the formation of a yellow color. Because of the limited amounts of disaccharide available, it was not possible to identify the products from degradation by hot alkaline solutions. The mechanism of the degradation under these drastic conditions is unknown.

Experimental

2-*O*-D-Xylopyranosyl-L-arabinose.—Hemicellulose-B, prepared from corn cobs, was partially hydrolyzed under conditions similar to those reported by Whistler and McGilvray.[7] After neutralization, the hydrolyzate was eluted from a charcoal–celite column in the usual way.[8] The 5% ethanol eluate was concentrated and chromatographed on a cellulose column, using butanol saturated with water. The first component to be eluted was 2-*O*-D-xylopyranosyl-L-arabinose which was obtained in a crystalline form by concentration of the eluent. Crystallinity was proved by X-ray diffraction. After recrystallization from aqueous ethanol the disaccharide had m.p. 167–168°, $[\alpha]^{25}D$ + 32.9 (*c* 0.97 in water).

Anal. Calcd. for $C_{10}H_{18}O_9$: C, 42.65; H, 6.44. Found: C, 42.85; H, 6.57.

When an aqueous ethanol solution of 2-*O*-D-xylopyranosyl-L-arabinose was allowed to evaporate rapidly in a vacuum desiccator, fine needles of the disaccharide hydrate were obtained, m.p. 80–81°. Recrystallization of this hydrate by seeding an aqueous ethanol solution with the higher melting form or heating the lower melting form at 45° over phosphorus pentoxide gave 2-*O*-D-xylopyranosyl-L-arabinose, m.p. 166–167°, $[\alpha]^{25}D$ + 47.0 → 32.5° (*c* 1.15, in water).

Anal. Calcd. for $C_{10}H_{18}O_9 \cdot 2H_2O$: C, 37.74; H, 6.98. Found: C, 37.86; H, 7.09.

Action of Lime Water upon 2-*O*-D-Xylopyranosyl-L-arabinose.—Sixty-four and eight-tenths mg. of 2-*O*-D-xylopyranosyl-L-arabinose was dissolved in 25 ml. of 0.033 *N* lime water and maintained at 25°. Periodically, 2-ml. aliquots were withdrawn and run into 10 ml. of 0.01 *N* sulfuric acid. After 1/4 hour, the solution was titrated with 0.01 *N* sodium hydroxide solution to the first semipermanent end-point with phenolphthalein. The solution was then diluted to 50-ml. and 2-ml. samples were taken to determine the reducing value by the method of Hagedorn and Jensen.[9] Samples of the solution were also examined by paper chromatography which revealed the presence of 2-*O*-D-xylopyranosyl-L-arabinose only.

Time (hr.)	Equiv. acid produced	Reducing value	Time (hr.)	Equiv. acid produced	Reducing value
0	0.000	1.000	10	0.038	...
1	.016	...	48	.044	0.962
3	.022	...	72	.044	.962

After the solution had been heated at 100° for 1 hour the acid produced was 2.51 equiv. The solution had attained a deep yellow color and chromatographic analysis indicated that most of the 2-*O*-D-xylopyranosyl-L-arabinose had undergone degradation. D-Xylose was detected in trace amounts.

(8) R. L. Whistler and D. F. Durso, THIS JOURNAL, **72**, 677 (1950).

(9) H. C. Hagedorn and B. N. Jensen, *Biochem. Z.*, **135**, 46 (1923).

