Tetrahedron Letters No.6, pp. 489–493, 1967. Pergamon Press Ltd. Printed in Great Britain.

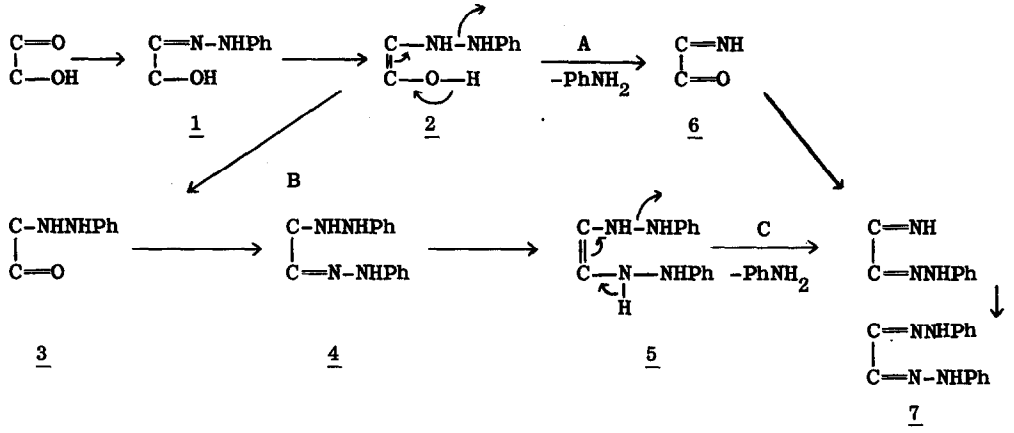
ON THE MECHANISM OF OSAZONE FORMATION

Alfred Hassner and P. Catsoulacos

Department of Chemistry, University of Colorado, Boulder, Colorado

(Received 10 October 1966)

The details of the formation of bisphenylhydrazones (osazones) from ketols or aldols have long intrigued the organic chemist. A direct oxidation mechanism first suggested by Fischer[2] has not received much support. After Weygand proposed routes A and B for osazone formation[3], evidence in favor of either pathway was presented by different investigators.[4]

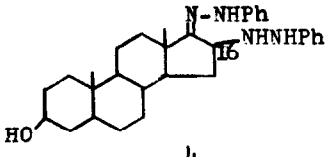


Both mechanisms involve tautomerizations. The difference between path A and B is essentially whether aniline is lost from enol amine 2 (step A) or from ene diamine 5 (step C). A recent study[5] pertinent to this subject, prompts us to report our independent findings that shed light on the mechanism of osazone formation from various α-substituted ketones. The conversion of a ketol phenylhydrazone, i.e. 1, to a phenyl hydrazinoketone, i.e. 3, is known as the Amadori rearrangement and is essentially the reverse of reactions observed by us for α-amino ketosteroids.[6] For this reason and because of the well defined stereochemistry in such systems, we chose as a substrate steroidal α-bromo-, α-hydroxy- and α-acetoxyketones 8 and 9. By heating bromo ketone 8 (X:Br)[7] or

acetoxy ketone 8 (X:OAc)[8] with phenylhydrazine in ethanol we were able to obtain in yields of up to 70% the phenylhydrazino phenylhydrazone 4,[9] an often postulated but never isolated intermediate in path B.[5] Phenylhydrazone 4 (λ_{max} 280 mμ, ε 16,840; ν_{max} 3300 (s), 1600 cm^{-1} (s); nmr τ 5.05 triplet, H at C-16) is a stable white solid which is readily convertible to the yellow osazone 7 on treatment with phenyl hydrazine in the presence of acetic acid or pyridine.

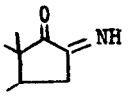
The plausibility of the conversion of 4 to 7 via 5 and path C is shown by the following facts. When 4a was treated with p-nitrophenylhydrazine in acetic acid medium the mixed osazone 12 was isolated. The structure of 12 is apparent from its formation in the reaction of 14 with p-nitrophenylhydrazine, a sequence which must involve a step analogous to C. Phenylhydrazone 14, in turn, was obtained from ketone 13. It was shown that under conditions of formation of 12, osazone 7a does not exchange with p-nitrophenylhydrazine to yield 12. Whereas the isolation of 4 and the formation of 12 from 4 and 14 clearly demonstrate that path B is possible, evidence for path A can be obtained by the conversion in 80% yield of hydroxy phenylhydrazone 11 (R:H), λ_{max} 274 mμ, ε 17,300, to keto phenylhydrazone 15 by means of p-nitro phenylhydrazine in the presence of acetic acid at 25°. This transformation probably involves intermediate 6. Ketone 15 (ν_{max} 1710, 1600 cm^{-1}; λ_{max} 370 mμ, ε 35,800) is converted to 12 with phenylhydrazine.

