Duality of the Reaction of a β-Dicarbonyl System with Nitrous Acid

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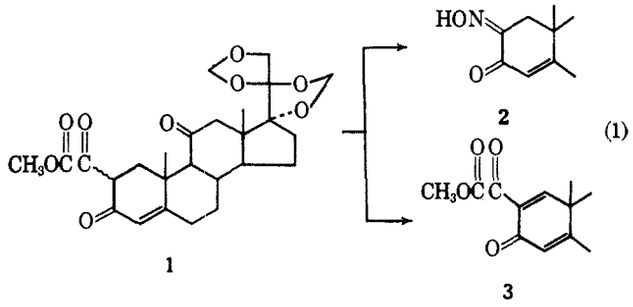
As part of a general study on the reaction of electrophilic reagents with alkoxalyl or formyl keto steroids[1-3] conducted in this laboratory, we investigated the reaction of nitrous acid with 17α,20;20,21-bismethylenedioxy-2-methoxalylpregn-4-ene-3,11-dione (**1**).[4] Application of this common procedure[5] to a related 2-hydroxymethylene-Δ⁴-3-keto steroid[6] is known to occur with deacylation and result in the formation of the α-oximino ketone. However, in the instance of **1**, this reaction proceeds, at least in part, in an unexpected manner (eq 1).



Thus, treatment of **1** with 1 equiv of sodium nitrite in the presence of acetic acid resulted in loss of the nitrite (negative starch–iodide test) but incomplete consumption of **1** (positive test for an enol with ferric chloride). Chromatography of the resulting mixture gave **1** (31%), 25% of the expected 2-hydroxyimino ketone **2**, and 15% of the 2-methoxalyl Δ¹,⁴-ketone **3**. The structure of this unexpected product was indicated by microanalysis (absence of nitrogen) and the pmr spectrum (an additional olefinic proton resonance at δ 8.50 when compared with that of **1**) and confirmed when dehydrogenation of **1** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[7,8] gave 79% of material which was identical in all respects with the nitrous acid product. On treatment with 10 equiv of sodium nitrite, complete conversion of **1** was observed; under these conditions the 1-dehydro derivative **3** predominates (52%) and **2** is a minor (7%) product.

(1) For a summary of these reactions, see G. R. Allen, Jr., and M. J. Weiss, *J. Org. Chem.*, **27**, 4681 (1962). Ethoxalyl and/or formyl keto steroids also have been utilized for the preparation of methylthio[2] and phenyl derivatives.[3]

(2) H. M. Kissman, R. E. Schaub, and M. J. Weiss, *J. Med. Chem.*, **10**, 252 (1967).

(3) J. F. Poletto, G. R. Allen, Jr., and M. J. Weiss, *ibid.*, **10**, 106 (1967).

(4) C. E. Holmlund, L. I. Feldman, H. M. Kissman, and M. J. Weiss, *J. Org. Chem.*, **27**, 2122 (1962).

(5) O. Touster, *Org. Reactions*, **7**, 327 (1953).

(6) H. Mrozik, P. Buchschacher, J. Hannah, and J. H. Fried, *J. Med. Chem.*, **7**, 584 (1964).

(7) Utilization of this reagent for conversion of 2-hydroxymethylene-[8a] and 2-cyano-3-keto steroids[8b] into the corresponding 1-dehydro derivatives has been reported.

(8) (a) J. A. Edwards, M. C. Calzada, L. C. Ibanez, M. E. Cabezas Rivera, R. Urquiza, L. Cardona, J. C. Orr, and A. Bowers, *J. Org. Chem.*, **29**, 3481 (1964); (b) H. M. Kissman, A. M. Hoffman, and M. J. Weiss, U. S. Patent 3,035,051 (May 15, 1962).

Experimental Section

General.—Melting points were determined in an open capillary tube on a Mel-Temp apparatus and are corrected. Ultraviolet spectra are for methanol solution unless stated otherwise. Rotations were determined at 25° in chloroform solution at 0.7–2% concentrations. Pmr spectra were determined with a Varian A-60 spectrometer using tetramethylsilane as an internal standard; deuteriochloroform was used as the solvent. Thin layer chromatography was carried out on silica gel G (Stahl) using benzene–acetone–water (2:1:2) as the eluent.

