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Minor Products in Photoreactions of α-Diketones with Arenes. Abstraction of Hydroxylic Hydrogen by Triplet Carbonyl

Mordecai B. Rubin* and Arie L. Gutman[1]

Department of Chemistry, Technion-Israel Institute of Technology, Haifa, Israel

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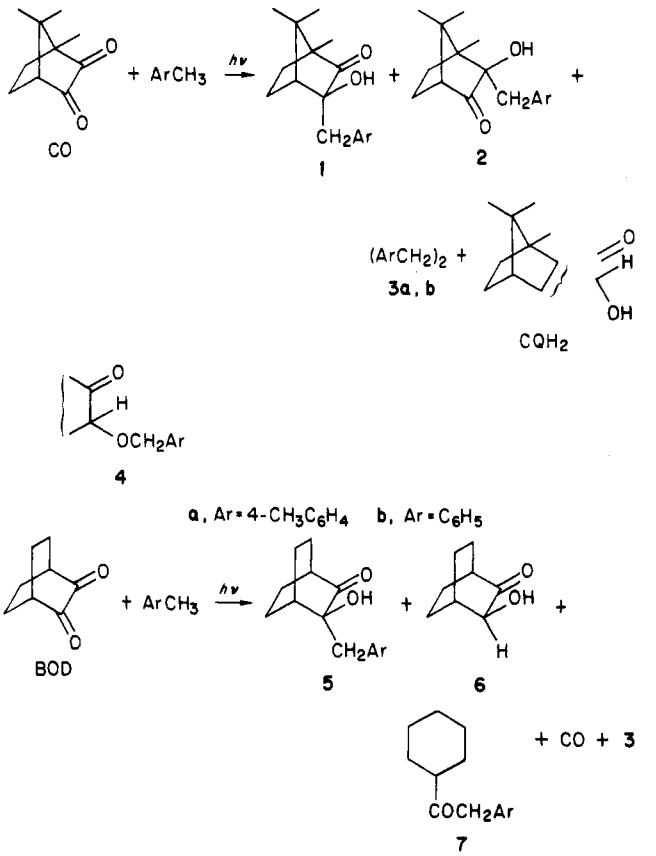
Photochemical reactions of cyclic saturated α-diketones in toluene or *p*-xylene produce 1:1 adducts as major products and smaller amounts of reduced diketone and bibenzyls, as expected from previous work. In addition, reaction of BOD gave 2% of the decarbonylation product, *p*-methylbenzyl cyclohexyl ketone; reaction of camphorquinone gave a mixture of decarbonylation products (10% total) including saturated and unsaturated monoketones. These compounds were secondary products arising from reaction of photoexcited diketone with the initially formed adducts; quenching and sensitization studies showed that triplet states of α-diketones were involved in both primary and secondary reactions. The decarbonylation products were also formed by reaction of benzophenone triplets or of *tert*-butoxy radicals with adducts. Deuterium labeling of the adducts was employed to demonstrate that the decarbonylation process involves abstraction of hydroxylic hydrogen.

One of the characteristic photoreactions[2] of α-dicarbonyl compounds is abstraction of a hydrogen atom from a wide variety of substrates to give semidione and substrate derived radicals which proceed to product(s) via coupling or disproportionation reactions. Some years ago we reported[3] a reaction of this type between camphorquinone (CQ) and substituted toluenes which gave about 70% of crystalline adducts[4] **1** and **2**, the appropriate bibenzyl (**3**), and about 10% of mixed hydroxycamphors (CQH_2). More recently it was shown[5] in a similar reaction of CQ or of bicyclo[2.2.2]octane-2,3-dione (BOD) with aromatic aldehydes that quantum yields and product compositions depended on experimental conditions and could be varied markedly, particularly by variations in light intensity. These results prompted a reinvestigation of the reactions of CQ and BOD with toluenes in order to determine if such a dependence on experimental conditions could be observed and to account for the unidentified 20% of reaction products. It was of particular interest to establish if O-benzylated products, such as **4**, were formed. While no evidence for **4** has been obtained, the new photocleavage reaction of α-hydroxy ketones observed forms the substance of this report. For convenience in NMR analysis, most of the work was performed with *p*-xylene.



Reaction Products

Initial experiments were performed with BOD since the symmetry of this diketone eliminates complications due to regio- and stereoisomerism of products. Irradiation of a solution of BOD in *p*-xylene under nitrogen at wavelengths longer than 380 nm furnished a mixture of the expected products: adduct **5a** (70%), reduced diketone **6** (17%), and bibenzyl **3a** (6%).[6] In addition gas chromatographic analysis showed the presence of about 2% of an additional product of relatively short retention time. Pure material corresponding to this peak was isolated by preparative scale TLC and shown, by spectroscopic properties and unexceptional synthesis (see Experimental Section), to be *p*-methylbenzyl cyclohexyl ketone (**7a**). The

