The Bischler-Napieralski Reaction in Liquid Sulfur Dioxide. Formation of N, N'-bis-β-Phenethyl Acet- and Benz-amidines and N, N'-Diphenyl Acet- and Benz-amidines

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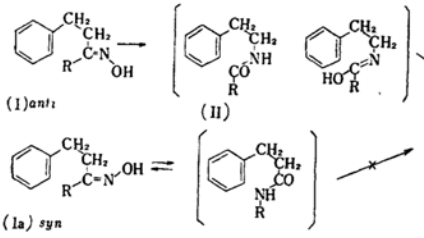
It has been shown in a previous paper[1] that dihydroisoquinoline and phenanthridine-derivatives may be produced from the corresponding ketone oximes by simultaneous Beckmann rearrangements and cyclodehydrations in liquid sulfur dioxide under appropriate conditions. As shown in Chart I, the *syn*- and *anti*-configurations of the starting materials should be taken into account in considering the reaction process.

Chart I



In the above-mentioned simultaneous rearrangement and cyclodehydration, the total yield of the condensed ring compound was lower than forty-five per cent and this low yield was apparently due to the presence of a considerable amount of the Ia (*syn*) isomer.

In order to clarify this point, the expected intermediate from the *anti* oxime (I), viz. the acid amide (II), was subjected to the Bischler-Napieralski reaction with phosphorus pentoxide in liquid sulfur dioxide by modifying Bradsher and Sinclair's method of cyclodehydration[2]. In a preliminary examination, it was ascertained that 1-methyl-3, 4-dihydroisoquinoline ($R=CH_3$, III) was obtained from *N*-phenethyl acetamide ($R=CH_3$, II) in a maximum yield of 24.5%, and that 10.7% of the acid amide (I) was recovered.

In addition, it was found that the procedure gave a basic substance besides usual Bischler-Napieralski reaction product III.

This result aroused the authors' interest in examining the general behavior of acid amides toward condensing reagents in liquid sulfur dioxide.

Among various reagents examined, phosphorus oxychloride, polyphosphoric acid and thionyl chloride gave no reaction product and only phosphorus pentoxide was effective. The results are shown in Table I.

As is shown in Table I, the relation between the dihydroisoquinoline and the basic substance produced at 20°C in liquid sulfur dioxide explains that the side reaction was induced in preference to the

TABLE I. SYNTHESES OF 1-METHYL-3, 4-DIHYDROISOQUINOLINE FROM *N*-β-PHENETHYL ACETAMIDE IN LIQUID SO_2[a, b]

No.	Molar ratio of amide to P_2O_5	Reaction Temp. °C	Reaction Time hr.	Amide, recovered, yield, %	1-Methyl-3, 4-dihydro isoquinoline, yield, %	Basic substance, yield, %
1	1 : 5	20	6	35.3	3.5	23.0
2	1 : 5	70	6	10.7	24.5	33.8
3[c]	1 : 17	210	0.5	—	83	0

a) Reactions were carried out with 6.5 g. (0.04 mol.) of amide in 100 ml. of liq. SO_2 under shaking.

b) $POCl_3$, polyphosphoric acid, or $SOCl_2$ used as the reagent in liq. SO_2 (molar ratio of amide to reagent was 1 : 5) at 20°C for 6 hr. or at 70°C for 6 hr., caused no reaction.

c) Reaction was carried out in tetralin[3].

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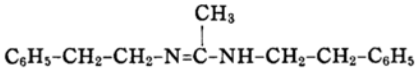
[1] R. Tada, H. Sakuraba and N. Tokura, This Bulletin, 31, 1003 (1958).

[2] C. K. Bradsher and E. F. Sinclair, *J. Org. Chem.*, 22, 79 (1957).

Bischler-Napieralski reaction.

This basic substance produced was assumed to be the hitherto unknown *N, N'*-bis-β-phenethyl acetamidine (IV).



