Notes

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Tozo Fujii, Chin C. Wu, and Shun-ichi Yamada : Preparation and Nuclear Magnetic Resonance Spectra of Alkoxyamines.

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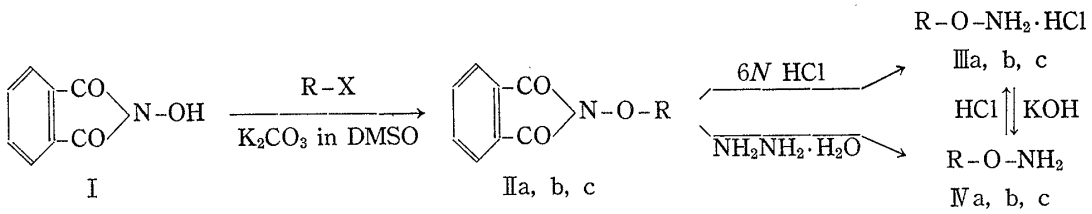
The choice of suitable solvents for nuclear magnetic resonance (NMR) spectroscopy of adenine derivatives is extremely limited. Since such compounds usually are insufficiently soluble in the common NMR solvents in which correlation of chemical shifts of protons with molecular structures has been extensively investigated,[1] other solvents such as D_2O,[1e,2] liquid SO_2,[3] deuterated dimethyl sulfoxide (DMSO-d_6),[4] and dimethyl sulfoxide (DMSO)[5] have to be used. Among these the last one seems to be the most attractive because it is capable of giving fairly concentrated solutions of the salts as well as the free bases of many adenine derivatives and because of its miscibility with D_2O which can simplify the experimental procedure to detect protons exchangeable for deuterons. It is thus convenient to use DMSO rather than the more expensive DMSO-d_6, unless important signals of the solute are overlapped with those of the solvent and ^{13}C satellites. In connection with an interest in NMR spectroscopical study on the N-alkoxyadenine derivatives which have been synthesized recently in our laboratory,[6] it has been desirable to us to catalogue the NMR chemical shifts in DMSO for the protons of methoxyamine (Ⅳa), ethoxyamine (Ⅳb), benzyloxyamine (Ⅳc), and their hydrochlorides (Ⅲa,b,c) on comparison with those of the corresponding primary amines, alcohols, and ethers.



a : R=CH_3 b : R=C_2H_5 c : R=$C_6H_5CH_2$

Chart 1.

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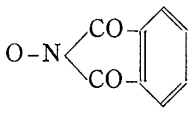
1) *a*) G. V. D. Tiers : "Table of τ Values for a Variety of Organic Compounds," Minnesota Mining and Manufacturing Co., St. Paul, Minn., 1958; *b*) *Idem* : J. Phys. Chem., **62**, 1151 (1958); *c*) L. M. Jackman : "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, New York, N. Y., 1959, p. 50; *d*) N. S. Bhacca, L. F. Johnson, J. N. Shoolery : "Varian NMR Spectra Catalog," Vol. I, Varian Associates, Palo Alto, Cal., 1962; *e*) N. S. Bhacca, D. P. Hollis, L. F. Johnson, E. Pier : *Ibid.*, Vol. Ⅱ, 1963.
2) C. D. Jardetzky, O. Jardetzky : J. Am. Chem. Soc., **82**, 222 (1960).
3) N. J. Leonard, J. A. Deyrup : *Ibid.*, **84**, 2148 (1962).
4) L. B. Townsend, R. K. Robins, R. N. Loeppky, N. J. Leonard : *Ibid.*, **86**, 5320 (1964).
5) N. J. Leonard, T. Fujii : Unpublished data, see footnote 40 in ref. 4.
6) *a*) T. Fujii, T. Itaya, S. Yamada : This Bulletin, **13**, 1017 (1965); *b*) *Idem* : *Ibid.*, **14**, 1452 (1966); *c*) T. Fujii, C. C. Wu, T. Itaya, S. Yamada : Chem. & Ind. (London), **1966**, 1598; *d*) T. Fujii, T. Itaya, C. C. Wu, S. Yamada : *Ibid.*, **1966**, 1967.

