

Studies on the Syntheses of Azole Derivatives. Part II (1).
Syntheses of *N*-(1- or 2-Substituted)indazolones *via* Diazotization (2).

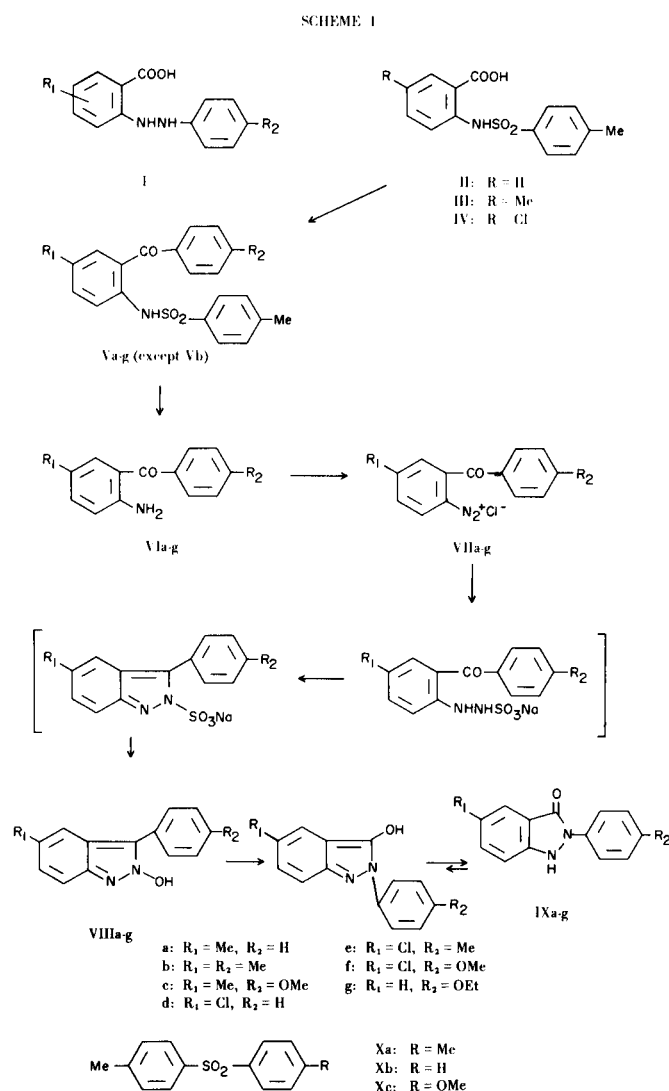
Tetsuji Kametani (3), Kaoru Sota, and Masahisa Shio

Pharmaceutical Institute, Tohoku University and
Research Laboratory, Taisho Pharmaceutical Co., Ltd.

Syntheses of 2,5-disubstituted-indazolones (IXa-g) and 3-hydroxy-1-substituted-1*H*-indazoles (XIVa,b) were achieved by diazotization of 2-benzoylaniline (VIa-g) and *N*-benzoylhydrazine (XIIa-c), respectively.

The previous paper (1) reported the syntheses of indazole derivatives in order to investigate the relationship between the structure and activity of azole derivatives. We now wish to report an extension of the previous work to the syntheses of *N*-arylindazolone derivatives (IX and XIV) possessing an aryl group at the N-1 or N-2 position *via* benzene diazonium chloride (VII and XIII).

