CONTRIBUTION TO THE CHEMISTRY OF PEREZONE

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Abstract—The sequence of reactions described confirms that perezinone (IIb) is a quinone methide related to the 2H-naphtho [1,8-bc] furan system. The structures of two oxidation derivatives isolated earlier are established.

As a consequence of the elucidation of the structural features of α - and β -pipitzols,¹ the structure of perezone postulated by Kögl and Boer² was revised,³⁻⁶ the position of its OH group changed, and the new structure (Ia) confirmed by unequivocal synthesis.⁷ At the same time, the earlier structure² of perezinone was also revised and established⁸ as IIa.

We now report additional results concerning the structural features of perezinone (IIa) which permit us to assign structures to its oxidation products.

During the preparation of perezinone (IIa) by sulfuric acid dehydration of hydroxyperezone (Ic), Remfry⁹ and earlier workers^{10, 11} isolated two by-products.

The first of these compounds, oxoperezinone (IIb), could be obtained in acceptable yields by treatment of an acetic acid solution of perezinone (IIa) with selenium dioxide, and was identical with a sample obtained following Remfry's⁹ directions.

Oxoperezinone, (IIb; $C_{15}H_{16}O_4$) is soluble in sodium hydroxide giving a violet colour and furnishes a positive ferric chloride test. Its structure can be rationalized in terms of its preparation from perezinone (IIa) and from its spectral properties.

Comparison of the UV spectra of perezinone (IIa)⁸ and oxoperezinone (IIb, λ_{max} 343, 361 mµ; ε , 11,200, 13,800), showed a shift to higher wavelength, suggesting that the new O atom in IIb is directly conjugated with the chromophore of perezinone (IIa) as a CO group. The IR spectrum of IIb was not directly informative since it is complex in the carbonyl region, but the NMR spectrum* permits us to assign position 3 to the new CO group. Singlets at 7.31 (1H, disappearing on equilibration with D₂O) and at 1.96 (3H, aromatic Me group) indicate the presence of the quinone methide system. Singlets at 1.62 and 1.66 (3H each) correspond to the *gem*-dimethyl group, whereas a doublet (J = 7 c/s) centered at 1.3 (3H) is due to a secondary Me group. The allylic proton appears as a multiplet centered at 3.5 and the C-4 methylene protons as a multiplet centered at 2.67 representing the AB part of an ABX system ($J_{AB} = 16$ c/s, $J_{AX} = 4$ c/s, $J_{BX} = 6$ c/s and $\Delta v = 19$ c/s) in which the X proton is further coupled to the secondary Me group.

The mass spectrum of oxoperezinone (IIb) showed a parent peak at m/e 260 corresponding to the molecular ion and intense peaks at m/e 245, 229 and 218, the latter corresponding to a 3,8-dimethyl-2,6-dihydroxy-1,4-naphthoquinone ion or its

^{*} All chemical shifts are reported in ppm as δ units, and were measured at 60 Mc/s.

tautomeric 3,8-dimethyl-1,4-dihydroxy-2,6-naphthoquinone ion. Therefore, oxoperezinone is adequately represented by formula IIb.

Hydrogenation of perezinone (IIa) afforded IIIa.⁸ In a similar fashion, the structure of oxoperezinone (IIb) was demonstrated unequivocally by hydrogenation with Adams catalyst in acetic anhydride solution in the presence of sodium acetate, which affords a diacetate ($C_{19}H_{22}O_6$). It showed IR bands corresponding to ester CO groups at 1765 and to cyclohexanone at 1715 cm⁻¹. Its NMR spectrum is completely in accord with structure IIIb. Singlets at 1.18 and 1.76 are assigned to the gemdimethyl group. A doublet (J = 7 c/s) centered at 1.22 (partially superimposed on one of the singlets of the gem-dimethyl group) corresponds to the secondary Me group, whereas a singlet at 1.98 is ascribed to the aromatic Me group. The two acetyl groups are responsible for a singlet (6H) at 2.28. A multiplet centered at 3.25 is assigned to the allylic proton at C-5 and a singlet at 3.65 (1H) is attributed to an allylic proton which is also alpha to a CO group. The methylene protons appeared as a complex signal centered at 2.45.