LAFAYETTE, INDIANA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF SOUTHERN CALIFORNIA]

Synthetic Analogs of Cortical Hormones. II. 3-Substituted α-2,5-Trihydroxyacetophenone Derivatives

BY MILTON C. KLOETZEL AND B. Y. ABADIR[1]

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The synthesis and some reactions of 3,5-diacetoxy-α-diazoacetophenone and of 3-acetoxy-, 3-nitro- and 3-bromo-2,5-diacetoxy-α-diazoacetophenone have been described. The diazo ketones yielded α-halo ketones by reaction with hydrogen halides, α-ketols by hydrolysis with hot dilute sulfuric acid, and (except for the 3-nitro diazo ketone) α-ketol acetates by reaction with hot acetic acid. The α-ketol acetates also were obtained by treatment of the respective α-bromo ketones with silver acetate in hot toluene or acetic acid. α,2,5-Triacetoxy-3-nitroacetophenone and 3-bromo-α,2,5-trihydroxyacetophenone produced appreciable eosinopenia in adrenalectomized mice. 2,5-Diacetoxy-3-acetylaminobenzoic acid, obtained by catalytic reduction of 3-nitrogentisic acid in acetic anhydride, also produced some eosinopenia in adrenalectomized mice.

Biological similarities between cortisone and salicylates,[2] and between salicylates and sodium gentisate,[3] have been reported recently. However, α,2,5-trihydroxyacetophenone (XXIII), a compound which appeared of interest because of superficial structural relationships to all of these active substances, was found to produce no lowering of the eosinophil count in adrenalectomized mice.[4]

Since it appeared likely that the biological activity of a compound such as α,2,5-trihydroxyacetophenone might be dependent, at least to some extent, upon the potential of its hydroquinone–quinone system, a series of α,2,5-trihydroxyacetophenone derivatives containing electron-attracting and electron-repelling substituents in the 3-position have been synthesized and submitted to pharmacological testing. The substances here described include two, α,2,5-triacetoxy-3-nitroacetophenone (XVIII) and 3-bromo-α,2,5-trihydroxyacetophenone (XXII), which showed appreciable activity in lowering the eosinophil count of adrenalectomized mice.

α,2,5-Triacetoxy-3-nitroacetophenone (XVIII), α,2,5-triacetoxy-3-bromoacetophenone (XIX) and α,2,3,5-tetraacetoxyacetophenone (XX), as well as α,3,5-triacetoxyacetophenone (XXIV), were obtained from the corresponding diazo ketones (VII, VIII, IX and XXV, respectively) by means of the general reaction sequence which has been described previously[4] for the preparation of α,2,5-triacetoxyacetophenone and which is illustrated in Fig. 1.

Hydrolysis of diazo ketone VIII with hot 15% sulfuric acid also yielded directly 3-bromo-α,2,5-trihydroxyacetophenone (XXII). However, under similar conditions, diazo ketone VII yielded a monoacetyl derivative of α,2,5-trihydroxy-3-nitroacetophenone (XXI).

When an attempt was made to prepare α,2,5-triacetoxy-3-nitroacetophenone (XVIII) by the action of boiling acetic acid on 2,5-diacetoxy-α-diazo-3-nitroacetophenone (VII), the only crys-

(1) Postdoctorate Research Fellow, 1951–1952.

(2) H. F. Hailman, *J. Clin. Endocrinol. and Metabolism*, **12**, 454 (1952).

(3) K. Meyer and C. Ragan, *Science*, **108**, 281 (1948).

(4) M. C. Kloetzel, R. P. Dayton and B. Y. Abadir, *J. Org. Chem.*, **20**, 38 (1955).

