for this behavior because it is not clear at which stage the unusual N-alkylation occurs. The nitrogen-free products from 1 and benzhydryl halides, on the other hand, presumably arose via decomposition of 3 or of an intermediate RON=NOAg. Finally, we have confirmed the presence of an elimination process by detecting cyclohexene in reaction mixtures of 1 and cyclohexyl bromide.

Experimental Section

Silver hyponitrite, precipitated from 1% solutions of the sodium salt at pH 7-8 (acetate buffer) with dilute silver nitrate, was dried below 1 Torr in an Al foil wrapped container and stored at -16 °C. The samples were redried in the same way for at least 30 min just before use. Solvents were reagent grade, and the halides were obtained from commercial sources and were usually redistilled or recrystallized before use. The analysis was performed by Spang Microanalytical Laboratory, Eagle Harbor, MI. NMR spectra (referenced to TMS) were recorded with a Varian EMI360 or XL-200 instrument and IR spectra with a PE Model 283B or a Nicolet Model 7199 spectrometer. Gas chromatography was carried out with an HP Model 5880 instrument and a 50 m × 0.2 mm i.d. capillary column (PONA, HP Cat. No. 19091S).

***N*-(Diphenylmethoxy)-*N'*-(diphenylmethyl)diazene *N'*-Oxide (2).** Chlorodiphenylmethane (2.05 g, 10 mmol) was dissolved in 10 mL of 2:1 benzene–mixed hexanes with stirring. Silver hyponitrite (2.74 g, 10 mmol, excess to minimize unreacted halide) was added slowly at room temperature, and the mixture was stirred magnetically for 3.5 h. The solution was filtered, and the filtrate was cooled in a liquid nitrogen–acetone slush bath. The resulting white crystals were recrystallized from methanol to give 11% yield of the product; mp 131-133 °C. IR (Nujol): 2840-2980 (br), 1480 (m), 1450 (s), 1375 (s), 1264 (w), 1285 (w), 1025 (s), 1000 (s), 940 (w), 910 (w), 800 (m), 755 (s), 740 (s), 695 (s), 660 (m), 600 (s), 565 (m), 555 (s), cm^{-1}. The ^1H NMR spectrum in $CDCl_3$ showed 1:1 singlets at δ 6.39 and 6.50 and an aromatic peak at δ 7.01-7.50. Anal. Calcd for $C_{26}H_{22}N_2O_2$: C, 79.19; H, 5.58; N, 7.11. Found: C, 79.14; H, 5.53; N, 7.12.

Isolation of the hyponitrite 3 has been described elsewhere.[4] The reactions in various solvents for the product study by ^1H NMR spectroscopy were conducted on a smaller scale in a manner similar to the syntheses of 2, with a stoichiometric excess of 1 added to the halide dissolved in 6-8 times its weight of solvent at 0 °C. After being stirred at 0 °C for about 20 min and at room temperature until no further changes in the appearance of the solid phase were evident, the mixture was filtered or centrifuged, the AgX was washed with the solvent of reaction, and the combined filtrate and washings were concentrated under reduced pressure. The residue was dissolved in $CDCl_3$, and the spectrum was recorded.

Allyl hyponitrite was prepared by addition of 0.2 g (0.7 mmol) of 1 to 2 mL of allyl bromide stirred in an ice bath. After 1 h the ice had melted, and the mixture was filtered and then concentrated with appropriate precautions to ca. 0.1 g of a shock-sensitive liquid that was stable for days at -16 °C. ^1H NMR ($CDCl_3$): δ 4.73 (d of mlt, J = 5 Hz, 2 H), 5.3 (mlt, 2 H), 6.0 (mlt, 1 H). After standing overnight at room temperature, a varnishlike deposit had formed on the inner wall of the NMR tube beneath the liquid level. The spectrum was again recorded, and revealed a new multiplet centered at δ 3.5 whose position and fine structure matched those of the CH_2 group of authentic allyl alcohol in $CDCl_3$. Acrolein, the other anticipated product, is known to polymerize in the presence of free-radical initiators.[10] IR (ν, neat): 3079 (w), 2930 (m), 1733 (w), 1636 (w), 1428 (s), 1339 (m), 1205 (m), 1019 (vs), 922 (vs), 684 (m). MS: m/z (relative intensity) 143 (0.2), 142 (0.3), 141 (1.5), 125 (1.4), 120 (0.2), 112 (6.2), 88 (12.5), 85 (5.0), 82 (4.0), 81 (8), 57 (14), 55 (23), 54 (15), 42 (8), 41 (100).

