Base-Induced Reactions of Phenacyl Chloride

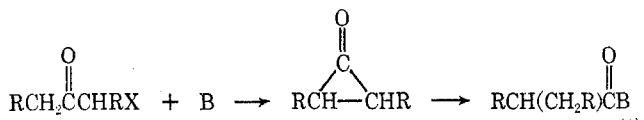
RALPH J. DE PASQUALE[1] AND MARTIN VOGEL

Department of Chemistry, Rutgers—The State University, New Brunswick, New Jersey

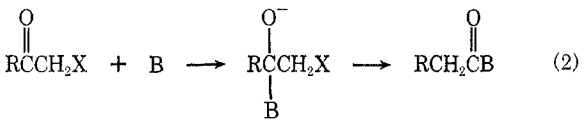
Received January 17, 1969

In benzene at reflux temperature, the reaction between phenacyl chloride and excess sodium hydride affords *trans*-1,2,3-tribenzoylcyclopropane and 3-chloro-2,4-diphenylfuran. With potassium *t*-butoxide at room temperature, acetophenone, diphenacyl, and phenacyl chloride are recovered after hydrolysis; the product ratio is sensitive to the mode of hydrolysis. Heating the butoxide reaction mixture prior to hydrolysis gives four rearranged products: *t*-butyl phenylacetate, phenylacetic acid, dibenzyl ketone, and ω-benzylacetophenone.

The reactions of α-halo ketones with alkoxides or hydroxides leads to both rearranged and unrearranged products.[2] Rearranged products[3] can be produced by both Favorskii (eq 1) and semibenzylic (eq 2) processes for α-halo ketones with and without α′ hydrogens.

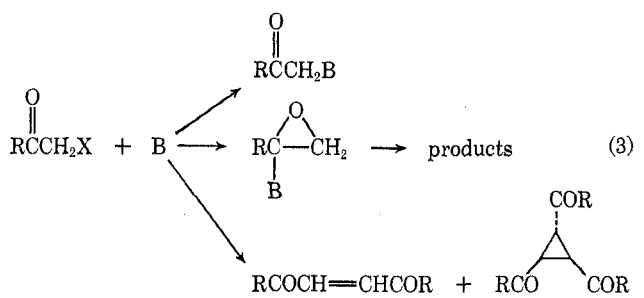


(1)



(2)

Unrearranged products include α-hydroxy or alkoxy ketones,[4] epoxides or products derived from them,[5] 1,2-diacylethylenes, and 1,2,3-triacylcyclopropanes (eq 3).[6] Alternate routes involving keto carbenoids[7] and



(3)

their anionic precursors[8] have been proposed for the formation of acylethylenes and cyclopropanes.

This paper deals with the reactions between phenacyl halides and sodium hydride or potassium *t*-butoxide in cyclohexene and benzene. Phenacyl halides were used since they have no α′ hydrogens and cannot undergo Favorskii rearrangement.

Results and Discussion

Sodium Hydride Reactions.—The reaction between phenacyl chloride and excess sodium hydride in refluxing cyclohexene or benzene gives *trans*-1,2,3-tribenzoylcyclopropane (I) and 3-chloro-2,4-diphenyl furan (II). The reaction with phenacyl bromide gives the cyclopropane derivative and the corresponding bromofuran. The products yields as a function of the reaction conditions are summarized in Table I.

TABLE I

REACTION OF PHENYL HALIDES WITH SODIUM HYDRIDE AT SOLVENT REFLUX TEMPERATURE

$NaH/C_6H_5CO-CH_2Cl(Br)$ mole ratio	Phenacyl halide addition time and solvent	Yield of halofuran, cyclopropane, and acetophenone, %
	Phenacyl Chloride	
15:1	1 hr, C_6H_6	16.8, 17.2, 0.0
15:1	2 hr, C_6H_6	13.2, 14.0, 0.0
15:1	4 hr, C_6H_6	7.8, 11.0, 0.0
9:1	1 hr, C_6H_6 or cyclohexene	20–21, 20–21, 0.0
	Phenacyl Bromide	
15:1	1 hr, C_6H_6 or cyclohexene	6–7.5, 21–22, 4.0
15:1	4 hr, cyclohexene	0–1, 2.6, 0.0

When cyclohexene was used as a solvent, neither phenacyl chloride nor bromide gave any *cis*- or *trans*-dibenzoylethylene or 7-benzoylnorcarane. The chlorofuran, tribenzoylcyclopropane, and 7-benzoylnorcarane do not decompose or isomerize under simulated reaction conditions.

