Chemistry and the Macromolecular Research Center, The University of Michigan, the Petroleum Research Fund (R.K.H.), and the National Science Foundation (CGO) (Grant DMR 78-13400).

Registry No. (±)-1, 77415-53-3; (±)-1 dipicrate, 77415-54-4; (±)-1·2HBr, 77415-55-5; (*R*)-(−)-1, 77480-26-3; (*R*)-(−)-1·2HBr, 77480-27-4; (*S*)-(+)-1, 77480-28-5; (*S*)-(+)-1·2HBr, 77480-29-6; (±)-2, 77480-30-9; (*R*)-(+)-2, 77415-56-6; (*S*)-(−)-2, 20088-86-2; 3, 20822-61-1; (±)-4, 77415-57-7; (±)-5, 77480-31-0; (*R*)-(−)-5, 20088-81-7; (*R*)-(−)-5 quinine, 77415-58-8; (*S*)-(−)-5, 77415-59-9; (*S*)-(+)-5 quinine, 77415-60-2; (±)-6, 77415-61-3; (*R*)-8, 77415-62-4; (±)-9, 77415-63-5; (±)-9 reineckate, 77415-64-6; (±)-9 *N,O,O*-trimethanesulfenyl derivative, 77415-65-7; (*R*)-9, 77480-32-1; (*R*)-9 *N,O,O*-trimethanesulfonyl derivative, 77480-33-2; (±)-10, 77415-66-8; (*R*)-(+)-10, 20088-82-8; (±)-11, 77415-67-9; (*R*)-(+)-11, 20088-83-9; (*S*)-(−)-12, 40710-02-9; (±)-12 monomethyl ester, 43010-65-7; (*S*)-12 monomethyl ester quinine, 77481-54-0; (*S*)-12 monomethyl ester, 77480-34-3; (*S*)-12 dimethyl ester, 4727-78-0; (±)-13, 39122-18-4; (*S*)-(+)-13, 39122-19-5; (±)-14, 77415-68-0; (*S*)-(−)-14, 20088-85-1; (*R*)-(+)-14, 77480-35-4; 15, 77415-69-1; 16, 77415-70-4; 17, 77415-71-5; (±)-18, 77415-72-6; (±)-18 dipicrate, 77415-73-7; (±)-19, 77415-74-8; (*R*)-(+)-19, 77480-36-5; 20 (isomer 1), 77415-75-9; 20 (isomer 2), 77480-37-6; ethyl cyanoacetate, 105-56-6; ethyl bromoacetate, 105-36-2; (±)-dimethyl 2-ethyl-2-methylsuccinate, 77480-38-7; (±)-2-ethyl-2-methylsuccinic acid, 77480-39-8; (±)-3-ethyl-3-methylpyrrolidine, 77415-76-0; (±)-3-ethyl-3-methylpyrrolidine picrate, 77415-77-1; (*R*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetic acid, 20445-31-2; (*S*)-α-methoxy-α-(trifluoromethyl)phenylacetoxyl chloride, 20445-33-4; malononitrile, 109-77-3; (*S*)-(−)-11, 20088-84-0.

A Study of the Structure of Hydrazones of Indole-2,3-dione and 1-Methylindole-2,3-dione with Nuclear Magnetic Resonance Spectroscopy

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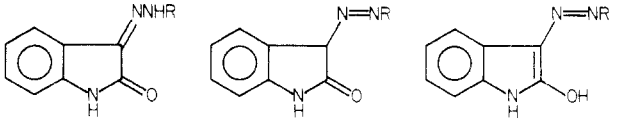
Nuclear magnetic resonance was used to determine the structure of mono- and disubstituted hydrazones of indole-2,3-dione and 1-methlindole-2,3-dione. The assignment of the hydrazone form to all of the monosubstituted derivatives is supported by infrared data. The ^{15}N isotopomer of indole-2,3-dione 3-phenylhydrazone confirms the hydrazone structure. These compounds all show strong intramolecular hydrogen bonding. The disubstituted hydrazones are found to exist as geometric isomers. No tautomeric forms involving the ring NH were detected.

Introduction

Although azo compounds derived from indol-2-one and the comparable hydrazones of indole-2,3-dione have been known for many years,[1] no definitive studies have been reported on the structure of these compounds. In an earlier paper,[2] we had reported that the 1-methyl-2-(phenylazo)indol-2-one probably existed in chloroform as a hydrazone. This assignment was based upon a low-field singlet in the NMR spectrum falling within a 2-ppm range of the shift of similar hydrazone heterocyclics.

The monosubstituted hydrazones of isatin (indole-2,3-dione) can exist in at least three tautomeric forms, 1–3.



