Anal. Calcd for $C_7H_{15}NOBr_2$: C, 29.08; H, 5.18; N, 4.84. Found: C, 29.26; H, 5.33; N, 4.67.

***trans*-Carboxyvinyltrimethylammonium Bromide (16).**—To a stirred mixture of 30 g (0.36 mol) of methyl propiolate in 80 ml of water was added with cooling 90 g of 25% aqueous trimethylamine solution at 25°. The dark mixture was stirred for an additional 3 hr, followed by removal of water and excess trimethylamine under vacuum (30–40° bath). The brown residue was dissolved in 200 ml of 48% aqueous HBr. The water and excess acid were removed on an evaporator. Recrystallization of the dark residue from methanol–ether yielded 44 g (59%) of **16**: mp 120° dec; ir (Nujol) 1724 (C=O) and 1661 cm^{-1} (C=C); uv max (CH_3OH) 208.5 nm (ϵ 2160); nmr (D_2O) δ 3.49 [s, $(CH_3)_3N$, 9 H], 6.61 and 7.49 (d, vinyl, 2 H) with J = 13.8 Hz.

Anal. Calcd for $C_6H_{12}O_2NBr$: C, 34.30; H, 5.72; N, 6.66. Found: C, 34.96; H, 6.09; N, 6.89.

Tetrafluoroborate Salt of 16a.—*trans*-Carboxyvinyltrimethylammonium tetrafluoroborate (**16a**) was prepared in an analogous fashion to that described for the bromide salt. Recrystallization from methanol–ether gave mp 135–136°; ir (Nujol) 1724 (C=O), 1661 (C=C), and 1053 cm^{-1} (BF_4^-); nmr δ 3.20 [s, $(CH_3)_3N^+$, 9 H], 6.41 and 7.22 (d, vinyl, 2 H) with J = 13.8 Hz.

Anal. Calcd for $C_6H_{12}NO_2BF_4$: C, 33.13; H, 5.76; N, 6.45; F, 35.25. Found: C, 33.63; H, 5.27; N, 6.55; F, 34.80.

Bromination of 16 in Methanol.—A solution consisting of 2.2 g (11.0 mmol) of **16** in 100 ml of methanol was treated dropwise with 8 g (50.0 mmol) of bromine in 40 ml of methanol at 35°. After the solution was stirred for 20 hr at 35–40°, the volatiles were removed under water aspirator vacuum. The residual red oil was redissolved in 100 ml of methanol, and an equal volume of ether was added. The precipitated yellow solid was again dissolved in methanol and treated with ether to yield 2.4 g (96%) of *trans*-methoxycarbonylvinyltrimethylammonium bromide (**1a**): mp 164–165°; ir (Nujol) 1658 (C=C) and 1715 cm^{-1} (C=O); nmr δ 3.37 [s, $(CH_3)_3N^+$, CH], 3.86 (s, OCH_3, 3 H), 6.63 and 7.47 (d, vinyl, 2 H) with J = 13.9 Hz.

Anal. Calcd for $C_7H_{14}NO_2Br$: C, 37.51; H, 6.25; N, 5.98; Br, 35.69. Found: C, 37.96; H, 6.40; N, 5.77; Br, 35.79.

2-Carboxy-1,2-dibromoethyltrimethylammonium Bromide (17).—A mixture of 44 g (0.21 mol) of **16** and 50 g (0.33 mol) of bromine in 250 ml of chloroform was stirred vigorously at 45° for 24 hr. The yellow solid was filtered, washed with 200 ml of acetonitrile, and purified by recrystallization from methanol to yield 62 g (82%) of **17**: mp 162–163°; nmr δ 3.58 [s, $(CH_3)_3N^+$, 9 H], 5.86 (d, β-CH, 1 H), and 6.57 (d, α-CH, 1 H) with J = 1.5 Hz.

Anal. Calcd for $C_6H_{12}NO_2Br_3$: C, 19.47; H, 3.26; N, 3.79; Br, 64.82. Found: C, 19.87; H, 3.37; N, 3.87; Br, 65.25.

Dehalogenation of 17 with Potassium Carbonate.—Five grams (0.014 mol) of **17** in 100 ml of water was treated with a potassium carbonate solution (0.94 g in 25 ml of water, 0.0068 mol) at 45–50°. Carbon dioxide was evolved during the addition. The solution was then heated at 60° for 2 hr. The water was removed under vacuum and the residual solid was extracted with ethanol. An equal volume of ether was added to the cooled extract to yield 2.2 g (55%) of (*Z*)-2-bromo-2-carboxyvinyltrimethylammonium bromide (**18**): mp 187° dec; ir (Nujol) 3401 (–OH), 1724 (C=O), and 1631 cm^{-1} (C=C); uv max (CH_3OH) 216 nm; nmr δ 8.06 (s, vinyl, 1 H), and 3.68 [s, $^+N(CH_3)_3$, 9 H].

Anal. Calcd for $C_6H_{11}O_2NBr_2$: C, 24.93; H, 3.81; N, 4.84. Found: C, 24.06; H, 3.58; N, 4.44.

Registry No.—**1a**, 40463-91-0; **1b**, 40463-92-1; **1c**, 40463-93-2; **1d**, 40463-94-3; **1e**, 40463-95-4; **2**, 40463-96-5; **3**, 14800-49-8; **4a**, 40463-98-7; **4b**, 14800-51-2; **5a**, 40464-00-4; **5b**, 40464-01-5; **8a**, 40550-39-8; **8b**, 40464-02-6; **9**, 996-85-0; **11**, 40464-04-8; **12**, 40464-05-9; **13**, 40464-06-0; **14**, 40464-07-1; **16**, 40464-08-2; **16a**, 40464-09-3; **17**, 40464-10-6; **18**, 40464-11-7; methyl propiolate, 922-67-8; 2-chloroethyl propiolate, 40464-12-8; trimethylammonium chloride, 593-81-7; trimethylammonium bromide, 2840-24-6; triethylammonium bromide, 636-70-4; tributylammonium bromide, 37026-85-0; pyridine hydrochloride, 628-13-7; dimethyl acetylenedicarboxylate, 762-42-5; acetylenedicarboxylic acid, 142-45-0; bromine, 7726-95-6; 1-bromovinyltrimethylammonium tetrafluoroborate, 40464-14-0; hydrogen tetrafluoroborate, 16872-11-0.