Cyclohexene from 1 and Cyclohexyl Bromide. A solution of the bromide (815 mg, 5.00 mmol) in hexanes (10 mL) was treated with 1 (689 mg, 2.50 mmol) at 0 °C, followed by stirring at 25 °C for a total of 5 h. The mixture was filtered, and the filtrate was diluted to 25 mL with hexanes. Gas chromatography (column) revealed a peak with the same retention time as cyclohexene. An olefin signal in the ^1H NMR spectrum of the solution at δ 5.65 was enhanced upon addition of authentic cyclohexene. The yield was determined as 34% (based on halide) by comparison of the GC peak area with that from a standard solution of the olefin.

Measurements shown in Figure 1 were carried out with magnetically stirred samples in small, serum-capped round-bottom flasks with a glass-encased thermocouple wire (copper-constantan) pierced through the cap. The flask was placed in a styrofoam cup and surrounded by expanded polystyrene insulation.

Acknowledgment. This work was supported in part by the Research Office, Michigan Technological University, and by a Dean's Fellowship to T.B.

(10) Schulz, R. C. Polymerization of Acrolein. In *Vinyl Polymerization*; Ham, G. E., Ed.; Marcel Dekker: New York, 1969; Vol. 1, Part I, Chapter 7.

On the Mechanism of Formation of Azines from Hydrazones

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Introduction

During the past several years we have been involved in synthesis of mixed azines, $X_2C{=}N{-}N{=}CY_2$, where X and Y are moieties derived from ketones. $X_2C{=}O$ was typically naloxone (1) or naltrexone (2), i.e. opioid antagonists, and $Y_2C{=}O$ represented steroidal ketones.[1-5] These azines were typically prepared by a reaction of $X_2C{=}O$ (1 or 2) with the hydrazones of steroidal ketones, i.e. $Y_2C{=}N{-}NH_2$. The resulting azines, such as the mixed azines between estrone (3) and 1 or 2 (4, 5), showed a range of unexpected biological activities ranging from the ultra-long-lasting opioid antagonist activity[4] to specificity for the opioid δ receptor subtype.[5] In order to further study the receptor requirements for the long-lasting and δ-specific activity, we prepared a series of azines of 1 or 2 with various nonsteroidal ketones, which were chosen for their steric shape and electronic distribution. Hydrazones of such ketones were prepared first, with the objective to couple them with 1 or 2.

In the course of synthesis of these hydrazones by treatment of the corresponding ketones with an excess of hydrazine hydrate, with or without acid catalyst, we made the following observations. Some ketones gave virtually quantitative yields of hydrazones. Some other ketones, on the other hand, gave very low yields of hydrazones but high yield of azines. Some sterically hindered ketones gave hydrazones in low yields with a great difficulty; yet the hydrazones, once formed, were easily converted into the azines upon standing.

The objective of this paper is to present these various ketone categories and to suggest some possible factors which influence the formation of hydrazones and azines. The ketone models, although chosen with the biological objectives in mind, do emcompass several important ketone categories, such as cyclic, sterically hindered, conjugated, etc.

(1) Kolb, V. M.; Gober, J. R. *Life Sci. Suppl. 1* **1983**, *33*, 419-422.
(2) Kolb, V. M.; Hua, D. H. *J. Org. Chem.* **1984**, *49*, 3824-3828.
(3) Kolb, V. M.; Hua, D. H.; Duax, W. L. *J. Org. Chem.* **1987**, *52*, 3003-3010.
(4) Koman, A.; Kolb, V. M.; Terenius, L. *Pharm. Res.* **1986**, *3*, 56-60.
(5) Koman, A.; Kolb, V. M.; Terenius, L. *Pharm. Res.* **1987**, *4*, 147-149.

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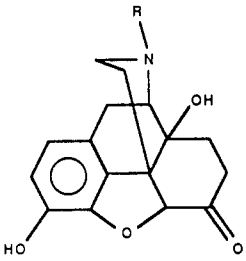

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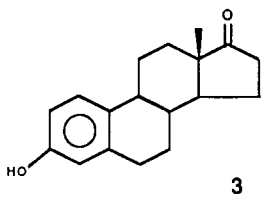
R = -CH_2- 2