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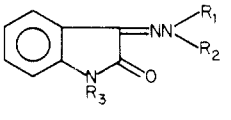
The possibility of tautomers involving the ring NH can be eliminated by studying the monosubstituted derivatives of *N*-methylisatin. On the other hand, the disubstituted hydrazones can exist only in the hydrazone form (4).



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Results and Discussion

NMR Spectra of Monosubstituted Hydrazones of Isatin and *N*-Methylisatin. The NMR spectrum of isatin 3-phenylhydrazone (see Table I) in Me_2SO shows two low-field singlets at 10.91 and 12.71 ppm and in dioxane at 9.27 and 12.75 ppm. The ^{15}N isotopomer of the 3-phenylhydrazone (where the ^{15}N is adjacent to the phenyl group) in Me_2SO contains a doublet centered at 12.75 ppm (J = 97 Hz) and a singlet at 10.95 ppm. The presence of this doublet and the magnitude of the coupling constant provide firm evidence for attachment of the proton to the ^{15}N nitrogen. Consequently, the compound exists in the hydrazone form (1). The higher field resonance can be assigned to the NH proton of the ring. The spectra of isatin 3-methylhydrazone (**5b**) also indicate a hydrazone structure. In both Me_2SO and $CDCl_3$ the methyl peak occurs as a doublet centered at 3.30 (J = 4.1 Hz) and 3.53 ppm (J = 3.9 Hz), respectively, while the lower field peak in Me_2SO occurs as a quarter centered at 10.87 ppm (J = 4.0 Hz) and a very broad signal at 10.98 ppm in $CDCl_3$. The proton of the ring NH appears as a singlet in Me_2SO at 10.61 and 8.71 ppm in $CDCl_3$. Decoupling experiments demonstrated that the doublet and quartet are a result of mutual coupling and therefore the doublet almost surely can be assigned to the NCH_3 group and the quartet to the NH proton of structure 1.

Comparable results are found with isatin 3-benzylhydrazone (**5c**) in Me_2SO. This NMR spectrum contains a lower field triplet centered at 11.32 ppm (J = 4.6 Hz) and a doublet centered at 4.78 ppm (J = 4.6 Hz) due to the methylene protons. Decoupling experiments again reveal the interaction of these protons.

The NMR spectra of *N*-methylisatin 3-phenylhydrazone (**5d**) in Me_2SO and $CDCl_3$ contain only one low-field signal at 12.78 and 12.72 ppm, respectively. The NMR spectra of *N*-methylisatin 3-methylhydrazone (**5e**) also contain only one low-field signal, a quartet centered at 10.83 ppm in Me_2SO and a very broad signal at 10.87 ppm in $CDCl_3$. The methyl peaks in both solvents are doublets (Table I)

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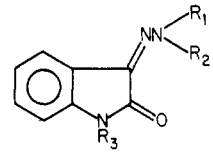
0022-3263/81/1946-2764$01.25/0

Table I. NH and CH_3 Chemical Shifts in Hydrazones of Isatin or *N*-Methylisatin



compd	R_1	R_2	R_3	solvent	concn, wt %	CH_3[a] δ	CH_3[a] J^b ($w_{1/2}$[c])	ring NH[a] δ	ring NH[a] J^b ($w_{1/2}$[c])	hydrazone NH[a] δ	hydrazone NH[a] J^b ($w_{1/2}$[c])
5a	C_6H_5	H	H	*p*-dioxane	5.5			9.27	bs (8.1)	12.75	bs (6.3)
				Me_2SO-d_6	5.5			10.91	bs (6.3)	12.71	bs (4.5)
5b	CH_3	H	H	$CDCl_3$	3.3	3.53	d, 3.9	8.71	bs (18)	10.98[d]	bs (18)
				Me_2SO-d_6	5.5	3.30	d, 4.1	10.61	bs (7.5)	10.87	bq, 4.0
5c	$C_6H_5CH_2$	H	H	Me_2SO-d_6	6.5	4.78	d, 4.6	10.72	bs (7.0)	11.32	bt, 4.6
5d	C_6H_5	H	CH_3	$CDCl_3$	3.3			3.24[e]	ss	12.72	bs (6.3)
				Me_2SO-d_6	5.5			3.32[e]	ss	12.78	bs (6.3)
5e	CH_3	H	CH_3	$CDCl_3$	7.0	3.34	d, 3.6	3.23[e]	ss	10.87	bs (15.3)
				Me_2SO-d_6	4.0	3.34	d, 3.6	3.31[e]	ss	10.83	bq
5f[f]	C_6H_5	CH_3	H	$CDCl_3$	2.2	3.96	ss	9.49	bs (8.1)		
						3.72	ss	8.44	bs (9.0)		
				Me_2SO-d_6	5.5	3.87	ss	10.75	bs (8.7)		
						3.62	ss	[g]			
5g[f]	CH_3	CH_3	H	$CDCl_3$	7.0	3.76	ss	10.50	bs (10.5)		
						3.48	ss	9.32	bs (9.0)		
				Me_2SO-d_6	5.5	3.48	ss	10.37[h]	vb		
						3.14	ss				
5h[f]	C_6H_5	CH_3	CH_3	$CDCl_3$	4.4	3.97	ss	3.23[e]	ss		
						3.70	ss				
				Me_2SO-d_6	4.9	3.94	ss	3.22[e]	ss		
						3.67	ss				