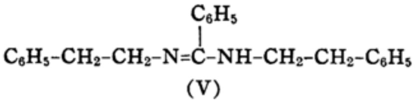
$$C_6H_5{-}CH_2{-}CH_2{-}N{=}\overset{CH_3}{\overset{|}{C}}{-}NH{-}CH_2{-}CH_2{-}C_6H_5$$

(IV)

This amidine (IV), distilling at 205~215°C (6~7 mmHg) or 180~190°C (2~3 mmHg) was obtained as a pale yellow oil ($n_D^{15}=1.5748$) and yielded a picrate of m. p. 118~119°C. The elementary analyses of both the base and the picrate satisfied formula IV. The ultraviolet spectrum of the base showed a maximum at $\lambda_{max}^{MeOH}=250\,m\mu$ ($\varepsilon_{max}=385$), indicating the presence of a nonconjugated benzene ring. Its infrared spectrum showed absorption at $\nu_{max}^{KBr}=1635$ ($>$C=N–), 3440 ($>$NH), 1352 (methyl), 2915 and 2860 (methylene), and 745 and 695 cm^{-1} (benzene, mono-substituted). The hydrolysis of this base with ten per cent aqueous sodium hydroxide solution, yielded *N*-β-phenethyl acetamide and *N*-β-phenethylamine. Thus the structure of the base was etablished as being IV.

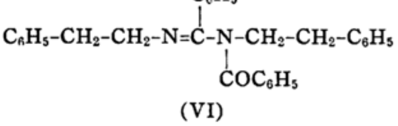
Similarly, it was also shown that a basic substance was afforded by the reaction of *N*-β-phenethyl benzamide ($R=C_6H_5$, II) with phosphorus pentoxide in liquid sulfur dioxide. This basic matter produced was identified as the known *N, N'*-bis-β-phenethyl benzamidine (V).

Further, it was also found that another substance was present in the reaction mixture in the latter case. This substance was assumed to be the hitherto unreported *N*-benzoyl-*N, N'*-bis-β-phenethyl benzamidine (VI).



$$C_6H_5{-}CH_2{-}CH_2{-}N{=}\overset{C_6H_5}{\overset{|}{C}}{-}NH{-}CH_2{-}CH_2{-}C_6H_5$$

(V)



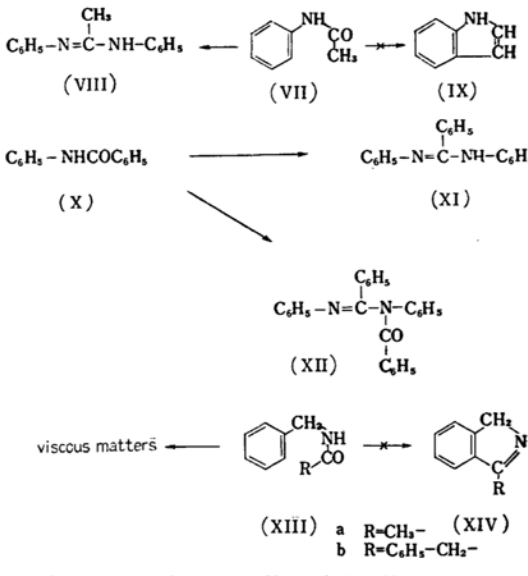
$$C_6H_5{-}CH_2{-}CH_2{-}N{=}\overset{C_6H_5}{\overset{|}{C}}{-}\underset{COC_6H_5}{\underset{|}{N}}{-}CH_2{-}CH_2{-}C_6H_5$$

(VI)

This amidine (VI), melting at 110~110.5°C, was obtained as faintly orange crystals. The elementary analysis satisfied formula VI. The ultraviolet spectrum of the amidine showed a maximum at $\lambda_{max}^{MeOH}=241\,m\mu$ ($\varepsilon_{max}=18647$). Its infrared spectrum showed absorptions at $\nu_{max}^{KBr}=1626$ ($>$C=N–), 1643 ($>$N–CO–), 2935 and 2860 (methylene), and 747 and 695 cm^{-1} (benzene, mono-substituted). The hydrolysis of this neutral substance with 2 N sulfuric acid gave benzoic acid, *N*-β-phenethyl benzamide and *N, N'*-bis-β-phenethyl benzamidine. Thus its structure may be represented by VI.