A mechanistic scheme compatible with these results follows (p 1058).

In path A the phenacyl halide enolate anion displaces halide from the phenacyl halide eventually leading to the cyclopropane. In path B the enolate anion adds to the carbonyl group of the phenacyl halide and ultimately provides the furan derivatives. The formation of halo furans in this scheme resembles the Feist–Bernary synthesis.[9]

It is plausible that the cyclopropane derivative (I) could arise from the reaction between a ketocarbene (*via* α elimination) and its dimer dibenzoylethylene. Previous workers have shown that divalent carbon fragments can be trapped with alkenes and cycloalkenes.[10,11] The photochemical decomposition of diazo ketones is thought to involve both triplet (primarily) and singlet carbenes, whereas the base-induced α-elimination reactions of diphenyldibromethane presumably involve a carbene–metal halide complex. These results suggest that under our conditions, cyclohexene, the solvent, should compete favorably with dibenzoylethylene for a keto carbene intermediate

(1) To whom inquiries should be addressed: Shell Development Co., Emeryville, Calif. 94608.

(2) (a) W. McPhee and E. Klingsberg, *J. Amer. Chem. Soc.*, **66**, 1132 (1944); (b) J. Harley-Mason, *J. Chem. Soc.*, 518 (1949).

(3) A. S. Kende and R. Adams, *Org. Reactions*, **11**, 261 (1960).

(4) A. A. Sacks and J. G. Aston, *J. Amer. Chem. Soc.*, **73**, 3902 (1951).

(5) A. M. Ward, *J. Chem. Soc.*, 1541 (1929).

(6) M. Charpentier-Morize and P. Colard, *Bull. Soc. Chim. Fr.*, 1982 (1962).

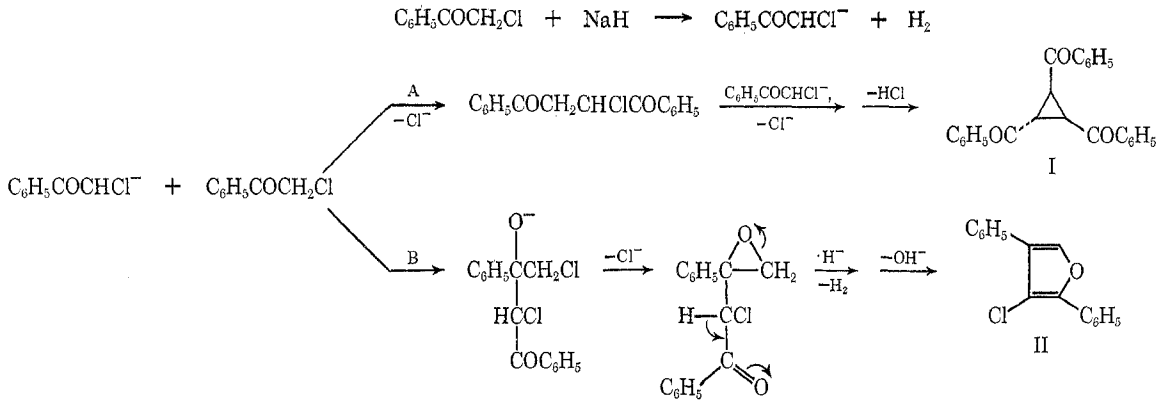
(7) (a) M. Siemiatycki and H. Strezelecka, *Compt. Rend.*, **250**, 3489 (1960); (b) V. Horak and L. Kohout, *Chem. Ind.* (London), 978 (1964).

(8) (a) G. Bonavent, M. Causse, and M. Guitard, *Bull. Soc. Chim. Fr.*, 2462 (1964); (b) H. Nozaki, K. Kondo, and M. Takaku, *Tetrahedron Lett.*, 251 (1965).

(9) A. F. Feist, *Chem. Ber.*, **35**, 1545 (1902).

(10) (a) D. O. Cowan, M. M. Couch, and G. S. Hammond, *J. Org. Chem.*, **29**, 1922 (1964); (b) M. Jones, Jr., and W. Ando, *J. Amer. Chem. Soc.*, **90**, 2200 (1968); (c) A. Padwa and R. Layton, *Tetrahedron Lett.*, 2167 (1967).

