetramine adduct IV proved to be unstable even at room temperature. Thus the dry solid on standing for a few weeks gradually decomposed to an orange gum.

(6) Additional work has shown peracetic acid to be the reagent of choice for the conversion of sulfides to sulfones in a large number of instances.

(7) In the preparation of VII it was necessary to run the reaction at a relatively low temperature and to avoid an appreciable excess of peracetic acid. Indeed, when twice the theoretical amount of peracetic acid was used and the reaction allowed to rise to 55–60° the side chain was cleaved to give a 92% yield of an acid which proved to be identical with a compound previously described as 4-methylsulfonylbenzoic acid.¹²

slurried with 25 ml. of water and 50 g. of ice, was added 13 ml. of acetic anhydride followed by the immediate addition of a solution of 16.5 g. of sodium acetate trihydrate dissolved in 60 ml. of water. The stirred reaction mixture was allowed to warm gradually to 20° and treated with concentrated hydrochloric acid till acid to congo red. After recooling the mixture to 5°, the acetylated product VI was collected on a filter, washed with a little ice-water and dried; yield 3.4 g. (0.0133 mole) (66.5%). Recrystallization from 75 ml. of water or acetonitrile gave white needles or transparent octahedra, respectively, m.p. 200.6–202.5°.

Anal. Calcd. for $C_{11}H_{13}NO_4S$: S, 12.56; N-acetyl, 16.86. Found: S, 12.51; N-acetyl, 17.30.

Racemic α -Acetamido- β -hydroxy-4-methylsulfonylpropiophenone (VII).—A slurry of 5 g. (0.0196 mole) of α -acetamido-4-methylsulfonylacetophenone (VI), 1.47 ml. (0.0196 mole) of formalin, 0.1 g. of sodium bicarbonate and 25 ml. of 95% ethanol was stirred and heated at 38–40°. At no time during the reaction did complete solution occur, the slurry at any given time consisting of a mixture of the starting acetamidoketone VI and hydroxymethylated material VII. The course of the reaction was followed by removing small samples at varying time intervals and determining the melting point of each. After 2.5 hours of heating the melting point of a sample was 195–200° (uncor.). The mixture was then allowed to stir overnight at room temperature (m.p. 175–194°), an additional 0.73 ml. (0.009 mole) of formalin added and the mixture again heated at 35–45° for five hours. At this time a sample melted at 167–169° (uncor.) which indicated that the reaction was complete. The white solid was collected on a buchner funnel, washed with cold water and dried; yield 4.0 g. (71.5%). Recrystallization from nitroethane gave white crystals, m.p. 166.3–167.8°.

Anal. Calcd. for $C_{12}H_{15}NO_5S$: S, 11.24. Found: S, 11.28.

DL-threo-2-Acetamido-1-(4-methylsulfonylphenyl)-1,3-propanediol (VIII).—To a refluxing solution of 43.3 g. (0.212 mole) of aluminum isopropoxide in dry isopropyl alcohol was added 26 g. (0.091 mole) of the ketone VII. Refluxing was continued for 20 minutes and the isopropyl alcohol removed *in vacuo* to yield a yellow, solid residue. The latter was stirred and heated on a steam-bath for 30 minutes with 250 ml. of 10% aqueous sodium chloride solution and the precipitated aluminum hydroxide removed by filtration. After evaporation of the yellow filtrate to dryness, the product was extracted from the accompanying sodium chloride by means of hot nitroethane. The aluminum hydroxide filter cake was likewise extracted with hot nitroethane and the combined nitroethane extracts (about 750 ml.) from these two sources were evaporated *in vacuo* to a volume of about 500 ml. The latter solution was filtered hot with charcoal and the yellow filtrate chilled to give 9.1 g. (34.7%) of white solid. Two recrystallizations from nitroethane yielded white leaflets, m.p. 172.7–173.7°.

Anal. Calcd. for $C_{12}H_{17}NO_5S$: N, 4.88; S, 11.16. Found: N, 4.93; S, 11.12.

