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NEW STABLE MESOIONIC OXAZOLONES BY THE DOUBLE CYCLIZATION OF PHENYLGLYCINE-o-CARBOXYLIC ACID

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Huisgen and his school[1] described in an exhaustive manner the "münchnones", unstable mesoionic oxazolones with azomethine ylide structure, and their 1,3-dipolar cycloaddition reactions which closely parallel those of the related sydnones. Fused mesoionic oxazolones with an oxazolo[3,2-a]pyridinium skeleton (1) had already been obtained by Lawson and Miles[2], but they were invariably acylated at the 4-position of the oxazole ring. Compounds lacking a substituent at C-4 could be obtained only in solution by deprotonation of the perchlorate salts with triethylamine and could be kept only for a short period of time[3]. Attempts to prepare analogous quinoline derivatives failed: the 2-quinolone did not react with chloroacetic acid and refluxing of phenylglycine-o-carboxylic acid in acetic anhydride in the presence of 3-picoline was reported to give only N,O-diacetylindoxyl[2,4].

We now report the successful double cyclization in refluxing acetic anhydride, of the N-acetyl-phenylglycine-o-carboxylic acid (2) to the mesoionic oxazolone 5 possessing an oxazolo[3,2-a]quinolinium structure[5]. The straw-white crystals with m.p. 130-131°, obtained in 62% yield, could be kept for several months without a sensible alteration. Unstable in benzene and dioxane solution, the new mesoionic compound remained unchanged after several weeks in acetone and acetonitrile, while a moderate stability in chloroform, ethanol and pyridine permitted measurements of spectra. Its remarkable feature is the free, nonacylated position at C-3[6]. The corresponding C-H stretching vibrations show the characteristic value of 3178 cm^{-1} which closely parallels those of the sydnone group[7]. UV: λ_{max}^{EtOH} nm (log ε) = 328 (3.52), 267 (4.107), 234 (4.501).

Synthesis of tosylate 8 (m.p. 155°), by elimination of the acetyl group of 5 with boron trifluoride etherate and treatment with tosyl chloride of the resulting lactone 7, allowed an unambiguous assignment of the IR carbonyl absorption of the mesoionic oxazolone ring which overlaps that of the acetoxy group (ν_{CO} = 1760 cm^{-1}). Compared with related azlactones (ν_{CO} = 1820 cm^{-1}), the value indicates a considerable double-bond character quite similarly to the sydnones[7]. On the other hand, the synthesis of 6 (m.p. 163°) by the cyclization of 3 in acetic anhydride permitted to distinguish the chemical shifts of protons 3 and 10, long-range coupled to each other (J = 2 cps) in compound 5. The former appears at low field, in the aromatic region [δ = 7.12 ppm in

