J. Org. Chem. **1986**, *51*, 1604–1607

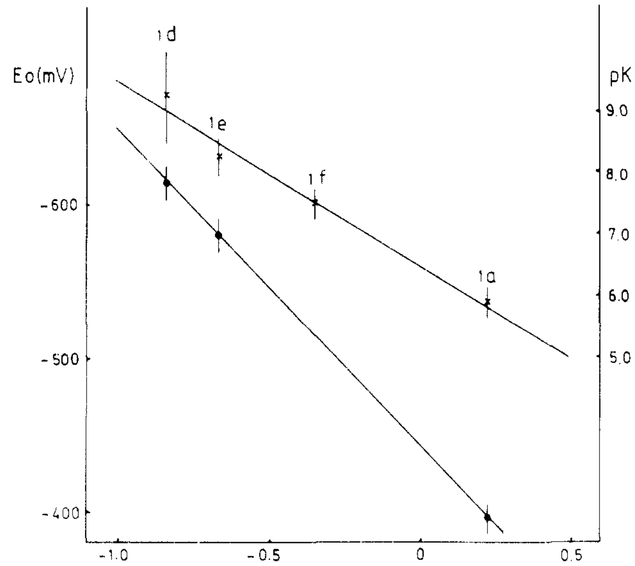

Figure 2. E_0 values of compounds **1a,d,e** vs. σ_p (●); pK_2 values of compounds **1a,d–f** vs. σ_p (×).

between reduction potentials and sigma values in organic systems, we determined the σ_p value of that substituent by the relationship found between the E_0 values of compounds **1a,d,e** and their respective σ_p values[14] (Figure 2).

From this relationship we calculated a σ_p (*p*-aminophenyl) value of −0.34. The correlation of the σ_p values of the four substituents with pK_2 is shown in Figure 2, from which we could derive a pK_2 value for the unsubstituted 5-deazaflavin of 6.5 ± 0.2.

As mentioned in the literature,[12] kinetic $E_{1/2}$ values rather than thermodynamic potentials have been obtained due to dimerization of the respective radicals. Values for thermodynamic $E_{1/2}$ potentials are either equal to or more negative than the respective values for kinetic $E_{1/2}$ potentials, depending on the rates of radical dimerization.

Despite the fact that we have carried out our measurements at rather arbitrary concentrations of **1a–g** we still found a good relationship between $E_{1/2}$ and pH values which points to an apparent lack of a concentration dependence of $E_{1/2}$; i.e., the dimerization rate is low compared to the overall electrode reaction rate.

Comparison of the data in Table II with respect to the substituent at C(8) leads to the conclusion that $E_{1/2}$ potentials shift to more negative values and that pK_1 and pK_2 values increase with increasing electron-donating character of the substituent. The fact that the E_0 and pK_2 values meet the Hammett relation points at the importance of through resonance in the reduction and dissociation process.

Experimental Section

Half-wave potentials for 1e⁻ reduction of 5-deazaflavins have been determined by differential pulse polarography with a Quickstep instrument.[15] A saturated Ag/AgCl electrode was used as reference against the static mercury drop electrode (repeating mode). The following buffers were used: 0.1 M KCl/HCl buffer, pH 1.34 and 1.90; 0.1 M phosphate buffer, pH 6.22 and 7.00; 0.1 M Tris buffer, pH 8.14 and 9.65. Concentrations of 5-deazaflavin solutions were varied between 30 and 100 μM. The temperature was 20 ± 2 °C.

Acknowledgment. We are indebted to Dr. H. P. van Leeuwen and Dr. H. G. de Jong, Laboratory for Physical and Colloid Chemistry, Agricultural University, Wageningen, for reading the manuscript.

Registry No. **1a**, 98629-96-0; **1d**, 98629-99-3; **1e**, 98630-00-3; **1f**, 98630-01-4.

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Hybridization of the Lone Pair Electrons in Amines and the Corresponding N–H Bond in Protonated Amines

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Theoretical studies on amines by ab initio,[1] semiempirical,[2] and more recently, molecular mechanics[3] calculations are well documented. However, to the best of our knowledge, no report on the hybridization of the lone pair electrons in amines has appeared in the literature. We recently reported a localized molecular orbital (LMO) calculation of the hybridization of the lone pair electrons in carbanions.[4] Rehybridization has been found to occur in either direction depending on the structure of the carbanions. For example, the s character of the lone pair orbital of the methyl anion is significantly enhanced over that of the corresponding C–H bonding orbital of the parent methane molecule, while decreases in s character are found in other acyclic anions. Since an amine is isoelectronic with its corresponding carbanion, it would be interesting and desirable to compare the hybridization of the lone pair orbitals in amines with that in carbanions. We now wish to describe an LMO study on the hybridization of the lone pair electrons in amines and, for the purpose of comparison, the hybridization of the N–H bond in protonated amines.

