Sodium Dichloroisocyanurate Oxidation of a Sterically Hindered Tetrahydro-9(10*H*)-acridinone

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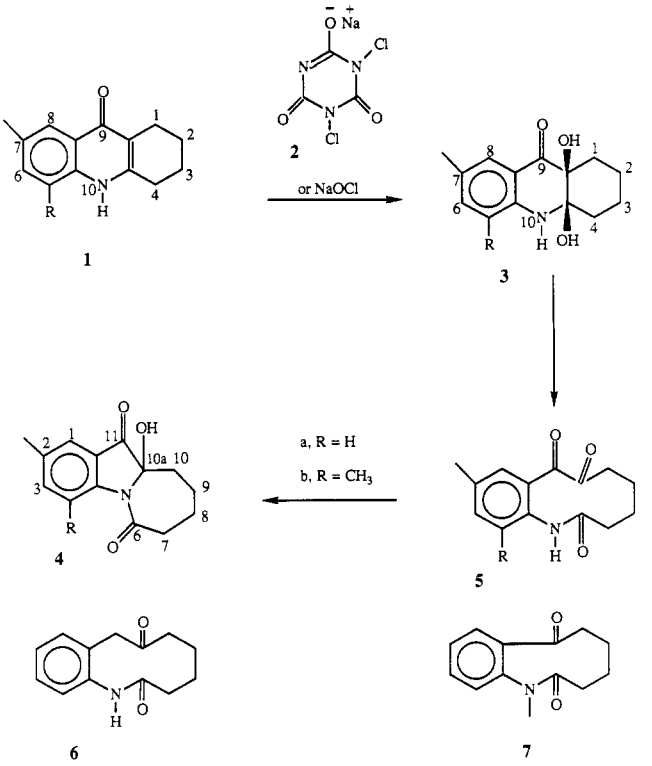
Treatment of 1,2,3,4-tetrahydro-9(10*H*)-acridinone (**1a**) with sodium dichloroisocyanurate (**2**) yields either *cis*-1,2-diol **3a** or azepino[1,2-*a*]indole **4a** as principal product depending on the molar proportion of **2** employed; diol **3a** itself is converted by **2** to end-product **4a** supposedly via a macrocycle intermediate **5a** undergoing ring closure (Scheme I).[1] Here we present further developments which lead us to propose that a more plausible pathway to **4a** from **3a** involves a *N*-chloro 1,2-diol intermediate which undergoes ring contraction to the product.

The postulation of **5a** as the immediate precursor for **4a** has literature analogies: for example the deoxygenated entity **6** is depicted as undergoing a like cyclization.[2] Indeed, the related relatively stable N-substituted macrocycle **7** has been isolated after a singlet oxygen photooxidation experiment.[3] Notwithstanding this apparent supportive evidence for **5a**, molecular mechanics simulation has indicated no significant stereochemical driving force for the conversion **5a** → **4a**.[4]

An indication of the stability and fate of azepinoindole **4a** in basic solution was obtained from ^1H and ^{13}C NMR spectroscopy: ring opening of the substrate anion (**4a***) with generation of macrocycle **5a** (or its anion **5a***) in a significant equilibrium (Scheme II) should be reflected in appropriately altered spectral absorptions. In the proton spectrum of **4a** (CD_3SOCD_3) attention was especially focused on the anisotropically deshielded H-4 doublet at δ 8.36; in a basic medium (CD_3SOCD_3–D_2O–NaOD) this signal was hardly effected (at δ 8.32), indicating a preserved amide CO group (as in **4a***). The ^{13}C absorptions of **4a** (CD_3SOCD_3) considered of diagnostic value (and their proposed assignments) were at δ 92.3 (C-10a), 176.9 (C-6), and 202.5 (C-11); in the same basic medium there were likewise only three signals in the δ 160–220 region; namely at δ 103.4, 179.5, and 212.0, respectively. This observation effectively ruled out macrocycle **5a** but was reconcileable with **4a***, and even with **5a***; however, **5a*** is not expected to show substantial deshielding of the aforementioned proton. In summary, the ^1H and ^{13}C NMR spectral observations were jointly consistent with an intact azepinoindole structure present exclusively, or at least, predominating, in both the neutral (**4a**) and basic (**4a***) media under the prevailing conditions.

