[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

SOME REACTIONS OF AMIDINES AS AMMONO-CARBOXYLIC ACIDS OR ESTERS[1]

E. C. WAGNER

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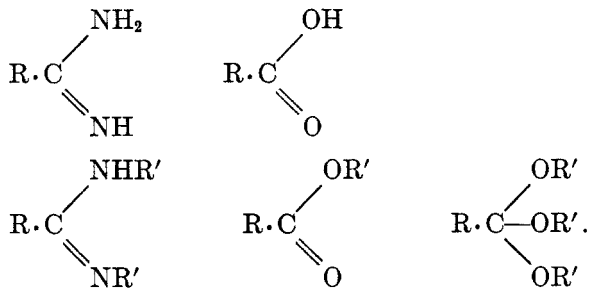
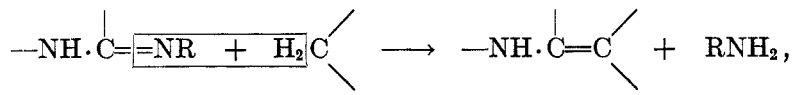
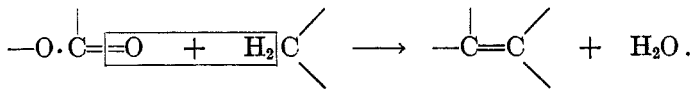
Amidines may be regarded as ammonia-system analogs of carboxylic acids or esters:



There is some evidence that this structural analogy is validated by a functional analogy. Examples include the condensation of isatin-α-anil and indoxyl, and the condensations of formamidines with reactive methylene compounds (1). Others are discussed by Franklin (2). Both the above examples involve the essential reaction



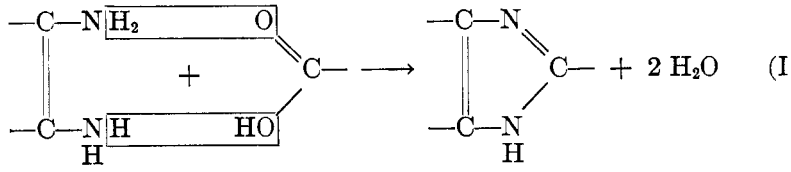
which is the ammonia-system counterpart of the reaction



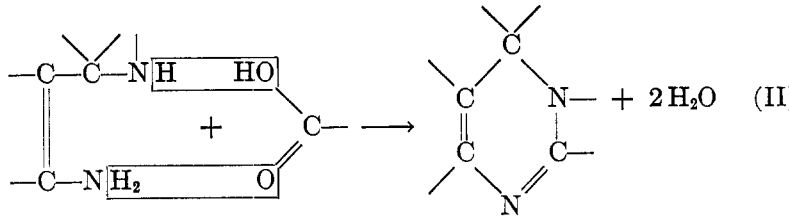
In these reactions only part of the amidine structure is involved, so that the functional analogy suggested above is only partially revealed. A reaction whose extension permits a more searching test of the analogy is the closure of 1,3-diazole (imidazole) or 1,3-diazine (pyrimidine) rings by action of formic acid or ester, or of their homologs, upon compounds with

[1] Presented in part at the 97th meeting of the American Chemical Society, Baltimore, Md., April 3 to 7, 1939.

two nitrogen atoms in $-NH_2$ or $-NH-$ groups separated by two or three carbon atoms:

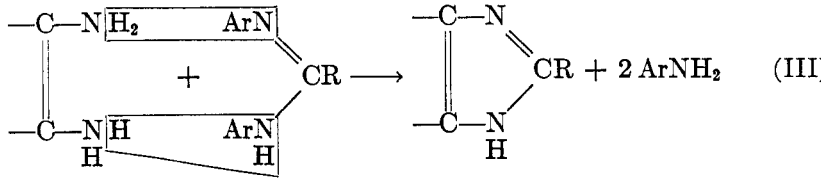


(I)

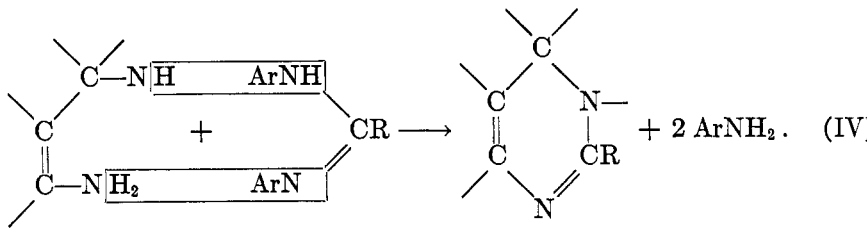


(II)

