

CHEMICAL PROPERTIES OF 3H-1,2,4-DIOXAZOLES. (*)

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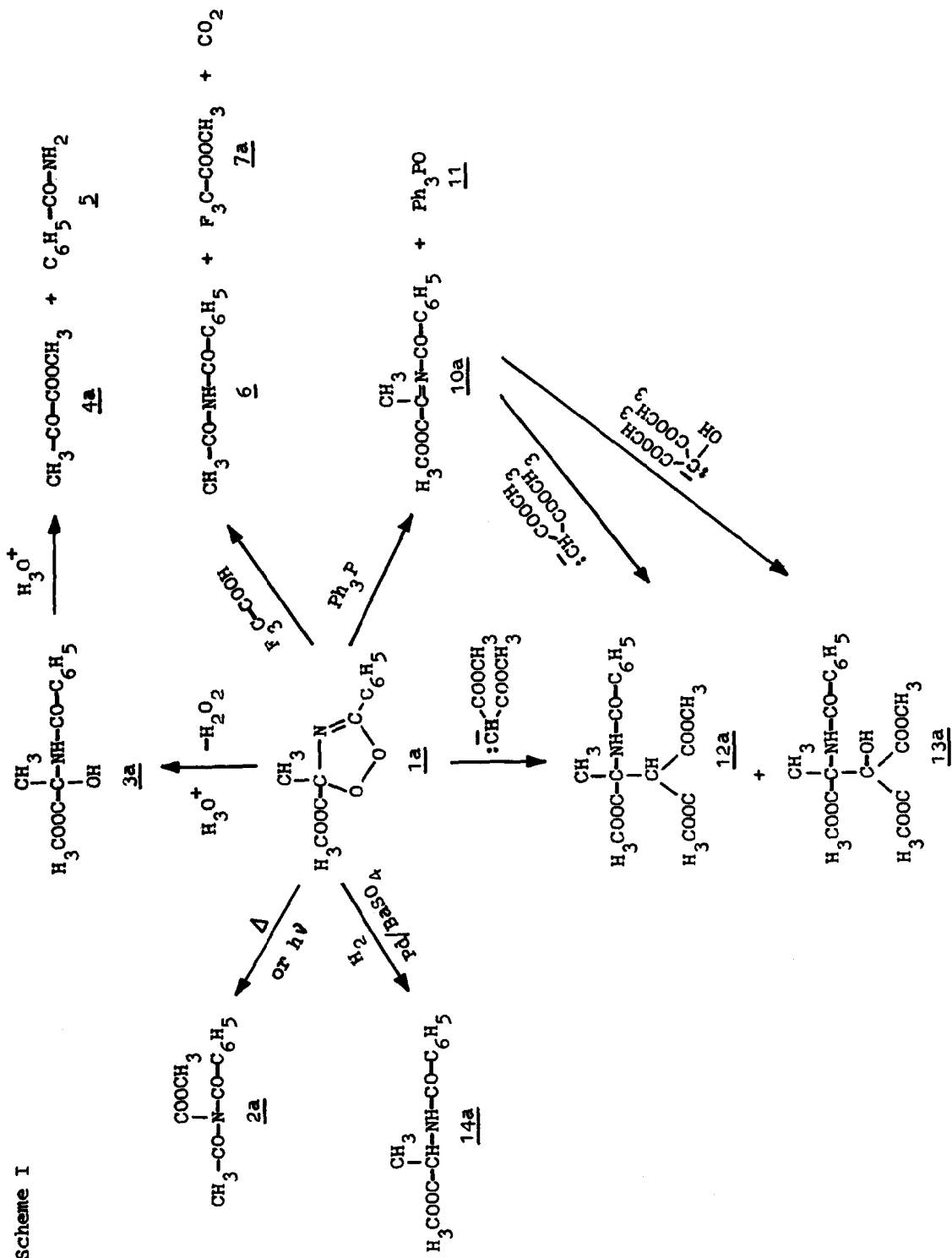
We have recently described the conversion of 5-alkoxy-4-methyl-2-phenyl-oxazoles into 3-alkoxycarbonyl-3-methyl-5-phenyl-1,2,4-dioxazoles 1 (yields ca. 50%).¹ As the dioxazoles 1 are the first examples of this ring system, and also the first peroxyimidates, we considered it interesting to study their reactivity and in this paper we show that dioxazoles 1 can be considered as key intermediates in the synthesis of many several compound types.

