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Quinoxalines. XXII.[1] Aryl Migration of 2-Aroylquinoxalines to 2-Arylquinoxalines

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The reaction of 2-aroylquinoxalines (**1**) with sodium hydroxide in dimethyl sulfoxide (DMSO) was found to result in aryl migration, fission of the C^2–C=O bond, and addition of DMSO to the C=O group, giving 2-arylquinoxalines (**2**), quinoxaline (**4**), aroic acids (**5**), and α-aryl-α-(methylsulfinylmethyl)-2-quinoxalinemethanols (**6**). Compounds **6** could be separated into two racemates, (α*R**,S*R**)-**6** and (α*R**,S*S**)-**6**.

In order to establish the generality of the aryl migration, other aroylated aromatic heterocycles were examined. 3-Aroylpyrido[2,3-*b*]pyrazines (**7**) and 1-benzoyl-4-isoquinolinecarbonitrile (**10**) both underwent similar aryl migration to give 3-arylpyridopyrazines (**14**) and 1-phenyl-4-isoquinolinecarbonitrile (**18**), respectively. On the other hand, the reaction of 1-benzoylisoquinoline (**9**) and 2-benzoylquinoline (**11**) resulted not in migration, but in the addition of DMSO to give 1-isoquinolinemethanol (**16**) and 2-quinolinemethanol derivatives (**20**), respectively. In the case of 1-benzoylphthalazine (**8**), migration did not occur, but instead 4-benzoyl-1(2*H*)-phthalazinone (**15**) was formed.

Keywords——2-aroylquinoxaline; 2-arylquinoxaline; 2-quinoxalinemethanol; aryl migration; racemate; 3-arylpyrido[2,3-*b*]pyrazine; 1-isoquinolinemethanol; 2-quinolinemethanol; 1-phenyl-4-isoquinolinecarbonitrile; 4-benzoyl-1(2*H*)-phthalazinone

It was reported that when mixtures of 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (I) and sodium hydroxide in dimethyl sulfoxide (DMSO) are stirred for 1 h at room temperature, migration of the aryl group to the 4-position occurs, *i.e.*, the benzilic acid rearrangement, resulting in the formation of the corresponding 4-aryl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxylic acids (II).[2] It was also reported that in the case of 7-aroyl-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidines (III), the reaction results in aryl migration, followed by oxidative decarboxylation, giving 7-aryl-3-phenyl-3*H*-1,2,3-triazolo[4,5-

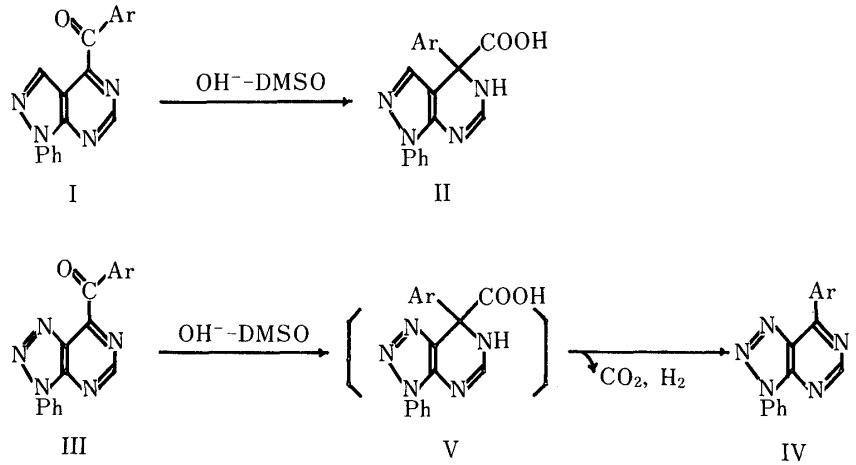
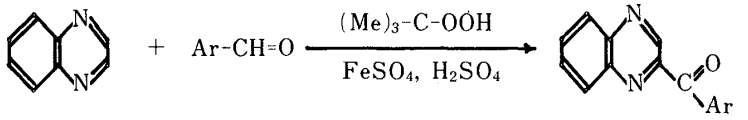


Chart 1

d]pyrimidines (IV) by way of 7-aryl-6,7-dihydro-3-phenyl-3*H*-1,2,3-triazolo[4,5-*d*]pyrimidine-7-carboxylic acids (V).[3]

In the expectation that a similar migration would take place, we examined reaction of 2-aroylquinoxalines (**1**) with sodium hydroxide in DMSO, and found that the reaction proceeded through three paths. The first path is the expected aryl migration, followed by oxidative decarboxylation, giving 2-arylquinoxalines (**2**) by way of 2-aryl-1,2-dihydro-2-quinoxalinecarboxylic acids (D). The second is the fission of the C^2–CO bond to yield quinoxaline (**4**) and aroic acids (**5**). The third path is the nucleophilic addition of DMSO to the carbonyl group of **1** to give α-aryl-α-(methylsulfinylmethyl)-2-quinoxalinemethanols (**6**). In the present paper, we describe our detailed investigation of the aryl migration, the fission, and the nucleophilic addition, as well as the generality of the aryl migration based on the results obtained from application of the aryl migration to other aroylated aromatic heterocycles such as 3-aroylpyrido[2,3-*b*]pyrazines (**7**),[4] 1-benzoylphthalazine (**8**),[5] 1-benzoylisoquinoline (**9**),[6] 1-benzoyl-4-isoquinolinecarbonitrile (**10**),[4] and 2-benzoylquinoline (**11**).[6]

The starting materials (**1**) were prepared according to the method reported by Minisci and Gardini.[7] Thus, when saturated solutions of iron(II) sulfate and *tert*-butyl hydroperoxide were added dropwise simultaneously to a stirred and cooled mixture of an aromatic aldehyde (**12**), **4**, and 4 M sulfuric acid in acetic acid, **1** was obtained in a moderate yield, as shown in Chart 2. The structures of **1c**, **1e**, and **1g** were suggested by the elemental analyses, and confirmed by analyses of the infrared (IR) absorption and proton-nuclear magnetic resonance (^{1}H-NMR) spectra, as described in the experimental section.