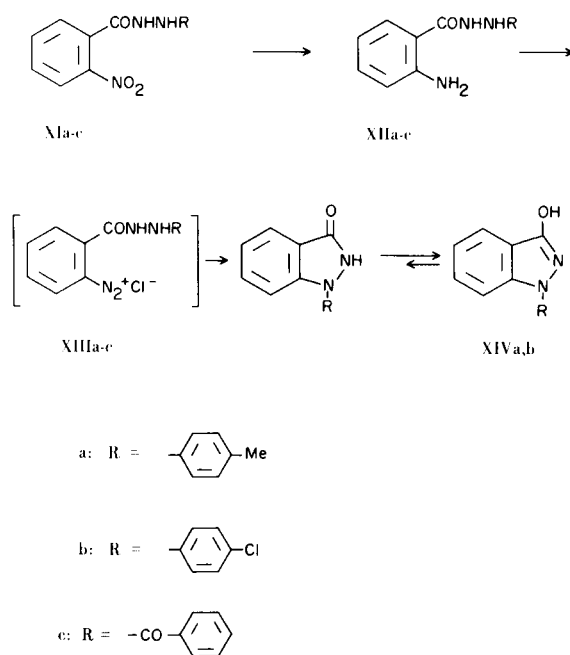
Generally, 2-arylindazolones are synthesized through the cyclization of 2-hydrazinobenzoic acid (I: $R_1 = R_2 = H$) (4). In our case, instead of using the substituted-2-hydrazinobenzoic acid as a starting material, we have investigated the cyclization of 4-substituted-2-benzoyl-*N*-(*p*-toluenesulfonyl)anilide (V) by Auwers' procedure (5). 5-Methyl-2-(*p*-toluenesulfonylamino)benzoic acid (IV) as starting materials were prepared from 5-methylisatin and 5-chloroisatin, respectively, by standard methods. The Friedel-Crafts reaction (6) of the corresponding acid chlorides of the above benzoic acids afforded the benzophenones (Va-g). Treatment of Va-g with sulfuric acid or sulfuric acid-glacial acetic acid gave the corresponding detosylated products (VIa-g), which upon diazotization with sodium nitrite afforded 3-aryl-2-hydroxyindazoles (VIIIa-g). Some of the indazoles (VIIIb,c,e,f,g) were used for the following reaction without purification since they were either extremely unstable or difficult to purify; however compounds VIIIa,d were characterized. The absorption band at *ca.* 3200 cm^{-1} in their ir spectra (nujol) due to the hydroxy group supported the structure of the desired products. The isomerisation of VIIIa-g in hot 2% sodium hydroxide solution afforded the desired corresponding 5-substituted-2-arylindazolone (IXa-g) (5). As shown in Table II, the yields varied by changing the substituents (R_1 and R_2). Thus it is apparent that substituents on the benzene ring could be easily introduced by this method.



The Friedel-Crafts reactions of the above 2-(*p*-toluenesulfonylamino)benzoic acid chlorides, obtained by chlorination of III and IV with phosphorus pentachloride, with two molar equivalents of aluminium chloride in toluene gave 2-aminobenzophenones (VIa,b) as by-products. This phenomenon was not observed in the case of the detosylated free anthranilic acid in the above reaction. Furthermore, the tosylated compounds, using excess aluminium chloride afforded appreciable yields of VIb,e. Treatment of 2-benzoyl-*N*-(*p*-toluenesulfonyl)anilide (V) with aluminium chloride in a variety of solvents, for example, benzene, carbon disulfide, anisole, and so on, afforded the interesting results shown in Table I. The formation of diarylsulfone (X) was observed when solvents such as toluene, benzene, and anisole were used. Although the use of carbon disulfide as solvent did not afford X, detosylation and formation of 4-anisyl-4'-tolylsulfone (Xc) was observed upon addition of anisole to the solvent.

Finally, the synthesis of indazolones possessing an aryl group at the N-1 position from hydrazides (XI) (7) was investigated as shown in Scheme 2.

SCHEME 2



The condensation of 2-nitrobenzoyl chloride with a variety of arylhydrazines, namely, *p*-tolyl-, *p*-chlorophenyl-, benzoyl-, *p*-ethoxyphenyl-, *p*-butoxyphenyl-, and α -naphthylhydrazine (9) resulted in formation of hydrazides XIa,b,c in the three former cases, whereas only tars were formed in the three latter cases. All the attempts to

purify the tars in the latter cases gave no corresponding compound XI. These results can be attributed to the considerable unstability of the latter three hydrazines used. Reduction of XIa,b,c afforded the 2-amino-derivatives (XIIa,b,c), two of which were further converted to the indazoles (XIVa and XIVb) on diazotization by König's method. However, XIIc did not give 1-benzoyl-3-hydroxy-1*H*-indazole (XIV: R = -COC₆H₅), but instead gave 3-benzoylamino-3,4-dihydro-4-oxo-1,2,3-benzotriazine (10) in 45% yield. In addition, from the biological point of view, compounds IX and XIV were examined for their effects on carrageenin-induced edema in rats.

EXPERIMENTAL (11)

2-Benzoyl-4-methyl-*N*-(*p*-toluenesulfonyl)anilide (Va).

To a suspension of 10 g. (0.033 mole) of the carboxylic acid (III) in 130 ml. of dry benzene was added 8 g. (0.033 mole) of phosphorus pentachloride and the mixture was heated under reflux for 20 minutes until evolution of hydrogen chloride gas had ceased. To the above reaction mixture was added 17 g. (0.12 mole) of aluminium chloride and the heating under reflux was continued for 30 minutes. The cooled reaction mixture was poured into 500 ml. of ice water containing 15 ml. of 12 *N* hydrochloric acid to decompose the excess aluminium chloride. After the organic solvent had been distilled off, decantation of water left a yellow syrup, which was basified with dilute aqueous sodium hydroxide solution and extracted with benzene. The extract was washed with water, dried, and evaporated to give a residue, which after recrystallization from ethanol gave 9.5 g. of yellow needles, m.p. 132-133°.