(1) Taken in part from: Gutman, A. L. M.Sc. Thesis, Technion, 1978.
(2) For reviews, see: Rubin, M. B. *Top. Curr. Chem.* **1969**, *13*, 251. Monroe, B. M. *Adv. Photochem.* **1971**, *8*, 77. Rubin, M. B. *Top. Curr. Chem.*, in press.
(3) Rubin, M. B.; LaBarge, R. G. *J. Org. Chem.* **1966**, *31*, 3283.
(4) For results relating to the stereochemistry of **1** and **2**, see: Rubin, M. B.; Ben-Bassat, J. M. *Tetrahedron*, **1970**, *26*, 3579.
(5) Rubin, M. B.; Inbar, S. *J. Am. Chem. Soc.* **1978**, *100*, 2266.
(6) Theoretically, yields of **3** and **6** should be equal. Control experiments showed that considerable **3** was lost by volatilization under the conditions of the workup.

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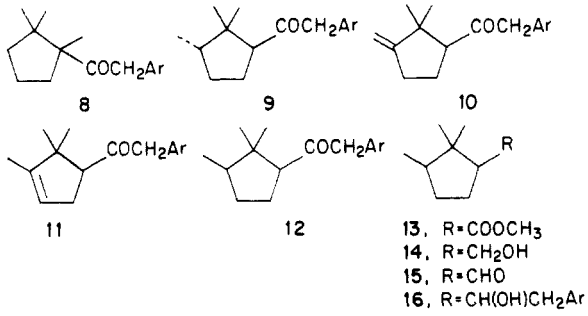
product composition was not changed by careful exclusion of oxygen (freeze–pump–thaw degassing), by the use of monochromatic light (436 nm), by varying initial BOD concentration, or by varying light intensity. In the presence of 1×10^{-3} M anthracene, complete quenching was observed. At lower anthracene concentrations, partial quenching did not affect product ratios. Similar results were obtained with toluene including formation of the corresponding ketone **7b**. The presence of carbon monoxide in the head space of the reaction vessel was established by qualitative tests.

An anticipated, reaction of CQ with *p*-xylene produced a more complex product mixture. In addition to the previously reported **1–3** and CQH_2, gas chromatographic analysis showed three overlapping peaks of approximately equal intensities with retention times similar to those observed for **7a,b** and corresponding to about 10% of the total product. Repeated preparative TLC afforded pure ketones (**8** and **9**) corresponding to two of these peaks as well as a mixture of two unsaturated ketonic compounds (**10** and **11**) with retention time corresponding to the third peak. Identification of **8–11** was based on the following considerations.



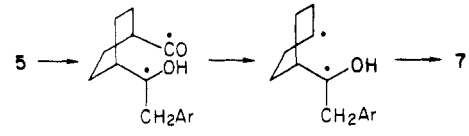
Mass spectra (M^+ 244) indicated that **8** and **9** (like **7a**) had compositions corresponding to loss of one molecule of carbon monoxide from adducts **1** or **2** analogous to the relationship between **7a** and **5a**. Infrared and NMR spectra were in full agreement with formulation as trimethylcyclopentyl *p*-methylbenzyl ketones. Further, the NMR spectrum of **8** showed three aliphatic methyl singlets consistent with its formulation as 1,2,2-trimethylcyclopentyl *p*-methylbenzyl ketone (**8**). Accordingly, **9** should be one of the isomeric (cis or trans) 2,2,3-trimethylcyclopentyl ketones and exhibit, in addition to the aromatic methyl group, two singlets and a doublet for the three aliphatic methyl groups. These signals overlapped in the observed spectrum, but the problem was resolved by addition of the shift reagent $Eu(DPM)_3$ which resulted in separation of the signals to give the expected spectrum.[7] Finally, **9** was assigned the trans stereochemistry on the basis of its nonidentity with *cis*-2,2,3-trimethylcyclopentyl *p*-methylbenzyl ketone (**12**) prepared from methyl *cis*-2,2,3-trimethylcyclopentanecarboxylate[8] (**13**) via Grignard reaction of the derived aldehyde **15** with (*p*-methylbenzyl)magnesium chloride followed by oxidation to **12** as detailed in the Experimental Section.

The third monoketonic fraction (M^+ 242) exhibited the NMR spectrum characteristic of a mixture of methylcyclopentenyl and methylenecyclopentyl ketones. The pertinent features of the spectrum were very similar to those reported[8] for methyl 2,3,3-trimethyl-3-cyclopentene carboxylate and 2,2-dimethyl-3-methylenecylcopentanecarboxylate and related compounds. The ratio **10/11** was approximately 2:1 based on integration of the appropriate olefinic and allylic proton signals. Catalytic hydrogenation (Pd/C, atmospheric pressure) of the mixture provided a single, saturated (M^+ 244) ketone not identical with **9**. Examination of models suggests that hydrogenation of both **10** and **11** should occur from the side of the molecule trans to the acyl group in agreement with the assignment above.

