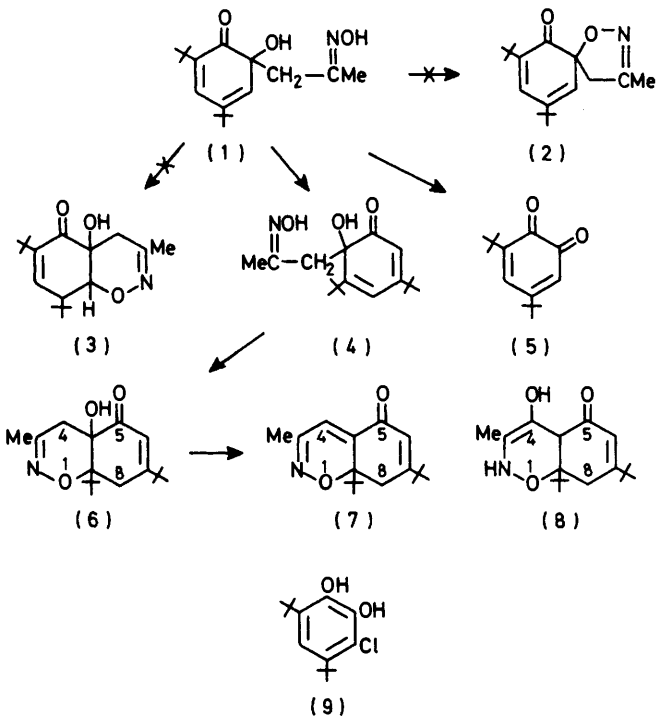
Cyclisation of Phenolic Oximes. Part 4.[1] Cyclisation of 6-Acetonyl-6-hydroxy-2,4-di-t-butylcyclohexa-2,4-dienone Oxime with Hydrogen Chloride

By **Alexander R. Forrester,* Ronald H. Thomson,** and **Soo On Woo,** Chemistry Department, University of Aberdeen, Meston Walk, Old Aberdeen AB9 2UE

The title dienone with hydrogen chloride rearranges to 6-acetonyl-6-hydroxy-3,5-di-t-butylcyclohexa-2,4-dienone oxime before cyclising to 4,4a,8,8a-tetrahydro-4a-hydroxy-3-methyl-7,8a-di-t-butyl-1,2-benzoxazin-5-one.

THE key step in a recently described [1] synthesis of a stereoisomer of the sponge metabolite aerothionin was the oxidative cyclisation of a phenolic oxime to a spiroisoxazoline. In the course of that work [2] we attempted to dehydrate the hydroxy-oxime (1) to the spiroisoxazoline (2) by treatment with hydrogen chloride in benzene. However, the major products were the *o*-benzoquinone (5) and an isomer [$C_{17}H_{27}NO_3$ (15%)] of the starting material. The latter showed hydroxy and conjugated carbonyl i.r. absorption at 3 470 and 1 665 cm^{-1} (chloroform solution), respectively. Comparison of its proton n.m.r. spectrum with that of the starting



material strongly indicated that the hydroxyimino-group had cyclised into the cyclohexadienone ring. The oxime hydroxy (δ 8.75) and cyclohexadienone (δ 6.92) proton signals of the starting material were replaced by tertiary hydroxy (δ 4.10) (1 H) and vinylic (1 H) (δ 6.10) singlets and the spectrum also included two 2 H signals at δ 2.76 (broad singlet) and δ 2.94 (doublet). This spectrum is not consistent with the dihydro-oxazine structure (3) formed by intramolecular addition of the oxime hydroxy group to the adjacent >C=C<. Further, the oxazine (3) should be easily dehydrated to an aromatic product but the new compound was recovered from a hot solution in benzene containing hydrogen chloride.

In conjugated cyclohex-enones [3,4] and -2,4-dienones ^{13}C-3 normally resonates at lower field than ^{13}C-2, but we found that it was the higher field vinylic carbon signal which was split into a doublet in the ^{13}C n.m.r. off-resonance decoupled spectrum. This indicates that the new compound, unlike the starting material, has no substituent on the carbon adjacent to the carbonyl group. We infer that the hydrogen chloride caused not only retro-aldol cleavage to the *o*-benzoquinone (5) but also rearrangement *en route* to the product. The structure [5] of the acetonylquinone from which the oxime (1) was prepared is not in doubt since the ketone and its oxime have ^{1}H n.m.r. spectra characteristic [6] of 2,4- and not 3,5-disubstituted cyclohexa-2,4-dienones (=CH at δ 6.9 and 6.1). Thus, we interpret the reaction with hydrogen chloride as involving initial rearrangement to an isomeric oxime (4) followed by cyclisation to the oxazine [(1) ⟶ (4) ⟶ (6)]. Structure (6) is consistent with all the spectroscopic data and was further supported by (*a*) proton spin decoupling experiments which showed that the C-8 protons (δ 2.94) are coupled strongly to the C-6 (δ 6.10) and the C-4 (δ 2.76) protons and weakly coupled to the 3-methyl protons, (*b*) satisfactory assignment of all the signals in the ^{13}C spectrum (see Experimental section), and (*c*) the mass spectrum, which showed major fragment peaks corresponding to $M^+ - OH - C_4H_9$ (50%) and $M^+ - OH - C_4H_8 - CH_3CNO$ (100%).

