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1-Acylindoles. VII.[1] On Formation Reaction of Indoles from Phenylhydrazines with Several Acidic Catalysts

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When a phenylhydrazine is reacted with phenylacetone or methyl ethyl ketone, the reaction using hydrogen chloride, zinc chloride, *ortho*-phosphoric acid or boron trifluoride–etherate as a condensing agent gives 2-methyl-3-phenylindole or 2,3-dimethylindole respectively, but the reaction using polyphosphoric acid affords the above-mentioned 2-methylindole derivative as well as 2-benzyl- or 2-ethyl–indole respectively, amount of which product tends to increase with increasing a ratio of phosphorous pentoxide to *ortho*-phosphoric acid.

In reacting a N^1-(p-chlorobenzoyl)phenylhydrazine with phenylacetone, the reaction in the presence of every catalyst gives 2-methyl-3-phenylindole derivatives as a main product, and even when used polyphosphoric acid it is too difficult to yield 2-benzylindole derivative.

Several mechanisms on these results are suggested.

According to stability of a double bond of C_α–C_β and that of C_α–C_β' in transition state of a hydrazone derivative (III), Fischer's indole formation from III causes production of 2-methylindole derivative (IV) or 2-methyleneindole derivative (V).

Cyclization of III in the presence of a catalyst such as a mineral or Lewis acid usually gives IV alone, but V is not detected in the reaction product.

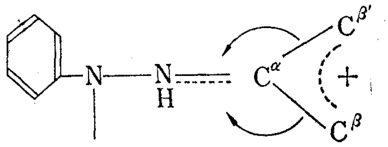
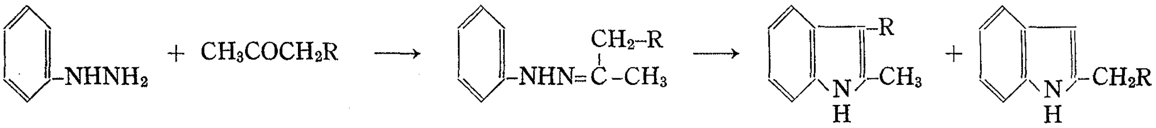


Chart 1



I II III IV V

IIa : R=C_6H_5
IIb : R=Me

IIIa : R=C_6H_5
IIIb : R=Me

IVa : R=C_6H_5
IVb : R=Me

Va : R=C_6H_5
Vb : R=Me

Chart 2

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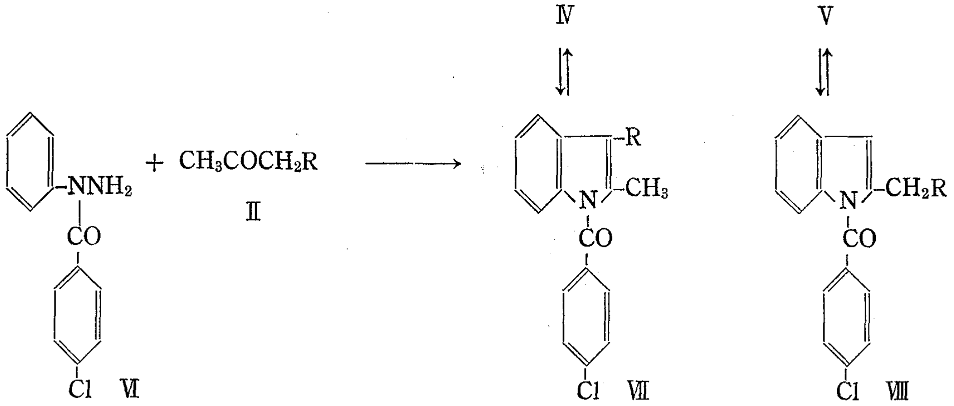
[1] Part VI: H. Yamamoto and T. Atsumi, *Bull. Chem. Soc. Jap.*, **41**, 2431 (1968).

[2] Location: *Kasugade-cho, Konohana-ku, Osaka.*

However, polyphosphoric acid (PPA) evokes a specific reaction in this cyclization. Buu-Hoi, *et al.* reported[3] previously about this problem. According to their report, when used hydrochloric acid or zinc chloride in the indole formation, phenylacetone phenylhydrazone usually give 2-methyl-3-phenylindole, but the reaction carried out in the presence of PPA gave 2-benzylindole besides 2-methyl-3-phenylindole.