The Stereochemistry of 1-Alkyl-2-acyl-1,2-dihydroisoquinaldonitriles[1]

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The pmr spectra and in particular the anisochronism (chemical shift differences) of diastereotopic groups (methyl or methylene) in a series of 1-alkyl-2-acyl-1,2-dihydroisoquinaldonitriles (**3** and **4**) have been studied as a function of substituent, temperature, and solvent. On this basis, stereochemical analysis of these systems was accomplished. The amide group configuration is the same in all cases and has been established. The ring configuration is believed to be the one in which the 1-alkyl group is pseudoaxial. In the cases where the 1-alkyl group is isopropyl, only a single conformer about the ring–alkyl bond is observed and on the basis of chemical shift arguments has been assigned. In the cases where the 1-alkyl substituent is either isobutyl or benzyl, more than one such conformer may be present as indicated by spectral temperature dependence; the predominant conformer is tentatively assigned.

Though the preparation of 1-alkyl derivatives of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds) (**1**) has been well documented,[3–9] only a few examples of these compounds (**3**) have been isolated and characterized.[5–7]

Several interesting stereochemical questions, therefore, remain unanswered for these systems. Among them are those concerning the ring conformation of the 1 substituent, the configuration of the amide moiety, and the conformation about the ring–alkyl bond. Additionally, in recent years there has been much interest in the anisochronism (chemical shift difference) of diastereotopic groups.[10]

In the interest of addressing these questions in the context of the relatively large anisochronisms[1] of the diastereotopic groups, a detailed study of these compounds was undertaken.

(1) A portion of this work was previously communicated: *Tetrahedron Lett.*, 5549 (1968), and Abstracts, 159th National Meeting of the American Chemical Society, Houston, Tex., Feb 1970, p O–008.

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(3) F. D. Popp in "Advances in Heterocyclic Chemistry," Vol. 9, A. R. Katritsky and A. J. Boulton, Ed., Academic Press, New York, N. Y., 1968, p 1.

(4) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

(5) F. D. Popp and J. M. Wefer, *J. Heterocycl. Chem.*, **4**, 183 (1967).

(6) J. Sam and A. J. Bej, *J. Pharm. Sci.*, **56**, 1441 (1967).

(7) J. L. Neumayer, B. R. Neustadt, and J. W. Weintraub, *Tetrahedron Lett.*, 3107 (1967).

(8) B. C. Uff and J. R. Kershaw, *J. Chem. Soc. C*, 666 (1969).

(9) M. P. Cava, M. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem.*, **34**, 2665 (1969).

(10) K. Mislow and M. Raban in "Topics in Stereochemistry," Vol. 1, N. L. Allinger and E. L. Eliel, Ed., Interscience, New York, N. Y., 1967.

Results

The pertinent parts of the pmr spectra of series **3** and **4**[11] are recorded in Tables I–IV. Two signals were observed only for the diastereotopic groups indicated.

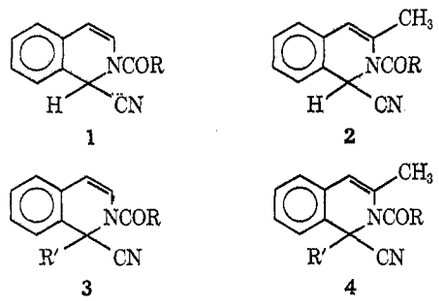
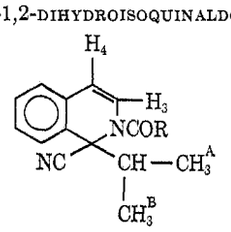


TABLE I

PMR SPECTRA OF 1-ISOPROPYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$

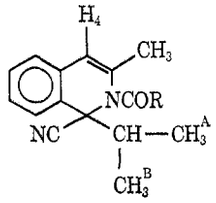


Compd	R	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{CH}	δ_{H_3}	δ_{H_4}
3p	OCH_2CH_3	0.83	1.16	0.33	2.75	7.08	5.82
3f	o-$C_6H_4CH_3$	0.87	1.18	0.31	2.94	6.30	5.67
3d	o-C_6H_4Cl	0.92	1.22	0.30	3.00	6.34	5.79
3g	p-$C_6H_4CH_3$	0.88	1.17	0.29	2.94	6.63	5.86
3a	CH_3	0.80	1.08	0.28	2.74	6.78	5.90
3e	p-C_6H_4Cl	0.88	1.16	0.28	2.92	6.57	5.92
3b[a]	C_6H_5	0.92	1.20	0.28	2.93	6.48	5.77
3b	C_6H_5	0.89	1.16	0.27	2.91	6.52	5.81
3c	$CH(CH_3)_2$	0.83	1.10	0.27	2.74	6.89	5.96

[a] 6,7-Dimethoxy derivative.

TABLE II

PMR SPECTRA OF 1-ISOPROPYL-2-ACYL-3-METHYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$

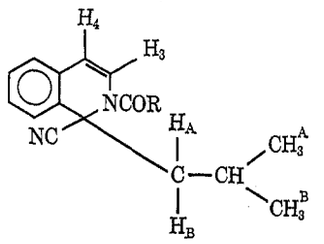


Compd	R	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{CH}	$\delta_{3\text{-}CH_3}$	δ_{H_4}
4f	α-$C_{10}H_7$	0.91	1.38	0.46	2.60	1.41	6.04
4e	o-$C_6H_4CH_3$	0.87	1.29	0.42	2.58	1.56	6.08
4d	o-C_6H_4Cl	0.91	1.32	0.41	2.62	1.68	6.22
4c	$CH(CH_3)_2$	0.84	1.24	0.40	2.54	2.29	6.44
4h	OCH_2CH_3	0.82	1.22	0.40	2.55	2.28	6.22
4b	C_6H_5	0.87	1.26	0.39	2.58	1.68	6.14
4i	$OCH_2C_6H_5$	0.81	1.19	0.38	2.5	2.18	6.17
4a	CH_3	0.82	1.19	0.37	2.50	2.30	6.40

Examining first the data of Table I, one notes the relatively high anisochronisms of the isopropyl methyl groups of **3**, R′ = *i*-Pr.[12] However, the magnitude of the anisochronism does not appear to be greatly dependent upon the nature of the *N*-acyl group, R. The results for series **4** as shown in Table II exhibit a somewhat wider range of anisochronism and these, in contrast, are dependent upon the acyl group, R. In fact, the dependence appears to be steric in nature. This can be rationalized in terms of a steric buttressing effect by the 3-methyl substituent on the acyl group R, resulting in a greater steric interaction with the 1-isopropyl group, and thus differentially affecting the chemical shifts of the methyl groups. This effect can be seen clearly by comparison of corresponding pairs of series **3** and **4**, *e.g.*, **3e** with **4e** and **3d** with **4d**.

