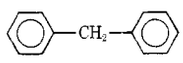
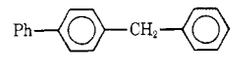
Table II. Summary of Equilibrium Constants

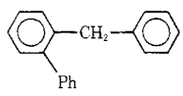
R_1H[a]	R_2H[a]	K	log K	n[b]	pK (per H)[c]
TPM	*p*-BBP	1.47 ± 0.28	0.17 ± 0.07	10	31.92 ± 0.12[d]
DCH	*p*-BBP	3.26 ± 0.37	0.51 ± 0.05	6	31.72 ± 0.14[d]
p-BBP	*o*-BBP	50.30 ± 12.7	1.69 ± 0.11	6	33.51 ± 0.12[e]
T*p*TM	*o*-BBP	1.46 ± 0.45	0.16 ± 0.13	8	33.50 ± 0.14[e]

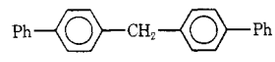
[a] Abbreviations and pK_{CsCHA} values for indicators used are as follows: TPM, triphenylmethane, 31.45; T*p*TM, tri-*p*-tolylmethane, 33.04; DCH, 5*H*-dibenzo[*a*,*d*]cycloheptа-1,3-diene, 31.21. [b] Number of determinations. [c] pK of R_2H followed by the accumulated probable error, relative to pK_{CsCHA} (9-phenylfluorene) = 18.49. [d] Weighted average pK_{CsCHA} of *p*-BBP is 31.82 ± 0.12. [e] Weighted average pK_{CsCHA} of *o*-BBP is 33.51 ± 0.12.

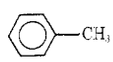
Table III. Effect of *p*-Phenyl Substituents on pK_{CsCHA} of Arylmethanes[a]

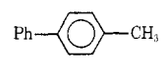

DPM; 33.4[b]

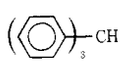

p-BBP; 31.8[c]

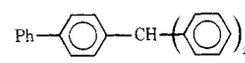

o-BBP; 33.5[c]


DBM; 30.8[b]


toluene; (41.2)[d,e]


p-MB;[e] 39.0[b,e]


TPM; 31.4[b]


BDPM;[e] 30.2[b]

[a] pK_{CsCHA} per hydrogen. Abbreviations used are as follows: *p*-MB, *p*-methylbiphenyl; BDPM, *p*-biphenylyldiphenylmethane. [b] Reference 1b. [c] This work. [d] A. Streitwieser, Jr., M. R. Granger, F. Mares, and R. A. Wolf, *J. Am. Chem. Soc.*, **95**, 4257 (1973). [e] A. Streitwieser, Jr., and F. Guibe, *J. Am. Chem. Soc.*, in press.

The pK value of 31.82 obtained for *p*-benzylbiphenyl (*p*-BBP) appears reasonable in view of the pK's already reported for diphenylmethane (DPM) and di-*p*-biphenylylmethane (DBM)[1b] (Table III). The results show an expected attenuation of substituent effects: substitution of a phenyl group into the para position of toluene gives a pK decrease of 2.2, the first *p*-phenyl substituent in diphenylmethane gives a ΔpK of 1.6, and the second gives a further ΔpK of 1.0. For comparison, a single *p*-phenyl substituent in triphenylmethane (TPM) causes a pK lowering of 1.3 pK units (Table III).

From Dreiding models it seems likely that steric interactions will prevent the biphenylyl group from achieving coplanarity in the anion of *o*-BBP and probably interfere with the conjugation to the central carbon. The experimental result that *o*-BBP has essentially the same acidity as the unsubstituted DPM (ca. 1.7 pK units less acidic than *p*-BBP) suggests that this effect is just balanced by the inductive effect of the *o*-phenyl group.

Experimental Section

Melting points were determined on a Büchi apparatus and are not corrected. Visible spectra were measured on a Cary 118 spectrometer (20 nm/in.; 1 nm/s).