The current further investigation on several catalysts including PPA shows that the formation ratio of two products, 2-methylindole derivative (IV) and 2-methyleneindole derivative (V), is changed according to variation of composition of PPA. When N^1-(*p*-chlorobenzoyl)-phenylhydrazine (VI) is reacted with a ketone derivative (II) in the presence of hydrogen chloride, zinc chloride or boron trifluoride–etherate, 1-(*p*-chlorobenzoyl)-2-methylindole derivative (VII) or its deacylated indole derivative (IV) is always yielded. On the other hand, when used PPA as catalyst, the reaction also affords VII or IV, but V is scarcely obtained.



VIIa : R=C_6H_5 VIIIa : R=C_6H_5
VIIb : R=CH_3 VIIIb : R=CH_3

Chart 3

Table I. Ring Closure of Phenylacetone Phenylhydrazone (IIIa)

Catalysis and solvent	Reaction conditions		Yield[a] (%)			Ratio of	
	Temperature (°C)	Time (hr)	IVa	Va	Total	IVa	Va
HCl in glac. AcOH	75—80	5	68.3	0.0	68.3	—	
BF_3–ether in glac. AcOH	refl.	3	73.0	0.0	73.0	—	
$ZnCl_2$ in glac. AcOH	refl.	3	78.1	0.0	78.1	—	
85% H_3PO_4	130—135	1/3	73.0	0.0	73.0	—	
PPA P_2O_5–H_3PO_4 1/2 : 1	130—135	1/3	62.3	9.4	71.7	6.6	1
1 : 1	130—135	1/3	28.9	36.3	65.2	1	1.3
3/2 : 1	130—135	1/3	18.3	40.7	59.0	1	2.2
2 : 1	130—135	1/3	14.7	44.8	59.5	1	3

[a] Analyzed by gas chromatography.

When a mineral acid such as hydrogen chloride and *ortho*-phosphoric acid or a Lewis acid such as zinc chloride and boron trifluoride is used as catalyst of Fischer's cyclization, the double bond of N^2=C may be rearranged to C^{α}–$C^{\beta'}$ bond selectively, because the reaction gives only or mainly IV, or no or scarcely V. When used PPA, however, the reaction gives

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3) N.P. Buu-Hoi, P. Jacquinon et Mme O. Perin, *Bull. Soc. Chim. France,* **1965**, 2849.

TABLE II. Ring Closure of Methyl Ethyl Ketone Phenylhydrazone (IIIb)

Catalysis and solvent	Reaction conditions		Yield[a] (%)			Ratio of
	Temperature (°C)	Time (hr)	IVb	Vb	Total	IVb Vb
HCl in glac. AcOH	75—80	5	78.1	0.0	78.1	—
BF_3–ether in glac. AcOH	refl.	3	78.0	0.0	78.0	—
$ZnCl_2$ in glac. AcOH	refl.	3	82.1	0.0	82.1	—
85% H_3PO_4	130—135	1/3	78.1	0.0	78.1	—
PPA P_2O_5–H_3PO_4 1/2 : 1	130—135	1/3	60.0	19.8	79.8	3 : 1
1 : 1	130—135	1/3	36.8	30.4	67.2	1 : 1
3/2 : 1	130—135	1/3	33.4	32.6	66.0	1 : 1
2 : 1	130—135	1/3	25.7	29.6	55.3	1 : 1

[a] Analyzed by gas chromatography.

V in addition to IV. Moreover, a production amount of V increases with increasing the ratio of phosphorous pentoxide to *ortho*-phosphoric acid, especially the tendency is notable in the derivative which R is a phenyl group.

The mechanism of this reaction is still obscure, but the cyclization is considered to be caused from hydrogen drawing effect of P→O group. Drawing of a hydrogen atom in C^{β} may be much more facile than that of $C^{\beta'}$ because of the steric hindrance, so the former is considered to be protonated easier than the latter. It is explained by this suggestion that production ratio of Va is greater than that of Vb because of steric hindrance of R.

It is deduced from this result that deacylation observed during cyclization reaction in PPA does not occur in the stages of acyl–phenylhydrazine derivative (VI).

