piperidine is reported[42] to be 37 ppm. Cf. $PhNHNH_2$ for which the shifts are 87 and 62 ppm, respectively.[43] The mass spectrum was obtained by GC/MS, *m/e* (%) 185 (19), 170 (10), 129 (7), 127 (7), 113 (9), 112 (100), 87 (14), 85 (7), 84 (44), 83 (10), 82 (22), 74 (17), 68 (6). After 4 days, only 4-piperidinecarboxamide (3) was detected by gas chromatography. It was identified by using an authentic standard.

Reduction of Isoniazid. Isoniazid (1) was reduced as above, and 4-piperidinecarboxylic acid hydrazide (2) was identified by GC/MS as an intermediate after 6.3 h: MS, *m/e* (%) 143 (10), 127 (25), 125 (5), 113 (15), 112 (95), 111 (5), 110 (5), 109 (5), 98 (10), 94 (10), 87 (30), 85 (35), 84 (100), 83 (20), 82 (75). After 20 h, only the amide (3) was found. It was identified by comparison with an authentic standard.

Acknowledgment. We thank Dr. Larry Keefer for helpful discussion, Drs. Bruce Hilton and Gwen Chmurny for NMR spectra, and Mr. John Roman for mass spectra. This work was sponsored by the National Cancer Institute under Contract No. NO1-CO-23910 with Program Resources, Inc.

Registry No. 1, 54-85-3; 2, 42596-58-7; 3, 39546-32-2; 4, 305-33-9; 5, 99706-49-7; pyridine, 110-86-1; 2-methylpyridine, 109-06-8; 2-ethylpyridine, 100-71-0; 2,6-dimethylpyridine, 108-48-5; 2,2'-bipyridine, 366-18-7; 2-phenylpyridine, 1008-89-5; 3-chloropyridine, 626-60-8; *N*-methyl-3-pyridinecarboxamide, 114-33-0; *N,N*-diethyl-3-pyridinecarboxamide, 59-26-7; *N*-methyl-4-pyridinecarboxamide, 6843-37-4; *N*-ethyl-4-pyridinecarboxamide, 41116-48-7; *N*-phenyl-4-pyridinecarboxamide, 3034-31-9; *N*-methyl-2-pyridinone, 694-85-9; pyridine oxide, 694-59-7; *p*-nitropyridine oxide, 1124-33-0; quinoline, 91-22-5; 6-methylquinoline, 91-62-3; piperidine hydrochloride, 6091-44-7; 2-methylpiperidine hydrochloride, 5119-88-0; 2-ethylpiperidine hydrochloride, 1484-99-7; cis-2,6-dimethylpiperidine hydrochloride, 32166-02-2; 2,2'-bipiperidyl, 531-67-9; 2-cyclohexylpiperidine hydrochloride, 51523-81-0; *N*-methyl-3-piperidinecarboxamide, 5115-98-0; *N,N*-diethyl-3-piperidinecarboxamide, 3367-95-1; *N*-methyl-4-piperidinecarboxamide hydrochloride, 1903-75-9; *N*-ethyl-4-piperidinecarboxamide hydrochloride, 1981-39-1; *N*-phenylpiperidinecarboxamide, 73415-85-7; *N*-methyl-2-piperidinone, 931-20-4; 4-methoxypyridine, 620-08-6; 4-ethoxypyridine, 33399-46-1; 1,2,3,4-tetrahydroquinoline, 635-46-1; 6-methyl-1,2,3,4-tetrahydroquinoline, 91-61-2; nickel, 7440-02-0; aluminum, 7429-90-5; 2-cyclohexylpiperidine, 56528-77-9; isonicotinoyl chloride hydrochloride, 39178-35-3; isoquinoline, 119-65-3; 1,2,3,4-tetrahydroisoquinone, 91-21-4.

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Conformational Studies by Dynamic NMR. 31.[1] Enantiotopomerization and Torsional Processes in sp^2-Carbon Diaryl-Substituted Hindered Compounds

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The stereodynamical processes in phenyl 2,4,6-triisopropylphenyl ketone and the analogues C=S, C=NH, and $C=CPh_2$ have been investigated by NMR. In all these compounds the plane of the triisopropylphenyl ring is perpendicular to the plane of the sp^2 carbon, as shown by anisochronous methyl groups for the pair of *o*-isopropyl groups. The enantiotopomerization processes that render these methyls isochronous at high temperature have free energies of activation that increase with the dimension of the X group. A second process, involving the rotation of the unsubstituted phenyl ring, which is coplanar to the C=X moiety, was observed by high-field ^{13}C NMR at low temperature. The free energies of activation of this second process were much lower than those for enantiotopomerization. It has been shown that the conformational arrangement of the two aromatic rings (triisopropylphenyl perpendicular and Ph coplanar to CO) is maintained in the intermediate radical produced in the photoreduction of 2,4,6-triisopropylbenzophenone.