It was further examined in cases of the other acid amides whether such amidine formations might be encountered generally in liquid sulfur dioxide. When acetanilide (VII) was subjected to this reaction, a similar basic substance was afforded and identified as the known *N, N'*-diphenyl acetamidine (VIII). Moreover, when benzanilide (X) was subjected to this reaction, similar substances were obtained and identified as the known *N, N'*-diphenyl benzamidine (XI) and *N*-benzoyl-*N, N'*-diphenyl benzamidine (XII), respectively. However, when benzyl acet- (XIIIa) and benz-amide (XIIIb) were used, the corresponding amidines were not produced, and viscous substances which were difficult to identify were afforded. The ring closure to IX or XIV was also difficult (Chart II).

Chart II



These results are listed in Table II.

The reason why the formation of dihydroisoquinolines is limited is thus well elucidated as the result of the competitive formation of *N, N'*-bis-β-phenethyl amidines. The present authors are not sure that the viscous substances produced from XIII ($R=CH_3$ or C_6H_5) might be the polymerization products of the isoindole derivatives which have been known to be very unstable.

TABLE II. REACTION OF PHOSPHORUS PENTOXIDE ON ACID AMIDES IN LIQUID SO_2[a]

Amide	Reaction		Amide, recovered, yield, %	Amidine, yield, %		Other substance produced, yield, %	
	Temp., °C	Time, hr.					
N-β-Phenethyl acetamide	20	6	35.3	28.3 [b]		3.5 [h]	
	70	6	10.7	41.5 [b]		24.5 [h]	
N-β-Phenethyl benzamide	20	6	48.8	12.3 [c]	0 [d]	14.6 [i]	8.3 [j]
	70	6	0	9.2 [c]	12.7 [d]	80.6 [i]	8.3 [j]
Acetanilide	20	6	57.4	19.0 [e]		5.5 [k]	
	70	6	35.1	30.9 [e]		11.1 [k]	
Benzanilide	20	6	41.7	1.8 [f]	46.6 [g]	trace [j]	
	70	6	5.0	46.2 [f]	28.6 [g]	16.6 [j]	
N-Benzyl acetmide	20	6	—	—		57.6 [l]	8.4 [m]
	70	6	—	—		83.0 [l]	10.8 [m]
N-Benzyl benzamide	20	6	—	—		84.5 [l]	3.5 [m]
	70	6	—	—		85.7 [l]	3.5 [m]

a) Reaction was carried out with 0.04 mol. of amide in 100 ml. of liq. SO_2 under shaking. Molar ratio of amide to $P_2O_5=1:5$.

b) The amidine obtained was *N,N'*-bis-β-phenethyl acetamidine.

c) The amidine obtained was *N,N'*-bis-β-phenethyl benzamidine.

d) The amidine obtained was *N*-benzoyl-*N,N'*-bis-β-phenethyl benzamidine.

e) The amidine obtained was *N,N'*-diphenyl acetamidine.

f) The amidine obtained was *N,N'*-diphenyl benzamidine.

g) The amidine obtained was *N*-benzoyl-*N,N'*-diphenyl benzamidine.

h) 1-Methyl-3,4-dihydroisoquinoline.

i) 1-Phenyl-3,4-dihydroisoquinoline.

j) Benzoic acid.

k) Aniline.

l) Viscous neutral substance from benzene extract in the acidic condition.

m) Viscous basic substance from benzene extract in the basic condition.

Experimental

Reagents.—Amides were prepared by acetylation or benzoylation of the corresponding amines according to methods indicated in references; the amides were *N*-β-phenethyl acetamide[3] (b. p. 147∼148°C/3∼4 mmHg), *N*-β-phenethyl benzamide[3] (m. p. 114.5∼115.5°C), *N*-benzyl acetamide[4] (m. p. 61∼63°C) and *N*-benzyl benzamide[5] (m. p. 104∼105°C). Acetanilide (m. p. 113.5∼114.5°C) and benzanilide (m. p. 162.5∼163°C) were commercial ones of extra pure grade.