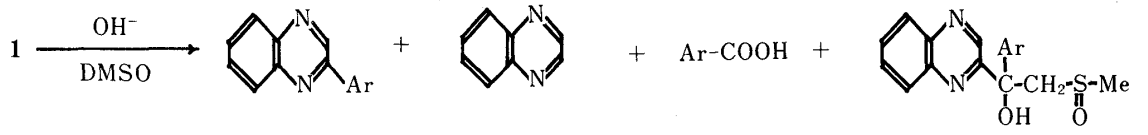
4	12	Ar	1	Yield (%)
	12a	C_6H_5	1a	55
	12b	C_6H_4–Cl (*p*)	1b	45
	12c	C_6H_4–Cl (*o*)	1c	30
	12d	C_6H_4–OMe (*p*)	1d	35
	12e	C_6H_4–OMe (*o*)	1e	17
	12f	C_6H_4–Me (*p*)	1f	24
	12g	C_6H_4–Me (*o*)	1g	23

Chart 2

When a mixture of **1** and sodium hydroxide in DMSO was stirred at 60 °C for 30 min, migration of the aryl group, fission of the C^2–CO bond, and nucleophilic addition of DMSO to the carbonyl group occurred, giving 2-arylquinoxalines (**2**),[8–12] **4**,[13] aroic acids (**5**), and α-aryl-α-(methylsulfinylmethyl)-2-quinoxalinemethanols (**6**). The results are summarized in Chart 3.

It was reported that the mechanism of the formation of IV from III involves a type of benzilic acid rearrangement, followed by oxidative decarboxylation of the initially formed dihydrocarboxylic acid (V), as shown in Chart 1.[3] A similar mechanism may also be applicable to the aryl migration of **1** to **2**, as shown in Chart 4. The influence of the strongly electron-deficient C^2 ring carbon causes fission of the C^2–C^α bond in A, which is generated by the equilibrium between **1** and sodium hydroxide in DMSO, giving **4** and **5**. On the other hand, addition of the carbanion (F), which is generated by removal of hydrogen from DMSO used as the solvent, to the carbonyl group of **1** leads to **6**.

Since **6** has two chiral atoms, the α-carbon atom and the sulfur atom in sulfinyl group, the



	Ar	2	Yield (%)	4	Yield (%)	5	Yield (%)	6	Yield (%)
1a	C_6H_5	**2a**	34	**4**	5	**5a**	3	**6a**	26
1b	C_6H_4–Cl (*p*)	**2b**	67	**4**	6	**5b**	6	**6b**	19
1d	C_6H_4–OMe (*p*)	**2d**	16	**4**	4	**5d**	3	**6d**	74
1e	C_6H_4–OMe (*o*)	**2e**	65	**4**	4	**5e**	4	**6e**	14
1f	C_6H_4–Me (*p*)	**2f**	13	**4**	6	**5f**	6	**6f**	67
1g	C_6H_4–Me (*o*)	**2g**	26	**4**	3	**5g**	6	**6g**	54