Highly hindered aromatic ketones have relatively high barriers to internal rotation; some of these values have been determined recently by variable-temperature NMR spectroscopy.[2,3] The larger barriers of these hindered ketones compared to the less crowded ones are due to a change in the conformation of the ground state. In compounds like acetophenone[4] or benzaldehyde,[5] the phenyl ring and the carbonyl group are essentially coplanar in the

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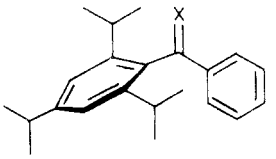
Scheme I



1, X = O
2, X = NH
3, X = S
4, X = CPh_2

torsional ground state and perpendicular in the transition state. The barrier to rotation is mainly dependent upon the degree of conjugation between the aromatic ring and the carbonyl group;[4,5] in this planar conformation the introduction of bulky substituents reduces the torsional barrier.[6] On the other hand, in the more stable conformation of very hindered aromatic ketones the plane of the aryl ring bearing the bulky substituents is twisted by an angle close to 90° with respect to the plane of carbonyl group, and the torsional transition state corresponds to the coplanarity between the aromatic and carbonyl groups. This interchange in the geometry of the ground and transition states as steric hindrance is varied has been observed by NMR in styrenes,[7] amines,[8] and hydrazones.[9]

In order to detect the existence of a perpendicular conformation by NMR spectroscopy and to measure the corresponding torsional barrier it is convenient to make use of prochiral probes, such as the isopropyl group. This moiety displays anisochronous methyl groups when the molecule has a conformation in which the plane bisecting the Me–CH–Me angle is not a molecular plane of symmetry.[10]

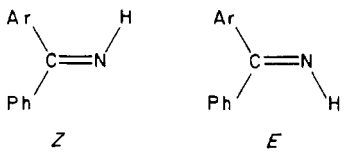
In 2,4,6-triisopropylbenzophenone (1) Ito and co-workers found by ^1H NMR that the methyl groups of the two *o*-isopropyl groups are anisochronous. This result indicates that the planes of the triisopropylphenyl ring and the carbonyl group are perpendicular. It is therefore conceivable that such an arrangement might also be observed in analogous molecules with atoms other than oxygen bonded to the sp^2 carbon. Accordingly we investigated in this work the corresponding imino (2), thiocarbonyl (3), and diphenylmethylene (4) derivatives (Scheme I).

If all these compounds actually stay in the perpendicular arrangement of Scheme I, it can be predicted that the barrier for the rotation of the 2,4,6-triisopropylphenyl group (a motion corresponding to an enantiotopomerization process) should increase as the dimensions of X increase. In the torsional transition state, when the triisopropylphenyl ring and the carbonyl groups become coplanar, the methyl components of the two *o*-isopropyl groups will be much closer to X than in the perpendicular ground state; the greater the size of X, the greater would be the hindrance to enantiotopomerization.

The conformation depicted in Scheme I is also expected to increase the torsional barrier of the phenyl group (coplanar to carbonyl) compared with unhindered analogues. Indications that this second motion is also amenable to quantitative studies by NMR comes from qualitative experiments on some derivatives of **1**.[2] This second barrier should be measurable by ^{13}C NMR at high field and at sufficiently low temperature.

Finally we also investigated by ESR spectroscopy whether the conformational arrangement of ketone 1 is maintained in the course of a reaction, such as photochemical reduction, that occurs via a radical intermediate.

Scheme II



Ar = 2,4,6-triisopropylphenyl

Table I. Free Energy of Activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the Enantiotopomerization and for the Phenyl Rotation Processes in Derivatives 1–4

compd	enantiotopomerization[a]	phenyl rotation[a]
1, X = O	16.3_5	9.4
2, X = NH	19.1	7.8_5
3, X = S	22.6_5	9.4_5
4, X = CPh_2	>27	<7.5

[a] The ^{13}C NMR measurements from which the values in columns two and three were derived were carried out respectively at 25.16 MHz in *o*-dichlorobenzene and at 75.46 MHz in CD_2Cl_2. The estimated errors are ±0.15 kcal mol^{-1}.

