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ACID-CATALYZED ISOMERIZATION AND CLEAVAGE OF DIOXIMES OF THE PHOTODIMERS OF γ-PYRONES

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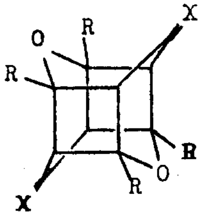
IN the course of studies on the chemistry of cage ketones of type I we have investigated the reactions of the corresponding dioximes, II, in strongly acid media. In no case were Beckmann rearrangement products obtained, but the reactions followed alternative pathways of some interest and novelty.

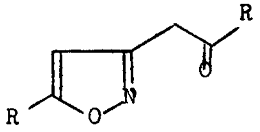


Ia R=CH_3,X=O

Ib R=C_2H_5,X=O

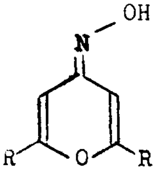
IIa R=CH_3,X=NOH

IIb R=C_2H_5,X=NOH



IIIa, R=CH_3

IIIb, R=C_2H_5



IVa, R=CH_3

IVb, R=C_2H_5

Brief treatment of IIa, dec. 305° (evac. cap.), the dioxime[2] of Ia[3],

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[2] This material is apparently a single stereoisomer, for it is converted to a single diacetate (cf. the case of IIb, below[10]).

[3] P. Yates and M.J. Jorgenson, J.Amer.Chem.Soc. 80, 6150 (1958).

with concentrated sulfuric acid on the steam bath gives three products, a colorless liquid, $C_7H_9O_2N$ [Found: C, 60.50; H, 6.46; N, 10.00; M.W. (Rast) 150], colorless needles, $C_7H_9O_2N$, m.p. 124-124.5° (Found: C, 60.63; H, 6.53; N, 10.35), and colorless needles[4], $C_{14}H_{18}O_4N_2$, m.p. 122-122.5° [Found: C, 60.51; H, 6.55; N, 10.29; M.W. (isothermal dist.) 250]. The liquid product, λ_{max}^{liq} 3.18, 5.82, 6.22, 6.77 and 7.40μ, λ_{max}^{EtOH} 218mμ (ϵ5700), τ (liq.) 4.00, 6.22, 7.72, 7.90 p.p.m. with area ratio ca. 1:2:3:3, forms a p-nitrophenylhydrazone, $C_{13}H_{14}O_3N_4$, m.p. 125-126°, λ_{max}^{EtOH} 218 mμ (infl., ϵ14,500), 250 mμ (ϵ13,000), and 384 mμ (ϵ28,000) (Found: C, 57.08; H, 5.27; N, 20.79), and gives a positive iodoform test. On the basis of these data and comparison of its spectra with those of model compounds, this product is assigned structure IIIa, confirmed by its independent synthesis by the oxidation of 3-(2-hydroxypropyl)-5-methylisoxazole, λ_{max}^{liq} 2.95, 3.18 and 6.22μ, λ_{max}^{EtOH} 216 mμ (ϵ4600) (Found: C, 59.40; H, 8.03; N, 10.16), itself prepared by reaction of 2,3-dihydro-2,6-dimethyl-4-pyrone[5] with hydroxylamine hydrochloride and pyridine followed by treatment with acid. The crystalline product m.p. 124-124.5°, has the following spectral properties: $\lambda_{max}^{CHCl_3}$ 2.76, 3.05 (br), 5.90 and 6.14μ, λ_{max}^{EtOH} 261 mμ (ϵ15,000), τ($CDCl_3$) 0.02, 3.54, 4.16 and 7.87 p.p.m. with area ratio ca. 1:1:1:6. It forms an acetate $C_9H_{11}O_3N$, m.p. 128.5-129.5°, $\lambda_{max}^{CHCl_3}$ 5.70, 5.94, 6.18 and 6.37μ, λ_{max}^{EtOH} 214 mμ (ϵ7500) and 266 mμ (ϵ16,900) [Found: C, 59.87; H, 6.05; N, 7.46; M.W. (Rast) 179], and is converted to 2,6-dimethyl-4-pyrone in poor yield on hydrolysis with hot dilute sulfuric acid in the presence of formaldehyde. On the basis of