Independent proofs of the structure of oxoperezinone (IIb), were obtained through the following series of experiments. Treatment of a pyridine solution of perezinone (IIa) with benzoyl chloride afforded a colorless dibenzoate ($C_{29}H_{26}O_5$; ester carbonyl band at 1738 cm⁻¹). Structure VII is deduced for this compound from its NMR spectrum. Ten protons are responsible for two complex signals centered at 8-00 (4H) and at 7.34 (6H) assigned to the aromatic protons of the benzoate groups. Singlets at 2-08 (3H) and at 1.51 (6H) are due to the aromatic Me and gem-dimethyl groups, respectively. A doublet (J = 7 c/s) centered at 1.12 is ascribed to the secondary Me group and the C-5 proton is responsible for a complex signal centered at 3-02. The vinylic proton at C-3 appeared as two doublets (J = 5 c/s) centered at 5-26. The methylene protons at C-4 appeared as a complex signal centered at 2.42. Treatment of the dibenzoate (VII) with m-chloroperbenzoic acid, followed by alkaline hydrolysis under a nitrogen atmosphere, afforded oxoperezinone (IIb).

Formula VIII is assigned to the peracid treatment product of the dibenzoate (VII) based on its composition $(C_{29}H_{26}O_7)$ and spectral properties: The IR spectrum of VIII showed a OH absorption band at 3550 cm⁻¹, olefinic double bonds at 1605 and 1618 cm⁻¹ and a band at 1720 cm⁻¹ attributable to a cyclohexanone. The NMR spectrum is fully in accord with structure VIII. The benzoate proton signals (10H) appeared as in perezinone dibenzoate (VII). Singlets (3H each) at 1:24, 1.71 and 2.08 correspond to the *gem*-dimethyl and aromatic Me groups, whereas doublet (J = 7 c/s) centered at 1.43 is due to the secondary Me group. A broad signal at 2.75 (1H, disappearing on equilibration with D₂O), corresponds to the tertiary OH group. The allylic proton is responsible for a multiplet centered at 3.32 and the C-4 protons appear as a complex signal centered at 2-64 (partially superimposed on the hydroxyl proton signal).

Oxoperezinone (IIb) is not very stable as a solid: after keeping a pure sample a few weeks, the crystal surface begins to become coated with a rather insoluble yellow compound. Somewhat above its m.p. oxoperezinone (IIb) begins to solidify, affording the same more polar (TLC) and insoluble substance, which has no m.p. but darkens at 300°. An adequate purity check on oxoperezinone (IIb) can be obtained by NMR spectroscopy, using a small singlet at 1.74 which corresponds to the *gem*-dimethyl group of the new compound dehydroöxoperezinone (IVa). This substance, which

can also be obtained by alkaline treatment of a methanolic solution of oxoperezinone (IIb) in the presence of air, showed IR bands at 1695 and 1605 cm⁻¹ attributable to a quinonoid chromophore. The presence of a phenolic hydroxyl group was demonstrated by preparation of the acetate (IVb, IR band at 1768 cm⁻¹) and the Me (IVc, NMR singlet at 3.98) derivative.

The NMR spectrum of IVa (in DMSO-d₆) showed sharp singlets at 1.70.(6H) and 1.75 (3H) corresponding to the gem-dimethyl and aromatic Me group respectively, and broad singlets at 6.70 (1H) and at 2.49 (3H) corresponding to an aromatic proton and a Me group, respectively; the NMR spectrum of the more soluble dehydroöxoperezinone acetate (IVb), showed singlets at 1.77 (6H, gem-dimethyl group), at 1.97 (C-8 methyl group) and at 2.41 (acetate). A doublet (J = 0.8 c/s) centered at 2.76 (3H) and a quartet (J = 0.8 c/s) centered at 7.12 (1H) indicate a long-range coupling of an aromatic Me group with a proton attached to the same double bond as the Me group. The magnitude of the long-range coupling constant, excludes the tautomeric 1hydroxy-2,6-amphi-quinone structure, since it would have coupling constants of similar magnitude to those found in α,β -unsaturated six-membered carbonyl group compounds, such as perezone (Ia)³⁻⁶ or lamberletin.¹²

The presence of the *o*-quinonoid chromophore was demonstrated by preparation of the quinoxaline (V). Similar chromophores as those presented by IVa, IVb and IVc, have been reported recently for mansonone H and its derivatives¹³ but unfortunately no UV data for comparison was described.