Attention was next focused on the 2,4-dimethyl-substituted azepinoindole **4b**: a space-filling (Catalin) model of this molecule indicated a steric impedance to the establishment of coplanarity between the 4-methyl group and the proximate amide carbonyl function. In consequence the corresponding macrocycle **5b** might transform to **4b** with difficulty or not at all, so improving the prospects for the detection and/or isolation of the former species. A more substansive assessment of the relative thermodynamic stabilities of azepinoindole **4a** and its macrocycle **5a** partner, and that of the corresponding **4b**–**5b** pair, was undertaken using the semiempirical SCF-MO methods MINDO/3,[5] MNDO,[6] and AM1.[7] For comparison we have

Scheme I



Scheme II

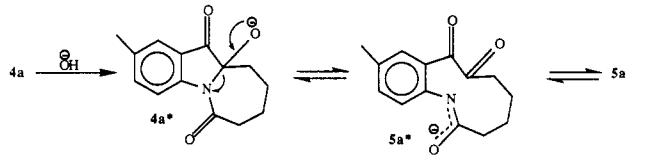
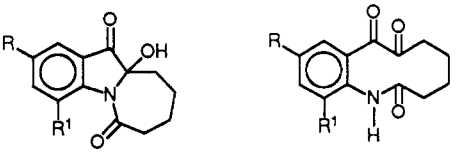


Table I. Calculated Heats of Formation (kcal mol^{-1}) for Compounds 4 and 5



a, R = CH_3, R^1 = H; **b**, R = R^1 = CH_3; **c**, R = R^1 = H; **d**, R = H, R^1 = CH_3

	a	b	c	d
		(i) MINDO/3		
4	−114.4	−114.5	−108.2	−108.4
5	−110.3	−113.8	−105.0	−106.4
4 − 5	−4.1	−0.7	−3.2	−2.0
		(ii) MNDO		
4	−92.0	−95.6	−84.2	−87.8
5	−80.8	−87.1	−73.8	−78.5
4 − 5	−11.2	−8.5	−10.4	−9.3
		(iii) AM1		
4	−83.7	−85.4	−75.1	−79.1
5	−84.6	−90.9	−77.0	−84.0
4 − 5	+0.9	+5.5	+1.9	+4.9

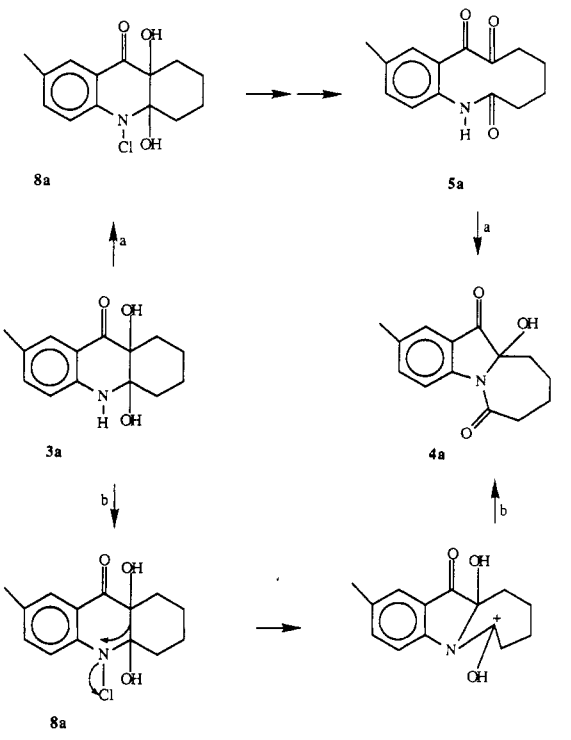
(1) Staskun, B. *J. Org. Chem.* **1988**, *53*, 5287.
(2) *The Chemistry of Heterocyclic Compounds—The Azepines*; Rosowsky, A., Ed.; Wiley and Sons: New York, 1984; Part I, pp 92–94.
(3) Saito, I.; Imuta, M.; Matsuura, T. *Chem. Lett.* **1972**, 1197.
(4) Boeyens, J. C. A.; Denner, L.; Marais, J. L. C.; Staskun, B. *S. Afr. J. Chem.* **1988**, *41*, 63.
(5) Bingham, R. C.; Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1975**, *97*, 1285, 1294, 1302, 1307.

