The Chemistry of 2*H*-3,1-Benzoxazine-2,4(1*H*)-dione (Isatoic Anhydride). 12. [1]. Synthesis of Araliopsine and Isoplatydesmine

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N-Methylisatoic anhydride reacts with the lithium enolate derived from 3,3-dimethyloxirane propanoic acid ethyl ester (**7**) to initially produce the acyclic β-ketoester **8**. Under neutral conditions, **8** spontaneously cyclizes to the alkaloid araliopsine (**1a**). In the presence of acid, **8** cyclizes to a mixture of **1a** and its leanear isomer isoplatydesmine (**2a**).

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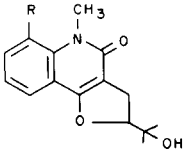
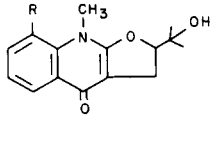
Araliopsine (**1a**) and its linear isomer isoplatydesmine (**2a**) are naturally occurring furoquinoline alkaloids in the *Rutaceae* family. Araliopsine and isoplatydesmine are both isolated from the root bark of *Araliopsis soyauxii* [2]. Isoplatydesmine can also be found in the leaves and twigs of the Hawaiian shrub *Pelea barbigera* [3].



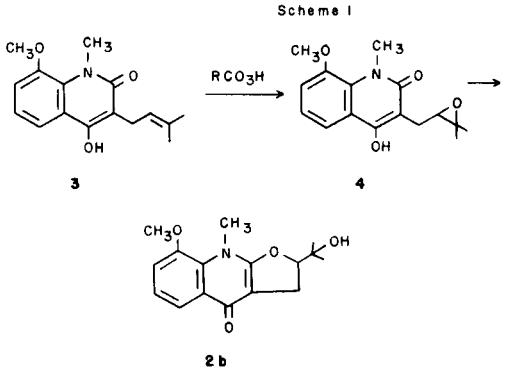
1a, R = H
1b, R = OCH_3



2a, R = H
2b, R = OCH_3

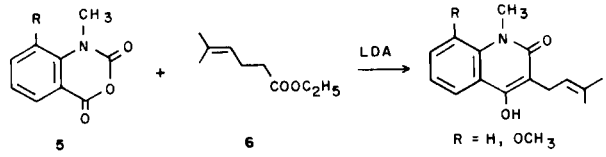
The methoxylated derivative balfourodine (**2b**) has been synthesized (Scheme 1) from the prenylated quinolone **3** by treatment with peroxylauric acid [4]. The initially formed epoxide **4** was not isolable and, under the reaction conditions, spontaneously cyclized to give only the linear isomer **2b**. None of the angular isomer **2a** was formed whether the reaction was performed under neutral or acidic conditions.

Scheme I



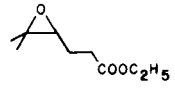
3 **4** **2b**

In a previous publication [6] we reported the facile preparation of prenylated quinolines by the reaction of *N*-methylisatoic anhydride derivatives (**5**) with the ester enolate derived from 5-methyl-4-hexenoic acid ethyl ester (**6**).



5 **6**

It can be envisioned that an analogous reaction of *N*-methylisatoic anhydride with an epoxide such as **7** should give an intermediate similar to **4** (demethoxy derivative) which then has the potential to produce the linear isomer isoplatydesmine (**2a**). This highly convergent strategy would represent a one-step synthesis starting from readily available materials.



7

Epoxide **7** is readily prepared in 69% yield from **6** by oxidation with *m*-chloroperoxybenzoic acid and its lithium enolate can be easily generated at −65° with lithium diisopropylamide (LDA). When *N*-methylisatoic anhydride is allowed to react with this enolate, a rapid reaction ensues and the starting materials are consumed in less than five minutes. The polarity of the product (thin layer chromatography) and its deep yellow color are characteristic properties of an acyclic intermediate [6] which, in this series, corresponds to **8** (Scheme 2). The nmr spectrum of the crude mixture still shows signals attributable to an ethyl ester and supports the acyclic structure. When **8** is allowed to stand at room temperature for 48 hours it is converted to a single new product which, by all physical data [2,5], is identical to araliopsine (**1a**). The formation of this angular isomer is quite unexpected since in the balfourodine series, Grundon [4] only isolated the linear isomer (Scheme 1).