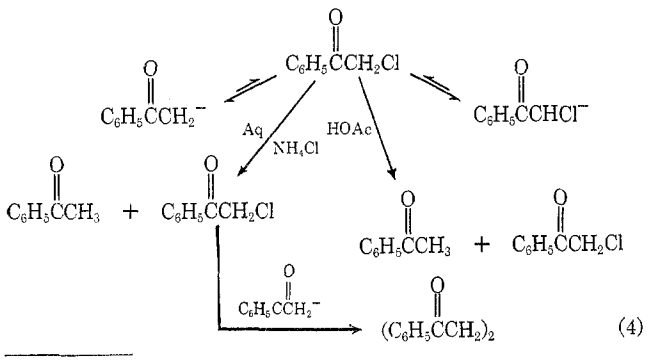
(11) G. L. Closs and L. E. Closs, *Angew. Chem.*, **74**, 431 (1962).



regardless of the fragment's multiplicity or degree of complexation. In the sodium hydride–phenacyl chloride–cyclohexene reaction, the absence of 7-benzoylnorcarane and the presence of *trans*-1,2,3-tribenzoylcyclopropane in the product mixture indicate that a phenacylidene fragment is an unlikely intermediate.

Potassium–*t*-Butoxide Reactions.—The addition of phenacyl chloride to fivefold excess potassium *t*-butoxide in benzene at room temperature results in the formation of a deep red solution. The solution gradually turns yellow on hydrolysis with aqueous ammonium chloride. Work-up affords diphenacyl (III) in 40–60% yield and acetophenone (IV) in 10% yield. When the red solution is hydrolyzed with acetic acid, it turns yellow rapidly and yields acetophenone (39%), phenacyl chloride (32%), and diphenacyl (<5%). An nmr spectrum of the initial red solution indicated that there was no phenacyl chloride, diphenacyl, or monoanion of diphenacyl in solution. An absorption at 5.5 ppm (singlet, phenacyl chloride or acetophenone enolate), which disappeared on hydrolysis, was observed.

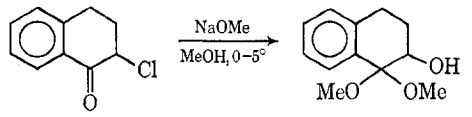
These results suggest that at the completion of the base addition only the enolate anions of phenacyl chloride and acetophenone, which are unreactive toward each other, remain. The presence of acetophenone enolate is likely because acetophenone is isolated after hydrolysis. Diphenacyl is apparently being formed during the subsequent neutralization step. The phenacyl chloride–acetophenone–diphenacyl distribution after hydrolysis depends on the neutralizing agent. It seems reasonable that the enolates are neutralized faster and more completely in the homogeneous acetic acid quench than in the heterogeneous aqueous ammonium chloride quench. In the ammonium chloride quench, diphenacyl formation[12] becomes important.



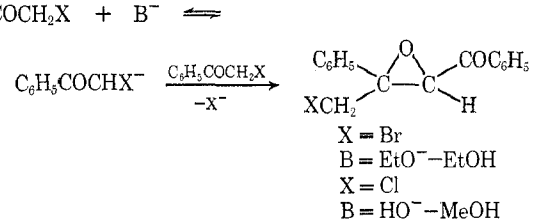
(4)

(12) Diphenacyl has been isolated previously in similar reactions: (a) O. Widman, *Chem. Ber.*, **42**, 3264 (1909); (b) P. R. Jones and J. R. Young, *J. Org. Chem.*, **33**, 1675 (1968).

Halo ketones without α' hydrogens react with alkoxides under mild conditions to provide alkoxy ethers and compounds derived from them[13] (eq 5) or



(5)



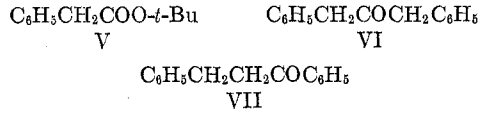
(6)

dimeric epoxides[14] (eq 6). Moreover, it has been reported that epoxyether formation competes with normal Favorskii rearrangement.[15] Cases have been reported[16] where tertiary α-halo ketones gave rise to rearranged acids on treatment with sodium hydroxide in refluxing xylene. This rearrangement is probably related to the benzylic acid rearrangement.

