Tetrahedron Letters No.17. pp. 1637-1639, 1967. Pergamon Press Ltd. Printed in Great Britain.

A TWO-STEP SYNTHESIS OF THE PYRONO-QUINONOID SYSTEM

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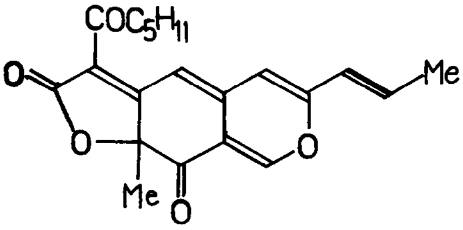
(Received 15 February 1967)

During our synthetic study of monascorubrin (I),[1] which contains the extended pyrono-quinonoid system, there was found a simple method to make the new pyrono-quinonoid nucleus.[2] In this paper, a two-step synthesis of such a nucleus from a γ-pyrone will be reported.

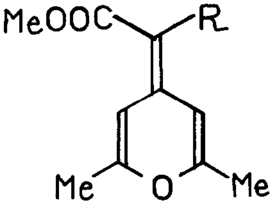
Generally, the carbonyl group of a γ-pyrone has low activity toward the common ketone reagents. It was found, however, that a condensation reaction took place between 2,6-dimethyl-γ-pyrone and methyl cyanoacetate or malononitrile in excess amounts of acetic anhydride to yield the extended γ-pyrone (II).[3] Attempted acid hydrolysis of II under vigorous conditions gave only an amide (III) (m.p. 180 - 181°C; m/e 223 (M^+); ν_{max}^{KBr} 3400, 3200, 1690, 1665, 1635, 1615, 1590 and 1520 cm^{-1}), in which both amide and carbomethoxy groups resisted further hydrolysis. If we consider cyanoacetic acid in excess acetic anhydride, the following equilibrium will be established.

$$CN\text{-}CH_2COOH + Ac_2O \rightleftharpoons CN\text{-}CH_2COOAc + AcOH$$

Under such conditions, the mixed anhydride species could react with the γ-pyrone. Thus, 2,6-dimethyl-γ-pyrone[4] in a large amount of acetic anhydride

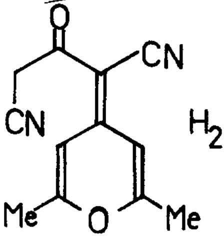


(I)

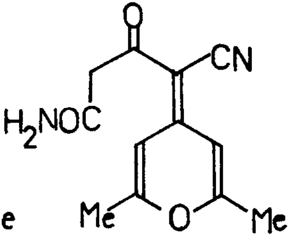


(II) R = CN
(III) R = $CONH_2$

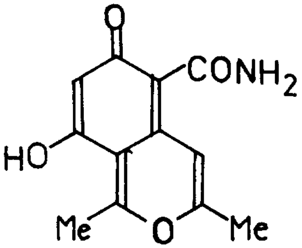
was refluxed with cyanoacetic acid for one hour to give the condensation product (IV) (m.p. 172 - 173°C) in 30% yield, whose structure was supported by the spectral data (m/e 214 (M^+), 174 and 146; ν_{max}^{KBr} 2220, 1670, 1627, 1570, 930 and 870 cm^{-1}; λ_{max}^{MeOH} 391, 368 sh, 260 and 228 mμ (log ε 4.47, 4.45, 3.86 and 3.86, respectively); NMR signals at 2.40 (6H, singlet), 3.88 (2H, singlet), 6.71 (1H, singlet) and 8.30 ppm (1H, singlet) (in $CDCl_3$)). When IV was treated with conc. sulfuric acid an amide (V) (m.p. 216 - 218°C; m/e 232 (M^+), 215 and 174) was produced, but when heated with polyphosphoric acid it afforded the cyclization product (VI) (m.p. 245 - 250°C (dec.); m/e 233 (M^+), 218 and 205; ν_{max}^{KBr} 3090 br, 2960, 1665, 1635 - 1590 br, 1505 br and 925 cm^{-1}; λ_{max}^{MeOH} 428 and 258 mμ (log ε 4.24 and 3.99, respectively); NMR signals at 2.90 (6H, near singlet) ~~and~~ 8.40 ppm (2H, near singlet) (in CF_3COOH)) in quantitative yield.



(IV)



(V)

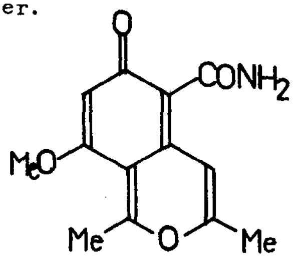


(VI)

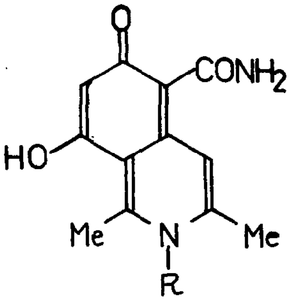
Treatment of VI with methanolic conc. sulfuric acid gave a methyl ether (VII) (m.p. 270 - 273°C (dec.); m/e 247 (M^+); λ_{max}^{MeOH} 430 and 260 mμ (log ε 4.44 and 4.09, respectively)). The most typical property of VI is shown below: the oxygen atom of VI was easily substituted by a primary amine or conc. ammonium hydroxide at room temp. to give VIII (m.p. 278 - 280°C; m/e 246 (M^+); λ_{max}^{MeOH} 398 and 260 mμ (log ε 4.16 and 3.93, respectively)) and IX (m.p. 280 - 283°C; m/e 232 (M^+); λ_{max}^{MeOH} 390 and 263 mμ (log ε 4.10 and 3.95, respectively)), respectively.

All m.ps are uncorrected. Satisfactory analyses were obtained for all new compounds described herein. UV spectra were recorded in MeOH on a Perkin Elmer 202 Spectrophotometer, mass spectra on a Hitachi RMU-6C Spectrometer (70 eV) and NMR spectra with TMS as an internal standard on a Varian

A-60 Spectrometer.



(VII)



(VIII) R = Me

(IX) R = H

REFERENCES

1. S. Kumasaki et al., Tetrahedron **18**, 1171 (1962); B. C. Fielding et al., Tetrahedron Letters **5**, 24 (1960).
2. Recently, the first synthesis of the pyrono-quinonoid system by another method has been reported by W. B. Whalley et al. (Chem. Comm. 620 (1966)).
3. Woods, J. Am. Chem. Soc., **80**, 1440 (1958); M. Ohta and H. Kato, Bull. Chem. Soc. Japan, **32**, 707 (1959).
4. We have found an easy method to make 2-substituted γ-pyrones.