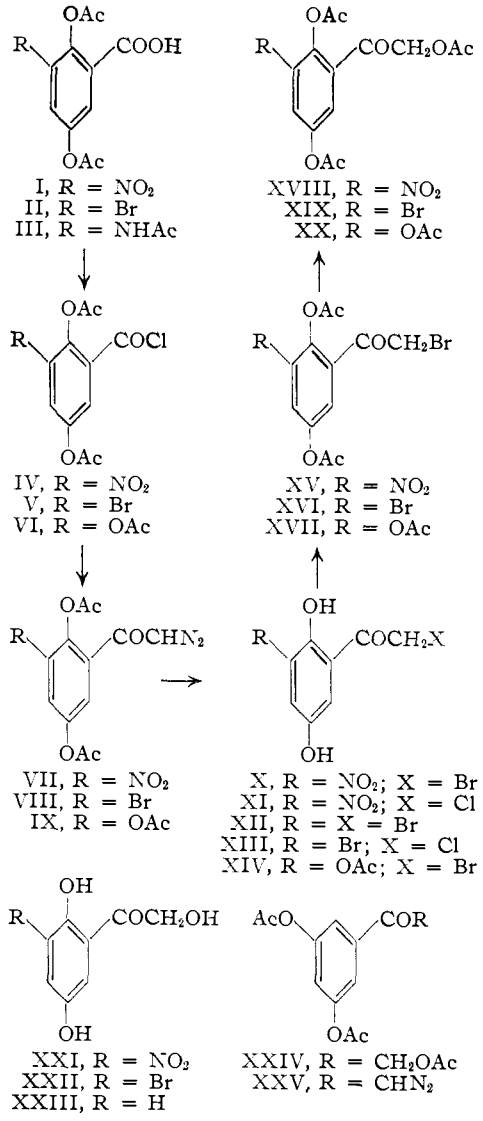
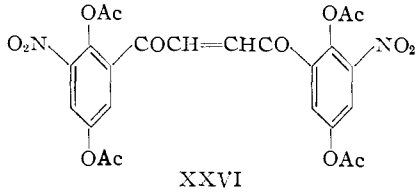


Figure 1

talline material that could be isolated was a yellow compound melting at 213–216°. Analytical data indicate that this substance may be a dibenzoylethylene derivative XXVI of the type previously observed by Grundmann[5] to result from the catalyzed thermal decomposition of α-diazoacetophenone.



XXVI

Although 3-nitrogentisic acid was successfully reduced over platinum oxide in water to give 3-aminogentisic acid, and in acetic anhydride to give 2,5-diacetoxy-3-acetylaminobenzoic acid (III), the synthesis of 3-amino-α,2,5-trihydroxyacetophenone derivatives was blocked by the failure of III to form a well-characterized acid chloride.

(5) C. Grundmann, *Ann.*, **536**, 29 (1938).

3-Bromo-α,2,5-trihydroxyacetophenone (XXII) caused an eosinopenia of 73% following administration of doses of 240 mcg./25 g. adrenalectomized mouse (compared to eosinopenia of 96% caused by cortisone acetate in doses of 60 mcg./25 g.). α,2,5-Triacetoxy-3-nitroacetophenone (XVIII) caused an eosinopenia of 70% following injection of doses of 240 mcg./25 g. adrenalectomized mouse (compared to average eosinopenia of 81% caused by cortisone acetate in doses of 60 mcg./25 g.). 2,5-Diacetoxy-3-acetylaminobenzoic acid (III) produced an eosinopenia of 46% following doses of 240 mcg./25 g. adrenalectomized mouse (compared to 96% caused by cortisone acetate in doses of 60 mcg./25 g.). α,2,5-Triacetoxy-3-bromoacetophenone (XIX), α,3,5-triacetoxyacetophenone (XXIV) and α,2,3,5-tetraacetoxyacetophenone (XX) produced insignificant or no eosinopenia in adrenalectomized mice.

Acknowledgment.—The authors are indebted to Eli Lilly and Co., Indianapolis, Ind., for generous financial aid which made this study possible, and to the Pharmacological Research Division of the Lilly Research Laboratories for performing the eosinophil lowering tests.

Experimental[6]

Reduction of 3-Nitrogentisic Acid. (a) **In Water.**—A solution of 2.0 g. of 3-nitrogentisic acid[7] in 50 cc. of water was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 200 mg. of platinum oxide. Absorption of hydrogen was quantitative within 3 hours. A small quantity of solid material which separated from solution during hydrogenation was brought back into solution by the addition of 3 cc. of concentrated hydrochloric acid. The filtered solution was warmed on a steam-bath and evaporated with the aid of a current of nitrogen until crystalline material began to separate. The cooled solution deposited 2.0 g. (97%) of **3-aminogentisic acid hydrochloride**. The salt was obtained in colorless needles when a concentrated methanol solution of the crude material was diluted with 15% hydrochloric acid. The compound darkens above 210° and has no distinct melting point. It gives a red color with ferric chloride solution.

