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The Structure of N-Aryloxyacylazoles

In connection with our work on synthetic plant growth regulators, over a hundred kinds of N-aryloxyacylazoles (I) have been synthesized mainly by the action of acyl chlorides on the azoles in pyridine.

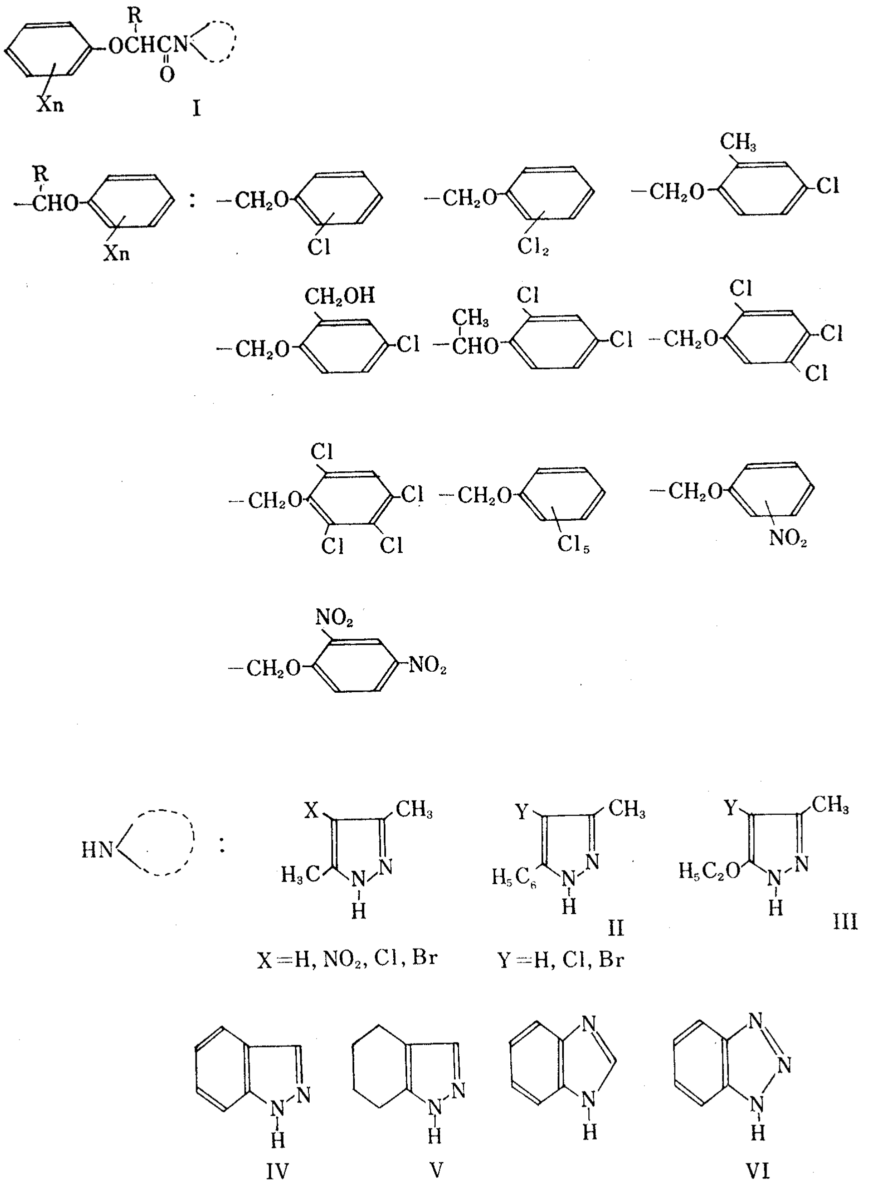

Chart 1.

When the unsymmetrically substituted pyrazoles (II, III) and condensed diazoles or triazoles such as indazole (IV), 4,5,6,7-tetrahydroindazole (V) and benzotriazole (VI) are acylated, two isomeric N-acylated compounds could be formed. Investigations of Auwers¹⁾ and Wahlberg²⁾ on this problem, however, demonstrated that acylation actually led to a single product in many cases.