0022-3263/90/1955-1969$02.50/0

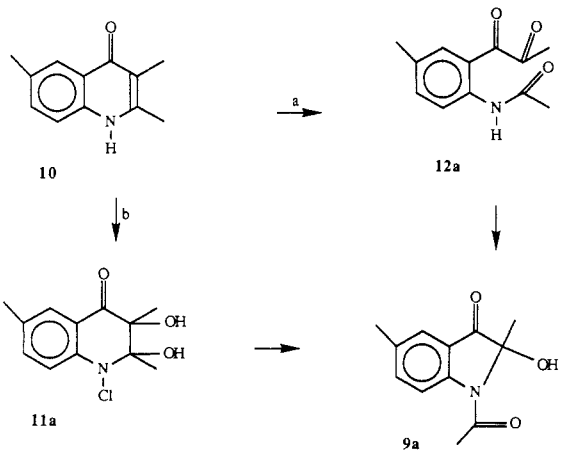
also included the unsubstituted compounds **4c** and **5c**, and the isomers to **4a** and **5a**, namely **4d** and **5d**. The results are summarized in Table I. The three methods differ quite strongly in their predictions concerning the relative thermodynamic stabilities of azepinoindoles **4** and the isomerous macrocycles **5**. According to both MINDO/3 and MNDO the azepinoindoles should be in all cases more stable than the corresponding macrocyclic isomers, whereas the AM1 calculations lead in all cases to the opposite prediction. Taking into account the limited accuracy of the semiempirical methods used, and assuming an approximate cancellation of entropy effects, it appears that the azepinoindoles **4** may well be more stable than the corresponding macrocycles **5**, and thus conversion of **5a** to **4a** may be a thermodynamically feasible process at ambient temperatures. Furthermore the calculations of all three types agree in their predictions that a methyl substituent on the benzene ring ortho to the nitrogen should have a relative destabilizing effect on the azepinoindoles (**4b**, **4d**) in comparison to their macrocycle partners (**5b**, **5d**). The energies of compounds **4a** and **4d** are here directly comparable (as are those of **5a** and **5d**), since the respective compounds may be set into relation using (hypothetical) homodesmic reactions.[8] In compounds **4** this effect appears to amount to ca. 4–6 kcal mol^{-1}, a corresponding destabilization of **5** by an *o*-methyl group being predicted to be generally smaller. Energy partitioning analysis[9,10] shows the effect to be due to less stabilizing neighboring pair interactions in, e.g., **4d** relative to **4a**, which can be traced back to an increase in two-center electron–electron repulsion and two-center core–core repulsion. This finding is in qualitative agreement with above-mentioned model considerations, as well as with chemical intuition, indicating unfavorable steric interactions between the *o*-methyl group and the amide carbonyl oxygen. The corresponding cyclization appears to be energetically less favorable.

