Photo Fries Rearrangements of 1-Naphthyl Esters in the Synthesis of 2-Acylnaphthoquinones[1]

David J. Crouse, Sheri L. Hurlbut, and Desmond M. S. Wheeler*

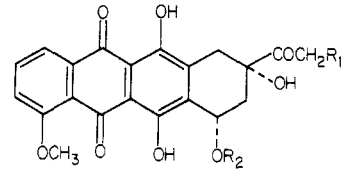
Department of Chemistry, University of Nebraska, Lincoln, Nebraska 68588

Received September 2, 1980

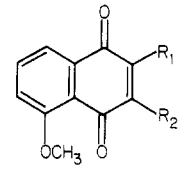
The photo Fries rearrangements of esters of 1-naphthol and 5-methoxy-1-naphthol to the corresponding 1-hydroxy-2-acylnaphthalenes have been carried out. The best yield (70%) was obtained by irradiating 5-methoxy-1-naphthyl acetate in ethyl acetate. By contrast the yield from 1-naphthyl acetate under similar conditions was 40%. Oxidation of 1-hydroxy-5-methoxy-2-naphthyl cyclohexyl ketone with thallium trinitrate gave the corresponding 1,4-quinone. These results provide a method for the regioselective synthesis of tricyclic analogues of adriamycinone.

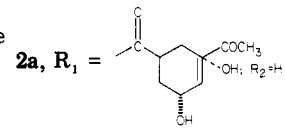
The synthesis of daunomycinone (**1a**), which also constitutes a total synthesis of the important anticancer antibiotic adriamycin (**1b**), has attracted much attention in recent years.[2] As **1b** is cardiotoxic, there is interest in making analogues of **1a** which could then be converted into analogues of **1b**. For an approach to the regioselective preparation of 2-acyl-5-methoxy-1,4-naphthoquinones (e.g., **2a**) as tricyclic analogues of daunomycinone,[3] we planned to make 2-acyl-1-hydroxy-5-methoxynaphthalenes (**3**) which could then be converted into the quinones (**2**). This route has been used previously:[4] the 2-acyl-1-naphthol (made by a Fries rearrangement)[5] is then converted to its 4-amino compound, which is then oxidized to the acylquinone. However, the nature of the substituents in the A ring that would be present in a synthesis of **2a** precludes the use of aluminum chloride and similar Lewis acids that are the usual catalysts for the Fries rearrangement. We decided to investigate the use of the photo Fries rearrangement for the conversion of esters of the type **4** into the corresponding hydroxy ketones **3** and then the conversion of **3** to **2**. This paper reports the results of these studies.

The photo Fries rearrangement[6] has received considerable attention since its discovery in 1960[7] but, as is usual with modern organic photochemistry, the studies have been devoted mainly to elucidating the mechanism of the reaction rather than its use in synthesis. Although there has been controversy about the details of the mechanism,[6] the reaction appears to involve acyl oxygen cleavage of the ester group to a pair of radicals, which recombine to give the ortho and para acyl products through a cage reaction.[8] Alternatively the phenoxy radical can pick up hydrogen to give the parent phenol, a byproduct that is usually obtained. Increasing the viscosity of the solvent cuts down the yield of phenol[6d] but does not increase the yield of the hydroxy ketone. Usually the yield of an acyl product is not good (about 20–30%) and so the reaction has not been used much in synthesis. There are two syntheses of natural products which use a photo Fries rearrangement: griseofulvin (although the photo Fries was later replaced by a normal Fries)[9a] and an early synthesis of daunomycinone.[10]

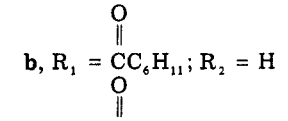


1a, $R_1 = R_2 = H$
b, $R_1 = OH$; R_2 = daunosamine

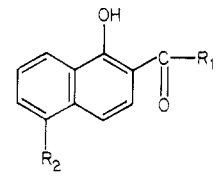




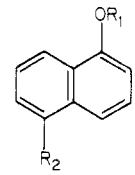
2a, R_1 =



b, $R_1 = CC_6H_{11}$; $R_2 = H$
c, $R_1 = CC_6H_{11}$; $R_2 = OH$



3a, $R_1 = CH_3$; $R_2 = H$
b, $R_1 = CH_3$; $R_2 = OCH_3$
c, $R_1 = C_6H_{11}$; $R_2 = H$
d, $R_1 = C_6H_{11}$; $R_2 = OCH_3$
e, $R_1 = C_6H_5$; $R_2 = H$
f, $R_1 = C_6H_5$; $R_2 = OCH_3$



4a, $R_1 = R_2 = H$
b, $R_1 = H$; $R_2 = OCH_3$
c, $R_1 = COCH_3$; $R_2 = H$
d, $R_1 = COCH_3$; $R_2 = OCH_3$
e, $R_1 = COC_6H_{11}$; $R_2 = H$
f, $R_1 = COC_6H_{11}$; $R_2 = OCH_3$
g, $R_1 = COC_6H_5$; $R_2 = H$
h, $R_1 = COC_6H_5$; $R_2 = OCH_3$

(1) Preliminary communication: Crouse, D. J.; Hurlbut, S. L.; Wheeler, D. M. S. *Synth. Commun.* **1979**, *9*, 877.