Anal. Calcd. for $C_7H_8ClNO_4$: C, 40.89; H, 3.92. Found: C, 40.61; H, 3.92.

(b) **In Acetic Acid.**—A solution of 2.0 g. of 3-nitrogentisic acid in 80 cc. of acetic acid, containing 200 mg. of suspended platinum oxide, absorbed 90% of the calculated volume of hydrogen necessary for reduction of the nitro group to the amino group within 4 hours at room temperature and atmospheric pressure. The solution was warmed to redissolve precipitated material and was then filtered from catalyst. To the filtrate was added 30 cc. of acetic anhydride and 2 drops of sulfuric acid and the mixture was heated on the water-bath for 20 minutes. Hydrolysis of excess acetic anhydride was accomplished with ice and after 2 hours the hydrolysis mixture was extracted with ether. Evaporation of the dried ether extract yielded 1.5 g. (51%) of **2,5-diacetoxy-3-acetylaminobenzoic acid (III)** which separated from dilute methanol in colorless needles. The compound decomposes vigorously at about 236°.

Anal. Calcd. for $C_{12}H_{13}NO_7$: C, 52.88; H, 4.44. Found C, 52.78; H, 4.20.

2,5-Diacetoxy-α-diazo-3-nitroacetophenone (VII).—A mixture of 15 g. of 3-nitrogentisic acid, 35 cc. of acetic anhydride and 3 drops of sulfuric acid was heated on a steam-bath for 8 hours. The cooled mixture was then stirred vigorously with 300 g. of ice and allowed to stand at 0° for several hours, whereupon 12 g. of crystalline **2,5-diacetoxy-3-nitrobenzoic acid (I)** separated. This acid (5.0 g.), once crystallized from benzene, was converted to the acid chlo-

(6) Melting points are uncorrected. Analyses are by Dr. Adalbert Elek, Elek Microanalytical Laboratories, Los Angeles, Calif., and by Mr. Joseph Pirie, University of Southern California.

(7) A. Klemenc, *Monatsh.*, **33**, 1243 (1912).

ride as described[4] for 2,5-diacetoxybenzoic acid. After four crystallizations from a mixture of benzene and Skellysolve B, the **2,5-diacetoxy-3-nitrobenzoyl chloride** (IV) melted at 88–89°, yield 4.0 g.

Anal. Calcd. for $C_{11}H_8ClNO_7$: C, 43.80; H, 2.67. Found: C, 43.92; H, 2.80.

The acid chloride (3.5 g.) was converted to the diazo ketone as previously described[4] for the preparation of 2,5-diacetoxy-α-diazoacetophenone. Crude **2,5-diacetoxy-α-diazo-3-nitroacetophenone** (VII) crystallized when triturated with Skellysolve B and finally yielded 3.45 g. (96%) of pale yellow needles after two crystallizations from benzene; m.p. 98–100° dec.

Anal. Calcd. for $C_{12}H_9N_3O_7$: C, 46.91; H, 2.95. Found: C, 47.62; H, 2.94.

Reactions of 2,5-Diacetoxy-α-diazo-3-nitroacetophenone (VII). (a) **With hydrogen bromide** the diazo ketone VII gave a 66% yield of **α-bromo-2,5-dihydroxy-3-nitroacetophenone** (X), in the manner previously described[4] for the preparation of α-bromo-2,5-dihydroxyacetophenone. The compound separated from benzene in yellow needles, m.p. 170–172°, and produced a yellow-brown color with ferric chloride solution.

Anal. Calcd. for $C_8H_6BrNO_5$: C, 34.80; H, 2.19. Found: C, 34.97; H, 2.26.

(b) **With hydrogen chloride** the diazo ketone VII yielded **α-chloro-2,5-dihydroxy-3-nitroacetophenone** (XI). The crude product crystallized upon trituration with Skellysolve B; yield 97%. Crystallization from a mixture of methanol and benzene produced yellow needles, m.p. 178–180°.