For preparation of the alkoxyamines (Ⅳa,b,c),[7] N-hydroxyphthalimide (I)[8] was converted into the N-alkoxyphthalimides (Ⅱa, b, c) in 90~94% yield with methyl, ethyl iodide, and benzyl chloride in DMSO*2 in the presence of anhydrous potassium carbonate, as shown in Chart 1, by modifying the known method in which the anionic form of I was alkylated in various solvents such as ether,[8a,b] water,[7g] N,N-dimethylformamide,[7b,c,f,h,i] and acetone.[7d] Although hydrolysis[7f] of Ⅱa and Ⅱb with hydrochloric acid[7g,h] for 30 mins. took place very smoothly to furnish Ⅲa and Ⅲb in good yields, that of Ⅱc in a mixture of acetic acid and 6*N* HCl for 1 hr. resulted in poor formation (36% yield) of benzyloxyamine hydrochloride (Ⅲc) owing to cleavage of the benzyl-O bond.*3 However, hydrazinolysis of Ⅱc with a slight modification of the reported procedure[7c,d] gave the free base (Ⅳc) in an excellent yield. The free bases (Ⅳa,b) of methoxyamine and ethoxyamine were liberated in the usual way from the hydrochlorides (Ⅲa,b)[7a,9] in good yields.

The NMR spectra of the N-alkoxyphthalimides (Ⅱa,b,c), alkoxyamines (Ⅳa,b,c), and their hydrochlorides (Ⅲa,b,c) thus prepared were measured on their DMSO solutions of at least three different concentrations within a range of 1 ~25% w/v. Then, the chemical shifts in τ-values for the protons were obtained by extrapolation to infinite dilution. Similar treatments were made also for benzylamine, and its hydrochloride,*4 for methanol, ethanol, and benzyl alcohol,[10] and for benzyl methyl ether,*4 diethyl ether, and benzyl ethyl ether.*4 In the cases of methylamine, ethylamine, and their

Table I. Methyl Groups Adjacent to Nitrogen and Oxygen Functions of the Type CH_3-X

X	τ_{CH_3}	X	τ_{CH_3}
NH_2	7.72[a]	$ONH_2 \cdot HCl$	6.20 (6.10)[d]
$NH_2 \cdot HCl$	7.64[b]		
OH	6.82[c]		6.04
$OCH_2C_6H_5$	6.71		
ONH_2	6.61 (6.44)[d]		

a) Measured on 7%w/v DMSO-d_6 solution.
b) Measured on 5%w/v DMSO-d_6 solution. The peak was a dull multiplet.
c) A doublet with J=5 c.p.s. Chapman and King reported a doublet at 6.83 τ for the methyl group of methanol when measured on DMSO solution.[10]
d) The value in parentheses is the one observed on 3% D_2O solution by Bauer and Ghosh.[7h]

*2 For a recent review of the use of DMSO as a versatile solvent and a reactant in organic reactions, see T. Sato : Yūki Gōsei Kagaku, **23**, 768, 867 (1965).

*3 Bauer, *et al.*[7e] reported a better reaction condition (reflux of Ⅱc in a mixture of AcOH and concd. HCl for 0.25 hr.) under which Ⅲc was obtained in 71% yield.

*4 We gratefully acknowledge the gift of a pure sample of this compound from Mr. T. Itaya of our Faculty.