In our experiments, potassium *t*-butoxide was used as a base. In the experiments cited, hydroxide, methoxide, and ethoxide ions were employed. *t*-Butoxide is the strongest, most hindered, and least nucleophilic of the four bases. In the halo ketone–potassium *t*-butoxide reaction these properties favor deprotonation of the halo ketone by alkoxide over any reaction involving addition to the carbonyl group.

Evidence regarding the mode of formation of acetophenone is scant. However, subsequent experiments suggest that this enolate is reversibly formed from phenacyl chloride, presumably by transfer of positive chlorine to some acceptor.

If the reaction mixture is refluxed prior to neutralization, *t*-butylphenylacetate (V), dibenzyl ketone (VI), ω-benzylacetophenone (VII), and phenylacetic acid (VIII) are formed. The yields of the four products V, VI, VII, and VIII were 30, 15, 5, and 21%, respec-



(13) (a) C. L. Stevens, J. J. Beereboom, Jr., and K. G. Rutherford, *J. Amer. Chem. Soc.*, **77**, 4590 (1955); (b) C. L. Stevens, W. L. Malik, and R. Pratt, *ibid.*, **72**, 4758 (1950).

(14) H. H. Wasserman, N. E. Aubery, and H. E. Zimmerman, *ibid.*, **75**, 96 (1953).

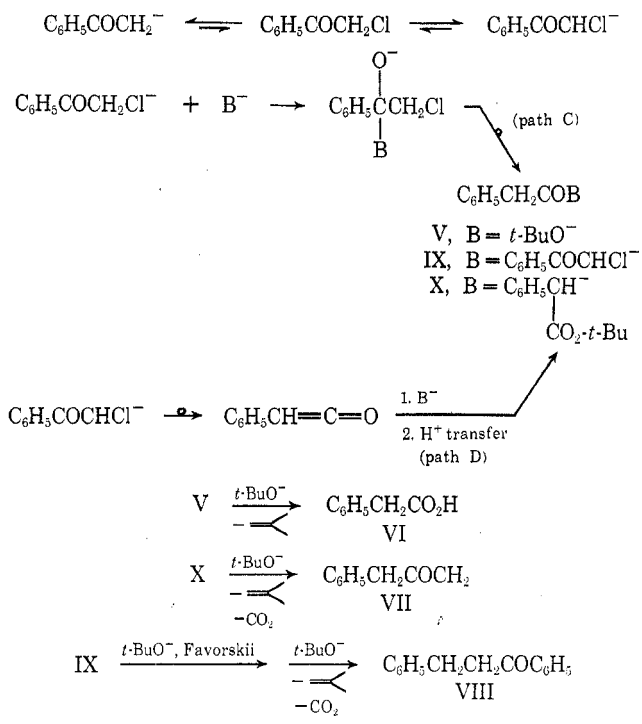
(15) C. L. Stevens and E. Farkas, *ibid.*, **74**, 618 (1952).

(16) (a) E. E. Smissman and G. Hite, *ibid.*, **81**, 2101 (1959); (b) B. Tchoubar, *Bull. Soc. Chim. Fr.*, **22**, 1363 (1955).

tively. The ratio of V to VI to VII was 6:3:1 regardless of the reflux time. Changing the solvent to cyclohexene gave the same products in approximately the same yields; 7-benzoylnorcarane was absent from the reaction mixture. The observed products are rearranged. To our knowledge, this is the first reported reaction in which alkoxide treatment of α-halo ketones without α' hydrogens provides rearranged products.

Possibly *t*-butyl phenylacetate could afford dibenzyl ketone *via* Claisen condensation followed by elimination of isobutylene and CO_2. However, when *t*-butyl ester V was treated with potassium *t*-butoxide under benzene reflux, no dibenzyl ketone was isolated. Only phenylacetic acid (21%) and unreacted ester (73%) were recovered. Isobutylene elimination must be the source of most of the phenylacetic acid in the phenacyl chloride–potassium *t*-butoxide reflux reaction.

Alternate paths leading to the rearranged products are suggested below.