Chart 3

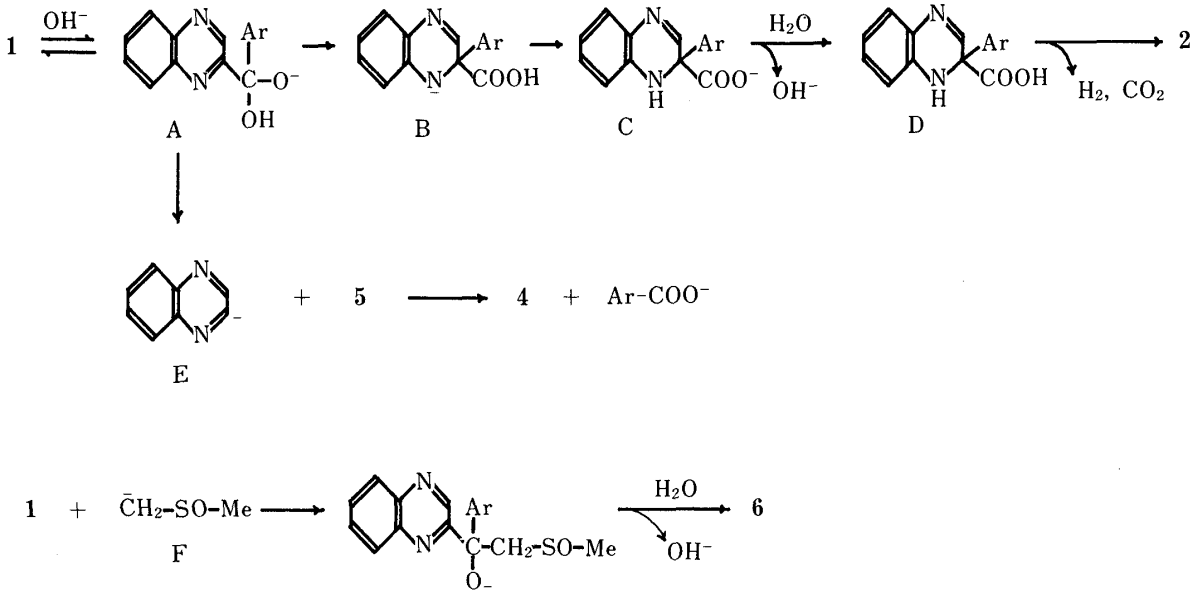


Chart 4

total number of stereoisomers will not exceed 4, *i.e.*, (α*R*,S*R*)-, (α*S*,S*S*)-, (α*R*,S*S*)-, and (α*S*,S*R*)-**6** designated according to the *R*–*S* system. In fact, **6**, which was obtained as a mixture of two racemates in a 1 : 1 ratio, could be separated into two racemates by chromatography on a column of SiO_2 with chloroform as the eluent (Table I). One is an equimolar mixture of (α*R*,S*R*)-**6** and (α*S*,S*S*)-**6**, indicated as (α*R**,S*R**)-**6**. The other is an equimolar mixture of (α*R*,S*S*)-**6** and (α*S*,S*R*)-**6**, indicated as (α*R**,S*S**)-**6**. Of course, neither of the racemates in chloroform solution showed any rotation of planepolarized light. An equimolar mixture of (α*R**,S*R**)-**6b** and (α*R**,S*S**)-**6b** was easily oxidized by potassium permanganate to give a single product α-(*p*-chlorophenyl)-α-(methylsulfonylmethyl)-2-quinoxalinemethanol (**13**) in 58% yield.

In the ^{1}H-NMR spectra of (α*R**,S*R**)-**6** in $CDCl_3$ and DMSO-d_6, the diastereotopic hydrogens of the methylene group constituted an AB system which appeared as a pair of doublets at 3.28—4.33 ppm. On the other hand, the diastereotopic hydrogens of (α*R**,S*S**)-**6** in $CDCl_3$ appeared as a pair of doublets, but in DMSO-d_6 they appeared as a singlet at 4.01—4.08 ppm, as shown in Table II. It is clear that the pair of doublets due to the diastereotopic hydrogens of the two racemates in $CDCl_3$ is the result of a relatively large contribution from internal hydrogen bonding between the hydroxyl group and oxygen of the sulfinyl group in a cyclic form, as shown in Chart 6. Examination of a Dreiding model reveals that the methyl

TABLE I. Yields, Melting Points, and Elemental Analyses of ($\alpha R^*, SR^*$)-**6** and ($\alpha R^*, SS^*$)-**6**

Compound	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
				C	H	N
($\alpha R^*, SR^*$)-**6a**	37	167.5[a,c]	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.97
				(65.36	5.16	9.00)
($\alpha R^*, SS^*$)-**6a**	13	173.5[a,c]	$C_{17}H_{16}N_2O_2S$	65.36	5.16	8.97
				(65.59	5.16	8.89)
($\alpha R^*, SR^*$)-**6b**	33	160—162[a,c]	$C_{17}H_{15}ClN_2O_2S$	58.87	4.36	8.08
				(59.14	4.39	7.95)
($\alpha R^*, SS^*$)-**6b**	11	179—180[a,c]	$C_{17}H_{15}ClN_2O_2S$	58.87	4.36	8.08
				(58.65	4.33	7.93)
($\alpha R^*, SR^*$)-**6d**	31	181[b,c]	$C_{18}H_{18}N_2O_3S$	63.14	5.30	8.18
				(63.28	5.39	8.03)
($\alpha R^*, SS^*$)-**6d**	7	174—175[b,c]	$C_{18}H_{18}N_2O_3S$	63.14	5.30	8.18
				(63.19	5.35	8.10)
($\alpha R^*, SR^*$)-**6e**	18	162[b,c]	$C_{18}H_{18}N_2O_3S$	63.14	5.30	8.18
				(63.03	5.19	8.06)
($\alpha R^*, SS^*$)-**6e**	12	165[b,c]	$C_{18}H_{18}N_2O_3S$	63.14	5.30	8.18
				(63.46	5.29	8.10)
($\alpha R^*, SR^*$)-**6f**	17	167[a,c]	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58
				(66.61	5.53	8.59)
($\alpha R^*, SS^*$)-**6f**	11	178[b,c]	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58
				(66.47	5.52	8.49)
($\alpha R^*, SR^*$)-**6g**	15	144[a,c]	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58
				(66.12	5.42	8.54)
($\alpha R^*, SS^*$)-**6g**	10	176[a,c]	$C_{18}H_{18}N_2O_2S$	66.23	5.56	8.58
				(66.08	5.55	8.30)

a) Colorless needles. *b*) Colorless particles. *c*) Recrystn. from benzene–petr. ether.

group of (αR^*,SS^*)-**6** practically touches C^3-H of the quinoxaline ring, but the methyl group of (αR^*,SR^*)-**6** does not. This means that the internal hydrogen bonding of (αR^*,SR^*)-**6** is more stable than that of (αR^*,SS^*)-**6**. Thus, even when (αR^*,SR^*)-**6** was dissolved in DMSO-d_6, having a high dielectric constant, (αR^*,SR^*)-**6** existed predominantly in the cyclic form, showing a pair of doublets due to the diastereotopic hydrogens. On the other hand, (αR^*,SS^*)-**6** in DMSO-d_6 existed predominantly in the open form, in which the diastereotopic hydrogens coincidentally appear as a singlet.

In order to establish the generality of the aryl migration, other aroylated aromatic heterocycles were examined.

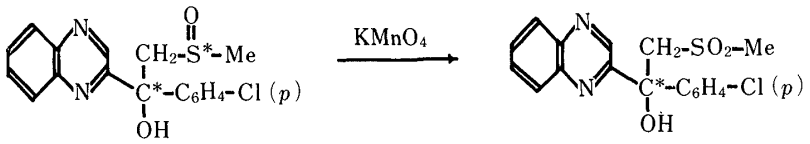
In the preceding paper,[3] we reported that when the reaction mixture obtained after stirring III with sodium hydroxide in DMSO was directly subjected to potassium ferricyanide oxidation, III was easily converted into the corresponding IV in good yield, and the yield obtained in the one-step preparation method mentioned above reflected the yield of the carboxylic acid (V) which was the formal product of the aryl migration. Application of the one-step preparation method to 3-aroylpyrido[2,3-*b*]pyrazines (**7**)[4] yielded the corresponding 3-arylpyrido[2,3-*b*]pyrazines (**14**), as shown in Chart 7. The structures of **14c** and **14d** were suggested by the elemental analyses and confirmed by analyses of the IR and ^{1}H-NMR spectral data, as described in the experimental section.