7) *a*) C.H. Andrews, H. King, J. Walker : Proc. Roy. Soc. (London), **B133**, 20 (1946), and references cited therein; *b*) E.L. Schumann, R.V. Heinzelman, M.E. Greig, W. Veldkamp : J. Med. Chem., **7**, 329 (1964), and references cited therein; *c*) A.F. McKay, D.L. Garmaise, G.Y. Paris, S. Gelblum: Can. J. Chem., **38**, 343 (1960); *d*) B.J.R. Nicolaus, L. Mariani, E. Testa : Ann. Chim. (Rome), **53**, 281 (1963) (C.A., **59**, 9851 (1963)); *e*) L. Bauer, A. Shoeb, V.C. Agwada : J. Org. Chem., **27**, 3153 (1962); *f*) L. Bauer, K.S. Suresh : *Ibid.*, **28**, 1604 (1963); *g*) R.T. Major, R.J. Hedrick : *Ibid.*, **30**, 1270 (1965); *h*) L. Bauer, B.K. Ghosh : *Ibid.*, **30**, 4298 (1965); *i*) M.J. Kornet : J. Med. Chem., **9**, 269 (1966); *j*) R.M. Khomutov : Zhur. Obscheĭ Khim., **31**, 1992 (1961) (C.A., **55**, 27018 (1961)); *k*) N.K. Bliznyuk, A.F. Kolomiets, L.A. Kalutskii : U.S.S.R. 163,187 (1964) (C.A., **61**, 13192 (1964)); *l*) H. Hjeds : Acta Chem. Scand., **19**, 1764 (1965); *m*) W. Theilacker, K. Ebke : Angew. Chem., **68**, 303 (1956).

8) *a*) W.R. Orndorff, D.S. Pratt : Am. Chem. J., **47**, 89 (1912); *b*) W.R. Roderick, W.G. Brown : J. Am. Chem. Soc., **79**, 5196 (1957); *c*) E. Kühle, R. Wegler : Ann., **616**, 183 (1958).

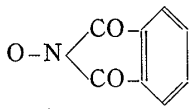
9) T.C. Bissot, R.W. Parry, D.H. Campbell : J. Am. Chem. Soc., **79**, 796 (1957).

10) O.L. Chapman, R.W. King : *Ibid.*, **86**, 1256 (1964). In their paper, hydroxyl proton splitting of alcohols in DMSO by spin-spin interaction with the α-protons has been reported.

hydrochlorides, the protons α to the nitrogen functions were obscured by the signals due to the methyl group and ^{13}C satellites of DMSO. Therefore, these four compounds were measured on 5~7 % w/v solutions in DMSO-d_6, which were able to reveal the peaks in question. Table I assembles the chemical shifts thus obtained for protons α to the nitrogen and oxygen functions of the type CH_3-X.

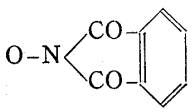
As might be expected,[1] the oxygen functions all produced larger paramagnetic shifts also in DMSO than observed for the nitrogen functions. Of particular interest was a deshielding effect of the ONH_2 group somewhat larger than that of the OR group. Protonation of the NH_2 and ONH_2 groups caused the methyl signals to move to lower fields. The methyl group deshielded most largely was found in N-methoxyphthalimide (IIa) among the compounds listed in Table I. For the compounds of the type CH_3-CH_2-X, τ-values of the α- and β-protons are given in Table II. Similarly, Table III provides the chemical shifts of the α-methylene and β-phenyl groups of the type C_6H_5-CH_2-X. Since the Shoolery's rule for calculating the alkyl proton frequencies

Table II. Protons α and β to Nitrogen and Oxygen Functions of the Type CH_3-CH_2-X

X	τ_{CH_3}[a]	τ_{CH_2}[b]
NH_2	9.00	7.43[c]
$NH_2 \cdot HCl$	8.82	7.18[d]
OCH_2CH_3	8.90	6.60
OH	8.94	6.54[e]
$OCH_2C_6H_5$	8.85	6.50
ONH_2	8.94 (8.85)[f]	6.45 (6.25)[f]
$ONH_2 \cdot HCl$	8.80 (8.72)[f]	5.93 (5.87)[f]
	8.67 (8.57)[g]	5.79 (5.67)[g]

a) Triplet with J=7 c.p.s.
b) Quartet with J=7 c.p.s.
c) Measured on 7 % w/v DMSO-d_6 solution.
d) Measured on 5 % w/v DMSO-d_6 solution. The methylene signal appeared as a dull multiplet.
e) A multiplet due to coupling with the hydroxyl proton.[10]
f) Observed on 3% D_2O solution by Bauer and Ghosh.[7h]
g) The value obtained in $CDCl_3$ by Bauer and Ghosh.[7h]

Table III. τ-Values of the α-Methylene and β-Phenyl Groups of the Type C_6H_5-CH_2-X

X	τ_{CH_2}	$\tau_{C_6H_5}$
NH_2	6.27	2.71
$NH_2 \cdot HCl$	5.98	2.58[a]
OCH_3	5.60	2.70
OCH_2CH_3	5.55	2.70
OH	5.50	2.72
ONH_2	5.43	2.70
$ONH_2 \cdot HCl$	4.96	2.62
	4.84	2.58[a]

a) Center of a multiplet.

has been applied most successfully to a system of the type Y-CH_2-X,[11] a similar treatment of the present data taken in DMSO would be of interest. At this time, however, we merely wish to call attention to the large deshielding effect of the ONH_2 group as shown also in Tables II and III.

