Beckmann Rearrangement in Liquid Sulfur Dioxide[1]. *IV.* *Syntheses of 1-Methyl-3,4-dihydro-isoquinoline and 9-Phenyl-phenanthridine*

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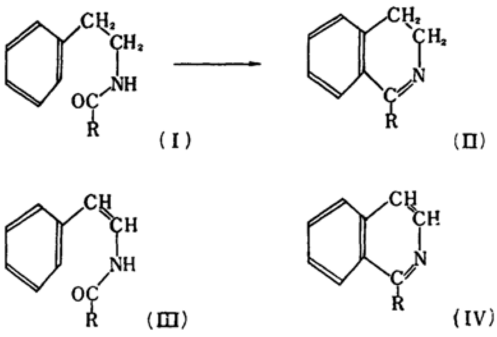
The increasing interest in the syntheses of isoquinoline derivatives which are found in alkaloids extensively has developed three important methods[2] since the beginning of this century. The Bischler-Napieralski reaction consists in the cyclodehydration of *N*-phenethylamides of aliphatic or aromatic carboxylic acids (I) to 1-alkyl- or 1-aryl-3, 4-dihydroisoquinolines (II), or of *N*-styrylamides of aliphatic or aromatic carboxylic acids (III) to 1-alkyl- or 1-aryl-isoquinolines (IV), by heating at a high temperature with phosphorus pentoxide:

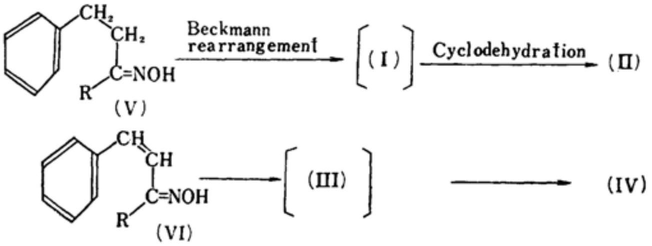
Chart 1.



R=alkyl or aryl

The starting materials for such a cyclodehydration, acid amides I or III, may be conveniently derived from oximes V or VI by the Beckmann rearrangement. Though several attempts[3-6] have been made to synthesize isoquinoline derivatives from such oximes without isolating the intermediate acid amides, the synthetic value of such simultaneous methods has still been in doubt[2] and the yields of isoquinolines were very scarce except in a few special cases. Only when the benzene rings bore electron donating groups such as alkyl, alkoxyl, etc., the yields of the isoquinolines were promoted[7,8].

Chart 2.



In the preceding papers[1], the authors reported that liquid sulfur dioxide was a superior solvent for the Beckmann rearrangement. Generally, the rearrangement in this solvent was accomplished instantaneously at the room temperature giving excellent yields.

In addition, the authors have recently been able to get another piece of information concerning the usefulness of liquid sulfur dioxide. Bradsher and Sinclair[9] employed phosphorus pentoxide in liquid sulfur dioxide at -10°C for cyclodehydration of *o*-benzylacetophenone and its derivatives to obtain anthracene derivatives in good yields.

As a preliminary examination, *N*-phenethylacetamide (I, $R=CH_3$) was subjected to the Bischler-Napieralski reaction with phosphorus pentoxide in liquid sulfur

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[1] Part III of this series: R. Tada and N. Tokura, This Bulletin, **31**, 387 (1958).

[2] Roger Adams, "Org. Reactions", Vol. VI, pp. 74—100, John Wiley and Sons, New York (1951).

[3] S. Komatsu, *Mem. Coll. Kyoto Imp. Univ.*, **7**, 147 (1924). *Chem. Abstr.*, **18**, 2126 (1924).

[4] C. Goldschmidt, *Ber.*, **27**, 1954, 2795 (1894), ibid., **28**, 818 (1895).

[5] C. S. Gibson, K. V. Hariharan, K. N. Menon and J. L. Simonsen, *J. Chem. Soc.*, **1926**, 2247.

[6] P. A. S. Smith, *J. Am. Chem. Soc.*, **76**, 436 (1954).

