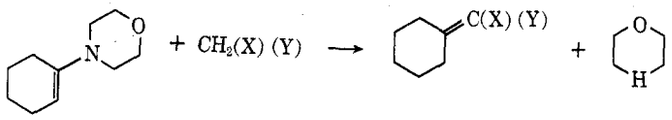
TABLE I
REACTION OF 1-MORPHOLINO-1-CYCLOHEXENE WITH ACTIVE METHYLENE COMPOUNDS



Registry no.	No.	Methylene X	Methylene Y	Reacting conditions: Solvent	Temp, °C	Time	Mp or bp, °C (mm)	Yield, %	Registry no.	Ir,[a] cm⁻¹ CN	Ir,[a] cm⁻¹ C=O	Ir,[a] cm⁻¹ C=C	Nmr,[b] δ, CH_2 (cis)
372-09-8	1	CN	COOH	DMF	25–30	30 min	110–112[c]	81.4	37107-50-9	2230	1705	1590	2.72 (CN) 3.01 (COOH)
105-56-6	2	CN	$COOC_2H_5$	None	25–30	20 hr	152–157 (10)[d]	59.1	6802-76-2	2225	1725	1595	2.63 (CN) 2.93 ($COOC_2H_5$)
109-77-3	3	CN	CN	DMF[e]	25–30	30 min	138–146 (10–8)[f]	58.7	4354-73-8	2245		1595	2.55 (CN)
107-91-5	4	CN	$CONH_2$	Abs EtOH[g]	Reflux	10 min	105–110[g]	76.1	704-16-5	2215	1670	1585	2.62 (CN) 2.92 ($CONH_2$)
141-82-2	5	COOH	COOH	DMF	25–30	7 days	135–140	19.6[h]	4354-70-5		1690	1620	2.80 (COOH)
	6	COOH	COOH	DMF	58–65	15 hr	70–83[i]	60.0	1552-91-6		1695	1645	2.23 (H) 2.82 (COOH)
1071-46-1	7	COOH	$COOC_2H_5$	DMF	55–70	8 hr	99–103 (8)	28.7[j]	1552-92-7		1715	1650	2.17 (H) 2.84 ($COOC_2H_5$)

[a] Infrared spectra were determined in chloroform (1, 4), neat (2, 3, 7), in carbon tetrachloride (6), and as a Nujol mull (5). [b] Nmr response of methylenes cis to the substituent in chloroform (1, 4), neat (3, 7), carbon tetrachloride (2, 6), and pyridine (5). [c] Reported mp 110–110.5°: A. C. Cope, *et al.*, "Organic Syntheses," Collect. Vol. IV, Wiley, New York, N. Y., 1963, p 234. [d] Reported bp 98–99° (0.1 mm), ref 2. Nmr taken by T. Izewski. [e] An equivalent of acetic acid was required to buffer the mixture. Omission of the acetic acid resulted in an 83% yield of dimer, mp 107–140°. After recrystallization the melting point was 171–175°, as reported by M. R. S. Weir and J. B. Hyne, *Can. J. Chem.*, **42**, 1440 (1964). [f] Reported bp 98–101° (0.08 mm), ref 2. [g] An equivalent of acetic acid was required to buffer the mixture, avoiding complex products formed in base [*cf.* F. B. Thole and J. F. Thorpe, *J. Chem. Soc.*, **99**, 422 (1911)]. Product crystallized directly from reaction mixture. The reported melting point is 110.5–111.5°, ref 2. [h] A 25% excess of malonic acid was used and the dibasic acid was accompanied by an 18.9% yield of monobasic acid. Crystallization from ethyl acetate–hexane furnished purified product, mp 146–147.5°, reported mp 150° [G. A. R. Kon and E. A. Speight, *J. Chem. Soc.*, 2727 (1926)]. [i] The monbasic acid, cyclohexylideneacetic acid, was the product when the malonic acid to enamine ratio was 2:1. Crystallization from alcohol–water results in mp 90–92°, as reported by Papa and Schwenck (ref 4). [j] Ethyl hydrogen malonate was generated *in situ* by action of the potassium salt and chloroacetic acid. Ethyl cyclohexylideneacetate was the product. The reported boiling point is 88–90° (10 mm) [W. S. Wadsworth and W. D. Emmons, *J. Amer. Chem. Soc.*, **83**, 1733 (1961)].