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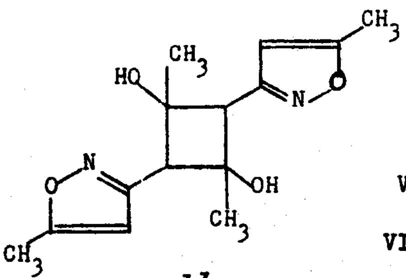
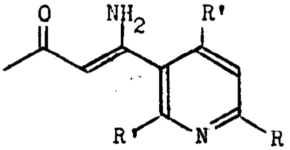
[4] *Cf.* M.J. Jorgenson, Ph.D. Thesis, Radcliffe College, 1959.

[5] Prepared by partial hydrogenation of 2,6-dimethyl-4-pyrone over Pd/$CaCO_3$ followed by separation from accompanying reduction products by distillation and chromatography: *cf.* J.J. de Vrieze, *Rec.Trav.Chim.* **78**, 91 (1959).

these data it is assigned structure IVa, confirmed by its independent synthesis by the action of hydroxylamine hydrochloride and sodium carbonate on 2,6-dimethyl-4-thiopyrone. The crystalline product, m.p. 122-122.5°, has the following spectral properties: λ_{max}^{Nujol} 2.81, 2.86, 3.17, 6.25μ, λ_{max}^{EtOH} 218 mμ(ε12,500), τ($CDCl_3$) 3.87, 6.00, 6.60, 7.60 and 8.50 p.p.m. with area ratio ca. 1:1:1:3:3. It is rapidly converted to compound IIIa by the action of hot aqueous 10% sodium hydroxide and by gentle heating above its m.p., attempted acetylation with acetic anhydride and pyridine on the steam bath for 2 hr gives a mixture of IIIa and starting material. Consideration of these data and rational routes for the acid-catalyzed isomerization of IIa (*vide infra*) leads to the assignment of structure V to the compound, m.p. 122-122.5°. Hydrogenation of V in acetic acid over platinum gives a colorless oil, $\lambda_{max}^{CHCl_3}$ 2.88, 2.99, 3.07, 3.16 (sh), 6.18, 6.28, 6.42 and 6.58μ, which forms a crystalline acetyl derivative, $C_{16}H_{22}O_3N_2$, m.p. 102.5-103°, $\lambda_{max}^{CHCl_3}$ 2.87, 3.0 (br), 5.79, 6.18, 6.29, 6.42 and 6.59μ, λ_{max}^{EtOH} 275mμ(infl. ε8000) and 304 mμ(ε20,500) (Found: C, 66.14; H, 7.49; N, 9.41). The hydrogenation product and its acetyl derivative are formulated as VI and VII, respectively, on the basis of this and the following evidence. Dehydration of VI with concentrated sulfuric acid gives VIII, m.p. 125.5-128.5° (resolidifies 129°, remelts 131°), $\lambda_{max}^{CHCl_3}$ 2.84, 3.06, 6.03, 6.14 (sh), 6.17, 6.28 and 10.36μ, λ_{max}^{EtOH} 246mμ(ε12,200) and 303mμ(ε27,000), τ($CDCl_3$) 0.00, 3.07, 3.52 (multiplet), 5.00, 7.60, 7.75, 8.02 and 8.17 p.p.m. with area ratio of last five peaks ca. 2:6:6:9:3 [Found: C, 72.85; H, 8.08; N, 11.91; pk_a' (50% EtOH/H_2O) 4.95]. Hydrogenation of VIII in ethanol over Pd/C gives the dihydro compound IX, m.p. 113-115° (resolidifies, remelts 130°), $\lambda_{max}^{CHCl_3}$ 2.84, 3.05, 6.16, 6.28, 6.40 and 6.55 (br)μ, λ_{max}^{EtOH} 275mμ (infl., ε 8400) and 303mμ(ε20,000), τ($CDCl_3$) 0.72 (br), 3.32, 3.82 (br), 5.12, 7.55, 7.72, 8.05 (superimposed on other, broad bands) and 9.07