TABLE III. Ring Closure Reaction of Methyl Ethyl Ketone (IIb) with N^1–(*p*-Chlorobenzoyl)phenylhydrazine (VI)

Cyclizing agents	Reaction conditions		Yield of VIIb (%)		
	Temp. (°C)	Time (hr)	First corp	Sec. corp	Total
HCl in glac. AcOH	75—80	5	79.4	5.7	85.1
BF_3–ether in glac. AcOH	refl.	3	79.4	4.0	83.4
$ZnCl_2$ in glac. AcOH	refl.	5	79.4	8.8	88.2

TABLE IV. Ring Closure Reaction of Phenylacetone (IIa) with N^1-(*p*-Chlorobenzoyl)phenylhydrazine (VI)

Cyclizing agents	Reaction conditions		Yield of VIIa (%)		
	Temp. (°C)	Time (hr)	First corp	Sec. corp	Total
HCl in glac. AcOH	75—80	5	67.5	3.5	71.0
BF_3–ether in glac. AcOH	refl.	3	79.2	18.9	83.4
$ZnCl_2$ in glac. AcOH	refl.	3	64.0	4.3	68.3

	Reaction conditions		Yield (%) of			
	Temp. (°C)	Time (min)	VIIa	IVa	Va	Total
PPA (P_2O_5–H_3PO_4) 1 : 1	125—130	5	26.4	29.2	0.4	59.0

Because, if the deacylation would occur in these stages, a considerable amount of 2-benzylindole (Va) should have to be obtained besides 2-methyl-3-phenylindole (IVa) by using PPA. However, the reaction on treatment of PPA give almost only 2-methyl-3-phenylindole (IVa) and 1-(*p*-chlorobenzoyl)-2-methyl-3-phenylindole (VIIa) in the current experiment.

It is concluded from these results that a deacylation does not procede a new C–C bond formation of Robinsons' mechanismic intermediate.[4] This conclusion coincides with that deduced from the other model experiments.[5]

When a *p*-chlorobenzoyl group is substituted to N^1-position, 2-benzylindole (Va) or 1-(*p*-chlorobenzoyl)-2-benzylindole (VIIIa) was scarcely or not obtained from N^1-(*p*-chlorobenzoyl)-phenylhydrazine even on treatment of PPA. Because of probable steric hindrance of *p*-chlorobenzoyl group, the benzyl group may be apt to be conformed in anti position of the *p*-chlorobenzoyl group. Therefore, C$^{\beta'}$ may be located in a place near to the *ortho* carbon atom of the main phenyl ring (A ring), but C$^{\beta}$ may be sterically too far from the A ring to form a new C–C bond smoothly. From these points the *p*-chlorobenzoyl group is seemed to hinder the cyclization of 2-benzylindole sterically.

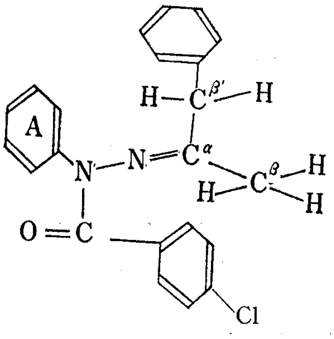

Chart 4

Experimental

Melting points are uncorrected. Infrared (IR) absorption spectra were recorded on a Shimadzu IR–27G spectrophotometer and nuclear magnetic resonance (NMR) spectrophotometry were taken on a Varian A–60 spectrophotometer.

1 Materials

Phenylacetone (IIa)——According to the method described in Organic Syntheses[6] was prepared IIa, bp 112—116°/33 mmHg(lit.,[2] bp 109—112°/24 mmHg).

Phenylacetone Phenylhydrazone (IIIa)——A mixture of 48.6 g of phenylacetone and 40.0 g of phenylhydrazine (I) (purity 98%) was heated in a water bath for 10 min and the mixture was extracted with ether. The ether layer was dried over anhydrous sodium sulfate and the solvent was evaporated to a solidal substance, which was recrystallized from cyclohexane to give 53 g (84.4%) of colorless needles, mp 84.5—87° (lit.,[7] mp 83°).