The results described above would be of great help to interpreting NMR spectra of N-alkoxyadenine derivatives[6] and of others which have to be measured on DMSO solutions.

Experimental*5

N-Methoxyphthalimide (IIa)——Anhydrous K_2CO_3 (42 g., 0.304 mole) was added slowly to a solution of N-hydroxyphthalimide (I)*6,8) (77.7 g., 0.476 mole) in dimethyl sulfoxide (DMSO) (380 ml.) with stirring. To the resultant reddish brown mixture was added dropwise with continuous stirring methyl iodide (115 g., 0.812 mole) in such a rate that the inner temperature of the mixture did not exceed 30°. After addition was complete, the mixture was kept stirring at room temperature for 20 hrs., poured into cold water (2 L.), and allowed to stand at 0~5° for a while. The colorless crystals which separated were filtered, and washed with water (100 ml. × 3 times). The combined solution of the filtrate and washings was then extracted with benzene (100 ml. × 3 times). The benzene solution was washed with water (200 ml. × 3 times), dried over anhyd. Na_2SO_4, and evaporated *in vacuo* to dryness leaving a small amount of pale brown crystals as the second crop. The crystals of the first and second crops were combined and recrystallized from EtOH (200 ml.) to give 75.7 g. (89.7%) of IIa as colorless needles of m.p. 132~133.5°(reported[7g] m.p. 133°). One more recrystallization from EtOH did not raise their melting point. *Anal.* Calcd. for $C_9H_7O_3N$: N, 7.91. Found: N, 7.78. NMR (25% in DMSO): 6.01 τ (singlet, OCH_3) and 2.20 τ (C_6H_4).

N-Ethoxyphthalimide (IIb)——A mixture of I (152 g., 0.932 mole) and anhyd. K_2CO_3 (96.7 g., 0.699 mole) in DMSO (800 ml.) was allowed to react with ethyl iodide (290 g., 1.86 moles) for 18 hrs. in the same way as described above. The resultant reaction mixture was poured into water (*ca.* 2.5 L.) under cooling with ice. The colorless crystals that separated were filtered, washed with water (100 ml. × 3 times). The filtrate and washings were combined and extracted with benzene (300 ml. × 3 times). The combined benzene layer was washed successively with H_2O (300 ml. × 3 times), dil. aq. $NaHSO_3$ solution (200 ml.), 10% aq. Na_2CO_3 solution (100 ml.), and H_2O (300 ml. × 3 times), dried over anhyd. Na_2SO_4, and evaporated *in vacuo* giving an additional amount of IIb as colorless crystals. The crystals of the first and second crops thus obtained were combined and recrystallized from EtOH (200 ml.) to furnish 167 g. (93.7%) of IIb as colorless prisms of m.p. 97~98°. For analyses, they were recrystallized from isopropyl ether giving colorless prisms of m.p. 98°(lit. m.p. 97~98°,[7g] 99~101°[7h]). *Anal.* Calcd. for $C_{10}H_9O_3N$: C, 62.82; H, 4.75; N, 7.33. Found: C, 62.52; H, 4.60; N, 7.53. NMR (25% in DMSO): 8.67 τ (triplet, J=7 c.p.s., CH_3), 5.77 τ (quartet, J=7 c.p.s., O-CH_2-Me), and 2.17 τ (C_6H_4).