Procedure. The procedure for measuring the spectra of the cesium salts has been described in detail.[4] The equilibrium constants in Table II were determined using the previously reported procedures.[1,5] This table is arranged such that the more acidic hydrocarbon is given as R_1H in equilibrium 1, and K is always >1. Table III summarizes the results as pK values. These values actually relate to the equilibrium of each hydrocarbon in eq 1 with 9-phenylfluorene, with a pK of 18.49 assigned to the latter, and are given on a per hydrogen basis.

***o*- and *p*-Benzylbiphenyl.** A commercial sample of benzylbiphenyl (Eastman Organic Chemicals; a mixture of the ortho and para isomers) was initially purified by subliming out the biphenyl present as a contaminant [32–35 °C (1 mm)]. The residual mixture (150 mg) was cleanly separated by preparative thin-layer chromatography (TLC) on a 20 × 20 cm silica gel F-254 plate (Brinkman Co.) with cyclohexane as eluent to give (after recrystallization from 95% EtOH) 13 mg of biphenyl [R_f 0.95; mp 68–69 °C (lit.[6a] mp 69–70 °C)], 59 mg of *o*-benzylbiphenyl [R_f 0.83; mp 54–55 °C (lit.[6b] mp 54 °C)], and 22 mg of *p*-benzylbiphenyl [R_f 0.70; mp 83–84 °C (lit.[6b] mp 85 °C)].

Acknowledgment. This work was supported by NIH USPH Grant GM-12855.

Registry No.—*p*-BBP, 613-42-3; *o*-BBP, 606-97-3.

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(1) (a) A. Streitwieser, Jr., E. Ciuffarin, and J. H. Hammons, *J. Am. Chem. Soc.*, **89**, 63 (1967). (b) A. Streitwieser, Jr., J. R. Murdoch, G. Häfelinger, and C. J. Chang, *ibid.*, **95**, 4248 (1973). A summary is available for Japanese readers: A. Streitwieser, Jr., and L. L. Nebenzahl, *Yuki Gosei Kagaku Kyokai Shi*, **33**, 889 (1975).
(2) The pK of *p*-benzylbiphenyl in Me_2SO–MeOH has been reported by E.-C. Steiner and J. M. Gilbert, *J. Am. Chem. Soc.*, **87**, 382 (1965).
(3) Steric inhibition of resonance has been observed by Bowden and Stewart when comparing the effect of *o*- and *p*-nitro groups on the acidity of diphenylmethane: K. Bowden and R. Stewart, *Tetrahedron*, **21**, 261 (1965).
(4) G. Häfelinger and A. Streitwieser, Jr., *Chem. Ber.*, **101**, 672 (1968).
(5) A. Streitwieser, Jr., J. H. Hammons, E. Ciuffarin, and J. I. Brauman, *J. Am. Chem. Soc.*, **89**, 59 (1967).
(6) (a) W. H. Zartman and H. Adkins, *J. Am. Chem. Soc.*, **54**, 3398 (1932); (b) G. Goldschmiedt, *Monatsh. Chem.*, **2**, 432 (1881).

Synthesis of 2,6-Diacetonylpiperidine. X-ray Diffraction Analysis of Its *N*-Benzoyl Derivative[1]

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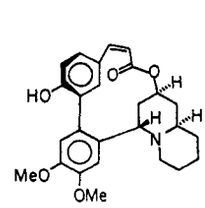
Received February 1, 1978

The 39 alkaloids which have been isolated from members of the *Lythraceae* plant family[2] may be classified according to three structural types. The type I alkaloids, quinolizidine lactones, are represented by cryogenine (**1**).[2a] The type II alkaloids, e.g., lythrancine I (**2**),[2b] are also quinolizidine alkaloids, but with a carbocyclic ring. Finally, the type III alkaloids are piperidine alkaloids, e.g., lythranidine (**3**).[2c] Some of the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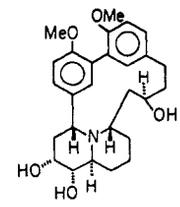
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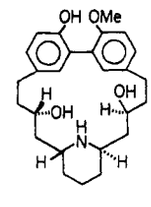
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type I alkaloids have been investigated for use as sedatives, antiinflammatory agents, and as diuretics.[3] There have been no reports of pharmacological studies on the type II or III al-