Anal. Calcd. for $C_8H_6ClNO_5$: C, 41.49; H, 2.61. Found: C, 41.56; H, 2.75.

(c) **With Sulfuric Acid.**—A mixture of 200 mg. of diazo ketone VII, 2 cc. of ethanol and 10 cc. of 20% sulfuric acid was heated under reflux for 1 hour. Extraction with ether and subsequent evaporation of the dried extract gave a yellow gum which crystallized after being dissolved in a small quantity of fresh ether. Two crystallizations from ether yielded 100 mg. (60%) of a **monoacetyl derivative** of **α,2,5-trihydroxy-3-nitroacetophenone** in yellow prisms, m.p. 145–147° dec. The compound produced a yellow-brown color with ferric chloride.

Anal. Calcd. for $C_{10}H_9NO_7$: C, 47.06; H, 3.55. Found: C, 47.30; H, 3.40.

Complete acetylation of the aforementioned monoacetyl derivative (50 mg.) was accomplished in the usual manner by heating on a steam-bath for 3 hours with acetic anhydride and sulfuric acid; yield 25 mg. (38%) of **α,2,5-triacetoxy-3-nitroacetophenone** (XVIII), which separated from ethanol in cream colored leaflets, m.p. 81–82°.

Anal. Calcd. for $C_{14}H_{13}NO_9$: C, 49.56; H, 3.86. Found: C, 49.59; H, 3.89.

The same triacetate XVIII, was prepared also in the following manner. α-Bromo-2,5-dihydroxy-3-nitroacetophenone (X, 500 mg.) was acetylated by warming with acetic anhydride and sulfuric acid. The crude, viscous diacetate (XV, 400 mg.) then was heated under reflux for 40 minutes with 186 mg. of silver acetate and 12 cc. of anhydrous toluene. The residue obtained by evaporation of the filtered solution was evaporatively distilled in vacuum to give a nearly colorless oil which dissolved in ethanol and finally yielded 225 mg. (40%) of crystalline triacetate XVIII, m.p. 81–82°.

(d) **With Acetic Acid.**—The diazoketone (VII, 500 mg.) was added gradually to boiling glacial acetic acid (8 cc.). Evolution of nitrogen was vigorous. The solution was finally boiled for 4 minutes and then evaporated to dryness under reduced pressure. Crystallization of the residue from dioxane yielded 300 mg. of cream colored needles, presumably ***sym*-bis-(2,5-diacetoxy-3-nitrobenzoyl)-ethylene** (XXVI), m.p. 205–207°. Further crystallizations eventually raised the m.p. to 213–216°. No other crystalline product could be isolated.

Anal. Calcd. for $C_{24}H_{18}N_2O_{14}$: C, 51.62; H, 3.25. Found: C, 51.74; H, 3.25.

The aforementioned compound (100 mg.) was boiled for several minutes with 15 cc. of water, 0.5 cc. of concentrated hydrochloric acid and 2 drops of hydriodic acid. The cooled reaction mixture was extracted with ether and dried. Evaporation of the ether left 60 mg. of yellow solid which separated from benzene in small cubes. The compound decomposed at 232°. Analysis indicated that hydrolysis had removed only two acetyl groups per molecule.

Anal. Calcd. for $C_{20}H_{14}N_2O_{12}$: C, 50.64; H, 2.97. Found: C, 50.70; H, 2.88.

2,5-Diacetoxy-3-bromo-α-diazoacetophenone (VIII).—Bromine (54 g.) was added dropwise to a mixture of 50 g. of gentisic acid and 100 cc. of acetic acid and the mixture was then heated on the steam-bath until all solid had dissolved (30 minutes). Upon cooling, 47 g. (62%) of 3-bromogentisic acid separated in colorless needles, m.p. 238–239° dec. This acid, previously prepared by bromination of gentisic acid in ether, has been reported[5] to melt at 238°.