TABLE III

PMR SPECTRA OF 1-ISOBUTYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$

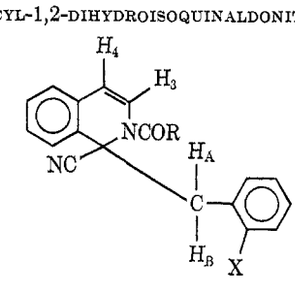


Compd	R	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
3h	CH_3	1.98	2.57	0.59	0.76	0.78	0.02	6.66	5.68
3j	o-$C_6H_4CH_3$	2.17	2.73	0.56	0.84	0.87	0.03	6.32	5.66
3i	C_6H_5	2.23	2.50	0.27	0.78	0.94	0.16	6.53	5.80
4g	α-$C_{10}H_7$				0.95	1.10	0.15	1.46[a]	6.04

[a] 3-CH_3 resonance.

TABLE IV

PMR SPECTRA OF 1-BENZYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES IN $CDCl_3$



Compd	R	X	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	δ_{H_3}	δ_{H_4}
3k	CH_3	H	3.28	3.74	0.45	6.40	5.47
3l	o-$C_6H_4CH_3$	H	3.56	3.92	0.36	6.16	5.45
3m	C_6H_5	H	3.51	3.73	0.22	6.35	5.54
3n[a]	C_6H_5	I	3.79	3.97	0.17	6.54	5.72
3o	C_6H_5	CH_3	3.63	3.63	0.00	6.43	5.68

[a] Through courtesy of J. L. Neumeyer, Northeastern University, Boston, Mass. [J. L. Neumeyer, H. H. Oh, K. K. Weinhardt, and B. R. Neustadt, *J. Org. Chem.*, **34**, 3786 (1969)].

The isobutyl derivatives listed in Table III possess pmr spectra containing ABX patterns attributed to the CH_2CH group. A unique inverse variation of $\Delta\delta_{AB}$ and $\Delta\delta_{CH_3}$ with the *N*-acyl group, R, occurs. For **3h** and **3j** large $\Delta\delta_{AB}$'s and small $\Delta\delta_{CH_3}$'s are displayed. On the other hand, **3i** reveals a relatively small $\Delta\delta_{AB}$ and large $\Delta\delta_{CH_3}$. A large $\Delta\delta_{CH_3}$ is also discernible for **4g**, but $\Delta\delta_{AB}$ could not be obtained directly. The anisochronisms ($\Delta\delta_{AB}$) for the benzyl derivatives **3k–o** (Table IV) are arrayed in a pattern analogous to that in the isobutyl compounds. These results do not appear to be sterically related to the *N*-acyl group R, however, since in both the isobutyl and benzyl deriva-

(11) H. W. Gibson, *J. Heterocycl. Chem.*, **7**, 1169 (1970).

(12) The largest reported isopropyl methyl anisochronisms to date are 0.73[13] and 0.75 ppm.[14] Generally much smaller values (0.1 ppm) are observed.

(13) M. Katjar and L. Radics, *Chem. Commun.*, 784 (1967).

(14) H. Kessler and B. Zeeh, *Tetrahedron*, **24**, 6825 (1968).

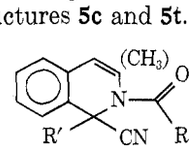
tives the acetyl compounds more closely resemble the toluyl than does the benzoyl; compare **3h**, **3j**, and **3i**, also **3k**, **3l**, and **3m**. Note also that in **3o** $\Delta\delta_{AB}$ is zero. It has been reported[14] that in 1-(3-benzyloxy-4-methoxy-2-nitrobenzyl)-5,6,7-trimethoxy-1,2-dihydroisoquinaldonitrile the benzylic protons are equivalent at δ 3.68.

Discussion

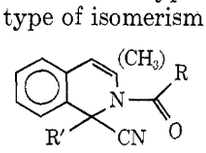
Nitrogen Inversion.—The umbrella-like inversion of nitrogen is generally a facile, low-energy (few kcal/mol) process even for amides.[15] Therefore, in these compounds two invertomers are present. While interconversion is rapid at the temperatures used in this study owing to the low energy of activation, the relative contributions of the invertomers will be dependent on the total energy content of each. For the sake of simplicity let us consider an average situation in which the three groups bonded to nitrogen are in a plane, as would be the case for equal energy invertomers, but let us bear in mind that the average conformation may be biased toward one invertomer.

Ring Inversion.—There is also a possibility of ring inversion in the title compounds. Ring inversion would result in transposition of pseudoaxial and pseudoequatorial groups at the 1 position (Figure 1). When the groups involved are of different conformational energy, this ring inversion would be manifested by a temperature-dependent equilibrium, and this in turn would normally result in changes in pmr spectra. In view of the lack of significant change in the pmr signals in these systems from low (−50°) to high (150°) temperatures (see below), it is concluded that a single ring form or two ring conformations of equal energy are present. The latter possibility is deemed highly unlikely for the following reason. It is known from dihydronaphthalene systems that interactions of equatorial groups at the 1 position with the peri (8) proton is severe and because of this the conformationally larger 1 substituent assumes the axial position.[16] From conformational energies (*A* values) determined in cyclohexyl systems, the effective bulk of alkyl groups such as those used in this study is known to be much greater than that of the cyano group.[17] In light of these facts the cyano group would be expected to occupy the more hindered pseudoequatorial position. The absence of a temperature effect is interpreted in terms of this being a very highly favored conformation. The possibility of coincidental isochronism of protons associated with two different ring conformers seems remote.

Amide Configuration.—Another factor which must be taken into account is the possibility of cis–trans amide configurational isomerism of the type shown in structures **5c** and **5t**. This type of isomerism is well



5c



5t

(15) P. G. Lister and J. K. Tyler, *Chem. Commun.*, 152 (1966).