Results and Discussion

The ^{13}C NMR spectra of 1–4 at room temperature display three signals of equal intensity for the six methyls of the three isopropyl groups. One signal corresponds to the pair of isochronous methyl carbons of the 4-isopropyl group. The others are due to anisochronous methyl carbons of the *o*-isopropyl groups. That these latter methyl groups are anisochronous is proved by the observation that there are only two ^{13}C NMR signals for the methine carbons: one for the 4-isopropyl group and another, twice as intense, for those in positions 2 and 6. These facts are evidence for the conclusion that 1–4 all have the same conformation[2] wherein the plane of the triisopropylphenyl ring is perpendicular to the planes of the C=O, C=N, C=S, and C=C moieties.

Imine **2** could exist, in principle, in the *E* and *Z* forms[11] (Scheme II).

It has been shown, however, that in $Ph_2C{=}NH$ (^{15}N enriched) the iminic hydrogen is exchangeable at room temperature and that only at −60 °C is its motion sufficiently slow to exhibit a J_{NH} coupling.[12] Accordingly, asymmetric imines (e.g., RPhC=NH where R = *sec*-butyl) exist as *E* and *Z* isomers only at low temperature.[12] This effect has been detected only in pentane but not in other solvents ($CDCl_3$ or CH_3CN). Since this exchange is second order with respect to the imine (intermolecular)[12] it is likely that the *E*–*Z* interconversion rate is accelerated by trace of impurities in the solutions, as observed for analogous hydrogen exchanges.[13] Accordingly, although we did not observe doubling of the C-13 signals in **2** due to *E*–*Z* isomerism even at −100 °C (in CD_2Cl_2 at 75.46 MHz), we cannot conclude that **2** exists in a single *E* or *Z* form. In

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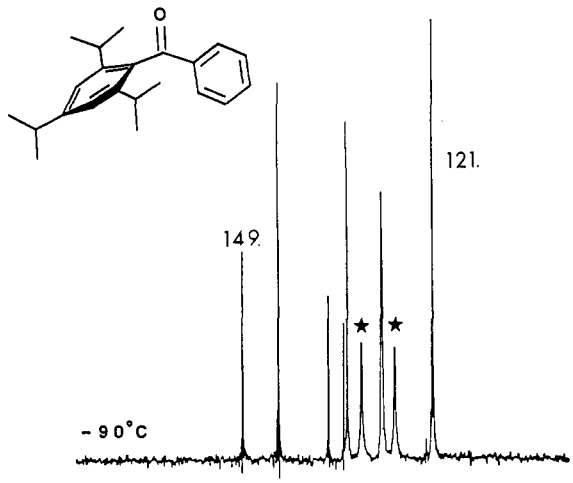


Figure 1. Aromatic region of the 75.46-MHz ^{13}C spectrum of 1 in CD_2Cl_2 at -90 °C. The signal corresponding to the pair of ortho carbons of C_6H_5, which is a single line at room temperature, is split into two lines (starred) below -65 °C.

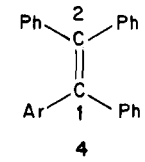
view of the results of ref 12 it is very likely that the *E–Z* interconversion is fast in the whole temperature range examined.

On raising the temperature the methyl signals of the *o*-isopropyl groups of **1** and **2** broaden and eventually coalesce; the corresponding signals of **3** broaden but the coalescence point was not obtained, whereas in the case of **4** both the ^{13}C and the ^1H (100 MHz) NMR signals do not broaden, even at 190 °C.

Line shape analysis gave the free energies of activation ($\Delta G^{\ddagger}$ in kcal mol^{-1}) for the enantiotopomerization of **1–3**; for **4** only the lower limit could be established. The values listed in Table I follow the trend **1** < **2** < **3** < **4**, as expected from the size of the C=X moieties. If the C=X bond length is indicative of the steric hindrance experienced by the *o*-isopropyls in the transition state of enantiotopomerization, then the order would be **1** (C=O, 1.22 Å[14]) < **2** (C=N, 1.31 Å[15]) < **3** (C=S, 1.63 Å[16]). The CPh_2 group as X makes derivative **4** by far the most hindered of these compounds. The observation of a value of $\Delta G^{\ddagger}$ larger than 27 kcal mol^{-1} for the enantiotopomerization in **4** indicates that in derivatives of **4** that lack a plane of symmetry (e.g., compounds with one substituent in position 3 of the 2,4,6-triisopropylphenyl ring) separation of the *R* and *S* enantiomers should be achieved at room temperature, as reported for similar hindered styrenes.[17]

The electronic effects of the C=X moiety should play a much less substantial role than the steric effects since the degree of conjugation between the hindered phenyl ring and the C=X group is likely to be quite small. The experimental observations indicate that their planes are almost orthogonal in the rotational ground state. On the other hand, the effect of conjugation is expected to be more important in determining the torsional barrier of the unsubstituted phenyl ring. The following experiments show that the C=X and the C_6H_5 groups are almost coplanar when X = O, NH, or S (**1**, **2**, or **3**, respectively). This second motion, i.e., the Ph—C=X torsional process, can