Anal. Calcd. for C₂₁H₁₉NO₃S: C, 69.02; H, 5.24; N, 3.83. Found: C, 69.15; H, 5.22; N, 4.12.

2-(4-Methoxybenzoyl)-4-methyl-*N*-(*p*-toluenesulfonyl)anilide (Vc).

To a suspension of 10 g. (0.033 mole) of carboxylic acid (III) in 200 ml. of carbon disulfide was added 10 g. (0.048 mole) of phosphorus pentachloride. After evolution of hydrogen chloride gas had become mild, the stirred reaction mixture was refluxed for 20 minutes. After cooling to room temperature, 12 g. (0.12 mole) of anisole and 4.4 g. (0.033 mole) of aluminium chloride were added with stirring to the mixture. Stirring was continued for 10 minutes and an additional amount of 4.4 g. (0.033 mole) of aluminium chloride was added. After the evolution of hydrogen chloride gas had again become mild, the reaction mixture was refluxed for 30 minutes. Compound Vc (13.5 g.) was obtained as colorless prisms, m.p. 106-107° (from ethanol), according to the same procedure as for Va.

Anal. Calcd. for C₂₂H₂₁NO₄S: C, 66.81; H, 5.35; N, 3.54. Found: C, 66.59; H, 5.41; N, 3.54.

2-Benzoyl-4-chloro-*N*-(*p*-toluenesulfonyl)anilide (Vd).

The same treatment of the acid chloride, prepared from 10 g. of carboxylic acid (IV) by chlorination with 8 g. of phosphorus pentachloride, with 17 g. of aluminium chloride in 130 ml. of benzene afforded 9.6 g. of Vd as colorless needles, m.p. 118-119° (from ethanol).

Anal. Calcd. for C₂₀H₁₆ClNO₃S: C, 62.23; H, 4.18; N, 3.63. Found: C, 62.13; H, 4.05; N, 3.92.

TABLE I
Friedel-Crafts Reaction of 2-(4-Substituted-benzoyl)-N-(p-toluenesulfonyl)anilide (V)
with Aluminium Chloride

| V | | Solvent | AlCl ₃ (Molar Equivalent) | Reaction | | Yield (%) of Product | |
|----------------|-------------------|--------------------------------|--|---------------------|------------|----------------------|--------------------------|
| R ₁ | R ₂ | | | Temp. (°C) | Time (hr.) | VI | X (R of X) |
| H | CH ₃ | toluene | 2.5 | 45-55 | 1 | 30.8 | 32.9 (CH ₃) |
| H | CH ₃ | toluene | 2.0 | 60-70 | 1 | 39.2 | 41.8 (CH ₃) |
| H | CH ₃ O | toluene | 2.0 | 45-55 | 0.5 | 29.7 | 29.4 (CH ₃) |
| H | CH ₃ | benzene | 2.0 | 50-60 | 3 | --- | --- |
| H | CH ₃ | benzene | 2.0 | boil | 3 | 10.0 | 9.5 (H) |
| H | CH ₃ | benzene | 4.0 | boil | 3 | 15.4 | 14.1 (H) |
| H | CH ₃ | anisole | 4.0 | room temp. 50-60 | 0.5 1 | 23.8 | 25.0 (OCH ₃) |
| H | CH ₃ | anisole | 2.0 | room temp. 50-60 | 1 3 | 21.4 | 21.0 (OCH ₃) |
| H | CH ₃ O | CS ₂ | 2.0 | reflux | 1 | --- | --- |
| H | CH ₃ O | CS ₂ | 2.0 | reflux | 5 | --- | --- |
| H | CH ₃ | CS ₂ anisole (a) | 8.0 | reflux | 36 | 3.5 | 3.4 (OCH ₃) |

(a) Anisole of 1.5 molar equivalents to V was added.

TABLE II
The Characters of 2-Arylindazolone (IXa-g)