The expectation that these reactions might be duplicated by use of amidines has been realized for certain of the N,N′-diaryl formamidines and acetamidines, the essential changes being ammonia-system counterparts of (I) and (II), viz.,

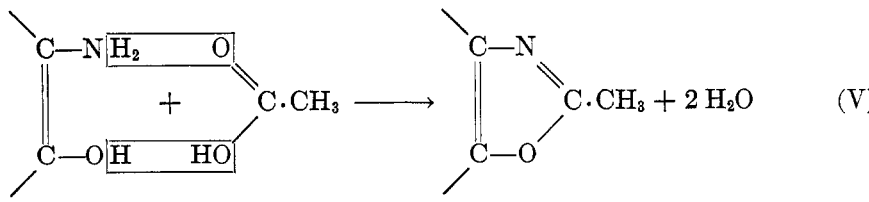


(III)

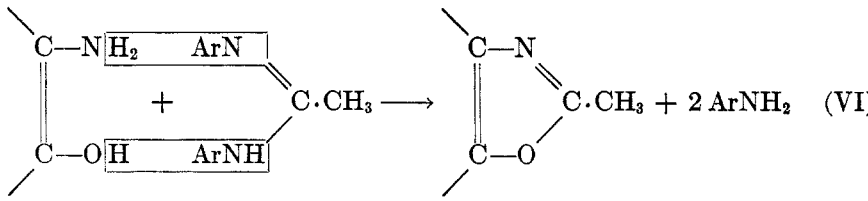


(IV)

Similarly the formation of the oxazole ring by acetic acid (anhydride) was duplicated by use of diaryl acetamidine:



(V)



(VI)

It appears that formamidines enter into such reactions more readily than do amidines of homologous or other acids. Acetamidines were used in a few trials, successfully in reactions (III) and (VI) and unsuccessfully in reaction (IV). Preliminary experiments indicated diphenylbenzamidine to be unreactive according to equation (III) under conditions favorable to reactivity of formamidines and acetamidines.

Reactions with amidines were carried out in general by simple fusion of the reactants, used either in equivalent amounts or with the amidine in excess. The following reactions are described in the experimental section.

I. Formation of imidazole ring (reactions I and III): (a) Conversion of *o*-phenylenediamine to benzimidazole by formic acid and by diarylformamidines; (b) Conversion of *o*-phenylenediamine to 2-methylbenzimidazole by acetic anhydride and by diphenylacetamidine.

II. Formation of pyrimidine ring (reactions II and IV): (a) Conversion of *o*-aminobenzylarylamines to 3,6-disubstituted dihydroquinazolines by formic acid and by diarylformamidines; (b) Conversion of anthranilanilides to 3-substituted-4-ketoquinazolines by formic acid, by ethyl orthoformate and by diarylformamidines; (c) Conversion of 1,8-diaminonaphthalene to perimidine by formic acid and by diphenylformamidine.

III. Formation of oxazole ring (reactions V and VI): Conversion of *o*-aminophenol to 2-methylbenzoxazole by acetic anhydride and by diphenylacetamidine.

In two other cases preliminary experiments showed formamidines to react like formic acid or ethyl formate, viz., (a) Conversion of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline to the corresponding dihydroquinazoline by formic acid (3) and by di-*p*-tolylformamidine, a reaction whose course is as yet obscure; and (b) Conversion of phenylbiguanide to a single product (m.p. 230°, and presumably a *sym*-triazine derivative) by either ethyl formate (4) or diphenylformamidine.

EXPERIMENTAL

The required *o*-aminobenzylarylamines were prepared by the procedure described in a previous paper (5). The anthranilanilides were made from isatoic anhydride and suitable amines by the method of Kolbe (6). Diarylformamidines were made by interaction of arylamines and ethyl orthoformate (7). Diarylacetamidines were

prepared from arylamines, N-arylacetamides and phosphorus trichloride by a modification of the method of Sen and Ray (8). The other compounds were Eastman Kodak Company chemicals. Diaminonaphthalene was obtained also by hydrogenation of 1,8-dinitronaphthalene in an Adams and Vorhees apparatus, using Raney nickel, about thirty pounds per square inch pressure of hydrogen, and dioxane as solvent. The hydrogenation was slow and incomplete, the yield of diamine as hydrochloride being 55%. The reduction liquid was intensely purple in color, and yielded a dark blue by-product.