Further structural confirmation was sought by dehydration of the oxazine (6) with acetic anhydride in pyridine. Two products were obtained, neither of which was an acetate. One was clearly an anhydro-derivative from its mass, i.r. (no ν_{OH}), and n.m.r. spectra. It showed two vinylic proton signals at δ 5.37 and 5.82, the

[1] A. R. Forrester, R. H. Thomson, and Soo On Woo, *Annalen*, 1978, 66.
[2] A. R. Forrester, R. H. Thomson, and Soo On Woo, *J.C.S. Perkin I*, 1975, 2340, 2348.
[3] R. Hollenstein and W. von Philipsborn, *Helv. Chim. Acta*, 1972, 2030.
[4] L. F. Johnson and W. C. Jankowski, 'Carbon-13 NMR Spectra,' Wiley, New York, 1972, spectra 387, 386, 482.
[5] R. Magnusson, *Acta Chem. Scand.*, 1960, **14**, 1643.
[6] W. Regel and W. von Philipsborn, *Helv. Chim. Acta*, 1968, **51**, 867.

latter being split by coupling with one of the two methylene protons which were themselves strongly coupled mutually (18 Hz). The u.v. spectrum ($\lambda_{max.}$ 245 and 310 nm) was also consistent with the oxazine structure (7), which we assign to this product.

The second product was an isomer (mass spectrum) of the oxazine (6). A significant feature of its n.m.r. spectrum was the three exchangeable proton signals. One of these, δ 15.7, is typical of a hydroxy signal of a strongly chelated enol (*e.g.* acetylacetone), the second, δ 6.2, also a broad signal, was shifted in acid solution and is assigned to NH, and the third, δ 5.82, which exchanged more slowly than the other two and only when acid was present, is assigned to $-CH{\cdot}CO-$. These and other structural features, including conjugated carbonyl absorption (i.r., u.v.) and strongly coupled methylene protons (*J* 18 Hz) are accommodated by structure (8). Its formation from (7) presumably occurs by addition of a molecule of water during work-up.

The rearrangement (1) ⟶ (4) is not an intermolecular process since the *o*-benzoquinone (5), acetoxime, and hydrogen chloride in benzene gave the same 1,4-adduct (9) as that obtained when acetoxime was absent. Dreiding models of the oximes (1) and (4) show that, in the conformation most favourable for intramolecular cyclisation of the oxime hydroxy group non-bonding interactions between t-butyl and the oxime side chain are greater in (1) than in (4). Hence, if (1) and (4) were in equilibrium then preferential formation of (6) would ensue. The instability of other acetone-*o*-quinone adducts under the conditions used for oxime formation has prevented us from examining the behaviour of related oximes in acid solution.

EXPERIMENTAL

Reaction of 6-*Hydroxy*-6-(2-*hydroxyiminopropyl*)-2,4-*di-t-butylcyclohexa*-2,4-*dienone with Hydrogen Chloride*.—Dry hydrogen chloride was bubbled through a solution of the oxime (586 mg) in benzene (40 ml) for 1 h. The mixture was left overnight. Next day the solvent was removed *in vacuo* at room temperature. Chromatography (t.l.c.) of the residual oil on silica with chloroform–ether (4 : 1) as eluant gave (*a*) 3,5-di-t-butyl-1,2-benzoquinone (164 mg, 33%), identical with an authentic specimen, and (b) 4,4a,-8,8a-*tetrahydro*-4a-*hydroxy*-3-*methyl*-7,8a-*di-t-butyl*-1,2-*benzoxazin*-5-*one* (6) (90 mg, 15%) as needles, m.p. 143—145° (from light petroleum–benzene) (Found: C, 69.7; H, 9.8; N, 4.6%; M^+, 293.198 1. $C_{17}H_{27}NO_3$ requires C, 69.6; H, 9.3; N, 4.8%; *M*, 293.199 1), $\nu_{max.}$ (KBr) 3 115br, 1 670, and 1 635 cm^{-1}; $\nu_{max.}$ ($CHCl_3$) 3 470, 1 665, and 1 625 cm^{-1}; $\lambda_{max.}$ (EtOH) 235 nm (log ε 4.26); δ_H 1.16 (9 H, s, Bu^t), 1.26 (9 H, s, Bu^t), 2.0 (3 H, s, Me), 2.76 (2 H, br, s, CH_2), 2.94 (2 H, d, CH_2), 4.1 (1 H, s, OH), and 6.1 (1 H, br, s, CH); δ_C 200.2(CO), 173.7(C-7), 140.1(C-3), 118.9(C-6), 83.3(C-4a), 79.2(C-8a), 46.1(C-4 or -8), 38.9(C of Bu^t), 37.6 (C of Bu^t), 30.2(C-4 or -8), 28.3(CH_3), 27.9(CH_3), and 12.91-(3-CH_3), *m/e* 294(5%), 293(25, M^+), 237(6), 236(10), 221(8), 220(50), 219(36), 205(11), 165(28), 164(22), 163(100), 149(6), 109(6), 107(10), 93(6), 41(25), and 39(6).