Calculations

The ground-state geometries of the amines and the protonated amines under investigation were fully optimized at the INDO level by using a locally modified CINMIN program.[5] The optimization procedure of this program uses an adapted version of the method due to Rosenbrock.[6] The MO's obtained were transformed into localized orbitals, LMO's, by the technique of Edmiston and Ruedenberg[7] using the ORBLOC subroutine.[8] These LMO's are energy-localized orbitals which minimize the sum of all interorbital repulsions and the sum of the self-energies

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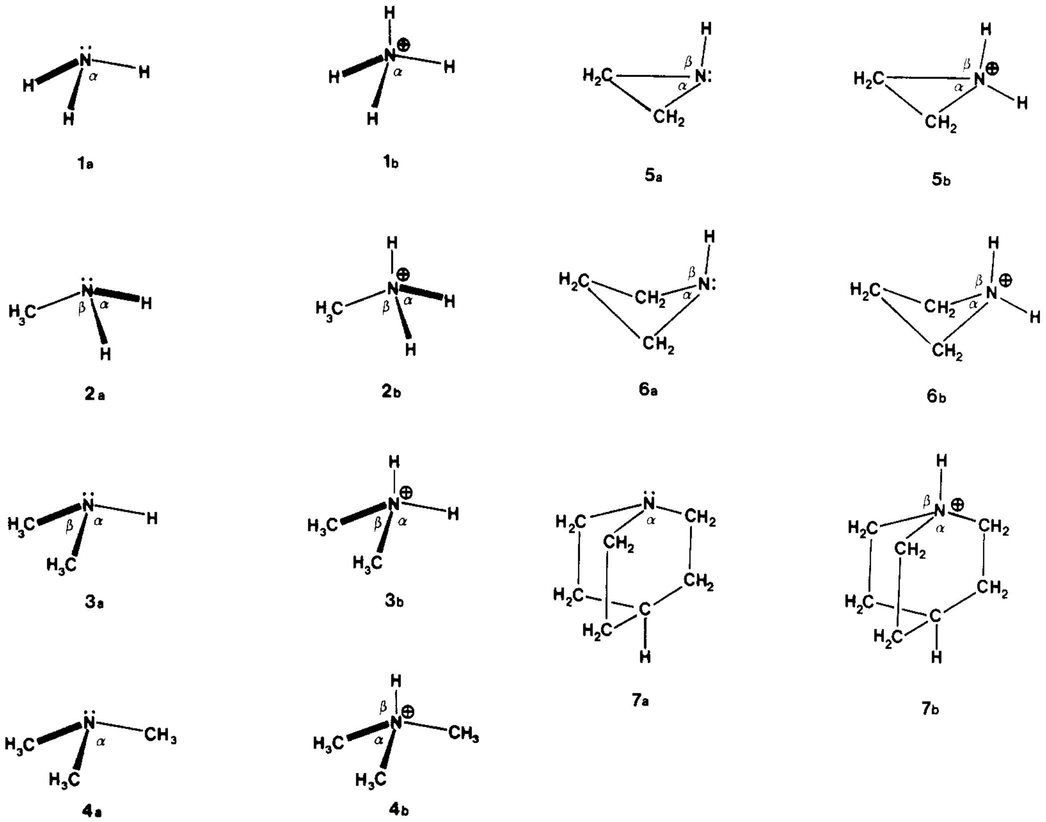

Figure 1. Optimized bond angles at the nitrogen atoms of some amines and protonated amines: **1a**, α = 106.5°; **1b**, α = 109.5°; **2a**, α = 106.2°, β = 111.5°; **2b**, α = 107.3°, β = 111.5°; **3a**, α = 111.3°, β = 113.5°; **3b**, α = 105.7°, β = 110.3°; **4a**, α = 112.2°; **4b**, α = 109.7°, β = 109.2°; **5a**, α = 61.0°, β = 113.0°; **5b**, α = 59.7°, β = 119.5°; **6a**, α = 87.0°, β = 118.8°; **6b**, α = 84.4°, β = 116.8°; **7a**, α = 106.9°; **7b**, α = 108.4°, β = 110.5°.

