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SOME SYNTHETIC APPLICATIONS OF THE REACTION OF REDUCTIVE OPENING OF THE ISOXAZOLE RING

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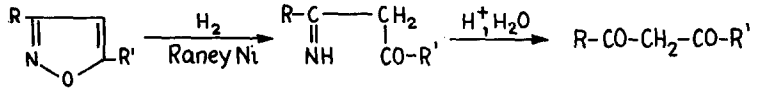
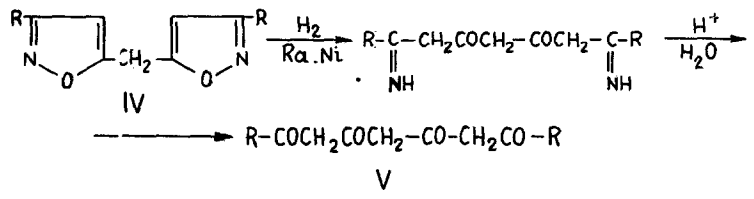
Increasing attention has been given in these last years to the study of β-polyketonic systems as possible biogenetic precursor of a number of natural products from fungi and higher plants[1], nowithstanding the incompleteness of our knowledge of the biosynthetic mechanisms actually involved in their formation. A serious handicap to this study is the difficult availability of β-polyketones for which no satisfactory general synthesis is so far known. Investigations on the reactivity of β-polyketones have therefore till now been limited to β-diketones and β-triketones; some interesting results have however been reached, such as their conversion into aromatic systems of phenolic type[2,3], imitating the postulated biosynthetic path.

It is known that catalytic hydrogenation in mild conditions of isoxazoles (I) results in the rupture of the N-O linkage with the formation of monoiminoketoderivatives (II)[4] which can readily be converted into the corresponding β-diketones (III) by acidic hydrolysis:



I II III

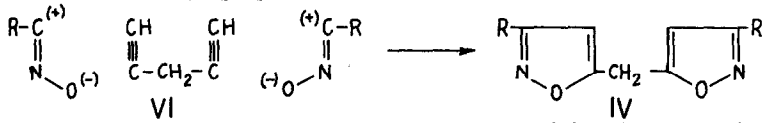
This reaction, when applied to diisoxazolylmethanes (IV), should have offered a convenient route to β-tetraketones (V) according to schema:



IV

V

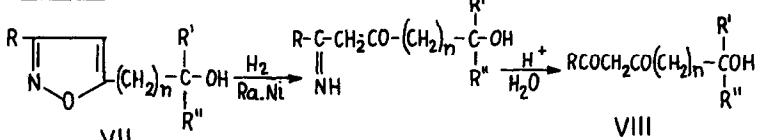
In fact, we could recently achieve by this way the synthesis of dibenzoylacetylacetone (V, R = C_6H_5)[5]. Since diisoxazolylmethanes of type (IV) are readily prepared by addition of two molecules of nitrile oxide RCNO on diethynylmethane (VI)[6]:



VI IV

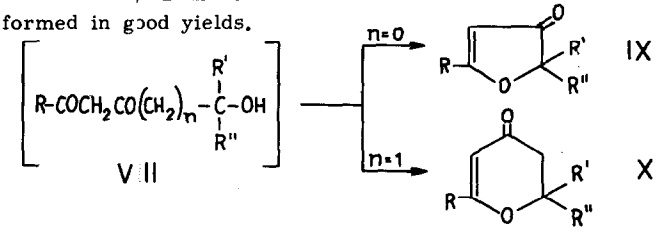
This reaction provides a valuable general method for the synthesis of β-tetraketones[7].

With the aim of exploiting this reaction for the synthesis of β-diketoalcohols (VIII) following the general schema:



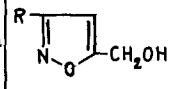
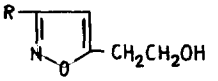
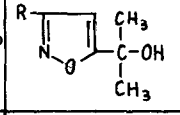
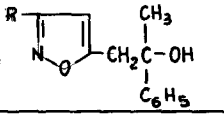
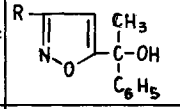
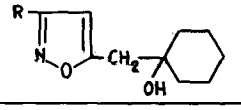
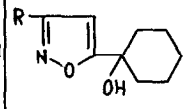
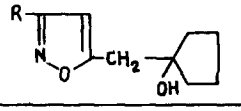
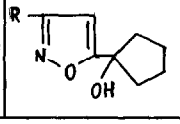
VII VIII

a number of 5-isoxazolylcarbinols (VII)[8] were submitted to catalytic hydrogenation and subsequent acidic hydrolysis. For the members n = 0 and n = 1 reported in Table 1, instead of expected γ-hydroxy- and δ-hydroxy-β-diketones (VII, with respect. n = 0 and n = 1), the corresponding β-furanones (IX) and 2,3-dihydro-γ-pyrones (X) were formed in good yields.