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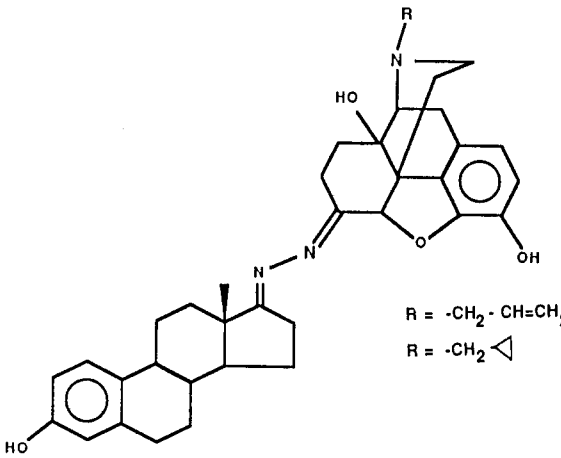


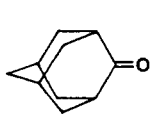
R = -CH_2-CH=CH_2 4

R = -CH_2- 5

Experimental Section

Melting points were taken on a Mel-Temp apparatus and are not corrected. The IR spectra were taken on a Perkin-Elmer 1320 spectrophotometer. The ^{13}C and ^1H NMR spectra were taken on JEOL FX 200-MHz and Bruker 360-MHz instruments at the University of Wisconsin—Madison. Some ^1H NMR spectra were taken on JEOL PMX-60 instrument. All spectra were taken in $CDCl_3$ unless otherwise noted. All the ketones used in this study were obtained from Aldrich Chemical Co.

2-Adamantanone Hydrazone (7) and Azine (8). 2-Adamantanone (**6**) (1.00 g; 0.00667 mol) was dissolved in 10 mL of 95% EtOH. Hydrazine hydrate (Aldrich; 3 mL; 0.063 mol) was added. The mixture was stirred at room temperature overnight. After that time the reaction was quenched by pouring into water. A solution thus obtained was extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried, and evaporated to give a white solid (0.96 g; the theoretical yield for the hydrazone is 1.09 g). IR (Nujol): ν 3360 (broad), 3210 (broad), NH_2 of the hydrazone **7**, 1640 (strong), C=N of the azine **8** and hydrazone **7**, cm^{-1}. The peak at 1722 cm^{-1} for the C=O of 2-adamantanone (**6**) was not found.



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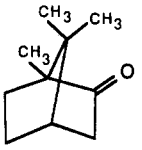
^{13}C NMR spectroscopy showed a mixture of the hydrazone **7** (minor) and azine **8** (major). ^{13}C NMR data for the hydrazone **7**: C-1 28.84; C-2 162.11; C-3 39.59; C-4 37.36[a]; C-5 27.98; C-6 36.52; C-8 38.94[a]; for the azine **8**: C-1 31.69; C-2 171.09; C-3 39.56; C-4 38.03[b]; C-5 27.92; C-6 36.61; C-8 39.32[b] ppm (the shifts with the same superscript may be interchanged). None of the peaks for 2-adamantanone (**6**) were found: C-1 46.66; C-2 217.30; C-3 46.66; C-4 38.90; C-5 27.19; C-6 35.98; C-7 27.19; C-8 38.90 ppm.

Very similar results were obtained when the acid catalyst (6 drops of 50% v/v HCl) was used or when the reaction was run for shorter time (3 h) under N_2, and the extraction was done with CH_2Cl_2. When a mixture of hydrazone **7** and azine **8** was refluxed in EtOH, open to air for 3 h, the product was all azine **8**.

Camphor Hydrazone (10) and Azine (11). (*R*)-(+)-Camphor (**9**) (1.0 g; 0.0066 mol) was treated with hydrazine hydrate under the same conditions as described in the above experiment. When no acid catalyst was added the reaction gave almost exclusively the recovered **9** (IR: C=O at 1745 cm^{-1}), a small amount of camphor azine (**11**) (C=N at 1670 cm^{-1}), and just a trace of camphor hydrazone (**10**) (as indicated by the broad bands for the NH_2 at 3345 and 3200 cm^{-1}, and C=N at 1620 cm^{-1}). When acid catalyst was added and reflux (3 h) was employed, the reaction products were the azine **11** (major), hydrazone **10** (minor), and some recovered **9**. A prolonged reflux (12–17 h) resulted in a mixture of azine **11** and hydrazone **10** and just a trace of the starting **9**. ^{13}C NMR for the hydrazone **10**: C-1 51.77; C-2 164.57; C-3 35.07; C-4 44.01; C-5 27.36; C-6 32.56; C-7 47.77; C-8 11.10; C-9 18.63; C-10 19.36. For azine **11**: C-1 52.27; C-2 172.86; C-3 35.07; C-4 43.89; C-5 27.21; C-6 32.18; C-7 47.68; C-8 11.10; C-9 19.01; C-10 19.51. For camphor (**9**): C-1 57.11; C-2 218.50; C-3 42.80; C-4 42.63; C-5 26.64; C-6 29.48; C-7 46.30; C-8 8.83; C-9 18.76; C-10 19.36 ppm. ^1H NMR for hydrazone **10**: CH_3-8 0.734; CH_3-9 0.965; CH_3-10 0.901. For azine **11**: CH_3-8 0.786; CH_3-9 1.034; CH_3-10 0.928. For camphor: CH_3-8 0.84; CH_3-9 0.97; CH_3-10 C.0.92 ppm.