Mechanistic Investigation

Analysis of reaction profiles of irradiations of CQ and of BOD with *p*-xylene showed that ketones **7a** and **8 + 9 + 10 + 11** were not primary products of reaction but only began to accumulate after appreciable conversion to adducts had occurred. Thus, the possibility could be ruled out that these ketones were formed by a mechanism involving initial α-cleavage of diketone followed by decarbonylation and coupling with *p*-methylbenzyl radicals.

A second possible α-cleavage mechanism could also be ruled out. This involves, as illustrated for **5**, decarbonylation of the intermediate biradical **17** followed by intramolecular hydrogen atom transfer and would account nicely for formation of saturated monoketones. However,



direct excitation of **5** (or of **1** and **2**) is not possible under the experimental conditions used ($\lambda_{irr} > 380$ nm or $\lambda_{irr} = 436$ nm). Further, prolonged irradiation of **5a** at 313 nm in benzene solution led to partial destruction without formation of **7a** as established by gas chromatographic analysis. It also appears unlikely that energy transfer from excited (triplet) BOD ($E_T \sim 52$ kcal/mol) to **5** would be of any significance.[10] Irradiations of **5a** at 313 nm using the triplet sensitizer *m*-methoxyacetophenone ($E_T \sim 72$ kcal/mol) provided no evidence for triplet sensitized cleavage of **5a** although this sensitizer was effective in sensitizing the BOD–*p*-xylene reaction and produced the same product mixture as obtained from direct irradiation at longer wavelengths. Conceivably, α-cleavage of adducts does, in fact, occur, but rebonding of the resulting biradical is faster than other possible reactions.

These sensitization experiments and the quenching by anthracene mentioned earlier show that the triplet state of diketone is involved in all the observed photochemistry and suggest that reaction of triplet dione with adduct(s) is responsible for formation of decarbonylation products. This could be established by irradiation of mixtures of 5a with *either* CQ or BOD at long wavelength in benzene solution. In both cases, **7a** was formed in about 30% yield with low ($<5 \times 10^{-4}$) quantum yield; other products were not identified. Further, irradiation of **1** with BOD or CQ produced a mixture of **9–11** while comparable reaction of **2** produced **8**. Other procedures which also produced decarbonylated products from the adducts included irradiation of solutions containing adducts and benzophenone

(7) Both **9** and **12** showed very similar dependences of NMR shifts on shift reagent concentration so that no stereochemical information could be deduced from such experiments.

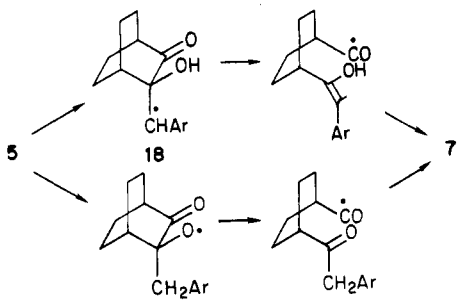
(8) Danieli, B.; Palmisano, G. *Chem. Ind. (London)* **1976**, 565.

(9) Baas, P.; Cerfontain, H. *Tetrahedron* **1979**, *35*, 1135.

(10) Triplet energies of α-hydroxy ketones should be appreciably higher than those of corresponding α-diketones. Attempts to observe phosphorescence from **7e** gave extremely weak emission at 435 nm (corresponding to E_I ca. 65 kcal/mol) which cannot be assigned with any confidence to **7a** since it could only be detected at maximum instrument sensitivity.

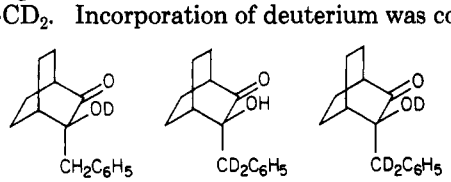
and thermolysis or photolysis of mixtures of adducts and di-*tert*-butyl peroxide.

The combination of all these results strongly suggests that a hydrogen atom abstraction by triplet dione carbonyl, triplet benzophenone, or by *tert*-butoxy radicals is the initial step in the formation of decarbonylated products. A priori, the most probable point of attack would be the benzylic methylene group leading to formation of radical **18**, which could then proceed to product by bond cleavage and loss of CO as illustrated for **5a**. A less likely alternative, as illustrated, is initial abstraction of a hydroxylic hydrogen to give oxy radical **19** followed by bond cleavage, etc. These possibilities were tested by examination of deuterium isotope effects.



The simpler approach consisted of irradiating BOD in D_2O-saturated *p*-xylene and comparing the product ratio of **5a–7a** with that obtained in a control experiment using ordinary water. While the amount of **5a** formed was identical in both experiments, the experiment using heavy water produced one-half the amount of **7a** obtained in the H_2O experiment. This result implicates the hydroxyl hydrogen as the point of attack in formation of **7** since it can readily be exchanged by deuterium either at the stage of semidione radical or in **5**. Deuterium transfer from deuteriated semidione radical to *p*-methylbenzyl radical (reversal of the initial H-abstraction step) would produce monodeuteriated *p*-xylene, but in the presence of an enormous excess of *p*-xylene, this could hardly account for the observed effect.