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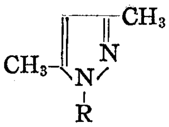
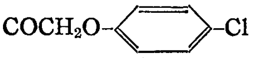
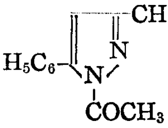
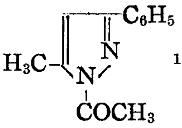
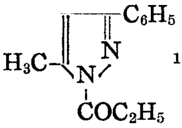
1) K. v. Auwers, K. Dietrich : J. prakt. Chem., **139**, 65 (1934).
2) H. E. Wahlberg : Arkiv Kemi., **20**, 153 (1962).

Now we used the nuclear magnetic resonance spectra[*1] in determining the structures of isomers formed by the acylation of II, III, IV, V, and VI. It should be noted in this connection that Reddy, *et al.*4) observed a constant down-field shift of about 19 c.p.s. (40 Mc. in CDCl$_3$) of the proton adjacent to the acetyl position and also a down-field shift of the methyl protons at the same position of about one-third of the magnitude in the nuclear magnetic resonance spectra of the imidazoles and purines.

Pyrazole Derivatives

We observed in the nuclear magnetic resonance spectra of the N-acylated 3,5-dimethylpyrazoles (VII∼XII) that the chemical shifts of the methyl groups in the 3- and 5-positions differed appreciably from each other, and that the lower signals were assigned to the methyl groups adjacent to the acyl group as shown with the authentic compounds (XIII∼XV).1) (Table I, nuclear magnetic resonance spectra of all the pyrazole derivatives reported here were measured in carbon tetrachloride containing tetramethylsilane as an internal reference at 60 Mc. with a Varian A-60 spectrometer).

Table I. Nuclear Magnetic Resonance Spectra of Some 1-Acylpyrazoles

		Chemical shift (τ) of the methyl group		
	R =	3-CH$_3$	5-CH$_3$	Δ_τ 3∼5
VII	COC$_6$H$_5$	7.79	7.37	0.42
VIII	CONH$_2$	7.79	7.45	0.34
IX	COCH$_3$	7.82	7.52	0.30
X	COC$_2$H$_5$	7.82	7.50	0.32
XI	COCH$_2$OC$_6$H$_5$	7.81	7.48	0.33
XII		7.80	7.47	0.33
XIII	 1)	7.75	—	
XIV	 1)	—	7.41	
XV	 1)	—	7.41	

Further, Table I shows that changes in the structure of the acyl group of N-acylpyrazoles have little effect on the chemical shift of either methyl group.

Chemical shifts (τ) of the methyl group of N-aryloxyacylpyrazoles now derived from unsymmetric methylpyrazoles (II, III) were observed to be about 7.41 which indicated the existence of the methyl group adjacent to the acyl group.

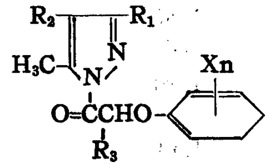
[*1] After this work was completed, a paper3) entitled "Proton Nuclear Magnetic Resonance Spectra of 1-Acyl Pyrazoles" was published, in which the structures of N-acetylated pyrazoles were discussed on the basis of the nuclear magnetic resonance spectra of the annular protons.

3) J.K. Williams: J. Org. Chem., 29, 1377 (1964).

4) G.S. Reddy, L. Mandell, J.H. Goldstein: J. Chem. Soc., **1963**, 1414.

These nuclear magnetic resonance data, therefore, strongly suggest that N-aryloxyacylpyrazoles derived from II and III should be 1-aryloxyacyl-3-phenyl (or ethoxy)-5-methylpyrazoles (Table II).