(2) In 1978 Dr. T. R. Kelly circulated a list of close to 60 research groups who are working on problems related to 1. For a general survey, see: Remers, W. A. "The Chemistry of Antitumor Antibiotics"; Wiley: New York, 1979; Vol. 1, Chapter 9. The following is a sample of recent papers: Jackson, D. K.; Narashimhan, L.; Swenton, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 3989; Jung, M. E.; Lowe, J. A.; Lyster, M. A.; Brown, R. N. "Abstracts of Papers", American Chemical Society/Chemical Society of Japan Chemical Congress, Honolulu, HI, Apr 1979; American Chemical Society: Washington, DC, 1979; ORGN 281; Hauser, F. M.; Prasanna, S. *J. Org. Chem.* **1979**, *44*, 2596; Amaro, A.; Carreno, M. C.; Farina, F. *Tetrahedron Lett.* **1979**, 3983; Russell, R. A.; Collin, G. J.; Sterns, M.; Warrener, R. N. *Ibid.* **1979**, 4229; Carrupt, P. A.; Vogel, P. *Ibid.* **1979**, 4533; Rama Rao, A. V.; Deshpande, V. H.; Laxma Reddy, N. *Ibid.* **1980**, 2661; Terashima, S.; Tanno, N.; Koga, K. *Ibid.* **1980**, 2749, 2753; Bridson, J. N.; Bennett, S. M.; Butler, G. *J. Chem. Soc., Chem. Commun.* **1980**, 413; Barton, D. H. R.; Dawes, C. C.; Franceschi, G.; Foglio, M.; Ley, S. V.; Magnus, P. D.; Mitchell, W. L.; Temperelli, A. *J. Chem. Soc., Perkin Trans. 1* **1980**, 643; Parker, K. A.; Kallmarten, J. *J. Org. Chem.* **1980**, *45*, 2620.

(3) (a) Wheeler, D. M. S. *Cancer Chemother. Rep.* **1975**, *59* (Part I), 258. (b) Crouse, D. J.; Wheeler, D. M. S. *Tetrahedron Lett.* **1979**, 4797. (c) Crouse, D. J.; Wheeler, M. M.; Goemann, M.; Tobin, P. S.; Basu, S. K.; Wheeler, D. M. S., unpublished work.

(4) Comparatively little work on 2-acylnaphthoquinones has been reported. (a) Ulrich, H.; Richter, R.; *Methoden Org. Chem. (Houben-Weyl), 4th Ed.* **1977**, *7/3a*, 300 ff. (b) Spruit, C. J. P. *Recl. Trav. Chim. Pays-Bas* **1947**, *66*, 655.

(5) Blatt, A. H. *Org. React.* **1942**, *1*, 342. Henecka, H. *Methoden Org. Chem. (Houben-Weyl), 4th Ed.* **1973**, *7/2*, 379. Gerecs, A. "Friedel-Crafts and Related Reactions"; Olah, G. A., Ed.; Interscience: New York, 1964; Vol. III, Chapter 33.

(6) (a) Bellus, D. *Adv. Photochem.* **1971**, *8*, 109. (b) Sternberg, V. I. "Organic Photochemistry"; Chapman, O. L., Ed.; Arnold: New York, 1967; Vol. I, Chapter 3. (c) Pfau, M.; Julliard, M. *Bull. Soc. Chim. Fr.* **1977**, 785. (d) Sandner, M. R.; Hedaya, E.; Trecker, D. J. *J. Am. Chem. Soc.* **1968**, *90*, 7249. (e) Finnegan, R. A.; Knutson, D. *Tetrahedron Lett.* **1968**, 3429. (f) Plank, D. A. *Ibid.* **1968**, 5423.

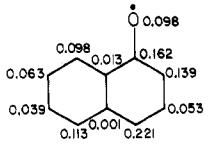
(7) Anderson, J. C.; Reese, C. B. *Proc. Chem. Soc.* **1960**, 217. Kobza, H. *J. Org. Chem.* **1962**, *27*, 2293.

(8) Kalmas, C. E.; Hercules, D. M. *J. Am. Chem. Soc.* **1974**, *96*, 449. Adam, W. *J. Chem. Soc., Chem. Commun.* **1974**, 238.

0022-3263/81/1946-0374$01.00/0

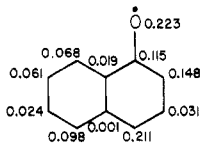
Chart I. Odd π-Electron Densities

calculations by Ohto using SCF MO[11a]

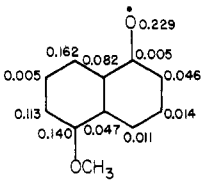


(a)

calculations by HMO using $\alpha_0 = 1$; $\alpha_0 = 2, \beta = 0.8$



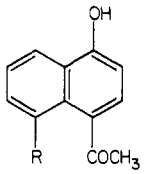
(b)



(c)

The reaction has also been used in the synthesis of flavanoids.[9b,c]

The photo Fries rearrangement of naphthalene esters has been little studied.[11] Ohto and co-workers[11a] found that 1-naphthyl acetate (**4c**) on irradiation with ultraviolet light gave 41% of the 2-acetonaphthone (**3a**), 27% of the 4 isomer (**5a**), and 18% of 1-naphthol (**4a**). Their calcu-



5a, R = H
b, R = OCH_3

lations, using a SCF-MO method (see Chart Ia), showed that the odd π-electron density at the 4 position of the 1-naphthoxy radical was higher than that at the 2 position and they suggested that the proximity of the 2 position favored the recombination of the radicals to give more of the 2 as opposed to the 4 product. More recently Farina and co-workers[12] studied the photo Fries rearrangements of a series of 1,4-diacetoxynaphthalenes; only one group migrated and the yield of the ortho product (no para one was possible) was good (usually 60–75%).