[a] ss, sharp singlet; bs, broad singlet; vbs, very broad singlet; d, doublet; bt, broad triplet; bq, broad quartet. [b] ±1 Hz. [c] Half-height width of peak in hertz given in parenthesis. [d] Decoupling shows that this peak is a collapsed quartet. [e] CH_3 peak of ring NCH_3. [f] Equilibrium spectrum. [g] Integration shows other peak in aromatic region. [h] Peak is asymmetric, probably two overlapping signals.

which can be reduced to singlets by irradiation at the low-field resonance.

As can be seen from the above data, the position of the lower field signal for each compound remains relatively constant with a change in solvent. Methylation of the ring nitrogen also has no effect on the position of this signal. Therefore, the low field of this NH resonance and its relatively constant value strongly suggest intramolecular hydrogen bonding to the carbonyl group. The chemical shift of the hydrogen proton resonance (and the strength in) follows the order of the para Hammett σ constants: $C_6H_5 > C_6H_5CH_2 > CH_3$ (12.7 > 11.3 > 11 ppm in Me_2SO).

Preliminary studies with a thio derivative of isatin (indole-2-thione 3-phenylhydrazone) also show the hydrazone structure to be the favored tautomeric form. For this compound the proton resonance of the hydrazone is shifted to 15.62 ppm in Me_2SO and 15.65 ppm in dioxane, which suggests stronger hydrogen bonding than with the isatin derivative. This is in agreement with the results found with 3-alkyl-4-(arylazo)isoxazole-5-thiones,[3] with the 4-aminomethylene derivative of pyrazoline-5-thione,[4] and with 4-(phenylazo)-3-methyl-1-phenyl-5-pyrazoline-5-thione.[5]

NMR Spectra of Disubstituted Hydrazones of Isatin. In contrast to the monosubstituted hydrazones of isatin, the disubstituted hydrazones which have a fixed hydrazone structure (**4**) exhibit an equilibrium between two forms. The NMR spectra of solutions of isatin methylphenylhydrazone (**5f**) in $CDCl_3$ taken immediately after preparation show only one methyl signal at 3.96 ppm and one low-field signal at 8.44 ppm. Time studies show that the original peaks decrease in intensity to the same extent as the increase in intensity of both a new methyl signal at 3.72 ppm and a new low-field signal at 9.44 ppm. Equilibrium is achieved after 48 h. The UV–vis spectrum of this compound in chloroform did not change over the same 48-h period, λ_{max} 421 nm. The isatin dimethylhydrazone (**5g**) shows similar behavior (Table I) with equilibrium occurring after 5 days.

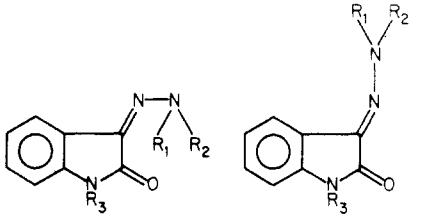
Table II. Syn-Anti Equilibrium Data at 37 °C

compd	solvent	*syn*-CH_3/*anti*-CH_3	*K*	time, days, for equilibrium
5f	$CDCl_3$	1.91/1.1	1.7	2
	Me_2SO-d_6	2.1/0.9	2.3	2
5g	$CDCl_3$	3.8/2.2	1.7	5
	Me_2SO-d_6	4.6/1.4	3.3	5
5h	$CDCl_3$	2.27/0.73	3.1	2
	Me_2SO-d_6	2.09/0.94	2.2	2

The above behavior of the disubstituted hydrazones could be attributed to either geometric isomerism or to the formation of tautomeric forms involving the ring NH proton. As similar behavior is observed with *N*-methylisatin methylphenylhydrazone (**5h**) where the possibility of tautomeric forms is eliminated, it is reasonable to conclude that these compounds exist as geometric isomers. (Equilibrium data are presented in Table II.)

(3) L. A. Summers, P. F. H. Freeman, and D. J. Shields, *J. Chem. Soc.*, 3312 (1965).
(4) L. N. Kurkovskaya, N. N. Shapet'ko, I. Kuitko, Yu. Koshelov, and E. M. Sof'ina, *Zh. Org. Khim.*, **9**, 821 (1973).
(5) F. A. Snavely and S. Un, unpublished results.