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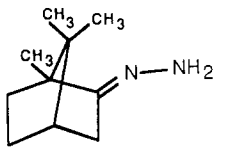

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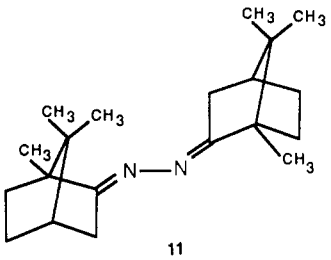

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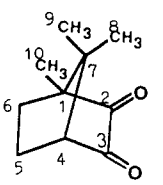
Camphorquinone Hydrazone (13). Camphorquinone (**12**) (1.00 g; 0.00602 mol) was treated with hydrazine hydrate under the conditions described above, without acid catalyst, for 21 h at room temperature. The IR of the product (yellow solid) revealed that no camphorquinone (**12**) was left (no C=O double peak at 1742–1760 cm^{-1}). Major peaks were 1710 (C=O), 1582 (C=N of hydrazone **13**), 3460 and 3422 (NH_2 of the anti **13**), 3300 and 3225 (NH_2 of the syn **13**; NH_2 syn is presumably at lower wavenumber, since it can be H-bonded intramolecularly). ^{13}C NMR spectroscopy revealed that the mixture was composed of two hydrazones (**13**), syn (C-3 at 144.40 ppm) and anti (C-3 at 149.44 ppm). No azine was found. ^1H NMR analysis showed the ratio of syn to anti **13** to be 3:2. The chemical shifts and assignments in ^{13}C and ^1H NMR spectra are as described in the ref 6.



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When the reaction was run under the reflux conditions (in THF) for 13.5 h, again the anti and syn **13** were obtained, with no azine present, but with starting material present in ca. 60%. When this mixture or a mixture of syn and anti **13** obtained by

(6) Cullen, D. L.; Mangion, M. M.; Crist, B. V.; Lightner, D. A. *Tetrahedron* **1983**, *39*, 733–742.

crystallization was refluxed in THF, open to air, for 3 h, the azine still was not observed.

Acetophenone Hydrazone (15) and Azine (16). Acetophenone (14) (1.00 g; 0.00833 mol) was treated with hydrazine hydrate at room temperature overnight, without catalyst, according to the procedure described for 2-adamantanone (6) (vide supra), except that the product was extracted with $CHCl_3$ and also Et_2O due to the poor solubility in $CHCl_3$. The product obtained was an oil composed of hydrazone 15 and azine 16 in a ratio of 20:1 (by ^1H NMR; CH_3 for hydrazone 15 at 2.03 ppm; for the azine 16 at 2.25 ppm; for the starting ketone 14 at 2.53 ppm). After 3 h of standing in the NMR tube the ratio of 15:16 changed to 18:1. After 24 h of standing in the NMR tube the ratio became 12:1. In the neat oil after 24 h of standing, yellow crystals formed. The NMR of this mixture showed a 1.9:1 ratio of 15 to 16. Upon prolonged standing (ca. 3 weeks or sooner if left open to air) all azine 16 is obtained. Some characteristic IR bands, acetophenone (14): 1605 (strong), 1588 (medium) cm^{-1}. Hydrazone 15: 3380, 3218 (strong), 3300 (medium) (NH_2), 1630 (weak), 1591 (strong) cm^{-1}. Azine 16: 1605 (strong), 1568 (medium) cm^{-1}. When the product was extracted with Et_2O which contained BHT, and then let stand open to air for 24 h, a mixture of 15 to 16 in a ratio 11.5:1 was obtained, similar to the ratio of 12:1 obtained above.

***p*-Nitroacetophenone Hydrazone (18).** When *p*-nitroacetophenone (17) (1.00 g; 0.00606 mol) was treated as above with hydrazine hydrate, a product precipitated out of the reaction mixture. This product was a pure hydrazone 18. IR (Nujol): ν 3416, 3318, 3230 (medium) (NH_2), 1615, 1600, 1565 (C=N and C=C), 1500 and 1325 (NO_2, assym and sym) cm^{-1}. NMR: CH_3 at 2.10 ppm in $CDCl_3$–DMSO-d_6; CH_3 of the starting ketone 17 at 2.74 ppm.

