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AN UNUSUAL REARRANGEMENT DURING PYRIDINE SYNTHESIS.

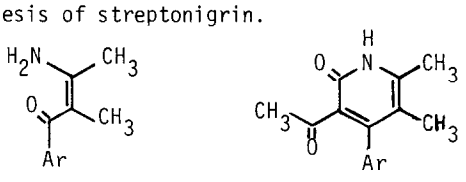
ANOMALOUS CONDENSATION OF A β-KETO ENAMINE WITH A TETRONIC ACID.

Andrew S. Kende*, Joachim E. Veits, Dennis P. Lorah and Frank H. Ebetino

Department of Chemistry, University of Rochester, Rochester, New York 14627

The condensation of β-keto enamine 1 with 5-methyltetronic acid takes an anomalous course. Single crystal X-ray analysis and chemical evidence establish the rearranged pyridine structure 15 for this condensation product.

We have recently described a total synthesis of the antitumor quinone streptonigrin.[1] A key step in this synthesis was the thermal condensation of the known[2] β-keto enamine 1 with methyl acetoacetate to give the acylpyridone 2 in high yield. The structure of 2 is firmly established by its elaboration to the quinoline diester 3 independently synthesized by Boger and Panek,[3] and also by its ultimate conversion to the aminoquinone 4, identical with a sample prepared by Weinreb et al[4] during their pioneering total synthesis of streptonigrin.



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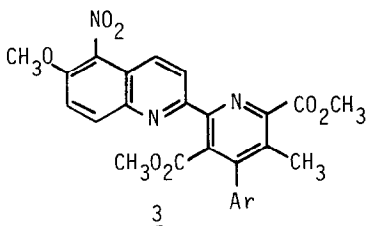

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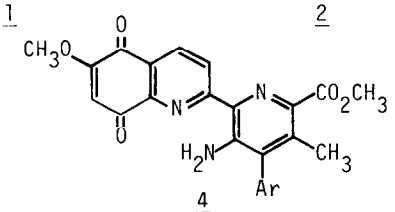

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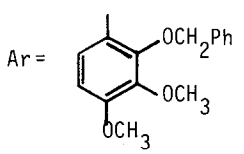
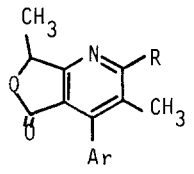


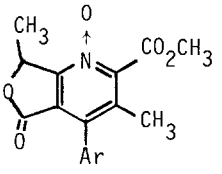
In an attempt toward a more convergent synthesis of streptonigrin we explored the direct condensation between β-keto enamine 1 and 5-methyltetronic acid.[5] Melting of these two reactants first at 140°C, then holding the melt at 120°C for 3 hrs led in 54% yield to a crystalline $C_{25}H_{25}NO_5$ γ-lactone, mp 108.5-110°C [IR($CHCl_3$): 1760 cm^{-1}; ^{1}H-NMR (400 MHz, DMSO-d_6): δ 1.48(3H,d), 2.03(3H,s), 2.54(3H,s), 3.82(3H,s), 3.88(3H,s), 4.71 (1H,m), 4.91(1H,m), 5.48(1H,d), 6.95(4H,m), 7.16(3H,m)] assigned the 4-arylpyridine structure 5. Oxidation of 5 (SeO_2, HOAc, 100°C, 18 hrs) gave aldehyde 6 (82%) which on further oxidation ($NaClO_2$, NH_2SO_3H, NaOAc, rt, 2 hrs)[6] afforded 80% of lactonic acid 7, mp 251-252°C (dec). The methyl ester 8 (K_2CO_3, CH_3I, Me_2CO, reflux, 3 hrs, 67%) was converted to the corresponding N-oxide 9 (m-CPBA, $CHCl_3$, rt, dark, 48 hrs, 75%) which was submitted to rearrangement [$(CF_3CO)_2O$, pyridine, rt, dark, 23 hrs, 50%] producing the methylene

lactone 10, readily hydrolyzed by base to the pseudo acid 11, mp 160°C(dec) [IR($CHCl_3$): 1775, 1740; 85%].

Friedländer condensation of 11 with the p-toluidine imine 12 of 3-(p-methoxy)-benzyloxy-6-aminobenzaldehyde under the modified Borsche conditions previously described[1] gave on reesterification with CH_2N_2 66% of a quinoline diester (13) which was selectively deblocked (CF_3CO_2H, 0°C, 1 hr) to a quinolinol assigned structure 14, mp 194-195°C.



