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PYROLYSIS OF 21-DIAZO-20-KETO-5α-PREGNANE[1]

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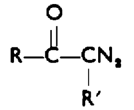
Abstract—The pyrolysis of 21-diazo-20-keto-5α-pregnane (VI) gives a 2,4-di(17β-androstanyl)-4-hydroxy-2-butenoic lactone (XII) by way of the initially formed 1,3-cycloaddition product XIII.

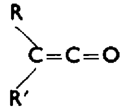
INTRODUCTION

Although ketenes are commonly postulated as intermediates generated by the thermal decomposition of α-diazoketones (I), aldoketenes (IIa) or dimers thereof are not generally detected when appropriate α-diazoketones (Ia) are decomposed in inert solvents. Ketoketenes (IIb) have been isolated from the analogous decompositions of α-diazoketones Ib.[2-4]



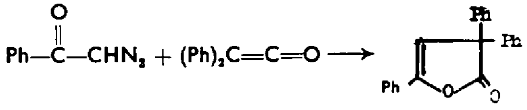
$R{-}C({=}O){-}C(R')N_2$

Ia, R' = H
Ib, R' ≠ H



IIa, R' = H
IIb, R' ≠ H

A plausible hypothesis explaining this contrasting behaviour may be constructed. It has been shown[5,6] that ketenes react with α-diazoketones to give 1,3-cycloaddition products (e.g. III + IV → V)[5] and nitrogen.



III IV V

Aldoketenes and their dimers, then, may not be obtained from the pyrolysis of α-diazoketones Ia because the ketene produced may react facilely with undecomposed α-diazoketone. The differences in observed products from pyrolyses of α-diazoketones Ia and Ib could be caused by differences in the reactivity of the intermediate ketene formed, and not by a fundamental difference in mechanism.

In direct contradiction to this hypothesis and in contrast to the pyrolysis of α-diazoacetophenone[5] is the finding that 21-diazo-20-keto-5α-pregnane (VI) may be decomposed thermally and in high yield to a dimer of an intermediate 17β-androstanylketene, 2,4-di(17β-androstanyl)-1,3-cyclobutanedione (VII).[7]

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[1] Acknowledgement is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for partial support of this research.

[2] G. Schroeter, *Chem. Ber.* **42,** 2336 (1909).

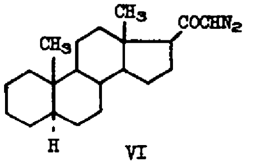
[3] H. Staudinger and H. Hirzel, *Chem. Ber.* **49,** 2522 (1916).

[4] L. Horner and E. Spietschka, *Chem. Ber.* **85,** 225 (1952).

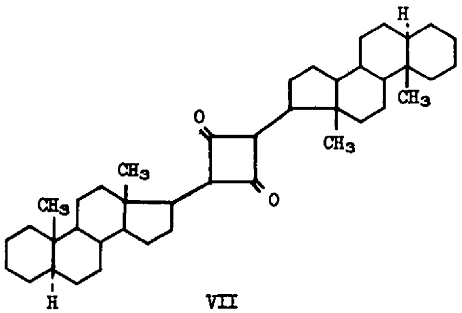
[5] P. Yates and T. J. Clark, *Tetrahedron Letters* No. 13, 435 (1961).

[6] W. Ried and H. Mengler, *Angew. Chem.* **73,** 218 (1961); *Liebig's Ann.* **651,** 54 (1962).

[7] F. Greuter, *Thesis*, Eidgenössische Technische Hochschule, Zürich (1959).



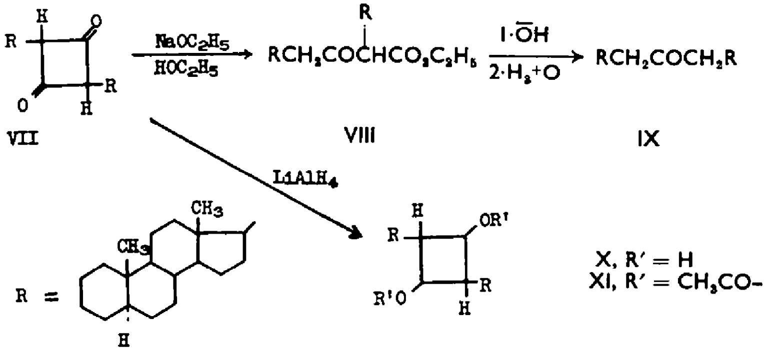
VI



VII

The present research sought to confirm or amend the structural assignment previously made for the product from the pyrolysis of the diazoketone VI in order to clarify the facts upon which mechanistic interpretations of possible ketene dimerizations or 1,3-cycloadditions in this reaction must depend.