The hydrazone 18 was left stand open to air. Its IR and NMR spectra indicated no change, even upon 7 months of standing.

***p*-Methoxyacetophenone Hydrazone (20) and Azine (21).** When *p*-methoxyacetophenone (19) (1.00 g; 0.00666 mol) was treated as above with hydrazine hydrate, mostly hydrazone 20 with a trace of azine 21 was obtained (ratio of 19:1). IR (Nujol): 3392 (strong) 3305, 3250 (medium) (NH_2), 1640, 1609 (C=N and C=C) cm^{-1}. NMR, hydrazone 20: CH_3 at 2.08 ppm. Azine 21: CH_3 at 2.32 ppm. The CH_3 peak of the starting material 19 was at 2.52 ppm. Upon standing for 24 h the solid product composed of 20 with a trace of 21 showed only slightly increased amount of the azine 21.

Observation of Breakdown of Camphor Hydrazone (10) to Camphor (9) upon Standing. Camphor (9) was reacted with hydrazine hydrate with acid catalyst under the prolonged reflux conditions (12–17 h). These reaction conditions gave product, which consisted of a mixture of hydrazone 10 (C=N at 1620), azine 11 (C=N at 1670), and just a trace of camphor (9) (C=O at 1745). The reaction was run several times and was worked up slightly differently: extraction with $CHCl_3$, wash of $CHCl_3$ was saturated $NaHCO_3$, extraction with CH_2Cl_2, wash of CH_2Cl_2 with H_2O. Also, a reaction was run in which 100 mg of BHT was added at the beginning of the reaction ($CHCl_3$ extraction, wash with $NaHCO_3$). The reaction products were left to stand open to air and were monitored by IR, typically at the following times: 0 h (time immediately after the workup), 2 h, 4 h, 2 days, 3 days, 5 days, 7 days, and 17 days.

In all the experiments except the one in which BHT was added, an increase in the C=O absorption was observed. This increase was accompanied by a decrease in the C=N hydrazone band (1620). The C=N azine band (1670) appeared to stay constant. This monitoring of the IR spectra indicated that hydrazone 10 was breaking down to camphor (9). On the other hand, azine 11 appeared to be stable. The breakdown of hydrazone 10 was observed as soon as in 2.5 h (for CH_2Cl_2 extraction), to 2 days (for $CHCl_3$ extracts, regardless if they were washed with $NaHCO_3$ or not). After 5 or 7 days the C=O band became noticeably strong. The sample with BHT did not exhibit a C=O band even after 17 days, indicating that no breakdown of hydrazone 10 to camphor (9) occurred.

Results and Discussion

In our previously published work[1-5] we have prepared hydrazones of naloxone (1), naltrexone (2), and estone (3) in excellent, almost quantitative yields. In cases of 1 and 2, a trace of the corresponding azine was observed. However, the amount of azine did not appear to increase substantially upon standing of the hydrazones, even over a period of a couple of years. Although the ketones 1 (or 2) and 3 are substantially different, they have in common a phenol group, which could act as a built-in antioxidant.

In the present work, we investigated reaction of a series of nonphenolic ketones of varying structures with hydrazine hydrate and found wide differences in both formations of hydrazone and azine. First, we shall present the results for individual ketones and then we shall discuss some trends in common for all of them.

First, we reacted camphor (9) with hydrazine hydrate with an acid catalyst (HCl) at room temperature (the reaction was extremely slow without acid catalyst). We obtained recovered camphor (9) in large amounts. The rest of the material was mostly camphor azine (11) and a trace of camphor hydrazone (10) (by IR, ^{13}C NMR, and ^1H NMR spectroscopy). The yields were largely improved when the reaction mixture was refluxed (ethanol as solvent). These preparations gave us mostly camphor azine (11) instead of the expected camphor hydrazone (10). This was surprising. The camphor azine (11) could form from camphor hydrazone (10) during the workup. However, while it is known in the literature that azines form from hydrazones upon standing,[7,8] usually the process is slow and does not yield much azine. According to our observations it appears that camphor hydrazone (10) converts into the azine 11 quite rapidly upon standing. On the other hand, the camphor azine (11) could also form in the reaction mixture, by two pathways. One would be the coupling of the initially formed camphor hydrazone (10) with camphor (9) and the other would be the acid-catalyzed conversion of camphor hydrazone (10) to camphor azine (11).