In the case of 1-benzoylphthalazine (**8**),[5] aryl migration did not occur, but instead 4-benzoyl-1(2*H*)-phthalazinone (**15**) was formed in 23% yield. Compound **15** showed an amino

TABLE II. IR and ^{1}H-NMR Spectral Data for ($\alpha R^*, SR^*$)-**6** and ($\alpha R^*, SS^*$)-**6**

Compound	IR ν_{max}^{KBr} cm^{-1}		^{1}H-NMR (ppm)							
	OH	SO		C^3-H (s)	Aromatic H (m)	OH (s)[c]	CH_2 (dd) H_a	CH_2 (dd) H_b	CH_2 (dd) J	CH_3 (s)
($\alpha R^*, SR^*$)-**6a**	3160	1040	*a)*	9.09	7.16—8.13 (9H)	6.50	4.28	3.33	13	2.69
			b)	9.00	7.17—8.13 (9H)	6.85	4.33	3.64	13	2.75
($\alpha R^*, SR^*$)-**6b**	3160	1000	*a)*	9.08	7.14—8.14 (8H)	6.52	4.26	3.28	13	2.70
			b)	8.98	7.20—8.15 (8H)	7.05	4.27	3.68	13	2.72
($\alpha R^*, SR^*$)-**6d**	3100	1000	*a)*	9.09	6.71—8.13 (8H)	6.35	4.21	3.73	13	2.72, 3.73
			b)	8.98	6.75—8.19 (8H)	6.90	4.28	3.65	13	2.72, 3.69
($\alpha R^*, SR^*$)-**6e**	3150	1020	*a)*	8.75	6.71—8.14 (8H)	5.91	4.15 (2H, s)			2.72, 3.48
			b)	8.56	6.80—8.14 (8H)	6.91	4.09 (2H, s)			2.43, 3.32
($\alpha R^*, SR^*$)-**6f**	3160	1010	*a)*	9.16	7.00—8.12 (8H)	6.38	4.26	3.34	12	2.71, 2.28
			b)	8.90	6.95—8.10 (8H)	6.75	4.25	3.58	12	2.70, 2.22
($\alpha R^*, SR^*$)-**6g**	3120	980	*a)*	8.74	7.08—8.12 (8H)	6.44	4.14	3.48	12	2.71, 2.02
			b)	8.62	7.05—8.13 (8H)	6.80	4.28	3.68	12	2.71, 1.93
($\alpha R^*, SS^*$)-**6a**	3400	1030	*a)*	9.01	7.20—8.11 (9H)	6.18	4.25	3.71	14	2.68
			b)	9.07	7.19—8.06 (9H)	6.78	4.06 (2H, s)			2.61
($\alpha R^*, SS^*$)-**6b**	3120	1030	*a)*	8.94	7.13—8.04 (8H)	6.19	4.20	3.64	14	2.67
			b)	9.06	7.39—8.03 (8H)	6.96	4.04 (2H, s)			2.66
($\alpha R^*, SS^*$)-**6d**	3120	1020	*a)*	9.01	6.75—8.10 (8H)	6.09	4.23	3.67	14	2.70, 3.74
			b)	8.99	6.90—8.13 (8H)	6.76	4.01 (2H, s)			2.61, 3.69
($\alpha R^*, SS^*$)-**6e**	3080	1020	*a)*	8.88	6.90—8.17 (8H)	6.25	4.31	3.66	12	2.76, 3.59
			b)	8.55	6.80—8.15 (8H)	6.91	4.08 (2H, s)			2.42, 3.31
($\alpha R^*, SS^*$)-**6f**	3140	1030	*a)*	8.94	7.00—8.05 (8H)	6.02	4.20	3.65	12	2.69, 2.29
			b)	9.02	7.01—8.18 (8H)	6.78	4.01 (2H, s)			2.60, 2.26
($\alpha R^*, SS^*$)-**6g**	3080	1040	*a)*	8.74	7.05—8.15 (8H)	6.05	4.12	3.83	12	2.65, 1.92
			b)	8.82	7.10—8.14 (8H)	6.76	4.03 (2H, s)			2.55, 2.00

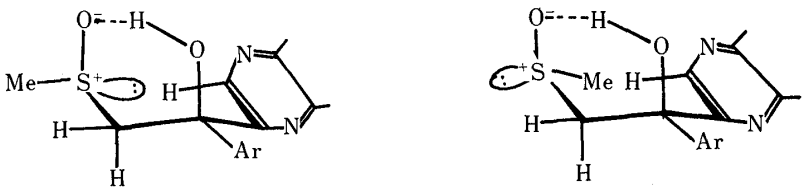
a) ^{1}H-NMR in $CDCl_3$. *b)* ^{1}H-NMR in DMSO-d_6. *c)* Exchangeable with D_2O.



an equimolar mixture of ($\alpha R^*, SR^*$)-**6b** and ($\alpha R^*, SS^*$)-**6b**

13 58%

Chart 5



($\alpha R^*, SR^*$)-**6** ($\alpha R^*, SS^*$)-**6**

Chart 6

absorption peak (3160 cm^{-1}, a broad peak) and a carbonyl absorption peak (1690 cm^{-1}) in the IR spectrum.

In the isoquinoline area, the reaction of 1-benzoylisoquinoline (**9**) resulted in the

formation of α-(methylsulfinylmethyl)-α-phenyl-1-isoquinolinemethanol (**16**), which was easily oxidized to α-(methylsulfonylmethyl)-α-phenyl-1-isoquinolinemethanol (**17**) by potassium permanganate. Compound **16**, which was a mixture of two racemates in a 1 : 1 ratio, could be separated into two racemates, having melting points of 249—250 °C[14] and 175 °C, respectively, by chromatography on a column of SiO_2 with chloroform as the eluent. Both racemates in $CDCl_3$ and in DMSO-d_6 showed a pair of doublets at 3.21—4.16 ppm due to the diastereotopic hydrogens of the methylene group in the ^{1}H-NMR spectra, but the precise structures, (α*R**,S*R**)-**16** and (α*R**,S*S**)-**16**, have not been assigned yet.