Space-filling models indicate that the methyl group in the syn form (**5a**) always lies within the deshielding region of the induced field of the carbonyl group. Consequently, the protons of the methyl group are shifted downfield. In the anti form (**5b**) the methyl group is placed away from



syn-5a *anti*-5b

the carbonyl group and is relatively unaffected. Thus the methyl group of the syn form would be expected to be more downfield with respect to the methyl group of the anti form. Since in all of the disubstituted compounds the downfield methyl peak was the predominant signal, and, as the downfield peak initially was the only methyl peak present, it seems reasonable to conclude that the major isomer in solution and the predominant form in the solid phase is the syn isomer.

IR Spectra. The IR spectra of the phenylhydrazone and the methylhydrazone of isatin in chloroform have sharp absorption maxima in the 3420–3450-cm^{-1} region, a broad band at 3200 to 3210 cm^{-1}, and strong absorptions in the 1660–1680-cm^{-1} region. The maximum at 3200–3210 cm^{-1} is missing with the methylphenylhydrazone and the sharp band in the 3420–3450-cm^{-1} region is missing with *N*-methylisatin phenylhydrazone. It seems reasonable, therefore, to assign the 3420–3450-cm^{-1} region to the NH ring proton, the broad band at 3200–3210 cm^{-1} to the intramolecularly hydrogen-bonded proton, and the 1660–1680-cm^{-1} absorption to the carbonyl group. In the more basic solvents, dioxane and Me_2SO, the sharp peak in the 3420–3450-cm^{-1} region disappears and a large broad band appears at 3100–3200 cm^{-1} which suggests strong hydrogen bonding of the ring NH proton with the solvent. Inspection of the NMR spectra support this hydrogen bonding of the NH ring proton to these basic solvents (the position of the ring NH proton resonance is shifted about 1.8 ppm downfield from its position in $CHCl_3$) as well as the strong intramolecular hydrogen bond of the NH hydrazone proton.

Experimental Section

Compounds. The 3-(substituted hydrazones) of isatin and *N*-methylisatin were prepared by dissolving a 1:1 molar mixture of isatin or *N*-methylisatin and the appropriate hydrazine in glacial acetic acid and heating on a steam bath for about 30 min. Crystallization was induced by adding water and the products were recrystallized from 95% ethanol. **5a**: orange-yellow crystals; mp 211–212 °C (lit.[6] mp 209–210 °C. **5b**: orange-yellow crystals; mp 178–180 °C (lit.[7] mp 179 °C. **5c**: yellow needles; mp 154–155 °C. **5d**: yellow needles; mp 138–139 °C (lit.[8] mp 140 °C). **5e**: orange-yellow crystals; mp 109–110 °C. **5f**: orange crystals; mp 174–175 °C (lit.[9] mp 172–173 °C. **5g**: yellow crystals; mp 122–123 °C (lit.[7] mp 124°C). **5h**: orange crystals; mp 119–121 °C.

N-Methylisatin was prepared from isatin according to the literature.[10]

The ^{15}N isotopomer of isatin 3-phenylhydrazone was prepared by diazotization of [^{15}N]aniline and coupled to indol-2-one. The probability of isotope scrambling under the conditions used[11] has been shown to be very low and the azo compound can therefore be safely assumed to carry the ^{15}N attached to the benzene ring. The melting point was the same as that of the ^{14}N homologue.

Indole-2-thione 3-phenylhydrazone was prepared by refluxing a solution of isatin 3-phenylhydrazone in pyridine to which P_2S_5 was added over a 15-min period. After 2 h water was added and the red needles were recrystallized from 95% ethanol; mp 224–225 °C.

Melting points were obtained under nitrogen on a Perkin-Elmer DSC-1 differential scanning calorimeter and on a Fisher Scientific melting-point block.

Spectra. NMR spectra were recorded on a 90-MHz Perkin-Elmer R-32 spectrometer. Ethanol-free (alumina was used to remove ethanol) deuteriochloroform was used as a solvent, while other solvents were dried over molecular sieves. Integrated areas were in good agreement with the theoretical values. IR spectra were recorded on a Perkin-Elmer 621 spectrophotometer and calibrated with polystyrene film.

Acknowledgment is made by S.U. to the DuPont College Science Grant for partial support of this work.

Registry No. 5a, 17310-26-8; **5b**, 59026-21-0; **5c**, 77305-83-0; **5d**, 15096-16-9; **5e**, 69414-14-8; *syn*-**5f**, 77305-84-1; *anti*-**5f**, 77305-85-2; *syn*-**5g**, 77305-86-3; *anti*-**5g**, 77305-87-4; *syn*-**5h**, 77305-88-5; *anti*-**5h**, 77305-89-6; indole-2-thione 3-phenylhydrazone, 77305-90-9.

(6) E. Fischer, *Chem. Ber.*, **17**, 577 (1884).
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