In a series of experiments with camphor (9), it was shown that a prolonged reflux time and acid catalysis are needed to carry the reaction to completion. In all cases, even when some unreacted camphor was recovered, the azine 11 was observed as the major product and the hydrazone 10 was the minor product. This indicated that the reaction rate of the formation of camphor hydrazone (10) from camphor (9) and hydrazine hydrate is slow, but the formation of azine 11 is fast, to the point that pure hydrazone 10 could not be isolated.

It is not expected that the azine 11 forms in situ by coupling of hydrazone 10 with the ketone 9, since the reaction conditions—excess of hydrazine hydrate—favor the formation of the hydrazone 10.

If one assumes that the azine 11 is formed in solution (during the reaction) or in the solid state or viscous state (upon standing following the workup) from two molecules of hydrazone 10 by a classical addition–elimination mechanism [Addition of a hydrazone to another hydrazone; elimination of hydrazine. One hydrazone acts as a nucleophile (attack by NH_2), the other hydrazone acts as an electrophile (C=N bond).], one wonders why the reaction is so fast. Namely, the camphor keto group is sterically hindered, and the hydrazone C=N group should be similarly hindered. The steric hindrance is caused by the methyl group at position 10. This is supported by an example in the literature[6] which shows that of the two keto groups in camphorquinone, only the one next to the

(7) Smith, P. A. S. *Derivatives of Hydrazones and Other Hydronitrogens Having N–N Bonds*; Benjamin: London, 1983; pp 43–79 and references cited therein.

(8) Overberger, C. G.; Anselmo, J.-P.; Lombardino, J. G. *Organic Compounds with Nitrogen–Nitrogen Bonds*; The Ronald Press Co.: New York, 1966; pp 9–21 and references cited therein.

CH_3-10 (C-2) does not react with NH_2NH_2 at room temperature without catalyst, while the other (C-3) makes hydrazone easily. Therefore, the C-8 CH_3 of camphor is not responsible for observed steric hindrance of C-2 keto group.[6]

When 2-adamantonanone (**6**) was treated with excess hydrazine hydrate at room temperature for 3 h with or without an acid catalyst, no starting material was recovered. Surprisingly, 2-adamantanone azine (**8**) was obtained as the major product and the hydrazone **7** as a minor to a very minor product (depending on the reaction conditions). This was very surprising also because the azine **8** was formed almost exclusively even when no acid was present as catalyst. Namely, the hydrazone–azine formation was found to be acid catalyzed,[3] but no mention was made about fast noncatalyzed hydrazone–azine conversion which we observed.

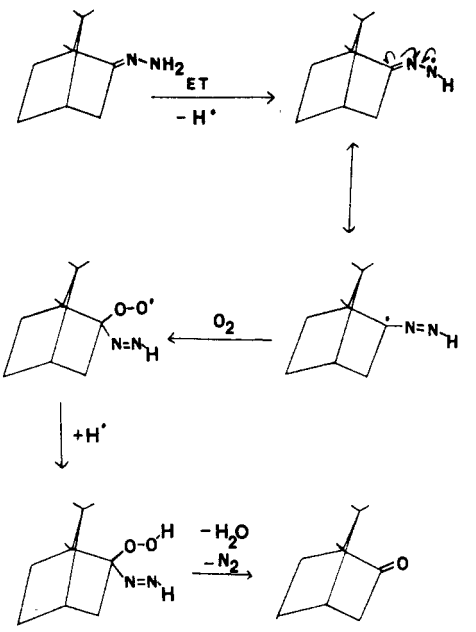
In our experiments in which camphorquinone (**12**) was treated with hydrazine hydrate, camphorquinone hydrazones (**13** syn and anti by IR, ^{13}C NMR, ^1H NMR spectroscopy) were obtained exclusively, and no azine was observed. This was quite surprising. The unhindered C-3 keto group was expected to form the azine as in the other unhindered cases. All attempts to make camphorquinone azine, e.g. by refluxing hydrazones **13** open to air, resulted in the recovery of **13** only. This raised the possibility that the conjugated double bonds at C-2 and C-3 were affecting the availability of the electrons on the hydrazone nitrogen. Namely, the electron density of the N-lone pair from the NH_2 of the hydrazone, which acts as a nucleophile at the C=N of the other hydrazone molecule (if the azine is formed by an addition–elimination process) would be depleted by the resonance of the N-lone pair with the conjugated C=N and C=O double bonds. This type of conjugation would also diminish the electrophilicity of the C=N of the hydrazone molecule which acts as an electrophile.

