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HYPOIODITE THERMOLYSIS-CYCLIZATION ROUTE TO POLYCYCLIC KETONES. DIRECTION OF THE CC-BOND SCISSION. REARRANGEMENT OF 6-PROTOADAMANTANOL TO 2- AND 4-HOMOBRENDANONE

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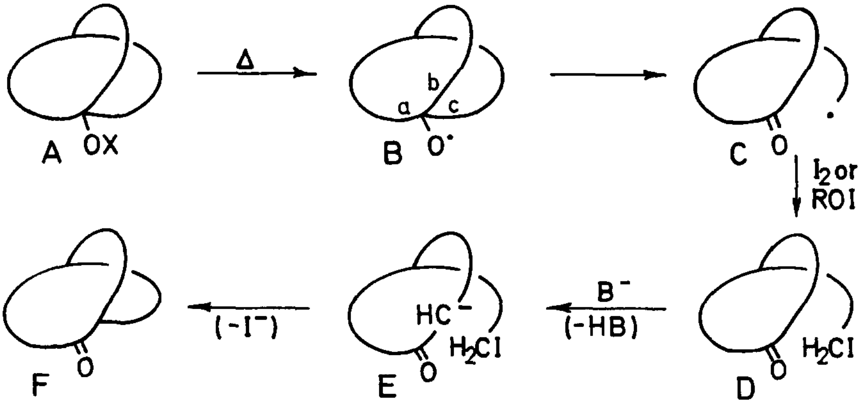
Summary: Thermolysis of 6-protoadamantyl hypoiodite followed by intramolecular, base-promoted, cyclization of the resulting iodoketones yields 70% of a 3:2 mixture of 4-homobrendan-4-one and 2-homobrendan-2'-one. Direction of the α-CC bond scission in the hypoiodite appears to be controlled by the relative strain energies of the iodoketones.

The hypoiodite thermolysis-cyclization sequence appears to be an excellent method for preparation of polycyclic ketones by rearrangement of the appropriate bridgehead alcohols.[1-5] 4-Protoadamantanone was obtained from adamantanol in 71-82% yield;[3] 1-homoadamantanol yielded 74% of 10-homoprotoadamantan-4-one,[4] while 3-homoadamantanol gave 78% of a 3:2 mixture of 4-homoadamantanone and 4-homoprotoadamantan-4-one.[5] The most plausible mechanism[1] (Scheme I) involves formation of the hypoiodite (A, X=I) in situ from the alcohol (A, X=H),