Scheme I summarizes the results pertinent to 1a (alkyl = CH₃); for sake of completeness it also shows the thermal and photochemical rearrangement of 1a into diacylcarbamate 2a already described.¹

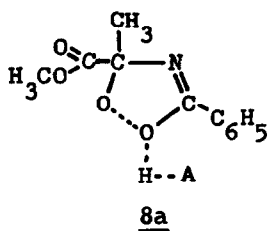
Treatment of 1a in acetone with 2N hydrochloric acid at room temperature (3 hr) led to 3a, 4a and 5; in the product mixture hydrogen peroxide was present. Hemiaminal 3a,² isolated by silica-gel chromatography (ca. 30%), yielded 4a and 5 by further acid hydrolysis.

Dioxazole 1a dissolved in anhydrous trifluoroacetic acid with carbon dioxide evolution. Inspection of the ¹H nmr spectrum, after the signals of 1a had disappeared (3 hr), showed only the presence of 6³ and 7a. Removal of the solvent and 7a in vacuo gave diamide 6 (ca. 100%).

The above results are consistent with an hypothesis according to which the presence of protic acids leads to the transition state 8a. In aqueous medium (2N HCl) 3a and hydrogen peroxide are formed, the reaction occurring probably



via displacement of the oxygen at position 2 by water. When the reaction is



carried out in anhydrous conditions, electron-transfer in 8a from the carbonyl carbon to the oxygen at position 2 gives rise to 6.

Dioxazole 1a was recovered almost quantitatively⁴ after 6 days at room temperature from a pyridine solution, whereas triphenylphosphine reacts with 1a very rapidly (10 min) at room temperature in carbon tetrachloride. In addition to 11, ketimine 10a was quantitatively⁵ obtained showing that the phosphine displaces the oxygen at position 2.

This displacement occurred also in the presence of a stronger base such as sodium dimethyl malonate. When a 1:1 mixture of the base (from sodium hydride and dimethyl malonate in dry benzene) and 1a in dry benzene was stirred at room temperature for 3 hr, usual workup gave a mixture which was chromatographed on silica-gel. Elution with increasing concentration (up to 80%) of ether in light petroleum gave 12a⁶ [(ca. 40%; m.p. 107-110°; $\text{ir } \nu_{\text{max}}^{\text{CHCl}_3}$ 3360, 1760, 1745, 1737, 1663 cm^{-1} ; $^1\text{H nmr}$ (CDCl_3) τ 2.05-2.64 (6H, m, aromatic H and NH), 5.53 (1H, s, CH), 6.22 and 6.27 (9H, two s, 3xOCH₃), 8.08 (3H, s, CH₃)] and 13a⁶ [(ca. 20%; m.p. 149-152°; $\text{ir } \nu_{\text{max}}^{\text{CHCl}_3}$ 3365, 3100 (broad), 1760, 1745, 1735, 1660 cm^{-1} ; $^1\text{H nmr}$ (CDCl_3) τ 1.95 (1H, bs, NH), 2.05-2.65 (5H, m, aromatic H), 4.75 (1H, bs, OH), 6.17, 6.19 and 6.22 (9H, three s, 3xOCH₃), 8.22 (3H, s, CH₃)]. With a 3:1 ratio of sodium malonate to 1a, the yield of 12a increased (12a 55% ; 13a 6%) showing that the key step of the reaction is the displacement of the oxygen at position 2 from 1a to form 10a. In this way malonate anion is

oxidized to tartronate anion which competes with the malonate anion in the successive addition to 10a. The observation that 10a⁷ reacted with sodium malonate and sodium tartronate to give 12a (ca. 72%) and 13a (ca. 50%) respectively supports this hypothesis.

Catalytic hydrogenation of 1a (in cyclohexane, Pd/BaSO₄ catalyst, 50°, 2 atm) gave quantitatively 14a.⁸

The reactions reported in Scheme I were carried out also using 1b (alkyl = C₂H₅); the yields of the reactions were very similar to those reported for 1a; 12b⁶ (m.p. 64-67°) and 13b⁶ (m.p. 109-112°) were isolated by silica-gel chromatography.

REFERENCES AND NOTES

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- 4 Only trace amounts of 2a were present; similar results were found in benzene solution.
- 5 Ketimine 10a is hydrolyzed even by atmospheric moisture; its quantitative formation was confirmed by addition of dry ethanol to the crude reaction mixture. The obtained methyl 2-benzoylamino-2-ethoxypropionate was isolated by silica-gel chromatography.¹
- 6 All the new compounds described in this paper gave satisfactory elemental analysis; ir and ¹H nmr spectra are consistent with the proposed structures.
- 7 The reactions were carried out in situ using 10a obtained from 1a by Ph₃P.
- 8 J.W. Cornforth in "The Chemistry of Penicillin" p. 688, Princeton Univ. Press, Princeton, New Jersey, 1949.