of all overlap charge distributions.[7] The percent s character of the lone pair orbital of an amine and the corresponding bonding orbital of the N-H bond of the protonated amine was then calculated from the atomic coefficients c's of the orbital associated with the nitrogen atom by the relation in eq 1.

$$\%\mathrm{s} = \frac{c(2\mathrm{s})^2}{c(2\mathrm{s})^2 + c(2\mathrm{p}_x)^2 + c(2\mathrm{p}_y)^2 + c(2\mathrm{p}_z)^2} \times 100\% \quad (1)$$

Results and Discussion

The calculated percent s character of the lone pair orbitals of the amines and that of the corresponding N-H bonding orbitals of the protonated amines are listed in Table I. These results are also compared in Table I with those for the carbon analogues. The optimized bond angles around the nitrogen atoms of the amines and their protonated derivatives are summarized in Figure 1, while their fully optimized geometries are shown in Figure 4 in the supplementary material.

As shown in Figure 1, all amines are definitely pyramidal and the corresponding protonated conjugate acids are roughly tetrahedral. The bond angles around the nitrogen atom in the acyclic amines **1a**–**4a** increase with increasing number of methyl substituents. This is understandable within the framework of the idea of B-strain.[9] However, the bond angles and the extent of the increase of bond angles for methyl substituted amines **2a**–**4a** are somewhat smaller than those for the carbanion analogues. As can be seen from Table I, the lone pair electrons in methyl, dimethyl, and trimethyl amines have higher s character than those in the corresponding carbanions. However, both NH_3 and CH_3^-, on the other hand, have almost the same bond angle and percent s character for their lone pair orbitals. These calculated results perhaps can be accounted for as follows. The lone pair electrons are more tightly bound and thus closer to the nucleus in an amine than in a carbanion because nitrogen is more electronegative than carbon and the anionic carbon carries a formal negative charge. Hence, the lone pair electrons on the anionic carbon have a greater tendency to delocalize onto the carbon–carbon bond(s) of a substituted methyl anion and increases its (their) double bond character. Consequently, a greater bond-pair–bond-pair repulsion and thus larger bond angles result according to Gillespie's VSEPR theory.[10] This in turn causes the percent s character of the lone pair orbital of a substituted methyl anion to be

Table I. Proton Affinities of Amines and Percent s Character of Amines, Protonated Amines, and Carbanions

amines	PA, kJ/mol[a]	% s(amine)	% s(N-H)	Δs	% s(carbanion)[b]
1	-1347 (-853.5)	42	26	16	48
2	-1364 (-896)	32	24	8	15
3	-1374	25	22	3	2
4	-1378 (-942)	22	20	2	1
5	-1417	51	31	20	32
6	-1422	33	25	8	7
7	-1453	33	21	12	33

[a] Observed values are in parentheses; ref 14. [b] The corresponding N atoms in **1a**–**7a** are replaced by C^-; ref 4.

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(9) Brown, H. C.; Batholomay, H.; Taylor, M. D. *J. Am. Chem. Soc.* **1944**, *66*, 435.

(10) Gillespie, R. J. "Molecular Geometry"; Van Nostrand Reinhold: London, 1972; *J. Chem. Educ.* **1974**, *51*, 367; **1970**, *47*, 18.