Acetoxy ketone 8a (X:OAc) and its phenylhydrazone 10a both yield 4a on warming with phenylhydrazine. The only logical pathway from 10a (R:OAc) to 4a is 1,4-elimination of acetic acid from 10a to form azo compound 16, to which phenylhydrazine adds in a 1,4-manner. Formation of unsaturated azo compounds in the reaction of α-halo or acetoxy ketones with hydrazines has been demonstrated.[5,10] The subtle steric and conformational influences in this steroid system are demonstrated by the fact that the isomeric acetoxy phenylhydrazone 11 (R:Ac) is recovered unchanged on exposure to phenylhydrazine in alcohol. Neither of the α-hydroxy phenylhydrazones 10a (R:H) or 11 (R:H) react with phenylhydrazine in alcohol, but both react in acetic acid solution to yield

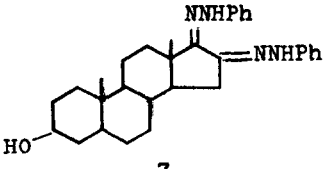


4

4a, Δ^5

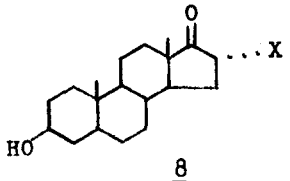


6



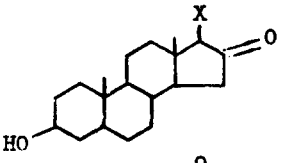
7

7a, Δ^5

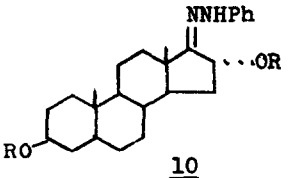


8

8a, Δ^5

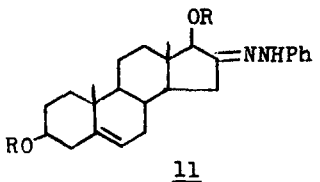


9

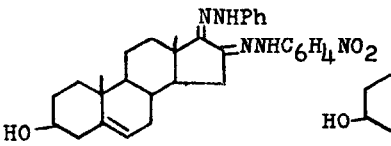


10

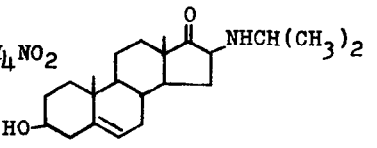
10a, Δ^5



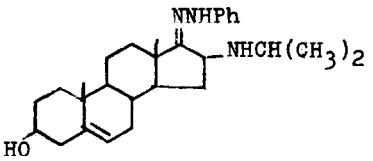
11



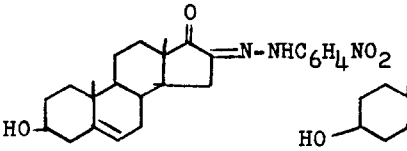
12



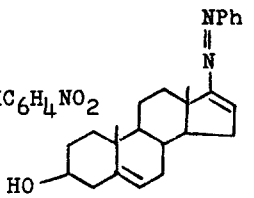
13



14

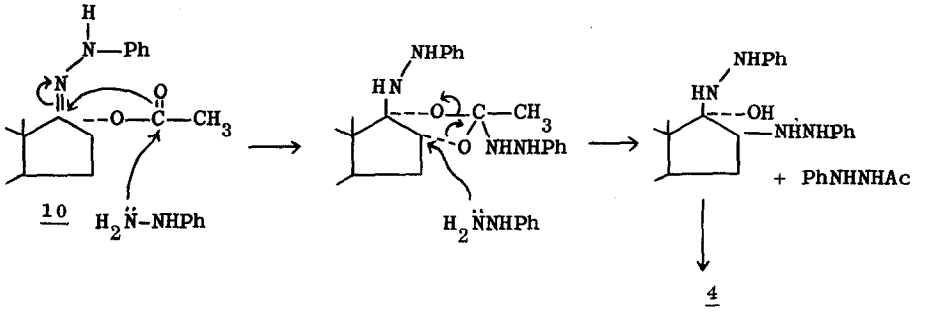


15



16

osazone 7a. The fact that the rates of conversion of alcohols 10a and 11 (R:H) to osazone 7a are not appreciably different, whereas acetates 10a and 11 (R:OAc) show vastly dissimilar reactivities, suggests that in the absence of acid a different mechanism is operating for the reaction of phenylhydrazine with alcohol 10 (R:H) than with acetate 10 (R:OAc). The possibility that the difference in reactivity between 10 (R:Ac) and 10 (R:H) can be accounted for on the basis of the following reaction sequence has been discarded, since 4 results in yields higher than 50% when 10 is exposed to one equivalent of phenylhydrazine



in hot ethanol. On the other hand it is easy to see why elimination from 10 would take place when OR is a good leaving group (i.e. OAc or Br) but not if OR is OH. Heating of 10a (R:OAc) with pyridine gives a crude product, the infrared spectrum of which indicates a marked diminution of the C=N-NHPh absorp- at 1600 cm^{-1}, and NH absorption at 3330 cm^{-1}, while new bands at 1665 cm^{-1} attributable to N=N have appeared. This crude product (presumably a mixture of 10 and 16) cannot be purified[11] but is converted readily with phenylhydrazine into 4. The alcohol 10 (R:H) is unaffected by phenylhydrazine in hot pyridine.