3-Bromo-2,5-diacetoxybenzoic acid (II) was obtained when 30 g. of 3-bromogentisic acid was warmed for 15 minutes with 100 cc. of acetic anhydride and 4 drops of sulfuric acid and the cooled mixture was poured onto 600 g. of ice. After standing for 5 hours at 8° the mixture yielded 35 g. (86%) of crystalline product, m.p. 135–137°. This m.p. was raised to 142–144° when the solid was crystallized three times from a mixture of benzene and methanol; yield 24 g.

Anal. Calcd. for $C_{11}H_9BrO_6$: C, 41.66; H, 2.86. Found: C, 41.89; H, 3.20.

2,5-Diacetoxy-3-bromobenzoyl chloride (V) was prepared in 57% yield as described previously[4] for other analogs, and separated from *n*-heptane in colorless needles, m.p. 96.5–98°.

Anal. Calcd. for $C_{11}H_8BrClO_5$: C, 39.37; H, 2.43. Found: C, 39.60; H, 2.20.

The diazo ketone VIII was prepared as described[4] for preparation of analogous diazo ketones and solidified when triturated with ice-cold ether. Crystallization from a mixture of ether and benzene gave a 50% yield of yellow needles, m.p. 94–95°.

Anal. Calcd. for $C_{12}H_9BrN_2O_5$: C, 42.83; H, 2.66. Found: C, 42.61; H, 3.00.

Reactions of 2,5-Diacetoxy-3-bromo-α-diazoacetophenone (VIII). (a) **With hydrogen chloride**, as described previously for other analogs, diazo ketone VIII gave a quantitative yield of **3-bromo-α-chloro-2,5-dihydroxyacetophenone** (XIII), which produced a green color with ferric chloride solution; m.p. 130–131° after crystallization from benzene.

Anal. Calcd. for $C_8H_6BrClO_3$: C, 36.19; H, 2.28. Found: C, 36.50; H, 2.50.

(b) **With hydrogen bromide**, diazo ketone VIII gave **α,3-dibromo-2,5-dihydroxyacetophenone** (XII) which separated from benzene in yellow prisms, m.p. 82–83°, and produced a green color with ferric chloride solution.

Anal. Calcd. for $C_8H_6Br_2O_3$: C, 31.00; H, 1.95. Found: C, 31.31; H, 2.23.

Bromo ketone XII was acetylated in the customary manner with acetic anhydride. Crude **2,5-diacetoxy-α-3-dibromoacetophenone** (XVI), obtained in 86% yield, melted at 134–137°. Recrystallization from ethanol raised the m.p. to 140–141°.

Anal. Calcd. for $C_{12}H_{10}Br_2O_5$: C, 36.57; H, 2.55. Found: C, 36.96; H, 2.68.

(c) **With Acetic Acid.**—Rapid evolution of nitrogen occurred when 200 mg. of diazo ketone VIII was added slowly to 5 cc. of boiling acetic acid. After being refluxed for 20 minutes, the solution was evaporated under reduced pressure and the residue was evaporatively distilled in vacuum. Trituration of the distillate with Skellysolve B and subsequent crystallization from a mixture of benzene and Skellysolve B yielded 130 mg. (60%) of **α,2,5-triacetoxy-3-bromoacetophenone** (XIX) in colorless cubes (or sometimes needles), m.p. 104–105°.

Anal. Calcd. for $C_{14}H_{13}BrO_7$: C, 45.06; H, 3.51. Found: C, 45.05; H, 3.61.

The same triacetate XIX was obtained by heating 2,5-diacetoxy-α,3-dibromoacetophenone (XVI) with silver acetate in acetic acid as described[4] for preparation of α,2,5-triacetoxyacetophenone; yield 42% of material, m.p. 104–105°, which did not depress the m.p. of triacetate prepared from diazo ketone VIII and acetic acid.

(8) F. v. Hemmelmayr, *Monatsh.*, **30**, 253 (1909).