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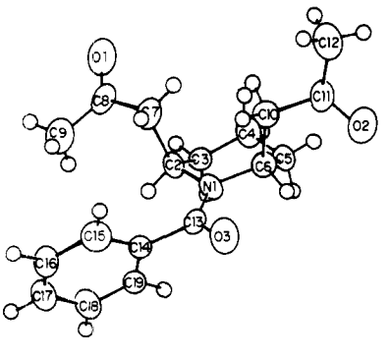
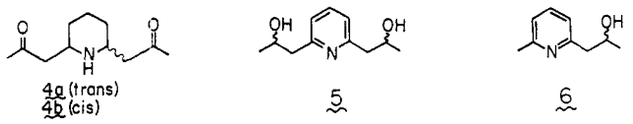


Figure 1. A labeled drawing of *N*-benzoyl-2,6-diacetonylpiperidine showing 50% probability ellipsoids for the nonhydrogen atoms.

kaloids. There has likewise been no report of synthetic studies on these latter two classes of alkaloids.

The type II and III alkaloids have been proposed to arise biogenetically from a common precursor, *trans*-2,6-diacetonylpiperidine (**4a**).[4] This dione is also an attractive starting material for the syntheses of these alkaloids. Elaboration of **4** into the type II or III skeletons may be envisioned to occur via pelletierine[5] and/or Claisen–Schmidt condensations. Thus, we began our synthetic studies on these alkaloids with a study of the preparation of **4.**

Our initial route utilized a bisfunctionalization of 2,6-lutidine. Thus, a THF solution of lutidine was treated with 2 equiv of lithium diisopropylamide at −70 °C to yield a dark-red solution.[6] The solution became light yellow when an excess of acetaldehyde was distilled into it. Normal workup of this solution afforded a crude oil. Separation of the components of this oil by chromatography afforded a 43% yield of the diol, **5,** presumably as a mixture of diastereomers, as well as a 25%

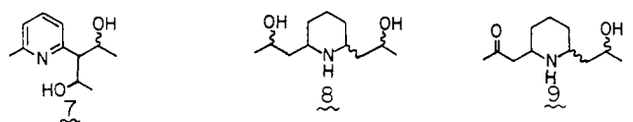


4a (trans)
4b (cis)

5

6

yield of the monofunctionalized lutidine, **6.**[7] There is no evidence for the occurrence of the nonsymmetric diol, **7.** Hydrogenation of **5** resulted in an 86% yield of the piperidine diol, **8.** This latter compound was very difficult to purify and was routinely utilized without further purification.



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8

9

The final step in this sequence, the oxidation of the diol to the dione, proved to be unexpectedly difficult. The presence of the secondary amine limits the choice of oxidation reagents. All of the methods investigated suffered from either low material recovery (i.e., Jones or Fieser oxidations) or low percent conversions (i.e., pyridinium chlorochromate,[8] polymer-bound CrO_3,[9] Oppenauer, or Moffat oxidations). The former problem was a result of the formation of an emulsion upon basification of the oxidation mixture. The latter series of reagents was studied in an attempt to avoid this problem. The best results in the entire series were obtained with Jones reagent. Thus, a 26% yield of **4,** as well as an 8% yield of **9,** was obtained after chromatography of the crude oil from the Jones oxidation. The overall yield of **4** by this route was 9.6%. The oxidation of the pyridine diol, **5,** to the corresponding dione by these reagents was likewise not very successful. Attempts to selectively block the nitrogen in **8** were unsuccessful. Since there did not appear to be much chance for improvement in the oxidation step we considered other synthetic routes.

