Tetrahedron Letters No. 48, pp 4775 - 4778. 0040-4039/78/1122-4775$02.00/0

TOTAL SYNTHESIS OF THE STREPTONIGRIN QUINONE CARBON FRAMEWORK

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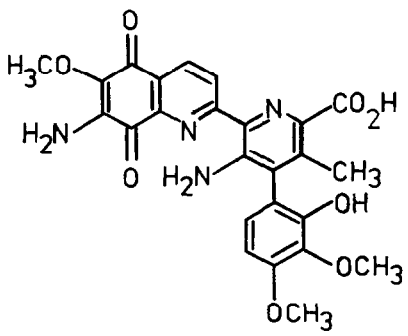
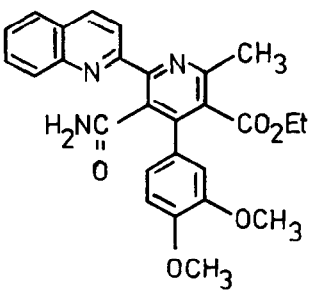
The antitumor antibiotic streptonigrin was shown in 1963 by Rao, Biemann and Woodward to possess the tetracyclic aminoquinone structure I.[1] Since that time streptonigrin has been the focus of vigorous synthetic activity, but to date no total synthesis of this challenging polyfunctional molecule has been published.[2] Of the several dozen papers in this area, those of note include the construction of the model quinoline II by Kametani,[3] the complete C-D ring by Cheng,[4] and the tricyclic quinolinequinone III by Hibino and Weinreb.[5]



I



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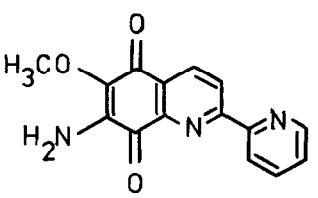
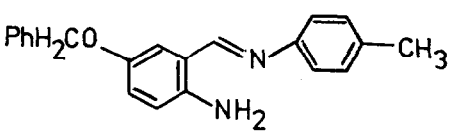


III

We wish to report the first synthesis of a tetracyclic aminoquinone containing the entire carbon framework of the streptonigrin molecule. Our approach, which is both modular and convergent, makes use of selective functionalization procedures which are compatible with the electron-rich trioxyphenyl D-ring. The basic strategy employs the modified Friedländer condensation of the aminoimine IV with the substituted acetylpyridine V.



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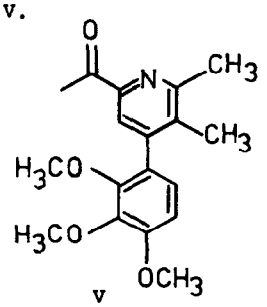
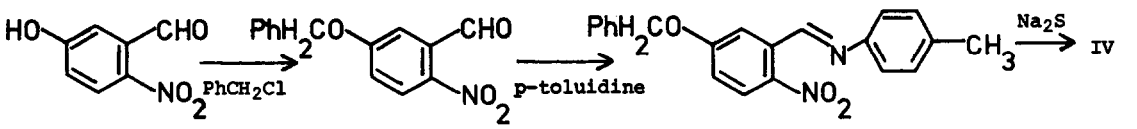


V

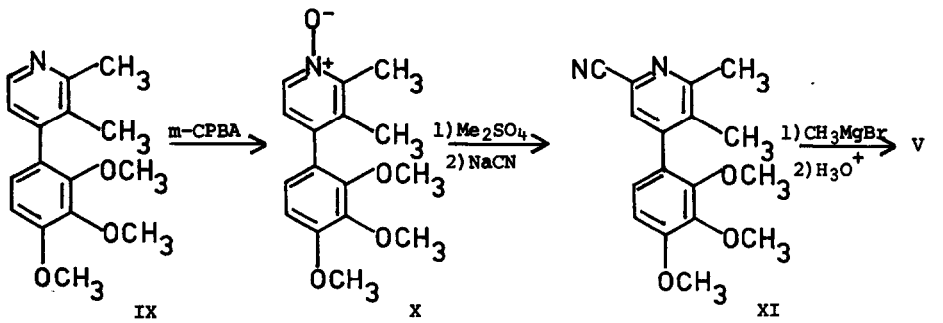
Precursor IV to the A-ring was prepared in three steps and 54% overall yield from the known 6-nitro-3-hydroxybenzaldehyde (VI).[6] O-Benzylation with benzyl chloride (K_2CO_3, KI, DMF, r.t., 24 hrs) gave the benzyl ether VII, mp 74-75°, which was condensed with p-toluidine (C_6H_6,

reflux, 15 hrs) to give the nitroimine VIII which was subsequently reduced with sodium sulfide (MeOH, reflux) to yield IV, mp 98°.