5 R=CH_3
6 R=CHO
7 R=CO_2H
8 R=CO_2CH_3



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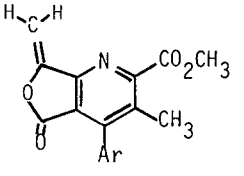

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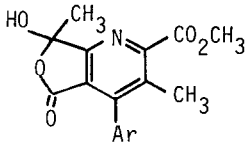

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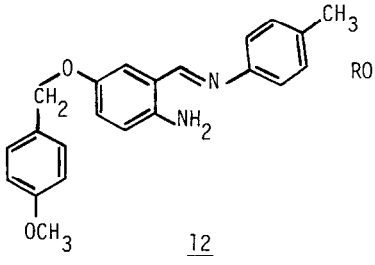

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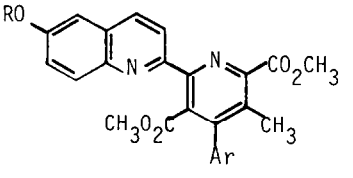


13 R = p-$CH_3OC_6H_4CH_2$
14 R=H

Nitration (CH_3NO_2, 90% HNO_3, 0°C for 20 min, then rt, 30 min) and O-methylation (CH_2N_2, or CH_3I/K_2CO_3 in acetone) gave a 5-nitro-6-methoxyquinoline diester, mp 187-189°C [^{1}H-NMR (400 MHz, $CDCl_3$): δ 2.26(3H,s), 3.87(3H,s), 3.95(3H,s), 3.96(3H,s), 3.99(3H,s), 4.08(3H,s), 4.70-5.10(2H,m), 6.84(1H,d,J=9 Hz), 6.96(1H,d,J=9 Hz), 7.03-7.14(5H,m), 7.57 (1H,d,J=10 Hz), 8.10(1H,d,J=10 Hz), 8.19(1H,d,J=10 Hz), 8.36(1H,d,J=10 Hz;48%)]. However, the properties of this diester differed dramatically from authentic 3, prepared by us and by Boger and Panek as described previously. In particular, the 400 MHz ^{1}H-NMR of authentic 3 taken under the same conditions as the preceding spectrum showed greatly different signals [δ 2.26(3H,s), 3.62(3H,s), 3.90(3H,s), 3.93(3H,s), 4.02(3H,s), 4.06(3H,s), 4.93(2H, AB quartet, J=11 Hz), 6.72(1H,d,J=9 Hz), 6.86(1H,d,J=9 Hz), 6.95-7.20(5H,m), 7.48(1H,d,J=10 Hz), 8.05(1H,d,J=10 Hz), 8.15(1H,d,J=10 Hz), 8.64(1H,d,J=10 Hz).

To resolve this startling discrepancy, we considered that the regiochemistry of pyridine ring formation from β-keto enamine 1 and the tetronic acid may be fundamentally different from that obtained in the original synthesis involving 1 and methyl acetoace-

tate. In authentic 3 the $PhCH_2O$ methylene protons showed clear nonequivalence at 400 MHz (AB quartet centered at δ 4.93), whereas in the tetronic acid-derived isomer the $PhCH_2O$ methylenes were observed as an unresolved broad multiplet at δ 4.70-5.10. Since this nonequivalence probably arises from hindered rotation[7] at the aryl-pyridine bond, we concluded that the aryl substituent in the tetronic series was in a less hindered environment. In addition, all of the quinoline diesters in the "authentic" series exhibited a unique $COOCH_3$ methyl signal at about δ 3.7, whereas in the tetronic series the most upfield OCH_3 signal was around δ 3.9. Our hypothesis was that all of our structures 5 through 14 were incorrect, and that the tetronic series comprised structures in which the aryl group was at C-2 rather than C-4 of the newly created pyridine ring. This hypothesis was confirmed by single crystal X-ray structure determination of the $C_{25}H_{25}NO_5$ γ-lactone derived from β-keto enamine 1 and 5-methyltetronic acid (Fig. 1). Based on this rearranged structure (15), the pseudoacid "11" must be reformulated as 16, and the quinolines "13", "14" and the new methoxynitroquinoline diester must be 17, 18, and 19 respectively.