In an effort to determine what effect, if any, the presence of acid will have on the course of the transformation, interemediate **8** was treated with one equivalent of various acids (Table 1). In all cases, after 24 hours, a mixture of **1a**

Table 1

Product Distribution in the Acid-Assisted Cyclization of **8** [a]

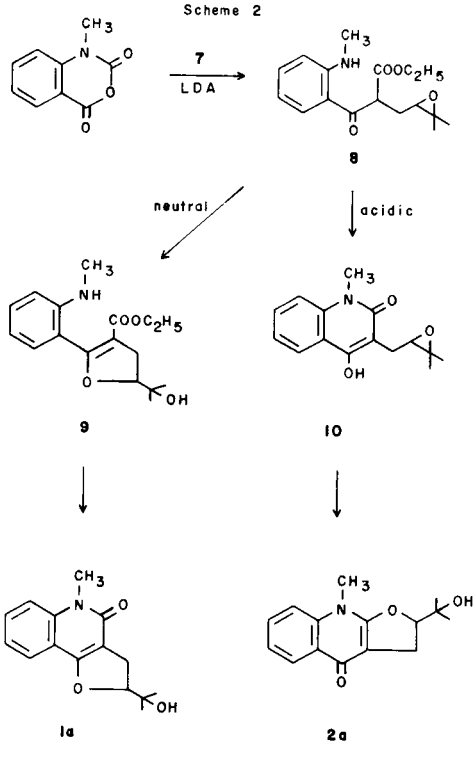
Acid	% **1a**	% **2a**
2*N* HCl	70	30
CH_3COOH	66	34
CF_3COOH	82	18
m-ClC_6H_4COOH	67	33
CH_3SO_3H	70	30
CF_3SO_3H	51	49

[a] All reactions were performed in methylene chloride with the exception of the first (2*N* HCl) in which tetrahydrofuran was used. The product ratios were determined from the nmr of the crude reaction mixtures.

and **2a** is formed. The ratio of isomers is not greatly affected by acid strength although trifluoromethanesulfonic acid produces nearly a statistical mixture. However, with strong acids a significant amount of decomposition occurs in the reaction mixture. The cleanest conversion is achieved with *m*-chlorobenzoic acid. All spectral properties of **2a** are identical with reported values [2,3,5].

It appears that the course of transformations mentioned above is dependent on two possible modes of cyclization of **8**. Under neutral conditions, intramolecular attack of the enolizable ketone on the epoxide to generate the dihydrofuran **9** apparently occurs at a much faster rate than amide formation (giving **10**). Once **9** is formed, the only option the molecule has is to form the amide bond therefore giving the angular isomer **1a**.

Scheme 2



In the presence of acid, the amide forming cyclization **8** → **10** is enhanced to such a rate as to be competitive with the **8** → **9** cyclization. Once **10** is formed, the acid catalyzed intramolecular cyclization of the oxygen in the 2-position of the quinolone with the epoxide only produces the linear isomer **2a** [4]. The two competing pathways therefore give the observed mixtures of **1a** and **2a** as shown in Table 1.

It should be noted that the yields described in this paper are by no means optimized. In each case the reactions were performed only once. The preparation of optically pure epoxide **7** is currently under investigation. The described methodology using such a chiral epoxide should furnish the natural enantiomers of each alkaloid.

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 Varian T-60, 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). The mass spectra were determined on an LKB 9000 spectrometer. Ultraviolet spectra were recorded on a Cary 14 spectrometer.

The carbon-13 magnetic resonance spectra were obtained in the Fourier transform mode on a Jeol FX-90-Q spectrometer system. The spectra were obtained at an observing frequency of 22.5 MHz. Sample concentrations were *ca.* 0.1 molar in 5 or 10 mm (od) sample tubes. General nmr spectral and instrumental parameters employed were: Internal deuterium lock to the solvent; spectral width of 5000 Hz; a pulse width of 6 μs corresponding to a 45° pulse angle; and a pulse repetition time of 1.8 seconds. For all spectra, 8K time-domain points were used. All shifts reported are referenced to internal TMS and are estimated to be accurate to ±0.05 ppm.

All of the described reactions are performed under a nitrogen atmosphere using tetrahydrofuran which has been distilled over lithium aluminum hydride. Unless otherwise stated, all solutions of organic compounds were washed with saturated sodium chloride solution and dried over sodium sulfate. No attempt has been made to optimize the yields of the described reactions.

3,3-Dimethyloxiranepropanoic Acid Ethyl Ester (**7**).