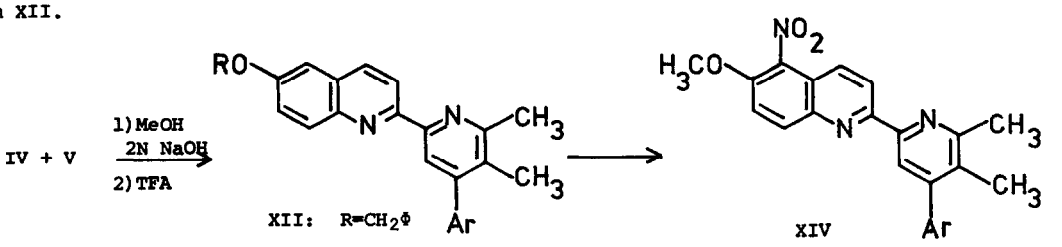
VI VII VIII

The C-D bicyclic precursor V is in turn easily accessible from the known pyridine IX[7] by the methoxypyridinium variant of the Reissert-Kaufmann reaction.[8] Thus the conversion of pyridine IX to the N-oxide X (m-CPBA, $CHCl_3$, r.t., 12 hrs), mp 144-145°, followed by methylation (Me_2SO_4, 100°) and subsequent reaction with NaCN in DMF gave the Reissert-Kaufmann nitrile XI, mp 111-113°. Reaction of this nitrile with CH_3MgBr followed by hydrolysis produced the acetylpyridine V, mp 120-121°, nmr: δ2.16, 3H, s; 2.64, 3H, s; 2.74, 3H, s; 3.62, 3H, s; 3.94, 6H, s; 6.82, 2H, s; 7.80, 1H, s, in 24% overall yield from IX.

