Communications to the Editor

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Proton Magnetic Resonance Spectra of the Benzazine and Benzodiazine N-Oxides

Recently[1] we have found that the ring proton signals in nuclear magnetic resonance (NMR) spectra of pyridazine 1-oxide (I) and its derivatives appear in the order of $H_3<H_6<H_5<H_4$, and have also concluded that, because of the presence of the N-O group anisotropy,[*1] the signal of proton H_6 attached to the carbon atom adjacent to the N-O group (*ortho*-position) is shifted by about -2.65 p.p.m.[*2] from a position expected from an

Table I. Nuclear Magnetic Resonance Parameters of Benzazine and Benzodiazine N-Oxides[a)]

Compound	Chemical shift (τ)					Coupling constant J (c.p.s.)				
	H_1	H_2	H_3	H_4	H_8[b)]	$J_{2,3}$	$J_{2,4}$	$J_{3,4}$	$J_{4,8}$	
Quinoline 1-oxide (II)	—	1.43	2.73	2.26	1.25	6.0	1.1	8.5		
2-Methylquinoline 1-oxide	—	—	2.74	2.35	1.21	~0	~0	8.5	0.8	
3-Bromoquinoline 1-oxide	—	1.40	—	2.13	1.3	—	1.4	—	0.8	
4-Methylquinoline 1-oxide	—	1.55	2.88	—	1.19	5.8	~0	~0.4	—	
4-Chloroquinoline 1-oxide	—	0.93	2.28	—	1.26	6.6	—	—	—	
5-Nitroquinoline 1-oxide	—	1.50	1.83	—		6.8	—	—	—	
6-Methylquinoline 1-oxide	—	1.57	2.82		1.41	5.8	1.2	8.5		$J_{7,8}$ 9.5
6-Methoxyquinoline 1-oxide	—	1.62		2.33	1.36	5.8	1.1	8.8	0.8	$J_{7,8}$ 9.2
7-Methylquinoline 1-oxide	—	1.53	2.83		1.47	6.0	1.0	8.5	0.8	$J_{7,8}$ 0.3
8-Hydroxyquinoline 1-oxide	—	1.79	2.79	2.26	—	5.8	1.0	8.6	—	$J_{6,7}$ 7.4
Isoquinoline 2-oxide (III)	1.23	—	1.86			—	—	7.0		$J_{1,3}$ 1.7
Cinnoline 1-oxide (IV)[c)]	—	—	1.67	2.50	1.33	—	—	6.2	0.9	
4-Methylcinnoline 1-oxide[c)]	—	—	1.87	—	1.35	—	—	1.0	—	
3-Methoxycinnoline 1-oxide[c)]	—	—	—	3.08	1.52	—	—	—	1.0	
Cinnoline 2-oxide (V)[c)]	—	—	1.79	1.94		—	—	7.0		
4-Methylcinnoline 2-oxide[c)]	—	—	1.90	—		—	—	1.0	—	
Phthalazine 2-oxide (VI)	1.40	—	—	0.91		—	—	—		$J_{1,4}$($J_{1,5}$) 0.9
4-Ethoxyphthalazine 2-oxide	1.72	—	—	—		—	—	—	—	$J_{1,5}$ 0.8
Quinazoline 1-oxide (VII)[d)]										
4-Methoxyquinazoline 1-oxide	—	1.17	—	—	1.35	—	—	—	—	$J_{7,8}$ 8.0
Quinazoline 3-oxide (VIII)	—	0.86	—	0.89		—	1.8	—		
4-Metnylquinazoline 3-oxide	—	0.98	—	—		—	—	—	—	
Quinoxaline 1-oxide (IX)	—	1.64	1.33	—	1.45	3.5	—	—	—	$J_{7,8}$ 4.8
Quinoxaline 1,4-dioxide (X)	—	1.76	1.76	—	1.37		—	—	—	$J_{7,8}$ 6.8

a) The spectra were taken with a Varian A-60 analytical NMR spectrometer system on 10% (w/v) solutions in deuterochloroform containing tetramethylsilane as an internal reference. Chemical shifts are expressed on τ-scale.

b) Centers of the signals (these protons, in general, appeared as the K parts of ABCK systems in these cases.).

c) M. Ogata, H. Kano, K. Tori: This Bulletin, **10**, 1123 (1962).

d) This compound has not been synthesized as yet.

