ACID-CATALYZED CYCLIZATION OF 2-HYDROXY-3-PYRROLONE DERIVATIVES. 2-METHOXY-3(2H)-FURANONES AS PRECURSORS OF POLYCYCLIC NITROGEN HETEROCYCLES

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Abstract - Condensation of 2-methoxy-3(2H)-furanones with β-substituted ethylamines followed by treatment with various acid catalysts gives rise to polycyclic nitrogen heterocycles by way of two intramolecular cyclizations. The pathway depends upon the nature of the β-substituent. β-Aryl substituents underwent alkylation through the 2-position of the hetero ring while β-amino- and β-thio groups cyclized to the 5-position.

Weigele and co-workers reported some years ago that primary amines reacted with 2-methoxy-3-(2H)-furanones to produce 2-hydroxy-3(2H)-pyrrolone derivatives.[1] In view of recent interest in nitrogen heterocycle synthesis by generation of an electrophilic center next to a nitrogen atom from aminal-like precursors,[2] it seemed to us that appropriately N-substituted 2-hydroxy (or 2-alkoxy) 3-(2H)-pyrrolones might be enticed to undergo intramolecular cyclization in the presence of acid catalysts. Thus a series of N-(β-arylethyl) derivatives of 2,4-diphenyl-2-hydroxypyrrolone were prepared and so treated in refluxing solvent. It was observed that the highest yields of cyclization products were obtained when the aryl group was electron-rich and particularly when an electron-releasing meta substituent (para to the position undergoing alkylation) was present. The results are summarized in Scheme I and Table I.

Scheme I

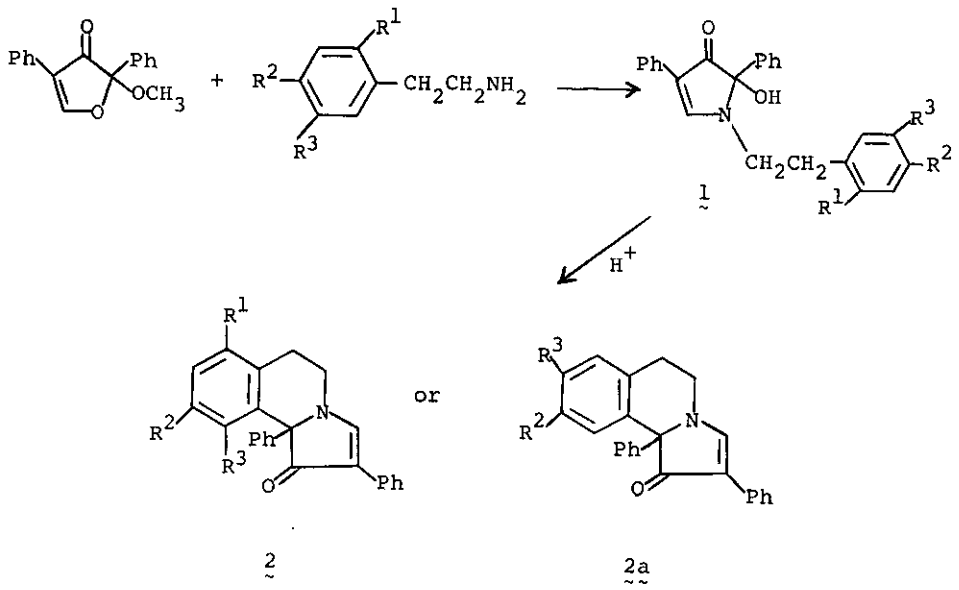
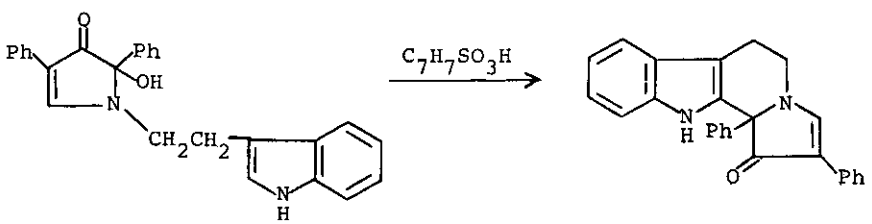


Table I[3]