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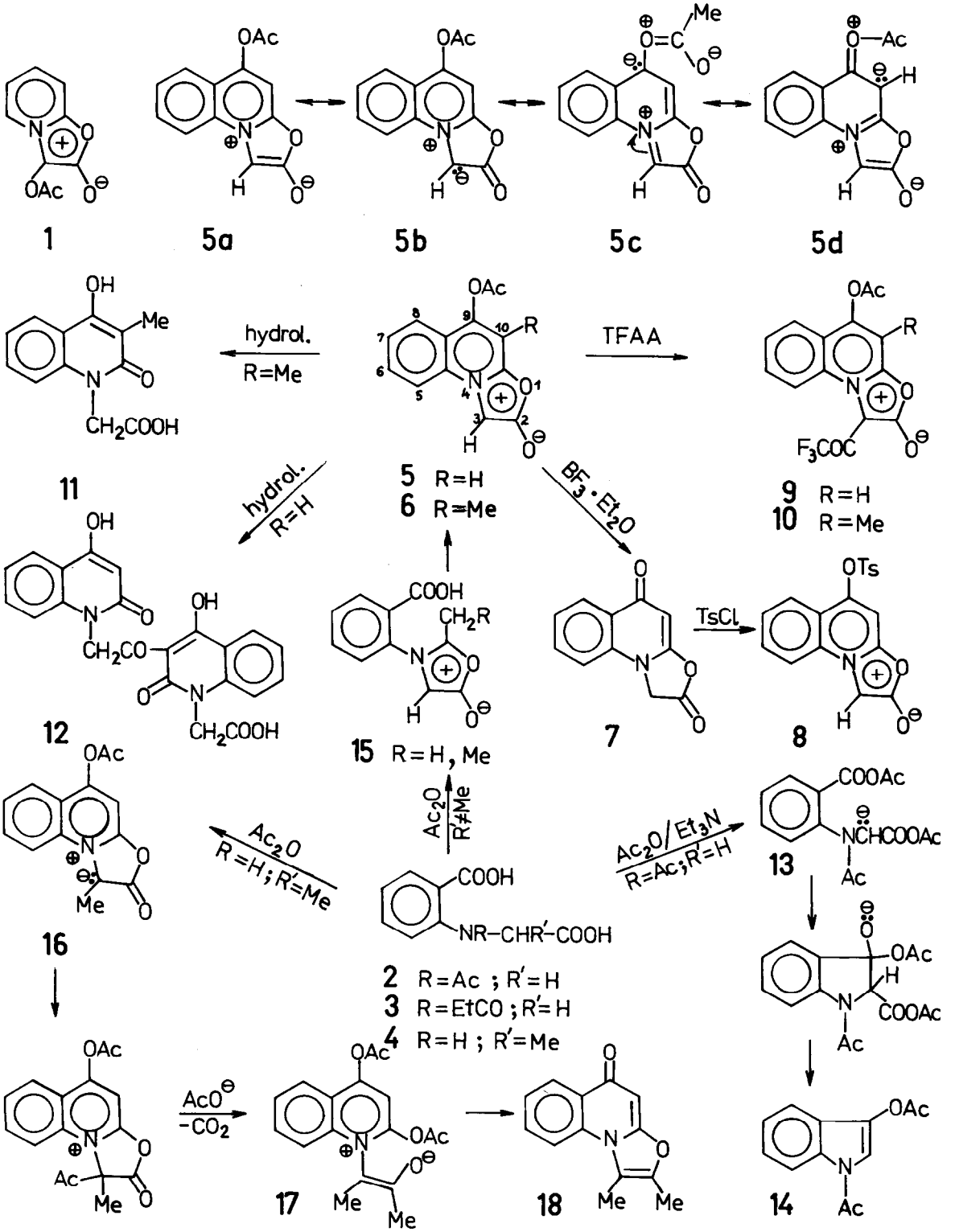

1
5a
5b
5c
5d
hydrol.
R=Me
11
hydrol.
R=H
12
5 R=H
6 R=Me
TFAA
9 R=H
10 R=Me
BF3·Et2O
7
TsCl
8
15 R=H, Me
Ac2O
R≠Me
Ac2O
R=H; R'=Me
16
2 R=Ac ; R'=H
3 R=EtCO ; R'=H
4 R=H ; R'=Me
Ac2O/Et3N
R=Ac; R'=H
13
AcO⊖
-CO2
17
18
14

$CDCl_3$] in support of the mesoionic structure, while the latter at δ = 5.72 ppm indicates a strong nucleophilic reactivity.

Attempts to acylate 5 and 6 were unsuccessful except with trifluoroacetic anhydride which gave the 3-trifluoroacetyl derivatives 9 (m.p. 209°) and 10 (m.p. 220°). In the presence of traces of trifluoroacetic acid deuteration of the 3-position of the same compounds 5 and 6 occured readily.

Alkaline or acid hydrolysis of 6 led to the 4-hydroxy-3-methyl-α-quinolone-N-acetic acid (11; m.p. 246°). In the case of 5 hydrolysis is accompanied by self-acylation of the nucleophilic site at 10-C with formation of the acid 12 (m.p. 217°).

The fact that the fused mesoionic oxazolone 5 is not acylated at the 3-position, in contrast to its unsubstituted pyridinium analogue 1[2], can be rationalised by considering the canonical forms 5a and 5b which correspond to a vinylogous quinoline oxide and to an ylidic structure respectively. The back-donating effect[8] characteristic to both of them is enhanced by the push-pull action of the acetoxy substituent which facilitates the flow of electrons in the pyridine ring by increasing the contribution of tetrapolar canonical structures such as 5c through an inductive stabilizing effect. The contribution of another tetrapolar canonical structure 5d is mostly responsible for the high-field absorption of proton 10. We expect that the acetoxy group will have the same stabilizing effect on the pyridinium analogue of 5, which is now under study.

