# The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 14 [1]. A Facile Entry Into The Acronycine Ring System



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6-Demethoxyacronycine (**9**), containing the acronycine nucleus, has been readily synthesized in two steps *via* the reaction of *N*-methylisatoic anhydride with the enolate derived from 2,6,7,8-tetrahydro-2,2-dimethyl-5*H*-1-benzopyran-5-one (**8**) followed by oxidation with DDQ.

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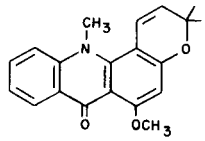
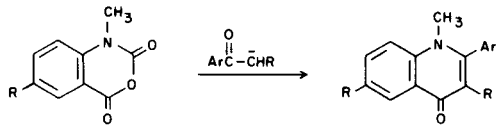
Acronycine (**1**) belongs to a small group of acridone alkaloids which are exclusively found in the Rutaceae family of higher plants [2,3,4]. It is a constituent of *Acronychia baueri* [5,6] and *Vepris amphody*.



**1**

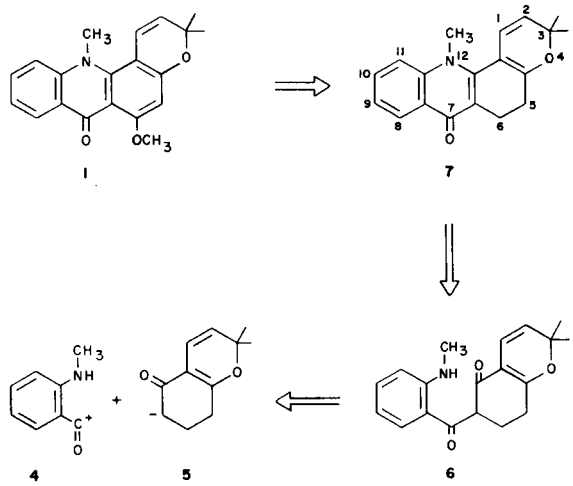
In a recently published report from this laboratory, we described the synthesis of some simple 2-aryl-4-quinolone alkaloids (**3**). The 4-quinolone system was constructed in a single step by reaction of an appropriately substituted isatoic anhydride (**2**) with an aromatic ketone enolate [7].



**2** **3** R = H, $OCH_3$

Since the acronycine nucleus contains a 4-quinolone system fused to a benzopyran heterocycle, it was envisioned that this reaction could be applied to the expeditious construction of the acronycine framework (see retrosynthetic scheme).

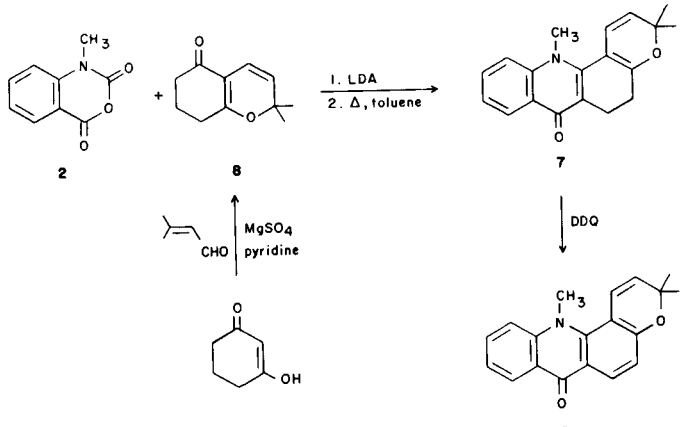
Retrosynthetically, dearomatization and demethoxylation of the C ring of **1** gives **7** which still contains the entire skeleton of the natural product. Disconnection of the 12,12a-bond, which presumably can be formed easily by a dehydrative process, leads to precursor **6**. *N*-Methylisatoic anhydride (**2**, R = H), a synthetic equivalent of **4**, can supply the anthranilic portion of **6** while the enolate derived from 2,6,7,8-tetrahydro-2,2-dimethyl-5*H*-1-benzopyran-5-one (**8**) provides the charged species **5** required to form the eventual 6a,7-bond of **7**.



**1** **7** **4** **5** **6**

Retrosynthetic Scheme

Benzopyran **8** was conveniently prepared from cyclohexane-1,3-dione and 3,3-dimethylacrolein according to the procedure of deGroot and Jansen [8]. The generation of **5** was easily accomplished by the deprotonation of **8** with lithium diisopropylamide at −65°. The reaction of *N*-methylisatoic anhydride (**2**) with two equivalents of **5** [9] proceeded smoothly at −65° with **2** being completely consumed within one hour. The chromatographic polarity and yellow color of the new product suggest that it possesses structure **6** [10]. Heating **6** in toluene for 30 minutes re-



**2** **8** **7** **9**

sults in the formation of a new, more polar, product. Chromatographic separation of the reaction mixture furnished **7** in 56% yield. In addition, the extra equivalent of **8** used in the reaction can be almost entirely recovered for recycling purposes if desired.

Although **7** appeared to be pure by thin layer chromatography, its nmr spectrum exhibited extraneous *N*-methyl (δ 3.73) and C-methyl (δ 1.51) signals (approximately 20% of the mixture). The product resisted purification by chromatography because of the chromatographic superimposition of both materials. Even hplc chromatography only showed a slightly broadened singlet in its chromatogram. Repeated recrystallizations did not enhance the ratio of products in either direction. The remainder of the nmr spectrum, however, corresponded to the proposed structure for **7** (see experimental).