N-Benzyloxyphthalimide (IIc)——A mixture of I (30 g., 0.184 mole), anhyd. K_2CO_3 (19.3 g., 0.14 mole), and DMSO (200 ml.) was treated with benzyl chloride (45.6 g., 0.36 mole) for 24 hrs. in the same way as the methylation of I. The resultant reaction mixture was poured into cold water (600 ml.) and the whole was kept at 0~5° for a while. The colorless crystals which separated out were filtered, washed with water (20 ml. × 3 times), and recrystallized from EtOH (900 ml.) to afford 43.7 g. (93.6%) of IIc as colorless needles of m.p. 142~143°(reported[7d] m.p. 145~147°). One more recrystallization did not raise the melting point. *Anal.* Calcd. for $C_{15}H_{11}O_3N$: N, 5.53. Found: N, 5.58. NMR (16% in DMSO): 4.85 τ (singlet, O-CH_2-C_6H_5), 2.61 τ (center of multiplet, C_6H_5), and 2.21 τ (C_6H_4).

Methoxyamine Hydrochloride (IIIa)——A mixture of IIa (109 g., 0.615 mole) and 6*N* HCl (1.1 L.) was heated under reflux with stirring. The insoluble IIa went into solution when the mixture almost began to boil, and then bulky precipitate of phthalic acid immediately appeared. After heated for 30 mins., the mixture was kept in a refrigerator overnight. The phthalic acid that deposited was filtered and washed with cold water (100 ml. × 2 times). The filtrate and washings were combined and evaporated *in vacuo* to dryness. The residue was dissolved in EtOH (400 ml.) and benzene (200 ml.) was added to this solution. The mixture was evaporated *in vacuo* again to dryness. The colorless residue thus obtained was recrystallized from EtOH-Et_2O to give 48.7 g. (94.8%) of IIIa as colorless scales of m.p. 150~151° (reported[7g] m.p. 150~151°). Two more recrystallizations from EtOH-Et_2O did not raise their melting point. *Anal.* Calcd. for CH_6ONCl: N, 16.77. Found: N, 16.89. NMR (25% in DMSO): 6.16 τ (singlet, CH_3) and *ca.* −0.5 τ (broad, $\overset{\oplus}{N}H_3$).

*5 All melting points are corrected. However, no correction is made for the boiling points observed.

*6 Its nuclear magnetic resonance (NMR) spectrum (25% in DMSO) exhibited two single peaks at 2.21 τ (C_6H_4) and −0.8 τ (N-OH).

11) Ref. 1*c*, p. 59.

Ethoxyamine Hydrochloride (IIIb)——A mixture of IIb (167 g., 0.873 mole) and 6*N* HCl (1.67 L.) was treated in the same way as the case of IIIa. The hydrochloride (IIIb) was obtained as colorless scales of m.p. 129~131°(lit. m.p. 129~131°,[7g] 133~134°[7h]) when recrystallized from EtOH-Et_2O. Yield, 79.1 g., or 92.8%. *Anal.* Calcd. for C_2H_8NOCl: N, 14.36. Found: N, 14.32. NMR (25% in DMSO): 8.76 τ (triplet, J=7 c.p.s., CH_3), 5.87 τ (quartet, J=7 c.p.s., O-CH_2-Me), and *ca.* −0.6 τ (broad, $\overset{\oplus}{N}H_3$).

Benzyloxyamine Hydrochloride (IIIc)——Treatment of a mixture of IIc (5.0 g., 0.0197 mole) and 6*N* HCl (50 ml.) similar to the hydrolysis described above was ineffective probably owing to the poor solubility of IIc in the aq. acid. Although addition of AcOH (50 ml.) to this mixture was able to bring IIc into solution while hot, hydrolysis over a period of 1 hr. followed by a similar isolation procedure to that described above was unsatisfactory giving IIIc in 36% yield. Formation of benzyl chloride during the hydrolysis was evident.