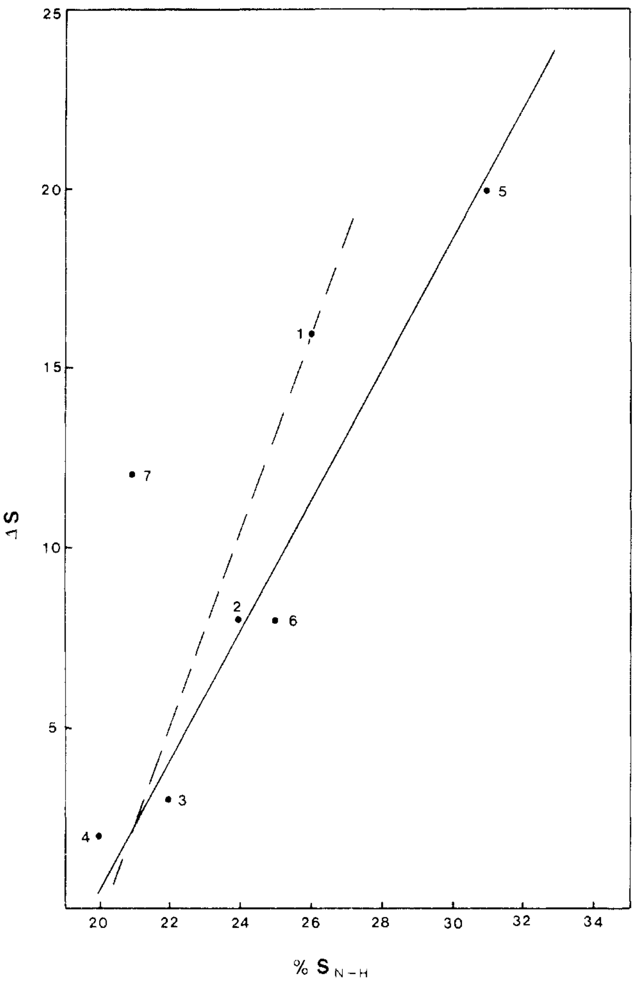

Figure 2. Relationship between the enhanced percent s character, Δs, of amines and the percent s character of the N–H bond of the corresponding protonated amines.

much smaller than that of the corresponding amine. Such a simple explanation is supported by the finding that INDO calculations give a shorter carbon–carbon bond for a carbanion than for its parent conjugate acid.

A plot of the percent s character of the N–H bond in protonated amines against Δs, which is defined in eq 2, is shown in Figure 2. A linear relationship (r = 0.94) was

$$\Delta s = \%s(\text{N–H orbital in protonated amine}) - \%s(\text{lone pair orbital in amine}) \quad (2)$$

obtained from the plot for the substrates **1**–**6**. However, a better correlation (r = 0.96) results if only the four acyclic amines are taken into consideration. Such a linear relationship suggests that the hybridization for the nonbonding orbitals in the amines is closely related to the hybridization of the N–H bonding orbitals of the corresponding protonated amines. It is interesting to note that the data of quinuclidine **7a** and its conjugate acid **7b** deviate from the linear relationship described above. A significant enhancement in s character occurs in **7a** over **7b**, even though the former is a tertiary amine. Perhaps, this is because the system **7a** is rigid and has essentially no B-strain. More importantly, its C–N–C bond angle has been calculated to be about 5° smaller than that of trimethylamine, presumably due to the rigidity of the system. A similar situation has been also found in the carbanions and their parent molecules.[4]

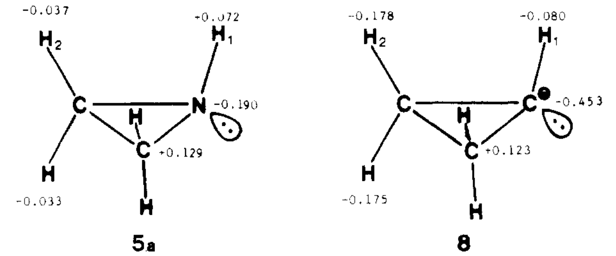

Figure 3. Calculated charge distribution of aziridine **5a** and cyclopropyl anion **8**.

A more striking contrast between the nitrogen compounds studied and the corresponding carbanion analogues is the tremendous increase in percent s character in aziridine **5a** over its conjugate acid **5b** in comparison with the case in cyclopropyl anion **8** and cyclopropane. Furthermore, the C–N–H_1 bond angle in **5a** is found to be 113.0°, which is much smaller than the C–C_a–H_1 angle of 126.9° in **8** (where C_a denotes the anionic carbon atom) as shown in Figure 3. This apparent anomaly of aziridine is not difficult to visualize. According to discussions given above, the structure around the anionic carbon of **8** will be much less pyramidal than that around the nitrogen atom of aziridine. Since the cyclic framework is rigid, the C_a–H_1 bond has therefore to tilt away from the C–C bonds so as to minimize the repulsion. In addition, Mulliken population analysis shows that the H_1 atom attached to the electronegative N atom is positively charged (+0.072) while that attached to the very "electropositive" C_a atom is negatively charged (–0.080). The methylene H_2 atoms, on the other hand, all carry a negative charge (–0.037 in **5a** and –0.178 in **8**). Consequently, the electrostatic interaction between H_1 and H_2 in **5a** is attractive while that in **8** is repulsive. Hence, the C–N–H_1 angle in **5a** should be much smaller than the C–C_a–H_1 angle in **8** and the lone pair electrons of the former should have accordingly more s character as found in the calculation.