Reaction of 17α,20;20,21-Bismethylenedioxy-2-methoxalylpregn-4-ene-3,11-dione (1) with Nitrous Acid. A.—A solution of 2.44 g (5.0 mmoles) of **1** in 25 ml of methylene chloride and 25 ml of glacial acetic acid was cooled in an ice bath under argon and then treated with 350 mg (5.1 mmoles) of sodium nitrite. After 50 min (netative starch–iodide test; positive test for an enol with ferric chloride), the reaction was distributed between methylene chloride and water. The organic solution was washed with saline, dried over magnesium sulfate, and evaporated. Tlc of the residue showed three components, one of which had the same mobility as **1**. The mixture was chromatographed on silica gel; the material eluted with chloroform was recrystallized from acetone–hexane to give 530 mg of **1**, mp 205–210°, identical with authentic **1**[4] by tlc, mixture melting point, and infrared spectral comparisons. The filtrate from this crystallization was evaporated and the residue crystallized with ether to give 650 mg of crystals, mp 185–205°, two components on tlc. Elution of the column with acetone gave 550 mg (25%) of **2-hydroxyimino-17α,20;20,21-bismethylenedioxypregn-4-ene-3,11-dione (2)** which was recrystallized from methanol: mp 227–230° dec; $[\alpha]_D$ +89°; λ_{max} 261 mμ (ε 13,400); λ 2.93, 5.85, 5.95, 6.18 μ.

Anal. Calcd for $C_{23}H_{29}NO_7 \cdot {}^1/_2H_2O$: C, 62.71; H, 6.87; N, 3.18. Found: C, 63.04; H, 7.05; N, 3.12.

The mixture (560 mg) obtained above was purified by partition chromatography[9] on diatomaceous silica using a heptane–ethyl acetate–2-methoxyethanol–water (70:30:17:4) system. The fraction eluted at peak hold-back volume 1.0 (V_m/V_s = 2.7) was evaporated to give 220 mg (31% total) of **1**, mp 205–209°. The fraction eluted at peak hold-back volume 3.0 was evaporated to give 370 mg (15%) of **17α,20;20,21-bismethylenedioxy-2-methoxalylpregna-1,4-diene-3,11-dione (3)** which was recrystallized from acetone–hexane to give white crystals, mp 239–241°, identical by the usual criteria with that described below. Tlc of the reaction products from a similar experiment carried out without the exclusion of air showed the presence of **1**, **2**, and **3**.

B.—In a manner similar to that described above, 1 mmole of **1** was treated with 690 mg (10 mmoles) of sodium nitrite without exclusion of air. After 15 min a negative test for an enol with ferric chloride and a positive starch–iodide test were observed. Tlc of the reaction mixture showed the presence of two components having the mobility of **2** and **3**. These materials were separated by chromatography on silica gel as described above. The chloroform eluate gave 232 mg (52%) of **3** as white crystals, mp 239–241°. Material from a similar experiment had the following properties: mp 242.0–243.5°; $[\alpha]_D$ −22.8°; λ_{max} 238 mμ (ε 13,600), 244 (14,200) (0.1 *N* HCl), 246, 344 (13,400; 10,700) (0.1 *N* NaOH);[10] λ 5.74, 5.85, 5.99, 6.12, 6.22, 8.05–8.30, 9.10, and 9.20 μ ($CHCl_3$); pmr, δ 0.87 (13-CH_3), 1.55 (10-CH_3), 3.91 (OCH_3), 3.98, 5.01, 5.03, 5.21 (OCH_2O), 6.14 (4-H), and 8.50 (1-H).

Anal. Calcd for $C_{26}H_{30}O_9$: C, 64.18; H, 6.22. Found: C, 64.03; H, 6.31.

The acetone eluate gave 31 mg (7%) of **2** which was recrystallized from methanol, mp 226–230° dec.

