Studies on Herbicides and Plant Growth Regulators

Part III. Synthesis and Structures of N-Aryloxyacylazoles*

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With the aim of obtaining plant growth regulators, we have synthesized 1-aryloxyacylbenzimidazoles, 1-aryloxyacylindazoles, 2-aryloxyacyl-4,5,6,7-tetrahydroindazoles and 1-aryloxyacylbenzotriazoles by the acylation of azoles, and 1-aryloxyacyl-4,5,6,7-tetrahydroindazoles by the reaction of aryloxyacylhydrazines with 2-(hydroxymethylene)cyclohexanone. The structures of these compounds are discussed on the basis of nuclear magnetic resonance data.

In the preceding paper,¹⁾ we have described the synthesis, structural evidence and some reactions of N-aryloxyacylpyrazoles. The infrared absorption spectra of these compounds exhibited the carbonyl bands at the region of higher frequencies ($1730\sim 1780\text{ cm}^{-1}$) as expected, and their high chemical reactivities were observed.

It has been known²⁾ that N-acetyl-benzimidazole and -benzotriazole exhibit the carbonyl bands at higher frequencies ($1729, 1735\text{ cm}^{-1}$ respectively) and bear high chemical reactivities. Our assumption, therefore, was that N-aryloxyacyl derivatives of these azoles should be highly reactive, and might be qualified as a novel type of plant growth regulator different from the substituted aryloxyacyl amines.

The present paper deals with the synthesis, structure and some reactions of N-aryloxyacyl derivatives of benzimidazole, benzotriazole and structurally related azoles, i.e. indazole and 4,5,6,7-tetrahydroindazole.

Synthesis of N-Aryloxyacylazoles

1-Aryloxyacylbenzimidazoles, 1-aryloxyacylindazoles, 2-aryloxyacyl-4,5,6,7-tetrahydroindazoles and 1-aryloxyacylbenzotriazoles were prepared by the reaction of aryloxyacyl chlorides with the azoles at $5\sim 10^\circ\text{C}$ in pyridine (Method A). Some 1-aryloxyacyl-4,5,6,7-tetrahydroindazoles were obtained by the reaction of aryloxyacylhydrazines with 2-(hydroxymethylene)cyclohexanone (Method B). The melting points, yields and elemental analyses of the compounds obtained are summarized in Table I.

Structure

The acylation of indazole should, theoretically, lead to two isomers, namely I and II. Auwers et al.³⁾ have recorded that the acylation of indazole at lower temperatures ($-15\sim 0^\circ\text{C}$) led to 2-acylindazoles (II) in many cases, while at higher temperatures gave rise to 1-acylindazoles (I).

We carried out the acylation of indazole at higher temperature ($5\sim 10^\circ\text{C}$) to obtain the corresponding 1-aryloxyacylindazoles. It was assumed that, in the NMR spectrum of 1-aryloxyacylindazoles, the 3-proton signal would

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1) Part I. M. Ochiai, *Chem. Pharm. Bull.*, **12**, 1101 (1964). Part II. M. Ochiai and T. Kamikado, *Chem. Pharm. Bull.*, **14**, 628 (1966).

2) H. A. Staab, *Angew. Chem.*, **74**, 704 (1962).

3) a) K. v. Auwers, *Ber.*, **58**, 2081 (1925); b) K. v. Auwers und W. Demuth, *Ann*, **451**, 282 (1926).