I. Formation of imidazole ring

Ring-closure by acids. Benzimidazole was obtained in 85% yield from *o*-phenylenediamine and formic acid by the method of Wundt (9), described in modified form in Organic Syntheses (10). Methylbenzimidazole was obtained from *o*-phenylenediamine and acetic anhydride in dilute hydrochloric acid by the method of Phillips (11). The yield of crude material was nearly quantitative, and was decreased to 85.5% after crystallization from water (m.p. 176° obs.), with 7.8% recoverable from the mother liquor as picrate (m.p. 212–215° obs.) (12).

Ring-closure by amidines. Benzimidazole was obtained by heating a mixture of *o*-phenylenediamine and somewhat more than one equivalent of diphenyl- or di-*p*-tolyl-formamidine at about 125° for several hours. The mixture was submitted to steam distillation, and the distillate was acidified with hydrochloric acid and evaporated to dryness to recover as hydrochloride the amine liberated in the reaction.[2] The residual liquid in the flask was made alkaline with sodium hydroxide and steam distillation was resumed, in order to decompose unused amidine and remove the resultant amine. The liquid was then acidified slightly with acetic acid, neutralized with sodium bicarbonate, digested with charcoal, filtered, and concentrated by evaporation. When the solution was chilled, benzimidazole separated as crystals of m.p. 171° obs., raised to 172° by recrystallization from water. A further small quantity of benzimidazole could be recovered as picrate (m.p. 223° obs.) from the first mother liquor.

By this procedure 1.08 g. (0.01 mole) of *o*-phenylenediamine and 3.0 g. (about 0.015 mole) of diphenylformamidine gave benzimidazole in 81.4% yield, with 3.9% more recovered as picrate; total indicated yield 85.3%. The aniline liberated in the reaction (2.84 g. of aniline hydrochloride) was 83% of the theoretical. The yield of benzimidazole was 63% when one equivalent of diphenylformamidine was used.

2-Methylbenzimidazole. A mixture of 1.08 g. (0.01 mole) of *o*-phenylenediamine and 3.15 g. (0.014 mole) of phenyl-*o*-tolylacetamidine was heated for two hours at 180°. The mass was treated with sodium hydroxide and the mixture submitted to steam distillation to remove aniline and *o*-toluidine. The liquid in the flask was acidified with acetic acid, made barely alkaline with ammonium hydroxide, digested with charcoal, filtered hot, and then chilled. The methylbenzimidazole weighed 0.84 g. (63.6% of the theoretical), melted at 176° obs., and was identified by mixed melting point test.

II. Formation of pyrimidine ring

(1) Formation of substituted dihydroquinazolines from o-aminobenzylarylamines. Ring-closure by formic acid or orthoformic ester. By heating the *o*-aminobenzyl-

[2] Steam distillation in absence of acid or alkali does not decompose these diarylamidines appreciably.

arylamine with excess of 90% formic acid on the water-bath (13) small yields (20 to 39%) of the corresponding dihydroquinazolines were obtained (14), viz.,

3-*p*-tolyl-6-methyldihydroquinazoline, m.p. 160° obs.,

3-*p*-chlorophenyl-6-chlorodihydroquinazoline, m.p. 186–7°, obs.,

3-*p*-bromophenyl-6-bromodihydroquinazoline, m.p. 200° obs.

Ethyl orthoformate was used similarly by v. Walther and Bamberg (13), who reported a 70% yield of 3-tolyl-6-methyldihydroquinazoline from 2-amino-5-methyl-N-tolyl-benzylamine.