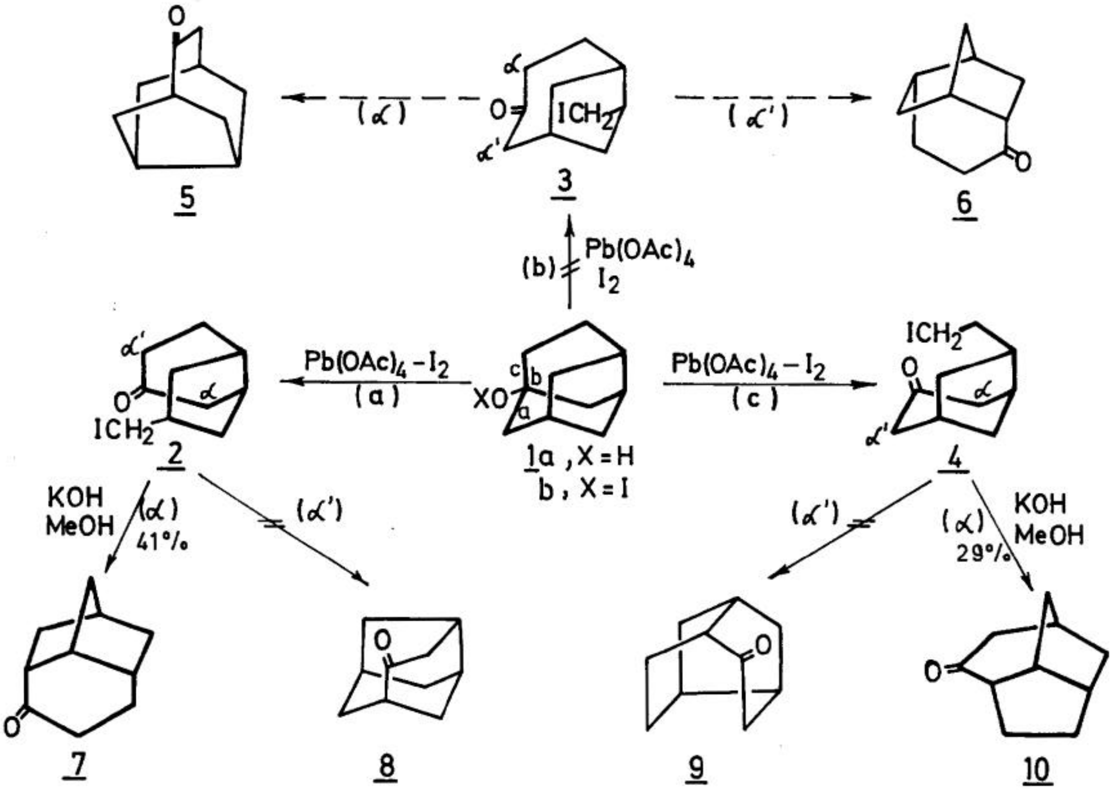
Scheme I



followed by homolytic cleavage of the O-I bond and rearrangement of the resulting alkoxy radical (B) by scission of one α-CC bond (a, b, or c) to give the carbonyl-alkyl radical (C) and the corresponding iodoketone (D). Intramolecular, base-promoted, C-alkylation of the iodoketone will produce the polycyclic ketone (F). Since two α-carbonyl methylene groups in the iodoketone are activated, two isomeric polycyclic ketones could be formed from each iodoketone. Consequently, the structure of the polycyclic ketone(s) depends on both the direction of the CC-bond scission in the alkoxy radical and the course of the intramolecular C-alkylation of the iodoketone.

In this work we studied the first of these two reactions, the α-CC bond scission, using 6-protoadamantanol (1a) as the starting material. Contrary to the systems studied previously,[1-5] all three α-CC bonds in 1 (Scheme II), are nonequivalent ($a \neq b \neq c$) and, consequently, three isomeric iodoketones, 2, 3, and 4, could be formed through the CC-bond scission. The intramolecular C-alkylation of 2, 3, and 4 could theoretically produce six ketones: 5, 6, 7, 8, 9, and 10.

Scheme II



6-Protoadamantyl hypoiodite (1b) was prepared and thermolyzed in a single operation by treatment of 1a[6] (7 mmol) with lead tetraacetate (17 mmol) and iodine (15 mmol) in a dry benzene solution (60 ml) at 70 °C for 2 h. The solid materials were removed by filtration and the filtrate was washed with aqueous $Na_2S_2O_3$ and $NaHCO_3$ and dried. Evaporation of the solvent produced an approximatively 3:2 mixture (by ^1H NMR) of two iodoketones.[7] The crude iodoketones were cyclized by KOH (35 mmol) in methanol (50 ml; reflux 2 h) to yield a 3:2 mixture of two products which was purified on a neutral alumina (activity III) column using pentane as eluent. The overall yield of the pure products ($\geqslant$96% by GLC) was 70% (based on 1a). The products were separated on a 10% charcoal-silica gel column with a 0→5% ethylacetate-cyclohexane mixture as eluent.

The spectral data of both products are in accord with all six proposed structures: 5, 6, 7, 8, 9, and 10. To assign the correct structures to the products, they were reduced to the parent hydrocarbons by Wolff-Kishner reaction. The major product (41%) was identified as *4-homo*brendan-4-one[8] (**7**, tricyclo$[5.2.1.0^{3,8}]$decan-4-one) by ^{13}C NMR, ^{1}H NMR, IR, and mass spectrometry, and GLC comparison of its parent hydrocarbon, *4-homo*brendane,[9] with an authentic sample.[10] The ^{13}C NMR spectrum of the hydrocarbon derived from the minor product (29%) showed 10 signals.[11] Such a spectrum can correspond only to structures **8** and **10**.[12] However, the IR, ^{13}C NMR, ^{1}H NMR, and mass spectra of the minor product[13] and its parent hydrocarbon[11] were entirely different from those of authentic samples of 5-protoadamantanone[14] (**8**) and protoadamantane, respectively. Consequently, structure **10** was assigned to the minor product. This new tricyclic system (tricyclo$[5.2.1.0^{4,8}]$decane) can be conveniently named[15] *2-homo*brendane. According to our knowledge no *2-homo*brendane derivative has been prepared previously.