TABLE I. N-ARYLOXYACYLAZOLES

Appearance	M.p.* °C	Yield (%)	Formula	Calcd.			Found		
					C	H	N	C	H	N
4-Cl	141~143	68	C ₁₅ H ₁₁ ClN ₂ O ₂	62.81	3.87	9.77	62.44	3.78	9.55
	2,4-Cl ₂	148	19	C ₁₅ H ₁₀ Cl ₂ N ₂ O ₂	56.08	3.14	8.73	56.06	3.14	8.46
	2-CH ₃ -4-Cl	154	15	C ₁₆ H ₁₃ ClN ₂ O ₂	64.94	4.36	9.32	64.67	4.39	9.35
	2,4,5-Cl ₃	186~187	14	C ₁₅ H ₉ Cl ₃ N ₂ O ₂	50.67	2.56	7.88	50.47	2.46	7.92
	2,6-Cl ₂	168~170	67	C ₁₅ H ₁₀ Cl ₂ N ₂ O ₂	56.08	3.14	8.73	56.45	3.14	8.44
	2,5-Cl ₂	131~132	16	"	"	"	"	56.31	3.34	8.54
	2-NO ₂	118	5	C ₁₅ H ₁₁ N ₃ O ₄	60.40	3.73	14.14	60.57	3.83	13.84
	4-NO ₂	182	23	"	"	"	"	60.25	3.47	13.93
	4-Cl	129~131	53	C ₁₅ H ₁₁ ClN ₂ O ₂	62.81	3.87	9.77	62.46	3.89	9.63
	2,4-Cl ₂	135	45	C ₁₅ H ₁₀ Cl ₂ N ₂ O ₂	56.08	3.14	8.73	56.16	3.27	8.75
2,4,5-Cl ₃	210~212	63	C ₁₅ H ₉ Cl ₃ N ₂ O ₂	50.67	2.56	7.88	50.93	2.52	8.10
	2,4-Cl ₂	81~82	37	C ₁₆ H ₁₂ Cl ₂ N ₂ O ₂	57.33	3.61	8.36	57.47	3.47	8.10
	4-Cl	100~102	72	C ₁₅ H ₁₅ ClN ₂ O ₂	61.95	5.20	9.62	61.88	5.32	9.70
	2,4-Cl ₂	111~112	9	C ₁₅ H ₁₄ Cl ₂ N ₂ O ₂	55.40	4.34	8.62	55.67	4.36	8.76
4-Cl	120	53	C ₁₅ H ₁₅ ClN ₂ O ₂	61.95	5.20	9.62	62.12	5.28	9.63
	2,4-Cl ₂	96~97	50	C ₁₅ H ₁₄ Cl ₂ N ₂ O ₂	55.40	4.34	8.62	55.48	4.38	8.96
	2-Cl	162~164	73	C ₁₄ H ₁₀ ClN ₃ O ₂	58.44	3.50	14.60	58.38	3.62	14.27
	4-Cl	123~124	54	"	"	"	"	58.50	3.62	14.49
	3-Cl	105~106	54	"	"	"	"	58.43	3.34	14.69
	2,4-Cl ₂	170~171	44	C ₁₄ H ₉ Cl ₂ N ₃ O ₂	52.20	2.82	13.05	51.93	2.83	12.93
	2-CH ₃ -4-Cl	141~142	41	C ₁₅ H ₁₂ ClN ₃ O ₂	59.79	4.02	13.93	59.54	3.86	13.80
	2,4,5-Cl ₃	165	47	C ₁₄ H ₈ Cl ₃ N ₃ O ₂	47.15	2.25	11.78	47.17	2.16	11.66
	2,5-Cl ₂	188~190	70	C ₁₄ H ₉ Cl ₂ N ₃ O ₂	52.20	2.82	13.05	52.03	2.75	12.87
	2-NO ₂	162~164	67	C ₁₄ H ₁₀ N ₄ O ₄	56.37	3.38	18.79	56.29	3.30	18.75
4-NO ₂	189~190	65	"	"	"	"	56.52	3.48	18.34
	2,4-Cl ₂	98~99	45	C ₁₄ H ₁₁ Cl ₂ N ₃ O ₂	53.60	3.30	12.51	53.31	3.14	12.50

• All melting points are uncorrected.

