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ETHYL OXAOROTATE - A NEW SYNTHETIC ROUTE TO 1,3-OXAZINE-2,6-DIONES

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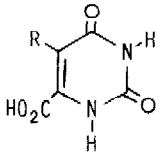
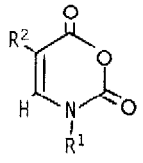
We wish to report a simple synthesis of oxazinediones--the oxygen isosters of uracils--which extends the range of substitution patterns obtainable for these biologically interesting heterocycles, and to present data on the synthesis and hydrolytic stability of a key member of this series--ethyl oxaorotate 7a--the hitherto unreported analog of orotic acid

The metabolic centrality of orotic acid 1 and its derivatives has instigated vigorous study of the chemotherapeutic properties of these heterocycles 5-Fluoroorotic acid 2 has shown anti-neoplastic activity,[1] and various salts and amides of orotic acid have shown activity against protozoan-induced diseases As the oxazinedione 3 ring system[2] and its derivatives have shown anti-leukemic[3] and growth-inhibiting properties[4], congeners of oxaorotic acid 4 should be of pharmaceutical interest

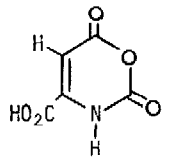
The previously described routes to the oxazinedione nucleus hypochlorite oxidation of maleimide,[2a] reaction of trimethylsilyl azide with maleic anhydride,[2b,c,d] polyphosphoric acid-induced cyclization of a β-aminoacrylic acid,[3a] and lead tetracetate oxidation of maleamic acid,[5] are inapplicable to the synthesis of 4 due to both inaccessibility of the requisite starting materials and/or possible formation of the wrong isomer as product



1 R = H
2 R = F



3a $R^1 = R^2 = H$
b $R^1 = H$, $R^2 = CH_3$
c R^1 = deoxyribosyl, $R^2 = H$
d R^1 = ribosyl, $R^2 = H$
e $R^1 = H$, $R^2 = F$



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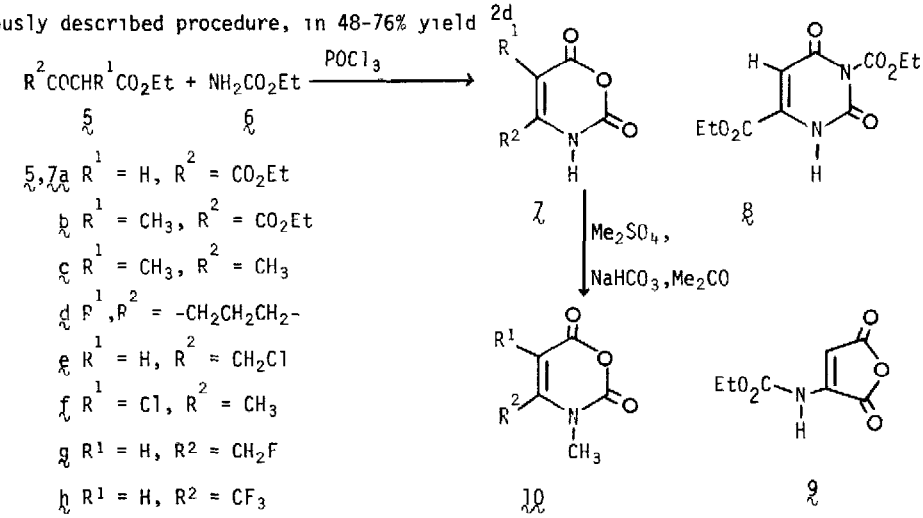
The ready availability of variously substituted β-keto esters and urethane 6 pointed toward their combination as an easy route to oxazinediones, particularly 4. Accordingly, heating a mixture of 20 mmol each of 6 and diethyl oxaloacetate 5a in 10 ml of phosphoryl chloride at 90° for 2 5 hr , and subsequent removal of volatiles by Kugel-rohr distillation left a red residue, which was dissolved in 50 ml of benzene, extracted with 4X50 ml of water, and the aqueous extracts extracted with 3X100 ml of EtOAc Evaporation of the dry EtOAc layer gave 0 45 g (22%) of ethyl oxaorotate, mp 138-140, 7a, ir 1805, 1745, 1730, 1710, 1650 cm^{-1}, pmr δ 8 5 (s,1), 6 31 (s,1), 4 45 (q,2), and 1 40 (t,3) ppm [6] Chromatography of the benzene layer gave 0 45 g (9%) of ethyl 3-carboethoxyorotate 8, this compound predominated at higher reaction temperatures At lower temperatures, N-ethoxycarbonylaminomaleic anhydride 9 was a major by-product