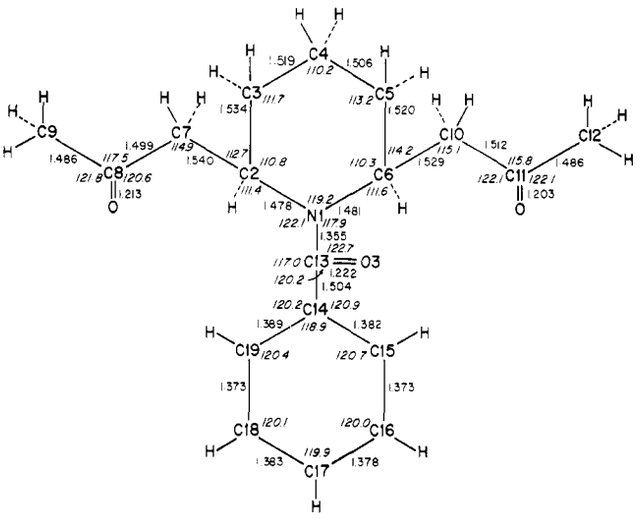
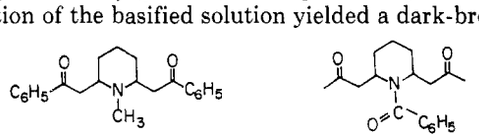


Figure 2. Bond distances and bond angles for *N*-benzoyl-2,6-diacetonylpiperidine. The average standard deviations are 0.006 Å and 0.4°, respectively.

Dione **4** is structurally similar to the *Lobelia* alkaloids, e.g., lobelanine (**10**). Lobelanine had been prepared by Schöpf and Lehmann by the condensation of glutaraldehyde, methylamine, and benzoylacetic acid in a buffered solution.[10] A similar condensation was attempted by stirring a solution of glutaraldehyde, ammonium chloride, and acetoacetic acid in a phosphate buffer (pH 2–3) overnight. Methylene chloride extraction of the basified solution yielded a dark-brown oil



10

11

which could be further purified by Kŭgelrohr distillation. The yield of **4** by this method was 12%. The condensation has also been attempted at pH's 4, 6, and 10, but the yields were even lower. The simplicity of this method makes the yield acceptable.

The NMR, IR, and mass spectra, as well as the TLC behavior, of **4** prepared from lutidine are identical with those of the material obtained from the glutaraldehyde condensation. Likewise, the hydrochlorides have the same melting–decomposition points. Thus, the two procedures probably yield the same diastereomer of **4.** All of our further studies have utilized material prepared by the condensation route.

The catalytic hydrogenation of 2,6-lutidine has been reported to afford *cis*-2,6-dimethylpiperidine.[11] The synthesis of lobelanine produced the cis isomer.[12] Thus, it could also be assumed that the diastereomer of **4** obtained in this study was the cis isomer. However, we wished to definitely establish the stereochemistry of the product. The NMR spectrum of **4** was not useful for this purpose since a first-order spectrum could not be obtained using lanthanide shift reagents nor could we prepare a characterizable 2,4-dinitrobenzenesulfonamide of **4** in order to apply the method of Raban et al.[13] However, the preparation of the crystalline benzamide, **11,** in 90% yield from **4** suggested the application of X-ray diffraction.

The molecular conformation of **11** as determined by the X-ray diffraction study (see Experimental Section) is shown in Figure 1. The bond lengths and bond angles involving nonhydrogen atoms are given in Figure 2. Several related structural features of the molecule are apparent from these results: the acetonyl groups at C-2 and C-6 are cis to one another; the amide group (N-1, C-13, and O-3) is planar; and the piperidine ring exhibits a flattened chair conformation. The

cis diaxial substitution avoids the contacts involving the planar amide group and the acetonyl groups which would occur if the latter were equatorial ($A^{1,3}$ strain).[14] At the same time flattening of the piperidyl ring, which results from the planarity of the amide, serves to prevent contact between the methylene hydrogens on C-7 and C-10. Even with the acetonyl groups in axial positions, the phenyl ring is unable to assume coplanarity with the amide carbonyl group due to the steric conflict between the hydrogen on C-2 of the piperidyl ring and the hydrogen on either C-19 or C-15 of the phenyl ring.

The cis relationship of the acetonyl groups in **11** indicates that **11** was obtained from *cis*-2,6-diacetonylpiperidine (**4b**). This is the first application of X-ray crystallography to a compound related to the Lobelia alkaloids. It verifies the stereochemical findings previously made on these alkaloids.[12]

Thus, the material which we have prepared by two different routes has the improper stereochemistry for synthesis of the type II and III *Lythraceae* alkaloids. Work is now in progress to find methods for the conversion of **4b** into **4a**.