(16) M. J. Cooks, A. R. Katritsky, F. C. Pennington, and B. M. Semple, *J. Chem. Soc. B*, 523 (1969); D. C. Ayres and J. A. Harris, *Chem. Commun.*, 1135 (1969).

(17) E. L. Eliel, N. A. Allinger, S. J. Angyal, and G. A. Morrison, "Conformational Analysis," Interscience, New York, N. Y., 1965, pp 440–442.

RING CONFORMATIONS

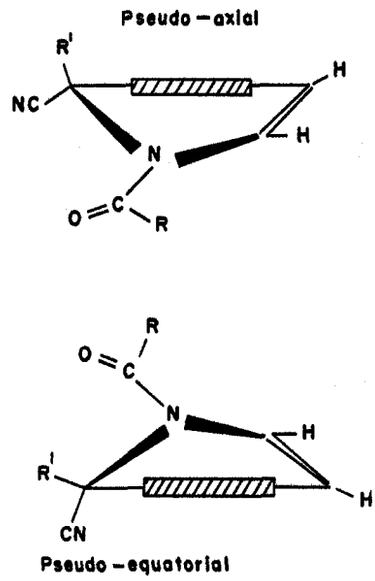


Figure 1.—Ring conformations of 1-alkyl-2-acyl-1,2-dihydroisoquinaldonitriles.

known and has been extensively studied.[18–25] Generally, the activation energies are relatively large (15–20 kcal/mol), and hence at normal temperatures interconversion is slow enough that signals for both forms are observable in pmr spectra. In fact, in at least one case the isomeric forms have been isolated.[22]

The fact that no signal doubling for protons other than those in diastereotopic environments occurs in the compounds under examination at room temperature indicates the presence of a single isomer or that the activation energy is low enough to allow rapid interconversion of the two. (The possibility of isochronism of all other protons in the two isomers is very remote.) The spectra of compounds **3b**, **3i**, **3j**, and **3k** were obtained at a temperature of −50°; there was no evidence of a "freezing out" of two isomeric forms, *i.e.*, no signal doubling occurred. The spectrum of **3b** was determined in a variety of solvents (Table V) and

TABLE V

SOLVENT DEPENDENCE OF PMR SPECTRUM OF 1-ISOPROPYL-2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILE (**3b**)

Solvent	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
$CDCl_3$	0.89	1.16	0.27	6.52	5.81
C_6H_6	0.78	1.11	0.33	6.17	5.37
$(CH_3)_2SO$	0.82	1.09	0.27	6.59	5.97
$C_6H_5NO_2$	0.90	1.22	0.32	6.59	5.86

(18) H. S. Gutowsky, J. Jonas, and T. H. Siddall, III, *J. Amer. Chem. Soc.*, **89**, 4300 (1967).

(19) Y. Shvo, E. C. Taylor, K. Mislow, and M. Raban, *ibid.*, **89**, 4910 (1967).

(20) Y. L. Chow, C. J. Colon, and J. N. S. Tarn, *Can. J. Chem.*, **46**, 2821 (1968).

(21) R. F. C. Brown, L. Radom, S. Sternhell, and I. D. Rae, *ibid.*, **46**, 2577 (1968).

(22) T. H. Siddall, III, W. E. Stewart, and A. L. Marston, *J. Phys. Chem.*, **72**, 2135 (1968).

(23) R. A. Johnson, *J. Org. Chem.*, **33**, 3627 (1968).

(24) A. M. Monro and M. J. Sewell, *Tetrahedron Lett.*, 595 (1969).

(25) J. P. Chupp, J. F. Olin, and H. K. Landwehr, *J. Org. Chem.*, **34**, 1192 (1969).

again no signal doubling was discernible. These results suggest that only a single amide configuration is present in these compounds in the temperature range employed.

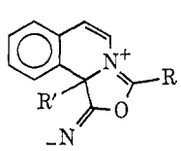
Aromatic solvent induced shifts (ASIS)[19] were employed to establish the configuration of the amide function. It is known that groups s-trans to the amide carbonyl oxygen experience a large upfield shift and groups s-cis to the carbonyl oxygen are subjected to a small downfield or upfield shift when the solvent is changed from carbon tetrachloride to benzene.[19] Owing to the limited solubility of these compounds in carbon tetrachloride, chloroform was used. Using materials soluble in both solvents, it was shown that the differences are slight; shifts in chloroform were 3 to 6 Hz downfield from those in carbon tetrachloride. The results of this solvent study are recorded in Table VI. On the basis of predicted ASIS effects, the protons of the R′ group (A and B) of isomer **5c** would undergo a large upfield (+) shift, while H_3 (or 3-CH_3) and H_4 would be slightly shifted upfield (+) or downfield (−). In contrast the protons of R′ in **5t** would be expected to exhibit a small shift in either direction, while H_3 (or 3-CH_3) and H_4 should undergo large upfield (+) shifts. In each case the data conclusively indicate configuration **5t**, in which the R group of the amide is cis to H_3 (or 3-CH_3) and the carbonyl function is cis to the R′ and cyano groups. This configuration is in accord with structure **6**, in which the interaction of the cyano and carbonyl moieties has been invoked to explain the lack of nitrile absorption in the infrared spectra of Reissert compounds (**6**, R′ = H).[4] Weak, barely detectable nitrile absorptions are found at 2245–2255 cm^{-1} (4–5 wt % solutions in $CHCl_3$) in all the compounds of series **3** and **4** except **4a**, which showed no such absorption. The nitrile absorbances were 1–5% of the carbonyl absorbances, which occurred at 1672–1694 cm^{-1}. Nitrile absorption intensities are known to be extremely variable, sometimes undetectable.[26] Therefore, the low nitrile absorption intensities in series **3** and **4** cannot be taken as proof of extensive contribution of form **6** to stabilization of amide configuration **5t**; at most it can be said that the results are consistent with this proposal.