The presence of the furan ring in IVa was demonstrated by preparation of the methoxydiacetate (VIb). It showed CO absorption at 1765 cm⁻¹ in the IR region and NMR singlets at 3.85 (3H, OMe group), 2.23 and 2.22 (6H, two acetyl groups), 2.10 (3H, C-8 Me group) and 1.74 (6H, gem-dimethyl group). A doublet (J = 0.7 c/s) centered at 2.60 (3H) and a quartet (J = 0.7 c/s) centered at 6.87 (1H) correspond to the C-5 Me and C-4 proton, respectively.

Dehydroöxoperezinone (IVa) could be isolated in low yields after treatment of the acyloin (VIII) with BF_3 -etherate complex in benzene solution.

The IIb-IVa alkaline transformation can be rationalized in terms of the intermediary nonisolable hydroquinone (VIa, a tautomer of IIb) which is then oxidized in air. It can also be concluded that in this case, the *o*-quinone (IVa) is more stable than the tautomeric hydroxy-*amphi*-quinone.

Although perezone was isolated in 1852,¹⁴ all previous attempts to acetylate this product resulted in a mixture of α - and β -pipitzol acetates.⁹ In the preparation of leucoperezone triacetate (IX) following Kögl's directions,² but using zinc shot instead of dust, we were able to isolate *perezone acetate* (Ib) in acceptable yield. It showed IR bands for enolic acetate at 1770 cm⁻¹, quinone CO groups at 1660 and 1650 cm⁻¹, and olefinic double bonds at 1620 cm⁻¹. The NMR spectrum of the acetate (Ib) is similar to that of perezone (Ia).³ Instead of the OH signal at 7.05,³ there appeared a singlet (3H) at 2.30 corresponding to the acetyl group. The quinonoid vinylic proton and Me group are involved in an AB₃ system (doublet, J = 7 c/s, 3H at 1.99 and quartet, J = 1.7 c/s, 1H at 6.52) as in the case of perezone (Ia).³-6

EXPERIMENTAL

M.ps are uncorrected. Analyses were by Dr. A. Bernhardt, Mülheim, Germany. Chromatography was on alumina (Alcoa F-20) and chromatoplates on Silica G (Merck). UV spectra were taken in 95% EtOH.



Unless noted otherwise NMR spectra were taken in CDCl₃ using TMS as internal standard on a Varian A-60 and IR spectra in chf soln using NaCl prisms.

 H_2SO_4 treatment of hydroxyperezone (lc). A soln of Ic⁸ (10 g) in H_2SO_4 98% (80 ml) was heated on the steam bath for 30 min, cooled, diluted with ice water, filtered and the ppt washed with water. The combined filtrate and washings were saturated with NaCl and extracted twice with hexane and then with CHCl₃. The dried ppt, mixed with Na₂SO₄ anhyd (15 g), was extracted in a Soxhlet with the hexane used in the extraction of the filtrate. From the hexane soln, IIa (54 g) crystallized as yellow plates, m.p. 146–147°, λ_{max} 207, 245, 324, 333 (sh), 360 (sh) mµ; ε , 16,750, 1000, 23,450, 21,350, 4700; λ_{max}^{H+} 207, 246, 324, 333 (sh), 362 (sh), mµ; ε , 16,750, 1100, 23,400, 21,350, 4600; λ_{max}^{OH-} 223, 334, 384, 436 mµ; ε , 13,600, 20,200, 2850, 1600. It was identified with an authentic sample⁸ by standard methods.