Experimental Section

General. NMR spectra were recorded with a Varian T-60 spectrometer and are reported in ppm downfield from tetramethylsilane. Infrared spectra were recorded with a Perkin-Elmer 457 spectrophotometer. Mass spectra were recorded on a Nuclide mass spectrometer. Melting points were obtained with a Thomas-Hoover melting point apparatus and are uncorrected. The elemental analyses were performed by Galbraith Laboratories, Inc. An Aldrich Kügelrohr apparatus was utilized for bulb-to-bulb distillation. All commercially available reagents were used without further purification unless otherwise specified.

1. 2,6-Di(2-hydroxypropyl)pyridine (5). To a 0 °C solution of 70 g (0.69 mol) of diisopropylamine in 250 mL of dry tetrahydrofuran (THF), 63 mL of 8 N *n*-butyllithium in hexane (0.50 mol) was slowly added. After stirring for 15 min, 26.75 g (0.25 mol) of 2,6-lutidine in 60 mL of dry THF was added dropwise. Stirring was continued for 45 min after the addition was completed. Acetaldehyde (28 mL) was distilled into the deep red solution and the now yellow reaction mixture was allowed to warm to room temperature (3 h). The mixture was diluted with 100 mL of water, basified with 6 N sodium hydroxide, and extracted with methylene chloride (3 × 250 mL). The extracts were dried (Na_2SO_4) and concentrated in vacuo to yield 34.9 g of a brown oil.

Column chromatography of 10.1 g of this crude oil on 200 g of alumina (activity grade III) gave, upon elution with 25% acetonitrile in ether, 2.70 g (25% yield) of 2-methyl-6-(2-hydroxypropyl)pyridine (**6**)[7] as an oil: IR (film) 3340, 1595, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.25 (d, J = 6 Hz, 3 H), 2.47 (s, 3 H), 2.83 (d, J = 6 Hz, 2 H), 4.22 (h, J = 6 Hz, 1 H), 5.3 (br s, 1 H), 7.2 (m, 3 H). Signal at δ 5.3 disappears after shaking with D_2O.

Further elution of the above column with acetonitrile gave 6.10 g (43% yield) of 2,6-di(2-hydroxypropyl)pyridine (**5**) as an oil: IR (film) 3325, 1595, 1580 cm^{-1}; NMR ($CDCl_3$) δ 1.23 (d, J = 6 Hz, 6 H), 2.87 (d, J = 6 Hz, 4 H), 4.23 (h, J = 6 Hz, 2 H), 4.78 (br s, 2 H), 7.3 (m, 3 H). Hydrochloride (from isopropyl alcohol): mp 139–140 °C dec. Anal. Calcd for $C_{11}H_{18}ClNO_2$: C, 57.01; H, 7.84; N, 6.05; Cl, 15.30. Found: C, 57.28; H, 8.01; N, 5.84; Cl, 15.47.

2. 2,6-Di(2-hydroxypropyl)piperidine (8). To a solution of 3.17 g (16 mmol) of **5** in 30 mL of acetic acid was added 1 g of 0.5% rhodium on aluminum oxide. The slurry was exposed to hydrogen in a Parr hydrogenator for 24 h. The catalyst was removed and the solution was concentrated. The resulting solution was diluted with 30 mL of water, basified with 6 N sodium hydroxide, and extracted with methylene chloride. The extracts were dried (Na_2SO_4) and concentrated to yield 2.81 g (86% yield) of **8** as a brown oil: IR (film) 3300 cm^{-1}; NMR ($CDCl_3$) δ 0.9–2.0 (m, 16 H), 1.14 (d, J = 6 Hz), 2.8 (m, 2 H), 3.4–4.2 (m, 4 H), 3.7 (br s, 4 H). After shaking with D_2O δ 3.7 changed to 2 H, m.