TABLE VI

AROMATIC SOLVENT INDUCED SHIFTS OF PMR SPECTRA OF 1-ALKYL-2-ACYL-1,2-DIHYDROISOQUINALDONITRILES

Compd	$\Delta\delta_{CDCl_3-C_6D_6}$, Hz[a] A[b]	B[b]	H_3	H_4
3c	+6.2	+0.8	+24.9	+18.8
3l	+2.6	−0.5	+23.9	+28.6
4c	+3.0	+9.0	+23.4[c]	+23.8
4d	+4.5	+2.5	+14.9[c]	+21.8

[a] + sign denotes upfield shift upon changing to C_6D_6; − sign, downfield shift. [b] A and B denote the diastereotopic groups of R′, *i.e.*, the CH_3 groups of R′ = *i*-C_3H_7 and the CH_2 protons of R′ = $CH_2C_6H_5$. [c] 3-CH_3 resonance.



6

The ASIS results are corroborated by the data of Table VII, relating the chemical shift of the acetyl methyl protons of compounds **3** and **4**, R = CH_3, to the alkyl substituent R′ and the presence of the 3-methyl group. In the **3** series variation of R′ from methyl (**3q**) to ethyl (**3r**) to isopropyl (**3a**) to isobutyl (**3h**) to benzyl (**3k**) alters δ_{CH_3} by only 0.07 ppm. Comparison of the 1-isopropyl compounds **3a** and **4a** reveals the effect of the 3-methyl group; the acetyl methyl protons undergo an upfield shift of 0.11 ppm. Additionally in compound **3c** the methyl protons of the *N*-isobutyryl group are diastereotopic with pmr signals at δ 1.22 and 1.28. In **4c** the corresponding resonances appear at δ 0.97 and 1.22.[27] Thus, addition of the 3-methyl function resulted in a slight (0.06 ppm) upfield shift in the downfield signal, but the upfield resonance underwent a large (0.25 ppm) upfield displacement. These data are consistent with the conclusion that the configuration of the amide group is that shown in **5t**; that is, the acyl R group is cis to the 3 position of the isoquinoline ring. Therefore, signals arising from protons in the R group are highly sensitive to the 3 substituent but relatively insensitive to the R′ group at the 1 position. In these terms the anisochronisms for the *N*-isobutyryl methyl signals are readily rationalized. If in accordance with other work[28] the carbonyl group prefers to eclipse one of the methyl groups, the other methyl group will be in close proximity to the 3 position. The two methyl groups will then be affected by different magnetic anisotropies. In **3c** the difference is small; in **4c** the carbonyl anisotropy is similar to that in **3c**, but, owing to the presence of the 3-methyl group, the isobutyryl methyl group in that region (the upfield signal) is subjected to a much different anisotropy and is shifted further upfield and a larger anisochronism results.

TABLE VII

THE EFFECT OF 1-ALKYL SUBSTITUENT ON THE CHEMICAL SHIFTS OF THE ACETYL METHYL PROTONS OF **3** AND **4** (R = CH_3) IN $CDCl_3$

Compd	R′	δ_{CH_3}
3q	CH_3	2.35
3r	CH_2CH_3	2.33
3a	$CH(CH_3)_2$	2.33
3h	$CH_2CH(CH_3)_2$	2.30
3k	$CH_2C_6H_5$	2.28
4a	$CH(CH_3)_2$	2.22

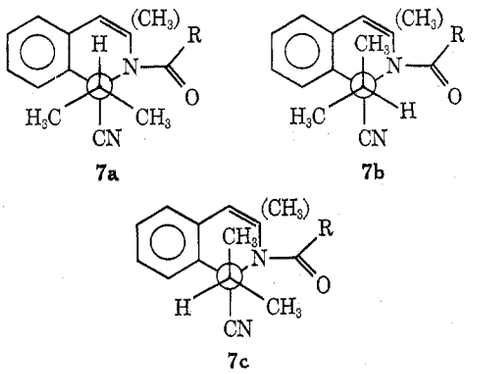
Conformation About the C_1–R′ Bond.—A further point of obvious consequence to the anisochronism of diastereotopic groups in R′ of **3** and **4** is the conformation about the C_1–R′ bond. Three noneclipsed conformations are possible for each compound. Conformations of the 1-isopropyl derivatives of **3** and **4** are shown in **7a**, **7b**, and **7c** as viewed along the methine–C_1 bond.

When the energy barrier due to eclipsing of groups in passing from one conformer to another is sufficiently low, all of the conformers will be represented in propor-

(26) L. J. Bellany, "The Infrared Spectra of Complex Molecules," Wiley, New York, N. Y., 1966, pp 265–267.

(27) This anisochronism (0.25 ppm) is very large; for structurally similar *N*-benzyl-*N*-(*o*-tolyl)-2-methylpropionamide the methyl anisochronism is 4 Hz (0.07 ppm).[19]

(28) G. J. Karabatsos and N. Hsi, *J. Amer. Chem. Soc.*, **87**, 2864 (1965).



7a 7b

7c

tion to their free energy content. The presence of two or more rotamers of unequal energy is manifested as a temperature dependence of the relative populations. If the chemical shifts of the groups involved vary from conformer to conformer, as is usually the case, this temperature dependence is conveniently detected by pmr spectroscopy. In some cases, owing to preferential solvation the relative conformer populations are sensitive to changes in solvent and such changes can also be discerned by pmr.

The effect of temperature from −50 to 150° on the spectrum of 1-isopropyl-2-benzoyl-1,2-dihydroisoquinaldonitrile (**3b**) is listed in Table VIII. The solvent

TABLE VIII

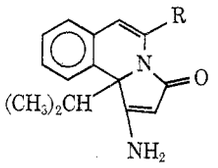
TEMPERATURE DEPENDENCE OF PMR SPECTRUM OF 1-ISOPROPYL-2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILE (**3b**)

Temp, °C	$\delta^{A}_{CH_3}$	$\delta^{B}_{CH_3}$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
−50[a]	0.96	1.23	0.27	6.59	5.89
−30[a]	0.96	1.23	0.27	6.58	5.88
40[a]	0.89	1.16	0.27	6.52	5.81
40[b]	0.90	1.22	0.32	6.59	5.86
95[b]	0.92	1.22	0.30	6.57	5.82
150[b]	0.93	1.20	0.27	6.57	5.82

[a] Solvent $CDCl_3$. [b] Solvent $C_6H_5NO_2$.

dependence of the spectrum of **3b** is listed in Table V. As can be seen, the spectrum in chloroform-*d* from −50 to 40° undergoes only minor chemical shift changes; the anisochronism ($\Delta\delta_{CH_3}$) is constant. In nitrobenzene solvent from 40 to 150° there is a slight change in $\Delta\delta_{CH_3}$ from 0.32 to 0.27 ppm, about a 10% decrease. This small change is believed to be related, not to changes in conformer ratio, but rather to the solvation of **3b** by the aromatic solvent, leading to a differential shielding dependent upon stereochemistry and electron density.[29] Thus, as the temperature is increased to 150° the solvation is effectively shorter lived and chemical shifts and anisochronisms closely resemble those in chloroform-*d* at room temperature. Nitrobenzene is not a highly electron-rich nucleus and thus its solvating power is less than that of benzene. The solvent dependence (Table V) seems to reflect only the same difference between aromatic and nonaromatic solvents with no gross changes taking place.