Methyl Ethyl Ketone Phenylhydrazone (IIIb)——According to the above-mentioned procedure, a crude product was prepared from 50.5 g of IIb and 75.5 g of I. Purification by distillation afforded 99 g of IIIb, bp 97.5—98.5°/0.7—0.55 mmHg (lit.,[8] bp 190°/100 mmHg).

2-Methyl-3-phenylindole (IVa)——A mixture of 2.5 g of I hydrochloride (purity 98%) and 2 g of IIa was heated in 15 ml of glacial acetic acid at 70—75° for 3 hr and the mixture was poured into ice water and extracted with benzene. A concentrate of the benzene layer was distilled *in vacuo* to give 3.0 g (97%) of yellow liquid, bp 177—178°/0.5 mmHg. Treatment of *n*-hexane and recrystallization from petroleum benzine gave colorless needles of IVa, mp 63—64° (lit.,[9] mp 58—60°). IR $\nu_{\text{max}}^{\text{paraffin}}$ cm^{-1}: 3300. NMR (τ, TMS in $CDCl_3$): 7.65 (3H, singlet), 2.34—2.94 (9H, multiplet).

2-Benzylindole (Va)——According to the method of Clemo, *et al.*,[6] heat rearrangement of 3-benzylindole in the presence of $AlCl_3$–NaCl afforded Va, bp 145—150°/0.55 mmHg, mp 84—85° (colorless plates from petroleum ether) (lit.,[10] mp 84°).

2,3-Dimethylindole (IVb)——A mixture of 7.2 g of I hydrochloride and 8.7 g of IIb was heated in 50 ml of glacial acetic acid at 75—80° for 3 hr and the reaction mixture was poured into water and the separated crystals were collected by filtration to give 6.7 g (92.5%) of crude product, mp 106°. Recrystallization

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[4] R.B. Carlin and E.E. Fischer, *J. Am. Chem. Soc.*, **70**, 3421 (1948).
[5] H. Yamamoto and T. Atsumi, *Bull. Chem. Soc. Jap.*, **41**, 2431 (1968).
[6] "Organic Syntheses," Vol. 18, 1938, p. 54.
[7] B. Trenkler, *Ann.*, **248**, 106 (1888).
[8] A. Arnold, *Ber.*, **30**, 1015 (1897).
[9] D.W. Ockenden and K. Schofield, *J. Chem. Soc.*, **1953**, 613.
[10] G.R. Clemo and J.C. Seaton, *J. Chem. Soc.*, **1954**, 2582.

from petroleum ether on treatment with alumina gave 4.2 g of colorless scales of IVb, mp 107—108° (lit.[11], mp 108—109°). IR$\nu_{\max}^{\text{paraffin}}$ cm^{-1}: 3400. NMR(τ, TMS in $CDCI_3$) : 7.87(6H,singlet), 2.70—3.17(4H,multiplet).

2-Ethylindole (Vb)——According to the method of Organic Syntheses,[12] 29.8 g (84%) of crude Vb, mp 42—50° was prepared by heating 40.0 g of N-propionyl-*o*-toluidide with sodium amide at 230—245° for 30 min. Recrystallization from petroleum ether gave colorless plates of Vb, mp 51—52° (lit.[13] mp 45—46°). IR $\nu_{\max}^{\text{paraffin}}$ cm^{-1}:3400. NMR (τ, TMS in $CDCl_3$): 8.80 (3H, triplet), 7.40 (2H, quartet), 3.87 (1H, doublet), 2.80—3.10 (4H, multiplet).

N^1-(*p*-Chlorobenzoyl)-phenylhydrazine (VI)——According to the procedure of Lockmann,[14] colorless prisms of VI, mp 128—129° (from 50% aqueous ethanol), (lit.,[10] mp 128—129°), were prepared from acetaldehyde N^1-(*p*-chlorobenzoyl)-phenylhydrazone. Hydrochloride salt, mp 191° (decomp.) (colorless needles, form ethanol) (lit.,[14] mp 192—193°).