In the acid-catalyzed Fries rearrangement of phenols use of low temperatures favors the para product; higher temperatures favor the ortho product.[5] This result has been observed in the acid-catalyzed Fries rearrangement of 1-naphthyl esters.[13] Presumably the 4 position, which is more reactive, is also more sterically hindered than the 2. The fact that the thermal Fries rearrangement to the 4 position is hindered sterically suggested that in the photoreaction the presence of a 5-methoxy group in a 1-naphthyl ester would promote rearrangement to the 2 position by increasing the hindrance at 4. This paper describes our work on the photorearrangements of the acetates, cyclohexylcarboxylates, and benzoates of 1-naphthol (**4a**) and 5-methoxy-1-naphthol (**4b**). The esters **4c–h** were prepared from the naphthols and appropriate acid chlorides. The esters **4c**,[14] **4d**,[15] **4e**,[16] and **4g**[17] were known; the esters **4f** and **4h** had the correct composition and spectra.

Table I. Rearrangements of Esters 4c-h[a]

starting ester	solvent	% yields: *o*-hydroxy ketone	naphthol	ester
4d	methanol	50		
4d	*tert*-butyl alcohol	58	14	9
4d	ethylene glycol/ diglyme	29	12–17	5
4d	benzene	42	7	10
4d	dimethyl formamide	19	5	11
4d	acetone	7		
4d	ethyl acetate	71		
4c	ethyl acetate	38	tr	15
4e	ethyl acetate	33	29	24
4f	ethyl acetate	38	tr	11
4g	ethyl acetate	47	15	7
4h	ethyl acetate	44	17	0

[a] Rearrangements by irradiation for 30 min in ethyl acetate under N_2 using a Hanovia 450-W medium-pressure mercury lamp. The products from the reactions of **4e-4h** were separated by flash chromatography on silica gel using benzene/petroleum ether (1:3) as the eluent. The products from **4c** and **4d** were separated by TLC on silica gel developed by benzene; R_f values: **3b**, 0.65; **4d**, 0.48; **4b**, 0.28.

Rearrangements of Acetates. The photorearrangement of the 5-methoxy acetate **4d** to the 2-acetyl compound **3b** was studied under a variety of conditions to determine the best conditions for making **3b**. While **3b** was always isolated, its yield depended on the solvent used in the reaction (Table I). The structure of **3b** was determined from its composition and spectra. The ortho relationship of the acetyl and hydroxyl groups was confirmed by the spectral data of **3b**, especially the absorptions characteristic of 1-hydroxy-2-acetonaphthone (cf. ref 18) in the ultraviolet spectrum, the low frequency of the CO group in the IR,[19] and the positions of the phenolic proton (δ 13.8) and the acetyl methyl group (δ 2.6) in the NMR spectrum; the latter signal is downfield of any of the (much smaller) acetyl methyl peaks observed in the spectrum of the crude material.

The variation of the yield of **3b** with solvent under standard conditions is given in the top half of Table I. Apparently the most important factor in accounting for the variation in yields is the ability of the solvent to donate hydrogen atoms (or as with benzene, an electron) to the radicals formed in the reaction; on this basis the yield of product should increase in going from benzene to methanol to *tert*-butyl alcohol.[20] Ethyl acetate, the best solvent for the reaction, should be a poorer donor than *tert*-butyl alcohol; neither the polarity nor the viscosity of the solvent appears to be important in influencing the yield of the hydroxy ketone (cf. ref 6a,d–f).

(9) (a) Taub, D.; Kuo, C. H.; Slates, H. L.; Wendler, N. L. *Tetrahedron* **1963**, *19*, 1. (b) Ramakrishnan, V. T.; Kagan, J. *J. Org. Chem.* **1970**, *35*, 2901. (c) Obara, H.; Takahashi, H.; Hirano, H. *Bull. Chem. Soc. Jpn.* **1969**, *42* 560.

(10) Kende, A. S.; Belletire, J.; Bentley, T. J.; Hume, E.; Airey, J. *J. Am. Chem. Soc.* **1975**, *97*, 4425.

(11) (a) Ohto, Y.; Shizuka, H.; Sekiguchi, S.; Matsui, K. *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1209. (b) The mechanism of the rearrangement of **4c** has been studied in some detail but the results have apparently not been published (ref 6a, p 114).

(12) Escobur, C.; Farina, F.; Martinez-Utrilla, R.; Paredes, M. C. *J. Chem. Res. (S)* **1977**, 266; *J. Chem. Res. (M)* **1977**, 3154.

(13) (a) Joshi, G. G.; Shah, N. M. *J. Indian Chem. Soc.* **1952**, *29*, 225. (b) Stoughton, R. W. *J. Am. Chem. Soc.* **1935**, *57*, 202.

(14) Chattaway, F. D. *J. Chem. Soc.* **1931**, 2495.

(15) Fischer, O.; Bauer, C. *J. Prakt. Chem.* **1916**, *94*, 13.

(16) Bhargava, S. S.; Jain, S. K.; Sahara, G. S. *Indian J. Chem.* **1967**, 543.

(17) Autenrieth, W.; Muhlinghaus, P. *Chem. Ber.* **1907**, *40*, 744.

(18) (a) Spruit, C. J. *Recl. Trav. Chim. Pays-Bas* **1949**, *68*, 309. (b) Bergmann, E. D.; Hirshberg, Y.; Pinches, S. *J. Chem. Soc.* **1950**, 2351.

(19) Hunsberger, I. M. *J. Am. Chem. Soc.* **1950**, *72*, 5626.

(20) Cf.: Turro, N. J. "Modern Molecular Photochemistry"; Benjamin: Menlo Park, CA, 1978; p 374.

The starting ester, **4d**, and the naphthol, **4b**, were also isolated in some experiments. We never isolated the para isomer **5b**; indeed, no para hydroxy ketone was obtained from any of our experiments.