The Soxhlet cartridge was extracted with the CHCl₃ soln. From this, 85 mg of IVa crystallized as bronzecolored needles which did not melt but darkened at 300°, gave a positive FeCl₃ test (greenish-brown), were soluble in NaOHaq (red color); λ_{max} 206, 219, 271, 395, 364 mµ; ϵ , 16,100, 16,700, 18,700, 19,250, 12,200, 8350; λ_{max}^{H+2} 206, 220, 265, 270, 295, 363, 438 mµ; ϵ , 16,250, 17,000, 19,400, 20,300, 12,400, 8800, 1500; λ_{max}^{OH-2} 238 (sh), 245, 253, 293, 312, 400, 486 mµ; ϵ , 14,850, 15,800, 16,200, 10,500, 11,600, 16,900, 2300. IR bands (KBr disk) at 1695 (quinonoid CO group) and at 1605 cm⁻¹ (broad with shoulders at 1590 and 1640 cm⁻¹, C=C double bonds). (Found: C, 69-92; H, 5-60; O, 24-95; Calc for C₁₃H₁₄O₄: C, 69-76; H, 5-66; O, 24-78%). Identified by IR and TLC comparison with a sample of the same structure obtained according to Remfry's directions.⁹ The mother liquors were concentrated and the residual oil crystallized from acetone-hexane, yielding 651 mg of IIb, m.p. 163-165°. The analytical sample showed m.p. 167-168° (orange-reddish needles) solidifying above the m.p., gave a positive FeCl₃ test (greenish-brown), was soluble in NaOHaq (violet color), λ_{max} 204, 225 (sh), 268, 325 (sh), 343, 361 mµ; ε , 7300, 3000, 750, 4900, 11,200, 13,800; these do not change on acidification; λ_{max}^{OHe} 230, 378, 565 mµ; ε , 3650, 10,000, 1600; IR bands at 3320 (OH group) and 1682, 1665, 1645, 1622, 1601 and 1592 cm⁻¹ (CO groups and C=C double bonds). (Found: C, 69-44; H, 6·27; O, 24·43. Calc. for C₁₅H₁₆O₄: C, 69·22; H, 6·20; O, 24·59%). This compound was identified by standard methods with a sample obtained following Remfry's⁹ directions.

SeO₂ oxidation of perezinone (IIa). A soln of IIa (500 mg) in AcOH (15 ml) was treated with SeO₂ (250 mg), left on a steam bath for 20 min, diluted with water and extracted with EtOAc. The organic layer was extracted several times with water and with Hg, dried and evaporated. The residue crystallized from acetone-hexane, yielding 153 mg of IIb, m.p. 160–163°. Recrystallization from the same solvents raised the m.p. to 167–168°. This compound was identified by standard methods with a sample obtained by H_2SO_4 action on Ic.

Alkaline treatment of perezinone (IIa). A soln of IIa (100 mg) and KOH (200 mg) in MeOH (20 ml) was stirred mechanically for 20 hr, acidified with dil HCl, concentrated to a small volume under reduced press, diluted with water and extracted with EtOAc. The organic layer was washed with water and dried. Upon concentration, IVa (25 mg) crystallized as yellow needles, which had not melted at 300°. These were identified with a sample of the same product obtained by H_2SO_4 action on Ic.

When the experiment was carried out as above, but under a N_2 atmosphere, IIa was recovered in almost quantitative yield.

Alkaline treatment of oxoperezinone (IIb). A soln of IIb (45 mg) in MeOH (5 ml) was treated with K_2CO_3 (60 mg) in water (1 ml). The mixture was heated under reflux for 45 min, acidified, and worked up as in the case of IIa. The product IVa (15 mg) was identified with an authentic sample. The mother liquors consisted of a mixture of the product and starting material, as judged by TLC.

Alkaline treatment under a N2 atmosphere resulted in recovery of IIb.

Dehydrogenation of oxoperezinone (IIb). A sample of IIb (100 mg) was heated slowly in an oil bath to 210°, cooled, and the solid crystallized from EtOAc—MeOH. This yields IVa (53 mg) identified with an authentic sample.

Leucodehydroöxoperezinone diacetate (IIIb). A soln of IIb (100 mg) in Ac₂O (20 ml) was hydrogenated with PtO₂ (20 mg) until the absorption of H₂ ceased, NaOAc (250 mg) was added, and the mixture was stirred magnetically at room temp for 20 hr in an H₂ atm. The soln was then filtered and evaporated to dryness under reduced press. The residue dissolved in Et₂O was washed with water, dried and evaporated to dryness. Crystallization of the oily residue from hexane afforded IIIb as white prisms (90 mg), m.p. 132-136°. The analytical sample showed m.p. 138-140°, gave a negative FeCl₃ test, λ_{max} 206, 288 mµ; ε , 18,300, 1700; IR bands at 1765 (acetyl groups), 1715 (cyclohexanone) and 1610 cm⁻¹ (C=C double bonds). (Found: C, 65.71; H, 6.48; O, 27.63. C₁₉H₂₂O₆ requires: C, 65.88; H, 6.40; O, 27.71%).