Table II. Nuclear Magnetic Resonance Spectra of 1-Aryloxyacylpyrazoles

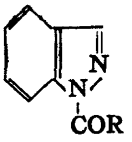


				Chemical shift (τ) of the methyl group	
R₁	R₂	R₃	Xn	τ	τ −7.41
C_6H_5	H	H	4-Cl	7.37	−0.04
〃	Cl	〃	〃	7.35	−0.06
〃	Br	〃	〃	7.37	−0.04
OC_2H_5	H	〃	〃	7.46	0.05
〃	Cl	〃	〃	7.45	0.04
〃	Br	〃	〃	7.45	0.04
C_6H_5	Cl	〃	2,4-di-Cl	7.37	−0.04
〃	Br	〃	〃	7.34	−0.07
OC_2H_5	H	〃	〃	7.47	0.06
〃	Cl	〃	〃	7.44	0.03
〃	Br	〃	〃	7.45	0.04
C_6H_5	H	CH_3	〃	7.37	−0.04
〃	Cl	〃	〃	7.36	−0.05
〃	Br	〃	〃	7.38	−0.03
OC_2H_5	H	〃	〃	7.45	0.04
〃	Cl	〃	〃	7.46	0.05
〃	Br	〃	〃	7.45	0.04
C_6H_5	H	H	2-CH_3-4-Cl	7.38	−0.03
〃	Cl	〃	〃	7.40	−0.01
〃	Br	〃	〃	7.40	−0.01
OC_2H_5	H	〃	〃	7.48	0.07
〃	Cl	〃	〃	7.47	0.06
〃	Br	〃	〃	7.47	0.06
C_6H_5	H	〃	2,4,5-tri-Cl	7.37	−0.04
OC_2H_5	〃	〃	〃	7.48	0.07
〃	Cl	〃	〃	7.46	0.05
〃	Br	〃	〃	7.43	0.02

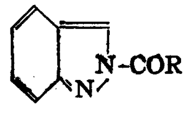
Indazole Derivatives

Acylation of indazole (IV) also should give rise to two isomers (XVI, XVII), in which the chemical shifts of the 3-proton would be expected to differ from each other.

This was confirmed with isomeric N-acetylindazoles (XIX, XX).



XVI



XVII

Chart 2.

It is evident in the Table III (nuclear magnetic resonance spectra were measured in dioxane, and other conditions were same as in the case of pyrazole derivatives) that the signal of the 3-proton of the 2-acetylindazole (XX)[5] shifts down-field to a larger extent as compared with the value observed with 1-acetyl compound (XIX),[5] the result being consistent with the earlier discussion[4] that the N-acylation of the imidazoles and purines causes larger down-field shift of the adjacent hydrogen signal.

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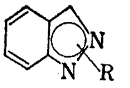
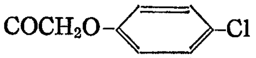
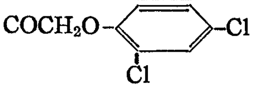
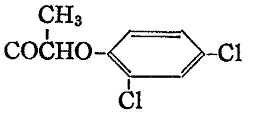
5) K. v. Auwers, H. G. Allardt: Ann., 438, 1 (1924); K. v. Auwers, W. Demuth: *Ibid.*, 451, 282 (1926).

Table III. Nuclear Magnetic Resonance Spectra of Some N-Acylindazoles

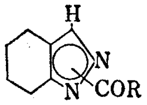
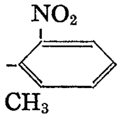
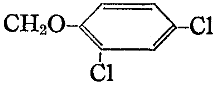
	 R =	Chemical shift (τ) of 3-H	τ −1.95
XVIII	H	1.95	
XIX	1-COCH$_3$[5)]	1.87	−0.08
XX	2-COCH$_3$[5)]	1.24	−0.63
XXI		1.80	−0.15
XXII		1.81	−0.14
XXIII		1.76	−0.19

Since the chemical shifts (τ) of the 3-proton of the N-aryloxyacylindazoles (XXI～XXIII) are near 1.87 rather than 1.24, these compounds derived from IV should be assigned to 1-aryloxyacylindazoles (XVI).

4,5,6,7-Tetrahydroindazole Derivatives

N-Acyl-4,5,6,7-tetrahydroindazoles were prepared by two methods; that is, by the action of acyl halides on V (method A), and by the reaction of acid hydrazides with 2-(hydroxymethylene)cyclohexanone (method B). The products obtained by both methods were isomeric. Nuclear magnetic resonance spectra of these compounds are shown in Table IV.

Table IV. Chemical Shift (τ) of 3-Proton of Some Acyl-4,5,6,7-tetrahydroindazoles (in dioxane)

	Product by the method A			Product by the method B		
R =	No.	3-H	τ −2.91[a)]	No.	3-H	τ −2.91[a)]
C$_6$H$_5$	XXIV	1.91	−1.00	XXIV′	2.53	−0.38
	XXV	1.88	−1.03	XXV′	2.67	−0.28
CH$_3$	XXVI	2.07	−0.84	XXVI′	2.59	−0.32
	XXVII	2.07 (m.p. 120°)	−0.84	XXVII′	2.55 (m.p. 100～102°)	−0.36
	XXVIII	2.00 (m.p. 96～97°)	−0.91	XXVIII′	2.53 (m.p. 111～112°)	−0.38

a) 2.91=τ of 3-proton of 4,5,6,7-tetrahydroindazole (V)

The larger down-field shift of the 3-proton was observed with the products obtained by the method A, thus indicating that these compounds have to be assigned to 2-acyl-4,5,6,7-tetrahydroindazoles. Our conclusion, therefore, should be reconciled with those reported by Auwers, *et al.*,[6)] who assigned the alternative structure to 2-acyl-4,5,6,7-tetrahydroindazole.