17α,20;20,21-Bismethylenedioxy-2-methoxalylpregna-1,4-diene-3,11-dione (3).—A mixture of 488 mg (1 mmole) of 17α,20;20,21-bismethylenedioxy-2-methoxalylpregn-4-ene-3,11-dione (**1**), 344 mg of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone, and 50 ml of dioxane was refluxed with stirring for 16 hr. The mixture was evaporated and the residue was mixed with 50 ml of benzene. The filtered solution was washed with water, 1% aqueous potassium hydroxide, and water to neutrality. The dried solution

(9) For a complete description of this technique as developed by C. Pidacks, see M. J. Weiss, R. E. Schaub, G. R. Allen, Jr., J. F. Poletto, C. Pidacks, R. B. Conrow, and C. J. Coscia, *Tetrahedron*, **20**, 357 (1964).

(10) A similar bathochromic shift in alkali has been reported for 2-formyl-Δ¹,⁴-3-keto steroids. This shift has been explained as being the result of addition of alkoxide at C-1, giving the anion of the 2-acyl-1-alkoxyl-Δ⁴-3-keto sterod, which is responsible for the observed spectra.[8a]

was evaporated and the residue crystallized from ether: 380 mg (79%); mp 239–241°. The identity of this material with that prepared by the nitrous acid procedure was shown by mixture melting point and ultraviolet, infrared, and pmr spectral comparisons.

Anal. Found: C, 64.29; H, 6.55.

Registry No.—1, 13509-81-4; 2, 13509-82-5; 3, 13509-83-6; nitrous acid, 7782-77-6.

Acknowledgment.—Spectral and rotational data were furnished by Mr. W. Fulmor and his associates. Microanalyses were determined by Mr. L. Brancone and his group and partition chromatography was carried out by Mr. C. Pidacks and his staff.

Synthesis and Proof of Structure of Benzodiiodoxole[1a-c]

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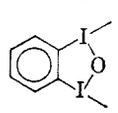
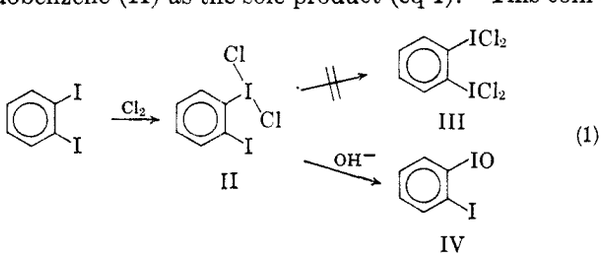
The synthesis, in our laboratories[2] and in others,[3] of a number of ring systems containing iodine as a heteroatom has been extended to the synthesis of a ring containing more than one annular iodine atom. We wish to report here the synthesis and proof of the structure of compounds containing the 1,3,2-benzodiiodoxole (I) ring as an example of such a system.



I

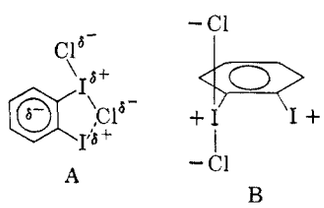
In a first attempt, we proceeded to oxidize 1,2-diiodobenzene with chlorine, obtaining 1-iodosodichloro-2-iodobenzene (II) as the sole product (eq 1). This com-



(1)

pound has not been prepared previously and is the first polyvalent iodine compound synthesized that is derived from 1,2-diiodobenzene.[4,5] 1-Iodosodichloro-2-iodobenzene is resistant, under the conditions used, to further chlorine addition on the second iodine atom, thus failing to give the desired 1,2-bis(iodosodichloro)-benzene (III).