Alkaline treatment of the mother liquors under N_2 , followed by air oxidation of the acidified soln, regenerated IIb.

Dehydroöxoperezinone acetate (IVb). A soln of Va (80 mg) in pyridine (2 ml) and Ac₂O (2 ml) was left at room temp overnight, heated 20 min on the steam bath and worked up as usual. Crystallization of the residue from hexane furnished orange needles (70 mg), m.p. 147–155°. The analytical sample of IVb showed m.p. 115–118°/157–160°, λ_{max} 205, 220, 255 (sh), 264, 274, 290 (sh), 335, 440, mµ; ϵ , 10,650, 13,400, 10,300, 14,000, 13,050, 4550, 1400, 1400; IR bands at 1768 (acetyl group) 1695 (quinonoid CO groups) and 1630 and 1590 cm⁻¹ (C=C double bonds). (Found: C, 67·85; H, 5·54; O, 26·57. C₁₇H₁₆O₅ requires: C, 67·99; H, 5·37; O, 26·64%).

Methoxydehydroöxoperezinone (VIc). A soln of IVa (50 mg) in Me₂CO (15 ml) containing anhyd K₂CO₃ (700 mg) and Me₂SO₄ (0.6 ml) was heated under reflux for 14 hr, diluted with water and extracted with EtOAc. The organic layer was washed with water, NaOHaq and water, dried and evaporated to dryness. The residue, dissolved in benzene-hexane 1:9, was chromatographed over alumina (2 g). The fractions eluted with benzene-hexane 1:1, with increasing proportions of benzene, and benzene, crystallized. They were combined and recrystallized from acetone-hexane, yielding IVc (45 mg) as fluffy yellow needles, m.p. 255-256°, λ_{max} 204, 222, 266, 291, 358, 435 mµ; ε , 11,500, 11,850, 13,500, 9600, 4850, 1250; IR bands at 1685 (quinonoid CO groups) and 1621 and 1590 cm⁻¹ (C=C double bonds). (Found: C, 70-57; H, 5-94; O, 23-74. C₁₆H₁₆O₄ requires: C, 70-58; H, 5-92; O, 23-50%).

Methoxydiacetate (VIb). The hydrogenation of IVc (55 mg) was carried out as in the case of IIb. The

product VIb (40 mg) crystallized from hexane as prisms, m.p. 165–170°. The analytical sample (white prisms from MeOH) had m.p. 183–184°, λ_{max} 205 (sh), 221, 247, 317 mµ; ϵ , 16,400, 27,200, 32,250, 5000, IR bands at 1765 (acetyl group) and 1620 cm⁻¹ (C=C double bonds). (Found: C, 67-28; H, 6-02; O, 26-66; C₂₀H₂₂O₆ requires: C, 67-03; H, 6-19; O, 26-79%).

Quinoxaline (V). A soln of IV (70 mg) in AcOH (8 ml) was treated with o-phenylenediamine (80 mg). The mixture was heated under reflux for 1 hr, left at room temp overnight, diluted with water and extracted with EtOAc. The organic layer was washed several times with water and dried. Upon concentration, V crystallized (55 mg) as yellow needles, m.p. 252-254°. The analytical sample (from EtOAc) showed m.p. 254-255°. (Found: C, 76.64; H, 5.75; N, 8.06; O, 9.47. $C_{22}H_{20}O_2$ requires: C, 76.72; H, 5.85; N, 8.13; O, 9.29%).