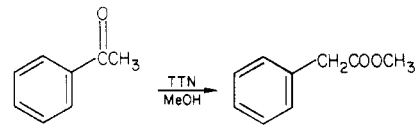
The irradiation of 1-naphthyl acetate (**4c**) was carried out under the conditions that gave the best yield with the methoxy compound **4d**. The 2-acetyl compound **3a**, a known compound,[13b] was isolated in 38% yield (Table I). Our yield was slightly less than Ohto's[11a] and we did not isolate the para compound. Thus, our yield of **3b** was greater than that of **3a**.

To examine the electronic effect that the methoxyl group may have on the reaction of **4d**, we have determined the odd π-electron densities in the 1-naphthoxy (Chart Ib) and 5-methoxy-1-naphthoxy (Chart Ic) radicals using a Hückel molecular orbital calculation. The distribution in Chart Ib corresponds qualitatively to that determined by Ohto (Chart Ia): the electron density in the ring with the oxygen radical is greater than that in the unsubstituted ring, and the density at C_4 is greater than that at C_2. Surprisingly the introduction of the methoxy group (Chart Ic) reverses this pattern; the ring with the methoxyl group has the greater density, and there is more density at C_2 than C_4. We conclude that the increase in yield of hydroxy ketone due to the methoxyl is an electronic effect, at least in part, rather than only steric as we had expected.

Rearrangement of Cyclohexanecarboxylates and Benzoates. The work was extended to a study of the rearrangements of the cyclohexylcarboxylates (**4e** and **4f**) and the benzoates (**4g** and **4h**). The reactions were run in ethyl acetate, using the conditions that gave the best yield of **3b** from **4d**. As shown in Table I, the 2-acyl compound (**3c–3f**) is the main product in each reaction. Compounds **3c**[21] and **3e**[22] are known; their spectra and the spectra and analytical data for **3d** and **3f** are in accord with the assigned structures. The yields of **3c** and **3e** parallel that of **3a** from **4c**; however, the yields of the methoxy ketones **3d** and **3f** are little different from those of the corresponding nonmethoxy compounds (**3c** and **3e**).[23]

Quenching of a naphthoxy radical to naphthol should be easier when the migrating group is benzoyl (transfer of electron) or cyclohexanoyl (abstraction of hydrogen) than when it is acetyl; this was confirmed by the larger amounts of phenol isolated in the reactions of **4e**, **4g**, and **4h** and to some extent with **4f**. This easier quenching of the radical may be large enough to swamp the effect observed in the rearrangement of **4d**.

Oxidation to Quinone. In other work[3c] we (following Taylor and McKillop's results with phenols)[26] found that oxidation of a naphthol with thallium trinitrate (TTN) gives good yields of the corresponding naphthoquinones, without going through several steps as with the amino route.[4] However, McKillop and Taylor[27] showed that oxidation with TTN of alkyl aryl ketones containing an enolizable hydrogen leads to rearrangement of the ketone to an ester (e.g., **6** → **7**). More recently, a Japanese group[28]



6 **7**

found that oxidation of a 2,5-dimethoxyacetophenone with TTN gave a rearranged ester or an ester quinone, depending on the conditions of the reaction. It was possible that in the reaction of **3d** with TTN a similar rearrangement might take place in preference to conversion to the quinone **2b**. In the event oxidation of **3d** gave the desired acylquinone **2b**. Apparently, the enolization of the tertiary hydrogen (which would be the rate-determining step in the rearrangement to the ester) is slower than the oxidation of the ring. The spectroscopic data and composition of **2b** are in accord with the structure; in particular the peak corresponding to the methine hydrogen adjacent to the ketone appears in the NMR of **2b** slightly downfield of its position in **3d**.

The oxidation of **3d** is best done with slightly less than 2 equiv of TTN. When more than 2 equiv of TTN were used, we isolated the 3-hydroxy compound **2c** rather than **2b**. The structure of **2c** follows from its spectra. The high-resolution mass spectrum shows that **2c** has one more oxygen than **2b** and that this oxygen is associated with the naphthalene system (several peaks corresponding to $C_{12}H_xO_5$). The IR spectrum shows that a hydrogen-bonded hydroxyl is present. The UV spectrum has quinoid peaks at 375 and 282 nm (corresponding to bathochromic shifts of peaks at 308 and 243 nm in **2b**);[29] these peaks, especially the peak at 282 nm, are indicative of a 2- or 3-hydroxynaphthoquinone[30a] and are also observed with 2-acetyl-3-hydroxy-1,4-naphthoquinone.[18a] The absence in the NMR spectrum of **2c** of the C_3-H peak at 6.7 ppm in **2b** confirms the hydroxyl group is at C_3. The NMR spectrum of **2c** also showed a pronounced downfield shift (from δ 2.9 to 3.7) of the signal corresponding to the methine hydrogen in the cyclohexane ring as compared with the corresponding signal in **2b** and **3d**. Examination of models shows that hydrogen bonding of the ketone carbonyl with the C_3-OH (or the C_1-OH in the other tautomeric form of **2c**) leaves the methine hydrogen in the deshielding zone of the carbonyl C_1 (or, of course, C-3 in the other tautomer). Moore and Scheuer[30d] reported that the introduction of a 3-hydroxyl group in a 2-acetylnaphthoquinone leads to a downfield shift of about 0.3 ppm in the methyl signal.[31] In their compound the methyl group can rotate freely about the O=C—C axis and so the signal is an averaged shift; with our compound steric factors will cause the cyclohexyl ring to point away from the quinone carbonyl and thus the methine hydrogen should show a greater de-

(21) Buu-Hoi, Ng. Ph.; Lavit, D. *Croat. Chem. Acta* **1957**, *29*, 287; *Chem. Abstr.* **1959**, *53*, 10684a.

(22) Arventi, B. I. *Bull. Soc. Chim. Fr.* **1937**, *4*(5), 999.