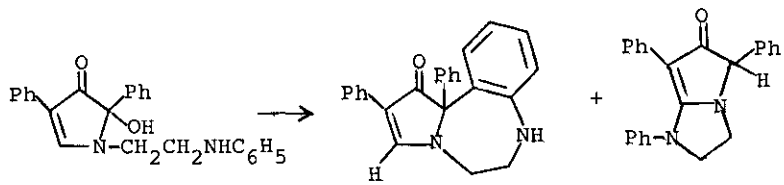
Pyrrolone 1	Catalyst (equiv.)	Solvent	Pyrroloquinoline	Mp, °C	Yield, %
$R^1=R^2=R^3=H$	$C_7H_7SO_3H$ (1.20)	C_6H_6	2, $R^1=R^2=R^3=H$	175-177	17
$R^1=R^3=H$, $R^2=OCH_3$	$AlCl_3$ (1.40)	CH_2Cl_2	2, $R^1=R^3=H$, $R^2=OCH_3$	169-170	33
$R^1=R^2=H$, $R^3=OCH_3$	HCO_2H (-)	HCO_2H[a]	2a, $R^2=H$, $R^3=OCH_3$	225-227	86
$R^1=H$, $R^2=R^3=OCH_3$	$C_7H_7SO_3H$ (0.35)	C_6H_6	2a, $R^2=R^3=OCH_3$	216-217	99
$R^2=H$, $R^1=R^3=OCH_3$	$C_7H_7SO_3H$ (0.62)	C_6H_6	2, $R^2=H$, $R^1=R^3=OCH_3$	216-218	26

[a]Reaction temperature was 25°C.

When tryptamine was used to prepare the pyrrolone, acid treatment resulted in cyclization in the α-position of the indole ring to produce a β-carboline derivative in 86% yield:

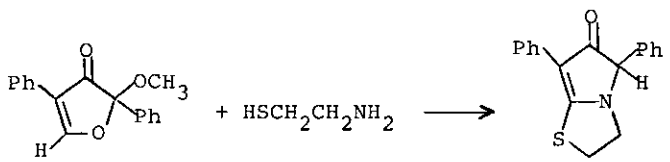


When the aromatic ring was connected to the side chain through a nitrogen atom, a most interesting result was obtained. Ring alkylation to give a benzodiazepine derivative 3 was still observed, but, depending upon the catalyst, this product was accompanied by various amounts of an isomer that proved to be compound 4:



	3	4
$C_7H_7SO_3H$	74%	14%
$AlCl_3$	82%	5%

A product of similar structure was obtained exclusively when N-methylethylenediamine was used. Finally, this kind of cyclized product (5) was obtained directly from the reaction of the 2-methoxy-3(2H)-furanone with β-mercaptoethylamine.



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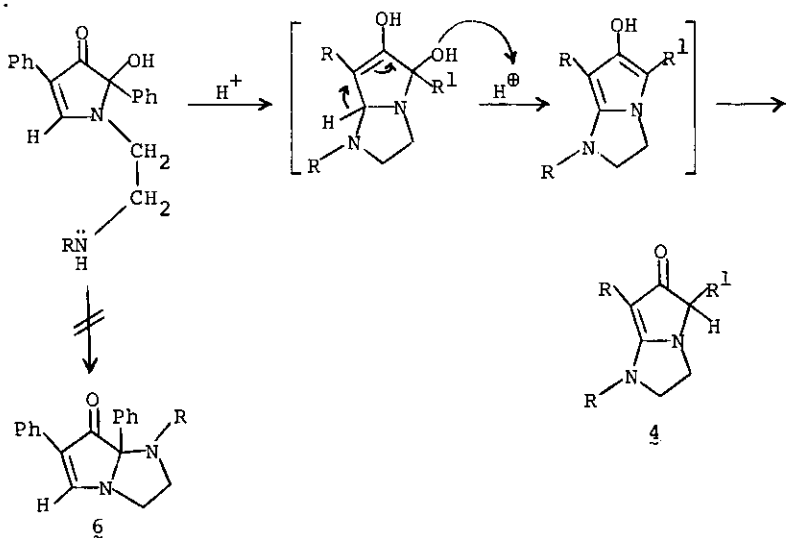
It is particularly striking that none of the 2-alkylation product of isomeric structure 6 was obtained from any of these reactions. The route to compounds of type 4 and 5 may be envisioned as follows:



6

4

The structural differentation of compounds of type 4 and 5 from 6 is based upon the disappearance from their nmr spectra of the sharp singlet at δ 7.7-8.4 common to all compounds in this pyrrolone series with a proton at C5, and the appearance of a sharp singlet at δ 4.4-4.6, which is compatible with the deshielded environment at C2.

Studies are underway to examine the scope of these reactions, particularly the effect of substituents in the pyrrolone on the 5,5-cyclization.

REFERENCES

1. M. Weigele, J. P. Tengi, S. DeBernardo, R. Czajkowski, and W. Leimgruber, J. Org. Chem., 1976, 41, 388 and preceding papers.
2. H. Kohn and Z.-K. Liao, J. Org. Chem., 1982, 47, 2787; B. E. Maryanoff, D. F. McCornsey, and B. A. Dukl-Ensweiler, J. Org. Chem., 1983, 48, 5062; S. Kano, Y. Yuasa, T. Yokomatsu, and S. Shibiya, J. Org. Chem., 1983, 48, 3835; G. A. Kraus and S. Yue, J. Org. Chem., 1983, 48, 2936.
3. Satisfactory analyses were obtained for all new compounds.

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