Scheme III



4

Ar = 2,4,6-triisopropylphenyl

be investigated at a much lower temperature than that required to detect the enantiotopomerization. The torsional barrier about the Ph–CO bond in alkyl aryl ketones (e.g., acetophenone), although quite low, can be measured[4] by ^{13}C NMR, whereas this is not the case for benzophenone. The conjugation of a single phenyl ring with C=O affords greater double bond character and thus greater torsional barrier than where the conjugation is shared between the two equivalent phenyls of benzophenone. Derivative **1**, however, resembles an alkyl phenyl ketone in that the 2,4,6-triisopropylphenyl group is perpendicular to the carbonyl plane and has therefore little conjugation with the C=O double bond. Accordingly the high field (75.46 MHz) ^{13}C spectra of **1** (Figure 1) display two signals at -90 °C for the ortho carbons of the phenyl group, but a single signal (129.5 ppm) at room temperature. Line shape analysis at intermediate temperatures yields the free energy of activation for this process (Table I). Compounds **2** and **3** also display diastereotopic ortho carbons and **3** displays diastereotopic meta carbons at low temperature. This proves that the observation of unique signals in **1** and **2** for the meta carbons is only due to accidental degeneracy.

On the other hand, although all the 18 signals of the unsaturated carbons of **4** are resolved at 75.46 MHz, none of them exhibited line broadening at the lowest attainable temperature (only -60 °C, owing to the low solubility of the compound). Since at the same temperature the lines of the ortho carbons of **1–3** were already appreciably broad, the barrier for the corresponding process in **4** must be definitely lower. This means that the phenyl ring geminally related to the trialkylphenyl ring is more twisted with respect to the ethylenic plane than in **1–3**. It could even be that the steric congestion of **4** forces the phenyl ring into an almost perpendicular arrangement, thus preventing the possibility of detecting different shifts for its ortho carbons.

The torsional barrier in **1** is much higher than that in acetophenone (9.4 vs. 5.4 kcal mol^{-1}); this means that the conjugation between the phenyl and CO groups is not the only reason that allows observation of this motion in **1**. Clearly also the two *o*-isopropyl groups protruding from the plane of the other ring interact with the unsubstituted phenyl in its transition state when the latter becomes perpendicular to the C=O plane. This steric interaction makes the passage through the transition state more difficult, thus enhancing the torsional barrier of **1** compared with acetophenone.

The simultaneous conjugative and steric effects make it difficult to rationalize the facts that the barrier of **2** is lower than and the barrier of **3** is equal to that of **1**. This seems to be the first example of a measurement of a Ph–CS torsional barrier in a thiocarbonyl compound, and thus we cannot compare the value for **3** with those of simpler thiocarbonyl compounds, as we did for ketones. On the other hand the effects that greatly reduce the barrier for the Ph–C1 rotation in **4** (Scheme III) can be better understood.

First the barrier in the simplest analogue of **4** (styrene) is even lower (3 kcal mol^{-1})[18] than that of acetone (5.4 kcal

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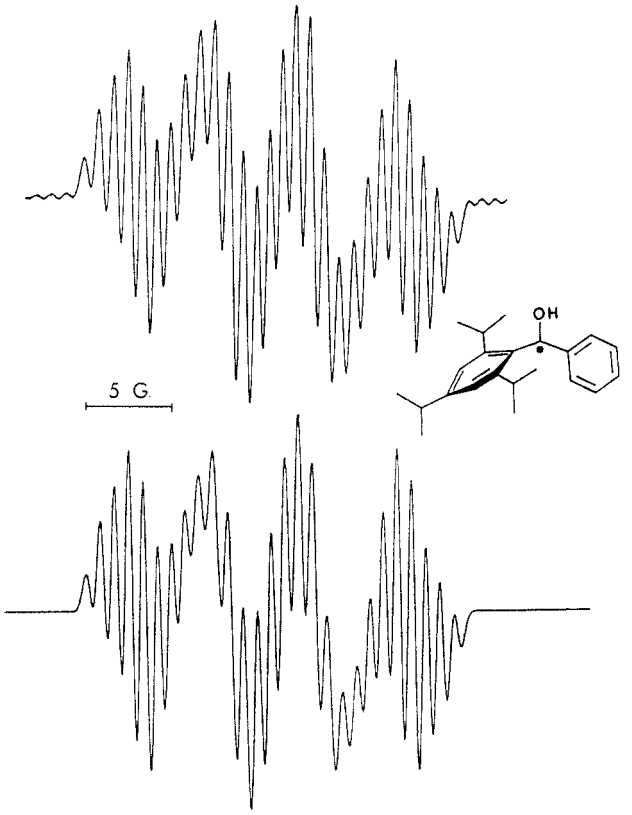