Liquid sulfur dioxide was used as a solvent. A commercial material was dried with sulfuric acid and distilled before use.

The commercial phosphorus -pentoxide, -oxychloride and thionyl chloride of extra pure grade were used. Polyphosphoric acid was prepared by the known method[6].

Apparatus and General Procedure.—Glass pressure vessels (300 ml. capacity) equipped with metal joints and needle valves were used as before[1]. A liquid sulfur dioxide solution of an amide was added to a mixture or a solution of the condensing reagent in liquid sulfur dioxide with ice-cooling. Since benzanilide is sparingly soluble in liquid sulfur dioxide, sulfur dioxide was added to the mixture of this amide and phosphorus pentoxide. Then the whole set was thoroughly shaken and kept for a definite time at a definite temperature.

When the reaction was over, the reaction mixture turned into a gelatinous mass. The excessive solvent (sulfur dioxide) was evaporated and the mixture was decomposed with chilled water. Then the products were treated for further examination.

Reaction of *N*-β-Phenethyl Acetamide (II) ($R=CH_3$) in Liquid Sulfur Dioxide.—To 50 ml. of sulfur dioxide containing the condensing reagent (five times moles against that of the amide) as indicated in Table I was added a solution of 6.5 g. (0.04 mol.) of *N*-β-phenethyl acetamide (II) ($R=CH_3$) in 50 ml. of sulfur dioxide. After the reaction under a definite condition with shaking, the solvent was evaporated and water was added to the solution with chilling. The acidic mixture was extracted with benzene. The benzene solution, after washing with sodium bicarbonate solution and drying with anhydrous sodium sulfate, was condensed and the residue was distilled in vacuo. The acid amide (II) ($R=CH_3$) was recovered as a pale yellow oil boiling at 160∼170°C (6∼7 mmHg). Hydrolyzing this acid amide to β-phenethyl amine with hydrochloric acid, a picrate of the amine was prepared, m. p. 167∼168°C. Reported melting point is 171°C[7]. The mixed melting point with an authentic sample showed no depression.

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[3] A. Bischler and B. Napieralski, *Ber.*, **26**, 1903 (1893).

[4] J. Strakosch, ibid., **5**, 697 (1872).

[5] E. Beckmann, ibid., **23**, 3334 (1890).

[6] R. C. Gilmore and W. J. Horton, *J. Am. Chem. Soc.*, **73**, 1412 (1951).

[7] H. Decker and W. Kropp, *Ber.*, **42**, 2078 (1909).

The residual aqueous solution was made alkaline with caustic alkali and was extracted with benzene. The benzene solution, after washing with water and drying with anhydrous sodium sulfate, was evaporated and the residue was distilled in vacuo. A colorless oil boiling at 100~105°C (7~8 mmHg) was obtained. This was 1-methyl-3, 4-dihydroisoquinoline (III) ($R=CH_3$). Picrate, yellow needles, m. p. 188~189°C. Reported melting point is 188~190°C[8]. No melting point depression was observed when the sample was mixed with an authentic sample.

Anal. Base Found: N, 9.72. Calcd. for $C_{10}H_{11}N$: N, 9.65%. Picrate Found: N, 15.10. Calcd. for $C_{16}H_{14}O_7N_4$: N, 14.97%.

Moreover, following the above fraction, a pale yellow oil boiling at 205~215°C (6~7 mmHg) was obtained. This oil was assumed to be *N*, *N'*-bis-β-phenethyl acetamidine (IV), b. p. 180~190°C (2~3 mmHg), $n_D^{15}=1.5748$, I. R. ν_{max}^{KBr}: 3440, 2915, 2860, 1635, 1352, 745 and 695 cm^{-1}, U. V. λ_{max}^{MeOH}: 250 mμ (ε_{max} 385). Picrate, yellow needles (from 95% ethanol) m. p. 118~119°C, mol. wt. (by the Counningham method)[9]: 464 (the molar ratio of picric acid : base = 1 : 1, calcd. as $C_{24}H_{25}O_7N_6$ 495).