[7] K. N. Gaind, S. Kopoar and J. N. Ray, *J. Indian Chem. Soc.*, **18**, 213 (1941).

[8] S. Sugasawa, *J. Chem. Soc.*, **1933**, 1583.

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

TABLE I

SYNTHESES OF 1-METHYL-3, 4-DIHYDROISOQUINOLINE FROM BENZYLACETONE OXIME IN LIQUID SO_2[a, b]

No.	Reagent	Molar ratio of oxime to reagent	Reaction		*N*-Phenethyl acetamide yield (%)	1-Methyl-3, 4-dihydroisoquinoline yield (%)
			temp. (°C)	time (hr.)		
1	P_2O_5	1 : 5	20	6	10.0	4.5[c]
2	P_2O_5	1 : 5	20	12	20.0	trace
3	P_2O_5	1 : 5	−10	12	trace	0
4	P_2O_5	1 : 5	70	6	15.0	15.9
5	$P_2O_5+SOCl_2$	1 : 5 : 5	70	6	trace	0
6	$P_2O_5+POCl_3$	1 : 5 : 10	50	12	40.0	13.6
7	$P_2O_5+POCl_3$	1 : 5 : 10	70	3	36.0	18.1
8	$P_2O_5+POCl_3$	1 : 5 : 10	70	6	24.0	40.9
9	$P_2O_5+POCl_3$	1 : 5 : 10	70	12	4.0	45.4[d]
10	$P_2O_5+POCl_3$	1 : 5 : 10	110	12	0.0	29.5
11	$P_2O_5+POCl_3$	1 : 5 : 10	70	12	10.0	13.6[e]
12	$P_2O_5+POCl_3$	1 : 5 : 10	70	12	6.0	18.1[f]

a) Reactions were caused to proceed with 5 g. (0.03 mole) of the oxime in 70 ml. of liq. SO_2.

b) $POCl_3$, $SOCl_2$, PCl_5, or SO_3, used as the reagent in liquid sulfur dioxide (molar ratio of oxime to reagent was 1 : 5) at 20°C for 12 hr. or at 70°C for 6 hr., caused no reaction.

c) Reaction with shaking.

d) No difference was observed between the reaction with shaking and that without shaking.

e) Reaction was caused to proceed without solvent (liquid SO_2).

f) Tetralin (70 ml.) was added to the reaction mixture.

dioxide by modifying Bradsher and Sinclair's cyclodehydration. It was ascertained that 1-methyl-3, 4-dihydroisoquinoline was obtained in a yield of over 40 per cent. The results and the related facts observed will be reported elsewhere.

From the facts mentioned above, it appeared reasonable to expect that the reaction of the oximes of phenethyl ketones with acidic reagents in liquid sulfur dioxide may well lead to the production of isoquinoline derivatives.

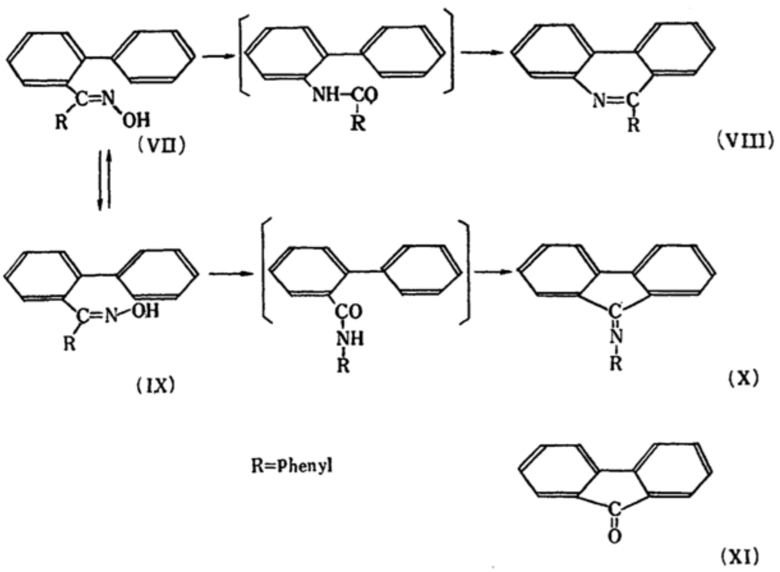
For the purpose of estimating the efficiency of this procedure benzylacetone oxime (V, $R=CH_3$) seemed suitable and it was subjected to the simultaneous rearrangement and cyclodehydration in liquid sulfur dioxide to obtain 1-methyl-3, 4-dihydroisoquinoline (II, $R=CH_3$). As shown in Table I, the best result (45.4% yield) was attained by treating the oxime with a mixture of phosphorus pentoxide and phosphorus oxychloride at 70°C in liquid sulfur dioxide.