Ring-closure by diarylformamidines. A mixture of the *o*-aminobenzylarylamine (0.01–0.02 mole), slightly more than one equivalent of the diarylformamidine and about 0.2 equivalent of the corresponding amine hydrochloride was heated on the water-bath for four hours or in an oil-bath at 130–140° for about two hours. The mixture was made alkaline with sodium hydroxide and was subjected to steam distillation. The residual solid was crystallized from dilute alcohol, and the mother liquor treated to recover a further quantity of product as picrate. Results were as follows:

o-AMINO-N-ARYLBENZYLAMINE	FORMAMIDINE	DIHYDROQUINAZOLINE	
		Yield %	m.p. C.°
2-Amino-5-methyl-N-(*p*-tolyl)-benzyl-amine	Diphenyl	78	161 obs.
2-Amino-5-chloro-N-(*p*-chlorophenyl)-benzylamine	"	69	186.5 "
	Di-*p*-chlorophenyl	69	187 "
2-Amino-5-bromo-N-(*p*-bromophenyl)-benzylamine	Diphenyl	48	198 "

In these reactions the amine hydrochloride was probably dispensable, as appears elsewhere in the experimental section. Its use in these early experiments was suggested by analogous use of amine salts in reactions which involve initial cleavage of methylene-N,N′-bis-arylamines (15).

An attempt to effect this ring-closure by means of an acetamidine was unsuccessful. After heating a mixture of 2-amino-5-methyl-N-(*p*-tolyl)-benzylamine and diphenylacetamidine in equivalent amounts for two hours at 190–200°, there was no steam-volatile oil present, and apparently little or no reaction had occurred. Most of the aminobenzylarylamine was recovered, in the form of its benzal derivative, and the other isolable compound was unchanged acetamidine.

(*2*) *Formation of substituted dihydroquinazolones from anthranilamide and anthranilanilides.*

Ring-closure by formic acid or ethyl orthoformate. Anthranilanilide, when heated with excess of formic acid or ethyl orthoformate for an hour at refluxing temperatures, yielded in either case 3-phenyldihydroquinazolone-4, m.p. 136° obs., or 139° corr., and identical with the product made by heating anthranilic acid and formanilide under open reflux for three hours at 130–140° (16). The picrates also were identical.

3-Phenyldihydroquinazolone-4 picrate. On mixing concentrated alcoholic solutions of 0.5 g. of the base and 1.10 g. of picric acid (slightly more than two equivalents), there separated 0.95 g. of the salt, a 94% yield of the 1:1 picrate. After crystallization from ethyl alcohol, the pure picrate melted at 177° obs., or 180.6° corr.

Ring-closure by formamidines. A mixture of the amide (0.01 mole) and diaryl-

formamidine (slightly more than 0.01 mole) was heated under reflux for two to three hours at temperatures which ranged from 130° to 160°. The reaction mixture was subjected to steam distillation to remove amine liberated in the reaction, and the residual crude product was dissolved in hot dilute alcohol and obtained by crystallization. Results are as follows:

AMIDE	FORMAMIDINE	DIHYDROQUINAZOLONE	
		Yield %*	m.p. C°
Anthranilamide	Di-*p*-tolyl	56	213 obs.
Anthranilanilide	Diphenyl	82	140 "
"	Di-*p*-chlorophenyl	82	137 "
p'-Bromo- "	Diphenyl	75	190 "

* Including product recovered as picrate.

An attempt to effect this ring-closure by means of an acetamidine was unsuccessful: no isolable quinazolone was obtained after heating anthranilanilide with 1.5 equivalents of diphenylacetamidine at 190° for two hours.

3,4-Dihydroquinazolone-4 picrate. When alcoholic solutions of 0.37 g. of dihydroquinazolone and 1.20 g. of picric acid (1.15 g. is two equivalents) were mixed 0.81 g. of the salt separated, an 85.3% yield of the 1:1 picrate. The melting point was 204° obs., with a color change from orange to yellow at 180–190°.

(*3*) *Formation of perimidine from 1,8-diaminonaphthalene.*

Ring-closure by formic acid. The procedure of Sachs (17) gave 78.7% and 79.7% of perimidine as light olive-green plates. The melting point ("about 222°") reported by Sachs could not be duplicated with certainty. On heating the substance in a capillary tube obvious decomposition was in progress around 220°. In several trials a drop separated around 226°. The nearly black mass appeared to be wholly liquid at 233° to 238°, with brown oily droplets on the walls of the tube. On the Dennis bar the melting point was equally uncertain, but was judged to be in the neighborhood of 238°. The picrate, reported by Sachs to melt at 226°, was found to decompose with effervescence around 249–250°. To establish more firmly the identity of the product with that described by Sachs it was analyzed for nitrogen: calc'd.: 16.6%; found: 16.3%.