In the light of these predictions 5,7-dimethylacridinone (**1b**) was accordingly treated with (i) a 0.5-molar proportion of sodium dichloroisocyanurate (**2**), and also with (ii) an excess (2-molar proportion) of the reagent. Reaction (i) furnished mainly diol **3b** (>58%) together with three minor byproducts, none of which corresponded (spectrally) to either azepinoindole **4b** or macrocycle **5b**. Structure **3b** for the diol was established from its spectral (IR, ^1H NMR, MS) properties and elemental analysis, and presumably the compound had a cis configuration of the vicinal hydroxyls.[1] Reaction (ii) also gave diol **3b** as chief product (>33%), likewise associated with the same aforementioned byproducts. The outcome in reaction (ii) contrasts markedly with that from acridinone **1a** and **2**, which gave predominatly azepinoindole **4a** (60%).[1] Diol **3b** was shown to be relatively less reactive than **3a** toward *N*-chloroimide **2**. Thus, under conditions in which **3a** was transformed to azepinoindole **4a** (80% yield), **3b** was recovered (~50%) unchanged and little if any of the corresponding **4b** was formed. The difference in reactivity between **3a** and **3b** is significant and mitigates against an initial oxidation of the vicinal hydroxyls in **3** with production of macrocycle **5**; these functions are relatively distant from the 5-methyl group in **3b** and would be expected to oxidize with comparable readiness. The observed disparity in behavior is explicable on the assumption that only diol **3a** undergoes initial conversion to a *N*-chloro derivative **8a** (Scheme III), the production of which determines subsequent events (vide infra). In contrast, the 5-methyl and 4a-hydroxyl functions in **3b** may together present a steric barrier that hinders approach of reagent **2** to the NH reaction site; in consequence production of **8b** is restricted or even prevented and diol **3b** is afterwards recoverable. As depicted in Scheme III the formation of azepinoindole **4a** from the *N*-chloro intermediate **8a** is envisaged to occur via either of two routes. Path a perseveres with macrocycle **5a** as the immediate precursor for **4a** although its derivation from **8a** is not clear. Path b is based on the work of Gassman[11] and involves alkyl migration to a divalent nitrogen (nitrenium ion) species (or related alternatives[11]), and currently is favored as the more plausible pathway (vide infra).

Scheme III

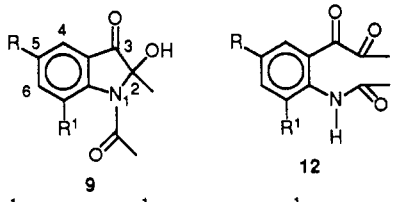


Scheme IV



(6) Dewar, M. J. S.; Thiel, W. *J. Am. Chem. Soc.* **1977**, *99*, 4899, 4907.
(7) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902.
(8) George, P.; Trachtman, M.; Bock, C. W.; Brett, A. M. *Tetrahedron* **1976**, *32*, 317. The term "homodesmotic" coined in that paper has meanwhile been superceded by the term "homodesmic" (used above) in analogy to "isodesmic". Compare: Schulman, J. M.; Disch, R. L. *J. Am. Chem. Soc.* **1984**, *106*, 1202, reference 4.
(9) Fischer, H.; Kollmar, H. *Theor. Chem. Acta* **1970**, *16*, 163.
(10) Dewar, M. J. S.; Lo, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 7201.
(11) Gassman, P. G. *Acc. Chem. Res.* **1970**, *3*, 26.

Table II. Calculated Heats of Formation (kcal mol^{-1}) for Compounds 9 and 12



9 12

a, R = CH_3, R^1 = H; b, R = R^1 = CH_3; c, R = R^1 = H; d, R = H, R^1 = CH_3

	a	b	c	d
		(i) MINDO/3		
9	−107.4	−107.7	−101.2	−101.7
12	−111.9	−114.3	−105.9	−108.4
9 − 12	+4.5	+6.6	+4.7	+6.7
		(ii) MNDO		
9	−93.1	−95.9	−85.4	−90.8
12	−88.4	−93.4	−80.6	−85.4
9 − 12	−4.7	−2.5	−4.8	−5.4
		(iii) AM1		
9	−79.2	−81.9	−71.7	−74.4
12	−86.9	−90.0	−77.9	−85.7
9 − 12	+7.7	+8.1	+6.2	+11.3

The production of dihydroindole **9a** from quinolinone **10** and **2**[1,4] (Scheme IV) may also be accounted for more satisfactorily in terms of the corresponding *N*-chloro precursor **11a** rather than as arising via 1,2-diketone precursor **12a** (corresponding to **5a** in Scheme III). In support we performed semiempirical SCF-MO calculations (MINDO/3, MNDO, AMI) on the dihydroindoles **9** and their hypothetical precursors **12**, and the results are summarized in Table II. Again the three methods yield quite different results. If we assume—as before—an approximate cancellation of entropy terms, then the ring closure from **12** to **9** should be thermodynamically feasible according to MNDO, but not feasible according to MINDO/3 and AM1. The open-chain compounds **12** should however be entropically favored relative to the cyclic isomers **9**, and we believe that the calculational results render reaction path a (Scheme IV) unlikely as a viable mechanism for the formation of compound **9a**.