The proton affinity (PA) of an amine is just the energy difference between the protonated amine and the parent amine itself because the energy of the proton is by definition zero.[11] The PA's of the amines studied are also given in Table I.

As can been seen from Table I, the calculated PA's are overestimated[12] as compared with the observed values.[13] However, the calculated PA's of the acyclic amines do reproduce correctly the observed trend. Indeed plots of the calculated PA's of the acyclic amines vs. the computed percent s character of the lone pair orbitals and the Δs values are linear (r = 1.0 for both plots). Similar excellent linear plots are also obtained when the experimental PA values are used instead (r = 1.0 and 0.99, respectively). It is noted that the PA's of the cyclic amines **5a**–**7a** do not fall within these plots.

Attempts to correlate quantitatively the pK_a values[14] of the conjugate acids **1b**–**7b** of the amines studied with the percent s character of their N–H orbitals or with the percent s character of the lone pair orbitals of the corre-

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[11] Hopkinson, A. C.; Holbrook, N. K.; Yates, K.; Csizmadia, I. G. *J. Chem. Phys.* **1968**, *49*, 3596.

[12] This is not surprising in view of the level of accuracy of the present calculation. Ab Initio calculations with minimal STO-3G basis set, for example, have given the PA's of OH^- and CH_3O^- in error by about 628 kJ m^{-1}. (Cf.: Random, L. In "Modern Theoretical Chemistry"; Schaefer, H. F., III, Ed.: Plenum: New York, 1977; Vol. 4 and references cited therein.) However, results of ab initio calculations with various basis sets on quite a number of spcies have shown that the smaller basis sets almost invariably give PA values whose magnitudes are too high and that one finds close agreement with experiment only when near-Hartree–Fock calculations are performed.

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sponding amines **1a**–**7a** or with the Δs values were not successful. However, a qualitative trend as anticipated does occur for the species **1a**–**3a** and for the secondary amines **3a**, **5a**, and **6a**, while the tertiary amine **4a** is found to be out of place owing to the steric B-strain. As we have suggested earlier,[4] acidity constant of a compound depends on several factors. Hybridization of an acid and its conjugate base, of course, may be one of the most important ones governing the relative energy difference between them. However, steric effect may also play a significant role.

Registry No. **1a**, 7664-41-7; **1a** (carbanion), 15194-58-8; **1b**, 14798-03-9; **2a**, 74-89-5; **2a** (carbanion), 25013-41-6; **2b**, 17000-00-9; **3a**, 124-40-3; **3a** (carbanion), 25012-80-0; **3b**, 17000-01-0; **4a**, 75-50-3; **4a** (carbanion), 65114-21-8; **4b**, 16962-53-1; **5a**, 151-56-4; **5b**, 24151-28-8; **6a**, 503-29-7; **6a** (carbanion), 60211-41-8; **6b**, 66203-35-8; **7a**, 100-76-5; **7a** (carbanion), 89849-42-3; **7b**, 49623-78-1; **8**, 1724-45-4.

Supplementary Material Available: Figure 4 showing the optimized geometries for all amines and protonated amines (4 pages). Ordering information is given on any current masthead page.

Thallium in Organic Synthesis. 65. A Novel Synthesis of Benzoxazoles from Anilides[1,2]

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Although benzoxazoles are conventionally prepared from *o*-aminophenols by cyclization with carboxylic acids, imino ethers, nitriles, etc.[3] a few procedures have been described which commence with an anilide and subsequently introduce the requisite ortho-situated oxygen substituent. Several groups have reported the formation of benzoxazoles by intramolecular trapping of an aryne intermediate generated in situ from 2- or 3-haloanilides.[4] Anodic oxidation of *N*-methyl-4-alkoxyanilides gives the corresponding benzoxazolium salts in good yield.[5] α,*N*-Diaryl nitrones rearrange upon prolonged heating (1–7 days) at 150 °C in the presence of *O*-methyl diphenylphosphinothioate to give 2-arylbenzoxazoles.[6] Benzoxazoles have also been prepared from aryl azides substituted in the para position with electron-withdrawing substituents by heating in PPA and a carboxylic acid.[7] Finally, 1,2-diacetamido-4-bromobenzene has been reported to undergo intramolecular oxidative coupling in low yield to a benzoxazole when treated with thallium(III) tris(trifluoroacetate) (TTFA) in refluxing TFA.[8]