Figure 2. Experimental (top) and computer simulated (bottom) ESR spectrum of radical **1a** obtained by photolysis of **1** in cyclopropane at −10 °C. The hfs constants used for the simulation are reported in Table II, the line width is 0.58 G.

mol^{-1}) and cannot be observed by low-temperature NMR. Second, the two phenyls bonded to C2 provide a remarkable steric hindrance. Owing to the fact that the unsubstituted phenyl ring at C1 is essentially coplanar with the C1=C2 plane, the steric effect of one of the two phenyls on C2 destabilizes its coplanar ground state, further reducing the Ph–C1 torsional barrier. In other words, the same steric properties that enhance the barrier to enantiotopomerization, owing to the perpendicular arrangement of 2,4,6-triisopropylphenyl ring, also reduce the Ph–C1 torsional barrier because of the coplanarity of the latter phenyl ring with the ethylenic moiety.

Whereas the conformation of a given molecule can often be determined with reasonable confidence, it is often more difficult to ascertain the conformation of the intermediates in a reaction. Here there is the opportunity of investigating the conformational preference of the intermediate in the reduction of ketone **1**. Reduction of the carbonyl group can be accomplished by various methods including photochemical processes that, in the case of diaryl or alkyl aryl ketones, yield the corresponding ketyl radicals as intermediates.[19,20] In the case of **1** there would be obtained a radical **1a** in which the two aromatic rings are bonded to an sp^2 carbon.

$$\underset{\mathbf{1}}{\mathrm{ArPhC{=}O}} \xrightarrow{h\nu} \underset{\mathbf{1a}}{\mathrm{ArPh\dot{C}OH}}$$

Ar = 2,4,6-triisopropylphenyl

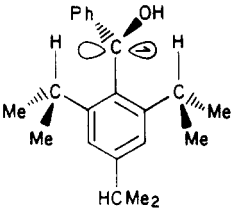
This reaction was carried out in the cavity of an ESR spectrometer and the spectrum of **1a** is shown in Figure

Table II. Hyperfine Splitting Constants (in G) Measured for Radical 1a (ArPhĊOH with Ar = 2,4,6-Triisopropylphenyl) in Cyclopropane at −10 °C[a]

	1a	$CH_3PhĊOH$
1 H (ortho)	5.15	4.94
1 H (ortho)	4.7	4.69
1 H (para)	5.7	5.88
2 H (meta)	1.7	1.60
1 H (OH)	0.85	0.64
others	0.85 (2 H)	14.12 (3 H)

[a] For comparison the values of a related alkyl phenyl radical ($CH_3PhĊOH$)[21] are also reported.

Scheme IV



1a

2. The hfs constants (a_H) that were obtained from the spectral analysis (Table II) give information about the conformational arrangement of the reaction intermediate. Of the three hydrogens with the smallest splittings (0.85 G) one was assigned to the hydroxylic hydrogen (Table II). Spectra taken in alkaline medium where the anion of **1a** ($ArPhĊO^-$) is produced showed that only two hydrogens, rather than three, have the smallest splitting. The a_H values in **1a** attributed to the hydrogens of the unsubstituted phenyl are much closer to those of the analogous alkylphenyl radicals (e.g., RPhĊOH where R = Me, Et, *i*-Pr[21,22]) than to those of diaryl radicals (e.g., $Ph_2ĊOH$[19,20,22]). The rationale for this behavior is that the bulky 2,4,6-triisopropylphenyl group maintains in the radical the perpendicular arrangement to the plane of the sp^2 carbon bearing the unpaired electron. The latter, accordingly, is essentially delocalized only on the C_6H_5 moiety, as in an alkylphenyl radical. Furthermore, the relative intensities of the spectral lines of **1a** require (see computer simulation in Figure 2) the nonequivalence of the two ortho hydrogens (Table II). This means that the rotation about the Ph–C bond is restricted and that the unsubstituted phenyl must be coplanar with the radical center. This feature is typical of alkylphenyl radicals[21,22] (where conjugation occurs with a single phenyl) but not of diaryl radicals of similar structure[22] (where conjugation occurs with both the aryls). The conformation we suggest for **1a** also requires a negligible spin density on the ring containing the isopropyls; there are not observable splittings for the two meta hydrogens or for the CH of the 4-isopropyl, contrary to the trialkyl-substituted radicals where delocalization of the unpaired electron occurs on both aryl groups (e.g., $Ar_2ĊO^-$ where Ar = 2,4,6-trimethylphenyl[22,23]).