To a solution of 1.56 g (0.01 mole) of **6** [6] in 20 ml of methylene chloride at 0° was added dropwise a solution of 2.0 g of *m*- chloroperoxy-

benzoic acid (85% pure). The mixture was allowed to warm to room temperature and was stirred there for 30 minutes. The resulting precipitate was filtered and the filtrate was washed with sodum sulfite solution and then with dilute sodium bicarbonate solution. The organic layer was dried over sodium sulfate and the solvent was removed under reduced pressure. The residue was distilled at 15 mm to give 1.2 g (69%) of **7**, bp 102-104°; ir (chloroform): 3005, 1720 cm^{-1}; nmr (deuteriochloroform): δ 4.15 (q, 2H), 2.9-2.25 (m, 3H), 2.0-1.7 (m, 2H), 1.35 (s, 3H), 1.3 (s, 3H), 1.3 (t, 3H).

Araliopsine (**1a**).

To a solution of 1.05 g of diisopropylamine in 35 ml of tetrahydrofuran (at −30°) was added 0.67 g of *n*-butyllithium (1.6*M* in hexane). After cooling to −65°, a solution of 0.9 g of **7** in 2 ml of tetrahydrofuran was added dropwise and the mixture was stirred at −65° for 40 minutes. To this was slowly added a solution of 0.93 g of *N*-methylisatoic anhydride in 20 ml of tetrahydrofuran. After stirring at −65° for 15 minutes, the mixture was quenched with a saturated ammonium chloride solution. The organic phase was separated and the aqueous layer was extracted with methylene chloride. The organic solutions were combined and dried over sodium sulfate. The solvent was removed under reduced pressure to give **8** as a yellow oil. After standing at room temperature for 48 hours, the material was chromatographed on a short column of silica gel (using 2% methanol/chloroform) to remove any polar materials. Evaporation of the solvent from the appropriate fractions furnished 0.45 g (33%) of **1a**, mp 141-144°, lit [2] mp 152°; ir (chloroform): 3600, 1660, 1625 cm^{-1}; nmr (deuteriochloroform): δ 7.82-7.05 (m, 4H), 4.88 (t, 1H, J = 9 Hz), 3.67 (s, 3H), 3.16 (d, 2H, J = 9 Hz), 2.18 (s, broad 1H, OH), 1.36 (s, 3H), 1.24 (s, 3H); ^{13}C-nmr (deuteriochloroform): δ 162.2, 161.2, 148.6, 130.9, 122.9, 121.6, 114.5, 112.4, 108.7, 91.9, 72.0, 29.2, 29.1, 25.6, 23.9; uv (ethanol): λ max (log ε): 232 (4.50), 285 (3.82), 296 (3.89), 319 (3.87), 337 (3.78); ms: (70 eV): m/e 259 (M^+).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.6; N, 5.4. Found: C, 69.3; H, 6.6; N, 5.2.

m-Chlorobenzoic Acid Catalyzed Cyclization of **8**-Formation of Araliopsine (**1a**) and Isoplatydesmine (**2a**).

The preparation of **8** was performed on the same scale as in the previous example. Intermediate **8** was then dissolved in 10 ml of methylene chloride. To this solution was added a suspension of 0.75 g of *m*-chlorobenzoic acid in 35 ml of methylene chloride and the resulting mixture was stirred at room temperature for 24 hours. The mixture was washed once with dilute sodium bicarbonate solution and the organic phase was dried over sodium sulfate. The solvent was removed under pressure and the residue was chromatographed on a Waters Prep-500 apparatus using 7% methanol/chloroform to elute the products (total yield 39%): 0.35 g of araliopsine (**1a**), spectral data identical to that otained in the previous example, 0.15 g of isoplatydesmine (**2a**), mp 213-215°, lit [3] mp 208-210°; ir (chloroform): 3600, 2976, 1625, 1590, 1530, 1464 cm^{-1}; nmr (deuteriochloroform): δ 8.42 (m, 1H), 7.64-7.23 (m, 3H), 4.84 (t, 1H, J = 9 Hz), 3.66 (s, 3H), 3.23 (d, 2H, J = 9 Hz), 2.74 (s, broad, 1H, OH), 1.34 (s, 3H), 1.29 (s, 3H); ^{13}C-nmr (deutriochloroform): δ 173.7, 161.3, 138.7, 131.0, 126.5, 123.2, 114.1, 99.3, 91.9, 71.6, 31.3, 27.8, 25.6, 24.3; uv (ethanol): λ max (log ε) 215 (4.47), 237 (4.36), 250 (4.17), 298 (3.96), 309 (4.06), 319 (4.00); ms (70 eV): m/e 259 (M^+).

Anal. Calcd. for $C_{15}H_{17}NO_3$: C, 69.5; H, 6.6; N, 5.4. Found: C, 69.0; H, 6.7; N, 5.3.

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