THE CHEMISTRY OF THE BENZIMIDAZOLES

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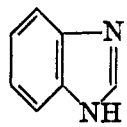
I. Introduction

The benzimidazoles contain a phenyl ring fused to an imidazole ring, as indicated in the structure for benzimidazole (I).

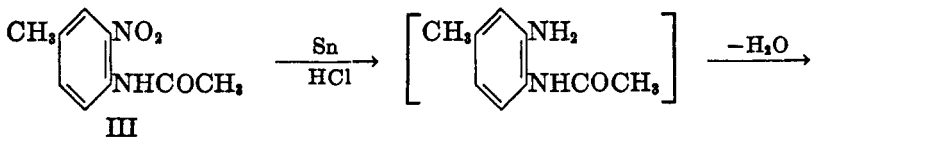


I

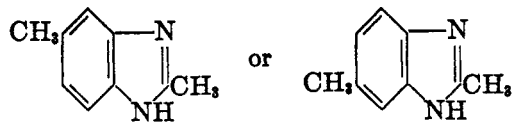
Benzimidazole

This important group of substances has found practical applications in a number of fields. Recently the interest in benzimidazole chemistry has been revived somewhat by the discovery that the 5,6-dimethylbenzimidazole moiety is part of the chemical structure of vitamin B_{12}.

Historically, the first benzimidazole was prepared in 1872 by Hoebrecker (327), who obtained 2,5(or 2,6)-dimethylbenzimidazole (II) by the reduction of 2-nitro-4-methylacetanilide (III).

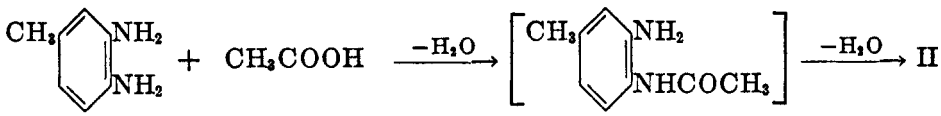


III

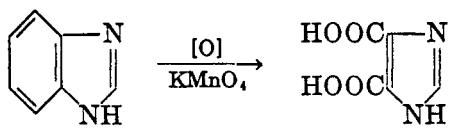


II

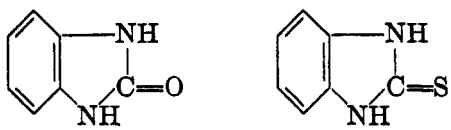
Several years later Ladenburg (446) obtained the same compound by refluxing 3,4-diaminotoluene with acetic acid.



Since compounds of this type were formed by the loss of water, they were called "anhydrobases" in the very early literature. It was subsequently shown (335, 339, 343) that "anhydrobases" of this type were formed only by compounds in which the nitrogen-containing groups were ortho to each other; that the ring formed was an imidazole ring was indicated by certain reactions of benzimidazoles, such as the fact that imidazoledicarboxylic acid may be obtained, although in small yield, by the oxidation of benzimidazole (40).

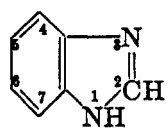


The benzimidazoles are known also as benziminazoles or benzoglyoxalines. They have been named also as derivatives of *o*-phenylenediamine, especially in the early literature. Thus, benzimidazole according to this nomenclature would be called methenyl-*o*-phenylenediamine and 2-methylbenzimidazole would be called ethenyl-*o*-phenylenediamine. Also, they have been named as derivatives of the grouping composing the imidazole portion of the ring. Thus, for example, benzimidazole has also been called *o*-phenyleneformamidine, and 2(3*H*)-benzimidazolone (IV) and 2(3*H*)-benzimidazolethione (V) are known also as *o*-phenyleneurea and *o*-phenylenethiourea, respectively.[1]



IV V

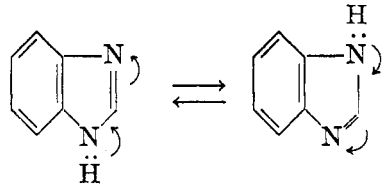
The numbering system for the benzimidazoles is as follows:



Occasionally the 2-position is designated as the μ-position.

[1] For examples in which benzimidazoles have been named as benzene derivatives see references 155, 192, 193, and 751.

Benzimidazoles which contain a hydrogen atom attached to nitrogen in the 1-position readily tautomerize. This may be depicted as follows (172):



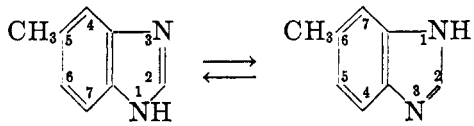
This tautomerism is analogous to that found in the imidazoles and amidines. The benzimidazoles, in fact, may be considered as cyclic analogs of the amidines. Because of this tautomerism in benzimidazoles certain derivatives which appear