The existence of small but significant splitting (0.85 G) for the methine hydrogens of the 2,6-isopropyls, accompanied by the absence of such a splitting for the CH in position 4, further supports the proposed perpendicular arrangement of the triisopropylphenyl moiety in **1a**. The mechanism of the spin transmission for this splitting is not

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related to the spin density on the ring (otherwise the 4-CH would also exhibit such a value) but to a direct overlapping of this pair of CH hydrogens with the unpaired electron. This overlapping can only be achieved if the ring with the three isopropyls is locked into a plane perpendicular to that of the radical center; in this arrangement the pair of methine hydrogens closely approaches the p_z orbital of the unpaired electron as shown in Scheme IV.

It thus appears that the conformation of ketone 1 is also maintained in the course of such a reaction pathway.

Experimental Section

Melting points are uncorrected. IR spectra were recorded with a Perkin-Elmer 257 grating spectrometer, and ^1H NMR spectra (60 MHz) were obtained with a Varian EM 360L instrument.

2,4,6-Triisopropylbenzophenone Imine (2). To a Grignard reagent, prepared[24] from 2.83 g (10 mmol) of 2,4,6-triisopropylbromobenzene and 0.243 g (10 mmol) of magnesium turnings in 14 mL of ether, was added at room temperature a solution of benzonitrile (1.03 g, 10 mmol) in 7 mL of ether. The mixture was refluxed for 4 h and then was decomposed by pouring it into 100 mL of acidified cold water: the yellow magnesium bromide salt of the imine precipitated from the solution and was filtered and washed with ether. Another small quantity was obtained from the organic layer dried with sodium sulfate and evaporated: total yield, 1.3 g (31.7%); ^1H NMR ($CDCl_3$) δ 0.9–1.7 (18 H, m, i-C_3H_7), 2.13–3.36 (3 H, m, i-C_3H_7), 7.33 (2 H, s, Ar), 7.40–8.76 (5 H, m, Ar); mass spectrum, m/e 409 (M^+), 307 ($M^+ + H - MgBr$), 306 ($M^+ - MgBr$). A quantity of 0.3 g of this salt in $CHCl_3$ (20 mL) was treated with gaseous ammonia; the white precipitate was filtered off, and the filtrate was evaporated. The residue was dissolved in ether and elimination of the solvent afforded the imine 2: 0.2 g (89%); mp 105–106 °C.; NMR ($CDCl_3$) δ 0.9–1.6 (18 H, m, i-C_3H_7), 2.5–3.33 (3 H, m, i-C_3H_7), 7.2 (2 H, s, Ar), 7.3–8.1 (5 H, m, Ar), 8.4 (1 H, br s, NH); the ^{13}C data are given in Table III; IR (KBr) 3260 cm^{-1} (NH); mass spectrum, m/e 307 (M^+), 306 ($M^+ - H$).

2,4,6-Triisopropylthiobenzophenone (3). 2,4,6-Triisopropylbenzophenone[25] (1) (2 g, 6.5 mmol) and the dimer of (4-methoxyphenyl)thionophosphine sulfide[26] (Lawesson reagent) (2.6 g, 6.5 mmol) in 30 mL of anhydrous xylene were refluxed under CO_2 for 28 h. The starting ketone was not completely consumed (TLC). The reaction mixture was then allowed to cool to room temperature and chromatographed on silica gel column (100:1 petroleum ether–ether). The blue fraction was collected and gave 0.72 g (34.3 %) of thioketone 3: blue crystals; mp 95–97 °C (from pentane–ether); ^1H NMR ($CDCl_3$) δ 1–1.5 (18 H, m, i-C_3H_7), 2.5–3.3 (3 H, m, i-C_3H_7), 7.13 (2 H, s, Ar), 7.28–8.33 (5 H, m, Ar); the ^{13}C data are given in Table III; IR (CS_2) [main bands] 2960, 2920, 2860, 1240, 1215, 1170, 770, 685 cm^{-1}; mass spectrum, m/e 324 (M^+), 309 ($M^+ - CH_3$), 281 (M^+ – isopropyl), 121 (PhC=S).

2-[2,4,6-Triisopropylphenyl]-2,3,3-triphenylthiirane. A solution containing 0.191 g (0.59 mmol) of 3 and 0.114 g (0.59 mmol) of diphenyldiazomethane[27] in 20 mL of anhydrous benzene was refluxed under N_2 for 4 h, with decolorization of the solution. The solvent was removed in vacuo and afforded 0.18 g (62.5%) of the thiirane: mp 174–175 °C (from n-hexane–ether); mass spectrum, m/e 490 (M^+), 458 ($M^+ - S$), 415 ($M^+ - SC_3H_7$-i).