In order to obtain further confirmation for this unexpected result, three deuterium-labeled compounds were prepared: **5b**-OD, **5b**-CD_2, and **5b**-OD-CD_2. Reaction of $C_6H_5CD_2MgCl$ with BOD yielded **5b**-CD_2, two exchanges with D_2O gave **5b**-OD from unlabeled **5b** and **5b**-CD_2-OD from **5b**-CD_2. Incorporation of deuterium was confirmed



by mass and NMR spectra. Since direct measurement of reaction rates was not feasible, competition reactions were used to determine the deuterium isotope effect. Degassed benzene solutions containing BOD (0.145 M), *p*-xylene (1 M), and unlabeled 5b (0.192 M) or one of the three labeled derivatives were irradiated at $\lambda > 380$ nm, and the ratio of 7b–7a was determined by gas chromatography. The results were as follows: approximately identical ratios of **7a–7b** (1:0.08) from reactions of **5b** or **5b**-CD_2 and smaller ratios (1:0.035) from reactions of **5b**-OD or **5b**-OD-CD_2. Thus we find a kinetic isotope effect of approximately two in both experiments.

In summary, the exclusion of other possible mechanisms and the observation of a deuterium isotope effect in two separate types of experiments indicates that decarbonylated products are formed by abstraction of hydrogen from the hydroxyl group of adducts by triplet diketone. While this conclusion is certainly an unexpected one, it is not without precedent. Previtali and Scaiano[11] have presented a theoretical treatment proposing that such a process involving O–H or N–H bonds cannot be disregarded and have summarized experimental support for this view up to 1974. Additional experimental support was provided by McLauchlan and Sealy[12] in 1976 who demonstrated the formation of alkoxy radicals in reactions of quinones with aliphatic alcohols by spin trapping. More recently, Wagner and Puchalsky[13] have shown that cleavage of acetophenone pinacol by triplet acetophenone or propiophenone also involves fairly efficient abstraction of hydroxyl hydrogen, leading to cleavage of the pinacol. The earliest example, to our knowledge, is the cleavage of 1-alkyl-1-cyclopropanols by benzophenone (and other carbonyl compounds) reported by DePuy et al.[14] in which quantum yields were comparable with those observed in benzophenone–isopropyl alcohol reactions and a deuterium isotope effect of 3 to 6 was observed. It was suggested that a concerted process involving abstraction of hydroxyl hydrogen and opening of the three-membered ring was involved in these cases. Such a process might also account for the higher yield of decarbonylated products observed in the more strained bornane system as compared with bicyclo[2.2.2]octanes in the present work. However, all (or part) of the explanation may lie in the higher quantum yield (~0.3) for BOD reactions with arenes as compared with CQ (~0.06) so that competition between adduct formation and subsequent reactions is more favorable with BOD under the reaction conditions used. Finally, it should be noted that quantum yields for formation of decarbonylated products were very low.

Experimental Section

Melting points are uncorrected. Infrared spectra were determined in chloroform solution unless noted otherwise. NMR spectra were determined in deuteriochloroform at 60 MHz with tetramethylsilane as internal standard and are given as ppm from Me_4Si (δ).

Gas chromatographic analyses were performed with a 6 ft × $^1/_8$ in. column of 1% XE-60 on 100–120 mesh Gaschrom Q at a flow of 25 mL of nitrogen/min. Injector and detector temperatures were 200 °C; initial column temperature was 160 °C, which, 10 min after injection, was raised during 1 min to 190 °C.

Preparative-scale irradiations were performed with a 900-W xenon lamp (Osram XBO 900) using a 1-cm layer of 1% sodium chromate solution to eliminate radiation below 420 nm. Irradiation vessels were evacuated on the water pump and filled with nitrogen several times before being closed. Small-scale irradiations were performed with 3 mL of solution in square Pyrex cells (1-cm light path), which were degassed by five freeze–pump–thaw cycles and then sealed. The light source was a 200-W high-pressure mercury (Osram HBO 200); the 313- and 436-nm lines were isolated with interference filters or a 1-cm glass filter was used to eliminate radiation below 380 nm.

Racemic camphorquinone was used; all products derived from CQ are therefore racemic.

Irradiation of Bicyclo[2.2.2]octane-2,3-dione (BOD) and *p*-Xylene. A solution of BOD (0.70 g) and *p*-xylene (17 mL) in benzene (25 mL) under nitrogen was irradiated until the yellow

(11) Previtali, C. M.; Scaiano, J. *J. Chem. Soc., Perkin Trans. 2* **1975**, 934.
(12) McLauchlan, K. A.; Sealy, R. C. *J. Chem. Soc., Chem. Commun.* **1976**, 115.
(13) Wagner, P. J.; Puchalsky, A. E. *J. Am. Chem. Soc.* **1980**, *102*, 7138.
(14) DePuy, C. H.; Jones, H. L.; Moore, W. M. *J. Am. Chem. Soc.* **1973**, *95*, 477.