TABLE 1

Equivalent tautomeric pairs in benzimidazole derivatives

POSITION OF SUBSTITUENT GROUP(S) IN FIRST TAUTOMER	POSITION OF SUBSTITUENT GROUP(S) IN SECOND TAUTOMER	DESIGNATION
4	7	4 (or 7)
5	6	5 (or 6)
2,4	2,7	2,4 (or 2,7)
2,5	2,6	2,5 (or 2,6)
4,5	6,7	4,5 (or 6,7)
4,6	5,7	4,6 (or 5,7)
2,4,5	2,6,7	2,4,5 (or 2,6,7)
2,4,6	2,5,7	2,4,6 (or 2,5,7)
4,5,6	5,6,7	4,5,6 (or 5,6,7)
4,5,7	4,6,7	4,5,7 (or 4,6,7)
2,4,5,6	2,5,6,7	2,4,5,6 (or 2,5,6,7)
2,4,5,7	2,4,6,7	2,4,5,7 (or 2,4,6,7)

at first to be isomers are in reality tautomers; although two nonequivalent structures can be written, only one compound is known. This may be illustrated with 5(or 6)-methylbenzimidazole:



VI VII

Thus, 5-methylbenzimidazole (VI) is a tautomer of 6-methylbenzimidazole (VII), and both structures (VI and VII) represent the same compound.

In designating such tautomeric compounds two numbers or sets of numbers are usually given designating the positions of the substituent group (or groups), the second number or group of numbers being placed in parentheses. According to this convention the compound designated by the pair VI–VII is written 5(or 6)-methylbenzimidazole. In table 1 are illustrated the equivalent tautomeric pairs in benzimidazole derivatives.

When the group attached to the nitrogen in the 1-position is larger than hydrogen, such tautomerism is not indicated and isomeric forms exist. Thus, 1,5-dimethylbenzimidazole and 1,6-dimethylbenzimidazole are separate and distinct compounds.

The present review is concerned only with the chemistry of the benzimidazoles. Those compounds which contain a fused phenyl and imidazole ring as part of a higher condensed system (e.g., naphthimidazoles, phenanthrimidazoles, benzobisimidazoles, etc.) are not included. The literature is reviewed through Volume 43 (1949) of *Chemical Abstracts;* also included are selected papers that have appeared in the literature in 1950.

II. Synthesis of Benzimidazoles

Practically all syntheses of benzimidazoles start with benzene derivatives possessing nitrogen-containing functions ortho to each other; that is, the starting material possesses the function designated by formula VIII.

VIII

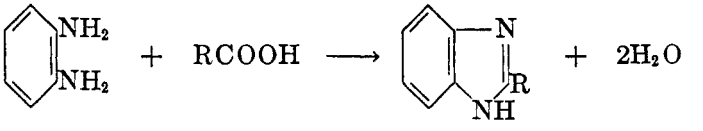
In the following discussion the synthetic methods have been grouped in the main according to the starting material used.

A. From *o*-phenylenediamines

1. *By reaction with carboxylic acids*

a. Monobasic acids

o-Phenylenediamines react readily with most carboxylic acids to give 2-substituted benzimidazoles, usually in very good yield. The reaction is carried out usually by heating the reactants together on a steam bath, by heating together under reflux or at an elevated temperature, or by heating in a sealed tube. The use of anhydrous acid is not necessary. Benzimidazole may be prepared in 83–85 per cent yield by using 90 per cent formic acid (107), and concentrations as



low as 25 per cent formic acid have been used successfully. Acetic acid gives a 68 per cent yield of 2-methylbenzimidazole (107). The acids that have been used in this general reaction are listed in table 2. As is evident from this table, a wide variety of acids have been employed.

Walther and von Pulawski (736) report that aromatic acids containing a nitro group in the ring lead to almost complete carbonization because of the

TABLE 2

Monobasic carboxylic acids used in the synthesis of benzimidazoles

ACID*	REFERENCES†
$HCOOH$	(107, 127, 307, 312, 560, 572, 576, 577, 581, 613, 728, 730)
CH_3COOH	(107, 127, 446, 572, 576, 581, 613, 616)
C_2H_5COOH	(127, 307, 572, 576, 613)
n-C_3H_7COOH	(127, 613, 661)
i-C_3H_7COOH	(127, 321, 661)
n-C_4H_9COOH	(613)
n-$C_5H_{11}COOH$	(127, 613, 661)
n-$C_6H_{13}COOH$	(613)
n-$C_7H_{15}COOH$	(613)
n-$C_8H_{17}COOH$	(613)
n-$C_9H_{19}COOH$	(613, 661)
n-$C_{10}H_{21}COOH$	(613)
n-$C_{11}H_{23}COOH$	(613, 661)
n-$C_{12}H_{25}COOH$	(613)
n-$C_{13}H_{27}COOH$	(613)
n-$C_{14}H_{29}COOH$	(613)
n-$C_{15}H_{31}COOH$	(613, 661)
n-$C_{16}H_{33}COOH$	(613)
n-$C_{17}H_{35}COOH$	(613, 623)
$CH_3CH{=}CHCH(CH_3)COOH$	(207)
$CH_3CH_2CH(CH_3)CH_2CH_2\overset{\overset{O}{\|}}{C}OOH$	(661)
$CH_2OHCOOH$	(93, 127, 166, 307, 361, 572, 671)
$CH_3CHOHCOOH$	(127, 307, 572, 576, 577)
d-$CH_3CHOHCOOH$	(174)
l-$CH_3CHOHCOOH$	(174)
$(CH_3)_2C(OH)COOH$	(671)
$CH_3CH_2CHOHCOOH$	(671)
CH_3OCOOH	(205, 356)
C_2H_5OCOOH	(204, 205)
$HSCH_2COOH$	(256)
$CH_2ClCOOH$	(109, 356, 415, 671)
$CH_3CHClCOOH$	(634)
CH_2ClCH_2COOH	(415)
C_6H_5COOH	(317, 572, 615, 616, 737)
$C_6H_5CH_2COOH$	(307, 356, 615, 616, 738)
$C_6H_5CH_2CH_2COOH$	(356, 615)
$CH_3(CH_2)_7\underset{\underset{C_6H_5}{\|}}{CH}(CH_2)_8COOH$	(412)
α-$C_{10}H_7COOH$	(616)
$(C_6H_5)_2CHCOOH$	(616)
$C_6H_5CHOHCOOH$	(92, 127, 262, 307, 572)
$C_6H_5CHOHCH_2COOH$	(263)
$(C_6H_5)_2C(OH)COOH$	(98, 307)