Path C involves appreciable buildup of the phenacyl chloride concentration. If this is the case, it is surprising that other products, *e.g.*, diphenacyl, I, II, alkoxy ethers (as eq 5), etc., were not observed. In path D the concerted[17] rearrangement of phenacyl chloride anion to phenylketene is analogous to the nitrogen analog[18] in the Hofmann rearrangement. It is reasonable that $C_6H_5COCH_2COCH_2$ resulting from reaction of acetophenone anion by either path C or D is not detected. This β diketone should readily cleave with *t*-butoxide,[19] affording V and regenerating acetophenone anion. Products resulting from the direct reaction of acetophenone anion (including acetophenone) were not observed after hydrolysis. This is consistent with a rapid acetophenone anion–phenacyl chloride equilibrium which shifts to the right as the reaction proceeds.

(17) The results do not exclude a stepwise ionization of phenacyl chloride anion to a keto carbene followed by rapid rearrangement to phenylketene. In the absence of further data, the concerted rearrangement is offered for simplicity.

(18) C. R. Hauser and W. B. Renfrow, Jr., *J. Amer. Chem. Soc.*, **59**, 121 (1937).

(19) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Co., Inc., New York, N. Y., 1959, p 339.

Experimental Section

All reactions were carried out in a nitrogen atmosphere. Vapor phase chromatography analysis was done on an F & M Model 500 instrument using a 10 ft × 0.25 in. 12% QF-1 on Anakrom ABS 70–80 mesh column. Infrared spectra were recorded on a Perkin-Elmer Infracord and a Beckman IR-5A spectrometer. Nuclear magnetic resonance spectra were recorded in carbon tetrachloride with tetramethylsilane as an internal standard on a Varian A-60 spectrometer. Capillary melting points were determined using a Mel-Temp apparatus and are uncorrected.

Reaction of Phenacyl Chloride with Sodium Hydride in Cyclohexene.—Sodium hydride–mineral oil dispersion (34.7 g, 0.810 mol) was washed with 300 ml of benzene. Cyclohexene (100 ml) was added to the sodium hydride and the stirred mixture was maintained at reflux while phenaycl chloride (13.9 g, 0.0900 mol) dissolved in 200 ml of cyclohexene was added dropwise over a 1-hr period. The red mixture was refluxed for an additional 15 min, allowed to cool, and rapidly filtered under vacuum. The solution was extracted with saturated aqueous ammonium chloride. A white solid (1.0 g) precipitated from the organic layer and was removed and recrystallized from benzene, mp 218–220° (lit.[8b] mp 218°). Its nmr spectrum was identical with that of *trans*-1,2,3-tribenzoylcyclopropane (I).

The cyclohexene layer was dried (Na_2SO_4) and concentrated *in vacuo*, leaving 7.2 g of tarry resin.

Elution of this material from neutral alumina with hexane afforded 2.4 g (23%) of 3-chloro-2,4-diphenylfuran (II), which was recrystallized from 95% ethanol, leaving white plates, mp 110°.

Anal. Calcd for $C_{16}H_{11}OCl$: C, 75.44; H, 4.32; Cl, 13.95. Found: C, 75.29; H, 4.47; Cl, 13.96.

The nmr spectrum of II showed two multiplets centered at 7.40 and 7.95 ppm (area 9:2) with a singlet at 7.47 ppm (the 5 proton). The infrared spectrum of II displayed major absorptions at 6.2, 6.75, 6.95, 9.5, and 11.0 μ; uv max (95% EtOH) 283 mμ (log ϵ 4.38).

An additional 0.3 g (21% overall) of I was eluted with methylene chloride. Analysis of the reaction mixture by vpc showed no detectable amounts of 7-benzoylnorcarane or *cis*- or *trans*-dibenzoylethylene by comparison with authentic samples. The reaction was repeated in benzene with similar results.

Reaction of Phenacyl Bromide with Sodium Hydride.—The procedure was the same as the previous one except that bromofuran was eluted from alumina with 90:10 hexane–benzene, yielding 1.1 g (7%) of 3-bromo-2,4-diphenylfuran, mp 122° (lit.[20] mp 122°).

Anal. Calcd for $C_{16}H_{11}OBr$: C, 64.24; H, 3.68; Br, 26.73. Found: C, 63.83; H, 3.77; Br, 27.27.

Its infrared and nmr spectra were very similar to those of II, uv max (95% EtOH) 286 mμ (log ϵ 4.49).

trans-1,2,3-Tribenzoylcyclopropane (2.3 g, 23%) and acetophenone (0.4 g, 4%) were also isolated.