Anal. Base Found: N, 10.99. Calcd. for $C_{18}H_{22}N_2$: N, 10.52%. Picrate Found: C, 57.92; H, 4.78; N, 14.29. Calcd. for $C_{24}H_{25}O_7N_5$: C, 58.17; H, 5.09; N, 14.14%.

No production of dihydroisoquinoline or amidine were observed with phosphorus oxychloride, polyphosphoric acid or thionyl chloride in liquid sulfur dioxide from II. Yields obtained with a variety of conditions are listed in Table I.

Hydrolysis of IV.—Two grams of this base was heated for 3.5 hr. under refluxing with 20 g. of 10% sodium hydroxide solution, then the mixture was acidified with hydrochloric acid. The mixture was extracted with benzene. The benzene solution, after washing with water and drying with anhydrous sodium sulfate, was concentrated and the residue was distilled in vacuo. A pale yellow oil (0.4 g.), boiling at 154~155°C (4~5 mmHg), was obtained. This was *N*-β-phenethyl acetamide. Hydrolyzing this acid amide to β-phenethyl amine with hydrochloric acid, a picrate of the amine was prepared. The melting point and the mixed melting point with an authentic sample were 167~168°C[7]. The residual solution was made alkaline with caustic alkali again and the product was extracted with benzene. The benzene extract, after washing with water and drying with anhydrous sodium sulfate, was concentrated and the residue was fractionated in vacuo. Two oils, boiling at 110~115°C (50~51 mmHg) and 205~215°C (6~7 mmHg) were obtained. The first colorless oil (0.4 g.) was *N*-β-phenethyl amine. A picrate of the amine was prepared. The melting point and the mixed melting point with an authentic sample were 167~168°C[7]. The second pale yellow oil (0.2 g.) obtained was the recovered *N*, *N'*-bis-β-phenethyl acetamidine. A picrate of the amidine was prepared. The melting point and the mixed melting point with the picrate of the amidine (reaction product in liquid sulfur dioxide) were 118~119°C.

Preparation of IV from II with Hydrogen Chloride.—*N*-β-Phenethyl acetamide was subjected to a reaction with hydrogen chloride stream at 150°C for two hours according to the preparation method of Wallach[14]. A basic pale yellow oil ($n_D^{15}=1.5718$) boiling at 175~185°C (1~2 mmHg) was obtained and yielded a picrate of m. p. 118~119°C. This melting point was not depressed on mixture with the picrate of the basic substance (b. p. 180~190°C/2~3 mmHg) obtained from *N*-β-phenethyl acetamide in liquid sulfur dioxide and assumed to be *N*, *N'*-bis-β-phenethyl acetamidine (IV).

Reaction of *N*-β-Phenethyl Benzamide (II) ($R=C_6H_5$) in Liquid Sulfur Dioxide.—A solution of 9 g. (0.04 mol.) of *N*-β-phenethyl benzamide in 50 ml. of sulfur dioxide was added to 50 ml. of sulfur dioxide containing the reagent (molar ratio of amide to P_2O_5 was 1 : 5). After the reaction for six hours and at 20°C with shaking, the solvent was allowed to evaporate and water was added with chilling. The acid mixture was extracted with benzene. The benzene solution, after washing with ammonia water and then with water, was dried with anhydrous sodium sulfate and was evaporated. The residue gave crystals melting at about 115°C. The crystals 4.4 g. (48.8%) were recrystallized from ethanol as colorless leaflets, melting at 116~116.5°C and were identified as the recovered *N*-β-phenethyl benzamide. When the reaction was carried out at 70°C, the benzene extract gave crystals of m. p. 110~110.5°C, faintly orange prisms (from ethanol). The crystals (1.1 g., 12.7%) were assumed to be *N*-benzoyl-*N*, *N'*-bis-β-phenethyl benzamidine (VI). I. R. ν_{max}^{KBr}: 2935, 2860, 1643, 1626, 745 and 695 cm^{-1}, U. V. λ_{max}^{MeOH}: 241 mμ (ε_{max} 18647), mol. wt. [Rast's method (camphor)]: 423, calcd. as $C_{30}H_{28}ON_2$, 432.