1-(*p*-Chlorobenzoyl)-2-methyl-3-phenylindole (VIIa)——A mixture of 2.3 g of VI hydrochloride and 1.1 g of IIa was heated in 15 ml of glacial acetic acid at 70—75° for 3 hr with stirring. After completion of the reaction, the reaction mixture was poured into 50 ml of water and extracted with 50 ml of benzene three times. The benzene layer was washed with water and dried over anhydrous sodium sulfate. The solution was concentrated under reduced pressure to a residue, which was solidified on treatment of acetone to yield 2.3 g (83.0%) of crude VIIa, mp 159—161°. Recrystallization from acetone on treatment with active charcoal gave 2.0 g (72.2%) of pale yellow needles of VIIa, mp 160.5—161°. IR $\nu_{\max}^{\text{Paraffin}}$ cm^{-1}: 1675, 1595. NMR (τ, TMS in $CDCl_3$): 7.61 (3H, singlet), 2.15—3.00 (13H, multiplet). *Anal.* Calcd. for $C_{22}H_{16}CNCl$: C, 76.41; H, 4.66; N, 4.05; Cl, 10.25. Found: C, 76.00; H, 4.34; N, 4.29; Cl, 10.23.

1-(*p*-Chlorobenzoyl)-2-benzylindole (VIIIa)——To a mixture of 0.7 g of sodium hydride (purity 50%), and 50 ml of N,N-dimethylformamide (DMF) was added dropwise a solution of 2 g of Va in 10 ml of DMF below 10° in nitrogen gas, and then stirred at room temperature for 3 hr. Thereafter, a solution of 2.3 g of *p*-chlorobenzoyl chloride in 5 ml of ether was added dropwise to the mixture below 10° with stirring. Stirring was continued on cooling for 1 hr and at room temperature for additional 20 hr. The mixture was poured into 200 ml of water and extracted with ether. By filtration was removed 0.7 g of *p*-chlorobenzoic anhydride, mp 193.5°. The ether extract was washed with water, dried and concentrated *in vacuo* to 3.3 g of an oily substance, which was dissolved in ether and chromatographed on silica gel. The eluate with *n*-hexane gave 0.9 g (26.1%) of an oily substance, which was solidified on treatment of petroleum ether to give crystals, mp 69—74°. Recrystallization from ethanol gave 0.5 g (14.5%) of colorless needles of VIIIa, mp 72.5—75°. IR $\nu_{\max}^{\text{paraffin}}$ cm^{-1}: 1667, 1595. NMR (τ, TMS in $CDCl_3$): 5.80 (2H, singlet), 3.60 (1H, singlet), 2.40—3.35 (13H, multiplet). *Anal.* Calcd. for $C_{22}H_{16}ONCl$: C, 76.41; H, 4.66; N, 4.05; Cl, 10.25. Found: C, 76.45; H, 5.15; N, 3.27; Cl, 10.03.

1-(*p*-Chlorobenzoyl)-2,3-dimethylindole (VIIb)——A mixture of 2.3 g of VI hydrochloride and 0.6 g of IIb (purity 97%) was heated in 17 ml of glacial acetic acid at 75—80° for 5 hr. An after-treatment of the reaction mixture by the same procedure with that of VIIa afforded 2.5 g of an oily substance, which crystallized on treatment of petroleum ether to give 1.9 g (84%) of crude VIIb, mp 74.5—77.0°. Recrystallization from ethanol-water and then ethanol gave 1.2 g (53%) of pale yellow needles of VIIb, mp 78.5—79°. IR $\nu_{\max}^{\text{paraffin}}$ cm^{-1}: 1680, 1610, 1595. NMR (τ, TMS in $CDCl_3$): 7.86 (3H, singlet), 7.75 (3H, singlet), 2.32—2.16 (8H, multiplet). *Anal.* Calcd. for $C_{17}H_{14}ONCl$: C, 71.95; H, 4.97; N, 4.94; Cl, 12.50. Found: C, 72.28; H, 4.87; N, 4.71; Cl, 12.41.