(23) In other experiments we irradiated **4d** and **4f** through a Pyrex filter for 1 h and obtained slightly lower yields than those reported in Table I. We also irradiated the cyclohexylcarboxylate **4f** in chlorobenzene and in Triton X-100, a nonionic micelle.[24,25] Rearrangement to the ortho product **3d** took place in both media, but problems associated with the workup of the reactions made it hard to isolate the product.

(24) For examples of photoreactions using micelles see: Turro, N. J.; Liu, K. C.; Chow, M. F. *Photochem., Photobiol.* **1977**, *26*, 413; Nakamura, Y.; Imakura, Y.; Kato, T.; Marita, Y. *J. Chem. Soc., Chem. Commun.* **1977**, 883.

(25) Triton X-100 was obtained from the Sigma Chemical Company, St. Louis, MO. Compound **4b** is insoluble in SDS (sodium dodecyl sulfate).

(26) McKillop, A.; Perry, D. H.; Edwards, M.; Antus, S.; Farkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282.

(27) McKillop, A. *Pure Appl. Chem.* **1975**, *43*, 463. Taylor, E. C.; Chiang, C.-S.; McKillop, A.; White, J. F. *J. Am. Chem. Soc.* **1976**, *98*, 6750.

(28) Maruyama, K.; Kozuka, T. *Bull. Chem. Soc. Jpn.* **1978**, *51*, 3586.

(29) The peaks for **2b** agree with published data for 2-acyl-1,4-naphthoquinones.[18a,30b,c]

(30) (a) Singh, I.; Ogata, R. T.; Moore, R. E.; Chang, C. W. J.; Scheuer, P. J. *Tetrahedron* **1968**, *24*, 6053. (b) Eugster, C. H.; Bosshard, P. *Helv. Chim. Acta* **1963**, *46*, 815. (c) Bosshard, P.; Fumagalli, S.; Good, R.; Trueb, W.; v. Philipsborn, W.; Eugster, C. H. *Ibid.* **1964**, *47*, 769. (d) Moore, R. E.; Scheuer, P. J. *J. Org. Chem.* **1966**, *31*, 3272.

(31) Moore and Scheuer[30d] explained their shift by suggesting that the introduction of the hydroxyl group led to strong hydrogen bonding involving not only **2c** but a tautomer in which the C_3 oxygen is a carbonyl group and the acetyl ketone has enolized toward the ring.

shielding than did Scheuer's methyl group. While the usual stability of 1,4- over 1,2-quinones suggest that the tautomer represented in **2c** is the more important one, we have no definitive evidence to confirm that view. Spruit[4b] has reported that oxidation with ferric chloride of 4-amino-1-hydroxy-2-acetonaphthone gave the 3-hydroxyquinone as well as the quinone; when the oxidation was done at 100 °C the hydroxy compound became the main product.

The sequence **4b** → **4f** → **3d** → **2b** provides a convenient regioselective route to 2-acylnaphthoquinones.[4] The shortness of the route compensates for the fair yields of the photochemical step. Work is now in hand to make a suitable ring A precursor for the synthesis of **2a**.[32] Another regioselective approach to 2-acylquinones is also under study.[3b,c]

Experimental Section

General. Melting points (uncorrected) were obtained in capillary tubes by using a Mel-Temp apparatus. NMR spectra were recorded on either a Varian Associates A-60D or T-60. All chemical shifts are reported in parts per million (δ) downfield from $(CH_3)_4Si$ as the internal standard. IR spectra were recorded on either a Perkin-Elmer 137 or a Beckman Acculab 4 grating spectrophotometer. UV spectra were determined on a Cary 14 recording spectrophotometer or a Hewlett-Packard 8450. Mass spectra were determined on an AEI MS-50 mass spectrometer. Elemental analyses were performed by MicroTech Laboratories, Inc., Skokie, IL.

Preparative TLC utilized Analtech 2013 silica gel of 1-mm thickness. Analytical TLC was done on Eastman 13181 silica gel. Column chromatography used Merck No. 9385 silica gel (400–230 mesh).

Preparation of Naphthyl Esters. General Procedure. The acid chloride (1.2 mL) was added dropwise to the appropriate naphthol (**4a** or **4b**,[33] 14 mmol) in pyridine (20 mL) at 0 °C. The solution was stirred overnight at room temperature and then poured into ice and concentrated HCl (25 mL). This was extracted with ether and the extracts were washed with brine, aqueous Na_2CO_3, and brine and then dried ($MgSO_4$). The ether was evaporated to give the crude ester in good yield as an oil or solid. The following esters crystallized from 95% ethanol (**4e–h**), hexane (**4c**), or hexane/EtOAc (**4d**). Crystalline yields were not optimized.

4c (1-naphthyl acetate): 47%; mp 45–46 °C (lit.[14] mp 48–49 °C); IR ($CHCl_3$) ν_{max} 1760 cm^{-1}; NMR ($CDCl_3$) δ 2.3 (s, 3 H, CH_3), 7.0–7.9 (m, 7 H, arom H).

4d (5-methoxy-1-naphthyl acetate): 58%; mp 61–63 °C (lit.[15] mp 68 °C); IR ($CHCl_3$) ν_{max} 1760 cm^{-1}; NMR ($CDCl_3$) δ 2.3 (s, 3 H, $COCH_3$), 4.0 (s, 3 H, OCH_3), 6.7–8.1 (m, 6 H, arom H).

4e (1-naphthyl cyclohexanecarboxylate): 39%; mp 50–51 °C (lit.[16] mp 52 °C); IR (CCl_4) ν_{max} 1770, 1610 cm^{-1}; NMR ($CDCl_3$) δ 1.2–3.0 (m, 11 H, alicyclic H), 7.1–8.0 (m, 7 H, arom H).