Among various reagents examined, sulfuric acid, sulfur trioxide, thionyl chloride and phosphorus pentachloride were ineffective and phosphorus pentoxide gave a small quantity of the product. But when a mixture of phosphorus pentoxide and phosphorus oxychloride was used at 70°C for twelve hours, the amount of the product reached the maximum (45.4%). As for the reaction temperature, a better yield was obtained at 70°C rather than below 0°C, which differed somewhat from the experience of Bradsher and Sinclair[9]. Shaking of the reaction vessel resulted only in a slight improvement. Addition of another solvent such as tetralin gave no good effect. Because phosphorus pentoxide was not dissolved but suspended in liquid sulfur dioxide, the addition of a large amount of phosphorus oxychloride served probably to keep the suspension homogeneous.

A considerable amount of acid amide (I, $R=CH_3$) was found in the reaction mixture. This explains the fact that the cyclodehydration is rather a slow reaction and the first step (the Beckmann rearrangement) proceeds promptly before the cyclodehydration takes place. When benzylideneacetone oxime (VI, $R=CH_3$) was subjected to this reaction, only a resinous product was produced. This suggests that a vinyl polymerisation occurred in liquid sulfur dioxide.

The preparation of 9-phenylphenanthridine (VIII) in liquid sulfur dioxide was attempted. Smith[6] reported that the yield of this substance from *o*-phenylbenzophenone oxime (VII) by heating with polyphosphoric acid was 17 per cent.

Chart 3.



With phosphorus pentoxide and phosphorus oxychloride in liquid sulfur dioxide, 9-phenylphenanthridine (VIII) was obtained in an improved yield of 29.4 per cent. Moreover, fluorenone (XI) was also isolated from the reaction mixture as was reported by Smith.

It is an established fact that a *trans*-migration occurs in the Beckmann rearrangement. When *o*-phenylbenzophenone oxime (VII) takes another geometrical structure IX, it may afford fluorenoneanil (X) as the product. This will produce fluorenone (XI) by hydrolysis in the acidic medium.

The method mentioned above, the simultaneous rearrangement and cyclodehydration in liquid sulfur dioxide under mild conditions, may give excellent syntheses of dihydroisoquinoline, phenanthridine and their derivatives and may be applied extensively with great advantages.

Experimental

Liquid sulfur dioxide.—Commercial sulfur dioxide was dried with sulfuric acid and distilled.

Reagents.—Phosphorus pentoxide, oxychloride, and pentachloride, sulfuric acid, sulfur trioxide and thionyl chloride were of extra pure grade.

Apparatus and general procedure.—Glass pressure vessels (300 ml. capacity) equipped with metal joints and appropriate cocks or valves were used as before1). A liquid sulfur dioxide solution of an oxime was added to a mixture or a solution of the dehydrating reagent in the same solvent with ice-cooling. The vessel was kept at a definite temperature during the reaction period for a definite time. If necessary, the vessel was shaken. Then the solvent was evaporated and recovered. The residue was dropped into ice water and the excessive reagent was decomposed. Then the products were separated for their identification.