1-(*p*-Chlorobenzoyl)-2-ethylindole (VIIIb)——A reaction of 2 g of Vb with 3.2 g of *p*-chlorobenzoyl chloride was carried out in 50 ml of DMF in the presence of 0.6 g sodium hydride (purity 50%) by the procedure described before in VIIIa. An after-treatment of the reaction mixture afforded 3.5 g of an oily substance, to which was added petroleum ether. By filtration was removed 0.65 g of insoluble *p*-chlorobenzoic acid, mp 239—240°. The filtrate was concentrated to 2.6 g (66.5%) of a brown oily residue, which was dissolved in ether and chromatographed on silica gel. The eluate with *n*-hexane afforded 1.6 g of an oily substance which was purified by distillation to give 1.4 g (35.8%) of a yellow oil of VIIIb, bp 146—151°/0.045 mmHg, mp 48—50.5°. IR $\nu_{\max}^{\text{paraffin}}$ cm^{-1}: 1688, 1595. NMR (τ, TMS in $CDCl_3$): 8.78 (3H, triplet), 7.15 (2H, quartet), 3.56 (1H, singlet), 2.25—3.25 (8H, multiplet). *Anal.* Calcd. for $C_{17}H_{14}ONCl$: C, 71.95; H, 4.97; N, 4.94; Cl, 12.50. Found: C, 72.15; H, 4.96; N, 4.80; Cl, 12.18. An eluate with *n*-hexane-ether (9:1) afforded 0.6 g of an oily substance, which recrystallized from petroleum ether gave 0.26 g of yellow scales of Vb, mp 50—51°, undepress when admixed with the authentic sample and identical IR spectra were obtained from the material and the authentic sample.

2 Hydrolyses of 1-Acylindole Derivatives

IVa from VIIa——To a solution of 0.3 g of VIIa in 10 ml of ethanol was added a small amount of aqueous potassium hydroxide (0.2 g) solution and the mixture was refluxed for 1 hr. After completion of the reaction,

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11) C.M. Atkinson, J.C.E. Simpson and A. Taylor, *J. Chem. Soc.*, **1954**, 165.

12) "Organic Syntheses," Vol 22, 1942, p. 94.

13) L.A. Aksanova, N.F. Kucherova and V.A. Zagorevskii, *Zh. Obshch Khim.* 34, 1609, (1964).

14) G. Lockemann, *Ber.*, 43, 2228 (1910).

the reaction mixture was concentrated *in vacuo* to a residue, to which was added water and extracted with benzene. The benzene layer was washed with water, dried over anhydrous sodium sulfate and distilled *in vacuo* to 0.17 g (quantitative) of an oily material, which was solidified on treatment of *n*-hexane to give 0.14 g (78%) of crystalline product, mp 58—59°. Recrystallization from petroleum benzine gave 0.09 g (50%) of pale brown needles of IVa, which was identified by mixture melting point and infrared absorption spectra. The aqueous layer was acidified with 2 N HCl to give 0.12 g (92.4%) of *p*-chlorobenzoic acid, mp 239—240°.

Va from VIIIa——A mixture of 0.2 g of VIIIa, 0.1 g of potassium hydroxide (purity 85%) and 10 ml of ethanol was treated by the above-mentioned procedure. In this case, a precipitate was separated only by adding water to a residue, collected by filtration and washed with water to give 0.15 g of crude product, mp 87—88°. Recrystallization from petroleum benzine with treatment of alumina gave 0.11 g (92%) of colorless prisms of Va, mp 87—89°, which was identified by mixture melting point and infrared absorption spectra. Acidification of aqueous layer afforded 0.09 g (quantitative) of *p*-chlorobenzoic acid, mp 230—241°.

IVb from VIIb——A mixture of 0.3 g of VIIb, 0.1 g of potassium hydroxide (purity 85%) and 10 ml of ethanol was treated by the procedure described above to yield 0.15 g (94.1%) of crude IVb, mp 102—103°, which was recrystallized from petroleum ether (bp 30—70°) with treatment of alumina, to raise the melting point to 105.5—107°, which was identified by mixture melting point and infrared absorption spectra. Acidification of aqueous layer afforded 0.14 g (84.5%) of *p*-chlorobenzoic acid, mp 241—241.5°.

Vb from VIIIb——A mixture of 0.2 g of VIIIb, 0.1 g of potassium hydroxide (purity 85%) and 10 ml of ethanol was treated by the procedure described before to give 0.1 g (quantitative) of crude product, mp 47—50°. It was recrystallized from petroleum ether to give colorless scales of Vb, mp 46—49°, which was shown to be identical with an authentic sample by mixture melting point determination and infrared absorption spectra. Acidification of aqueous layer afforded 0.08 g (72.7%) of *p*-chlorobenzoic acid, mp 240—241°.