Control Experiments.—In three separate experiments, 7-benzoylnorcarane, *trans*-1,2,3-tribenzoylcyclopropane, and 3-chloro-2,4-diphenylfuran were refluxed in benzene for 1.5 hr in the presence of a tenfold excess of sodium hydride. Following the general work-up, the three compounds were recovered in virtually quantitative yields.

Reaction of Phenacyl Chloride with Potassium *t*-Butoxide at Room Temperature.—Potassium *t*-butoxide (34.6 g, 0.300 mol) was added to 100 ml of anhydrous benzene. A solution of phenacyl chloride (9.24 g, 0.0600 mol) dissolved in 100 ml of benzene was added dropwise to the stirred slurry over a 1-hr period. An nmr spectrum of the red solution showed that phenacyl chloride had been consumed. After an additional 15 min of stirring, neutralization with saturated aqueous ammonium chloride (50 ml) followed by conventional work-up afforded 3.0–4.2 g (40–65%) of crude diphenacyl (III). Recrystallization from ethanol

(20) This compound has been previously isolated. However, it was not fully characterized: H. A. Weidlich and G. H. Daniels, *Chem. Ber.*, **72**, 1590 (1939).

afforded a pure sample, mp 145–146° (lit.[21] mp 145°). Analysis of the crude reaction mixture by vpc revealed only two major products (*ca.* 1:7 ratio) which were identified as acetophenone (10%) and diphenacyl; traces of phenacyl chloride and *t*-butylphenylacetate were also detected. Traces of benzoic acid were isolated from the aqueous extracts.

The previous reaction was repeated at one-twelfth the scale. The reaction was quenched with 6 ml of glacial acetic acid in *ca.* 1 sec. Conventional work-up afforded a 0.46-g mixture of diphenacyl–phenacyl chloride–acetophenone (*ca.* 1:7:7, vpc). A 39 and 32% yield of acetophenone and phenacyl chloride, respectively, were obtained by nmr integration.

Reaction of Phenacyl Chloride with Potassium *t*-Butoxide at Benzene Reflux.—The procedure was identical with that of the previous large-scale, room temperature experiment up to the termination of the addition of the phenacyl chloride–benzene solution. At this point, the benzene mixture was refluxed for 1.5 hr with stirring. The reaction mixture was worked up as usual leaving an oily residue.

Vpc showed three major components in a 6:3:1 ratio. These were collected by vpc and identified as *t*-butyl phenylacetate (V), dibenzyl ketone (VI), and ω-benzylacetophenone (VII), respectively, by comparison of their physical and spectral properties with independently synthesized samples. Phenacyl chloride and acetophenone were minor components (<5%) in the residue. Acidification of the aqueous extracts afforded 0.84 g (21%) of phenylacetic acid, mp 74–76° (lit.[22] mp 77°).

(21) C. Weygand and W. Meusel, *Chem. Ber.*, **76**, 498 (1943).
(22) B. Sobin and G. B. Bachman, *J. Amer. Chem. Soc.*, **57**, 2458 (1935).

The reaction was conducted several times on a smaller scale. From the vpc and nmr spectrum of these crude reaction mixtures, the yield of V (30%), VI (15%), and VII (5%) was calculated. The V:VI:VII product ratio was identical after either 0.5- or 1.5-hr reflux.

Changing the solvent to cyclohexene gave the same products with slightly different ratios; the absence of 7-benzoylnorcarane was confirmed by vpc of the reaction mixture and synthetic norcaryl ketone.

Control Experiments.—In separate experiments, dibenzyl ketone, ω-benzylacetophenone, 7-benzoylnorcarane, and diphenacyl were reacted with a fourfold excess of potassium *t*-butoxide at benzene reflux for 1.5 hr. After work-up, all were recovered in quantitative or near quantitative yield.

Reaction of *t*-Butylphenylacetate with Potassium *t*-Butoxide.—Potassium *t*-butoxide (0.535 g, 5.00 mmol) was added to 8 ml of anhydrous benzene. To this stirred slurry, *t*-butylphenylacetate (0.30 g, 1.6 mmol) was added and the mixture was refluxed for 1.5 hr and worked up in the usual manner.

Unreacted starting material (0.218 g, 73%) was obtained from the organic phase. From the combined aqueous extracts, a white, crystalline acid, mp 74–76°, was isolated (0.08 g, 21%), whose nmr and ir spectra were identical with the spectra of phenylacetic acid.

Registry No.—Phenacyl chloride, 532-27-4; 3-bromo-2,4-diphenylfuran, 23346-66-9; II, 23346-65-8.