3. Jones Oxidation of 2,6-Di(2-hydroxypropyl)piperidine (8). To a solution of 5.05 g (25 mmol) of **8** in 20 mL of acetone at 0 °C was added Jones reagent made from 55 mmol of CrO_3. After 2 h, excess sodium thiosulfate solution was added and the solution was basified with sodium hydroxide. The resulting emulsion could not be filtered but was washed several times with ether. The combined organic layers were dried (Na_2SO_4) and concentrated to yield 2.35 g of a brown oil. Chromatography of this oil on 80 g of alumina afforded two characterizable products. The first, **4**, eluted with ether–methylene chloride mixtures and was obtained in 26% yield (1.30 g): IR (film) 3320, 1705 cm^{-1}; NMR ($CDCl_3$) δ 0.8–1.9 (m, 6 H), 2.10 (s, 6 H), 2.45 (d, J = 6 Hz, 4 H), 2.7 (br s, 1 H), 2.8–3.3 (m, 2 H). After shaking with D_2O the δ 2.7 signal disappears. Mass spectra m/e 197 (21), 140 (85), 139 (92), 112 (58), 96 (100), 82 (94), 43 (72). Hydrochloride (from isopropyl alcohol): mp 202–202.5 °C dec. Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99; Cl, 15.17. Found: C, 56.37; H, 8.71; N, 5.89; Cl 15.26.

Further elution of the column with methylene chloride gave 0.41 g (8% yield) of **9** as a pink solid. Two successive sublimations (47 °C (0.05)) afforded a white solid: mp 73–4 °C; IR (KBr) 3400, 3260, 1715 cm^{-1}; NMR ($CDCl_3$) δ 0.8–2.0 (m, 11 H), 1.15 (d, J = 6 Hz), 2.12 (s, 3 H), 2.47 (d, J = 6 Hz, 2 H), 2.6–3.3 (m, 3 H), 4.0 (m, 1 H); mass spectra m/e 199 (10), 142 (57), 140 (100), 82 (84). Anal. Calcd for $C_{11}H_{21}NO_2$: C, 66.29; H, 10.62; N, 7.03. Found: C, 66.59; H, 10.90; N, 7.24. Hydrochloride (from isopropyl alcohol): mp 199.5–200 °C dec. Anal. Calcd for $C_{11}H_{22}ClNO_2$: C, 56.52; H, 8.62; N, 5.99; Cl, 15.17. Found: C, 56.42; H, 8.66; N, 5.96; Cl, 15.23.

4. 2,6-Diacetonylpiperidine (4). Condensation Method. To a three-neck flask equipped with a mechanical stirrer was added, in order, 200 mL of 25% glutaraldehyde solution (0.50 mol), 300 mL of deoxygenated water, 39.6 g (0.74 mol) of ammonium chloride in 500 mL of water, sodium acetoacetate solution [prepared by stirring a solution of 156 g (1.2 mol) of ethyl acetoacetate and 58 g of sodium hydroxide in 500 mL of water for 1.5 h], and 88 g (0.25 mol) of disodium hydrogen phosphate in 500 mL of water. The pH of the resulting red solution was initially adjusted to 2.5–3.0 by careful addition of concentrated hydrochloric acid. The mixture was allowed to stir for 24 h at room temperature. Finally, 33 mL of concentrated hydrochloric acid was added and the solution was heated for 1 h on a steam bath. After cooling, the mixture was basified and the resulting precipitate was removed by filtration. The aqueous solution was extracted with methylene chloride (8 × 250 mL) and the combined extracts were dried and concentrated to yield 18.2 g of a brown oil. Kügelrohr distillation of 1.14 g of this crude oil afforded 0.757 g (12% yield) of **4** as a yellowish oil which slowly darkened on standing. IR, NMR, and mass spectra were the same as in procedure 3. Picrate (from ethanol): mp 190.5–191 °C dec. Anal. Calcd for $C_{17}H_{22}N_4O_9$: C, 47.89; H, 5.20; N, 13.15. Found: C, 48.01; H, 5.17; N, 12.98. Hydrochloride (from isopropyl alcohol): mp 198–198.5 ° dec. Anal. Calcd for $C_{11}H_{20}ClNO_2$: C, 56.52; H, 8.62; N, 5.99; Cl, 15.17. Found: C, 56.70; H, 8.80; N, 6.09; Cl, 15.29.