Cummulative evidence is now available to indicate that the conversion of α-hydroxy-,α-acetoxy- and α-halo ketones to osazones can proceed by three pathways - Weygand's paths A and B and one involving azo intermediates of type 16 - depending on the nature of the α-substituent, the presence or absence of acid, and steric and conformational factors in the system.

References

1. a. Stereochemistry XXII. For paper XXI see A. Hassner, M. Lorber and C. Heathcock, J. Org. Chem., 32, in press.

   b. This work was supported by U.S. Public Health Service Grant CA-04474 from the National Cancer Institute.

2. E. Fischer Ber. 20, 821 (1887).

3. F. Weygand, Ber. 73, 1284 (1940).

4. a. Evidence in favor of Weygand's mechanism A was presented among others by: W. Theilacker and P. Troester, Ann., 572, 144 (1951); P. Ruggli and P. Zeller, Helv. Chim. Acta 28, 747 (1945); M.M. Shemjakin, V.I. Mamind, K.M. Ermolaev, and E.M. Bamdas, Tetrahedron, 21, 2775 (1965).

   b. In favor of mechanism B are: F. Weygand, H. Simon and J.F. Klebe, Ber., 91, 1567 (1958); H. Simon, K.D. Keil and F. Weygand, Ber., 95, 17 (1962); I. Dijong and F. Micheel, Ann. 684, 216 (1965) - here a combination of path B and intermolecular oxidation is postulated.

   c. An oxidation process was proposed by V.C. Barry and P.W.D. Mitchell, Nature 175, 220 (1955); S. Kitaoka and K. Onodera, J. Org. Chem., 28, 231 (1963).

   d. A path analogous to mechanism A but proceeding through an HO-C=NO intermediate has been considered by W.C. Stickler, Abstr. Meet. Am. Chem. Soc., Denver, Colorado, Jan. 22, 1964, p59C.

5. L. Caglioti, G. Rosini and F. Rossi, J. Am. Chem. Soc. 88, 3865 (1966).

6. A. Hassner and A.W. Coulter, Steroids 4, 281 (1964).

7. E.R. Glazier, J. Org. Chem., 27, 2937 (1962).

8. N.S. Leeds, D.K. Fukushima and T.M. Gallagher, J. Am. Chem. Soc., 76, 2943 (1954).

9. Satisfactory elemental analyses were obtained for all compounds reported here.

10. B.T. Gillis and J.D. Jagarty, J. Am. Chem. Soc., 87, 4576 (1965).

11. A pure azo compound can be isolated from an analogous reaction in the A-ring of steroids.