| IXa-g | Yield g. (%) | IXa-g M.p. (°C) Appearance | Formula | Analyses | | | IR (Nujol) cm ⁻¹ | |
|-------|-----------------------|---|---|------------------|--------------|----------------|-----------------------------|-------|
| | | | | Calcd. C | (Found) H | N | NH | ν C=O |
| a | 3.5 1.80 (48.6) | 253-255 (EtOH) [lit. (17), 252] colorless needles | C ₁₄ H ₁₂ N ₂ O | 74.99 (74.88) | 5.38 5.05 | 12.49 12.09 | 3150-2700 | 1650 |
| b | 1.8 0.35 (18.4) | 225-226 (EtOH) yellow prisms | C ₁₅ H ₁₄ N ₂ O | 75.60 (75.48) | 5.92 5.89 | 11.76 11.90 | 3150-2700 | 1651 |
| c | 3.0 0.95 (30.0) | 200-202 colorless needles | C ₁₅ H ₁₄ N ₂ O ₂ | 70.85 (70.69) | 5.55 5.53 | 11.02 10.94 | 3150-2700 | 1645 |
| d | 2.5 1.33 (50.3) | 229-231 (AcOH) [lit. (18), 233] colorless needles | C ₁₃ H ₉ ClN ₂ O | 63.81 (64.02) | 3.71 3.68 | 11.45 11.01 | 3100-2700 | 1647 |
| e | 1.8 0.81 (40.7) | 235-236 (EtOH) colorless scales | C ₁₄ H ₁₁ ClN ₂ O | 65.00 (64.92) | 4.28 4.47 | 10.83 10.64 | 3150-2700 | 1645 |
| f | 3.0 1.36 (43.8) | 217-218 (benzene) colorless needles | C ₁₄ H ₁₁ ClN ₂ O ₂ | 61.21 (61.14) | 4.04 4.10 | 10.20 10.00 | 3150-2700 | 1652 |
| g | 2.0 0.23 (10.9) | 167-168 (benzene) colorless needles | C ₁₅ H ₁₄ N ₂ O ₂ | 70.85 (70.98) | 5.55 5.45 | 11.02 10.83 | 3150-2700 | 1645 |

4-Chloro-2-(4-methylbenzoyl)-*N*-(*p*-toluenesulfonyl)anilide (Ve).

The same treatment of 2.5 g. (0.008 mole) of carboxylic acid (IV) with 1.8 g. (0.009 mole) of phosphorus pentachloride, followed by Friedel-Crafts reaction of the acid chloride with 2.1 g. (0.016 mole) of aluminium chloride in 25 ml. of dry toluene afforded 1.6 g. of Ve as colorless needles, m.p. 115-116° (from ethanol).

Anal. Calcd. for $C_{21}H_{18}ClNO_3S$: C, 63.07; H, 4.54; N, 3.50. Found: C, 63.40; H, 4.42; N, 2.51.

Evaporation of the mother liquor of Ve gave 250 mg. of di-*p*-tolylsulfone (Xa) as colorless needles, m.p. 157-158° (from ethanol) [lit. (12), m.p. 156°]. The remaining residue obtained after the removal of Xa was subjected to column chromatography on alumina. The benzene eluate gave 260 mg. of 4-chloro-2-(4-methylbenzoyl)aniline (VIe) as yellow needles, m.p. 109-110° (from ethanol-petroleum ether, 10:1), whose structure was identified by the comparison of spectroscopic data with those of an authentic sample (VIe) and by mixed melting point determination.

4-Chloro-2-(4-methoxybenzoyl)-*N*-(*p*-toluenesulfonyl)anilide (Vf).

According to the same procedure as in the case of Vc, the acid chloride, prepared from 10 g. (0.03 mole) of carboxylic acid (IV) and 10 g. of phosphorus pentachloride, was treated with 12 g. of anisole and 8.8 g. of aluminium chloride in 200 ml. of carbon disulfide to give 10.5 g. of Vf as colorless plates, m.p. 140-141° (from ethanol).

Anal. Calcd. for $C_{21}H_{18}ClNO_4S$: C, 60.65; H, 4.36; N, 3.37. Found: C, 60.69; H, 4.00; N, 3.73.

2-(4-Ethoxybenzoyl)-*N*-(*p*-toluenesulfonyl)anilide (Vg).

The acid chloride, prepared by treatment of 9.2 g. of carboxylic acid (II) with 6 g. of phosphorus pentachloride, was reacted with 10 g. of *p*-phenetole in the presence of 7 g. of aluminium chloride and 200 ml. of carbon disulfide to give 6.3 g. of Vg as colorless needles, m.p. 123-124° (from ethanol).

Anal. Calcd. for $C_{22}H_{21}NO_4S$: C, 66.81; H, 5.35; N, 3.54. Found: C, 67.14; H, 5.40; N, 3.74.

2-Benzoyl-4-methylaniline (VIa).

A solution of 9 g. of the tosyl derivative (Va) in 90 ml. of 98% sulfuric acid was heated on a water-bath for 1 hour, and, after cooling, the mixture was poured into 250 ml. of water. The insoluble substance was filtered off, and the filtrate was basified with 28% ammonia to give 3.5 g. of VIa as yellow needles, m.p. 63-64° (from petroleum ether-ethanol, 10:1).

Anal. Calcd. for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.75; H, 6.28; N, 6.63.

4-Methyl-2-(4-methylbenzoyl)aniline (VIb).