4f (5-methoxy-1-naphthyl cyclohexanecarboxylate): 73%; mp 77–79 °C; UV (CH_3CN) λ 321 nm (ϵ 2400), 308 (4100), 295 (5700), 225 (24 000); UV (EtOH) 322 (2140), 282 (3600), 235 (3540), 217 (2880); IR (KBr) ν_{max} 1750, 1605, 1585 cm^{-1}; NMR ($CDCl_3$) δ 1.2–3.0 (m, 11 H, alicyclic H), 4.0 (s, 3 H, CH_3), 6.7–8.3 (m, 6 H, arom H); mass spectrum, m/e (relative intensity) 284.1407 (5), 174.0682 (100), 159.0452 (10), 115.0547 (7), 83.0850 (31), 55.0564 (15); m/e calcd for $C_{18}H_{20}O_3$ 284.1413.

4g (1-naphthyl benzoate): 62%; mp 47–48 °C (lit.[17] mp 56°); IR (CCl_4) ν_{max} 1720, 1600 cm^{-1}.

4h (5-methoxy-1-naphthyl benzoate): 56%; mp 91–93 °C; UV (CH_3CN) λ 321 nm (ϵ 2920), 307 (5140), 294 (7090), 283 (6810), 229 (30,600); UV (EtOH) 309 (4230), 283 (4460), 234 (4450), 219 (3630); IR (KBr) ν_{max} 1735, 1600, 1500 cm^{-1}; NMR ($CDCl_3$) δ 4.1 (s, 3 H, CH_3), 6.9–8.7 (m, 11 H, arom H); mass spectrum, m/e (relative intensity) 278.0939 (12), 115.0545 (5), 105.0339 (100), 77.0391 (26); m/e calcd for $C_{18}H_{14}O_3$ 278.0943.

Irradiation of Esters. General Procedure. A solution of the ester (1 mmol) in ethyl acetate (160 mL), which had been purged with N_2 for 1 h, was irradiated under N_2 for 30 min with a 450-W Hanovia medium-pressure mercury lamp operated inside a standard Hanovia quartz immersion well. The solvent was removed to give a red oil which was chromatographed on silica gel with benzene/petroleum ether (1:3). With the exception of 1-hydroxy-2-acetonaphthone (cyclohexane) the yellow *o*-hydroxy ketones crystallized from methanol. The naphthols **4a** and **4b** and the esters **4c–h** were identified by TLC and spectral comparison with authentic samples. The results are given in Table I. The following *o*-hydroxy ketones were isolated.

3a (1-hydroxy-2-acetonaphthone): mp 98–99 °C (lit.[13b] mp 98–99 °C); UV (EtOH) λ 379 nm (ϵ 2130), 357 (2300), 282 (2490), 252 (2460), 234 (2450); IR ($CHCl_3$) ν_{max} 1635, 1610, 1580 cm^{-1}; NMR ($CDCl_3$) δ 2.53 (s, 3 H, CH_3), 7.02–8.47 (m, 6 H, arom H), 13.9 (s, 1 H, OH).

3b (1-hydroxy-5-methoxy-2-acetonaphthone): mp 119–120 °C; UV (CH_3CN) λ 309 nm (ϵ 3500), 295 (4100), 286 (4700), 255 (35 000); UV (EtOH) 379 (5400), 309 (2960), 296 (4230), 286 (5000), 253 (9230), 241 (8700); IR ($CHCl_3$) ν_{max} 1635 cm^{-1}; NMR ($CDCl_3$) δ 2.63 (s, 3 H, $COCH_3$), 3.92 (s, 3 H, OCH_3), 6.82–8.07 (m, 5 H, arom H), 13.8 (s, 1 H, OH). Anal. Calcd for $C_{13}H_{12}O_3$: C, 72.22; H, 5.56. Found: C, 71.96; H, 5.62.

3c (1-hydroxy-2-naphthyl cyclohexyl ketone): mp 99–101 °C (lit.[21] mp 104 °C); UV (EtOH) λ 380 (ϵ 1930), 353 (2000), 282 (2130), 253 (2080), 234 (2090); IR ($CHCl_3$) ν_{max} 1630, 1570 cm^{-1}; NMR ($CDCl_3$) δ 0.72–2.53 (m, 10 H, CH_2), 2.97–3.43 (m, 1 H, HCC=O), 6.75–8.50 (m, 6 H, arom H), 14.4 (s, 1 H, OH).

3d (1-hydroxy-5-methoxy-2-naphthyl cyclohexyl ketone): mp 103–104 °C; UV (CH_3CN) λ 309 (ϵ 3300), 296 (4400), 286 (5100), 257 (38 000); (EtOH) 398 (2740), 309 (2280), 282 (2280), 275 (2190), 252 (2270), 234 (2230); IR (KBr) ν_{max} 1625, 1605 cm^{-1}; NMR ($CDCl_3$) δ 1.2–2.10 (m, 10 H, CH_2), 3.05–3.55 (m, 1 H, HCC=O), 3.97 (s, 3 H, CH_3), 6.80–8.22 (m, 5 H, arom H), 14.2 (s, 1 H, OH). Anal. Calcd for $C_{18}H_{20}O_3$: C, 76.06; H, 7.04. Found: C, 75.73; H, 7.06.

3e (1-hydroxy-2-naphthyl phenyl ketone): mp 63–64 °C (lit.[22] mp 64–65 °C); UV (EtOH) λ 382 (ϵ 4480), 283, (6120), 252 (6100), 232 (6120); IR ($CHCl_3$) ν_{max} 1635, 1615, 1580 cm^{-1}; NMR ($CDCl_3$) δ 6.83–8.38 (m, 11 H, arom H), 13.8 (s, 1 H, OH).