When the oxime (293 mg) was dissolved in 0.2M-hydrogen chloride in benzene (50 ml) and the solution left for 48 h at room temperature, 2,6-di-t-butyl-*o*-benzoquinone (65 mg, 32%) and the oxazine (6) (70 mg, 23%) were isolated.

Treatment of the benzoxazine (6) (500 mg) with acetic anhydride (10 ml) in pyridine (5 ml) for 18 h at room temperature, followed by chromatographic separation of the resulting mixture on silica with chloroform–light petroleum (1 : 1), gave (i) 8,8a-*dihydro*-3-*methyl*-7,8a-*di-t-butyl*-1,2-*benzoxazin*-5-*one* (7) (90 mg), m.p. 94—96° (from hexane) (Found: C, 74.0; H, 9.2; N, 5.2%; M^+, 275.188 3. $C_{17}H_{25}NO_2$ requires C, 74.1; H, 9.2; N, 5.1%; *M*, 275.188 5), $\nu_{max.}$ (KBr) 1 675 and 1 630 cm^{-1}; $\nu_{max.}$ ($CDCl_3$) 1 665 and 1 625 cm^{-1}; $\lambda_{max.}$ (EtOH) 244 and 312 nm; δ_H 0.98 (9 H, s, Bu^t), 1.16 (9 H, s, Bu^t), 2.62 (3 H, s, Me), 2.32 (1 H, dd, *J* 19 and 3 Hz, 8-H), 2.94 (1 H, d, *J* 19 Hz, 8-H), 5.37 (1 H, s, 4-H), and 5.82 (1 H, s, 6-H), *m/e* 275(M^+,0.4%), 220(11), 219(56), 204(10), 163(79), and 162(100); and (ii) 2,4a,8,8a-*tetrahydro*-4-*hydroxy*-7,8a-*di-t-butyl*-1,2-*benzoxazin*-5-*one* (8) (115 mg), m.p. 150—151° (from light petroleum) (Found: C, 69.7; H, 9.2; N, 5.1. $C_{17}H_{27}NO_3$ requires C, 69.6; H, 9.2; N, 4.8%); $\nu_{max.}$ (KBr) 3 200, 1 675, and 1 625 cm^{-1}; $\nu_{max.}$ ($CHCl_3$), 3 405, 1 670, and 1 610 cm^{-1}; $\lambda_{max.}$ 227 and 282 nm; δ_H 1.05 (9 H, s, Bu^t), 1.09 (9 H, s, Bu^t), 2.04 (3 H, s, Me), 2.34 (1 H, dd, *J* 16 and 3 Hz, 8-H), 3.08 (1 H, d, *J* 16 Hz), 5.7 (1 H, m, 6-H), 5.82 (1 H, s, 4a-H), 6.2 (1 H, m, NH), and 15.7 (1 H, br, s, OH).

Reaction of 4,6-*Di-t-butyl*-o-*benzoquinone with Hydrogen Chloride*.—A solution of 3,5-di-t-butyl-1,2-benzoquinone (220 mg) and acetoxime (100 mg) in benzene was saturated with hydrogen chloride and then left for 16 h. Removal of solvent followed by short-path distillation of the residue gave 3-*chloro*-4,6-*di-t-butylcatechol* as a thick oil (Found: M^+, 256.122 8. $C_{14}H_{21}ClO_2$ requires *M*, 256.123 0); $\nu_{max.}$ 3 520 cm^{-1}; δ .30 (9 H, s, Bu^t), 1.35 (9 H, s, Bu^t), 5.55 (2 H, s, 2 OH), and 6.85 (1 H, s, ArH). The same product was obtained when acetoxime was omitted.

[7/1969 *Received*, 9*th November*, 1977]