Shelton[2] in their ion-exchange resin catalysis study of the Knoevenagel condensation.

We have, however, observed a reaction with malonic acid. If 1-morpholino-1-cyclohexene was allowed to stand with malonic acid for 7 days at room temperature a mixture of cyclohexylidenemalonic acid (20% yield) and cyclohexylideneacetic acid (19%) was obtained. By heating a 2:1 ratio of malonic acid and the enamine at 60–65° for 15 hr a good yield (60%) of cyclohexylideneacetic acid was produced. This procedure is much more effective than the direct Knoevenagel procedure said to give less than 5% yield.[3] Furthermore, the procedure is much more convenient than the Reformatsky reaction usually used.[4]

Ethyl hydrogen malonate[5] has also proved to be effective in producing ethyl cyclohexylideneacetate (29%). Here the potassium salt was more convenient and the product was apparently free of the endo isomer, ethyl 1-cyclohexenylacetate, based on nmr.

Experimental Section

All melting points and boiling points were uncorrected. A Varian A-60 nmr spectrophotometer was used for recording nmr spectra in parts per million (δ) with respect to tetramethylsilane. A Beckman IR-8 or Perkin-Elmer 337 was used to record infrared spectra.

Reaction of 1-Morpholino-1-cyclohexene with Active Methylene Compounds.—The enamine was added to an equimolar amount of active methylene compound ($CH_2(X)(Y)$) in dimethylformamide (250 ml/mol). After the exothermic reaction was over (or heating concluded), the product was treated with dilute hydrochloric acid and the reaction was worked up by extraction with ether. Acidic products were washed out with 10% sodium carbonate, precipitated with hydrochloric acid, and collected. Liquid, neutral products were distilled at reduced pressure. The results are assembled in Table I.

Registry No.—1-Morpholino-1-cyclohexene, 670-80-4.

(2) R. W. Hein, M. J. Astle, and J. R. Shelton, *J. Org. Chem.*, **26**, 4874 (1961).

(3) I. S. Dutt, *Quart. J. Chem. Soc.*, **1**, 297 (1925); *Chem. Abstr.*, **19**, 2475 (1925).

(4) E. Schwenk and D. Papa, *J. Amer. Chem. Soc.*, **67**, 1432 (1945); J. H. Tumlinson, *et al.*, *J. Org. Chem.*, **36**, 2616 (1971).

(5) D. S. Breslow, E. Baumgarten, and G. R. Hauser, *J. Amer. Chem. Soc.*, **66**, 1287 (1944).

^{1}H Nuclear Magnetic Resonance Structure Elucidation of Substituted Isoquinolines by Means of Eu(fod)$_3$[1a]-Induced Paramagnetic Shifts

R. L. ATKINS,[1b] D. W. MOORE, AND R. A. HENRY

Chemistry Division, Code 605, Michelson Laboratory, Naval Weapons Center, China Lake, California 93555

Received August 8, 1972

Research efforts in this laboratory have led to the synthesis of a number of substituted isoquinolines. The determination of the position of substitution in these and other heterocyclic systems is by no means a trivial task, and in many instances classical and spectroscopic determinations lead to equivocal results.

The recently developed lanthanide-induced shift reagents[2] have found extensive application in structure elucidation, and we report here the application of

(1) (a) Eu(fod)$_3$, tris(1,1,1,2,2,3,3-heptafluoro-7,7-dimethyloctane)-4,6-dionatoeuropium(III): R. E. Rondeau and R. E. Sievers, *J. Amer. Chem. Soc.*, **93**, 1522 (1971). (b) National Research Council Postdoctoral Research Associate, 1971–1972.