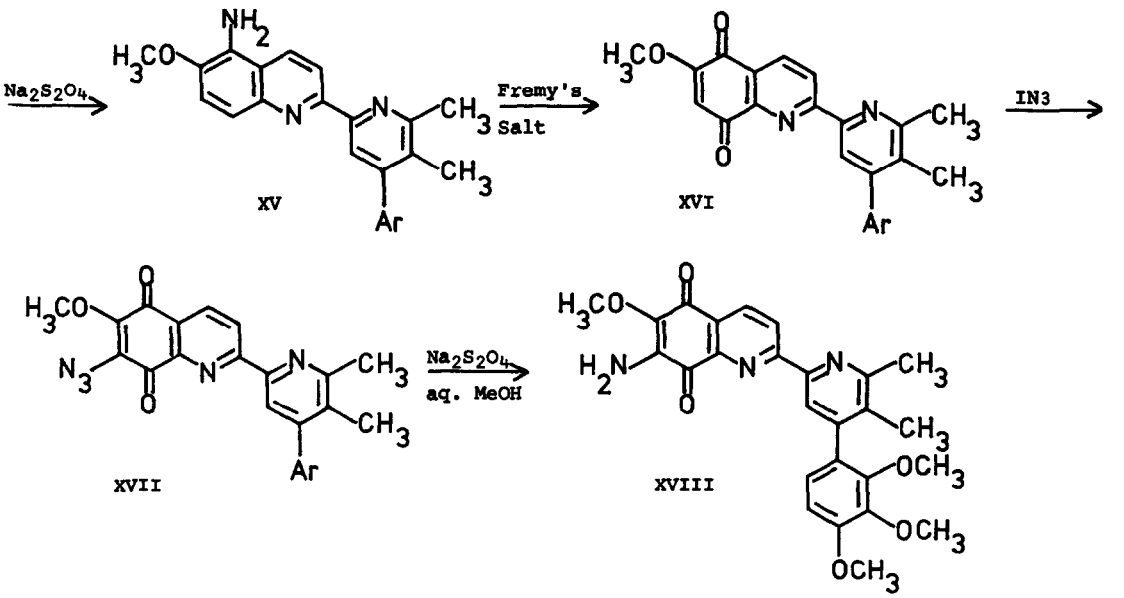


IX X XI

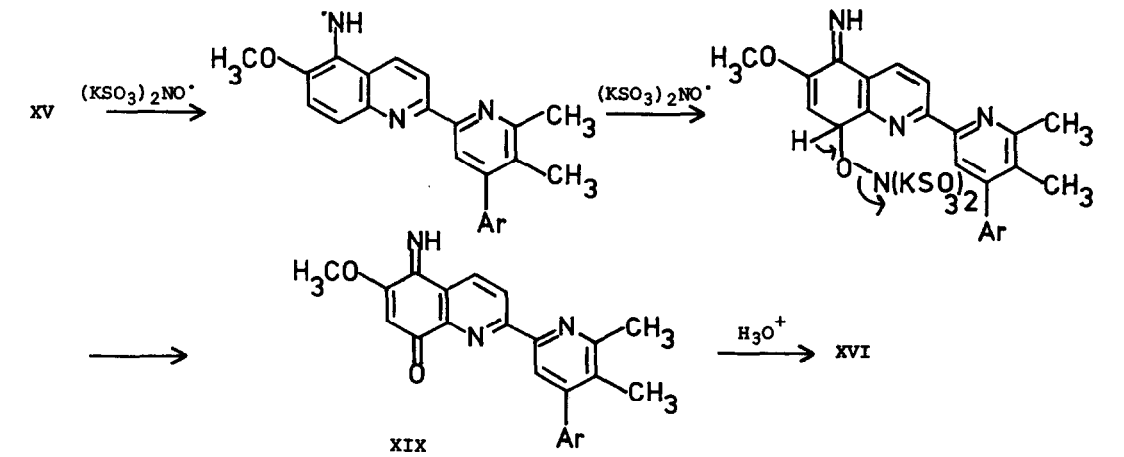
The modified Friedländer condensation between imine IV and acetylpyridine V proceeded in 72% yield (2N NaOH, MeOH, reflux, 24 hrs) to give the crystalline tetracyclic product XII, mp 188-190°, nmr δ2.12, 3H, s; 2.64, 3H, s; 3.60, 3H, s; 3.84, 3H, s; 3.88, 3H, s; 5.08, 2H, s; 6.74, 2H, q; 7.00-7.10, 2H, m; 7.20-7.44, 5H, m; 7.94, 2H, t; 8.20, 1H, s; 8.48, 1H, d. Debenzylation (CF_3CO_2H, reflux, 4 hrs) to phenol XIII, mp 255-256°, followed by selective nitration in the phenolic ring (70% HNO_3 in HOAc, r.t., 45 min) and direct O-methylation (Me_2SO_4, K_2CO_3, acetone, reflux, 24 hrs) gave the crystalline nitroquinoline XIV, mp 205-207°, in 32% yield from XII.



XII: R=$CH_2\Phi$
XIII: R=H
XIV



Dithionite reduction of XIV in aqueous THF gave the amine XV, mp 224-225°, in 75% yield. This could be oxidized with Fremy's salt (.167 M Na_2HPO_4, aq. acetone, r.t.) in 91% yield to the quinone XVI, mp 264-265°, nmr: δ2.20, 3H, s; 2.68, 3H, s; 3.66, 3H, s; 3.96, 9H, s; 6.34, 1H, s; 6.84, 2H, q; 8.40, 1H, s; 8.50, 1H, d; 8.90, 1H, d. In several Fremy's salt oxidations there was isolated a new substance to which we assign the quinone imine structure XIX. This substance showed ir peaks at 3500, 1690 and 1660 cm^{-1}, uv absorption maxima at 261 nm (ε 34,000) and 309 nm (ε 26,900), and nmr signals at δ 2.22, 3H, s; 2.76, 3H, s; 3.72, 3H, s; 4.04, 9H, s; 6.22, 1H, s; 6.96, 2H, q; 8.56, 1H, s; 9.02, 2H, s. The molecular ion at m/e = 459 in the mass spectrum and the observed analytical values (C, 67.73; N, 9.34; H, 5.48) were in precise accord with the $C_{26}H_{25}O_5N_3$ formulation XIX. Compound XIX could be quantitatively converted to the quinone XVI under mild conditions (THF, trace con. HCl, r.t., 24 hrs), and it probably is an intermediate in these para oxidations,[9] as shown below.