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6) K. v. Auwers, W. Buschmann, R. Heidenrich: Ann., **435**, 277 (1924); K. v. Auwers: *Ibid.*, **453**, 210 (1927).

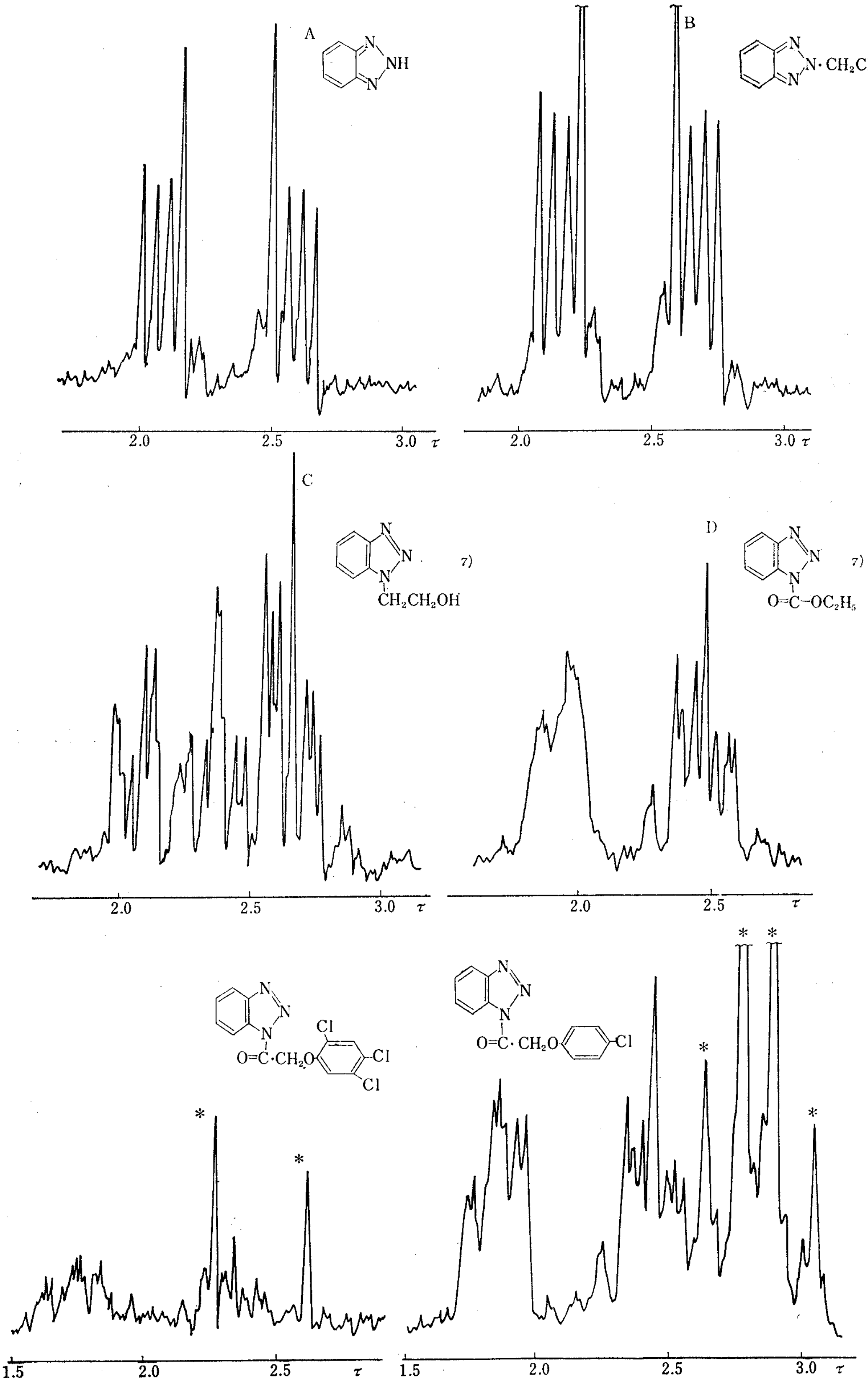

Fig. 1. Nuclear Magnetic Resonance Spectra of Benzotriazole Derivatives, at 60 Mc. in Dioxane containing Tetramethylsilane as an Internal Reference

* Ring protons of the phenoxy part.