The reaction of 1-benzoyl-4-isoquinolinecarbonitrile (**10**)[4] resulted in phenyl migration to give 1-phenyl-4-isoquinolinecarbonitrile (**18**)[15] together with 1-benzoyl-4-isoquinolinecarboxamide (**19**) which was formed by hydrolysis of **10**. In the previous paper,[2] we reported that the aryl migration of 4-aroyl-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidines (I) to 4-aryl-4,5-dihydro-1-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidine-4-carboxylic acids (II) requires a suitable electron-deficiency of the C^4-ring atom which is the migration terminus in a 1,2-shift of the aryl group. The effect of the cyano group as well as the N^2-ring atom presumably enhances the electron-deficiency of the C^1-ring atom of **10** rather than **9**. This effect causes **10** to undergo the aryl migration.

In the case of 2-benzoylquinoline (**11**),[6] the reaction resulted in the addition of DMSO to the carbonyl group to give α-(methylsulfinylmethyl)-α-phenyl-2-quinolinemethanol (**20**),[14] which is similar to the product (**16**) formed in the reaction of **9**. Compound **20**, which was easily convertible to α-(methylsulfonylmethyl)-α-phenyl-2-quinolinemethanol (**21**) by potassium permanganate oxidation, was a mixture of two racemates, (α*R**,S*R**)-**20** and

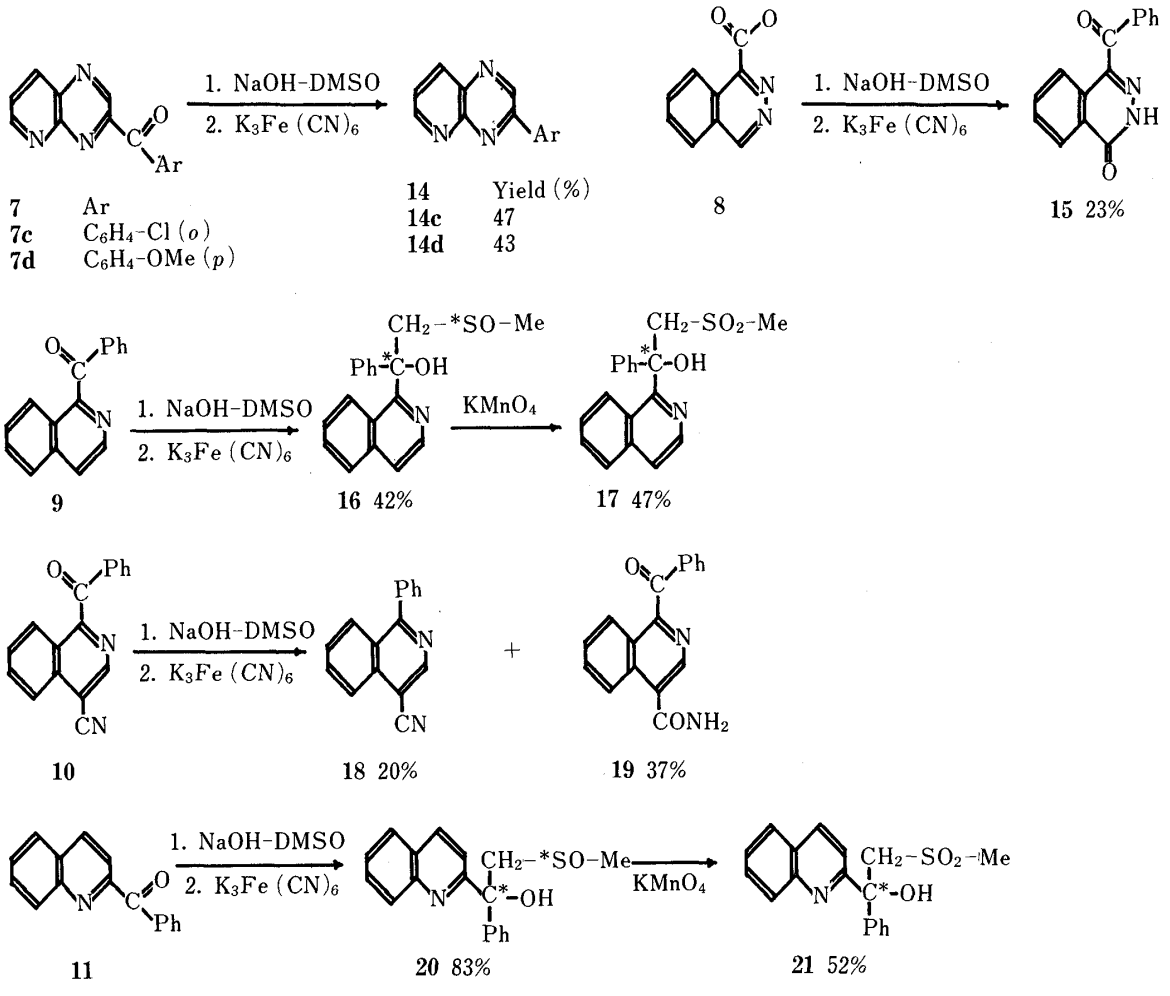


Chart 7

(αR*,SS*)-**20**, in a 1 : 1 ratio as estimated from the integration curve of the two pairs of doublets due to the diastereotopic methylene hydrogens in the ^{1}H-NMR spectra, but **20** has not yet been separated into the two racemates.