Earlier[7] it was found that pyrolysis of the diazoketone in an evacuated sealed tube at 150–160° for 15–20 minutes gave after chromatography a crystalline product which analyzed for $C_{42}H_{64}O_2$ and had the following spectral characteristics: $\lambda_{max}^{CCl_4}$ 5·66μ (1767 cm^{-1}); λ_{max}^{EtOH} 278–286mμ, log ϵ 2·21; λ_{max} 295mμ, log ϵ 3·70 in 0·01N alcoholic sodium hydroxide. The substance was assigned structure VII on the basis of the analytical and spectral data, and on its chemical transformations.



The "1,3-cyclobutanedione" VII was converted by sodium ethoxide in ethanol-benzene to $C_{44}H_{70}O_3$, which could be degraded to $C_{41}H_{66}O$ by sequential treatment with base and acid. The latter two substances were assigned structures VIII and IX. The dimer was reduced with lithium aluminium hydride to give a diol (X) which could be converted to a diacetate (XI).

This interpretation of the structure of the dimer $C_{42}H_{64}O_2$ and its degradation products may be internally consistent, but it did not seem beyond question. For instance, the IR band of the dimer at 1767 cm^{-1} is far removed from the carbonyl band observed[8] for 2,4-dimethyl-1,3-cyclobutanedione at 5·8μ (1725 cm^{-1}).

RESULTS

The $C_{42}H_{64}O_2$ pyrolysis product was prepared and found to be the α,β-unsaturated lactone XII rather than the 1,3-cyclobutanedione VII.

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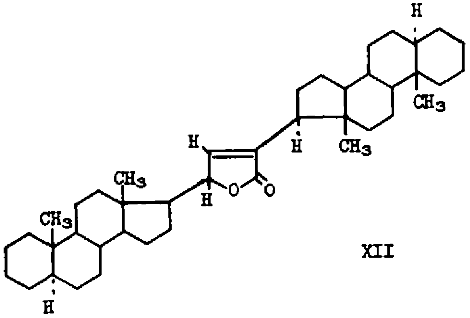
[8] E. B. Reid and S. J. Groszos, *J. Amer. Chem. Soc.* **75**, 1655 (1953). The extent to which solvent effects modify this particular discrepancy is not clear.



XII

The molecular formula $C_{42}H_{64}O_2$ was confirmed by mass spectroscopy: the molecular ion peak came at m/e 600, the theoretical value for the dimer. Previously,[7] the formula for this compound had depended on good combustion analysis data but unsatisfactory experimental molecular weights (456, 469, 473, 419 and 435).

The dimer had a carbonyl band in the IR at 1767 cm^{-1} in carbon tetrachloride which was found to be sensitive to the hydrogen bonding aptitude of the solvent: in chloroform this band fell at 1750 cm^{-1}. Both the position of the carbonyl band in carbon tetrachloride and the shift to lower wave numbers in chloroform are characteristic of α,β-unsaturated γ-lactones.[9]

Finally, the NMR spectrum of the dimer gave conclusive evidence in favor of structure XII. It showed three signals of weight one proton each at 425, 295 and 215 c/s (τ 2·92, 5·08 and 6·42), a complex pattern at 60–130 c/s (τ 7·8–9·0), and unsplit methyl peaks at 47 c/s (τ 9·22) (9 protons) and 33 c/s (τ 9·45) (3 protons). Thus the spectrum reveals three distinct protons and one shielded methyl group in addition to the characteristic signals for steroidal methine, methylene, and three methyl groups. The proton at 425 c/s is olefinic and β to a carbonyl group. The proton at 295 c/s is tertiary and deshielded by an adjacent carbon-carbon double bond and the lactone function. The approximately analogous proton in ascorbic acid adsorbs at 298 c/s.[10] The proton at 215 c/s may be assigned to the tertiary and allylic 17α-proton of the dimer. The methyl group at 33 c/s must be that one shielded by the proximate α,β-unsaturated lactone.[11]

These spectral data rigorously exclude structure VII as a possible expression for the dimer and offer persuasive support for the revised representation XII.

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No information concerning the stereochemistry of the dimer at C-4 of the lactone ring is available; no reinvestigation of the degradation products of the dimer was pursued.