Anal. Found: C, 83.08; H, 6.05; N, 6.41. Calcd. for $C_{30}H_{28}ON_2$: C, 83.30; H, 6.53; N, 6.41%.

The residual acid aqueous solution after benzene extraction was made alkaline with ammonia water and was again extracted with benzene. The benzene solution was dried and concentrated. When 2 N sulfuric acid was added to the residue, an oil was precipitated. The supernatant solution was decanted and ammonia water was added to the oil. The oil changed into crystals. The crystal (0.8 g., 12.3%, reaction at 20°C and 0.6 g., 9.2%, reaction at 70°C) obtained by filtration was recrystallized from ligroin (b. p. 100~120°C) as colorless needles, melting at 79.5~80°C (picrate, yellow plate, m. p. 170~170.5°C) and was identified as *N*, *N'*-bis-β-phenethyl benzamidine[10] (V) (m. p. and mixed m. p. 79.5~80°C) (picrate[11], m. p. and mixed m. p. 170~170.5°C).

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[8] E. Späth, F. Berger and W. Kuntara, ibid., **63**, 134 (1930).

[9] K. G. Cunningham, W. Dawson and F. S. Spring, *J. Chem. Soc.*, **1951**, 2305.

[10] G. L. Webster and J. S. Rodia, *J. Am. Chem. Soc.*, **75**, 1762 (1953).

[11] C. I. Brodrick and W. F. Short, *J. Chem. Soc.*, **1951**, 1344.

The supernatant solution decanted was made alkaline with ammonia water and was again extracted with benzene. The benzene solution, after washing with water and drying with anhydrous sodium sulfate, was concentrated and the residue was distilled in vacuo. A pale yellow oil (n_D^{18}=1.6293) boiling at 150~160°C (2~3 mmHg) was obtained. This base (1.2 g., 14.6%, reaction at 20°C and 6.6 g., 80.4%, reaction at 70°C) was 1-phenyl-3, 4-dihydroisoquinoline (III) (R=C_6H_5). Picrate, yellow needle, m. p. 173.5~174°C. Reported melting points 173~174°C[12]. No melting point depression was observed when mixed with an authentic sample.

Anal. Base Found: N, 6.31. Calcd. for $C_{15}H_{13}N$: N, 6.76%. Picrate Found: N, 12.82. Calcd. for $C_{21}H_{16}O_7N_4$: N, 12.84%.

The results and the related facts observed were shown in Table II.

The residual ammoniacal solution after extraction was acidified with sulfuric acid and was extracted again with benzene. The benzene solution, after washing with water and drying with anhydrous sodium sulfate, yielded a crystal after evaporation. This crystal (0.2 g., 8.3%, reaction at 20°C and 0.2 g., 8.3%, reaction at 70°C) was recrystallized from 50% ethanol to an m. p. of 121~121.5°C and was identified as benzoic acid by a mixed melting point determination.

Hydrolysis of VI.—Six tenths gram of VI was heated for two hours on a boiling water bath with 2 N sulfuric acid, then the mixture was made alkaline with ammonia water and was extracted with benzene. The benzene solution, after washing with water and drying with anhydrous sodium sulfate, was concentrated and was triturated with ether. The ether-insoluble residue (0.3 g.) melted at 114~115°C. This was *N*-β-phenethyl benzamide. From the ether solution, a viscous liquid (0.1 g.) was obtained and changed to a crystal melting at 69~70°C (recrystallization from ligroin, b. p. 100~120°C). A picrate of this basic matter was prepared. The melting point and the mixed melting point with the picrate[11] of the *N, N'*-bis-β-phenethyl benzamidine (V) were 170~170.5°C. The residual aqueous solution after extraction was acidified with sulfuric acid and was extracted with benzene. The benzene solution gave a crystal (0.1 g.) melting at 121~121.5°C. This was identified as benzoic acid by a mixed melting point procedure.