[*1] We have conjectured the presence of the diamagnetic anisotropy of the N-O group. The effect of this anisotropy probably includes the effect of the electric field due to the N-O group and of the lone-pair electrons on the oxygen atom. We consider that this anisotropic effect is similar to that observed for the carbonyl group (see, L.M. Jackman: "Application of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 121 (1959), Pergamon Press, New York, N.Y.).

[*2] This value has been obtained with a rough evaluation; the value for the case of pyrazine 1-oxide has been estimated to be about -2.7 p.p.m.[1]

1) K. Tori, M. Ogata, H. Kano: This Bulletin, **11**, 235 (1963).

LCAO-MO calculation.[2] It is reasonable to assume that in the NMR spectra of benzazine and benzodiazine N-oxides, the proton at a *peri*-position to the N-O group, like that at an *ortho*-positon, would show its signal peak at a lower field than other signals, owing to the anisotropic effect of the N-O group. Bearing this in mind, we assigned the signal peaks of the spectra of benzazine and benzodiazine N-oxides as listed in Table I. Some of the spectra are shown in Fig. 1.*[3]

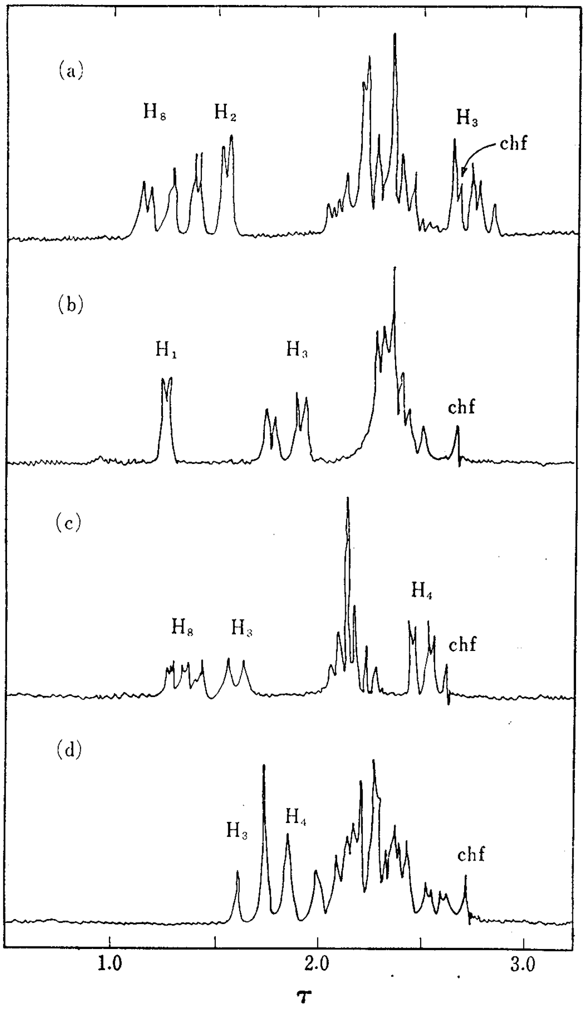
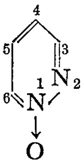


Fig. 1. Nuclear Magnetic Resonance spectra of (a) quinoline 1-oxide (II), (b) isoquinoline 2-oxide (III), (c) cinnoline 1-oxide (IV) and (d) cinnoline 2-oxide (V), at 60 Mc.p.s., in 10% solution in deuterochloroform



I

The signal of the proton H_8 of the 1-oxides (such as II, IV, VII, IX and X) was found at a lower field (about $1.2\tau\sim1.5\tau$) than were the other signals of the protons in the benzene ring. However, this is not the case with the spectra of 2- or 3-oxides (such as III, V, VI and VIII).