Benzoylation of perezinone (IIa). A soln of IIa (230 mg) in pyridine (2 ml) was treated with benzoyl chloride (2 ml), heated on the steam bath for 90 min, poured into ice water with stirring, and the gummy material extracted with EtOAc. The organic layer was washed with dil HCl and water, dried and evaporated. The oily residue was chilled, and extracted with pentane until the decanted pentane left no residue. The solid was then crystallized from acetone-hexane, yielding prisms (155 mg), m.p. 190-192°. The analytical sample of VII showed m.p. 195-196°, λ_{max} 203, 235, 269, 277 (sh), 317, 328 mµ; ε , 39,600, 47,200, 11,800, 9800, 8900, 9900. IR bands at 1738 (benzoyl groups) and 1605 (C=C double bonds). (Found: C, 76:49; H, 5:93; O, 17:81. C₂₉H₂₆O₅ requires: C, 76:63; H, 5:77; O, 17:60%).

Alkaline treatment of VII (KHCO₃ in MeOH under N₂ regenerated perezinone (IIa) in good yield.

m-Chloroperbenzoic acid treatment of perezinone dibenzoate (VII). A soln of VII (200 mg) in CHCl₃ (15 ml) containing the peracid (300 mg) was heated under reflux for 2 hr, evaporated to dryness and the residue dissolved in ether. The organic layer was washed with NaHCO₃ aq and water, dried and evaporated. Crystallization from ether-hexane furnished VIII as small prisms (95 mg), m.p. 221-223° (d). The analytical sample showed m.p. 234-235° (d), λ_{max} 205, 232, 280 mµ; ε , 28,500, 23,000, 23,000, 1R bands at 3550 (OH group) at 1745 (benzoyl groups), at 1722 (cyclohexanone) and at 1618 and 1605 cm⁻¹ (C=C double bonds). (Found: C, 71.70; H, 5.48; O, 22.89. C₂₉H₂₆O₇ requires: C, 71.59; H, 5.39; O, 23.02%).

 BF_3 treatment of the acyloin (VIII). A cold soln of VIII (40 mg) in benzene (5 ml) was treated with 2 drops of BF_3 - Et_2O complex. After 3 hr at room temp the greenish-red mixture was diluted with EtOAc, washed several times with water, dried and evaporated to a small volume. The crystalline residue was filtered, yielding dehydroöxoperezinone (IVa, 7 mg). This was identified with an authentic sample by standard methods.

Alkaline treatment of the acyloin (VIII). A suspension of VIII (30 mg) in MeOH (7 ml) with $KHCO_3$ (30 mg) in water (1 ml) was heated under reflux under N₂ for 20 min. The violet soln was acidified with dil HCl and worked up as usual. Crystallization from acetone-hexane yielded IIb (10 mg), m.p. 157-161°. It was recrystallized and identified by direct comparison with an authentic sample.

Acetylation of perezone (Ia). The quinone Ia (980 mg) was dissolved in Ac₂O (5 ml), Zn (16-30 mesh; 10 g) and NaOAc anh (200 mg) were added and the mixture refluxed for 30 min, the Zn filtered off and washed with hot Ac₂O, and the solution evaporated to dryness in vacuum. The oily residue was dissolved in Et₃O, washed with water, dried and evaporated. After four distillations (115-120°/0-07-0-08 mm Hg), pure Ib (550 mg) was obtained as an orange viscous liquid, λ_{max} 204, 257, 325 mµ; ε , 8400, 15,700, 700. IR bands at 1770 (acetyl group), 1660 with a shoulder at 1650 (quinone CO groups) and 1620 cm⁻¹ (C=C double bonds). (Found : C, 70-28; H, 7-76; O, 22-22. C₁₇H₂₂O₄ requires: C, 70-32; H, 7-64; O, 22-04%).

From the higher boiling fractions, a sample of leucoperezone triacetate² (IX, 110 mg) could be isolated. It showed λ_{max} 206, 267 mµ; ε , 23,200, 400; IR bands at 1765 (acetyl groups) and 1637 and 1590 cm⁻¹ (C=C double bonds). NMR signals at 1·18 (doublet, J = 7 c/s, 3H, secondary Me group) 1·51 and 1·64 (singlets, 3H each, gem-dimethyl), 2·07 (singlet, 3H, aromatic Me), 2·16 (singlet, 9H acetyl groups), 5·01 (broad triplet, 1H, vinylic proton) and 6·76 (singlet, 1H, aromatic proton).

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