Preparation of VI.—*N, N'*-bis-β-phenethyl benzamidine[10] was subjected to a reaction for four hours with benzoyl chloride in boiling benzene according to the method[13] of Oxley and Short. A neutral faintly orange prism melting at 110~110.5°C was obtained. This melting point was not depressed on mixture with the neutral substance (m. p. 110~110.5°C) obtained from *N*-β-phenethyl benzamide in liquid sulfur dioxide, thus establishing the structure of the latter to be *N*-benzoyl-*N, N'*-bis-β-phenethyl benzamidine (VI).

Reaction of Acetanilide (VII) in Liquid Sulfur Dioxide (Table II).—A solution of 5.4 g. (0.04 mol.) of acetanilide in 50 ml. of sulfur dioxide was added to a mixture of reagent (molar ratio of amide to P_2O_5 was 1 : 5) in 50 ml. of sulfur dioxide. When the reaction at 20°C for six hours with shaking was over, the reaction mixture was treated as in the previous case. From the benzene extract of the reaction mixture (acidic condition) there was recovered 3.1 g. (57.4%) of acetanilide, m. p. 113.5~114°C (recrystallization from benzene). No melting point depression was observed when mixed with an authentic sample.

The residual solution was made alkaline by sodium hydroxide solution. From the benzene extract of the solution, there was separated an oil, which changes to a crystalline matter. The crystal (0.8 g., 19.0%) was recrystallized from 50% ethanol as a colorless needle, melting at 131.5~132°C and was identified as *N, N'*-diphenyl acetamidine[14] (VII) (m. p. and mixed m. p. 131.5~132°C). I. R. ν_{max}^{KBr}: 3220, 1637, 1380, 757 and 690 cm^{-1}, U. V. λ_{max}^{MeOH}: 265 mμ (ε_{max} 18827), mol. wt. [Rast's method (camphor)]: 208, calcd. as $C_{14}H_{14}N_2$, 210. Picrate, yellow needle (from 95% ethanol): m. p. 168.5~169°C[15], mol. wt. (by the Cunningham method)[9]: 475, calcd. as $C_{20}H_{17}O_7N_5$ (the molar ratio, picric acid : base=1 : 1), 439.

Anal. Base Found: C, 79.76; H, 6.53; N, 13.55. Calcd. for $C_{14}H_{14}N_2$: C, 79.96; H, 6.71; N, 13.32%. Picrate Found: C, 54.86; H, 4.12; N, 15.76. Calcd. for $C_{20}H_{17}O_7N_5$: C, 54.67; H, 3.90; N, 15.94%.

From the filtrate, 0.3 g. (5.5%) of an oil was obtained by distillation in vacuo. Colorless oil, b. p. 96~102°C (49~50 mmHg) was identified as aniline by its benzoylation[16], m. p. and mixed m. p. 160°C.

When the reaction was conducted at 70°C for six hours, 1.9 g. (35.1%) of the acid amide was recovered and 1.3 g. (30.9%) of the amidine and 0.6 g. (11.1%) of aniline were obtained.

Reaction of Benzanilide (X) in Liquid Sulfur *Dioxide* (*Table II*).—To a mixture of benzanilide 7.9 g. (0.04 mol.) and the reagent (molar ratio of amide to P_2O_5 was 1 : 5), was added 100 ml. of sulfur dioxide. When the reaction at 20°C for six hours with shaking was over, the solvent was allowed to evaporate and water was added with chilling. The acid mixture was filtered. The filtrate was extracted with benzene. From the benzene solution, after washing with water and drying with anhydrous sodium sulfate, a trace of crystal was obtained. The crystal was recrystallized from 50% ethanol as a colorless needle, melting at 121~121.5°C and was identified as benzoic acid by a mixed melting point. The residue, after filtration, was washed with water and dried. Fractional crystallization of the residue from ethanol gave two kinds of crystals melting at about 160 and about 170°C, respectively. The first crystal 3.3g. (41.7%) was recrystallized from ethanol as a colorless leaflet, melting at

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[12] C. I. Brodrick and W. F. Short, ibid., **1951**, 1345.

[13] P. Oxley and W. F. Short, *J. Chem. Soc.*, **1948**, 1524.

[14] O. Wallach, *Ber.*, **15**, 208 (1882).