color of starting material had disappeared (40 h). Examination of the head space with a Drager carbon monoxide tube immediately after opening the cell indicated the presence of carbon monoxide. Gas chromatographic analysis showed four peaks with retention times of 2.0 (bibenzyl **3a**), 4.3 (hydroxy ketone **6**), 8.4, and 18.5 min (adduct **5a**). The solution was concentrated under vacuum on the steam bath and the oily residue dissolved in hexane (3 mL) and left overnight in the refrigerator. The crystals which separated were filtered to give 3-(*p*-methylbenzyl)-3-hydroxybicyclo[2.2.2]octan-2-one (**5a**, 0.40 g, 33%), mp 140–142 °C. The analytical sample of **5a** was obtained by recrystallization from hexane: mp 143–144 °C; ν_{max} 1720, 3540 cm^{-1}; NMR 7.20 (4 H), 2.90 (2 H), 2.35 (3 H), 1.2–2.2 (m, 11 H); MS, *m/e* 244 (M^+). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.69; H, 8.19. Found: C, 78.42; H, 8.00.

The filtrate was concentrated and chromatographed on thick-layer silica gel plates with benzene as eluant. The following products were isolated in order of increasing polarity: *p,p'*-dimethylbibenzyl (**3a**, 60 mg, 6%); an impure fraction (50 mg) which was rechromatographed in the same way to give pure *p*-methylbenzyl cyclohexyl ketone (**7a**, 20 mg, 1.7%) as a colorless oil, identical by comparison of IR and NMR spectra with the compound obtained from the synthesis described below, additional **5a** (430 mg, 37%, total yield 70%); 3-hydroxybicyclo[2.2.2]octan-2-one (**6**, 120 mg, 17%).

The product composition was not changed by varying light intensity, concentrations of either BOD or *p*-xylene, or by careful degassing using the freeze–pump–thaw method.

Irradiation of BOD and Toluene. A solution of BOD (0.50 g) in toluene (70 mL) was irradiated (10 h) and worked up as described above to give the following products: **3b** (50 mg, 10%); benzyl cyclohexyl ketone (**7b**, 0.020 g, 2%) as a colorless oil; 3-benzyl-3-hydroxybicyclo[2.2.2]octan-2-one (**5b**, 0.47 g, 60%) as white crystals. The analytical sample of **5b** was prepared by crystalization from hexane: mp 129–130 °C; ν_{max} 1720, 3550 cm^{-1}; NMR 7.30 (5 H), 2.89 + 2.84 (2 H, J_{AB} = 14 Hz), 2.2–2.5 (m, 2 H), 1.7–2.2 (m, 9 H); MS (relative intensity) *m/e* 230 (M^+ (5.60), 111 (100). Anal. Calcd for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88. Found: C, 77.97; H, 7.75. The final fraction was 3-hydroxybicyclo-[2.2.2]octan-2-one (**6**, 70 mg, 14%).

Synthesis of *p*-Methylbenzyl Cyclohexyl Ketone (7b). Reaction of commercial cyclohex-3-enecarboxaldehyde (3 g) in dry ether with (*p*-methylbenzyl)magnesium chloride in the usual way followed by chromatography on silica gel yielded, in addition to **3a**, cyclohex-3-enyl *p*-methylbenzyl carbinol (5.5 g, 60%) as a colorless oil which was crystallized from hexane to give 4.2 g of pure product; mp 58.5–59°: ν_{max} (KBr), 3250 cm^{-1}; NMR, 1.5–1.8 (3H), 1.8–2.2 (2H), 3.4–3.9 (1H), 5.72 (2H, br, singlet), 7.13 ppm (4H); MS, *m/e* 216 (M^+).

Reduction of the carbinol (1.7 g) in methanol over 10% palladium on charcoal gave cyclohexyl(*p*-methylbenzyl)carbinol (1.55 g) as a crystalline solid. The analytical sample was prepared by crystallization from hexane: mp 88 °C; ν_{max} (KBr) 3260 cm^{-1}; NMR 1.0–1.4 (6 H), 1.50 (1 H, disappeared after addition of deuterium oxide), 1.6–2.1 (5 H), 2.33 (3 H), 2.5–3.1 (1 H), 3.3–3.9 (1 H), 7.13 (4 H); MS, *m/e* 218 (M^+), 200. Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.39; H, 9.77.

A solution of the preceding (0.29 g) in acetone (3 mL) was treated with 8 N chromic acid solution (0.85 mL) with stirring. After a few minutes, a few drops of 2-propanol were added followed by water (15 mL), and the aqueous phase was extracted three times with ether. Drying and concentration furnished crude cyclohexyl *p*-methylbenzyl ketone (**7a**, 0.20 g, 70%) as an oil, which was purified by preparative TLC as described above followed by bulb-to-bulb distillation at 180–200 °C (0.2 mm) to give the analytical sample: mp 34–36 °C; ν_{max} 1705 cm^{-1}; NMR 1.1–2.1 (11 H), 2.33 (3 H), 3.70 (2 H), 7.13 (4 H); MS, *m/e* 216.1502 (M^+). Anal. Calcd for $C_{15}H_{20}O$: C, 82.28; H, 9.32; *m/e* 216.1514. Found: C, 82.30; H, 9.60.