We believe that these data are indicative of the presence of a single stable rotamer as has been previously suggested for some 1-isopropyl-1,2,3,4-tetrahydroisoquinoline compounds.[18] In considering the isopropyl conformation several observations are important. The unfield methyl signal (CH_3^A) is not much affected by the presence or absence of the 3-methyl substituent (Tables I and II, *e.g.*, **3f** and **4e**, **3d** and **4d**, **3a** and **4a**) nor by formation of cyclic compounds **8a** and **8b** from compounds **3a** and **4a**.[30] This implies that



8a, R = H; δ_{CH_3} 0.83; δ_{CH} 2.2 (DMSO)
8b, R = CH_3; δ_{CH_3} 0.81, 0.84; δ_{CH} 2.3 (DMSO)

the high-field methyl group occupies a position removed from the 3 position and the amide region. Conversely, the low-field methyl (CH_3^B) and the methine proton are affected by the presence of the 3-methyl substituent (Tables I and II) and conversion to **8**; therefore, it is inferred that they lie in the vicinity of the 3 position and the amide function. Based on these inferences, **7a** and **7b** are the two possible conformers and the high-field methyl group CH_3^A is gauche to the nitrile and benzo groups. In **7a** the methine proton is expected to move upfield as the 3-methyl group is added while in **7b** the downfield methyl (CH_3^B) is expected to move upfield, both due to increased shielding by the double bond. Experimentally it is found that CH_3^B undergoes a downfield shift (~0.1 ppm, regardless of R) while the methine proton shifts upfield (~0.3 ppm), and this points to conformer **7a**.

As expected for **7a** the methine proton reveals the anisotropy of the R group. For alkyl R groups it is shielded relative to aryl R's; of the aryl R's phenyl is most like the alkyls, *i.e.*, it is less deshielding (Tables I and II). A similar effect can be seen in the H_3 signal (Table I); with ortho-substituted aryl R groups H_3 is shielded relative to other aryl R groups. In Tables I and II it can be seen that CH_3^B is slightly more deshielded with ortho-substituted aryl R groups than with other aryl or alkyl R groups. Molecular models indicate crowding of aryl R groups and the 3 substituent (H or CH_3) so that either (1) R rotates to become orthogonal to the NCO plane or (2) the N–COR bond is not quite coplanar in that the R group lies below the 3 position, or (3) a combination of 1 and 2 occurs. The chemical shifts of the methine proton and the CH_3^B are informative in this regard. In the series **3** the methine proton is relatively sensitive to changes in R in comparison to series **4**. The isopropyl CH_3^B is, however, changed by a nearly constant (0.11 ppm) amount for all R's in comparing series **3** and **4**; similarly changes of R in the two series result in about the same changes in CH_3^B, *e.g.* compare **3b–d** and **4b–d**. Also the chemical shift of the group at the 3 position is inversely related to that of the methine proton, while the shifts of the methine and CH_3^B are directly related. These results taken together suggest that the degree of orthogonality is dependent on R and is relatively constant for a given R whether it is in series **3** or **4**, but that introduction of the 3-methyl group causes a nearly constant change in the nonplanarity of the NCOR

(29) R. G. Wilson, D. E. A. Rivett, and D. H. Williams, *Chem. Ind. (London)*, 109 (1969).

(30) These and related compounds will be described in a forthcoming publication; see also Abstracts, 164th National Meeting of the American Chemical Society, New York, N. Y., Aug 1972, p 0–4.

grouping. This places the R group somewhat more below the 3-methyl group, away from the 3-methine proton, which is thereby less sensitive to R, and raises the carbonyl oxygen toward CH_3^B, placing it in a more highly deshielding area. The methine and the 3 substituent in both series reveal the dependence of the degree of orthogonality on R, *i.e.*, ortho substituents increase orthogonality, hence shielding. In this regard note the position of the 3-CH_3 group in **4f**.[31]

In an effort to ascertain the conformation in the benzyl and isobutyl series, an examination of the effect of substituents on the chemical shifts of various protons in the 1-alkyl substituent is informative. First, by inspection of Tables III and IV it can be seen that the upfield protons (H_A's) for the two systems are similarly affected by changes in R, *i.e.*, $\Delta\delta_H^A$ is relatively constant (*e.g.*, compare **3h–k** to **3i–l**). Likewise the downfield protons (H_B's) are similarly affected by R. The conclusion is that the conformation about the C_1–CH_2 bond is on the average the same for both series of compounds. Similarly, through comparison of the low-field methylene protons (H_B's) of the isobutyl and benzyl systems (Tables III and IV) with the methine protons of the isopropyl series (Tables I and II) as a function of R it can be seen that the chemical shifts vary similarly, *i.e.*, $\delta_{H_A} - \delta_{CH}$ is relatively constant. This implies that the H_B's occupy the same position conformationally as does the methine proton. The H_A signals of the isobutyl and benzyl series do not seem to vary in the same manner as either CH_3^A or CH_3^B of the isopropyl series, however. Thus, the conformational relationship of isobutyl and benzyl series to the isopropyl series is tenuous.

The diastereotopic methylene groups in the isobutyl and benzyl series show very similar anisochronism changes with temperature (Tables IX and X). However, the isopropyl group of the isobutyl compounds is fairly mobile and shows relatively large anisochronism changes; changes in conformer populations about this bond due to changes in R or temperature could affect the diastereotopic methylene protons' magnetic anisotropy. Therefore, the parallelism of the behavior of the methylene groups of the two series does not necessarily arise directly from the same variable.