3f (1-hydroxy-5-methoxy-2-naphthyl phenyl ketone): mp 117–118 °C; UV (CH_3CN) λ 300 nm (ϵ 6600), 263 (29 000), 224 (14 000); UV (EtOH) 400 (3660), 306 (2740), 283 (2870), 252 (2890), 234 (2950); IR ($CHCl_3$) ν_{max} 1635, 1605, 1575 cm^{-1}; NMR ($CDCl_3$) δ 4.02 (s, 3 H, CH_3), 7.02–8.38 (m, 10 H, arom H), 14.2 (s, 1 H, OH); mass spectrum, m/e (relative intensity) 278.0945 (100), 200 (30), 185 (20); m/e calcd for $C_{18}H_{14}O_3$ 278.0943. Anal. Calcd for $C_{18}H_{14}O_3$: C, 77.70; H, 5.04. Found: C, 77.50; H, 5.11.

Oxidation of Hydroxy Ketone 3d to 2b. TTN/Celite reagent[3c] (2.06 g, ~1.3 mmol of Tl^{3+}) was added in one portion to a vigorously stirred solution of **3d** (0.202 g, 0.71 mmol) in CH_2Cl_2 (100 mL, 0 °C). This mixture was stirred for 30 min and filtered. TLC (silica gel, 10% ethyl acetate/benzene) indicated that the major component was a compound with R_f 0.2.[34]

The solution was evaporated and flash chromatographed on silica gel, using 5% ethyl acetate/benzene as the eluting agent. The fractions corresponding to R_f 0.2 (on silica gel with 10% ethyl acetate/benzene) were combined and evaporated in vacuo to give orange crystals (0.193 g). These crystallized from petroleum ether/ethyl acetate to give 5-methoxy-1,4-dioxo-1,4-dihydro-2-naphthyl cyclohexyl ketone (**2b**): mp 107–108 °C; 0.121 g (57%); UV (CH_3OH) λ 306 nm (ϵ 8100), 243 (11 600), 213 (14 000); NMR ($CDCl_3$) δ 1.1–2.0 (m, 10 H, CH_2), 2.8–3.1 (m, 1 H, HCC=O), 3.9 (s, 3 H, OCH_3), 6.7 (s, 1 H, HC=C), 7.1–7.7 (m, 3 H, arom H); IR ($CHCl_3$) ν_{max} 1690, 1655, 1580 cm^{-1}; mass spectrum, m/e (relative intensity) 298.1208 (43), 280.1092 (41), 265.0858 (23), 262.0986 (29), 216.0417 (35), 188.0470 (100), 160.0521 (48); m/e calcd for $C_{18}H_{18}O_4$ 298.1210.

3-Hydroxy-5-methoxy-1,4-dioxo-1,4-dihydro-2-naphthyl Cyclohexyl Ketone (2c). TTN/Celite reagent[3c] (0.926 g, 0.59 mmol of Tl^{3+}) was added in one portion to a vigorously stirred

(32) Tobin, P. S.; Basu, S. K.; Grosserode, R. S.; Wheeler, D. M. S. *J. Org. Chem.* **1980**, *45*, 1250.

(33) Bentley, W. H.; Robinson, R.; Weizmann, C. *J. Chem. Soc.* **1907**, *91*, 104. Rutdo, D.; Lee, S.; Shelden, R.; Moore, H. W. *J. Org. Chem.* **1978**, *43*, 2304.

(34) The R_f of **3d** is 0.5 and of **2c** is 0 under these conditions.

solution of **3d** (0.084 g, 0.29 mmol) in CH_2Cl_2 (50 mL, 0 °C). The mixture was stirred vigorously for 1 h and then filtered. The filtrate was evaporated in vacuo to give an orange solid (0.111 g) which was chromatographed on acid-washed silica gel. The column was eluted first with benzene/ethyl acetate (5%). Increasing the concentration of ethyl acetate eventually gave orange-colored fractions, which were evaporated to give orange crystals (0.066 g). These recrystallized from petroleum ether/ethyl acetate to give the hydroxyacylnaphthoquinone as orange crystals: mp 147–148 °C; 0.030 g (33%); UV (CH_3OH) λ 375 nm (ε 4200), 282 (9900), 239 (8000); NMR ($CDCl_3$) δ 1.1–1.9 (m, 10 H, CH_2), 3.4–4.0 (s and m overlap, 4 H, HCC=O and CH_3), 7.0–7.8 (m, 3 H, arom H); IR ($CHCl_3$) ν_{max} 3000 (br), 1690, 1665, 1655 cm^{-1}; mass spectrum, *m/e* (relative intensity) 314.1158 (100), 233.0444 (21), 232.0377 (38), 204.0417 (40) 203.0351 (75); *m/e* calcd for $C_{18}H_{18}O_5$ 314.1154, $C_{12}H_9O_5$ 233.0438, $C_{12}H_8O_5$ 232.0382, $C_{11}H_8O_4$ 204.0412, $C_{11}H_7O_4$ 203.0358.

Acknowledgment. This research was assisted by grants from the David Fund administered by the University of Nebraska Research Council and by NIH Biomedical Sciences Support Grant 5 S07RR07055-12-13. We are most grateful to the Midwest Center for Mass Spectrometry, Lincoln, NE 68588, for measuring mass spectra and to Drs. S. W. Staley, V. W. Day, and C. S. Day and Mr. C. S. Dustman for their kind assistance with the molecular orbital calculations. D.M.S.W. thanks Drs. N. J. Turro and E. C. Taylor for helpful comments.