[15] P. Oxley and W. F. Short, *J. Chem. Soc.*, **1947**, 384.

[16] L. Claisen, *Ber.*, **27**, 3182 (1894).

162.5~163°C and was identified as the recovered benzanilide.

The second crystal was recrystallized from benzene-ethanol as a faintly yellow prism, melting at 172~172.5°C. This crystal (3.5 g., 46.6%) was identified as *N*-benzoyl-*N, N'*-diphenyl benzamidine[13] (XII) (m. p. and mixed m. p. 172~172.5°C). I. R. $\nu_{\max}^{\text{KBr}}$: 1650, 1626, 763 and 690 cm^{-1}, U. V. $\lambda_{\max}^{\text{MeOH}}$: 255 m$\mu$ ($\varepsilon_{\max}$ 20890), mol. wt. [Rast's method (camphor)]: 366, calcd. as $C_{26}H_{20}ON_2$, 376. *Anal.* Found: C, 83.31; H, 5.25; N, 7.21. Calcd. for $C_{26}H_{20}ON_2$: C, 82.95; H, 5.36; N, 7.44%.

The residual acid aqueous solution was made alkaline with ammonia water and was extracted again with benzene. The benzene solution, after washing with water and drying with anhydrous sodium sulfate, was evaporated and the residue was given as a crystal. The crystal (0.1 g., 1.8%) was recrystallized from benzene as a colorless needle, melting at 146~146.5°C (picrate, yellow plate, m. p. 216.5~217°C with decomp.) and was identified as *N, N'*-diphenyl benzamidine[17] (XI) (m. p. and mixed m. p. 146~146.5°C, picrate[18], m. p. and mixed m. p. 216.5~217°C with decomp.).

When the reaction was conducted at 70°C for six hours, 0.4 g. (5.0%) of the acid amide was recovered and 0.4 g. (16.6%) of benzoic acid, 1.4 g. (18.6%) of *N*-benzoyl-*N, N'*-diphenyl benzamidine and 2.5 g. (46.2%) of *N, N'*-diphenyl benzamidine were obtained.

Reaction of *N*-Benzyl Acetamide (XIII) (R= CH_3) in Liquid Sulfur Dioxide.—To a mixture of the reagents (P_2O_5, 29 g., molar ratio of amide to P_2O_5 was 1 : 5) in 50 ml. of liquid sulfur dioxide was added a solution of 5.9 g. (0.04 mol.) of *N*-benzyl acetamide in 50 ml. of liquid sulfur dioxide. The reaction mixture was treated as described above after shaking for six hours at 70°C. A small amount of basic substance and a viscous residue were obtained in the reaction mixture (Table II).

Reaction of *N*-Benzyl Benzamide (XIII) (R= C_6H_5) in Liquid Sulfur Dioxide. — A solution of 8.4 g. (0.04 mol.) of the *N*-benzyl benzamide in 50 ml. of liquid sulfur dioxide was added to 50 ml. of sulfur dioxide containing the reagent (P_2O_5 five times moles against that of the amide). The reaction mixture was treated as in the previous case after shaking for six hours at 20 or 70°C. A small amount of resinous basic substance and a large amount of viscous acidic or neutral substance were separated from the viscous reaction mixture. But they were not further examined.

Summary

The Bischler-Napieralski reaction of *N*-β-phenethyl acetamide in liquid sulfur dioxide resulted in the formation of *N, N'*-bis-β-phenethyl acetamidine in addition to the expected 1-methyl-3, 4-dihydroisoquinoline. And the reaction product from *N*-β-phenethyl benzamide were *N, N'*-bis-β-phenethyl benzamidine and *N*-benzoyl-*N, N'*-bis-β-phenethyl benzamidine in addition to the expected 1-phenyl-3,4-dihydroisoquinoline. In the case of acetanilide, *N, N'*-diphenyl acetamidine was produced. Benzanilide afforded *N, N'*-diphenyl benzamidine and *N*-benzoyl-*N, N'*-diphenyl benzamidine under a similar condition. The similar reaction of benzyl acylamides in liquid sulfur dioxide failed to yield such amidines.

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