(d) **With Sulfuric Acid.**—A mixture of 200 mg. of diazo ketone VIII, 20 cc. of 15% sulfuric acid and 3 cc. of ethanol was heated under reflux for 20 minutes. Evaporation of an ether extract of the reaction mixture yielded 120 mg. (83%) of crystalline **3-bromo-α,2,5-trihydroxyacetophenone (XXII)** which separated from ether in cream colored prisms, m.p. 166–168°. The triol produced a green color with ferric chloride solution.

Anal. Calcd. for $C_8H_7BrO_4$: C, 38.88; H, 2.85. Found: C, 38.55; H, 2.99.

Hydrolysis of α,2,5-triacetoxy-3-bromoacetophenone (XIX, 40 mg.) was accomplished by heating under reflux for 5 minutes with a mixture of 10 cc. of water, 0.5 cc. of 36% hydrochloric acid and 2 drops of 48% hydroiodic acid. Upon cooling the solution, 15 mg. (58%) of crystalline triol (XXII) was obtained, which did not depress the m.p. of the triol prepared from diazo ketone VIII and sulfuric acid.

2,3,5-Triacetoxy-α-diazoacetophenone (IX) was prepared in 77% yield from 2,3,5-triacetoxybenzoyl chloride (VI)[9] in the manner previously described[4] and formed cream colored needles, m.p. 135–138°.

Anal. Calcd. for $C_{14}H_{12}N_2O_7$: C, 52.50; H, 3.77. Found: C, 52.85; H, 3.77.

2,3,5-Triacetoxy-α-bromoacetophenone (XVII).—The aforementioned diazoketone (2 g.) was slowly added to a saturated solution of hydrogen bromide in glacial acetic acid. After 10 minutes the acetic acid was removed under reduced pressure and the residue was heated on the steam-bath for 1 hour with 7 cc. of acetic anhydride and 1 drop of concentrated sulfuric acid. When the reaction mixture was poured onto ice there was obtained 1.6 g. of crystalline solid. Two crystallizations from ethanol yielded colorless needles, m.p. 81–82°.

Anal. Calcd. for $C_{14}H_{13}BrO_7$: C, 45.06; H, 3.51. Found: C, 45.19; H, 3.76.

α,2,3,5-Tetraacetoxyacetophenone (XX). (a) **From 2,3,5-Triacetoxy-α-diazoacetophenone (IX).**—The diazo ketone (150 mg.) was added slowly to boiling acetic acid (4 cc.) and the solution was then boiled for 5 minutes. The solvent was removed under reduced pressure and the residue was evaporatively distilled in vacuum. Upon scratching the distillate under ethanol it finally crystallized and one crystallization from ethanol produced colorless prisms (70 mg., 42%), m.p. 112–113°.

Anal. Calcd. for $C_{16}H_{16}O_9$: C, 54.54; H, 4.58. Found: C, 54.28; H, 4.78.

(9) R. E. Corbett, C. H. Hassall, A. W. Johnson and A. R. Todd, *J. Chem. Soc.*, 1 (1950).

(b) **From 2,3,5-Triacetoxy-α-bromoacetophenone (XVII).**—A mixture of 300 mg. of the bromo ketone, 132 mg. of silver acetate and 20 cc. of dry acetic acid was refluxed for one hour. The filtered solution was evaporated in vacuum and the residue was crystallized from ethanol; yield 150 mg. (53%) of tetraacetate (XX), which did not depress the m.p. when mixed with a sample prepared from the diazo ketone as previously described.

3,5-Diacetoxy-α-diazoacetophenone (XXV).—A mixture of 8 g. of 3,5-dihydroxybenzoic acid,[10] 30 cc. of acetic anhydride and 3 drops of sulfuric acid was warmed on a steam-bath for 25 minutes and then poured onto 200 g. of ice. The solid **3,5-diacetoxybenzoic acid** was crystallized from a mixture of benzene and ethanol and formed colorless prisms, m.p. 156–158°, yield 11.5 g. (93%).