Thus, thermolysis of 6-protoadamantyl hypoiodite (**1b**) proceeds through scission of bonds *a* and *c*, rather than *b*, producing iodoketones **2** and **4** in a ratio of 3:2, while iodoketone **3** is not formed. The relative strain energies of the iodoketones may be assumed to roughly parallel the relative strain energies of the hydrocarbons from which they are derived. The calculated strain energy of the hydrocarbon corresponding to iodoketone **3** (bicyclo[4.2.1]nonane: 20.95 kcal/mol)[16] is twice the strain energy of the hydrocarbons related to iodoketones **2** and **4** (bicyclo[4.3.0]nonane: 9.86 kcal/mol, bicyclo[3.2.1]octane: 12.06 kcal/mol).[16] Therefore, *the direction of the α-CC bond scission in the hypoiodite appears to be controlled by the relative strain energies of the iodoketones.*[17] This is in good agreement with the results of thermolyses of 3-noradamantyl and *4-homo*isotwist-3-yl hypoiodite.[18]

Iodoketones **2** and **4**, could theoretically yield ketones **7** and **8**, and **9** and **10**, respectively, by base-promoted cyclization (Scheme II). Both α-carbonyl methylene groups (α and α') in **2** as well as in **4** should be about equally active. However, the cyclizations of iodoketones **2** and **4** were found to be highly selective processes yielding ketones **7** and **10**, rather than **8** and **9**, respectively. Ketones **7** and **10** are formed through 5-membered ring closures, while the formation of ketones **8** and **9** would require closures of 6- and 7-membered rings. This is in good agreement with the rates of the base-promoted cyclizations of ω-halogenoalkylmalonic esters to the cycloalkane-1,1-dicarboxylates.[19] The relative rates of closure of 4-, 5-, and 6-membered rings were found[19] to be 1 : 6500 : 5, respectively. The closure of 5-membered rings was recently demonstrated to be also favored over 7-membered ring closures.[20]

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References and Notes

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7. 2 + 4: ^{1}H NMR ($CDCl_3$) δ 3.2 and 3.1 (d+t, 4H), 1.5-2.7 (m, 26H) ppm; ^{13}C NMR (C_6D_6) δ 209.7 and 210.5 (C=O) ppm; IR (film) 2940 (s), 2860, 1720 (s), 1455, 1420, 1350, 1230, and 1190 cm^{-1}.
8. ^{13}C NMR ($CDCl_3$) δ 215.4, 50.3, 46.9, 41.4, 37.9, 35.7, 33.8, 33.3, 31.3, and 27.7 ppm; ^{1}H NMR ($CDCl_3$) δ 0.8-3.0 (m) ppm; IR (film) 2950 (s), 2870, 1700 (s), 1455, 1290, 1250, and 1240 cm^{-1}; MS m/e 150 (M^{+}, 72%), 108 (27), 96 (69), 79 (69), and 66 (100); mp 81-83 °C.
9. (a) N. Takaishi, Y. Fujikura, Y. Inamoto, and K. Aigami, J. Org. Chem., 42, 1737 (1977). (b) The melting point of 4-homobrendane, prepared from 7 as well as from 4-homobrendan-4'-one,[10] was determined to be 106-108 °C rather than 65-67 °C as given in reference 9a.
10. We wish to thank Dr. Bernard Boyer for providing a sample of 4-homobrendan-4'-one, which was reduced to 4-homobrendane.
11. ^{13}C NMR (C_6D_6) δ 46.5, 42.8, 41.4, 38.0, 34.1, 33.5, 33.2, 32.9, 30.6, and 23.3 ppm; ^{1}H NMR (C_6D_6) δ 0.9-2.6 (m) ppm; IR (KBr) 2930 (s), 2860, 1470 and 1455 cm^{-1}; MS m/e 136 (M^{+}, 27%), 95 (30), 94 (27), 85 (60), 71 (83), and 57 (100); mp 133-135 °C.
12. The ^{13}C NMR spectra of the hydrocarbons corresponding to ketones 5, 6, and 9 would show 4, 6, and 6 signals, respectively.
13. ^{13}C NMR ($CDCl_3$) δ 217.2, 56.1, 49.1, 46.1, 41.6, 41.3, 34.6, 33.9, 33.6, and 32.6 ppm; ^{1}H NMR ($CDCl_3$) δ 1.0-2.8 (m) ppm; IR (film) 2940 (s), 2860, 1695 (s), 1450, 1350, 1220, and 1110 cm^{-1}; MS m/e 150 (M^{+}, 100%), 107 (88), 95 (60), 79 (90), and 67 (91); mp 121-124 °C.
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17. An alternative possibility suggesting the formation of the iodoketone (Scheme I, C → D) to be the rate determining step rather than the rearrangement of the alkoxy radical to the carbonyl-alkyl radical (B → C) cannot be rejected completely. Also, the carbonyl-alkyl radical could recombine to the alkoxy radical (C → B). According to this presumption all three carbonyl-alkyl radicals, corresponding to iodoketones 2, 4, and 3, could be formed, but the latter, unlike the former two, would recombine rapidly to the alkoxy radical rather than to yield iodoketone. However, this appears to be fairly unlikely, since no product derived from 3 was detected and all three carbonyl-alkyl radicals, being similar in structure, should behave alike.
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