With slight modification of the workup procedure, oxazinediones 7b-7f, inaccessible by other routes, were obtained in 22 to 43% yield from 6 and ketoesters 5b to 5f [6] New oxazinediones 7a to 7d were routinely converted to N-methyl derivatives 10a to 10d using our previously described procedure, in 48-76% yield

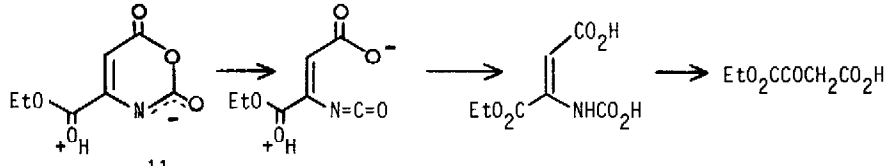


Fluorinated oxazinediones 7g and 7h could not be prepared using the procedure outlined above, and required treatment with polyphosphoric acid of the enamine isolated by reaction of equimolar quantities of ketoester and urethane with 0.33 molar equivalent of $POCl_3$

$$R^2COCH_2CO_2Et + H_2NCO_2Et + 1/3\ POCl_3 \longrightarrow EtO_2CNHC(R^2)=CHCO_2Et \xrightarrow{PPA} 7g,\ 7h$$

On the basis of current data, mechanistic speculation is unwarranted Any proposed scheme must account for such observations as formation of 8 and 9 in the reaction leading to 7a, a 5% yield of $EtO_2CNHCONH_2$ in the reaction leading to 7c, and formation of bis-carbamate $(EtO_2CNH)_2C(CF_3)CH_2CO_2Et$ in the reaction leading to 7h

Some quantitative measure of the stability under physiological conditions of 3 is desirable, as, bearing anhydride, enamine, and carbamate functionality, it possesses manifold pathways for hydrolytic decomposition The hydrolysis of 3a, studied by Skoda and coworkers,[5] is dependent on medium acidity, and produces formylacetic acid as final organic product The predicted half-life (in aqueous buffers at 37°) of 3a ranges from 10 days at pH 1 1, to 12 hr at pH 7 15, to 2 5 hr at pH 11 36 Our spectrophotometrically determined half-life at 25° for 7a was markedly shorter 72 hr at pH 1 1, and 6 hr at pH 7 15 Interestingly, the spectrophotometrically determined (at pH 2.20 λ_{max} 289 nm, at pH 9 80 λ_{max} 328, isosbestic point at 305 nm) pK_a of 7a is 6 14, one and one-half units less than the pK_a of 3a, 7 78 [5] We consider this to indicate contribution of zwitterion 11 to the ground-state structure of 7a If ring-opening of a species with un-protonated nitrogen (such as 11) initiates hydrolysis of the oxazinedione ring, then enhanced hydrolytic sensitivity for 7a is reasonable



11

We note further that, qualitatively, the rate of N-methylation of 7a was faster than that of 3a, and as methylation likely proceeds via an anion, involvement of 11 in ground-state structure would enhance the rate Clearly, further study of the hydrolytic behavior of oxazinediones is warranted to suggest synthetic modifications which will increase stability of these materials to physiological conditions

In summary, the advantages of the present synthesis are 1) it proceeds in one step albeit modest yield, from readily available starting materials, and 2) it opens a range of substitution patterns on the oxazinedione ring system which were previously synthetically unobtainable. The scope of this synthesis is under intense investigation

Acknowledgements

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6 Ir, nmr, and microanalytical data for all new compounds were in complete accord with structures assigned