(2) W. DeW. Horrocks, Jr., and J. P. Sipe, III, *ibid.*, **93**, 6800 (1971), and references cited therein.

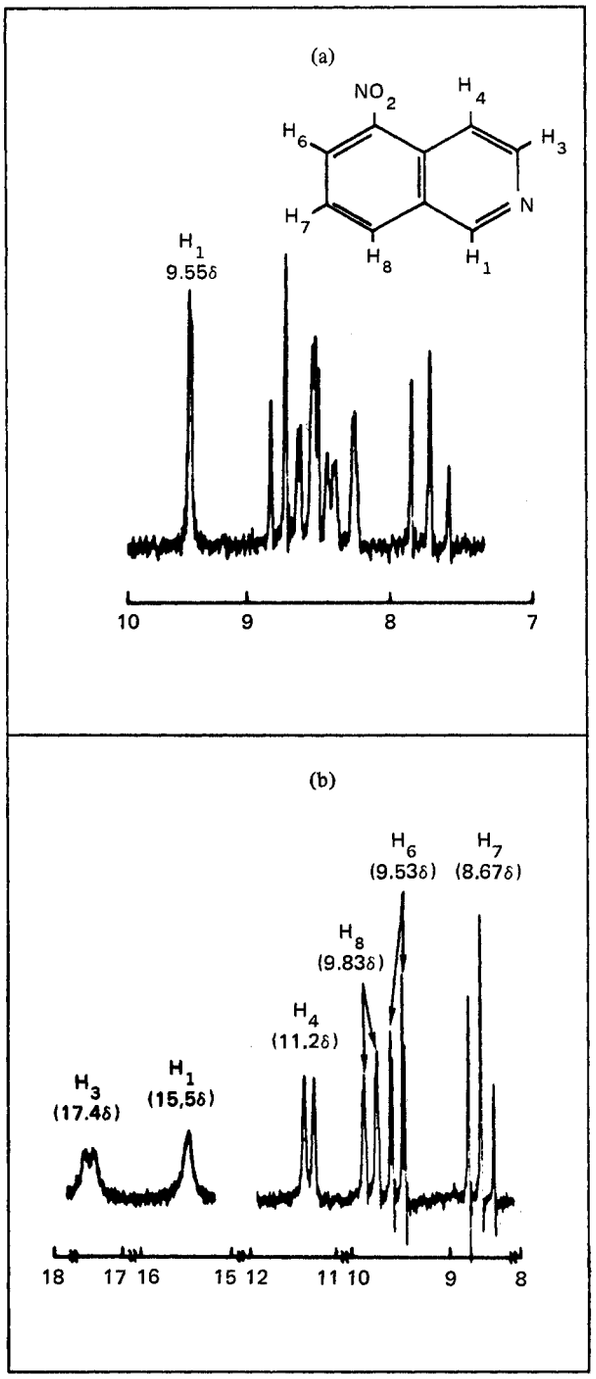


Figure 1.—60-MHz nmr spectra of 5-nitroisoquinoline (1): (a) 0.314 M in $CDCl_3$: (b) in the presence of 0.201 molar equiv of $Eu(fod)_3$.