It has been frequently reported that there is a quantitative relationship between chemical shifts and local π-electron distributions in aromatic molecules.[3] Charge densities on carbon atoms in the benzene rings of the examined compounds appear not to differ too much from one another. Actually, it has been shown in LCAO-MO calculations of quinoline 1-oxide (II)[4] and isoquinoline 2-oxide (III)[5] that

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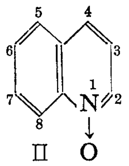
*[3] More detailed spectral data with more elaborate discussions will be presented in a pair of full papers by us.

[2] T. Kubota, H. Watanabe, I. Tanaka: Bull. Chem. Soc. Japan, to be published (presented at the 15th annual meeting of the Chem. Soc. Japan, in Kyoto, April, 1962).

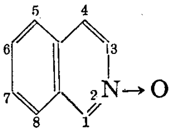
[3] For example, see H. Spiesecke, W.G. Schneider: Tetrahedron Letters, 468 (1961).

[4] T. Kubota: Nippon Kagaku Zasshi, **80**, 578 (1959).

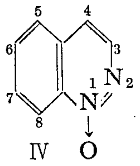
[5] *Idem*: Bull. Chem. Soc. Japan, **35**, 946 (1962).



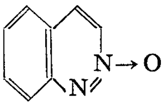
II



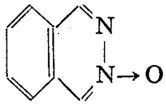
III



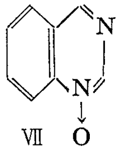
IV



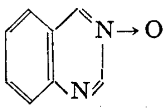
V



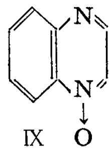
VI



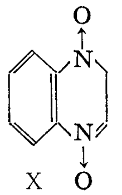
VII



VIII



IX



X

the π-electron charge density on the C_8 atom is slightly higher than those on the other carbon atoms in the benzene ring, and the densities on C_8 atom of II and III are almost equal. Therefore, it is apparent that the low-field shift of the H_8 proton signals of the 1-oxides should be ascribed to the anisotropic effect of the N-O group.

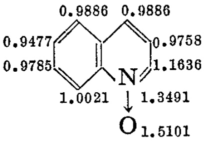
In order to estimate approximate shift values due to this anisotropic effect, proportional relationship[*4] proposed by Spiesecke and Schneider[3)] was applied to the quinoline 1-oxide (II) system as a typical example. The observed chemical shifts of the protons H_2, H_3, H_4 and H_8 in deuterochloroform solution (see Table I) and the results of the LCAO-MO calculation on II[4)],[*5] were used in this estimation. As a result, we obtained $-1.2\sim-1.4$ p.p.m. and $-3.0\sim-3.3$ p.p.m. for the shift values due to the anisotropic effect of the N-O group on the proton H_8 and H_2, respectively, taking account of the difference between the ring current effect on the protons H_2 and H_3 and that on the protons H_4 and H_8 (about 0.35 p.p.m.).[6)] This value of $-1.2\sim-1.4$ p.p.m. for the anisotropic effect on the proton H_8 is small as compared with that on the proton H_2. However, this value of $-1.2\sim-1.4$ p.p.m. may be reasonable for the N-O group anisotropy, since the values of -2.65 p.p.m.[1)] or $-3.0\sim-3.3$ p.p.m. estimated for the anisotropic effect of the N-O group on the *ortho* proton may involve the other various effects due to the N-O group, such as the inductive effect through the σ-bond.[*3]

Spin coupling between protons of different rings in aromatic compounds has been found in the case of the coupling between H_4 and H_8 of quinoline derivatives.[7)] This spin coupling was also observed in several compounds examined (see Table I). All the $J_{4,8}$ values of the N-oxide derivatives are about 1.0 c.p.s. and are similar to that of the quinoline derivatives.[7)]

We wish to express our gratitude to Prof. Emeritus, E. Ochiai of the University of Tokyo and Dr. K. Takeda, Director of this laboratory, for their helpful guidance through the course of this work.