TABLE II. NUCLEAR MAGNETIC RESONANCE SPECTRA OF SOME N-ACYLINDAZOLES

No.		Chemical shift (τ) of 3-H	$\tau-1.95$
	R =			I	II
III	H	1.95			
IV	1-COCH ₃	1.87	-0.08		
V	2-COCH ₃	1.24	-0.63		
VI	2-COCH ₂ O-C ₆ H ₄ -Cl	1.80	-0.15		
VII	2-COCH ₂ O-C ₆ H ₃ (Cl) ₂	1.81	-0.14		
VIII	2-COCH ₂ O-C ₆ H ₃ (Cl) ₂	1.76	-0.19		

appear at higher fields than that of 2-aryloxyacylindazoles being due to less electron withdrawing and anisotropic effects of the carbonyl group. Indeed, this was confirmed with model compounds, 1- and 2-acetylindazoles (IV, V),^{3b, 4)} as shown in Table II. Furthermore, our assumption was consistent with the earlier observation⁵⁾ that the N-acylation of

TABLE III. CHEMICAL SHIFT (τ) OF 3-PROTON OF SOME N-ACYL-4,5,6,7-TETRAHYDROINDAZOLES

Product by the method A			Product by the method B		
	No.	3-H	$\tau-2.91^*$	No.	3-H	$\tau-2.91^*$
R = C ₆ H ₅	IX	1.91	-1.00	IX'	2.53	-0.38
X	1.88	-1.03	X'	2.67	-0.28
CH ₃	XI ⁷⁾	2.07	-0.84	XI'	2.59	-0.32
CH ₂ O-C ₆ H ₄ -Cl	XII	2.07	-0.84	XII'	2.55	-0.36
CH ₂ O-C ₆ H ₃ (Cl) ₂	XIII	2.00	-0.91	XIII'	2.53	-0.38

* $2.91 = \tau$ of 3-proton of 4,5,6,7-tetrahydroindazole.

4) K. v. Auwers und H. G. Allardt, *Ann.*, **438**, 1 (1924).

5) G. S. Reddy, L. Mandell and H. H. Geldstein, *J. Chem. Soc.*, **1963**, 1414.

the benzimidazoles and purines caused fairly large down-field shift of the proton adjacent to the carbonyl group.

Since the chemical shifts of the 3-proton of the N-aryloxyacylindazoles obtained appeared near 1.87τ rather than 1.24τ , the compounds were assigned 1-aryloxyacylindazoles (VI~VIII).

N-Acyl-4,5,6,7-tetrahydroindazoles obtained by both methods (A and B) were isomeric. Auwers⁶⁾ assigned the 1-acyl structure to the products (IX, X) obtained by the method A. Similarly, the compounds (IX', X') obtained by the method B were assigned the 2-acyl structure without sufficient evidence for the assignments. The NMR spectra of N-aryloxy-

FIG. 1. NMR Spectra of Benzotriazole Derivatives, at 60 Mc. in Dioxane Containing Tetramethylsilane as an Internal Reference.

* Ring protons of the phenoxy part.

acyl-4,5,6,7-tetrahydroindazoles (XII, XIII, XII', XIII') obtained by our hands and of N-acyl compounds (IX~XI, IX'~XI') prepared according to the procedure of Auwers⁶⁾ are listed in Table III.

The larger down-field shift of the 3-proton signal was observed with the products obtained by the method A, thus indicating that these compounds have to be assigned the 2-acyl-4,5,6,7-tetrahydroindazoles. The structural assignments made by Auwers et al., therefore, have to be reinvestigated.

Acylation of benzotriazole should give an unsymmetric compound (XIV) and a symmetric one (XV). In the symmetric model compounds, the aromatic protons exhibited the pattern of A₂B₂ system in the NMR spectrum (Fig. 1, A, B), while in the unsymmetric compounds this pattern disappeared (Fig. 1, C, D).

Since the NMR spectra of N-aryloxyacylbenzotriazoles synthesized showed no A₂B₂ pattern, these compounds should be assigned 1-aryloxyacylbenzotriazoles (XIV).

Reactions of N-Aryloxyacylazoles

As was expected, N-aryloxyacylazoles obtained revealed the carbonyl bands at high frequencies in the IR spectra (Table IV). This suggests that these N-aryloxyacylazoles as has been known with N-aryloxyacylpyrazoles¹⁾ and other azolides²⁾ would be highly

TABLE IV. INFRARED DATA OF N-ARYLOXYACYLAZOLES AND YIELD OF 4-CHLOROPHENOXY-ACETANILIDE (XVI)

Structure	C=O (cm ⁻¹) in nujol	Yield of XVI (%)
	1755	98
	1745	87
	1735	89
	1742	93

Ar:

reactive for nucleophilic attack. This was substantiated by the fact that these compounds readily gave the anilide (XVI) upon treatment with aniline in benzene solution at 50°C for two hours. The results are summarized in Table IV.