VII IX X

Table 1. - 5-Isoxazolylcarbinols (VII, R = C_6H_5)

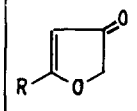
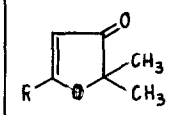
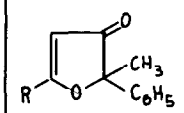
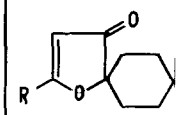
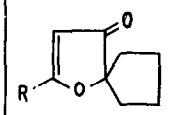
	n = 0	m. p.		n = 1	m. p.
VII_a		(9) 51°	VII_f		56°
VII_b		(10) 56°	VII_g		96°
VII_c		(10) liq. b. p. 200° (0, 5 mm)	VII_h		100°
VII_d		(10) 133°	VII_i		86°
VII_e		(10) 110-111°			

Among the β-furanones listed in Table 2 only 2-phenyl-5, 5-dimethylfuranone was already known as the major component of the essential oil of Mirtus bullata[11].

Of the 2, 3-dihydro-γ-pyrones reported in Table 3 2-phenyldihydropyrone had already been prepared by controlled hydrogenation of 2-phenyl-γ-pyrone[12], and 2-phenyl-6-methyl-6-phenyldihydropyrone had been obtained along with the unsatured β-diketone $C_6H_5COCH_2COCH{=}C\langle^{CH_3}_{C_6H_5}$ in the acid catalyzed dehydration of the corresponding hydroxy-β-diketone[13].

The reduction of 5-isoxazolylcarbinols (VII with n = 0, 1) followed by acidic hydrolysis affords a convenient general method for the synthesis

Table 2. - β-Furanones (IX, R = C_6H_5)

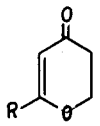
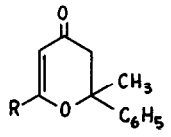
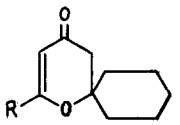
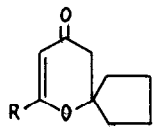
From isoxazolyl carbinol	Furanone	m. p.	I. R. nujol cm^{-1}	U. V. (EtOH) λ_{max}, mμ	2,4-DNP m. p.
VII_a		80-81°	1695 1615	244 (log ε 3,99) 306 (log ε 4,27) 220 (log ε 3,96)	-
VII_b		63°	1695 1610	242 (log ε 3,89) 305 (log ε 4,23) 220 (log ε 3,98)	222°
VII_c		68°	1695 1610	220+ (log ε 4,15) 244 (log ε 3,99) 306 (log ε 4,27)	-
VII_d		104-105°	1685 1615	220 (log ε 3,88) 245 (log ε 3,94) 305 (log ε 4,23)	-
VII_e		47°	1690 1610	220 (log ε 3,90) 244 (log ε 3,88) 304 (log ε 4,18)	257°

+ Shoulder

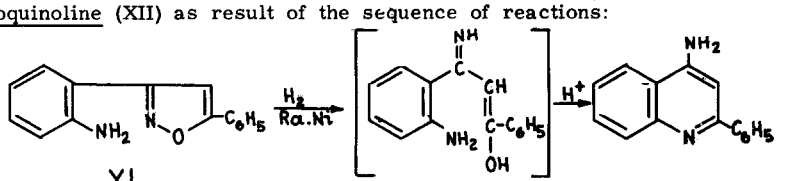
of β-furanones (IX) and β-dihydro-γ-pyrones (X); moreover the formation of these substances from intermediate β-diketols of type (VIII with n = 0, 1) suggests a possible biogenetic relationship between the two classes of compounds.

The potential capacity of suitably substituted isoxazoles of giving by reductive cleavage intermediates which may undergo cyclization to different heterocyclic systems, has prompted us to extend the investigations in this direction. Thus, researches still in progress have shown

Table 3. - Dihydro-γ-pyrones (X, R = C_6H_5)

From isoxazolyl carbinol	Dihydropyrone	m. p.	b. p. (mm)	I. R. nujol cm^{-1}	U. V. (EtOH) λ_{max}, mμ	2,4-DNP m. p.
VII_f		67°	--	1665	243 (log ε 3,65) 298 (log ε 4,15)	200°
VII_g		109°	--	1665	244 (log ε 3,85) 304 (log ε 4,25)	190°
VII_h		--	170° (0,3)	1665	245 (log ε 3,79) 305 (log ε 4,20)	180°
VII_i		--	140° (0,3)	1665	245 (log ε 3,47) 303 (log ε 3,84)	210°

that 3-o-aminophenyl-5-phenylisoxazole (XI), when hydrogenated in the presence of Raney Ni and treated with H_2SO_4, affords 2-phenyl-4-aminoquinoline (XII) as result of the sequence of reactions:



XI

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(6) A full account of this reaction will be published elsewhere.

(7) Since the addition can be carried out stepwise, it is possible to synthesize asymmetrical β-tetraketones by using two different nitrile oxides RCNO and R'CNO.

(8) Prepared by condensing ethynylcarbinols $HC{\equiv}C\text{-}(CH_2)_nC(R_1)(R_2)OH$ with nitrile oxides (from hydroxamic chlorides and Et_3N).

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