To test this proposal, acetophenone (**14**), a conjugated ketone, was treated with hydrazine hydrate. The uncatalyzed reaction gave the hydrazone **15** and a small amount of the azine **16**. The amount of azine **16** increased upon standing. Thus, the conjugation of hydrazone did not seem to completely prevent the formation of azine in this case. The *p*-methoxyacetophenone (**19**) gave similar results as acetophenone (**14**).

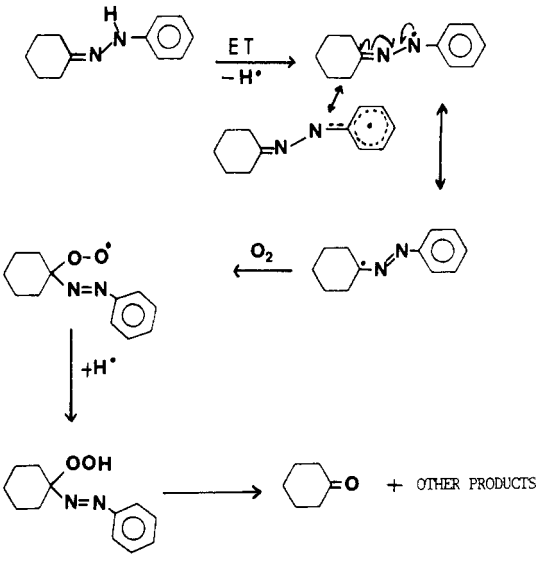
However, *p*-nitroacetophenone (**17**) gave the hydrazone **18**, which was not converted into the azine even after 7 months of standing open to air.

Another interesting observation that was made in this study was that camphor hydrazone (**10**) breaks down to camphor (**9**) upon standing. This breakdown seems to be prevented by the presence of BHT, an antioxidant. A possible mechanism for this decomposition is shown in Scheme I, which is based on some related findings in the literature, as follows. Only two cases of hydrazone to ketone decomposition are described in the literature. The first is the breakdown of cyclohexanone phenylhydrazone to cyclohexanone.[9] The breakdown occurred via a hydroperoxide intermediate (Scheme II). This reaction was autocatalytic. The first step is a radical cleavage of the N–H bond, followed by an allylic shift of the odd electron, and the reaction of the resulting radical with oxygen. The second example of hydrazone to ketone decomposition was the photooxygenation of acetone hydrazone.[10] The reaction follows a path similar to that shown in Scheme I.

Scheme I



Scheme II



The breakdown of cyclohexanone phenylhydrazone was not unexpected because the initially formed N radical (by breaking of the N–H bond) is resonantly stabilized by the phenyl group (from the phenylhydrazone moiety). We did not have the phenylhydrazone of camphor but a regular hydrazone which does not offer any obvious stabilization of the N radical. Also, the breakdown of acetone hydrazone to acetone cannot be compared directly to our case of camphor hydrazone because the acetone hydrazone was treated photochemically, also with photosensitizers added. In contrast, we have not used any such conditions.

In conclusion, the formation of hydrazones by treatment of ketones with hydrazine hydrate appears to be a reaction sensitive to steric hindrance. This is illustrated dramatically in case of a sterically hindered ketone camphor (**9**) where several hours of reflux and acid conditions are needed to yield hydrazone **10**. In contrast, the unhindered ketones (**1–3, 12, 14, 17, 19**) give high yields of hydrazones at room temperature, with no catalyst. A nucleophilic mechanism could account for this observation. The formation of azines from hydrazones seems to be much less sensitive to steric hindrance. Thus, camphor hydrazone

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(10) Dixon, D. W.; Barbush, M. *J. Org. Chem.* **1985**, *50*, 3194–3200.

is converted very easily to the corresponding azine, just by standing.

The (unhindered) ketones that were conjugated (camphorquinone 12; acetophenones 14, 17, 19) gave hydrazones with either no azines, or just small amounts of azines. In the cases where azines were formed (14, 19), their amount increases upon standing, faster if the hydrazone is a liquid (14), slower where it is a solid (19).

In cases of unconjugated ketones (1–3, 6), the ketones that have a phenol moiety gave hydrazones with no azines, or just a very small amount of azines. The azine amount increased upon standing, but extremely slowly (over a period of over a year). In contrast, the ketone 6, which does not have the phenol moiety, gave a mixture of hydrazone (minor) and azine (major), which was converted upon standing in the solid state to azine after a couple of months.