DL-threo-2-Amino-1-(4-methylsulfonylphenyl)-1,3-propanediol (IX).—The hydrolysis of the N-acetyl compound VIII was achieved by heating 30 g. (0.104 mole) of the latter with 67.8 ml. of concd. hydrochloric acid and 300 ml. of water for one hour on the steam-bath. The resulting solution was evaporated to a volume of 80 ml. and 11 g. of sodium chloride added to help salt out the very water-soluble amine IX. The solution was then rendered strongly alkaline with 40 ml. of 35% sodium hydroxide solution and, after warming to 70–80°, extracted with four 250-ml. portions of warm (70–75°) *n*-butyl alcohol. After drying over Drierite, the combined butanol extracts were evaporated *in vacuo* to a volume of 125 ml. and the concentrate chilled. The mixture of tan solid and gummy material which separated was collected on a filter, washed with *n*-butyl alcohol and sucked dry. The gum was separated from the solid manually and discarded; yield of solid 5.0 g. (19.5%), m.p. 119–122° (uncor.).

Two recrystallizations from absolute ethanol with charcoaling gave a white powder, m.p. 123.2–127.1°.

Anal. Calcd. for $C_{10}H_{15}NO_2S$: N, 5.71. Found: N, 5.82.

DL-threo-2-Dichloroacetamido-1-(4-methylsulfonylphenyl)-1,3-propanediol (X).—A mixture of 1.0 g. (0.00408 mole) of the free amine IX and 2 ml. (0.019 mole) of methyl dichloroacetate was heated on a steam-bath for 25 minutes with occasional stirring. The solid which separated was

filtered off, washed with a little methyl dichloroacetate and sucked dry; yield 1.27 g. (87.5%). Recrystallization from water gave white platelets, m.p. 181–183° (uncor.). A mixed melting point with an authentic sample of X¹ was not depressed.

α -Dichloroacetamido-4-methylsulfonylacetophenone (XI).—A mixture of 5 g. (0.02 mole) of the amine hydrochloride V, 6 ml. of dichloroacetyl chloride and 1 liter of dry benzene was refluxed overnight. The resulting clear solution was decanted from a small amount of solid and cooled to 10°. The product separated as white needles which were collected on a suction filter and washed with benzene; yield 5.6 g. (0.0173 mole) (86.5%). Recrystallization from 7 volumes of acetonitrile gave coarse white crystals, m.p. 181.0–182.2°.

Anal. Calcd. for $C_{11}H_{11}Cl_2NO_4S$: Cl, 21.87; N, 4.32. Found: Cl, 21.48; N, 4.26.

Racemic α -Dichloroacetamido- β -hydroxy-4-methylsulfonylpropiophenone (XII).—The preparation of this compound was similar to that described for VII above except that this reaction was even slower due to the insolubility of the starting material XI.

Five grams (0.0154 mole) of XI was heated at 35–45° intermittently for a total of 24 hours with 1.73 ml. (0.0231 mole) of formalin, 0.4 g. of sodium bicarbonate and 50 ml. of ethanol. Two additional portions (0.57 ml. each) of formalin were added after 5 and 11 hours, respectively. No appreciable improvement in the melting point of the mixture was noted after 11 hours of heating. After 24 hours of heating, the crude pale yellow product was collected on a buchner funnel, washed with water and dried; yield 2.0 g. (36.6%), m.p. 144–148° (uncor.). Two recrystallizations from nitroethane, with charcoaling, gave a white crystalline powder, m.p. 158.0–158.6°.

Anal. Calcd. for $C_{12}H_{13}Cl_2NO_5S$: Cl, 20.02; S, 9.05. Found: Cl, 20.03; S, 9.07.

Preparation of X from XII.—The reduction of 15 g. (0.0424 mole) of the α -dichloroacetamidoketone XII with aluminum isopropoxide was carried out in a manner similar to that described for the preparation of the acetamido derivative VIII with the exception that water was used as the extracting medium instead of nitroethane; yield 7.4 g. (49%) of crude light yellow product. Two recrystallizations from water, with charcoaling, gave white prisms, m.p. 181–183° (uncor.). A mixed melting point of the latter with an authentic specimen of X¹ was not depressed.