Synthesis of 1-methyl-3, 4-dihydroisoquinoline from benzylacetone oxime.—*Benzylacetone.*—Essentially the methods of Leuchs10) and Meerwein11) were followed. Metallic sodium (42 g.) was dissolved in 500 ml. of absolute ethanol and 500 g. of ethyl acetoacetate was added. To this mixture cooled below 30°C, 246 g. of benzyl chloride was added and the whole was stirred for 1 hour at room temperature. The reaction mixture was further refluxed for 1 hour and filtered. From the filtrate 350 g. of ethyl 2-benzylacetoacetate was obtained as a transparent liquid boiling at 140~145°C (5 mmHg). In an autoclave, a mixture of 350 g. of the ethyl 2-benzylacetoacetate and 200 ml. of water was heated for 30 min. at 250°C. The oily layer and the ethereal extract of the aqueous layer were combined, washed with 50 ml. of 0.1 N sodium hydroxide solution and with water successively, and distilled. Benzylacetone distilled at 105~110°C (10 mmHg). Yield, 160 g.

Benzylacetone oxime.—Prepared by the ordinary method12), m. p. 84~85°C. From 160 g. of benzylacetone, 134 g. of the oxime was obtained.

1-Methyl-3, 4-dihydroisoquinoline (*II*, *R*=CH_3).—A solution of 5 g. (0.03 mole) of benzylacetone oxime in 20 ml. of liquid sulfur dioxide was added to a mixture of the reagents (molar ratio of oxime, phosphorus pentoxide and phosphorus oxychloride was 1 : 5 : 10) in 50 ml. of the same solvent. After the reaction at 70°C for 12 hours, the solvent (sulfur dioxide) was allowed to

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10) H. Leuchs, *Ber.*, **44**, 1510 (1911).
11) H. Meerwein, *Ann.*, **398**, 249 (1913).
12) P. W. Neber and A. Uber, ibid., **467**, 63 (1928).

evaporate from the mixture. The residue was added to ice water and excessive reagents were decomposed. The mixture was extracted with ether. The ethereal solution, after being dried over calcium chloride, was condensed and the residue was distilled in vacuo. The rearranged product, acid amide (I, R=CH_3), was obtained as an oil boiling at 155∼157°C (5 mmHg); yield, 0.2 g. (4%). The acid amide was hydrolyzed to phenethylamine with hydrochloric acid, and a picrate of the amine was prepared. The melting point and the mixed melting point with an authentic sample were 167∼168°C (reported[13] m. p. 171°C).

The residual aqueous solution was made alkaline with caustic alkali and steam-distilled. The distillate was again made alkaline and extracted with ether. The ether solution, after being dried over magnesium sulfate, was condensed and the residue was distilled in vacuo. A pale yellow oil boiling at 95∼105°C (5∼6 mmHg) was obtained. This was 1-methyl-3, 4-dihydroisoquinoline. Picrate, yellow needles, m. p. 188∼189°C (reported[14] m. p. 188∼190°C). No depression of the melting point was observed when mixed with an authentic sample.

Anal. Base: Found; N, 9.74%. Calcd. for $C_{10}H_{11}N$; N, 9.65%. Picrate: Found; N, 15.13%. Calcd. for $C_{16}H_{14}O_7N_4$; N, 14.97%.

Dihydroisoquinoline was not produced with phosphorus oxychloride or with thionyl chloride. Sulfuric acid or sulfur trioxide appeared to produce water soluble substances which could not be separated. The effects of reaction conditions on the yield of 1-methyl-dihydroisoquinoline are listed in Table I.

An attempted synthesis of 1-methyl-isoquinoline from benzylideneacetone oxime (VI, R = CH_3).—Vorländer's[15] recipe was followed. A mixture of 320 g. of acetone, 210 g. of benzaldehyde washed with dilute soda solution, and 200 ml. of water was added to 50 ml. of 10% caustic soda solution in two hours at 10∼20°C. The reaction mixture was stirred further for two hours and was allowed to stand for 24 hours at room temperature. The solution was made acidic with hydrochloric acid and the oily layer was separated. The aqueous layer was thoroughly extracted with benzene. The oily layer combined with the benzene extract was washed with water and dried over calcium chloride. After the benzene and the unchanged benzaldehyde were distilled off, a pale yellow oil boiling at 105∼110°C (3 mmHg) was obtained. Yield, 180 g. The above benzylideneacetone was mixed with hydroxylamine hydrochloride in methanol. The crystals separated in a few days were recrystallized from 60% ethanol: benzylideneacetone oxime[16], m. p. 114∼115°C. Yield, 45 g.