Treatment of 9.1 g. (0.03 mole) of carboxylic acid (III) with 8 g. of phosphorus pentachloride, followed by Friedel-Crafts reaction of the resulting acid chloride with 16 g. (0.02 mole) of aluminium chloride and 100 ml. of dry toluene gave 2.0 g. of VIb as yellow prisms, m.p. 91-92° (from petroleum ether-ethanol, 10:1); ν max (nujol), cm^{-1} 3455, 3377 (NH₂), 1632 (C=O).

Anal. Calcd. for $C_{15}H_{15}NO$: C, 79.97; H, 6.71; N, 6.22. Found: C, 79.49; H, 6.68; N, 6.28.

2-(4-Methoxybenzoyl)-4-methylaniline (VIc).

A mixture of 12 g. of tosyl derivative (Vc), 30 ml. of glacial acetic acid, and 30 ml. of 98% sulfuric acid was heated on a water-bath for 15 hours as described above to afford 5.0 g. of VIc as yellow needles, m.p. 93-94° (from petroleum ether-ethanol, 10:1).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.63; H, 6.28; N, 5.90.

2-Benzoyl-4-chloroaniline (VIId).

The same treatment of 10 g. of Vd with 100 ml. of 98% sulfuric acid as above gave 2.9 g. of VIId as yellow needles, m.p. 96-97° (from petroleum ether-ethanol, 10:1).

Anal. Calcd. for $C_{13}H_{10}ClNO$: C, 67.40; H, 4.35; N, 6.04. Found: C, 67.50; H, 4.36; N, 5.99.

4-Chloro-2-(4-methylbenzoyl)aniline (VIe).

(a) A solution of 1.0 g. of Ve in 12 ml. of 98% sulfuric acid was heated in a water-bath for 1 hour, and after cooling, the mixture was poured into 30 ml. of water. The insoluble substance was filtered off, and the filtrate was basified with 28% ammonia to give 300 mg. of a yellow powder, m.p. 109-110°, whose recrystallization from petroleum ether-ethanol (10:1) afforded VIe as yellow needles, m.p. 109-110°; ν max (nujol), cm^{-1} 3420, 3310 (NH₂), 1620 (C=O).

Anal. Calcd. for $C_{14}H_{12}ClNO$: C, 68.38; H, 4.92; N, 5.70. Found: C, 68.27; H, 5.06; N, 5.57.

(b) Treatment of 5.1 g. (0.06 mole) of carboxylic acid (IV) with 4 g. of phosphorus pentachloride, followed by reaction of the acid chloride with 8.6 g. (0.064 mole) of aluminium chloride, and 50 ml. of dry toluene, and the usual work-up afforded the crude product, whose recrystallization from ethanol gave 1.2 g. of di-*p*-tolylsulfone (Xa). Evaporation of its mother liquor gave 4.1 g. of a reddish brown oil, which was chromatographed on alumina using benzene as an eluant. The first eluate gave 1.1 g. of an oil, whose structure could not be confirmed. Thus 250 mg. of Xa and 1.1 g. of yellow crystals, m.p. 103-105°, were obtained from the second and the third eluate, respectively, the latter of which were recrystallized from ethanol-petroleum ether (10:1) to give yellow needles, m.p. 109-110°, identical with VIc by comparison of its ir spectrum and mixed melting point test.

4-Chloro-2-(4-methoxybenzoyl)aniline (VIff).

The heating of 11 g. of Vf with 30 ml. of glacial acetic acid and 30 ml. of 98% sulfuric acid as described above afforded 3.5 g. of VIff as yellow needles, m.p. 97-98° (from ethanol).

Anal. Calcd. for $C_{14}H_{12}ClNO_2$: C, 64.20; H, 4.62; N, 5.35. Found: C, 64.44; H, 4.99; N, 5.46.

2-(4-Ethoxybenzoyl)aniline (VIg).

The treatment of 9 g. of Vg with 27 ml. of glacial acetic acid and 27 ml. of 98% sulfuric acid afforded 3.0 g. of VIg as yellow needles, m.p. 61-62° (from ethanol).

Anal. Calcd. for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.70. Found: C, 74.88; H, 6.29; N, 6.18.

2,5-Disubstituted-indazolone Derivatives (IX).

To a cooled suspension of 4-substituted-2-(4-substituted-benzoyl)aniline (VIa-g) in seven equivalents of 5 *N* hydrochloric acid was added a solution of two molar equivalents of sodium nitrite at 0-5°. The mixture was stirred for 15 minutes after the addition. To a cooled saturated aqueous solution of 1.5 molar equivalents of sodium sulfite was added dropwise the above upper layer and the stirring was then continued for 45 minutes. The yellow precipitate was collected by filtration. A solution of the above yellow solid in 2% aqueous sodium hydroxide solution was heated for 2.5 hours on a water-bath. The hot solution was filtered through celite to remove an insoluble substance. The filtrate was acidified with hydrochloric acid, and the crude compound (IX) was collected and recrystallized.