This finding leads us to reconsider the above discussion concerning the formation of **4a** from **5a**. If the open-chain diketone **12** is not involved in the formation of **9**, one has to assume that consequently the formation of **4a** does not take place via the macrocycle **5a** (Scheme III) which corresponds to **12**.[12] This supports indirectly the alternative (route b) mechanistic proposal of formation of **4a** and **9a**, respectively, via the *N*-chloro intermediates **8a** and **11a**, which may eliminate Cl^- under rearrangement, either stepwise (involving a nitrenium ion) or concertedly.

Calculations

Semiempirical SCF-MO calculations of type MINDO/3, MNDO, and AM1, were performed using the respective Hamiltonians as implemented in Stewart's MOPAC program package.[13] Geometries were fully optimized using the BFGS (Broyden–Fletcher–Goldfarb–Shanno) nonlinear optimization procedure.[14] Because of the size of the molecules of interest in the present investigation, and because of limited computation time available, a reasonably complete search on the potential energy hypersurfaces to locate all conformational minima was not possible. Instead the following procedure was adopted: The structures of **4c**, **5c**, **9c**, and **12c** were first optimized within the MINDO/3 procedure, starting from several different trial geometries. The lowest energy conformations obtained for these molecules were then used to construct starting geometries for the structures of the methyl-substituted derivatives (series **a**, **b**, and **d**), which were also first optimized using MINDO/3. These MINDO/3 optimized structures were then used as initial guesses in all calculations using MNDO and AM1. In each case the final optimizations were performed using stringent gradient and SCF criteria (MOPAC key-word "PRECISE"). Whereas the approach used here does not guarantee that we have indeed found the lowest energy conformation existing for each molecule according to each of the three methods employed, we feel sure that no conformations significantly lower in energy than the values reported here have been overlooked, and that our qualitative conclusions have not been thereby affected.

Experimental Section[15]

5,7-Dimethyl-1,2,3,4-tetrahydro-9(10*H*)-acridinone (1b). Compound **1b** was synthesized by heating together ethyl 1-oxocyclohexane-2-carboxylate and 2,4-dimethylaniline in the presence of polyphosphoric acid:[16] colorless crystals (from MeOH–DMF–H_2O); mp >250 °C (lit.[17] mp 318 °C); soluble in 2 M HCl; IR 3400–2900, 1630, 1620, 1560–1500 cm^{-1}; ^{1}H NMR (CD_3SOCD_3 + TFA) δ 1.85–1.90 (m, 4 H, $(CH_2)_2$), 2.49 (s, 3 H, CH_3), 2.69 (s, 3 H, CH_3), 2.77–2.82 (m, 2 H, CH_2), 3.18–3.23 (m, 2 H, CH_2), 7.65 (s, 1 H, 6-H), 8.1 (s, 1 H, 8-H); MS *m/z* 227 (M^+), 226 ($(M-1)^+$), 212.