The benzyl ketone **7a** decomposed rapidly; it could be stored for several weeks under nitrogen in the refrigerator.

Irradiation of Camphorquinone (CQ) and *p*-Xylene. A solution of CQ (3.6 g) and *p*-xylene (18 mL) in benzene (100 mL) under nitrogen was irradiated for 150 h with a Hanovia 450-W immersion lamp by using a color glass filter (cutoff 400 nm). Gas chromatographic analysis showed seven peaks. Four of these corresponded to the previously reported products 1–3 and CQH_2; minor peaks at 8.8, 9.8, and 10.3 min were unidentified. The reaction product was concentrated in vacuo on the steam bath to give a nearly colorless oil (5.1 g). A sample (0.3 g) was set aside and the remainder chromatographed on silica gel (170 g). Elution with hexane gave **3a** (0.35 g, 8%). Elution with 1:1 hexane–benzene gave a colorless oil (0.50 g, 10%) whose GC analysis indicated that it contained the unidentified substances. Elution with benzene gave a mixture (3.1 g, 60%) of adducts **1** and **2**. Elution with ethyl acetate gave CQH_2 (0.5 g, 17%).

The mixture of unidentified products eluted with 1:1 hexane–benzene was chromatographed successively on thick-layer silica gel plates with 4:1, 3:1, 2.5:1, and 2:1 hexane–benzene. The resulting broad band was divided into three equal parts, and after elution with chloroform and concentration, each third was rechromatographed in the same way. In this manner three colorless liquids were obtained.

1. 1,2,2-Trimethylcyclopentyl *p*-methylbenzyl ketone (8, 36 mg): ν_{max} (methylene chloride) 1690 cm^{-1}; NMR 0.95 (3 H), 1.15 (3 H), 1.20 (3 H), 1.4–2.0 (m, 6 H), 2.30 (3 H), 3.75 (2 H), 7.15 (4 H); MS, *m/e* (realtive intensity) 244.1803 (M^+), 139.1085, 111.4412 (100). Calcd for $C_{17}H_{24}O$: *m/e* 244.1827.

2. *trans*-2,2,3-Trimethylcyclopentyl *p*-methylbenzyl ketone (9, 30 mg): ν_{max} 1700 cm^{-1}; NMR 0.83 (d, *J* = 5 Hz, 3 H), 0.87 (6 H), 1.3–2.0 (m, 6 H) 2.30 (3 H), 2.6–2.9 (m, 1 H), 3.52 (2 H), 7.00 (4 H) (in $CDCl_3$, 0.05 M in europium tris(dipivalomethane) 1.73 (d, *J* = 7 Hz, 3 H), 2.07 (3 H), 2.48 (3 H), 2.98 (3 H); MS, *m/e* (relative intenstiy) 244.1818 (M^+), 139.1113, 111.4412 (100). Calcd for $C_{17}H_{24}O$: *m/e* 244.1827.

3. A mixture (28 mg) of 2,2-dimethyl-3-methylenecyclopentyl *p*-methylbenzyl ketone (10) and 2,2,3-trimethylcyclopent-3-enyl *p*-methylbenzyl ketone (11): ν_{max} 1705 cm^{-1}; NMR 0.9 (2.3 H), 1.00 (2 H), 1.30 (3 H), 1.60 (2.2 H), 1.7–2.2 (m, 2 H), 2.34 (3 H), 2.7–3.2 (1 H), 3.70 and 3.37 (combined 2 H), 4.85 (d, *J* = 2 Hz, 0.75 H), 5.30 (m, 0.5 H), 7.20 (4 H); MS, *m/e* 242.1674 (M^+), 137.0957, 106.2483. Calcd for $C_{17}H_{22}O$: *m/e* 242.1670.

Synthesis of *cis*-2,2,3-Trimethylcyclopentyl *p*-Methylbenzyl Ketone (12). A. From the Mixture of 10 and 11. A solution containing the mixture **10** and **11** (23 mg) in absolute ethanol (10 mL) was hydrogenated over 10% palladium on charcoal (15 mg) at room temperature and atmospheric pressure. Evaporation of solvent gave **12** (23 mg) as a colorless oil, which was identical in all respects with the material obtained from CQ by the following procedure.