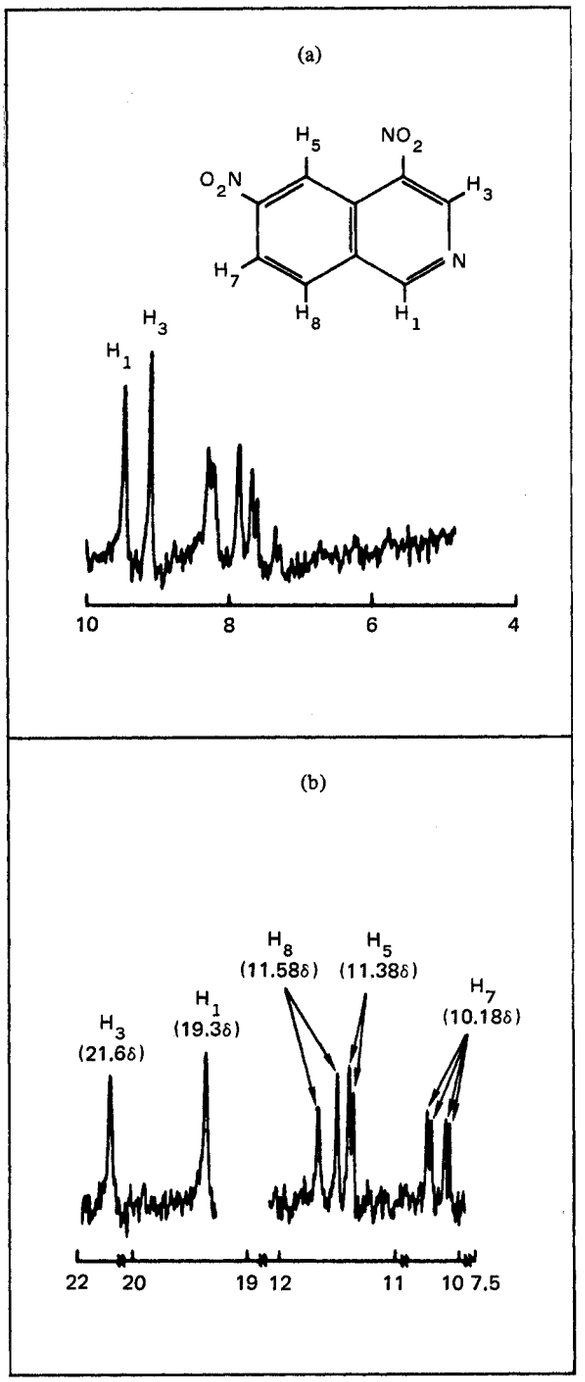


Figure 2.—60-MHz nmr spectra of 4,6-dinitroisoquinoline (2); (a) 0.640 M in $CDCl_3$: (b) in the presence of 0.428 molar equiv of $Eu(fod)_3$.

$Eu(fod)_3$ to a number of substituted isoquinolines, **1–8**. In every case spectral clarification was realized, and the position of substitution could be unambiguously assigned.

Figures 1 and 2 show the nmr spectra of two representative compounds. Spectrum 1a is the normal spectrum obtained at 60 MHz for 5-nitroisoquinoline, (1). In this spectrum only H_1 at δ 9.55 can unequivocally be assigned. The remaining protons appear as a complex series of 15 lines between δ 8.83 and 7.58. Spectrum 1b was obtained for a 0.314 M solution of **1** taken at 60 MHz in the presence of 0.201 molar equiv of $Eu(fod)_3$. In this spectrum the complexities of the original spectrum have been reduced to the point that a first-order analysis is possible allowing the unequivocal assignment of each resonance. The observed coupling constants are consistent with those reported for isoquinoline.[3]

Spectrum 2a was obtained for a previously unknown dinitroisoquinoline, **2**. From 2a it is not possible to distinguish the 4,6- from the 4,5-substituted isomer. Spectrum 2b was obtained for a 0.640 M solution of **2** in the presence of 0.428 molar equiv of $Eu(fod)_3$. The shift reagent has removed the fortuitous equivalence and overlap of chemical shifts observed in a and has made it possible to assign the structure of **2**

(3) F. Balkau and M. L. Heffernan, *Aust. J. Chem.*, **24**, 2311 (1971).