4a,9a-Dihydroxy-5,7-dimethyl-1,2,3,4,4a,9a-hexahydro-9-(10*H*)-acridinone (3b). (i) *N*-Chloroimide **2** (660 mg, 3.0 mmol) was added in one portion to a stirred solution of acridinone (**1b**) (1.36 g, 6.0 mmol) in a mixture of methanol (140 mL), 2 M NaOH (20 mL), and water (50 mL); the reagent granules gradually dissolved, and the reaction was accompanied by a mild exothermic effect. After 10 min the stirring was stopped, and the mixture was allowed to remain at room temperature for 1.5 h. The methanol-insoluble isocyanuric acid salt[1] was filtered off, and the combined alkaline filtrate and methanol washings were evaporatively concentrated to ~1/3 volume at room temperature. The residual mass was extracted with $CHCl_3$, and the washed (H_2O) and dried (Na_2SO_4) extract was evaporated to give an orange gum (1.3 g; TLC showed a mixture of about four components including diol **3b** as chief product). Acidification of the extracted aqueous (alkaline) phase with 2 M HCl afforded negligible material. Column chromatography[1] of the gum provided diol **3b** (920 mg, 3.5 mmol; 58%; R_f 0.49, essentially free of contaminants by TLC; ^{1}H NMR ($CDCl_3$) examination, however, revealed a minor impurity which was not characterized). Crystallization from aqueous acetone gave a sample of **3b** free of contaminants (TLC, ^{1}H NMR): yellow crystals; mp 95–217 °C;[18] IR 3300, 3260, 3160, 1650, 1620, 1590, 1510 cm^{-1}; ^{1}H NMR δ 1.48–1.85 (m, 8 H, $(CH_2)_4$), 2.18 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 3.00 (s, 1 H, OH, removed by D_2O), 3.99 (s, 1 H, OH, removed by D_2O), 4.40 (s, 1 H, NH, removed by D_2O), 7.12 (s, 1 H, 6-H), 7.51 (s, 1 H, 8-H); MS *m/z* 261 (M^+), 243 ($(M-18)^+$). Anal. Calcd for $C_{15}H_{19}NO_3$: C, 68.94; H, 7.33; N, 5.36. Found: C, 69.05; H, 7.43; N, 5.26. The appropriate fore-fractions preceding **3b** were combined and evaporated to give an orange gum A (200 mg; TLC showed a number of UV-fluorescent products including **3b**).

(12) This may be regarded as an application of Occam's Razor: "Entia non sunt multiplicanda praeter necessitatem".
(13) MOPAC 4.00 (QCPE No. 455); IBM version 4.01 by Egger, M.; Stewart, J. J. P. *QCPE Bull.* **1983**, *3*, 43.
(14) Thiel, W. *J. Molec. Struct.* **1988**, *163*, 415. Shanno, D. F. *J. Optim. Theory Appl.* **1985**, *46*, 87–94.
(15) Experimental details are described in ref 1.
(16) Staskun, B.; Foote, C. S. *S. Afr. J. Chem. Soc.* **1984**, *37*, 182.
(17) Huggill, H. P. W.; Plant, S. G. P. *J. Chem. Soc.* **1939**, 784.
(18) The diol melts over a wide range (as does diol **3a**, ref 19) perhaps owing to intermolecular and/or intramolecular dehydration processes occurring during heating.
(19) Boeyens, J. C. A.; Denner, L.; Marais, J. L. C.; Staskun, B. *S. Afr. J. Chem.* **1986**, *39*, 221.

(ii) Acridinone **1b** (1.36 g, 6.0 mmol) in methanol (140 mL), 2 M NaOH (50 mL), and water (20 mL) was reacted with sodium dichloroisocyanurate (**2**) (2.64 g, 12.0 mmol) as described in (i), for 1.5 h. The $CHCl_3$-extracted product [1.1 g, TLC showed a mixture containing the same components as in (i)] was chromatographed to afford diol **3b** [520 mg, 2.0 mmol, 33%, free of contaminants (TLC)] and an orange gum B (400 mg) corresponding to A. Flash chromatography [Merck Kieselgel 60 (230–400 mesh), benzene–acetone, 15:1 (v/v)] of the combined gums A and B succeeded in providing samples of three of the common byproducts in the (i)–(ii) reactions, viz, P1, P2, and P3 (approximate R_f values: 0.9, 0.8, 0.7, respectively) virtually free of contaminants, and also more of **3b**. As evidenced from their spectral (IR, ^1H NMR, MS)[20] properties, none of these minor products P1, P2, P3, corresponded to **4b** or to **5b**.