Acknowledgment—R. J. D. P. thanks Colgate Palmolive Co. and the Wright Fund for financial assistance.

Methylenation of Unsaturated Ketones. VIII.[1] Reaction of $\Delta^{1,4}$-, $\Delta^{1,4,6}$-, and $\Delta^{4,6}$-3-Keto Steroids with Phenyl(trichloromethyl)mercury[2]

B. BERKOZ, G. S. LEWIS, AND J. A. EDWARDS

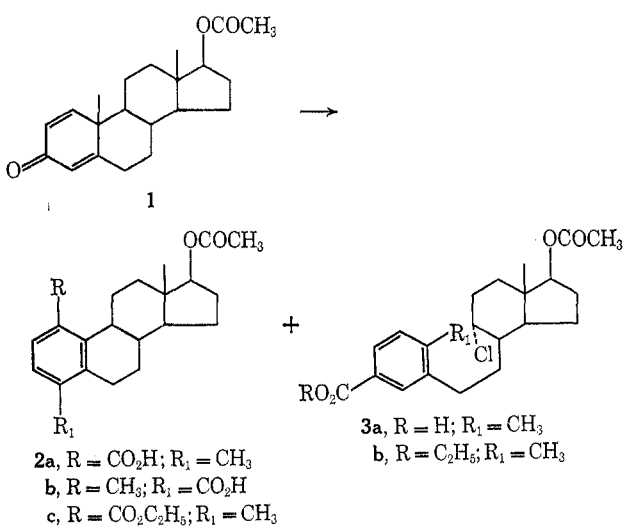
Institute of Organic Chemistry, Syntex Research, Palo Alto, California 94304

Received September 24, 1969

The $\Delta^{1,4}$- and $\Delta^{1,4,6}$-3-keto steroids **1** and **4** undergo dienol–benzene-type rearrangements on exposure to phenyl(trichloromethyl)mercury in benzene to yield ring-A aromatic carboxylic acids (**2a** and **3a** from **1**) and **5** from **4**. Although the $\Delta^{4,6}$-3 ketone **8a** is apparently resistant to attack by the mercurial reagent in boiling benzene, the corresponding 3β-acetoxy and 3-cycloethylenedioxy derivatives **8b** and **8c** are converted into the 6α,7α-dichloromethylene adducts **10a** and **10b** (plus **10d**), respectively, under the same conditions.

Phenyl(trichloromethyl)mercury is an exceptionally effective reagent for the dichloromethylenation of carbon–carbon double bonds. In an extensive series of investigations, Seyferth and coworkers showed that various olefins, as well as aliphatic α,β-unsaturated ketones, esters, and nitriles, react with the organomercurial in boiling benzene to afford the corresponding dichlorocyclopropanes in good yield.[3] This paper describes the results of an investigation aimed at evaluating phenyl(trichloromethyl)mercury as a reagent for preparing dichloromethylene steroids from linear and cross-conjugated dienone and trienone precursors.

Treatment of 17β-acetoxyandrosta-1,4-dien-3-one (**1**)[4] with 20 equiv of phenyl(trichloromethyl)mercury in boiling benzene followed by chromatography of the crude reaction mixture afforded the ring-A aromatic



acids **2a** (12%) and **3a** (13%).[5] The structure of the seco acid **3** follows from its elemental analysis and

(1) Part VII: C. Beard, B. Berkoz, N. H. Dyson, I. T. Harrison, P. Hodge, L. H. Kirkham, G. S. Lewis, D. Giannini, B. Lewis, J. A. Edwards, and J. H. Fried, *Tetrahedron*, **25**, 1219 (1969).
(2) Publication 363 from the Syntex Institute of Organic Chemistry.
(3) D. Seyferth, J. M. Burlitch, R. J. Minasz, J. Y.-P. Mui, H. D. Simmons, Jr., A. J. H. Trieber, and S. R. Dowd, *J. Amer. Chem. Soc.*, **87**, 4259 (1965).
(4) R. B. Woodward, H. H. Inhoffen, H. O. Larson, and K. Menzel, *Chem. Ber.*, **86**, 594 (1953).
(5) Some difficulty was experienced with the removal of phenylmercuric chloride from the reaction mixture. In this experiment the isolated yield proved to be a poor measure of reaction efficiency, since substantial product losses were incurred during chromatographic purification.