Anal. Calcd. for $C_{11}H_{10}O_6$: C, 55.46; H, 4.23. Found: C, 55.21; H, 4.36.

3,5-Diacetoxybenzoyl chloride was prepared from the aforementioned acid in 84% yield, and separated from a mixture of benzene and Skellysolve B in colorless needles, m.p. 84–85°.

Anal. Calcd. for $C_{11}H_9ClO_5$: C, 51.47; H, 3.53. Found: C, 51.60; H, 3.33.

3,5-Diacetoxy-α-diazoacetophenone (XXV) was prepared from 3,5-diacetoxybenzoyl chloride in the manner previously described for the isomeric 2,5-diacetoxy-α-diazoacetophenone[4]; yield 85% of yellow prisms from ether, m.p. 94–95°.

Anal. Calcd. for $C_{12}H_{10}N_2O_5$: C, 54.96; H, 3.84. Found: C, 54.98; H, 3.60.

3,5-Diacetoxy-α-bromoacetophenone was obtained when diazo ketone XXV was treated with hydrogen bromide in the manner described for preparation of bromo ketone XVII; m.p. 61–62°.

Anal. Calcd. for $C_{12}H_{11}BrO_5$: C, 45.73; H, 3.52. Found: C, 46.03; H, 3.34.

α,3,5-Triacetoxyacetophenone (XXIV) was prepared in 81% yield from diazo ketone XXV and in 75% yield from 3,5-diacetoxy-α-bromoacetophenone by methods analogous to those described for preparation of tetraacetate XX. The ester separated in colorless needles from methanol, m.p. 86–87°.

Anal. Calcd. for $C_{14}H_{14}O_7$: C, 57.14; H, 4.79. Found: C, 57.10; H, 4.92.

(10) N. L. Drake (Ed.), "Organic Syntheses," Vol. 21, John Wiley and Sons, New York, N. Y., 1941, p. 27.

LOS ANGELES, CALIFORNIA

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF WAYNE UNIVERSITY]

α-Iodoketones. Part 4.[1] The Reaction of N-Iodosuccinimide with Enol Acetates of Δ^4-3-Ketosteroids[2]

BY CARL DJERASSI, J. GROSSMAN AND G. H. THOMAS

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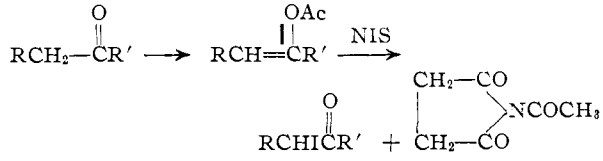
Enol acetates of Δ^4-3-ketosteroids react with N-iodosuccinimide at room temperature to produce the corresponding 6-iodo-Δ^4-3-ketones and some reactions of this class of compounds have been studied. Taking advantage of the greater reactivity toward N-iodosuccinimide of unsaturated enol acetates as compared to saturated ones, progesterone has been converted into 17α-hydroxyprogesterone *via* its dienol acetate by selective reaction with the $\Delta^{3,5}$-3-acetoxy system, followed by deiodination at C-6, perbenzoic acid oxidation at C-17(20) and base treatment.

We have recently recorded[3] a novel synthesis of α-iodo ketones which involves reaction of an enol acetate with N-iodosuccinimide (NIS).

The only α,β-unsaturated enol acetate which has so far been examined[1] has been the steroidal enol acetate II, derived from a Δ^{16}-20-ketosteroid (I),



and this led in excellent yield to the corresponding Δ^{16}-21-iodo-20-ketone (III), thus opening a new preparative path to the cortical hormone side chain.

(1) Part 3, C. Djerassi and C. T. Lenk, THIS JOURNAL, **76**, 1722 (1954).

(2) We are indebted to the Research Corporation of New York for a Frederick Gardner Cottrell grant in support of this work.

(3) C. Djerassi and C. T. Lenk, THIS JOURNAL, **75**, 3493 (1953).