As has already been known⁶⁾ with 1-benzoyl-4,5,6,7-tetrahydroindazole (IX'), 1-aryloxyacyl-4,5,6,7-tetrahydroindazoles (XII', XIII') isomerized on heating at 125°C to 2-aryloxyacyl compounds (XII, XIII).

EXPERIMENTAL

All melting points are uncorrected. Infrared absorption spectra were recorded with a Hitachi EPI-S2 infrared spectrometer and nuclear magnetic resonance

6) K. v. Auwers, *Ann.*, **453**, 211 (1927).

7) K. v. Auwers, W. Bushmann und R. Heidenreich, *ibid.*, **435**, 277 (1924).

8) F. Krollpfeiffer, H. Pötz und A. Rosenberg, *Ber.*, **71**, 596 (1938).

9) *Org. Syntheses*, **39**, 27 (1959).

spectra were measured in dioxane containing tetramethylsilane as an internal reference at 60 Mc. with a Varian A-60 spectrometer. For the preparation of compounds, typical runs are described.

1-(4-Chlorophenoxyacetyl)benzotriazole (Method A).

To a solution of 3.3 g of benzotriazole in 20 ml of pyridine was added dropwise with stirring a solution of 5 g of 4-chlorophenoxyacetyl chloride in 5 ml of acetone at 5~10°C over a period of 15 min. After being stirred at room temperature for 1 hr., the reaction mixture was poured into 200 ml of water and the separated solid was recrystallized from acetone to give colorless prisms, m.p. 123~4°C; yield, 3.7 g. Analytical data are given in Table I.

1-(4-Chlorophenoxyacetyl)-4,5,6,7-tetrahydroindazole (Method B).

To a solution of 0.6 g of 2-(hydroxymethylene)cyclohexanone⁹⁾ and 1 g of 4-chlorophenoxyacetylhydrazine in 50 ml of ethanol were added 2 drops of 10% hydrochloric acid. After being kept standing overnight at room temperature, the separated crystals were collected by suction and recrystallized from ethanol to give colorless crystals, m.p. 100~102°C; yield, 1 g. Analytical data are given in Table I.

Reaction of N-Aryloxyacylazoles with Aniline.

An equimolar mixture of N-(4-chlorophenoxyacetyl)-azole and aniline in dry benzene was kept standing at 50°C for 2 hrs. Benzene was evaporated under reduced pressure taking care to keep the temperature below 40°C, and the residue was poured into 10% hydrochloric acid. The separated solid was collected

and digested with 5% aqueous sodium hydroxide at 80°C for 5 min. to hydrolyse unreacted N-(4-chlorophenoxyacetyl)azole. After cooling, the separated solid was collected and washed with 10% hydrochloric acid and then with water, and recrystallized from 90% ethanol to give colorless needles, m.p. 125°C. The IR spectrum (in nujol) of this compound was identical with that of 4-chlorophenoxyacetanilide¹⁰⁾ prepared by the reaction of aniline with 4-chlorophenoxyacetyl chloride.

Thermal Isomerization of 1-Aryloxyacyl-4,5,6,7-tetrahydroindazole.

1-Aryloxyacyl-4,5,6,7-tetrahydroindazole obtained by the method B was heated at 125°C for 3 hrs. After cooling, the solidified material was recrystallized from ethanol to give colorless crystals in quantitative yield. Melting point, and NMR and IR spectra of the product confirmed the identity with 2-aryloxyacyl-4,5,6,7-tetrahydroindazole obtained by the method A.

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10) H. M. Hill, G. W. Senter and M. E. Hill, *J. Am. Chem. Soc.*, **72**, 2286 (1950).