Experimental

All melting points are uncorrected. IR spectra were recorded on a Jasco IRA-1 grating IR spectrometer. ^{1}H-NMR spectra were measured at 60 MHz on a Hitachi R-24 high-resolution NMR spectrometer. Chemical shifts are quoted in parts per million (ppm) with tetramethylsilane as an internal standard. The following abbreviations are used: s = singlet, d = doublet, m = multiplet, and br s = broad singlet. Mass spectra (MS) were recorded on a Hitachi RMS-4 MS spectrometer.

Preparation of 2-Aroylquinoxalines (1a—g)——Compounds **1a—g** were prepared according to the method reported by Minisci and Gardini.[7] Thus, saturated solutions of iron(II) sulfate (0.06 mol) and *tert*-butyl hydroperoxide (0.06 mol) were added dropwise simultaneously to a stirred and cooled (5—15 °C) solution of an aldehyde (**12**, 0.06 mol), quinoxaline (**4**, 0.02 mol), and 4 M H_2SO_4 (0.02 mol) in AcOH (30 ml). The mixture was then stirred for a further 10 min, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with benzene as the eluent. The first fraction gave **1**. The yields of **1a—g** are shown in Chart 2.

2-(*o*-Chlorobenzoyl)quinoxaline (**1c**): mp 124—125 °C, pale yellow leaflets recrystallized from benzene–petr. ether. *Anal.* Calcd for $C_{15}H_9ClN_2O$: C, 67.05; H, 3.38; N, 10.42. Found: C, 67.33; H, 3.43; N, 10.23. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). ^{1}H-NMR (in $CDCl_3$): 9.49 (1H, s, C^3-H), 7.22—8.24 (8H, m, aromatic H).

2-(*o*-Anisoyl)quinoxaline (**1e**): mp 130—131 °C, yellow plates recrystallized from benzene–petr. ether. *Anal.* Calcd for $C_{16}H_{12}N_2O_2$: C, 72.71; H, 4.58; N, 10.60. Found: C, 72.70; H, 4.57; N, 10.51. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). ^{1}H-NMR (in $CDCl_3$): 9.27 (1H, s, C^3-H), 6.87—8.20 (8H, m, aromatic H), 3.53 (3H, s, OCH_3).

2-(*o*-Toluoyl)quinoxaline (**1g**): mp 93—94 °C, pale yellow needles recrystallized from benzene–petr. ether. *Anal.* Calcd for $C_{16}H_{12}N_2O$: C, 77.40; H, 4.87; N, 11.28. Found: C, 77.69; H, 4.93; N, 11.21. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). ^{1}H-NMR (in $CDCl_3$): 9.44 (1H, s, C^3-H), 7.07—8.21 (8H, m, aromatic H), 2.47 (3H, s, Ar-CH_3).

Reaction of 1 with Sodium Hydroxide in DMSO——A mixture of **1** (4 mmol) and 50% NaOH (4 ml) in DMSO (10 ml) was stirred for 30 min at 60 °C, then poured onto an excess of ice, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and chromatographed on a column of Al_2O_3 with benzene as the eluent. The first, second, and third fractions gave 2-arylquinoxalines (**2**), quinoxaline (**4**), and α-aryl-α-(methylsulfinylmethyl)-2-quinoxalinemethanols (**6**), respectively. Compounds (**6**) were again chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave (αR*,SR*)-**6**, and the second fraction gave (αR*,SS*)-**6**.

The aqueous layer was neutralized with AcOH, and extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave aroic acids (**5**).

The yields of **2**, **4**, **5**, and **6** are shown in Chart 3. The elemental analysis data, yields and melting points of (αR*,SR*)-**6** and (αR*,SS*)-**6** are included in Table I, and the spectral data in Table II.

2-Phenylquinoxaline (**2a**, mp 78 °C[8]), 2-(*p*-chlorophenyl)quinoxaline (**2b**, mp 137 °C[9]), 2-(*p*-methoxyphenyl)quinoxaline (**2d**, mp 99 °C[10]), 2-(*o*-methoxyphenyl)quinoxaline (**2e**, mp 112 °C[11]), 2-(*p*-tolyl)quinoxaline (**2f**, mp 94 °C[12]), **4** (mp 29—30 °C[13]), benzoic acid (**5a**, mp 122 °C), *p*-chlorobenzoic acid (**5b**, mp 243 °C), *p*-anisic acid (**5d**, mp 184 °C), *o*-anisic acid (**5e**, mp 101 °C), *p*-toluic acid (**5f**, mp 180 °C), and *o*-toluic acid (**5g**, mp 107—108 °C) showed undepressed melting points on admixture with the corresponding authentic samples.

α-(*p*-Chlorophenyl)-α-(methylsulfonylmethyl)-2-quinoxalinemethanol (13)——Potassium permanganate (220 mg) was added to a stirred mixture of (αR*,SR*)-**6b** (156 mg, 0.45 mol) and (αR*,SS*)-**6b** (156 mg, 0.45 mol) in 10% AcOH (8 ml), and the whole was stirred for 3 h, then extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and passed through a column of SiO_2 to remove impurities. Compound **13** (58%, 199 mg) was recrystallized from benzene–petr. ether to give orange particles, mp 217 °C. *Anal.* Calcd for $C_{17}H_{15}ClN_2O_3S$: C, 56.27; H, 4.17; N, 7.72. Found: C, 56.51; H, 4.12; N, 7.66. IR ν_{max}^{KBr} cm^{-1}: 3060 (OH), 1290, 1130 (SO_2). ^{1}H-NMR (in DMSO-d_6): 9.15 (1H, s, C^3-H), 7.23—8.15 (8H, m, aromatic H), 7.08 (1H, br s, exchangeable with D_2O, OH), 4.24 (1H, d, C*–C$\begin{smallmatrix}H_a\\H_b\end{smallmatrix}$, J = 14 Hz), 4.64 (1H, d, C*–C$\begin{smallmatrix}H_a\\H_b\end{smallmatrix}$, J = 14 Hz), 3.03 (3H, s, CH_3).