Oxidation of Sulfides to Sulfones with Peracetic Acid.—The general procedure used in the oxidation of the sulfides¹ to the corresponding sulfones is as follows. Table I lists the volume of acetone used in each case and also the yield obtained.

TABLE I
OXIDATION OF SULFIDES¹ TO SULFONES WITH PERACETIC ACID

Sulfone prepared	Volume ^a of acetone	Yield of sulfone, %
VI	5	100
VII	8	85 ^b
VIII	10	73 ^c
XI	10	97
XII	9	86
XIII ^d	3	94

^a Volume of acetone per unit weight of sulfide.¹ ^b Only 5% of peracetic acid in excess of theory used and temperature maintained at 15° (see footnote 7). ^c Lowered yield due to solubility of product in large volume of solvent. ^d Racemic α -dichloroacetamido- β -hydroxy-4-ethylsulfonylpropiophenone (XIII).

To a slurry of 0.1 mole of the sulfide¹ in acetone¹² was added, in a dropwise fashion, 0.2⁺ mole¹³ of 40% peracetic

(12) Acetone is a convenient solvent for small scale laboratory preparations. However, the formation of acetone peroxide constitutes a potential hazard in large scale operations. Other suitable solvents may be used as, for example, acetonitrile or even water itself in many cases.

(13) Except in the case of VII (see footnote 7), the amount of peracetic acid in excess of that theoretically required was not at all critical.

acid.¹⁴ The temperature of the resulting exothermic reaction was maintained at about 40° by means of external cooling. After the addition was complete, stirring was continued for one hour and the resulting slurry of product and solvent cooled to 5°. The white crystalline solid was then collected on a suction filter, washed with fresh acetone and dried. In each case the sulfone was obtained in practically pure form directly from the reaction mixture. A mixture

(14) Obtained from Buffalo Electro-Chemical Co., Inc.

(15) The temperature, except in the case of VII (see footnote 7), can be varied within fairly wide limits. Thus in some cases the temperature was allowed to rise to 55–60° without detrimental effects.

melting point determination of the sulfones thus produced indicated that each was identical with a sample of the same sulfone prepared according to the reaction sequence outlined in Chart I.

Racemic α -Dichloroacetamido- β -hydroxy-4-ethylsulfonyl-propiophenone (XIII).—Prepared by the oxidation of racemic α -dichloroacetamido- β -hydroxy-4-ethylmercaptopropiophenone¹ according to the above procedure, m.p. 184.0–185.0°.

Anal. Calcd. for $C_{13}H_{15}Cl_2NO_5S$: Cl, 19.26; N, 3.81. Found: Cl, 18.96; N, 3.71.

RENSSELAER, NEW YORK

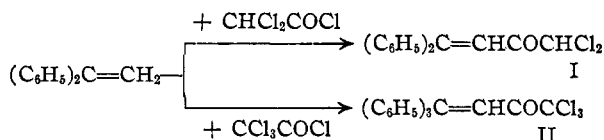
NOTES

The Uncatalyzed Condensation of 1,1-Diphenylethylene with Chlorinated Acetyl Chlorides

BY FELIX BERGMANN AND JOSEPH KLEIN

RECEIVED MARCH 4, 1953

The direct acylation of the β -carbon atom of 1,1-diphenylethylene is dependent on the presence of activating groups attached to the reacting COCl group. It has been shown, *e.g.*, that the $-COCl^1$ or the $-COOR^2$ radical, benzyl and aryl residues³ exert such an activating influence, which decreases in the order given. From a comparison of phosgene⁴ with oxalyl chloride it becomes evident that it is the neighboring carbonyl which increases the reactivity of the $-COCl$ group in the substitution under discussion. Therefore it appeared probable that any α -carbonyl would exert such an influence. Since the chlorides of glyoxylic acids and its homologs are unstable compounds—if existing at all—we applied the reaction to acid chlorides, in which the α -carbonyl is replaced by the CCl_2 group. Thus dichloroacetyl chloride, which is derived from glyoxylic acid chloride, was condensed with 1,1-diphenylethylene to form the ketone I. In a similar way, trichloroacetyl chloride, which is related to oxalyl chloride, gave the ketone II, accompanied by large amounts of the open-chain dimer of the hydrocarbon.⁵