Reaction of benzylideneacetone oxime (VI, R=CH_3).—A solution of 4.8 g. of the oxime in 20 ml. of liquid sulfur dioxide was added to a mixture of reagents (molar ratio of oxime to phosphorus pentoxide and phosphorus oxychloride was 1 : 5 : 10) in 50 ml. of liquid sulfur dioxide. The reaction mixture was treated as described above after 3 hours shaking at 70°C, or 6 hours shaking at room temperature. No significant amount of basic materials was found in the reaction mixture except resinous matters.

Synthesis of 9-phenylphenanthridine (VIII) from *o*-phenylbenzophenone oxime (VII).—*o-phenylbenzophenone.*—This was prepared from fluorene as follows: fluorenone obtained from the oxidation of fluorene[17] was cloven to *o*-phenylbenzoic acid[18] by alkali fusion. *o*-phenylbenzonitrile was prepared from this acid via its acid amide and was treated with phenylmagnesium bromide by Schlenk and Bergmann's[19] method to yield *o*-phenylbenzophenone. From 200 g. of fluorene, 25 g. of the ketone was obtained.

o-Phenylbenzophenone oxime (VII).—This was Prepared by the procedure of Smith[6]. Yield 18.3 g. from 25 g. of the ketone.

9-Phenylphenanthridine (VIII).—A solution of 5.4 g. (0.02 mole) of the oxime (VII) in 20 ml. of liquid sulfur dioxide was added to a mixture of the reagents (mole ratio of oxime: phosphorus pentoxide : phosphorus oxychloride, 1 : 5 : 10) in 50 ml. of liquid sulfur dioxide. After being allowed to stand at 70°C for 3 hours the reaction mixture was treated as described above. The resulting aqueous acidic mixture was made alkaline with ammonia and extracted with benzene. The extract was washed first with dilute, then with conc. hydrochloric acid, and finally with water. Neutralization of the acidic solution precipitated a basic material, which was recrystallized from ethanol to give crystalline 9-phenylphenanthridine. Yield, 1.5 g. (29.4%), m. p. 103∼104°C. Picrate: yellow needles, m. p. 247∼247.5°C (decomp.) (reported[20] m. p. 242°C (decomp.)). The mixed melting points of the base and of the picrate with the authentic samples respectively showed no depression.

Anal. Base: Found; N, 5.68%. Calcd. for $C_{19}H_{13}N$; N, 5.49%. Picrate: Found; N, 11.94%. Calcd. for $C_{25}H_{16}O_7N_4$; N, 11.57%.

When the benzene solution was condensed, 2.7 g. of dark yellow crystals was obtained. Recrystallization from ligroin (b. p. 60∼80°C) gave 2.4 g. of pale yellow plates, m. p. 83∼84°C, which showed no depression of the melting point on mixing with fluorenone (m. p. 83∼84°C).

When the reaction was conducted at 20°C for 12 hours, 0.2 g. (3.9%) of VIII and 1 g. of XI were obtained. A viscous orange liquid (4.2 g.) was also obtained along with XI from the benzene extracts in this case, the liquid being separated by fractional distillation under a reduced pressure. The liquid which distilled at 190∼200°C (1∼2 mmHg) contained nitrogen (N, 5.96%), but

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

[14] E. Späth, F. Berger and W. Kuntara, ibid., **63**, 137 (1930).

[15] D. Vorländer, *Ann.*, **294**, 275 (1897).

[16] C. Harries and A. S. de Osa. *Ber.*, **36**, 2998 (1903).

[17] J. Schmidt and H. Wagner, ibid., **43**, 1797 (1910).

[18] C. Graebe and A. Sc. Rateanu, *Ann.*, **279**, 259 (1894).

[19] W. Schlenk and E. Bergmann, ibid., **464**, 34 (1928).

[20] A. Pictet and A. Hubert, *Ber.*, **29**, 1188 (1896).

showed no change on refluxing with hydrochloric acid in ethanol.

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