Reaction of 3-Aroylpyrido[2,3-*b*]pyrazines (7) with NaOH in the Presence of $K_3Fe(CN)_6$——A mixture of **7** (1 mmol) and 50% NaOH (1 ml) in DMSO (8 ml) was stirred for 1 h. A solution of $K_3Fe(CN)_6$ (3.0 g) and 33% KOH (2.0 ml) in H_2O (26 ml) was added to the above reaction mixture, and the whole was vigorously shaken for 30 min, then extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and passed through a column of SiO_2 to remove impurities. Recrystallization from benzene–petr. ether afforded 3-arylpyrido[2,3-*b*]pyrazines (**14**).

From 3-(*o*-chlorobenzoyl)pyrido[2,3-*b*]pyrazine (**7c**), 3-(*o*-chlorophenyl)pyrido[2,3-*b*]pyrazine (**14c**), mp 187 °C, was obtained as yellow needles in 47% yield. *Anal.* Calcd for $C_{13}H_8ClN_3$: C, 64.61; H, 3.34; N, 17.39. Found: C,

64.76; H, 3.31; N, 17.43. ^{1}H-NMR (in $CDCl_3$): 9.30 (1H, s, C^2-H), 9.09 (1H, dd, C^6-H, $J_{6,7}=4$ Hz, $J_{6,8}=2$ Hz), 8.37 (1H, dd, C^8-H, $J_{7,8}=8$ Hz, $J_{6,8}=2$ Hz), 7.63 (1H, dd, C^7-H, $J_{7,8}=8$ Hz, $J_{6,7}=4$ Hz), 7.27—8.18 (4H, m, aromatic H).

From 3-(*p*-anisoyl)pyrido[2,3-*b*]pyrazine (**7d**), 3-(*p*-methoxyphenyl)pyrido[2,3-*b*]pyrazine (**14d**), mp 148 °C, was obtained as yellow needles in 43% yield. *Anal.* Calcd for $C_{14}H_{11}N_3O$: C, 70.87; H, 4.67; N, 17.71. Found: C, 71.27; H, 4.71; N, 17.72. ^{1}H-NMR (in $CDCl_3$): 9.30 (1H, s, C^2-H), 9.07 (1H, dd, C^6-H, $J_{6,7}=4$ Hz, $J_{6,8}=2$ Hz), 8.36 (1H, dd, C^8-H, $J_{7,8}=8$ Hz, $J_{6,8}=2$ Hz), 7.55 (1H, dd, C^7-H, $J_{7,8}=8$ Hz, $J_{6,7}=4$ Hz), 6.91—8.15 (4H, m, aromatic H), 3.86 (3H, s, OCH_3).

Reaction of 1-Benzoylphthalazine (8) with NaOH in the Presence of $K_3Fe(CN)_6$——A mixture of **8** (200 mg) and 50% NaOH (0.9 ml) in DMSO (5 ml) was stirred for 10 min. A solution of $K_3Fe(CN)_6$ (3.4 g) and 33% KOH (2.2 ml) dissolved in H_2O (30 ml) was added to the above reaction mixture, and the whole was vigorously shaken for 30 min, then extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and chromatographed on a column of Al_2O_3 with $CHCl_3$ as the eluent. The first fraction gave unchanged **8** in 60% yield (120 mg), and the second fraction gave 4-benzoyl-1(2*H*)-phthalazinone (**15**, 23%, 40 mg), which was recrystallized from MeOH to give colorless needles, mp 202 °C. *Anal.* Calcd for $C_{15}H_{10}N_2O_2$: C, 71.99; H, 4.03; N, 11.20. Found: C, 72.13; H, 4.05; N, 11.34. IR ν_{max}^{KBr} cm^{-1}: 3160 (NH), 1690 (C=O).

Reaction of 1-Benzoylisoquinoline (9) with NaOH in the Presence of $K_3Fe(CN)_6$——A mixture of **9** (320 mg) and 50% NaOH (1.4 ml) in DMSO (20 ml) was stirred for 16 h. A solution of $K_3Fe(CN)_6$ (4.5 g) and 33% KOH (2.8 ml) dissolved in H_2O (38 ml) was added to the stirred reaction mixture, and the whole was vigorously shaken for 30 min, then extracted with benzene. The extract was dried over Na_2SO_4, and chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave unchanged **9** in 38% yield (120 mg), and the second fraction gave a racemate of α-(methylsulfinylmethyl)-α-phenyl-1-isoquinolinemethanol (**16**), mp 250—251 °C,[14] which was recrystallized from benzene–petr. ether to give colorless needles in 21% yield (90 mg). *Anal.* Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.82; H, 5.62; N, 4.42. IR ν_{max}^{KBr} cm^{-1}: 3200 (OH), 1020 (SO). ^{1}H-NMR (in $CDCl_3$): 7.10—8.43 (11H, m, aromatic H), 6.61 (1H, s, exchangeable with D_2O, OH), 4.16 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=12$ Hz), 3.21 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=12$ Hz), 2.68 (3H, s, CH_3). ^{1}H-NMR (in DMSO-d_6): 7.36—8.56 (11H, m, aromatic H), 7.10 (1H, s, exchangeable with D_2O, OH), 4.29 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=12$ Hz), 3.41 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=12$ Hz), 2.71 (3H, s, CH_3).

The third fraction gave another racemate of **16**, mp 175 °C, which was recrystallized from benzene–petr. ether to give colorless needles in 21% yield (90 mg). *Anal.* Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.52; H, 5.54; N, 4.53. IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1020 (SO). ^{1}H-NMR (in $CDCl_3$): 7.15—8.41 (11H, m, aromatic H), 6.63 (1H, s, exchangeable with D_2O, OH), 4.17 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=13$ Hz), 3.86 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=13$ Hz), 2.63 (3H, s, CH_3). ^{1}H-NMR (in DMSO-d_6): 7.12—8.48 (11H, m, aromatic H), 6.87 (1H, s, exchangeable with D_2O, OH), 4.17 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=13$ Hz), 3.67 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=13$ Hz), 2.50 (3H, s, CH_3).