V



VI, R= $CH_2CHOHCH_3$, R'=CH_3

VII, R= $CH_2\underset{OCOCH_3}{CH}CH_3$, R'=$CH_3$

VIII, R=$CH=CHCH_3$, R'=CH_3

IX, R=$CH_2CH_2CH_3$, R'=CH_3

X, R=R'=H

(triplet, J=6 c./s.) p.p.m. [Found: C, 72.56; H, 8.65; N, 12.25; pK'_a (50% EtOH/H_2O) 5.35] [cf. X[6]: $\lambda_{max}^{CHCl_3}$ 2.84, 3.05, 6.14, 6.26, 6.40 and 6.57μ, λ_{max}^{EtOH} 225mμ (ε 8000), 248mμ (ε 6000) and 325mμ (ε 14,000), τ($CDCl_3$) 0.50 (br), 1.37 (doublet, J ~ 1 c/s), 1.57 (quartet), 2.25 (multiplet), 2.86 (multiplet), 3.25 (br), 4.65 and 7.95 p.p.m.].

Brief treatment of the dioxime IIa with polyphosphoric acid at 110° gives IIIa and V as the major products together with a product $C_{14}H_{14}O_2N_2$, m.p. 109-110.5°, $\lambda_{max}^{CHCl_3}$ 6.10, 6.24 and 6.37μ, λ_{max}^{EtOH} 210mμ (app., ε 42,000), 318mμ (ε 6100) and a series of peaks at 260-290mμ, τ($CDCl_3$) 2.90, 4.02, 7.17, 7.52, 7.70 and 7.92 p.p.m. with area ratio ca. 1:1:3:3:3:3 [Found: C, 69.03; H, 5.99; N, 11.07; M.W. (Rast) 255]. This compound can also be obtained in low yield by treatment of IIIa with polyphosphoric acid at 110-117° for 45 minutes and is assigned structure XI [cf. 3-methylanthranil: $\lambda_{max}^{CHCl_3}$ 6.08, 6.20, 6.33 and 6.39μ, ε_{210}^{EtOH} 12,000, λ_{max}^{EtOH} 316mμ (ε 5800) and a series of peaks at 245-280mμ, τ($CDCl_3$) 2.75 (multiplet) and 7.27 p.p.m.].

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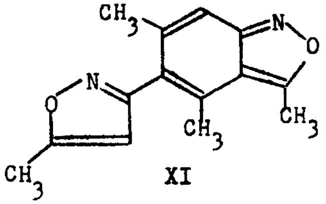
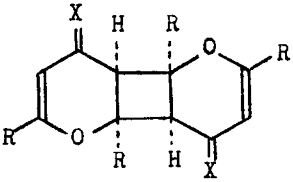
[6] Compound X, m.p. 92-93° (Found: C, 66.66; H, 6.32; N, 16.89), was prepared by treatment of 3-cyanopyridine with the sodium derivative of acetone in tetrahydrofuran.



XI



XIIa, R=CH_3, X=NOH
XIIb, R=C_2H_5, X=NOH
XIIIa, R=CH_3, X=O
XIIIb, R=C_2H_5, X=O

These observations can best be interpreted in terms of a reaction scheme in which the dioxime IIa is first converted by cleavage of one of its cyclobutane rings to an intermediate, XIIa; the breaking of the two C-C bonds may be formulated as occurring via protonation on nitrogen followed by retroaldol type bond fission.[7] Cleavage of the remaining cyclobutane ring in XIIa in like fashion would lead to the oxime IVa.[8] Compound XIIa could also serve as the source of V and IIIa via acid-catalyzed cleavage of both of its enol ether functions; cyclization of the resulting intermediate would then give V, while retroaldol type fission followed by cyclization could give IIIa (and also IVa). Routes to IIIa via IVa or V are unlikely since IVa and V do not give rise to IIIa under the conditions of the original reaction. The formation of XI can readily be formulated in terms of the self-condensation of IIIa.