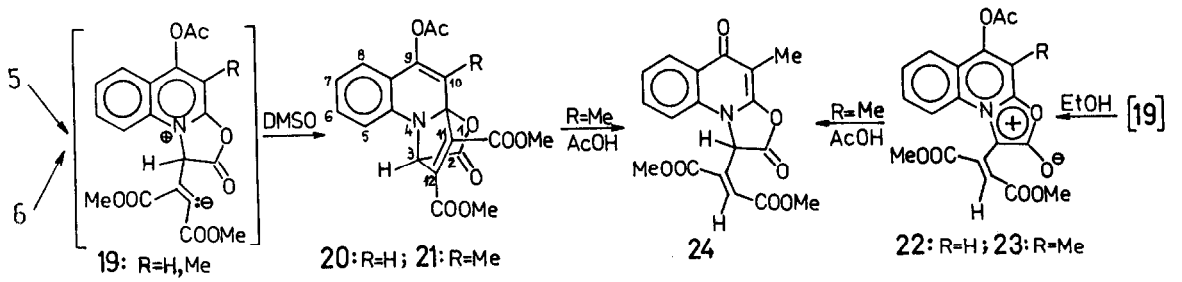
It is worth to be mentioned that the cyclization of 2 in refluxing Ac_2O-Et_3N[9] takes the different course of the well-known Heumann cyclization to N,O-diacetylindoxyl (14). In the absence of Et_3N no proton transfer occurs from the methylene of the mixed anhydride of 2 (13) and the cyclization to the intermediate oxazolone 15 is preferred, which possesses a very active methyl group as a result of the positively charged mesoionic ring. The double ring closure of 2 is thus completed to 5. In the presence of a weaker base such as pyridine a mixture of approximately equal parts of the two products 5 and 14 is formed.

When N-phenylalanine-o-carboxylic acid (4) was refluxed in acetic anhydride the cyclization followed a third path, that of the Dakin-West reaction[1b,10].

The ylidic canonical structure of the non-isolable mesoionic oxazolone 16 is destabilized or reactivated by the presence of the electron-donating methyl group. Thus the acylation becomes possible, followed by CO_2 elimination[11] and cyclization of the intermediate zwitterion 17 to the final fused oxazole 18 (m.p. 209°). UV: λ_{max}^{EtOH} nm (log ε) = 329 (4.052) and 259 (4.179); IR (CH_2Cl_2): ν_{CO} = 1630 cm^{-1}; PMR ($CDCl_3$): δ (ppm) = 6.07 (s, 1, 10-H), 8.50 (q, 1, 8-H).

The reaction of 5 and 6 with acetylenedicarboxylic ester follows two different paths depending on the solvent used. In aprotic solvents such as DMSO

or acetonitrile the N-bridged lactones 2o (m.p. 138°) and 21 (m.p. 167°) were formed by 1,3-dipolar cycloaddition. For 2o IR (KBr): ν_{CO} = 1765, 1745 and 1722 cm^{-1}; PMR ($CDCl_3$): δ (ppm) = 5.52 (d, 1, 3-H), 6.62 (d, 1, 1o-H), $J_{3,1o}$ = 1 cps. Similar stable cycloadducts have been recently isolated[12,13].



In methanol or ethanol the reaction takes another course with formation of the Michael type adducts 22 (m.p. 139°) and 23 (m.p. 167°), orange-red crystals. For 22 IR (CCl_4): ν_{CO} = 1775 and 173o cm^{-1}; PMR ($CDCl_3$): δ (ppm) = 6.o2 (s, 1, 1o-H), 7.18 (s, 1, ω-H).

The common intermediate of both reactions is the zwitterion 19. Both type of methylated adducts (21 and 23) on refluxing in glacial acetic acid gave the same deacetylated lactone 24 (m.p. 177°) which, in the case of 21, implies a heterolytic cleavage of the pyrroline ring. IR ($CHCl_3$): ν_{CO} = 178o, 1724 and 164o (sh) cm^{-1}; PMR ($CDCl_3$): δ (ppm) = 6.45 (s, 1, 3-H, the signal disappears on deuteration only in the presence of traces of trifluoroacetic acid), 6.88 (q, 1, 5-H), 7.18 (s, 1, ω-H), 8.2o (q, 1, 8-H).

Recently there has been considerable interest in the reaction mechanism of the 1,3-dipolar cycloadditions of münchnones, basically the problem being to decide between a concerted or biradical mechanism[14]. The above facts constitute an exception which can be rationalized by the adequately delocalized charges of the intermediate pyridinium zwitterion 19.

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