TABLE IX

TEMPERATURE DEPENDENCE OF THE PMR SPECTRUM OF 1-ISOBUTYL-2-BENZOYL-1,2-DIHYDROISOQUINALDONITRILE (**3i**)

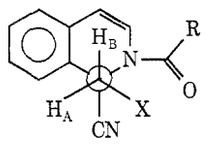
Temp, °C	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	$\delta_{CH_3}^A$	$\delta_{CH_3}^B$	$\Delta\delta_{CH_3}$	δ_{H_3}	δ_{H_4}
−54 (CD_3COCD_3)	2.20	2.41	0.21	0.71	0.97	0.26	6.90	6.03
40 ($CDCl_3$)	2.23	2.50	0.27	0.78	0.90	0.12	6.53	5.80

TABLE X

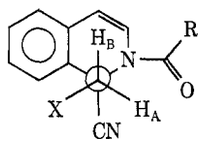
TEMPERATURE DEPENDENCE OF THE PMR SPECTRUM OF 1-BENZYL-2-ACETYL-1,2-DIHYDROISOQUINALDONITRILE (**3k**)

Temp, °C	δ_{H_A}	δ_{H_B}	$\Delta\delta_{AB}$	δ_{H_3}	δ_{H_4}
−30 (CD_3COCD_3)	3.37	3.88	0.51	6.87	5.62
40 (CD_3COCD_3)	3.40	3.86	0.46	6.73	5.69
40 ($CDCl_3$)	3.28	3.74	0.46	6.40	5.47

Nonetheless, the following rationale is offered. Based on the similarity of H_B to the methine proton of the isopropyl series, either **9a** or **9b** is the predominant conformer in these two series at 40°. Of these two conformers **9b** seems less strained in molecular models. Thus, **9b** is probably the major conformer in these two series. This is supported by the presence of the aromatic methyl signal of **3o** at a relatively high field, δ 1.83. Molecular models indicate that the ortho substituents would prefer to be away from the carbonyl group and lie over the benzo ring of the isoquinoline. The behavior of H_A with changes in R is then understandable in terms of nonplanarity and orthogonality of the NCOR group. Changing R from methyl to phenyl (**3h** to **3i**, **3k** to **3m**) apparently results in decreased planarity, raising the carbonyl oxygen relative to H_A, increasing the deshielding of H_A, while the phenyl rotates relatively freely resulting in only slight shielding of H_3. Changing to *o*-tolyl (**3j** or **3l**) then causes increased orthogonality (shielding of H_3 and deshielding of H_B) which to some extent alleviates the need for noncoplanarity so that H_A is not changed much from phenyl.



9a



9b

The behavior of **3m–o** (Table IV) is interesting. If one plots δ_{H_B} as a function of the Hammett substituent constant *for para substitution*, a straight line (slope 0.77 ± 0.07, correlation coefficient 0.996) results; a similar plot for δ_{H_A} is nonlinear. The variation of H_A and H_B in **3m–o** may then be due to changing conformation about the CH_2–aryl bond, which has been reported for other benzylic systems and ascribed to either hyperconjugation of the benzylic hydrogens or paramagnetic shielding.[32]

In summary, through consideration of the pmr spectra and in particular the anisochronisms of the diastereotopic groups as functions of substituent, temperature, and solvent, the following stereochemical questions were addressed: ring conformation *via* ring inversion, amide configuration, and conformation about the ring–alkyl bond.

Experimental Section

All compounds used in this study were of analytical purity.[11] Nmr solvents were obtained from Merck Sharpe and Dohme. Nmr spectra were recorded on a Varian A-60 instrument equipped with Model A-6040 temperature controller. Chemical shifts relative to internal tetramethylsilane are believed accurate to ±0.5 Hz. Temperatures were calibrated by use of ethylene glycol and methanol spectra. Temperature was ambient (~40°) unless otherwise indicated. Infrared spectra were determined using a Beckman IR-4 instrument and 0.1-mm matched sodium chloride cells.

Acknowledgments.—The author thanks Dr. John Fager and Mrs. Elizabeth Hezel for spectral determinations. The encouragement of Drs. Fred Stone, Dale McKenzie, and James McKeon is gratefully acknowledged. Drs. John Pochan, Frank Saeva, and Wolfgang Gunther are acknowledged for critically evaluating the manuscript.

(31) See paragraph at end of paper regarding supplementary material.

(32) R. R. Fraser, Gurudata, R. N. Renaud, C. Reyes-Zamora, and R. B. Swingle, *Can. J. Chem.*, **47**, 2767 (1969).

Registry No.—**3a**, 21203-36-1; **3b**, 6457-26-7; **3b** 6,7-dimethoxy derivative, 21286-81-7; **3c**, 30202-19-8; **3d**, 30202-20-1; **3e**, 30202-21-2; **3f**, 21203-35-0; **3g**, 30202-23-4; **3h**, 21400-79-3; **3i**, 21203-37-2; **3j**, 21202-98-2; **3k**, 30201-84-4; **3l**, 30201-86-6; **3m**, 16576-35-5; **3n**, 21876-56-2; **3o**, 16576-36-6; **3p**, 30201-97-9; **3q**, 30201-89-9; **3r**, 30201-87-7; **4a**, 30297-18-8; **4b**, 30297-19-9; **4c**, 30201-91-3; **4d**, 30201-92-4; **4e**, 30201-93-5; **4f**, 30201-94-6; **4g**, 40463-54-5; **4h**, 40463-55-6; **4i**, 40550-46-7.

Supplementary Material Available.—Photographs of Stuart–Briegleb models of **3b** and **4b** showing the conformational effects discussed here will appear following these pages in the microfilm edition of this volume of the journal. Single copies may be obtained from the Business Operations Office, Books and Journals Division, American Chemical Society, 1155 Sixteenth St., N.W., Washington, D. C. 20026. Remit check or money order for $3.00 for photocopy or $2.00 for microfiche, referring to code number JOC-73-2851.