TABLE I

Δδ VALUES OBSERVED FOR COMPOUNDS 1–8 IN THE PRESENCE OF Eu(fod)$_3$

Compd	No.	Concn	Proton 1	3	4	5	6	7	8
5-Nitroisoquinoline	1	0.314	29.4	42.5	13.6			4.7	
4,6-Dinitroisoquinoline[d]	2	0.640	22.8	27.7		5.3		3.4	5.4
3,4-Dibromoisoquinoline	3	0.222	2.2						1.8
3-Methylisoquinoline	4	0.203	17.3	22.1[a]	6.1	2.6			3.2
3-Bromoisoquinoline	5	0.131	3.2		3.9				2.0
4-Bromoisoquinoline	6	0.258	29.4	37.6		5.5			6.4
1-Cyanoisoquinoline[c]	7	0.126		2.6	0.7				1.3
Isoquinoline	8	0.446	28.1	29.9	9.7				
Isoquinoline[b]	8a	0.33	23.3	24.1	6.5	3.2	0.6	0.6	3.2

[a] This entry is the gradient observed for the 3-methyl substituent. [b] Data are taken from ref 3 and are the gradients observed for the protons of isoquinoline in the presence of Eu(dpm)$_3$. [c] A. Kaufmann and P. Dändliker, *Ber.*, **46**, 2924 (1923). [d] R. A. Henry, A. T. Nielsen, and D. W. Moore, *J. Org. Chem.*, **37**, 3206 (1972).

as 4,6-dinitroisoquinoline with absolute certainty. Again, the observed coupling constants are in accord with expectations.[3]

In a similar manner, the dibromide **3** was assigned as the 3,4-dibromoisoquinoline. In this case the four protons of the B ring did not reduce to a first-order system, but appear as a complex AA′BB′ system.

In all the isoquinolines examined the shift parameter Δδ [the slope of the straight line obtained by plotting the change of chemical shift in parts per million *vs.* the mole ratio of Eu(fod)$_3$ to substrate] varied monotonically with added shift reagent in the low-shift reagent to substrate domain (ratio less than 0.5). At higher ratios of shift reagent to substrate some deviations from linearity are observed, which are more pronounced for H_1 and H_3, and less severe for protons further removed from the coordination site. The methyl substituent of 3-methylisoquinoline (**4**) shows a marked deviation from linearity. The data for the shift gradients determined for compounds **1–8** are summarized in Table I.

Considerable line broadening was observed for resonances of protons near the coordination site. In the case of 3-methylisoquinoline the methyl resonance, which exhibits a 1.6-Hz line-width at half-height in the absence of Eu(fod)$_3$, is broadened to 22 Hz in the presence of 0.57 molar equiv of Eu(fod)$_3$. Similarly H_1 and H_3 of **1** (see Figure 1b) show extensive broadening in the presence of Eu(fod)$_3$. Protons further removed from the coordination site show little broadening.

Experimental Section

The pmr shifts were measured with a Varian HA-60-IL spectrometer. The solvent, $CDCl_3$, was dried over preheated (110° *in vacuo*) Linde 4 A Molecular Sieve to exclude water and HCl. TMS was used as an internal standard. The probe temperature was 30°. The shifted spectra were obtained by adding small increments of Eu(fod)$_3$.[4] Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn.

3,4-Dibromoisoquinoline (3).—This compound was formed in an attempt to prepare 3-bromoisoquinoline from the corresponding 3-amino derivative by using the procedure of Craig[5] for 2-bromopyridine.

3-Aminoisoquinoline (4.11 g, 0.029 mol) was dissolved with stirring and cooling in 32.5 g of 48% hydrobromic acid. Bromine (4.5 ml) was added over 40 min keeping the temperature between −5 and 0°. The perbromide which separated was initially gummy but toward the end of the addition the mass broke down to an easily dispersed orange solid. Sodium nitrite (4.9 g) in 7 ml of water was added over 50 min keeping the temperature below 0°. The mixture was stirred for an additional 2 hr (0°) and then neutralized by the dropwise addition of 11 g of sodium hydroxide in 50 ml of water. The tan product was filtered, washed well with cold water and dried, 6.5 g (80%), mp 86–87°. Recrystallization from 70% ethanol gave the product with mp 92–93°.