We have established in previous work that a wide variety of anilides undergo smooth ortho thallation when treated with TTFA in a mixture of TFA and ether.[9] We now report that benzoxazoles are readily formed upon photolysis of these ortho-thallated anilides in cyclohexane suspension (see Table I). In most cases, moderate yields were obtained within 2–6 h, although occasionally an increase in photolysis time resulted in a slight increase in yield. Of the substrates examined, only (3-chloro-2-acetamidophenyl)thallium(III) bis(trifluoroacetate), failed to produce a benzoxazole, perhaps because of the photolability of the C–Cl bond.

Since unsymmetrical biaryls can be obtained in almost quantitative yield by photolysis of arylthallium(III) bis(trifluoroacetates) in benzene,[10] an attempt was made to convert the above ortho-thallated anilides into 2-aminobiphenyl derivatives by irradiation in benzene. Photolysis of (2-acetamidophenyl)thallium(III) bis(trifluoroacetate) (**1a**) in benzene suspension at 300 nm for 3 h gave a very small amount (6%) of 2-acetamidobiphenyl; the major product formed was 2-methylbenzoxazole, indicating that intramolecular trapping of the aryl radical (formed by homolysis of the C–Tl bond) readily predominated over intermolecular capture by solvent.

This route to benzoxazoles, which commences with an aromatic amine and introduces the *o*-hydroxyl group by an intramolecular route, appears to be more flexible than conventional procedures which require an *o*-aminophenol as starting material. As a demonstration of the utility of this route to benzoxazoles, we have carried out a new synthesis of 2-(4-chlorophenyl)-α-methyl-5-benzoxazoleacetic acid (**3**) (benoxaprofen)[11] (see Scheme I). *m*-Nitropropiophenone (**4**) was reduced with hydrogen/Pt in ethanol to give *m*-aminopropiophenone, which was aroylated under Schotten–Baumann conditions with *p*-chlorobenzoyl chloride to give amide **5** (77% overall yield). This material was then converted with thallium(III) trinitrate (TTN) in a solution of methanol and trimethyl orthoformate (TMOF)[12] to **6**, which was thallated with TTFA in a mixture of ether and TFA; the arylthallium bis(trifluoroacetate) **7** precipitated directly from the reaction mixture in 38% overall yield. Photolysis of **7** in cyclohexane solution in a Rayonet reactor at 300 nm then gave benoxaprofen methyl ester (**8**) (90%), identical in all respects with an authentic sample.[13] Alkaline hydrolysis of **8** gave benoxaprofen (**3**).

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[1] For the previous paper in this series, see: Taylor, E. C.; Katz, A. H.; Alvarado, S. I.; McKillop, A. *J. Organomet. Chem.* **1985**, *285*, C9–C12.

[2] We are grateful to the National Science Foundation (Grant CHE 82-15419) for its support of this work.

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[11] This compound was introduced several years ago for the treatment of arthritis (Roberts, P. J. *Drugs Future* **1980**, *5*, 461. Huskisson, E. C. *Eur. J. Rheumatol. Inflammation* **1979**, *3*, 29), but fatalities resulting from its use led to its withdrawal from both the British and American markets. Several syntheses of this interesting representative of the α-methylarylacetic acid family of antiinflammatory agents have been reported (Dunwell, D. W.; Evans, D.; Hicks, T. A.; Cashin, C. H.; Kitchen, A. *J. Med. Chem.* **1975**, *18*, 53. Drew, R.; Meffin, P. J.; Hugel, H. M. *Synth. Commun.* **1985**, *15*, 1075); all of them employ the classical procedure for benzoxazole formation from an *o*-aminophenol precursor and standard methodology for the preparation of the α-methylacetic acid side chain.

[12] These reaction conditions for effecting the "acetophenone rearrangement" are critical, since propiophenones are known to undergo oxidation at the α-carbon atom in the absence of TMOF: McKillop, A.; Taylor, E. C. *Comprehensive Organometallic Chemistry*; Wilkinson, G., Stone, F. G. A., Eds.; Pergamon: Oxford, 1982 Vol. 7, p 465. McKillop, A.; Swann, B. P.; Taylor, E. C. *J. Am. Chem. Soc.* **1973**, *95*, 3340).

[13] We are grateful to Eli Lilly & Co. for providing us with an authentic sample of this material.