Thus, IIIc was prepared from the free amine (IVc) in the following manner: A solution of IVc (1.23 g., 0.01 mole) in MeOH (30 ml.) was added dropwise to 23 % w/v methanolic hydrogen chloride (15 ml.) under cooling. Colorless crystals immediately separated out. To this mixture was added abs. ether (150 ml.) and the whole was kept in an ice bath for 30 mins. The crystals that separated were filtered to give 1.25 g. (78.6%) of IIIc. Two recrystallizations from EtOH-Et_2O gave an analytically pure sample of colorless scales, which became pale brown at 203°, shrank at 235°, and did not melt below 245°(lit. m.p. 232°,[7e] m.p. >230° (subliming)[7d]). *Anal.* Calcd. for $C_7H_{10}ONCl$: C, 52.67; H, 6.32; N, 8.77. Found: C, 52.56; H, 6.24; N, 8.81. NMR (10% in DMSO): 4.91 τ (singlet, CH_2), 2.63 τ (C_6H_5), and *ca.* −1.0 τ (broad, $\overset{\oplus}{N}H_3$).

Methoxyamine (IVa)——This amine was prepared by a method essentially same as that of Bissot, *et al.*[9]: To the hydrochloride (IIIa: 56 g., 0.671 mole) placed in a small distillation flask was added dropwise a solution of KOH (95 g.) in H_2O (95 ml.). After addition was complete, the mixture was heated to collect a fraction boiling at 47~55° in a receiver which had been immersed in an ice-water bath. After dried over KOH pellets overnight, the crude free amine was transferred to another flask, dried over BaO for two days, and distilled to collect a fraction boiling at 46~49°(reported[9] b.p. 48.1°). Yield of IVa was 27.6 g., or 87.6%. NMR (25% in DMSO): 6.59 τ (singlet, CH_3) and 4.14 τ (NH_2).

Ethoxyamine (IVb)——Similar treatment of IIIb (79.1 g., 0.81 mole) with a solution of KOH (114 g.) in H_2O (114 ml.) as above gave the crude amine boiling at 64~74°, which was dried in the same way as IVa and distilled to give 45.6 g. (92.3%) of IVb as a colorless oil of b.p. 64~65°(lit.[7m] b.p. 69°). NMR (25% in DMSO): 8.94 τ (triplet, J=7 c.p.s., CH_3), 6.45 τ (quartet, J=7 c.p.s., O-CH_2-Me), and 4.28 τ (NH_2).

Benzyloxyamine (IVc)——A mixture of IIc (30.4 g., 0.12 mole), 80% hydrazine hydrate (8.28 g., 0.132 mole), and EtOH (900 ml.) was heated under reflux. Within 15 mins. after reflux had started, phthalhydrazide began to deposit. After refluxed for 2 hrs., the reaction mixture was cooled and concd. HCl (14.5 ml., 0.132 mole) was added. The voluminous phthalhydrazide was filtered, washed with EtOH (50 ml. ×3 times) and H_2O (300 ml.). The filtrate and washings were combined and evaporated *in vacuo* to dryness leaving colorless crystals, which were dissolved in H_2O (600 ml.). The resultant aqueous solution was basified with NaOH after filtration of some insoluble material and NaOH pellets were further added until an oily layer separated. The mixture was then extracted with ether (200 ml. ×4 times) and the ethereal solution was dried over KOH and evaporated under ordinary pressure. The oily residue was distilled *in vacuo* giving 13.4 g. (90.5%) of IVc as a colorless oil of $b.p_2$ 57.5~58°(lit. $b.p_{30}$ 118~119°,[12] b.p. 212~215°[7m]). NMR (25% in DMSO): 5.42 τ (singlet, CH_2), 4.04 τ (NH_2), and 2.71 τ (C_6H_5).

Measurement of the NMR Spectra for Tables I, II, and III——Proton magnetic resonance spectra were recorded at 23~26° on a Japan Electron Optics Laboratory 3H-60 NMR spectrometer operating at 60 Mc.p.s. As an internal standard, a few drops of 20% solution of tetramethylsilane in CCl_4 was used. Unless stated otherwise, chemical shifts quoted in τ-units were obtained by extrapolation to infinite dilution. In most cases, the line positions of the protons attached to carbon atoms were almost independent of concentrations if the spectra were run on 1~5% DMSO solutions. The DMSO used in this study was purified according to the direction given by Corey and Chaykovsky.[13]

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12) Beilstein, **6**, 440.

13) E. J. Corey, M. Chaykovsky: J. Am. Chem. Soc., **84**, 866 (1962).