Thus 5-methyl-2-phenyl-(IXa), 5-methyl-2-(4-tolyl)-(IXb), 2-(4-anisyl)-5-methyl-(IXc), 5-chloro-2-phenyl-(IXd), 5-chloro-2-(4-tolyl)-(IXe), 2-(4-anisyl)-5-chloro-(IXf) and 2-(4-ethoxyphenyl)indazolone (IXg) were obtained as shown in Table II.

2-Hydroxy-5-methyl-3-phenylindazole (VIIIa).

To a cooled and stirred solution of 3.0 g. of VIa in 13.3 ml. of 2.5 *N* hydrochloric acid was added an aqueous solution (10 ml.) containing 1.5 g. of sodium nitrite at 0.5°. After the addition, the mixture was stirred for 15 minutes. To a cooled saturated aqueous solution of 6 g. of sodium sulfite was added with stirring a clear upper solution of the above mixture. After stirring for 45 minutes, the yellow precipitate was collected and recrystallized from benzene to give 900 mg. of VIIIa as yellow prisms, m.p. 116° dec.; ν max (nujol), cm^{-1} 3200 (OH).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.32; H, 5.13; N, 12.44.

5-Chloro-2-hydroxy-3-phenylindazole (VIIId).

The same treatment as above of VIId with 4 ml. of concentrated hydrochloric acid, 1.5 g. of sodium nitrite, and 7 g. of sodium sulfate, afforded 1.4 g. of VIIIId as yellow prisms, m.p. 108° dec. (from ethanol); ν max (nujol), cm^{-1} 3220 (NH).

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.51; H, 4.03; N, 11.72.

The Reaction of 2-(4-Substituted-benzoyl)-*N*-(*p*-toluenesulfonyl)-anilide (V) with Aluminium Chloride.

(a) A stirred mixture of 1.46 g. of 2-(4-methylbenzoyl)-*N*-(*p*-toluenesulfonyl)anilide (V: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$) and 1.4 g. (2.5 moles) of aluminium chloride in 50 ml. of toluene was warmed at 45-55° in a water-bath for 1 hour and then poured into 50 ml. of ice-water containing 3 ml. of hydrochloric acid. The organic layer was separated, washed with water, dried, and evaporated to give the residue, whose ethanolic solution was set aside. In this case, 860 mg. (60.7%) of V was recovered as crystals. After removal of V, the filtrate was chromatographed on alumina using benzene as an eluant. The first eluate afforded 310 mg. (32.9%) of di-*p*-tolylsulfone (Xa), m.p. 157-158°. The second eluate afforded 250 mg. (30.8%) of 2-(4-methylbenzoyl)aniline (VI: $\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$) as orange needles, m.p. 94-95° (from ligroin) [lit. (5), m.p. 95°], whose ir spectrum was identical with that of an authentic sample (VI).

(b) A mixture of 1.46 g. of V ($\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$), 2.2 g. (4 moles) of aluminium chloride and 50 ml. of dry benzene for 3 hours was heated and treated as described above to afford a recovery of 1.19 g. (82.1%) of V, 130 mg. (14.1%) of phenyl 4-tolylsulfone (Xb) as colorless needles, m.p. 124-135° [lit. (13), m.p. 124.5°], and 130 mg. of VI ($\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$) (15.4%).

(c) A mixture of 1.46 g. of V ($\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$), 2.2 g. (4 moles) of aluminium chloride, and 50 ml. of anisole was stirred for 0.5 hour, and then heated at 50-60° for 1 hour. The same treatment of the reaction mixture as above gave 1.0 g. (68.4%) of the recovered material (V), 260 mg. (25.0%) of 4-anisyl-4'-tolylsulfone (Xc) as colorless needles, m.p. 104-105° [lit. (14), m.p. 103°] and 200 mg. (23.8%) of VI.

(d) A mixture of 1.46 g. of V ($\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$), 4.4 g. (8 moles) of aluminium chloride, and 650 mg. of anisole and 70 ml. of carbon disulfide was refluxed for 36 hours and 1.36 g. (93.1%) of V was recovered. Further, 36 mg. (3.4%) of Xc and 30 mg. (3.5%) of VI ($\text{R}_1 = \text{H}$, $\text{R}_2 = \text{CH}_3$) were obtained by the same procedure as above. These results were summarized in Table I.

N-(2-Nitrobenzoyl)-4-tolylhydrazine (XIa).

To a stirred and cooled solution of 9 g. of *p*-tolylhydrazine in 150 ml. of dry ether was added dropwise a solution of 7 g. of 2-nitrobenzoyl chloride in 10 ml. of ether. The vigorous reaction was observed on the addition of the above chloride. The reddish-yellow precipitate was collected by filtration and washed with hot water. Recrystallization of the crude product from ethanol-*n*-hexane afforded 8.5 g. of XIa as pale brown needles, m.p. 152-153°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_3$: C, 61.98; H, 4.83; N, 15.49. Found: C, 62.05; H, 4.50; N, 15.51.