Effect on Diols 3a and 3b of 2. A solution of **2** (125 mg, 0.57 mmol) in water (1.5 mL) was added in one portion to a stirred solution of diol **3b** (50 mg, ~0.2 mmol) in methanol (3 mL) and 2 M NaOH (1 mL). Stirring was continued for 10 min, and the mixture was then left for 1 h. Sparingly soluble isocyanuric acid (derivative)[1] was separated, and the filtrate was evaporated at room temperature. Alkali-insoluble material (30 mg) was identified as crude **3b** from its TLC and IR spectrum. Acidification of the alkaline (**3b**) filtrate afforded a minor amount of (unidentified) material. Diol **3a** (50 mg) under similar conditions reacted more rapidly and completely than did **3b** to yield alkali-soluble crude azepinoindole **4a** [(40 mg, 80%) characterized from its TLC and IR[4] spectrum].

(20) Staskun, B., work in progress.

NMR data of azepinoindole 4a in neutral and in basic medium: ^1H NMR (2 mg, 0.4 mL solvent) ($CDCl_3$) δ 1.4–2.3 (m, ≈6 H), 2.35 (s, 3 H, CH_3), 2.5–2.6 (m, 1 H), 3.08–3.22 (m, 1 H), 3.70 (br s, 1 H, OH, removed by D_2O), 7.4–7.5 (m, 2 H,), 8.34 (dd, J = 1 and 8 Hz, 1 H, 4-H); (CD_3SOCD_3) δ 1.35–2.1 (m, 6 H), 2.35–2.5 [m + s(CH_3), overlapping solvent peaks, ≈4 H], 3.0–3.15 (m, 1 H), 7.21 (s, 1 H, OH, removed by D_2O), 7.5–7.6 (m, 2 H), 8.36 (d, J = 8 Hz, 1 H, 4-H); [CD_3SOCD_3 (0.4 mL) + D_2O (0.1 mL) + 40% NaOD in D_2O (0.2 mL)] δ 1.0–1.6 (m, ≈3 H), 1.8–1.9 (m, 2 H), 2.16–2.33 (m + s(CH_3), ≈5 H), 3.4–3.55 (m, 1 H), 7.4–7.5 (m, 2 H), 8.32 (d, J = 8 Hz, 1 H, 4-H); ^{13}C NMR (60 mg, 0.4 mL solvent) (CD_3SOCD_3) δ 24.18, 26.64, 27.60, 38.57, 41.67, 92.34, (10a-C), 121.5, 124.7, 127.5, 137.5, 142.7, 153.6, 176.9, (6-C), 202.5 (11-C); [CD_3SOCD_3 (0.4 mL) + D_2O (0.1 mL) + 40% NaOD in D_2O (0.2 mL)] δ 24.86, 27.50, 29.17, 41.15, 42.04, 103.6 (10a-C), 122.5, 126.4, 127.9, 136.9, 142.3, 153.6, 179.5 (6-C), 212.1 (11-C).

Acknowledgment. The MOPAC program package was installed by Ingrid Turton. Computation time was supplied by the Computer Center of the University of the Witwatersrand. We thank the University and the Foundation for Research Development (Pretoria) for financial support.

Registry No. **1b**, 125302-77-4; **2**, 2893-78-9; **3a**, 117039-78-8; **3b**, 125302-78-5; **4a**, 117039-79-9; **4b**, 125302-80-9; **4c**, 125302-81-0; **4d**, 125302-82-1; **5a**, 125302-83-2; **5b**, 125302-84-3; **5c**, 125302-85-4; **5d**, 125302-86-5; **8a**, 125302-79-6; **9a**, 117039-81-3; **9b**, 125329-34-2; **9c**, 87066-84-0; **9d**, 125302-87-6; **12a**, 125302-88-7; **12b**, 125302-89-8; **12c**, 125302-90-1; **12d**, 125302-91-2; ethyl 1-oxocyclohexane-2-carboxylate, 1655-07-8; 2,4-dimethylaniline, 95-68-1.