

ACID-CATALYZED CYCLIZATION OF 2-HYDROXY-3-PYRROLONE DERIVATIVES.

2-METHOXY-3(2H)-FURANONES AS PRECURSORS OF POLYCYCLIC NITROGEN HETEROCYCLES

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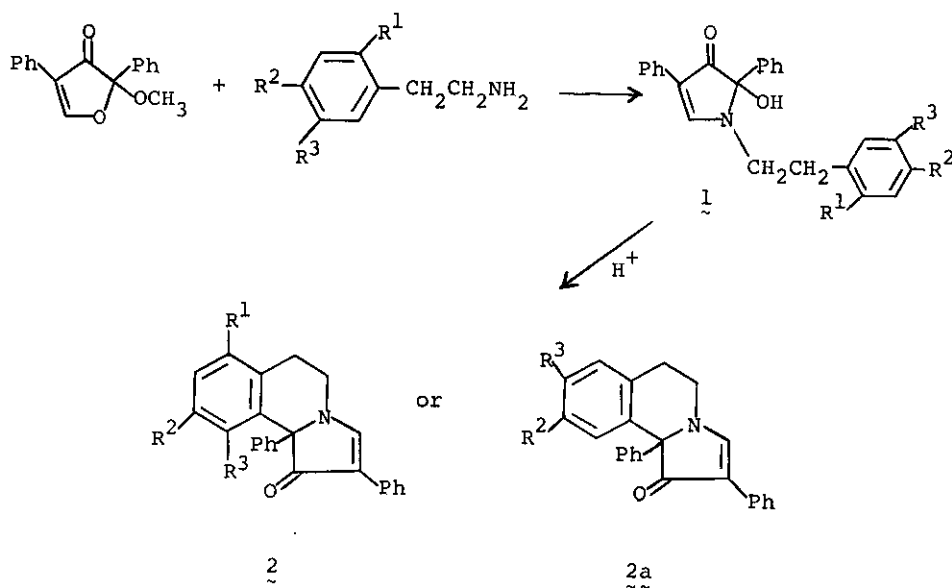
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Abstract - Condensation of 2-methoxy-3(2H)-furanones with β -substituted ethylamines followed by treatment with various acid catalysts gives rise to polycyclic nitrogen heterocycles by way of two intramolecular cyclizations. The pathway depends upon 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.

Weigle 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.

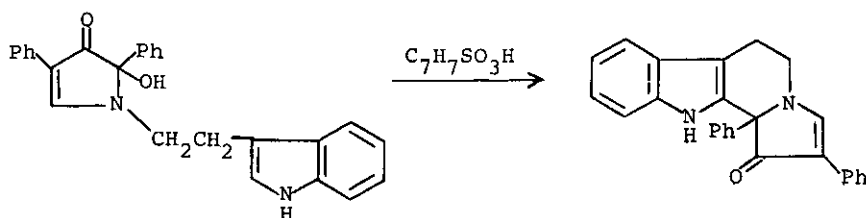
Scheme I

Table I³

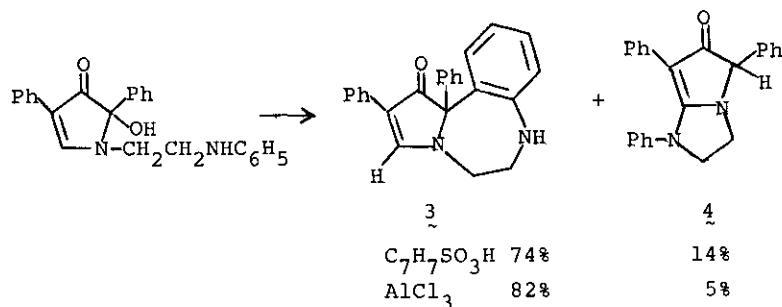
(No. of					
Pyrrolone 1	Catalyst (equiv.)	Solvent	Pyrroloquinoline	Mp, °C	Yield, %
R ¹ =R ² =R ³ =H	C ₇ H ₇ SO ₃ H (1.20)	C ₆ H ₆	2, R ¹ =R ² =R ³ =H	175-177	17
R ¹ =R ³ =H, R ² =OCH ₃	AlCl ₃ (1.40)	CH ₂ Cl ₂	2, R ¹ =R ³ =H, R ² =OCH ₃	169-170	33
R ¹ =R ² =H, R ³ =OCH ₃	HCO ₂ H (-)	HCO ₂ H ^a	2a, R ² =H, R ³ =OCH ₃	225-227	86
R ¹ =H, R ² =R ³ =OCH ₃	C ₇ H ₇ SO ₃ H (0.35)	C ₆ H ₆	2a, R ² =R ³ =OCH ₃	216-217	99
R ² =H, R ¹ =R ³ =OCH ₃	C ₇ H ₇ SO ₃ H (0.62)	C ₆ H ₆	2, R ² =H, R ¹ =R ³ =OCH ₃	216-218	26

^aReaction temperature was 25°C.

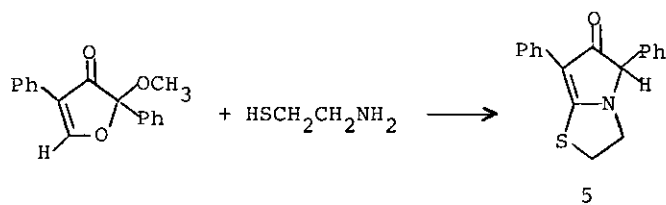
When tryptamine was used to prepare the pyrrolone, acid treatment resulted in cyclization in the α-position of the indole ring to produce a β-carboline derivative in 86% yield:



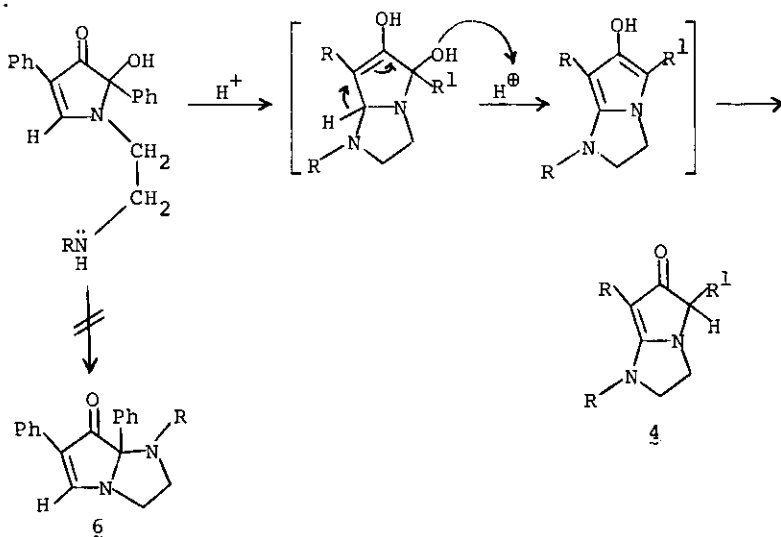
When the aromatic ring was connected to the side chain through a nitrogen atom, a most interesting result was obtained. Ring alkylation to give a benzodiazepine derivative **3** was still observed, but, depending upon the catalyst, this product was accompanied by various amounts of an isomer that proved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



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.



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:



The structural differentiation 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. Weigle, J. P. Teng, 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. Duki-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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