A Stereospecific Synthesis of C-6(7) Methoxypenicillin and -cephalosporin Derivatives

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A method for introducing the C-6(7) methoxy group on penicillins and cephalosporins *via* a route using presumably both carbanion and carbonium ion intermediates is described. Treatment of esters of C-6(7) benzylideneaminopenicillin and -cephalosporin with NaH and $MeSSO_2Me$ gave the corresponding C-6(7) methylthio derivatives. Hydrolytic removal of the benzylidene group of the above derivatives followed by treatment with $HgCl_2$ in methanol afforded benzyl 6-amino-6-methoxypenicillanate and *tert*-butyl 7-amino-7-methoxydeacetoxycephalosporanate. These compounds were converted to the appropriate penicillin and cephalosporin analogs by acylation and removal of the ester groups. Assignment of α configuration to the methoxy group is discussed.

A recent report that certain naturally occurring 7-methoxycephalosporins (cephamycins) have enhanced activity against gram-negative organisms[1,2] prompted us to investigate the synthesis of C-6(7) methoxypenicillin and -cephalosporin derivatives. Of the methods reported to date for synthesizing C-6(7)-disubstituted penicillins and cephalosporins,[2a] the C-6(7) methyl derivatives were made using appropriately protected carbanions[3,4] while the C-6(7) methoxy derivatives were synthesized by routes using carbonium ion[2] and acylimine[5] intermediates. We now report a facile synthesis of C-6(7) methoxy derivatives by a route using a combination of presumed carbanion and carbonium ion intermediates.

The Schiff base **1a**, prepared from equimolar amounts of benzaldehyde and **2a**,[6] on treatment with 1 equiv of NaH in anhydrous DMF followed by addition of 1 equiv of $MeSSO_2Me$[7] gave **1b** in 60% yield. Addition of 6 *N* HCl to **1b** in acetone precipitated **2b** HCl; the crystalline free base was generated by adding the salt to 5% $NaHCO_3$ solution. Treatment of **2b** in a mixture of anhydrous CH_3OH–DMF and pyridine with $HgCl_2$ gave the crystalline 7-methoxy derivative **2c** in 80% yield. Acylation of **2c** with 2-thienylacetyl chloride (TAC) and pyridine in CH_2Cl_2 gave **3a**. Trifluoroacetic acid (TFA) containing 10% anisole converted **3a** to **3c** in 67% yield. Alternatively, **3a** was prepared by first acylating (TAC–pyridine) **2b** and then treating the resulting **3b** with $AgNO_3$ in anhydrous MeOH. The 7-methylthiocephalosporin **3d** was obtained by treating **3b** with TFA containing anisole.

6-Methoxypenicillin G (**6b**) was prepared in a similar sequence of reactions. Thus, **4a**, prepared from **5a**[8] and benzaldehyde, reacted with NaH and $MeSSO_2Me$ to afford the methylthio derivative **4b** which was hydrolyzed by *p*-toluenesulfonic acid (*p*-TSA) hydrate to **5b** *p*-TSA. The salt was converted to the crystalline free base **5b** with 5% $NaHCO_3$ solution. Treatment of **5b** in anhydrous methanol–pyridine with $HgCl_2$ gave the crystalline methoxy derivative **5c**[9] which was converted *via* **6a** to the potassium salt of 6-methoxypenicillin G (**6b**) in a manner similar to that described previously (Chart I).[2]

We have assigned the α configuration to the CH_3S group in **2b** and **4b** based on the expected stereochemical course of the reaction by analogy to that for the synthesis of C-6(7) methyl β-lactam antibiotics.[3,4] Nmr studies using lanthanide shift reagents[10] and optical rotation data (Table I) also support the assignment. The α configuration of the methoxy group in **6a** was assigned on the grounds that the nmr and optical rotation data[11] of **6a** (Table II) are in agreement with those reported for 6α-methoxypenicillin G benzyl ester.[2] Since similar stereochemical course for introduction of the methoxy group in the cephalosporin and penicillin series is expected, we therefore assume the methoxy group in **2c** to have the α configuration.

The formation of **2c** and **5c** is stereospecific; epimers

(1) R. Nagarajan, L. D. Boeck, M. Gorman, R. L. Hamill, C. E. Higgens, M. M. Hoehn, W. M. Stark, and J. G. Whitney, *J. Amer. Chem. Soc.*, **93**, 2308 (1971).

(2) L. D. Cama, W. J. Leanza, T. R. Beattie, and B. G. Christensen, *J. Amer. Chem. Soc.*, **94**, 1408 (1972).

(2a) NOTE ADDED IN PROOF.—Since we submitted this paper, several publications which described related synthetic methods have appeared in the literature: W. A. Slusarchyk, H. E. Applegate, P. Funke, W. Koster, M. S. Puar, M. Young, and J. E. Dolfini, *J. Org. Chem.* **38**, 943 (1973); J. E. Baldwin, F. J. Urban, R. D. G. Cooper, and F. L. Jose, *J. Amer. Chem. Soc.*, **95**, 2401 (1973); G. A. Koppel and R. E. Koehler, *ibid.*, **95**, 2404 (1973).

(3) E. H. W. Böhme, H. E. Applegate, B. Toeplitz, J. E. Dolfini, and J. Z. Gougoutas, *J. Amer. Chem. Soc.*, **93**, 4324 (1971).

(4) R. A. Firestone, N. Schelechow, D. B. R. Johnston, and B. G. Christensen, *Tetrahedron Lett.*, 375 (1972).

(5) W. A. Spitzer and T. Goodson, *Tetrahedron Lett.*, 273 (1973).

(6) Method of J. Stedman, *J. Med. Chem.*, **9**, 444 (1966).

(7) M. D. Bentley, I. B. Douglass, and J. A. Lacadie, *J. Org. Chem.*, **37**, 333 (1972).

(8) J. C. Sheehan and K. R. Henery-Logan, *J. Amer. Chem. Soc.*, **84**, 2983 (1962).

(9) Reported in ref 2 as an "isolable intermediate" without melting point.

(10) Nmr studies on lanthanide-induced shift of the C-6 proton in **2a** and **2b** and in a mixture containing the epimer of **2a** suggest that the configuration of the amino group in **2a** and **2b** is identical.

(11) The nmr spectrum of **6a** displayed a *singlet* (6 H) for the *gem*-dimethyl protons while that of the epimer **6c**[2] showed a *pair* of singlets (3 H each) for the corresponding protons. The high specific rotations of **6a** and **6d** in contrast to that of **6c** and **6e** are consistent with the assignment.