Ring-closure by diphenylformamidine. A mixture of 1.58 g. of diaminonaphthalene (0.01 mole) and 2.0 g. of diphenylformamidine (0.01 mole) was heated at 160° for 90 to 150 minutes. Water was added to the cooled mass, which was submitted to steam distillation, the aniline being recovered and weighed as aniline hydrochloride. The solid residue in the flask was dissolved by addition of the minimum necessary hydrochloric acid. The solution was digested with charcoal, filtered, and the filtrate was treated with concd. hydrochloric acid in moderate excess (about one-fifth volume). The greenish-yellow crystalline perimidine hydrochloride thus salted out weighed 1.65 g. (80.7%). The aniline of reaction (1.97 g. of hydrochloride) was 79.7% of the theoretical. In other experiments the crude product (after the steam distillation) was crystallized from dilute alcohol, using decolorizing carbon, in some cases after first dissolving the crude material in dilute hydrochloric acid, digesting with charcoal, and precipitating by addition of sodium hydroxide and then sodium bicarbonate. The yields so obtained were comparable with the values above.

Perimidine thus obtained was similar in appearance and properties to the com-

pound made by use of formic acid, and a mixture of the two showed in the melting point determination the same behavior as either substance separately. The picrate of the base made by use of diphenylformamidine decomposed with effervescence at 247°, and a mixture with the picrate of the perimidine made by use of formic acid decomposed at the same temperature. The identity of the compounds made in the two ways was supported by the physical appearance of crystals obtained by sublimation. These were yellow-green needles, showing identical colors in polarized light, and a like extinction angle of about 14°.

III. Formation of the oxazole ring

Preparation of 2-methylbenzoxazole. The method of Ladenburg (18), which involves heating *o*-aminophenol with acetic anhydride, was used in the modification described by Phillips (19).

The same ring-closure was effected by use of diphenylacetamidine (instead of acetic anhydride), but the yield could be determined only approximately because of difficulty in separating the methylbenzoxazole from the aniline liberated in the reaction. The boiling points for these compounds (202° and 184°) appear to be favorable for separation by distillation, but this proved to be not feasible because of the high vapor pressure of methylbenzoxazole near the boiling point of aniline. Methylbenzoxazole was estimated by taking advantage of its ready conversion to *o*-acetaminophenol by mild acid hydrolysis (18), the acetaminophenol being obtained by chilling the solution. The procedure was as follows.

A mixture of *o*-aminophenol (0.02 to 0.05 mole) and slightly more than an equivalent amount of diphenylacetamidine was heated under reflux at 190–195° for two hours. The leek-like odor of methylbenzoxazole became noticeable after a short time and was finally strong. The methylbenzoxazole and aniline were removed together by distillation (184–205°). The mixture was suspended in water and treated with enough acetic acid to effect complete solution. The liquid was boiled gently for about thirty minutes, some charcoal was stirred in, and the mixture was filtered and the filtrate chilled. The acetaminophenol separated as colorless plates; m.p. 207° obs.; yield 56%. The filtrate smelled strongly of methylbenzoxazole, but after further boiling, and concentration by evaporation, no more acetaminophenol was obtained. By working up the mother liquor some *o*-aminophenol was isolated, corresponding to 4% of methylbenzoxazole, from which it had presumably been formed by complete hydrolysis.[3]

The *o*-acetaminophenol, after crystallization from dilute alcohol and then from 95% alcohol, melted at 208° obs., or 209.6° corr. It was identical with a specimen of *o*-acetaminophenol made from methylbenzoxazole prepared by the method of Phillips.

2-Methylbenzoxazole picrate. A solution of 2.7 g. (0.02 mole) of methylbenzoxazole in a little alcohol was added to a strong solution of 5.0 g. of picric acid (4.58 g. is 0.02 mole) in alcohol. The picrate separated only upon chilling the solution. The yield was 3.04 g. (42%), the picrate being fairly soluble in alcohol, probably because of separation into its components. The melting point was 117–118° obs.; melting was accompanied by volatilization of methylbenzoxazole, the odor of which was pronounced when the determination was made on a Fisher-Johns melting point

[3] As *o*-aminophenol sublimes on heating, it is possible that the recovered substance was aminophenol which had not reacted with diphenylacetamidine and which passed into the distillate with the methylbenzoxazole and aniline.

apparatus. This value, while close to the melting point of picric acid, is apparently a reproducible constant of the picrate, a mixture of which with picric acid melted badly from 103° to 115°.