5. *N*-Benzoyl-2,6-diacetonylpiperidine (11). A solution of 1 g (7.1 mmol) of freshly distilled benzoyl chloride in 10 mL of CH_2Cl_2 was added dropwise with stirring over a 1-h period of 0 °C under nitrogen to a solution of 0.6 g (2.59 mmol) of 2,6-diacetonylpiperidine hydrochloride in 100 mL of CH_2Cl_2 and 15 mL of 10% aqueous NaOH. The reaction mixture was stirred at 0 to 24 °C for 8 h. The CH_2Cl_2 layer was separated from the aqueous phase and the aqueous phase was extracted with three 50-mL portions of CH_2Cl_2. The organic layers were combined and concentrated. A CH_2Cl_2 solution of the crude extract was treated with 10% aqueous NaOH until the excess benzoyl chloride was destroyed. The organic layer was then dried (Na_2SO_4) and the solvent was removed in vacuo to leave 0.705 g (90% yield) of solid material. An analytical sample of **11** was obtained by recrystallization (ethanol): mp 109–110 °C; IR (KBr) 1715, 1695, 1630 cm^{-1}; NMR ($CDCl_3$) δ 1.7 (m, 6 H), 2.10 (s, 6 H), 2.76 (d, J = 7 Hz, 4 H), 4.83 (b m, 2 H). 7.26 (s, 5 H). Anal. Calcd for $C_{18}H_{23}O_3N$: C, 71.73, H, 7.69, N, 4.65. Found: C, 71.86, H, 7.79, N, 4.58.

6. Diffraction Experiment on 11. Single crystals of **11**, grown from an ethanolic solution, were found to belong to the monoclinic system with unit cell dimensions: a = 9.688 (3), b = 7.517 (3), c = 11.744 (4) Å, and β = 106.87 (3) °. The systematic absences ($0k0$, k = odd) are consistent with either $P2_{1/M}$ or $P2_1$. The latter space group was assumed on the basis of noncentrosymmetrical intensity statistics. The measured density of 1.17 g/cm^3 agrees well with the calculated density of 1.16 g/cm^3 for Z = 2 molecules per unit cell. Three-dimensional intensity data were collected on a Syntex $P2_1$ automated diffractometer using monochromatized Mo Kα radiation (λ = 0.71069 Å). The θ–2θ scan technique was used to measure 1178 unique reflections within the range $0° < 2\theta < 45°$ of which 1039 reflections were considered observed [$I > 1.25\sigma(I)$]. Lorentz and polarization corrections were applied to the data. The structure was solved using the Multan program package,[15] which employs a multiple solution–tangent refinement method. The 22 nonhydrogen atom parameters were refined with anisotropic temperature factors by a full matrix, least-squares technique. All 23 hydrogen atoms were located in difference Fourier maps and refined isotropically. The final weighted and unweighted R values are 0.048 and 0.039, respectively.

Acknowledgment. The authors gratefully acknowledge the financial support of this work by the National Institute of Neurological and Communicative Disorders and Stroke (Research Grant NS 120007) and the NSF for providing funds for a diffractometer facility (joint with Boston University).

Registry No.—**4b,** 66120-45-4; **4b,** HCl, 66120-46-5; **4** picrate, 66120-56-7; **5** isomer 1, 66120-47-6; **5** isomer 2, 66120-48-7; **5** isomer 1 HCl, 66120-49-8; **5** isomer 2 HCl, 66120-50-1; **6,** 66120-51-2; **8,** 66120-52-3; **9,** 66120-53-4; **9** HCl, 66120-54-5; **11,** 66120-55-6; 2,6-lutidine, 108-48-5; acetaldehyde, 75-07-0; glutaraldehyde, 111-30-8.

Supplementary Material Available: A table of final positional and thermal parameters (3 pages). Ordering information is given on any current masthead page.

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A Simple Carbon-13 Nuclear Magnetic Resonance Spectroscopic Method for Distinguishing between Open-Chain and Pseudoacid Chlorides

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Received December 6, 1977

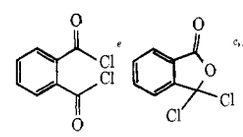
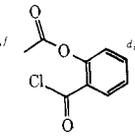
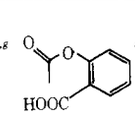
The structures of acid chlorides containing a carbonyl group at the γ position have been the subject of many reports. The possibility of the formation of cyclic forms (called pseudochlorides) of such molecules has been raised and substantiated in some cases. In many more instances, however, these structures have been postulated where evidence is weak or inconclusive. We wish to recommend a simple method that clearly distinguishes between pseudochloride and open-chain forms based on their ^{13}C magnetic resonance spectra.