[*4] $\delta=10.6\rho$, where δ is the chemical shift of a ring proton referred to benzene and ρ is the π-electron density on a corresponding carbon atom.

[*5]



6) J.A. Pople, W.G. Schneider, H.J. Bernstein : "High-resolution Nuclear Magnetic Resoance," 251 (1959). McGraw-Hill Book Co., Inc., New York, N.Y.

7) F.A.L. Anet : J. Chem. Phys., **32**, 1274 (1960).

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Preparation and Configuration of 17-Chloro-5α-androstan-3β-ols and Related Compounds

Westphal[1] prepared in 1939 17-chloro steroids by the reaction of 17β-hydroxy steroids with phosphorus pentachloride in chloroform, but the configuration of the chlorine atom at C-17 in these compounds has not been determined. The present communication describes a synthesis of two isomeric 17-chloro-5α-androstan-3β-ols and related compounds.

The preceding paper[2] it was described that the reaction of 3-oxo-4-en steroids with sulfuryl chloride in pyridine gave 3-oxo-4-chloro-4-en steroids in good yields. 5α-Androstan-3β,17β-diol acetate, when treated with sulfuryl chloride in pyridine in the same manner, gave a 17-chloro-5α-androstan-3β-ol acetate (I), 102~104°, $[\alpha]^{20}_{D}$ +27° (*Anal.* Calcd. for $C_{21}H_{33}O_2Cl$: C, 71.46; H, 9.43. Found : C, 71.43; H, 9.62).

A similar displacement of 17β-hydroxy-5α-androstan-3-one gave the corresponding 17-chloro-5α-androstan-3-one (II), m.p. 180~183°, $[\alpha]^{20}_{D}$ -23° (*Anal.* Calcd. for $C_{19}H_{29}OCl$: C, 73.88; H, 9.46. Found : C, 73.72; H, 9.44), which was also obtained from I by two steps, hydrolysis of I to 17-chloro-5α-androstan-3β-ol (III), m.p. 186~188°, $[\alpha]^{20}_{D}$ −37° and oxidation of III with chromium trioxide.

Testosterone was also converted into the corresponding 17-chloroandrost-4-en-3-one (IV), m.p. 150~153°, $[\alpha]^{20}_{D}$ +32°, UV : λ^{EtOH}_{max} 241 mμ (*Anal.* Calcd. for $C_{19}H_{27}OCl$: C, 74.36; H, 8.87. Found : C, 74.23; H, 8.90.), which seems to be identical with the 17-chloroandrost-4-en-3-one, m.p. 148°, reported by Westphal.[1]

In order to examine the nature of the displacement of the hydroxyl group by chlorine with sulfuryl chloride in pyridine, the reactions of androsterone and of isoandrosterone were carried out. When treated with this reagent, androsterone gave 3β-chloro-5α-androstan-17-one while isoandrosterone afforded 3α-chloro-5α-androstan-17-one. It is well known that the 3-hydroxyl group in saturated 5α-steroid is replaced by chlorine with inversion of configuration by phosphorus pentachloride, but with retention by thionyl chloride.[3] Thus the displacement of the hydroxyl group by chlorine with sulfuryl chloride-pyridine is similar to that with phosphorus pentachloride rather than with thionyl chloride, as far as inversion and retention of configuration is concerned. It is of interest to note that sulfuryl chloride-pyridine can be used as a general reagent for the displacement of the hydroxyl group by chlorine.

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[1] U. Westphal : Ber., **72**, 1233 (1939).
[2] H. Mori : This Bulletin, **10**, 429 (1962).
[3] R.E. Marker : J. Am. Chem. Soc., **57**, 1755 (1935). R.E. Marker, F.C. Whitmore, O. Kamm: *Ibid.*, **57**, 2358 (1935).

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