B. From CQ. Reduction of methyl *cis*-2,2,3-trimethylcyclopentane carboxylate[8] (2.5 g) in ether with lithium aluminum hydride (0.45 g) in the usual way gave (*cis*-2,2,3-trimethylcyclopentyl)carbinol (**14**, 1.8 g) as a colorless oil. Oxidation of this carbinol (1.55 g) with pyridinium chlorochromate (3.5 g) in methylene chloride maintaining the temperature below 20 °C was followed by the usual workup with ether. Washing the ether solution through a column of Florisil (30 g) gave *cis*-2,2,3-trimethylcyclopentanecarboxaldehyde (**15**, 1.3 g) as a colorless oil; NMR 9.82 (d, *J* = 2 Hz, 1 H). Reaction of a solution of **15** (1.2 g) in ether with (*p*-methylbenzyl)magnesium chloride followed by chromatography on silica gel afforded, in addition to **3a**, (*cis*-2,2,3-trimethylcyclopentyl)(*p*-methylbenzyl)carbinol (**16**, 1.06 g, 50% overall) as a colorless oil. Bulb-to-bulb distillation at 110–120 °C (0.1 mm) gave the analytical sample of **16**: mp −7 to −10 °C; ν_{max} 3500 cm^{-1}; NMR 0.70 (3 H), 0.80 (d, *J* = 5, 3 H), 0.95 (3 H), 1.1–1.5 (2 H), 1.5–1.9 (5 H), 2.33 (3 H), 2.6–2.9 (2 H), 3.7–4.1 (1 H), 7.10 (4 H); MS, *m/e* 246.1967 (M^+), 228.1872, 123.0657. Anal. Calcd for $C_{17}H_{26}O$; C, 82.87; H, 10.64; *m/e* 246.1983. Found: C, 81.83; H, 10.90.

A solution of **16** (0.16 g) in acetone (3 mL) was treated with 8 N chromic acid solution as described earlier to give a colorless oil (0.12 g, 75%) which was purified by preparative TLC as described earlier followed by bulb-to-bulb distillation at 90–100 °C (0.1 mm) to give the analytical sample of *cis*-2,2,3-trimethylcyclopentyl *p*-methylbenzyl ketone (**12**) as a clear oil: ν_{max} 1700 cm^{-1}; NMR, 0.60 (3 H), 0.85 (d, *J* = 5 Hz, 3 H), 1.13 (3 H), 1.3–2.0 (m, 5 H), 2.30 (3 H), 2.5–3.0 (m, 1 H), 3.55 (2 H), 7.03 (4 H); MS, *m/e* 244.2860 (M^+), 139.2447. Anal. Calcd for $C_{17}H_{24}O$: C, 83.55; H, 9.90; *m/e* 244.1827. Found: C, 83.41; H, 10.23.

3-Hydroxy-3-(α,α-dideuteriobenzyl)bicyclo[2.2.2]octan-2-one (5b-CD_2) and O-Deuteriated Compounds. A solution of BOD (0.30 g) in dry ether (30 mL) was added rapidly to the

Grignard reagent prepared from α-chloro-α,α-dideuteriotoluene[15] (0.50 g) and magnesium (0.15 g) in dry ether under nitrogen. The solution was refluxed for 0.5 h, cooled, and worked up in the usual manner to give an oily product (0.60 g), which was chromatographed on silica gel (150 g). Elution with hexane gave tetradeuteriobibenzyl (0.15 g). Elution with benzene gave **5b**-CD_2 as white crystals (0.19 g, 40%), which was crystallized from methylene chloride–hexane, mp 128–129 °C; the NMR spectrum was identical with the protio analogue except for absence of the two-proton signal at 2.9 ppm due to the benzylic methylene protons: MS, *m/e* (relative intensity) 232 (13.6).

The monodeuteriated compound, **5b**-OD was prepared by two crystallizations of **5b** from acetone–D_2O and gave the appropriate NMR spectrum.

The trideuteriated compound **5b**-CD_2-OD was prepared from **5b**-CD_2 in similar manner.

Reactions of 1 with Di-*tert*-butyl Peroxide. A. Thermolysis. A solution of **1** (0.15 g) and di-*tert*-butyl peroxide (0.50 g) in chlorobenzene was refluxed under nitrogen, and samples were withdrawn periodically for GC analysis; this indicated formation of a complex mixture. After 6 h, the solution was cooled and concentrated in vacuo (20 mm) to give a dark oil (0.18 g). Preparative TLC using benzene as eluant afforded recovered starting material (0.11 g) and a mixture (8 mg, 27% based on recovered starting material) of **9**–**11** in the ratio 2.5 (**9**):1 (**10** + **11**) (by NMR and GC analysis).

B. Photolysis. A solution of **7a** (45 mg) and the peroxide (0.50 g) in benzene (3 mL) was irradiated through a Pyrex filter. GC analysis showed peaks with retention time of 10 and 11 min corresponding to **9** and **10** + **11**.

Irradiation of Adducts with CQ or BOD. A solution of **2** (0.22 g) and CQ (0.50 g) in benzene (80 mL) under nitrogen was irradiated with a Hanovia 450-W mercury immersion lamp through a glass tube with a cutoff at approximately 380 nm. After 80 h, additional CQ was added and the irradiation continued for an additional 60 h when GC analysis indicated approximately 50% conversion to **8**. The solution was concentrated to give a yellow oil (1.03 g), which was chromatographed on silica gel (60 g). Elution with 1:2 hexane–benzene gave an oil (0.22 g), which afforded pure **8** (0.075 g, 40%) after preparative TLC (benzene eluant). Elution of the column with 1:9 benzene–hexane gave CQ (0.25 g, 31%), elution with benzene gave recovered **2** (0.11 g, 50%) and elution with ethyl acetate gave CQH_2 (0.38 g, 45%).