3 Cyclization of Phenylhydrazone Derivatives

Cyclization of III——a) With Hydrogen Chloride: A mixture of 0.03 mole of III and 30 ml of glacial acetic acid containg 0.045 mole of hydrogen chloride was heated at 70—80° for 5 hr. After completion of the reaction, the reaction mixture was poured into 200 ml of water and extracted with three portions of 50 ml of methylene dichloride. The organic layer was washed with 50 ml of water, 50 ml of 5% sodium bicarbonate aqueous solution and 50 ml of water in order, dried over anhydrous sodium sulfate and concentrate to an oily or crystalline residue, which was purified by distillation. A distillate was analyzed by gas chromatography.

b) With Boron Trifluoride-etherate: A mixture of 0.03 mole of III and 0.033 mole of boron trifluoride-etherate (purity of boron trifluoride 47%) in 30 ml of glacial acetic acid was refluxed in nitrogen gas for 3 hr. The reaction mixture was treated by the procedure described above to give a crude product, which was purified by distillation. A distillate was analyzed by gas chromatography.

c) With Zinc Chloride: A mixture of 0.03 mole of III and 0.03 mole of anhydrous zinc chloride (purity 90%) was refluxed in 30 ml of glacial acetic acid for 3 hr. The mixture was treated by the procedure described before to give a crude product, which was purified by distillation. A distillate was analyzed by gas chromatography.

d) With *ortho*-phosphoric Acid or Polyphosphoric Acid: To an adequate amount of 85% *ortho*-phosphoric acid was slowly added small portions of phosphorous pentoxide below 80° on external cooling with stirring. The resultant mixture was heated at 75—80° for 0.5—1 hr to give a clear solution of polyphosphoric acid (PPA). A mixture of one part of III and ten parts of 85% *ortho*-phosphoric acid or PPA was heated in nitrogen gas in an oil bath of 140—150°. The exothermic reaction was kept at 130—135° for 20 min. Thereafter, the mixture was poured into 200 ml of water and the solution was treated according to the procedure described before to yield a crude product, which was purified by distillation. The distillate was analyzed by gas chromatography.

4 Cyclization of N^1-(*p*-Chlorobenzoyl)phenylhydrazine (VI) with Phenylacetone (IIa) or Methyl Ethyl Ketone (IIb)

a) With Hydrogen Chloride: A mixture of 2.3 g (0.008 mole) of VI hydrochloride and 0.008 mole of IIa or IIb was stirred in 15 ml of glacial acetic acid at 75—80° for 5 hr. The reaction mixture was poured into 50 ml of water and extracted with 50 ml of three portions of benzene. Benzene layer was washed with water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to a crude product, which was purified by the same procedure with that of VIIa and VIIb described before. These products were identified by mixture melting point determination and comparison of infrared absorption spectra with those of authentic samples. The recrystallization filtrate was hydrolyzed with KOH-EtOH as described above and the benzene layer obtained was chromatographed with thin-layer of silica and it was affirmed to be neither spot of Va nor that of Vb. From this result, the reaction of VI with IIa and IIb in the presence of hydrogen chloride did not give both VIIIa and VIIIb.

b) With Boron Trifluoride-etherate: A mixture of 2 g (0.008 mole) of VI, 0.008 mole of IIa or IIb and 1.2 g (0.008 mole) of boron trifluoride-etherate (purity of boron trifluoride 47%) was refluxed in 15 ml of glacial acetic acid for 3 hr. The reaction mixture was treated and purified according to the procedure described before.

From thin-layer chromatographic study of the alkali hydrolyzed product, it is found that the reaction did not afford VIIIa and VIIIb.

c) With Zinc Chloride: A mixture of 2 g (0.008 mole) of VI, 0.008 mole of IIa or IIb and 1.3 g (0.008 mole) of anhydrous zinc chloride (purity 90%) was refluxed in 15 ml of glacial acetic acid for 3—5 hr. The reaction mixture was treated and purified according to the above mentioned procedure. From thin-layer chromatographic study of the alkali hydrolyzed product, this reaction did not afford VIIIa and VIIIb.

d) With PPA: A mixture of 2 g of VI, 1.1 g of IIa and 30 g of PPA in nitrogen gas was put in an oil bath before-heated at 140—150° and heated at 125—130° for 3—5 min. Thereafter, the mixture was poured into water while it was hot, and extracted with methylene dichloride. The organic layer was washed with water, 5% aqueous sodium bicarbonate solution and water in order, and dried over sodium sulfate. The solution was concentrated to an oily or crystalline residue, which was analyzed by gas chromatography.