Efforts to elucidate the structure of the contaminant of **7** have so far proved fruitless. An elemental analysis of the mixture containing **7** corresponds to the gross empirical formula of **7**. Capillary gas chromatography was the only successful means of achieving any separation of the products and subsequent mass spectra (chemical ionization) exhibited identical molecular ions for each compound. Furthermore, the electron impact mass spectra for each product furnished virtually identical fragmentation patterns. The infrared spectrum of the mixture showed a weakly absorbing carbonyl frequency at 1689 $cm^{-1}$ which may be attributable to the minor component. In addition, the carbon-13 spectra (deuteriochloroform) exhibited a pronounced signal at δ 202.03 which is characteristic for a ketone. These pieces of data suggest that the contaminant may be an isomer (possibly a double bond isomer).

Crude **7**, as described above was oxidized with DDQ in refluxing toluene. The C ring aromatized readily to give 6-demethoxyacronycine (**9**) in 88% isolated yield. The nmr spectrum of **9** was homogeneous and corresponded to the expected structure. No other impurities were observable. The high yield of the **7** → **9** transformation indicates that the by-product which contaminated **7** was also converted to **9**.

Efforts are presently underway to introduce the required methoxy substituent into the 6-position in order to complete the synthesis of the natural product **1**.

## EXPERIMENTAL

Melting points were determined on a Thomas-Hoover Unimelt apparatus and are uncorrected. The infrared spectra were recorded on Perkin-Elmer Model 257 and 457 spectrophotometers. Absorption frequencies are quoted in reciprocal centimeters. The proton nmr spectra were recorded on EM-360 and Jeol FX-90-Q spectrometers using TMS as an internal reference. Chemical shifts are quoted in parts per million (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet).

Enolate generating reactions were conducted under a nitrogen atmosphere using tetrahydrofuran which was freshly distilled over lithium aluminum hydride. No attempt has been made to optimize the yields of the described reactions.

5,6-Dihydro-3,3,12-trimethyl-7*H*-pyrano[2,3-*c*]acridin-7-one (**7**).

To a solution of 4.0 g (0.04 mole) of diisopropylamine in 150 ml of tetrahydrofuran (at −30°) was added 2.56 g of *n*-butyllithium (0.04 mole, 1.6*M* in hexane). After cooling to −65°, a solution of 7.2 g (0.04 mole) of **8** [8] in 25 ml of tetrahydrofuran was added dropwise and the mixture was stirred at −65° for 45 minutes. To the resulting suspension was added slowly a solution of 3.6 g (0.02 mole) of *N*-methylisatoic anhydride (**2**) in 100 ml of tetrahydrofuran and the mixture was stirred at −65° for 1 hour. The mixture was quenched with saturated ammonium chloride solution and the organic phase was separated. The aqueous layer was extracted twice with methylene chloride and then the organic phases were combined and dried over sodium sulfate. The solvent was removed under reduced pressure and the residue was chromatographed on a Waters Prep 500 apparatus using ethyl acetate to elute the product, 3.2 g (56%) of **7**) (3.3 g of **8** was also isolated). A sample of **7** was crystallized from ether, mp 187-190°; ir (chloroform): 1591 $cm^{-1}$; nmr (deuteriochloroform): δ 8.48 (m, 1H), 7.82-7.18 (m, 4H), 6.85 (d, 1H, J = 12 Hz), 3.83 (s, 3H), 3.03 (t, 2H), 2.54 (t, 2H), 2.06 (s, 3H), 1.97 (s, 3H).

*Anal.* Calcd. for $C_{19}H_{19}NO_2$: C, 77.8; H, 6.5; N, 4.8. Found: C, 77.4; H, 6.5; N, 4.6.

6-Demethoxyacronycine (**9**).

A mixture of 1.0 g of **7** and 0.85 g of DDQ in 100 ml of toluene was refluxed for 1 hour. The solvent was removed under reduced pressure and the residue was chromatographed on a column of silica gel using 10% methanol/chloroform to elute the product, 0.88 g (88%) of **9**. An analytical sample was crystallized from methylene chloride/ethyl acetate, mp 192-193°; ir (chloroform): 1620, 1600, 1590 $cm^{-1}$; nmr (deuteriochloroform): δ 8.40 (dd, 1H), 8.28 (d, 1H, J = 9 Hz), 7.75-7.11 (m, 3H), 6.78 (d, 1H, J = 9 Hz), 6.62 (d, 1H, J = 9.5 Hz), 5.57 (d, 1H, J = 9 Hz), 3.87 (s, 3H), 1.55 (s, 6H); ms: (70 eV) m/e 291 ($M^+$).

*Anal.* Calcd. for $C_{19}H_{17}NO_2$: C, 78.3; H, 5.9; N, 4.8. Found: C, 78.4; H, 6.0; N, 4.7.

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[9] When equimolar amounts of **2** and **5** are used, a significant quantity of unreacted **2** is observed in the reaction mixture. This may be attributed to partial quenching of the enolate **5** with the highly acidic proton of the developing β-diketone **6**.

[10] G. M. Coppola, *J. Heterocyclic Chem.*, **20**, 1217 (1983).