In a similar experiment using CQ and **1** there was obtained 35% of a 2:1 mixture of **9** and **10** + **11**, recovered CQ (67%), recovered **1** (50%), and CQH_2 (23%).

Similarly reaction of CQ or of BOD with **5a** afforded **7a**.

Irradiation of Adducts 1, 2, and 5a with Benzophenone. Degassed benzene solutions (3 mL) containing benzophenone (35 mg) and one of the adducts **1**, **2**, or **5a** (30 mg) were irradiated at 366 nm for 6 h. GC analysis indicated conversion of **1** to the mixture **9**, **10**, and **11**, of **2** to **8**, and of **5a** to **7a**.

Registry No. **1b**, 101980-79-4; **2b**, 102045-71-6; **3a**, 538-39-6; **3b**, 103-29-7; **5a**, 68903-63-9; **5b**, 66182-14-7; **5b**-CD_2, 101980-90-9; **6**, 63715-70-8; **7a**, 101980-77-2; **7b**, 61259-29-8; **7b** (alcohol), 101980-78-3; **8**, 101980-80-7; **9**, 101980-81-8; **10**, 101980-82-9; **11**, 101980-83-0; **12**, 101980-84-1; **13**, 101980-85-2; **14**, 101980-86-3; **15**, 101980-87-4; **16**, 101980-88-5; CQ, 465-29-2; CQH_2, 101980-91-0; BOD, 4216-89-1; 4-$CH_3C_6H_4CH_3$, 106-42-3; $C_6H_5CH_3$, 108-88-3; 3-cyclohexene-1-carboxaldehyde, 100-50-5; 4-methylbenzyl chloride, 104-82-5; 3-cyclohexenyl-*p*-methylbenzylcarbinol, 101980-89-6; (chloromethyl-d_2)benzene, 33712-34-4.

(15) Prepared by reduction of methyl benzoate with lithium aluminum deuteride followed by reaction with thionyl chloride according to the procedure of: Newman, M. S. *J. Am. Chem. Soc.* **1940**, *62*, 2295.

Facile Conversion of Natural Colchicine into (±)-Congeners and (+)-Enantiomers Including 2-Demethyl Analogues†

Raymond Dumont and Arnold Brossi*

Section on Medicinal Chemistry, Laboratory of Chemistry, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland 20205

J. V. Silverton

Laboratory of Chemistry, National Heart, Lung, and Blood Institute, National Institutes of Health, Bethesda, Maryland 20205

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Racemization of natural colchicine in refluxing acetic anhydride afforded after hydrolysis and chemical manipulation a variety of (±)-colchicinoids. Optical resolution of (±)-deacetylcolchicine and (±)-deacetylisocolchicine afforded the respective optical isomers, readily converted by N-acetylation into (−)- and (+)-colchicine and (−)- and (+)-isocolchicine. Selective ether cleavage of (±)- and (−)-colchicinoids with concentrated sulfuric acid afforded 2-demethyl analogues as major products. A single-crystal X-ray analysis of (±)-**1** showing unusual physical properties is reported.

Most biological effects of natural colchicine (**1b**) on mitosis and inhibition of tumors result from a disruption of the microtubule system. These effects are clearly related to its binding to α-tubulin, the subunit of tubulin protein.[1] Some biological effects of colchicine, however, cannot be explained by this mechanism. 2,3-Didemethylcolchicine (**21b**), i.e.,[2] binds only poorly to tubulin but shows pronounced antiinflammatory responses in artificially inflamed rat pads.[3]

Reevaluation of (±)- and unnatural (+)-colchicinoids in assays measuring antiinflammatory responses necessitated their preparation by more efficient procedures. This has now been accomplished, and the results take credit that several novel (±)-colchicinoids, target molecules of synthetic efforts, are now available for a comparison.

Racemic deacetylcolchiceine (**5**) was first obtained by Corrodi and Hardegger by base-catalyzed equilibration of the Schiff base obtained with benzaldehyde.[4] It was later shown that this process, affording considerable amounts

† Dedicated to Prof. A. Eschenmoser on the occasion of his 60th birthday.

(1) Capraro, H. G.; Brossi, A. *The Alkaloids*; Brossi, A., Ed.; Academic: New York, 1984; Vol. 23, pp 1–70.
(2) Rösner, M.; Hsu, F. L.; Brossi, A. *J. Org. Chem.* **1981**, *46*, 3686.
(3) The antiinflammatory properties of 2,3-didemethylcolchicine will be reported elsewhere.
(4) Corrodi, H.; Hardegger, E. *Helv. Chim. Acta* **1957**, *40*, 193.