α-(Methylsulfonylmethyl)-α-phenyl-1-isoquinolinemethanol (17)——Potassium permanganate (140 mg) was added to an equimolar mixture of the two racemates of **16** (180 mg) in 10% AcOH (6 ml), and the mixture was vigorously stirred for 3 h, then extracted with $CHCl_3$. The extract was dried over Na_2SO_4, and passed through a column of SiO_2 to remove impurities. Compound **17** was recrystallized from benzene–petr. ether to give colorless needles, mp 182 °C, in 47% yield (90 mg). *Anal.* Calcd for $C_{18}H_{17}NO_3S$: C, 66.03; H, 5.23; N, 4.28. Found: C, 66.23; H, 5.25; N, 4.23. IR ν_{max}^{KBr} cm^{-1}: 3520 (OH), 1300, 1120 (SO_2). ^{1}H-NMR (in $CDCl_3$): 7.12—8.43 (12H, m, aromatic H and OH), 4.64 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=14$ Hz), 4.05 (1H, d, C*–C$\underset{H_b}{\overset{H_a}{<}}$, $J=14$ Hz), 2.85 (3H, s, CH_3).

Reaction of 1-Benzoyl-4-isoquinolinecarbonitrile (10) with NaOH in the Presence of $K_3Fe(CN)_6$——The procedure for the reaction of **10** (280 mg) with 50% NaOH (1.1 ml) in DMSO (10 ml) in the presence of $K_3Fe(CN)_6$ (3.5 g) was essentially the same as described for the reaction of **7**. The $CHCl_3$ extract was chromatographed on a column of SiO_2 with $CHCl_3$ as the eluent. The first fraction gave 1-phenyl-4-isoquinolinecarbonitrile (**18**), which was recrystallized from benzene–petr. ether to give pale orange needles, mp 142 °C, in 20% yield (50 mg). Compound **18** showed undepressed melting point on admixture with an authentic sample.[15]

The second fraction gave 1-benzoyl-4-isoquinolinecarboxamide (**19**), which was recrystallized from benzene to give colorless needles, mp 207 °C, in 37% yield (110 mg). *Anal.* Calcd for $C_{17}H_{12}N_2O_2$: C, 73.90; H, 4.38; N, 10.14. Found: C, 74.31; H, 4.29; N, 10.09. IR ν_{max}^{KBr} cm^{-1}: 3360, 3180 (NH), 1690, 1650 (C=O). ^{1}H-NMR (in DMSO-d_6): 8.68 (1H, s, C^3-H), 8.10 (2H, br s, exchangeable with D_2O, NH_2), 7.43—8.50 (9H, m, aromatic H).

Reaction of 2-Benzoylquinoline (11) with NaOH in the Presence of $K_3Fe(CN)_6$——The procedure for the reaction of **11** (276 mg) with 50% NaOH (1.2 ml) in DMSO (20 ml) in the presence of $K_3Fe(CN)_6$ (4.1 g) was essentially the same as described for the reaction of **9**. The $CHCl_3$ extract was chromatographed on a column of SiO_2 with $CHCl_3$ as

the eluent. The first fraction gave a mixture of two racemates of α-(methylsulfinylmethyl)-α-phenyl-2-quinolinemethanol (**20**) in a 1 : 1 ratio. This product was recrystallized from benzene–petr. ether to give a colorless powder, mp 140—142 °C, in 83% yield (330 mg). *Anal.* Calcd for $C_{18}H_{17}NO_2S$: C, 69.43; H, 5.50; N, 4.50. Found: C, 69.73; H, 5.55; N, 4.55. IR ν_{max}^{KBr} cm^{-1}: 3160 (OH), 1020 (SO). ^{1}H-NMR (in $CDCl_3$): 7.13—8.10 (22H, m, aromatic H), 6.48 (1H, s, exchangeable with D_2O, OH), 6.39 (1H, s, exchangeable with D_2O, OH), 4.22 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 14 Hz), 4.17 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 13 Hz), 3.81 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 14 Hz), 3.48 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 13 Hz), 2.70 (6H, s, 2 × CH_3). ^{1}H-NMR (in DMSO-d_6): 7.20—8.30 (22H, m, aromatic H), 6.73 (1H, s, exchangeable with D_2O, OH), 6.64 (1H, s, exchangeable with D_2O, OH), 4.34 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 13 Hz), 4.07 (2H, s, CH_2), 3.64 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 13 Hz), 2.72 (3H, s, CH_3), 2.62 (3H, s, CH_3).

α-(Methylsulfonylmethyl)-α-phenyl-2-quinolinemethanol (21)——Potassium permanganate (140 mg) was added to a stirred mixture of **20** (200 mg) and 10% AcOH (6 ml), and the mixture was vigorously stirred for 3 h. Compound **21** (52%, 110 mg), mp 145 °C, was isolated as described for **17**. *Anal.* Calcd for $C_{18}H_{17}NO_3S \cdot 1/6C_6H_6$: C, 67.04; H, 5.33; N, 4.11. Found: C, 67.34; H, 5.39; N, 3.95. MS *m/e*: 327 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3440 (OH), 1130, 1310 (SO_2). ^{1}H-NMR (in $CDCl_3$): 7.10—8.05 (11H, m, aromatic H), 6.16 (1H, s, exchangeable with D_2O, OH), 4.50 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 16 Hz), 4.04 (1H, d, C*–C$\overset{H_a}{\underset{H_b}{<}}$, J = 16 Hz), 2.79 (3H, s, CH_3).

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