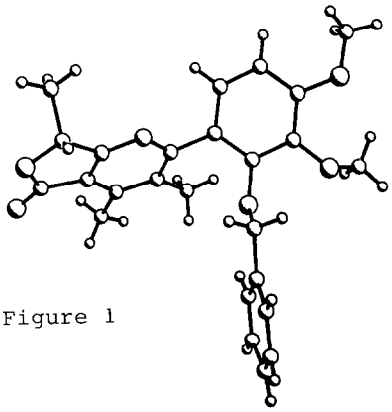
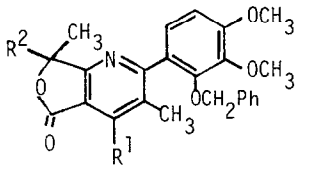
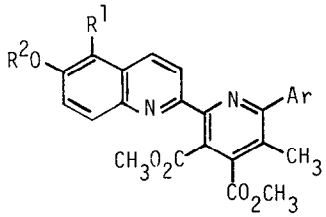


Figure 1



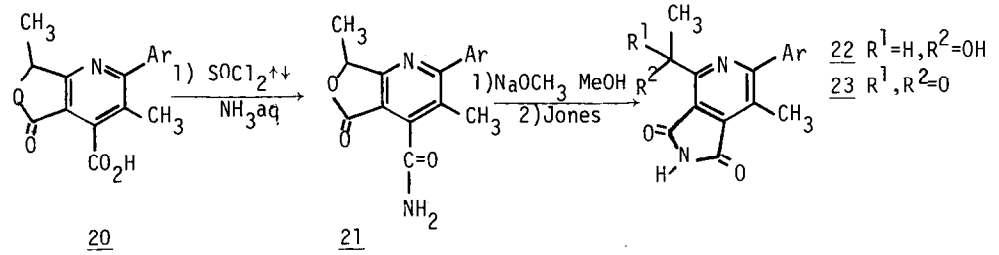
15 $R^1=CH_3, R^2=H$
16 $R^1=CO_2CH_3, R^2=OH$
20 $R^1=CO_2H, R^2=H$



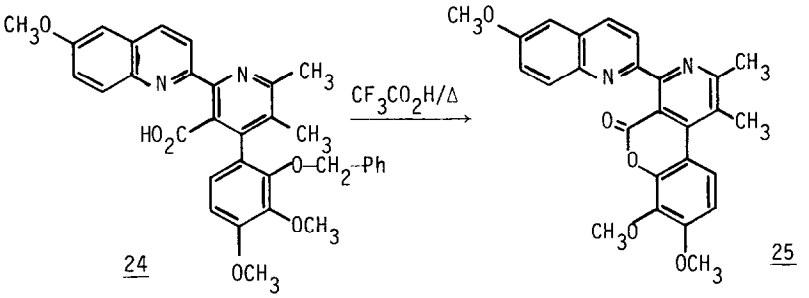
17 $R^1=H, R^2=p\text{-}CH_3OC_6H_4CH_2$
18 $R^1=R^2=H$
19 $R^1=NO_2, R^2=CH_3$

Chemical evidence for the correct structure 20 of the lactonic acid "7" was its conversion to amide 21 [mp 103-105°C; IR($CHCl_3$): 3500, 3390, 1760, 1680 cm^{-1}; 88%], the hydroxy imide 22 [mp 159-160°C; IR($CHCl_3$): 3420, 1770, 1725, 1595, 1095 cm^{-1}; ^{1}H-NMR (400 MHz,$CDCl_3$; partial) δ 1.54(3H,d,J=7 Hz), 5.34(1H,q); 54%] and ketoimide 23 [mp 153-155°C; IR($CHCl_3$): 3420, 1780, 1740, 1725, 1595, 1095 cm^{-1}; ^{1}H-NMR (400 MHz, $CDCl_3$, partial): δ 2.54(3H,s), 2.66(3H,s), 49%] by the sequence shown. Also consistent with the regiochemistry for the authentic series is the lactonization of methoxy acid 24 to 25 in 72% yield on brief warming in CF_3COOH [25: mp 252-253°C; IR ($CHCl_3$): 1735 cm^{-1}; ^{1}H-NMR (400 MHz,$CDCl_3$): δ 2.80(6H,s), 3.97(6H,s), 4.00(3H,s), 6.94(1H,d,J=9 Hz), 7.14(1H,d,J=3 Hz), 7.36(1H,dd,J=3, 9 Hz), 7.60(1H,d,J=9 Hz), 7.94(1H,d,J=9 Hz), 8.02 (1H,d,J=10 Hz), 8.17(1H,d,J=10 Hz). The shift of pyridine CH_3 to δ 2.8 from the usual δ 2.0-2.3 results from the enforced planarity of the diaryl lactone system.[11] In contrast,

none of the intermediates from the tetronic series could be induced to lactonize under similar conditions.



20 21



24 25

Formation of a 2-arylpyridine by condensation of 1 with a tetronic acid, but 4-arylpyridines with other acceptors (methyl acetoacetate, ethyl cyanoacetate,[2] diethyl malonate[8]) must involve a transamination in situ. Possible mechanisms are under study.[9,10]

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