Considerable strength is lent to the postulation of the intermediacy

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[7] Cf. C.A. Grob and W. Baumann, Helv.Chem.Acta. **38**, 594 (1955).

[8] Cf. the acid-catalyzed reversion of Ia to 2,6-dimethyl-4-pyrone.[3]

of XIIa by the results of a study of the reaction of dioxime IIb,[9,10] m.p. 263-267° dec. (Found: C, 64.61; H, 7.78; N, 8.42) with concentrated sulfuric acid. Under the same conditions as those used with IIa, four products are obtained. Two of these are analogous to products obtained from IIa: compound IIIb, a colorless liquid, λ_{max}^{liq} 5.81 and 6.24μ, λ_{max}^{EtOH} 217mμ(ϵ6600) (Found: C, 64.82; H, 7.67; N, 8.35) and compound IVb, m.p. 69.5-70.5°, $\lambda_{max}^{CHCl_3}$ 2.75, 3.05 (br), 5.93 and 6.17μ, λ_{max}^{EtOh} 265mμ(ϵ12,500) (Found: C, 64.17; H, 7.97; N, 8.16). The other two products, m.p. 212° dec, λ_{max}^{Nujol} 3-4, and 6.10μ, λ_{max}^{EtOH} 264mμ(ϵ33,600) (Found: C, 64.52; H, 7.69; N, 8.37) and m.p. 192.5-193°, λ_{max}^{Nujol} 3-4, 6.05 and 6.14 (sh)μ, λ_{max}^{EtOH} 263mμ(34,000) (Found: C, 64.79; H, 7.75; N, 8.22), are considered to be stereoisomers of structure XIIb: their spectra may be compared with those of XIIa, m.p. 218-220° dec., λ_{max}^{Nujol} 3-4, 6.02 (sh) and 6.08μ, λ_{max}^{EtOH} 262mμ(ϵ29,200) (Found: C, 60.13; H, 6.64; N, 9.81), prepared by the action of hydroxylamine on XIIIa, itself obtained by pyrolysis of Ia.[4] No product analogous to V is detected in the reaction of IIb with sulfuric acid or with polyphosphoric acid; the latter reagent gives rise to the same products as those obtained with sulfuric acid.

It is therefore proposed that the acid-catalyzed reactions of both IIa and IIb lead first to a compound of type XII; in the case of XIIa, this is rapidly converted to IIIa, IVa and V, while in the case of XIIb, it is more slowly converted to IIIb and IVb only.[11] The difference in behavior in the

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[9] The parent diketone, Ib, m.p. 261-262° dec. (Found: C, 70.94; H, 7.94) was prepared by irradiation of 2,6-diethyl-4-pyrone.

[10] This material is probably a mixture of two stereoisomeric forms of IIb since on acetylation it gives two diacetates, differing in the fingerprint region of their solution infra-red spectra but possessing superimposable nuclear magnetic resonance spectra.

[11] A related difference in behaviour of the diketones Ia and Ib has recently been observed: under conditions which suffice to bring about the acid-catalyzed reversion of Ia to monomer,[3] IIb yields XIIIb in high yield. (P. Yates and S.K. Roy, unpublished results.)

case of XIIb may be attributed to a combination of the following factors; enhanced steric hindrance to solvation of charged intermediates in the cyclobutane ring cleavage process and to nucleophilic attack in the enol ether cleavage process, and increased unfavorable *trans*-annular interactions.