The γ-diacid dichlorides are the most widely studied potential pseudochlorides. Phthaloyl chloride, for instance, has been isolated in two forms, and the higher melting isomer assigned the pseudochloride structure on the basis of dipole moment,[1] parachor,[2] and chemical reactivity.[3]

The γ-keto acid chlorides have been assigned the cyclic pseudochloride structure by chemical evidence,[4,5] infrared,[6] and ^1H NMR[7] spectroscopy.

The γ-ester acid chlorides are the group for which the evidence for the pseudochloride structure is least convincing.

Table I. ^{13}C Chemical Shifts of Aromatic Acid Chlorides

	Chemical shifts,[b] δ			
Carbon[a]				
C-1′	167.3	169.1	164.5	170.0
C-2′	167.3	104.6		
Acetate C=O			168.9	169.7
Acetate CH_3			20.7	21.0
C-1	134.3	136.0	124.3	122.2
C-2	134.3	150.6	150.5	151.3
C-3	130.1	122.8	124.3	122.3
C-4	133.4	136.3	136.1	134.8
C-5	133.4	125.6	126.4	126.1
C-6	130.1	132.0	134.2	132.5

[a] Carbons are numbered as follows: C-1 is in the aromatic ring σ bonded to a carbonyl carbon (which is C-1′); C-2 is in the aromatic ring and bears the ortho substituent (C-2′); C-3 to C-6 then follow in sequence. [b] Assignments within a column that differ by less than 1 ppm should be regarded as tentative. [c] For preparation see ref 16. [d] For preparation see ref 14. [e] Registry no. 88-95-9. [f] Registry no. 601-70-7. [g] Registry no. 5538-51-2. [h] Registry no. 50-78-2.

o-Acetoxybenzoyl chloride, for instance, has been found to exist in the open form by one set of chemical reactivity criteria[8] and to have a pseudochloride structure by another.[9] Infrared spectroscopy, in general, has given inconclusive results because of overlapping signals.[8] ^1H NMR spectroscopy has been employed to assign the open-chain structure to γ-carbomethoxypropionyl chloride on the basis of its methoxy proton signal at δ 3.66, compared to δ 3.29 for protons of this type in levulinic acid pseudomethyl ester, although the expected chemical shifts in the two pseudochlorides are not strictly comparable.[7]

Since molecules capable of existing as pseudochlorides were involved in synthetic work currently of interest in this laboratory, and because of the conflicting evidence available on the topic, the ^{13}C spectra of representative acid chlorides from each of the three groups were investigated. It was expected that π bonding and the magnetic anisotropy of the carbonyl group in the open-chain form would result in a large downfield chemical shift of this carbon signal in the ^{13}C spectra; such a large shift was not anticipated for the quaternary carbon in the pseudochloride structure.

Inspection of the first two entries of Table I substantiates this prediction. The lower melting phthaloyl chloride (entry 1) has carbonyl carbon absorptions at δ 167.3, reflecting its open-chain structure; the higher melting isomer (entry 2) has absorptions at δ 169.1 and 104.6, due to the carbonyl and quaternary carbons, respectively, in the cyclic pseudochloride structure. Moreover, the symmetry of the open-chain structure is revealed by having only three absorptions for the ring carbons; the nonsymmetrical pseudochloride has six additional peaks.

Clear evidence for the pseudochloride nature of levulinic acid chloride (entry 1, Table II) is seen in the ^{13}C spectrum, where only one carbonyl resonance is seen at δ 174.4. The resonance assigned to the quaternary carbon of the pseudochloride structure is again seen at δ 104.6, further substantiating the prediction made above.

Succinyl chloride (entry 2, Table II) is found to exist in the open-chain form, both on symmetry grounds (since only two resonances are seen in its ^{13}C spectrum) and by the chemical shift argument (the carbonyl resonance appears only at δ

0022-3263/78/1943-2708$01.00/0