1-[2,4,6-Triisopropylphenyl]-1,2,2-triphenylethylene (4). A solution of the thiirane (0.061 g, 0.124 mmol) and triphenylphosphine (0.032 g, 0.124 mmol) in 10 mL of benzene was refluxed under N_2 for 5 h; the solvent was removed and the residue chromatographed (preparative TLC, elution with benzene) to give, as the higher R_f fraction, the olefin 4 (0.057 g, 100%) and, as the lower R_f fraction, triphenylphosphine sulfide (0.036 g, 100%). 4: mp 148–152 °C (from ethanol); ^1H NMR ($CDCl_3$) δ 0.7–1.5 (18 H, m, i-C_3H_7), 2.4–3.66 (3 H, m, i-C_3H_7), 6.66–7.33 (17 H, m, Ar); the ^{13}C data are given in Table III; mass spectrum, m/e 458 (M^+), 292 ($M^+ - Ph_2C$).

Table III. Chemical Shifts of the ^{13}C Signals (ppm from Me_4Si) Obtained at 75.46 MHz for Compounds 1–4 in CD_2Cl_2 at Room Temperature[a]

	1	2	3	4
quaternary				
1 C	201 (CO)	178.5 (CNH)	243.4 (CS)	148.2, 144.25
	149.3	149.8	148.9	144.0, 143.5
	138.4	139.4	144.2	141.9, 138.2
	135.1	136.3	143.6	137.2
2 C	145.1	145.6	143.3	146.4
CH (aromatic)				
1 C	133.1	131.2	134.2	126.8, 126.7
				126.0
2 C	129.5	128.7	129.0	131.9, 131.4
	128.5	128.3	128.4	131.0, 127.5
	120.7	121.6	121.4	127.4, 127.3
				121.4
CH (aliphatic)				
1 C	34.4	34.8	34.8	34.2
2 C	31.1	31.3	30.9	30.4
Me (1,6-isopropyls)				
2 C	24.9	25.4	24.5	24.5
	23.3	23.6	23.1	23.3
Me (4-isopropyl)				
2 C	24.0	24.2	24.0	23.6

[a] The signals corresponding to one carbon or to a pair of equivalent carbons are indicated.

Spectral Measurements. The low-temperature ^{13}C NMR spectra of 1–4 were recorded in the FT mode at 75.46 MHz (Bruker CXP 300 spectrometer of the High Field NMR Service of CNR in Bologna). About 100 mg of 1–3 (or 50 mg of 4) was dissolved in 2 mL of CD_2Cl_2. Compounds 3 and 4 were also dissolved in a mixture of dimethyl ether and CD_2Cl_2 in order to reduce the viscosity of the CD_2Cl_2 solutions at low temperature. The sweep width was 16 kHz (212 ppm): a 16K memory was employed for the accumulations (a few hundred scans) and 32K for the FID transformation (zero-filling). A line broadening of 0.5 Hz was normally used. The temperatures within the probe of the superconducting spectrometer were determined by replacing the samples under examination with a sample containing a mixture of acetone-d_6 (1 mL measured at 0 °C) and CHF_2Cl (3 mL measured at −80 °C): the chemical shift difference δ between the carbonyl signal of acetone and the methine signal of CHF_2Cl is known[1] to depend upon the temperature according to the relationship t(°C) = 3286–36.23 δ, the error being about ±2°C.

The high-temperature (up to +150 °C) ^{13}C spectra of 1–4 were obtained in the FT mode at 25.16 MHz (Varian XL-100) in dichlorobenzene; a few drops of C_6D_6 provided the internal lock. In order to reach even higher temperatures (up to +190 °C) proton spectra (100 MHz) of 4 were also run in diphenylacetylene. The temperature was monitored with a thermistor. The concentrations for the ^{13}C high-temperature measurements were slightly higher in that the same amount of compound (see above) was dissolved in 1.5 mL of solvent. Owing to the lower sensitivity of the 100-MHz instrument a larger number of scans (up to a few thousand) and a wider line broadening (up to 2 Hz near the coalescence) were required. The sweep width was 5.5 kHz (219 ppm): 12K was used for both accumulation and FID transformation.

The assignments of the ^{13}C lines (Table III) to CH, CH_2, and CH_3 were obtained by off-resonance experiments. The relative intensities of the ^{13}C signals were measured by means of a gated-decoupling sequence that suppresses the NOE effects.

The computer simulations of the exchanging lines were performed with a two-site exchange program written for a personal computer connected to a plotter. The theory is based upon the modified Bloch equations,[28] and the results were cross-checked

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with the DNMR program[29] run on the CDC 6600 computer facilities of the University of Bologna.