Registry No. (*R*)-1, 71719-69-2; (*S*)-1, 75716-63-1; **2**, 75716-64-2; **3**, 75716-65-3; (*R*)-**6**, 71719-72-7; (*S*)-**6**, 71719-71-6; **7**, 45734-11-0; **8**, 75716-66-4; **9**, 75716-67-5; *O,O*-dimethyl phosphorothioic acid dicyclohexylammonium salt, 13941-61-2; dimethyl phosphonate, 868-85-9; 2-hydroxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane methyltriethylammonium salt, 75716-68-6; 2-methoxy-2-thiono-5,5-dimethyl-1,3,2-dioxaphosphorinane, 1005-97-6; **4f**, 75716-81-3; **4g**, 607-55-6; **4h**, 64725-89-9; acetyl chloride, 75-36-5; cyclohexanecarbonyl chloride, 2719-27-9; benzoyl chloride, 98-88-4.

Microbial Products. 5. Absolute Configuration of Aminoglycoside X-14847

Hubert Maehr,* Joanne M. Smallheer, and John F. Blount

Department of Chemical Research, Hoffmann-La Roche Inc., Nutley, New Jersey 07110

Received September 9, 1980

Analysis of the ^1H NMR spectrum of X-14847 nonaacetate reduces the number of possible structures for X-14847 to two. A study involving multiple cuprammonium complexation of the *N*-acetyl derivative which contains eight hydroxyl groups, generating five vicinal glycol groupings, permits the identification of X-14847 as 2-amino-2-deoxy-α-D-glucopyranosyl-1-*O*-D-*myo*-inositol. This assignment is confirmed by single-crystal Roentgen analysis of 2-[(5-bromo-2,4-dinitrophenyl)amino]-2-deoxy-α-D-glucopyranosyl-1-*O*-D-*myo*-inositol octaacetate prepared from X-14847 with 1-bromo-3-fluoro-4,6-dinitrobenzene and subsequent peracetylation.

We have recently described the isolation of a novel aminoglycoside, named X-14847, which is produced by *Micromonospora echinospora* sp. X-14847.[1] It exhibited very weak antibacterial activity and was identified as a 2-amino-2-deoxy-α-D-glucopyranosyl-*myo*-inositol.

Of the nine inositols, *myo*-inositol (**1**) belongs to the group of seven which are meso compounds. Since it contains one plane of symmetry bisecting two centers of opposite chirality, substitution of any one of the six hydroxyl groups gives rise to a specific stereoisomer so that six isomers had to be considered for the configuration of X-14847.

The ^1H NMR spectrum of 1,2-*O*-isopropylidene-*myo*-inositol 3,4,5,6-tetraacetate (**4**)[2] shows the protons of the acetoxy group within a close range [δ ($CDCl_3$) 2.00 (s, 6 H), 2.05 (s, 3 H), 2.10 (s, 3 H)] and the acetoxy signals of *myo*-inositol 3,4,5,6-tetraacetate (**3**)[3] fall into the same region [δ ($CDCl_3$) 1.98 (s, 3 H), 1.99 (s, 3 H), 2.07 (s, 3 H), 2.09 (s, 3 H)]. In agreement with the general observation that axial acetoxy groups attached to six-membered rings in the chair conformation absorb at lower field than the equatorial ones, the signal for the axial acetoxy group in the spectrum of *myo*-inositol hexaacetate (**2**),[4] therefore, could be assigned to the peak at δ 2.18 which is 0.2 ppm further downfield than the remaining five acetoxy signals. The chemical shifts of the acetoxy groups in methyl 2-(acetylamino)-2-deoxy-α-D-glucopyranoside triacetate (**9**)[5] range between δ ($CDCl_3$) 1.93 and 2.08 so that the low-field acetoxy peak at δ 2.28 in nonaacetate **12a** or **12b** could be assigned to the axial acetoxy group. The signals for H5 in **2** [δ ($CDCl_3$) 5.17 (t, $J_{4,5} = J_{5,6} = 10$ Hz)] and **12** [δ ($CDCl_3$) 5.11 (t, $J_{4,5} = J_{5,6} = 10$ Hz)] are very similar, requiring C5 in **12** to carry an acetoxy group as well. The hydroxyl groups located in the inositol symmetry plane in X-14847 are therefore unsubstituted.

The ring protons H2 [δ ($CDCl_3$) 5.60 (t, $J_{1,2} = J_{2,3} = 3$ Hz)], H4 and H6 [δ 5.51 (t, 2 H, $J_{1,6} = J_{3,4} = J_{4,5} = J_{5,6} = 10$ Hz)] in **2** absorb sufficiently far downfield so as not to interfere with the signals of **9**. Thus, the three triplets generated by H2 [δ 5.59 ($J_{1,2} = J_{2,3} = 3$ Hz)], H4 and H6 [δ 5.48 and 5.51 (2 t, $J_{1,6} = J_{3,4} = J_{4,5} = J_{5,6} = 10$ Hz)] are easily recognizable in the spectrum of X-14847 nonaacetate, confirming that the inositol hydroxyl groups at C4 and C6 in X-14847 are likewise free. The possible sugar-attachment sites in X-14847 are therefore limited to C1 and C3 of inositol, leaving structures **10a** and **10b** for consideration.

Similarly substituted *myo*-inositols are already known; (–)-bornesitol (**5a**) corresponds stereochemically to **10a** and

(1) Preceding paper in this series: H. Maehr, C-M. Liu, T. Hermann, B. L. T. Prosser, J. M. Smallheer, and N. J. Palleroni, *J. Antibiot.*, **33**, in press.
(2) R. Gigg and C. W. Warren, *J. Chem. Soc. C*, 2367 (1969).
(3) S. J. Angyal, P. T. Gilham, and C. G. Macdonald, *J. Chem. Soc.*, 1417 (1957).
(4) D. P. Langlois, *Methods Carbohydr. Chem.*, **2**, 83 (1963).
(5) R. C. G. Moggridge and A. Newberger, *J. Chem. Soc.*, 745 (1938).

0022-3263/81/1946-0378$01.00/0