In summary, the few ketones that we have studied indicate that the mechanisms of formation of azines is neither simple nor straightforward and deserves further study. Instead of a nucleophilic addition–elimination, an electron-transfer process could be operating. Such processes are usually not sensitive to steric hindrance and also show a different electronic demand than simple nucleophilic substitutions.

Synthesis and Iron Carbonyl Promoted Coupling Reactions of 7-(Aryloxy)norbornadienes

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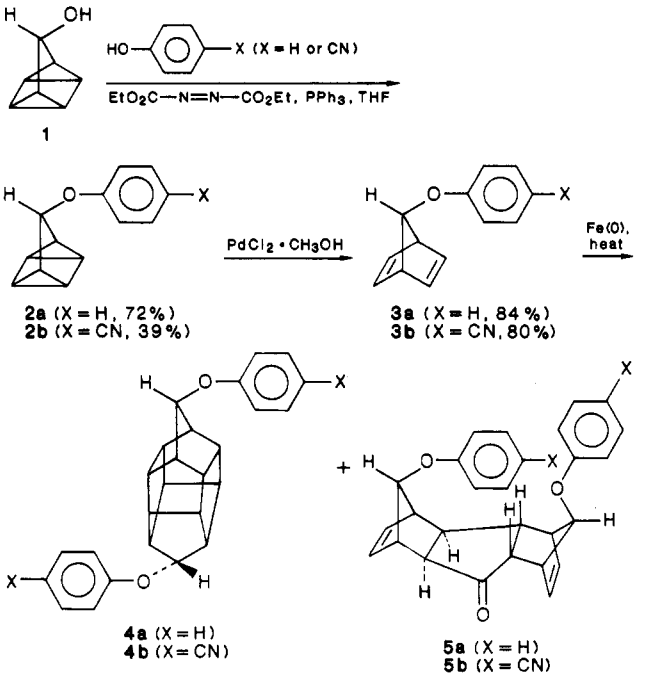
Thermal reactions of 7-substituted norbornadienes with iron carbonyls provide a convenient method for synthesizing a variety of unusual polycyclic compounds.[1,2] In this connection, we desired to study the corresponding reactions by employing 7-(aryloxy)norbornadienes as substrates. However, to our knowledge, no prior syntheses of 7-(aryloxy)norbornadienes have been reported. Accordingly, it was necessary to devise a method by which this class of compounds could be synthesized. The route summarized in Scheme I has been found to be useful for this purpose. The key synthetic step involves application of the Mitsunobu reaction[3] for converting 3-hydroxyquadricyclane (1) into 3-(aryloxy)quadriclanes **2a** and **2b**.

Scheme I



Thus, a tetrahydrofuran solution of 3-hydroxyquadricyclane (1)[4] was reacted with phenol in the presence of diethyl azodicarboxylate and triphenylphosphine in tetrahydrofuran solvent. This reaction afforded the corresponding 3-phenoxyquadricyclane (**2a**, Scheme I) in 72% yield. Valence isomerization of **2a** to the corresponding norbornadiene derivative, **3a**, was performed by treating **2a** with methanolic $PdCl_2$.[5] Similarly, Mitsunobu reaction[3] of 1 with *p*-cyanophenol afforded 3-(*p*-cyanophenoxy)quadricyclane (**2b**) in good yield. Treatment of **2b** with methanolic $PdCl_2$ promoted its valence isomerization to **3b**. We conclude that the route shown in Scheme I is useful for synthesing 3-(aryloxy)quadricyclanes and 7-(aryloxy)norbornadienes from the readily available[4] 3-hydroxyquadricyclane.

Next, the thermal reactions of **3a** and of **3b** with $Fe(CO)_5$ (di-*n*-butyl ether solvent, reflux 72 h) and with Fe_2CO_9 (dry benzene solvent, reflux 72 h) were studied. In all cases, oxidative workup was performed by stirring the reaction mixture with an acetone solution of excess ferric chloride heptahydrate for one week to decompose unreacted iron carbonyl and/or Fe(0) complexes that might be present.[6] The organic products were separated by column chromatography on silica gel by using a gradient elution scheme (see the Experimental Section).

Reactions of **3a** and **3b** with Fe(0) each afforded a cage dimer (**4a** and **4b**, respectively) and a dimer ketone (**5a** and **5b**, respectively) in low to moderate yields (Table I). The syn,exo,trans,endo,syn configuration of each dimer ketone, **5a**[1k] and **5b**,[8] was established by X-ray structural analysis. Surprisingly, the reaction of **3b** with $Fe(CO)_5$ afforded only

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