N-(2-Nitrobenzoyl)-4-chlorophenylhydrazine (XIb).

A solution of 8.8 g. of 4-chlorophenylhydrazine in 150 ml. of dry ether was treated with 6 g. of 2-nitrobenzoyl chloride in 10 ml. of ether by a similar procedure to the above XIa to give 7 g. of XIb as colorless needles, m.p. 171-172° dec. (from ethanol).

Anal. Calcd. for $\text{C}_{13}\text{H}_{10}\text{ClN}_3\text{O}_3$: C, 53.53; H, 3.46; N, 14.41. Found: C, 53.43; H, 3.62; N, 14.20.

N-(2-Nitrobenzoyl)benzoylhydrazine (XIc).

To a suspension of 9.0 g. of benzoylhydrazine in 100 ml. of benzene was added 6 g. of 2-nitrobenzoyl chloride and the mixture was then refluxed for 2 hours. After cooling, the crude product (XIc) precipitated was collected by filtration and the evaporation of the filtrate also gave XIc as a solid. The combined crude compound (XIc) was washed with hot water and then recrystallized from ethanol to give 8.2 g. of XIc as colorless prisms, m.p. 212-213°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{11}\text{N}_3\text{O}_4$: C, 58.94; H, 3.89; N, 14.72. Found: C, 59.13; H, 4.01; N, 14.72.

N-(2-Aminobenzoyl)-4-tolylhydrazine (XIIa).

To a solution of 70 ml. of 28% ammonium hydroxide saturated with hydrogen sulfide gas was added with stirring a solution of 7 g. of XIa in 70 ml. of ethanol, and the mixture was then refluxed for 0.5 hour. The ethanol was distilled off and the resulting aqueous solution was acidified with hydrochloric acid. After the removal of the insoluble substance, the solution was basified with 28% ammonia. Collection of the precipitate and recrystallization from ethanol gave 49 g. of XIIa as pale yellow needles, m.p. 178.5-179.5°.

Anal. Calcd. for $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}$: C, 69.69; H, 6.27; N, 17.43. Found: C, 69.43; H, 6.26; N, 17.44.

N-(2-Aminobenzoyl)-4-chlorophenylhydrazine (XIIb).

A solution of 5 g. of XIb in 60 ml. of ethanol was treated with 60 ml. of 28% of ammonium hydroxide saturated with hydrogen sulfide gas as above to give 2.8 g. of XIIb as colorless needles, m.p. 183-184° (from ethanol).

Anal. Calcd. for $\text{C}_{13}\text{H}_{12}\text{ClN}_3\text{O}$: C, 59.66; H, 4.62; N, 16.06. Found: C, 59.45; H, 4.94; N, 15.98.

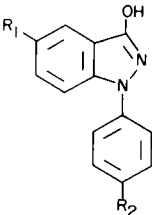
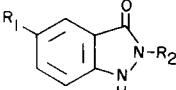
N-(2-Aminobenzoyl)benzoylhydrazine (XIIc).

Treatment of 8 g. of XIc with 150 ml. of ammonium hydroxide saturated with hydrogen sulfide by the same way described above afforded 3.9 g. of colorless silk-like crystals, m.p. 176-177°. Its ir spectrum was identical with that of an authentic sample (XIIc).

3-Hydroxy-1-(4-tolyl)-1*H*-indazole (XIVa).

To a cooled solution of 4 g. of XIIa in 80 ml. of 10% hydrochloric acid was added dropwise with stirring a solution of 2.5 g. of sodium nitrite in 20 ml. of water and a brown precipitate began

TABLE III
The Effect of 1-Aryl-3-hydroxy-1*H*-indazole and
2-Substituted-indazolone on Carrageenin-Induced Edema in Rats

| R ₁ | R ₂ | Rats | Dose (mg./kg.) | Inhibition (%) (Hours) | | | | |
|---|----------------|---------------------|-------------------|---------------------------|------|------|-------|-------|
| | | | | 2 | 3 | 4 | 5 | |
|  | H | H | 6 | 30 | 7.2 | --- | --- | 9.8 |
| | H | CH ₃ | 6 | 30 | 7.7 | -3.5 | -11.1 | -47.2 |
| | H | Cl | 6 | 30 | 79.5 | 38.6 | 20.4 | 8.3 |
|  | H | Ph | 6 | 30 | 16.7 | 11.5 | 13.0 | 14.9 |
| | Cl | Ph | 6 | 30 | 23.1 | 15.8 | -1.4 | --- |
| | H | -CH ₂ Ph | 6 | 30 | --- | 31.6 | --- | 24.5 |

to separate. After the addition, 200 ml. of ethanol was added and the mixture was refluxed for 45 minutes on a water-bath. The removal of the ethanol *in vacuo* gave XIVa, whose recrystallization from ethanol gave 2.1 g. (53.2%) of XIVa as colorless needles, m.p. 218-219°; ν max (nujol), cm^{-1} 2750-2600 (OH), 1550 ($-\text{C}=\text{N}-$).