Selective introduction of the amino group on the quinone A-ring proved to be difficult since XVI was relatively inert to nucleophilic attack by azide ion, and efforts to chlorinate or brominate the A-ring led to extensive D-ring halogenation. It was eventually found that reaction of XVI with iodine azide (ICl, NaN_3)[10] in DMF gave the azidoquinone XVII, mp 130-131°. Reduction with sodium dithionite converted XVII to the target aminoquinone XVIII. This compound, possessing the full streptonigrin carbon skeleton but differing in substituents on the C and D rings, was a bright purple substance having λ_{max} 260, 317, 484 (ε_{max} 49,000; 45,000; 2,200), nmr: δ2.16, 3H, s; 2.66, 3H, s; 3.62, 3H, s; 3.94, 6H, s; 4.08, 3H, s; 5.24, 2H, broad s, 6.88, 2H, q; 8.36, 1H, s; 8.44, 1H, d; 8.88, 1H, d, and a high resolution mass spectrum showing a molecular ion at m/e 475.1725 (calcd. 475.1743).[11] Modifications of this synthesis leading to streptonigrin itself are in progress.

There has been some speculation as to the relative importance of the aminoquinone moiety of streptonigrin for its antineoplastic activity.[12] It is thus of great interest that unlike streptonigrin, our synthetic aminoquinone showed no activity against P 388 leukemia in mice, implying an essential role for the C-D substituents in the natural antibiotic.

Acknowledgment: Partial support of this work by grant CA-18846 awarded by the National Cancer Institute, USPHS, and by the Hoffmann-La Roche Co., is gratefully acknowledged.

References and Notes:

1. K. V. Rao, K. Biemann and R. B.WWoodward, J. Am. Chem. Soc., 85, 2532 (1963).
2. For an excellent review of efforts toward streptonigrin synthesis see S. Hibino, Heterocycles, 6, 1485 (1977).
3. T. Kametani, K. Ogasawara, A. Koguka and K. Nyu, J. Pharm. Soc. Japan, 87, 1189 (1967).
4. T. K. Liao, P. J. Wittek and C. C. Cheng, J. Heterocyclic Chem., 13, 1283 (1976).
5. S. Hibino and S. M. Weinreb, J. Org. Chem., 42, 232 (1977); cf. D. Kim and S. M. Weinreb, ibid., 43, 125 (1978).
6. L. S. Hornig, J. Am. Chem. Soc., 74, 4570 (1952).
7. T. Kametani, K. Ogasawara, M. Shio and A. Kuzuka, J. Pharm. Soc. Japan, 86, 809 (1966).
8. E. Ochiai and I. Nakayama, J. Pharm. Soc. Japan, 65, 7 (1945).
9. Cf. L. Horner and K. Sturm, Chem. Ber., 88, 329 (1955).
10. F. W. Fowler, A. Hassner and C. A. Levy, J. Am. Chem. Soc., 89, 2077 (1967).
11. We are indebted to Drs. R. Hargreaves and J. S. Webb, Lederle Laboratories (American Cyanamid Co.) for the high resolution mass spectra, and to Dr. F. Durr (Lederle) for the screening results. All new compounds, including XVIII, gave C, H and N analyses as well as spectroscopic data in accord with the structures depicted.
12. K. V. Rao, Cancer Chemother. Rep., 4, 11 (1974); J. W. Lown and S. K. Sim, Canad. J. Chem., 54, 2563 (1976); J. W. Lown and S. K. Sim, Canad. J. Biochem., 54, 446 (1976).

(Received in USA 26 September 1978)