This is unexpected, since both 1,3-diodobenzene and 1,4-diodobenzene can be readily chlorinated to the corresponding bis(iodosodichloro)benzene derivatives.[6,7] The failure to obtain III indicates that the presence of an iodosodichloro function *ortho* to an iodine atom prevents the addition of a second chlorine molecule. The structure of the iodosodichloro group, as shown by X-ray crystallography,[8] is such that the two chlorine atoms are above and below the plane of the ring, thus precluding steric hindrance to chlorine addition. The easy addition of chlorine to both iodine atoms in *p*-diiodobenzene suggests that the resistance of II to chlorination is not due to a simple electron-withdrawing effect. Thus, if an iodosodichloro group would decrease the electron density on the second iodine to such an extent that chlorine addition would be hindered, it should be similarly operative both for the *ortho* and *para* positions. However, if this effect involved only nonbonding electrons of iodine and chlorine that cannot overlap with the π electrons of the benzene rings, then hindrance would only occur in the *ortho* and not the *para* positions (*i.e.*, A). Another possible explanation is the unfavorable dipole situation, which could also hinder chlorine addition to the second iodine atom (*i.e.*, B). Such a



A B

decrease in electron density at the second iodine would prevent an electrophilic chlorine (Cl^+) addition. It is of interest that Keefer and Andrews observed similar *ortho* effects on the reaction of the iodosodichloro function[9] and that Maciel[10] has interpreted the ^{19}F nmr spectra of the *m*- and *p*-fluoroiodobenzene dichlorides as indicating a negligible resonance interaction of the $-ICl_2$ function with the benzene ring.[11] Thus, all available evidence strongly favors a field effect (*e.g.*, B).

1-Iodosodichloro-2-iodobenzene (II) could be readily hydrolyzed to 2-iodoso-2-iodobenzene (IV) and again this compound revealed itself unable to accept a further chlorine atom on the second iodine. The absence of data concerning chlorination (on iodine) of other iodosobenzenes does not allow us to interpret these results at this moment. The only Hammett σ values

(1) (a) Publication No. 6 of the series Chemistry and Biochemistry of Polyvalent Iodine Compounds. Publication No. 5, *J. Pharm. Sci.*, **55**, 68 (1966). (b) I wish to acknowledge helpful discussion of this work with Drs. Harold Zaugg and L. J. Andrews. (c) This work was supported inp art by NSF-URP Grant GE-6377 and in part by Grant GM-10721 of the National Institutes of Health. (d) National Science Foundation Undergraduate Research Participant, 1964–1965.

(2) (a) W. Wolf and L. Steinberg, *Chem. Commun.*, 449 (1965); (b) E. Shefter and W. Wolf, *J. Pharm. Sci.*, **54**, 104 (1965); (c) W. Wolf and L. L. J. Hsu, Abstracts of Papers 54C, 146th National Meeting of the American Chemical Society, Denver, Colo., Jan 1964.

(3) (a) G. F. Baker, *et al.*, *J. Chem. Soc.*, 3721 (1965); (b) W. C. Agosta, *Tetrahedron Letters*, (31) 3681 (1965).

(4) C. Willgerodt, "Die Organischen Verbindungen mit Mehrwertigem Jod," F. Encke, Stuttgart, 1914, p 265.

(5) (a) F. M. Beringer and R. M. Grindler, *Iodine Abstr. Rev.*, **3**, 15 (1956); (b) after this work was completed, we became aware that J. Böeseken and Ch. Schneider (*Koninkl. Ned. Akad. Wetenschap. Proc. Ser. B*, **35**, 1140 (1932)) had synthesized a compound, by peracetic acid oxidation of 1,2-diiodobenzene, to which they attributed structure V. No experimental details or properties of the compound were described.

(6) C. Willgerodt and A. Desaga, *Ber.*, **37**, 1301 (1904).

(7) C. Willgerodt, *ibid.*, **27**, 590 (1894).

(8) E. Archer, *Acta Cryst.*, **6**, 88 (1953).

(9) R. M. Keefer and L. J. Andrews, *J. Am. Chem. Soc.*, **81**, 2374 5329 (1959).

(10) G. E. Maciel, *ibid.*, **86**, 1269 (1964).

(11) Since this paper was written, a proton nmr study of iodonium salts has been reported; F. M. Beringer and J. Galton, *J. Org. Chem.*, **31**, 1648 (1966). These authors suggest a strong resonance interaction between iodonium function and the benzene rings. It is of interest to note this apparent difference between the effects of the two types of trivalent iodine.