The ketone I behaved like a derivative of an α -ketoaldehyde, *e.g.*, with 2,4-dinitrophenylhydrazine two products were formed, a yellow hydrazone and a deep-red osazone. The keto group in the com-

pound II, however, is sterically hindered and thus unreactive.

The absorption spectra of these ketones, when compared with β,β -diphenylacrolein (Table I), reveal that at short wave lengths the chlorinated side chain has practically no influence, whereas for the long wave maximum I shows a shift of 100 Å. and II of 280 Å. toward the red.

TABLE I

ABSORPTION SPECTRA OF β,β -DIPHENYL- α,β -UNSATURATED CARBONYL COMPOUNDS IN 95% ETHANOL

Compound	Maxima at	
1. β,β -Diphenylacrolein	2260 (4.3)	3000 (4.1)
2. Ketone I	2310 (4.1)	3100 (4.1)
3. Ketone II	2250 (4.0)	3280 (4.2)

Experimental

Condensation of 1,1-Diphenylethylene with Dichloroacetyl Chloride.—The ethylene (12 g.) and dichloroacetyl chloride (74 g., 7.5 equiv.) were heated in a current of hydrogen to 112–115° for 60 hours. The excess acid chloride was distilled off, the residue dissolved in benzene, washed with water and sodium carbonate, and then fractionated. The portion distilling at 170–195° (1.5 mm.) was redistilled, yielding a yellow oil of b.p. 178–182° (2 mm.). This fraction (5 g.) proved to be the expected ketone, 1,1-diphenyl-3-keto-4,4-dichlorobutene-1 (I).

Anal. Calcd. for $C_{16}H_{12}OCl_2$: C, 65.9; H, 4.1; Cl, 24.4. Found: C, 65.7; H, 4.1; Cl, 24.5.

The reaction with Brady's reagent at room temperature for 24 hours gave a mixture, from which first yellow crystals separated. The substance crystallized from butanol in yellow plates of m.p. 168°. It gave a positive Beilstein test and, according to analysis, represents a monohydrazone of I.

Anal. Calcd. for $C_{22}H_{16}O_4N_4Cl_2$: C, 56.0; H, 3.4; Cl, 15.0. Found: C, 56.0; H, 3.7; Cl, 14.4.

From the mother liquor a deep red precipitate was obtained on standing, which crystallized from dioxane–butyl acetate in microcrystals of m.p. 248°. This derivative is chlorine-free and corresponds to an osazone of I.

Anal. Calcd. for $C_{28}H_{20}O_8N_8$: C, 56.4; H, 3.35; N, 18.8. Found: C, 56.4; H, 3.8; N, 18.8.

Condensation of 1,1-Diphenylethylene with Trichloroacetyl Chloride.—The ethylene (12.8 g.) and trichloroacetyl chloride (64 g., 5 equiv.) were refluxed for 30 hours at a temperature of 116–118° in a current of hydrogen. The mixture was treated as above and yielded a fraction of boiling point 195–215° (3 mm.), which crystallized upon trituration

(1) M. S. Kharasch, S. S. Kane and H. C. Brown, *THIS JOURNAL*, **64**, 333 (1942).

(2) F. Bergmann and A. Kalmus, *J. Chem. Soc.*, 4521 (1952).

(3) F. Bergmann, S. Israelashvili and D. Gottlieb, *ibid.*, 2522 (1952).

(4) F. Bergmann, M. Weizmann, E. Dimant, S. Patai and J. Szmuszkowicz, *THIS JOURNAL*, **70**, 1612 (1948).

(5) Monochloroacetyl chloride failed to condense with 1,1-diphenylethylene.