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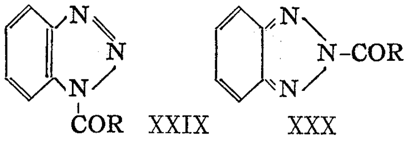
7) F. Krollpfeiffer, H. Pötz, A. Rosenberg: Ber., **71**, 596 (1938).



XXIX XXX

Chart 3.

Benzotriazole Derivatives

Acylation of benzotriazole (VI) should give an unsymmetric compound (XXIX) and a symmetric one (XXX). In the symmetric model compound, the aromatic protons exhibited the pattern of A_2B_2 system (Fig. 1, A, B), while in the unsymmetric compounds the pattern of this system disappeared (Fig. 1, C, D).

Since the nuclear magnetic resonance spectra of N-aryloxyacylbenzotriazoles synthesized showed no A_2B_2 system, these compounds should be assigned to 1-aryloxyacylbenzotriazoles (XXIX).

The authors wish to express their deep gratitude to Dr. T. Harukawa of these laboratories for his encouragement and to Takeda Chemical Industries, Ltd. for permission to publish this report. Thanks are also due to Miss F. Kasahara for the NMR spectra measurement.

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Structure and Stereochemistry of Norsecurinine and Dihydronorsecurinine

Two alkaloids have now been isolated from the roots of *Securinega virosa* Pax. et Hoffm. grown in Formosa. The first base has a molecular formula $C_{12}H_{13}O_2N$ [the hydrochloride, m.p. 225° (decomp.), IR ν_{max}^{Nujol} cm^{-1} : 1821, 1770, 1635, UV : λ_{max}^{EtOH} 254 mμ (ε (17,600), $[\alpha]_D^{20}$ $-309°$ (c=1.24, EtOH) (*Anal.* Calcd. for $C_{12}H_{14}O_2NCl$: C, 60.12; H, 5.88; N, 5.84. Found : C, 60.02; H, 5.36; N, 5.70); the methiodide, m.p. 231~232° (*Anal.* Calcd. for $C_{13}H_{16}O_2NI$: C, 45.23; H, 4.67; N, 4.05. Found : C, 45.19; H, 4.75; N, 4.16); the picrate, m.p. 258~260° (decomp.) (*Anal.* Calcd. for $C_{18}H_{16}O_8N_5$: C, 50.00; H, 3.73; N, 12.96. Found: C, 50.27; H, 3.47; N, 12.92)]. The free base [$[\alpha]_D^{23}$ -272° (c=6.9, EtOH), IR $\nu_{max}^{CCl_4}$ cm^{-1}: 1802, 1770, 1640, UV : λ_{max}^{EtOH} 256.5 mμ (ε 22,000), obtained as an oil from the hydrochloride] showed the same nuclear magnetic resonance, infrared and ultraviolet spectra as those reported by Iketubosin and Mathieson[1] for norsecurinine [m.p. 81~82°, $[\alpha]_D^{20}$ $-19.5°$ (c=0.2, EtOH), IR $\nu_{max}^{CCl_4}$ cm^{-1} : 1802, 1770, 1640, UV : λ_{max}^{EtOH} 255.5 mμ (ε 22,000); the methiodide, m.p. 194~195°; the picrate, m.p. 232~233°]. This proves both alkaloids to be identical. However, there is a considerable discrepancy in the physical constants between the specimens obtained by both groups. The lower specific optical rotation shown by the Iketubosin and Mathieson's specimen may be ascribable to contamination of its enantiomer as has been observed in case of *Securinega suffruticosa* Rehd. var. *amamiensis* Furusawa.[2]

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[1] G. O. Iketubosin, D. W. Mathieson : J. Pharm. and Pharmacol., 15, 810 (1963).

[2] S. Saito, T. Tanaka, T. Iwamoto, C. Matsumura, N. Sugimoto, Z. Horii, M. Makita, M. Ikeda, Y. Tamura : Yakugaku Zasshi, 84, 1126 (1964).