Conversion of Tetrahydroquinazoline to Dihydroquinazoline. The conversion of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline to the corresponding dihydroquinazoline by heating with formic acid under pressure was reported in an earlier paper (3). The same transformation was effected also by use of diphenylformamidine instead of formic acid.

A mixture of 0.99 g. of tolylmethyltetrahydroquinazoline and 1.7 g. (about 2 equivalents) of diphenylformamidine, in a test tube provided with a reflux condenser, was heated in a metal-bath for a hour at 190–200°. The test tube was broken, and the solid mass (which gave off an isonitrile odor) was transferred to a flask, where it was treated with water and about 3 g. of sodium hydroxide. The mixture was submitted to steam distillation to remove aniline. The residue was dissolved in hot 95% alcohol; on chilling the solution there separated 0.47 g. of unchanged tetrahydroquinazoline (m.p. 139° after recrystallization from alcohol). The mother liquor was treated with picric acid, and yielded 0.75 g. of a picrate of m.p. 203° obs. A mixture of this compound with the picrate of tolylmethyldihydroquinazoline (m.p. 204° obs.) melted at 203–204° obs. The yield of dihydroquinazoline obtained in the reaction was 38%.

Interaction of phenylbiguanide and ethyl formate or diphenylformamidine. By allowing arylbiguanides and ethyl formate[4] to stand in alcoholic solution, products separate which are believed to be derivatives of *sym*-triazines (4). The compound thus obtained from phenylbiguanide and ethyl formate is a white solid, of m.p. 230–232°. Formation of the same compound by use of a formamidine instead of ethyl formate was effected as follows. A mixture of 3.54 g. (0.02 mole) of phenylbiguanide and 4.0 g. of diphenylformamidine (0.02 mole) was heated near 145° for an hour. The mixture first melted and later solidified. The odor of ammonia and that of isonitrile were detectable during the heating. The cooled mass was dissolved in hot dilute hydrochloric acid. The solution was digested with decolorizing carbon, filtered, and then neutralized by addition of sodium hydroxide solution and finally solid sodium bicarbonate. The product separated as a white powder; m.p. 227–230° obs.; yield 1.52 g. (40.6% calculated as the triazine). A mixture of this product and that made by use of ethyl formate melted at 230° obs. This and analogous compounds are the subject of continued study.

Grateful acknowledgment is made to the Faculty Research Committee of the University of Pennsylvania for a grant to assist this study.

SUMMARY

A clear functional basis for regarding amidines as ammonia-system analogs of carboxylic acids or their esters was established experimentally by effecting with several diarylformamidines and acetamidines certain ring-closures characteristically effected also by formic acid or ester or by acetic acid or anhydride. The reactions were essentially alike in type, and yielded the same products whether the reagent was acid (ester) or

[4] This reaction was called to the writer's attention by Dr. J. K. Simons, Mellon Institute, Pittsburgh, Pa.

amidine, the former splitting out water (alcohol) and the latter splitting out amine. The ring-closures studied are of the following types:

1. Closure of imidazole ring. *ortho*-Phenylenediamine, when heated with either formic acid or diarylformamidines, was converted into benzimidazole. Similarly acetic acid or diphenylacetamidine gave 2-methylbenzimidazole.

2. Closure of pyrimidine ring. N-(2-aminobenzyl)-arylamines, when heated with formic acid, ethyl orthoformate, or diarylformamidines, yielded the corresponding 3-aryl-3,4-dihydroquinazolines. Anthranilamide or anthranilanilides, heated with formic acid, orthoformic ester, or diarylformamidines, yielded the corresponding 4-ketodihydroquinazolines. Peri-diaminonaphthalene, heated with formic acid or with diphenylformamidine, yielded perimidine.

3. Closure of oxazole ring. *ortho*-Aminophenol, when heated with either acetic anhydride or diphenylformamidine yielded 2-methylbenzoxazole

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