5 Gas Chromatography

Gas chromatographic quantitative analyses were carried out with a Yanagimoto GCG-550 FP gas chromatograph equipped with hydrogen flame ionization detector under following conditions.

a) Quantitative Analyses of IVa and Va: Sample: 70 mg of a distillate in acetone. Internal standard 50 mg of tribenzylamine (TBA). Column: Stainless steel tube. 1.5m × 3 mm. 5% PEG-20 M on Chromosorb W (60 × 80 mesh). Temperature: column, 240°; sample heater, 335°; detector, 240°. Carrier gas: nitrogen gas, 20 ml/min; hydrogen, 17 ml/min, air, 850 ml/min. Retention time; IVa, 10.4 min; Va, 8.7 min; TBA, 5.3 min. From areas of individual peaks, mole % figures were calculated for each product after a relative response date was determined by the internal standard method using TBA.

b) Quantitative Analyses of IVb and Vb: Sample: 70 mg of a distillate in chloroform. Internal standard substance: α-methylnaphthalene. Column: Stainless steel tube. 1.5 m × 3 mm. 10% AP-L on Chromosorb W (60—80 mesh). Temperature: column, 160°; sample heater, 230°; detector, 230°. Carrier gas: nitrogen, 25 ml/min; hydrogen, 20 ml/min: air, 900 ml/min. Retention time: IVb, 12.0 min; Vb, 10.6 min; α-methylnaphthalene, 7.3 min. Quantitative analysis was performed by the above-mentioned internal standard method using α-methylnaphthalene.

c) Quantitative Analysis of VIIa, IVa and Va: The mixture of VIIa, IVa and Va was analyzed by gas chromatography and thin-layer chromatography-ultraviolet spectrum.

i) Gas Chromatography—Sample: 70 mg of reaction product in acetone. Internal Standard: 50 mg of tribenzylamine (TBA). Column: Stainless steel tube. 1.5 m × 3 mm. 5% PEG-20 M on Chromosorb W (60—80 mesh). Temperature: column, 240°; sample heater, 275°; detector, 275°. Carrier gas: nitrogen, 20 ml/min; hydrogen, 20 ml/min; air, 900 ml/min. Retention time: Va, 8.5 min; VIIa and IVa, 10 min; TBA 5.5 min. Quantitative analysis was performed by above mentioned internal standard method using TBA.

ii) Thin-Layer Chromatography-Ultraviolet Spectrum—Ultraviolet quantitative analyses were carried out with Shimadzu RS-27 Recording Spectrophotometer. Thin-layer chromatography: Absorbent; Silica gel (Merck, Kieselgel G nach Stahl), 0.25 mm. Solvent; *n*-hexane-ether (4:1). Detector; iodine vapor. Sample; 20 mg of reaction product in chloroform. VIIa was extracted from absorbent with ethanol and ethanol layer was analyzed with ultraviolet spectrum.

6 Thin-Layer Chromatography

Silica gel (Merck, Kieselgel G nach Stahl) was used as TLC absorbent and Van Urk reagent[15] and iodine vapor were used as detectors. Among various solvent systems ether-*n*-hexane (1:3), *n*-hexane-ethyl acetate (4:1) or benzene is generally useful. Va, Vb, VIIIa and VIIIb were colored to pink immidiately after spray of Van Urk reagent but colors of VIIIa and VIIIb were lighter those of Va and Vb. IVa and IVb colored blue and violet respectively after the plate was kept at 50° for several min or at room temperature overnight. While, VIIa and VIIb were not colored or colored sometimes pale yellow. These spots were detected easily by iodine vapor.

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[15] K. Randerath, "Thin-Layer Chromatography," Academic Press, New York & London, 1963, p. 86.