Anal. Calcd for $C_9H_5Br_2N$: Br, 55.69; N, 4.88; mol wt, 285. Found: Br, 56.49; N, 4.99; mol wt (mass spectrum) 285, 287, 289.

3-Bromo- and 3-Hydroxy-4-bromoisoquinoline.—The latter compound precipitated as a hydrated sodium salt in about 22% yield during the preparation of 3-bromoisoquinoline (47% yield) by the method of Case.[6] Recrystallization from 95% ethanol gave yellow needles, mp 254–256° dec.

Anal. Calcd for $C_9H_5BrNONa \cdot 1.5H_2O$: C, 39.58; H, 2.95; Br, 29.26; N, 5.13; Na, 8.42. Found: C, 40.09; H, 2.54; Br, 28.98; N, 5.09; Na, 8.29.

The pure hydroxy compound was recovered by dissolving the salt in hot water and acidifying with acetic acid. A yellow-orange solid was obtained, mp 209–211°. Its spectral properties are similar to those reported for 3-hydroxyisoquinoline.

Anal. Calcd for C_9H_6BrNO: Br, 35.66; N, 6.25; mol wt, 224. Found: Br, 35.68; N, 6.26; mol wt (mass spectrum), 223, 225. Uv (95% ethanol) 229 nm (log ϵ_{max} 4.54), 241 (4.55), 282 (3.43), 294 (3.47), 307 (2.95), 357 (3.28), 428 (3.52); ir (Nujol) C=O, 1625, 1645 cm^{-1} (sh).

The isoquinolines **1**, **4**, **6**, and **8** were commercially available. Purities were checked by nmr and melting point.

Registry No.—**1**, 607-32-9; **2**, 35202-47-2; **3**, 36963-44-7; **4**, 1125-80-0; **5**, 34784-02-6; **6**, 1532-97-4; **7**, 1198-30-7; **8**, 119-65-3; Eu(fod)$_3$, 17631-68-4; 3-hydroxy-4-bromoisoquinoline sodium salt, 36963-49-2; 3-hydroxy-4-bromosioquinoline, 36963-50-5.

(4) Willow Brook Laboratories, Inc., Waukesha, Wis.

(5) L. C. Craig, *J. Amer. Chem. Soc.*, **56**, 231 (1934).

(6) F. H. Case, *J. Org. Chem.*, **17**, 471 (1952).

Mechanism and Stereochemistry of 1,4-Diol Ring Closure to Tetrahydrofuran

JOHN JACOBUS

Department of Chemistry, Clemson University, Clemson, South Carolina 29631

Received February 7, 1972

Four principal methods have been employed for the conversion of 1,4-diols to tetrahydrofuran derivatives; the transformation has been accomplished with strong acid,[1] sulfonyl chlorides,[2] alumina,[1a,2c,3] and dimethyl

(1) (a) G. A. Haggis and L. N. Owens, *J. Chem. Soc.*, 389 (1953); (b) S. F. Birch, R. A. Dean, and E. V. Whitehead, *J. Org. Chem.*, **19**, 1499 (1954).

(2) (a) D. D. Reynolds and W. O. Kenyon, *J. Amer. Chem. Soc.*, **72**, 1593 (1950); (b) K. Alder and W. Roth, *Ber.*, **88**, 407 (1955); (c) E. L. Whittbecker, H. K. Hall, Jr., and T. W. Campbell, *J. Amer. Chem. Soc.*, **82**, 1218 (1960).

(3) R. C. Olberg, H. Pines, and V. N. Ipatieff, *ibid.*, **66**, 1096 (1944).