Anal. Calcd. for $\text{C}_{14}\text{H}_{12}\text{N}_2\text{O}$: C, 74.99; H, 5.38; N, 12.49. Found: C, 74.75; H, 5.40; N, 12.46.

1-(4-Chlorophenyl)-3-hydroxy-1*H*-indazole (XIVb).

Treatment of 1.4 g. of XIIb with 50 ml. of 10% hydrochloric acid, 1.5 g. of sodium nitrite and 100 ml. of ethanol gave 740 mg. (57%) of XIVb as colorless silk-like crystals, m.p. 256-257°; ν max (nujol), cm^{-1} 2800-2650 (OH), 1568 ($-\text{C}=\text{N}-$).

Anal. Calcd. for $\text{C}_{13}\text{H}_9\text{ClN}_2\text{O}$: C, 63.81; H, 3.71; N, 11.45. Found: C, 63.64; H, 4.04; N, 11.38.

Investigation on the Effect on Planter Edema Induced by Carrageenin in the Rats (17).

Six male rats of Wistar strain were used as one group after 24 hours' fasting. The compounds used were suspended in 5% gum-arabic, and the above suspension (30 mg./kg.) was given to the rats orally one hour before injection of carrageenin. Carrageenin was suspended in physiological saline (0.1%). The suspension (0.1 ml.) after sterilization at 120° for 30 minutes in an autoclave was injected into the right foot pad of the rats. The difference of the foot volumes (18) between two measured values were determined. Inhibition ratio (%) in comparison with the control group on a carrageenin-induced edema is shown in Table III.

Acknowledgment.

We are grateful to Vice President S. Uehara and Director Dr. S. Ikawa, Taisho Pharmaceutical Co., Ltd. for their encouragement. We also thank Dr. I. Tanaka, Dr. T. Seki, Taisho Pharmaceutical Co., Ltd., Dr. K. Fukumoto and Dr. S. Shibuya, Pharmaceutical

Institute, Tohoku University, for their kind discussion. Further we also thank Mr. S. Hirata for mass spectral measurements.

REFERENCES

- (1) Part I, the preceding paper.
- (2) This forms Part CCCLXXVI of "Studies on the Syntheses of Heterocyclic Compounds," by T. Kametani.
- (3) Communications concerning this paper should be directed to Professor Tetsuji Kametani.
- (4a) E. Fischer and R. Blochmann, *Ber.*, **35**, 2315 (1902); (b) J. Kenner and E. Withan, *J. Chem. Soc.*, **119**, 1047 (1921). (c) G. Heller, *Ber.*, **49**, 2757 (1916).
- (5a) K. v. Auwers, *ibid.*, **29**, 1255 (1896); (b) K. v. Auwers and P. Stödter, *ibid.*, **59**, 529 (1926).
- (6) F. Ullmann and H. Bleier, *ibid.*, **35**, 4273 (1902).
- (7) A. König and A. Reissert, *ibid.*, **32**, 785 (1899).
- (8) F. Stolz, *ibid.*, **25**, 1663 (1892).
- (9) E. Fischer, *Ann. Chem.*, **232**, 237 (1895).
- (10) G. Heller, *J. Prakt. Chem.*, [2] **111**, 36 (1925).
- (11) All melting points are uncorrected and neutral alumina was used for the column chromatography.
- (12) A. Michael and A. Adair, *Ber.*, **10**, 583 (1877).
- (13) A. Michael and A. Adair, *ibid.*, **17**, 116 (1878).
- (14) G. R. Proctor and R. H. Thomson, *J. Chem. Soc.*, 2302 (1957).
- (15) S. Murahashi and S. Horiie, U. S. patent, 2,944,056 (1960).
- (16) S. Murahashi and S. Horiie, *J. Am. Chem. Soc.*, **78**, 4816 (1956).
- (17) C. A. Winter, E. A. Risley, and G. W. Nuss, *Proc. Soc. Exp. Biol. Med.*, **111**, 544 (1962).
- (18) E. Fujihira, Y. Komatsu, T. Mori, and M. Nakazawa, *J. Japan. Rheumatism Assoc.*, (*Riumachi*), **8**, 14 (1968).

Received February 24, 1970

Aobayama, Sendai, Japan