The superposition of the experimental and simulated spectra in the temperatures range where the line shape was more sensitive to the value of the rate constants (k) afforded k values (in s^{-1}) with errors that, at worst, did not exceed ±10%. This gives an uncertainty of the $\Delta G^{\ddagger}$ values not larger than ±0.07 kcal mol^{-1}. Within this accuracy the $\Delta G^{\ddagger}$ values measured at various temperatures were found to be equal and therefore an averaged value is reported in Table I for each compound. The uncertainty of the measurement of the temperatures (±2 °C) introduced a second source of error that corresponds to ±0.08 kcal mol^{-1}; the combination of the two errors indicates that the $\Delta G^{\ddagger}$ values should be accurate within ±0.15 kcal mol^{-1}.

The ESR spectra of **1a** were recorded with a Varian E-4 spectrometer equipped with a standard cooling system. The radical was generated by irradiating (500-W high-pressure Hg lamp) a vacuum-degassed solution of **1** in cyclopropane: as expected[19,20] addition of hydrogen-donor substances greatly intensified the signal. In order to obtain the radical anion of **1a**, a sodium mirror was deposited under vacuum into one arm of the sample and a small amount of methanol was added to the cyclopropane solution of **1** in the second arm: when the vacuum-sealed sample was tipped an alkaline environment (sodium methylate) was produced, and UV irradiation thus yielded the radical $ArPh\dot{C}O^-$.

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Registry No. 1, 33574-11-7; **1a**, 99686-14-3; **2**, 99686-11-0; **3**, 99686-12-1; **4**, 99686-13-2; $(Pr\text{-}i)_3C_6H_2Br$, 21524-34-5; PhCN, 100-47-0; $(Pr\text{-}i)_3C_6H_2C(Ph)=NMgBr$, 99686-15-4; 2-[2,4,6-triisopropylphenyl]-2,3,3-triphenylthiirane, 99686-16-5; diphenyldiazomethane, 883-40-9.

Studies of Extended Quinone Methides. The Hydrolysis Mechanism of 1-Methyl-2-(bromomethyl)-4,7-dihydroxybenzimidazole

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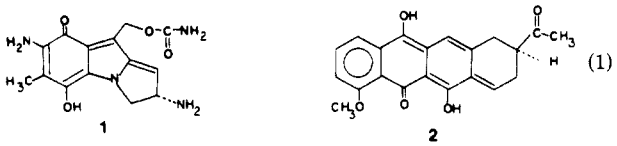
The hydrolysis of 1-methyl-2-(bromomethyl)-4,7-dihydroxybenzimidazole (**3**) was studied in anaerobic aqueous buffer to assess quinone methide formation and reactivity. Kinetic results, obtained over the pH range of 6.0–8.5 at 30.0 ± 0.2 °C, are consistent with rate-determining formation of the extended quinone methide **4**. The fate of **4** pertains to nucleophilic attack by added chloride and 2-hydroxyethyl mercaptide at the 2α-position to provide substituted hydroquinones. In a competing reaction, electrophilic trapping of the anionic form of **4** (4^-) occurs by 2α-protonation to provide 1,2-dimethylbenzimidazole-4,7-dione (**7**). Benzaldehyde was not observed to act as an electrophilic trap for 4^-, however. The following conclusions are drawn from these findings: **4** is an effective trap for nucleophiles, and 4^- is a poor trap for electrophiles. The facility of nucleophilic trapping is thought to pertain to the presence of nitrogen substitutions. These serve to make **4** electron deficient and thus promote nucleophilic trapping. Electrophilic trapping, on the other hand, will result in the formation of a high potential quinone.

It has been observed that many naturally occurring quinones are functionalized with a leaving group so as to permit quinone methide formation upon reduction.[1] Thus the reduction of mitomycin C and daunomycin would, upon 1,6-elimination of the leaving group, afford quinone methides **1** and **2** respectively (eq 1). As illustrated for



(1)

the quinone methide species in eq 2, the fate of these reactive species could pertain to both nucleophilic and electrophilic trapping. Nucleophilic trapping by a quinone methide may be responsible for the alkylation reactions exhibited by some naturally occurring quinones upon reduction.[2-4] Thus far the formation of **2** and its reactions with nucleophiles and electrophiles have been documented.[5,6] Yet to be studied are the myriad quinone systems which could form a quinone methide upon reduction. Nearly 200 naturally occurring quinones,[1] as well as many synthetic antitumor quinones,[7] fall into this category. Queries are thus posed concerning the formation of quinone methide intermediates from these structurally diverse systems and the relationship between structure and the relative facilities of nucleophilic and electrophilic trapping. Efforts in this laboratory have been directed toward studying quinone methide formation and reactivity

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