IR spectra of the reaction mixture during the pyrolysis of the α-diazoketone VI showed that as the band corresponding to the diazoketone at 2090 cm^{-1} disappeared, a new absorption at 1800 cm^{-1} grew; then this band decayed while a 1767 cm^{-1} signal developed. This evidence is consistent with a reaction path involving a 1,3-cycloaddition of a ketene and a diazoketone to give a β,γ-unsaturated lactone XIII which in turn rearranges to the conjugated isomer XII under the reaction conditions.[6]

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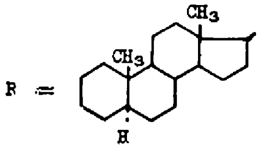
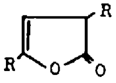
[9] R. N. Jones, C. L. Angell, T. Ito and R. J. D. Smith, *Canad. J. Chem.* **37**, 2007 (1959).

[10] Cf. spectrum No. 464 in *NMR Spectra Catalog* (Vol. 2 N. S. Bhacca, L. F. Johnson and J. N. Shoolery), Varian Associates, Palo Alto, California (1963).

[11] Cf. A. D. Cross and I. T. Harrison, *J. Amer. Chem. Soc.* **85**, 3223 (1963); and Refs. therein.





XIII

CONCLUSIONS

Thermal decomposition of 21-diazo-20-keto-5α-pregnane (VI) leads to XII *via* the β,γ-butenolide XIII. The key mechanistic aspects of this process are held to be electrophilic attack of an intermediate ketene on the α-diazoketone with resultant expulsion of nitrogen and formation of a 1,3-cycloaddition product XIII. Ketene dimerization reactions do not compete effectively against this mechanistic sequence under the pyrolytic conditions employed.

EXPERIMENTAL

21-*Diazo-20-keto-5α-pregnane* was prepared from commercial 3β-acetoxy-5-pregnen-20-one (General Biochemicals, Chagrin Falls, Ohio) in six steps by known procedures;[12–16] it was recrystallized from ligroine (b.p. 67–75°), m.p. 121–122°, dec. (lit.[15] m.p. 120–121°, dec.), $\nu_{max}^{CCl_4}$ 2090 cm^{-1}.

Thermal decomposition of 21-*diazo-20-keto-5α-pregnane.* 21-Diazo-20-keto-5α-pregnane (309 mg) was sealed under red. press. in an 8-mm diameter Pyrex tube and pyrolyzed in an oil bath at 160° for 25 min. The crude product was chromatographed on 11 g neutral alumina. Elution with ligroine–benzene (4:1, v/v) gave in the middle fractions 177 mg crystalline material showing a strong 1767 cm^{-1} band in the IR. Recrystallization of this solid from ligroine–benzene gave XII, m.p. 276–282°, $\nu_{max}^{CCl_4}$ 1767 cm^{-1} (lit.[7] m.p. 260–265°, $\nu_{max}^{CCl_4}$ 1767 cm^{-1}); $\nu_{max}^{CHCl_3}$ 1750 cm^{-1}; mol. wt. by mass spectroscopy, 600 (calc. for $C_{42}H_{64}O_2$: 600).

The NMR spectrum of a solution of this α,β-unsaturated lactone in $CDCl_3$, determined on a Varian A-60 instrument, exhibited peaks at 425, 295, and 215 cps downfield from the internal standard, tetramethylsilane, relative weight one proton each, complex signals at 60–130 c/s, and unsplit methyl absorptions at 47 c/s (9 protons) and at 33 c/s (3 protons).

The thermal decomposition of the diazoketone VI was followed by pyrolyzing 3-mg samples sealed in m.p. capillaries in an oil bath at 169° and determining the qualitative composition of the pyrolysate as a function of time by IR spectroscopy. In 40 sec, a strong band at 1800 cm^{-1} had developed; in 5 min the band at 2090 cm^{-1} was nearly gone and the 1800 cm^{-1} band had increased in intensity; in 20 min, a new band at 1767 cm^{-1} had appeared and was about twice as intense as the 1800 cm^{-1} absorption. No band in the region 1820–2000 cm^{-1} was observed in spectra of the mixtures of products from the pyrolyses.

[12] J. Staunton and E. J. Eisenbraun, *Organic Syntheses* **42,** 4 (1962).

[13] M. Steiger and T. Reichstein, *Helv. Chim. Acta* **20,** 1040 (1937).

[14] Pl. Plattner and A. Fürst, *Helv. Chim. Acta* **26,** 2266 (1943).

[15] Pl. Plattner, L. Ruzicka, and A. Fürst, *Helv. Chim. Acta* **26,** 2274 (1943).

[16] Huang-Minlon, *J. Amer. Chem. Soc.* **68,** 2487 (1946).