TABLE 2—*Continued*

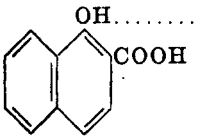
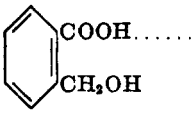
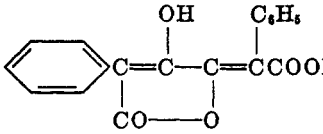
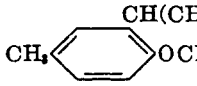
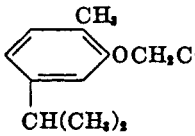
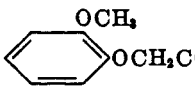
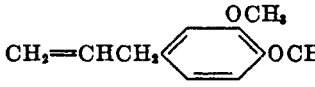
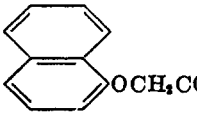
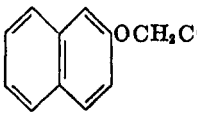
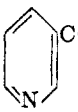
ACID*	REFERENCES†
	(725)
	(74)
	(654)
$C_6H_5OCH_2COOH$	(162, 204, 356)
p-$CH_3C_6H_4OCH_2COOH$	(159)
	(160)
	(159)
	(160, 162)
	(160, 162)
	(161)
	(161)
$(C_6H_5)_2CClCOOH$	(99)
p-$O_2NC_6H_4CH_2COOH$	(356)

TABLE 2—*Concluded*

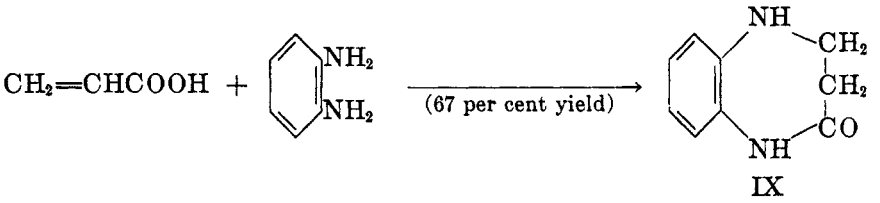
ACID*	REFERENCES†
o-$O_2NC_6H_4CH_2COOH$	(356)
p-$H_2NC_6H_4COOH$	(616)
p-$H_2NC_6H_4CH_2COOH$	(356)
$C_6H_5CONHCH_2COOH$	(356)
	(616)

* Acids derived from sugars are not included in this table. Benzimidazole derivatives of sugars are treated in a separate section (page 464).

† Owing to the large number of references in some cases, especially with the simpler acids, only representative references are given.

oxidative effect of the nitro group at the high temperatures employed in the reaction.

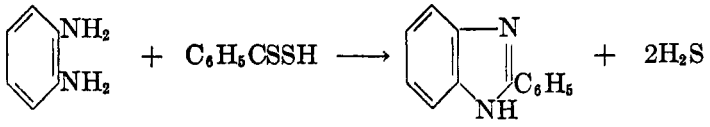
Acrylic acid does not give 2-vinylbenzimidazole. Instead, a seven-membered ring compound (IX) is apparently formed (24):



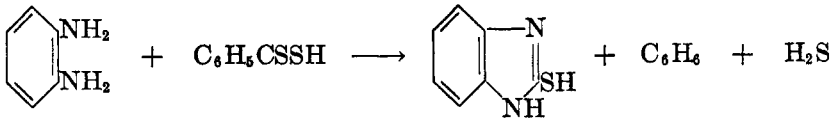
IX

Glycine and phenylglycine give no reaction (356). Anthranilic acid gives only a dyestuff (120). Phthalimidoacetic acid gives an amorphous product containing no oxygen.

Several dithio acids have been used in this reaction. Dithiobenzoic acid with *o*-phenylenediamine gives about a 55 per cent yield of 2-phenylbenzimidazole (767).

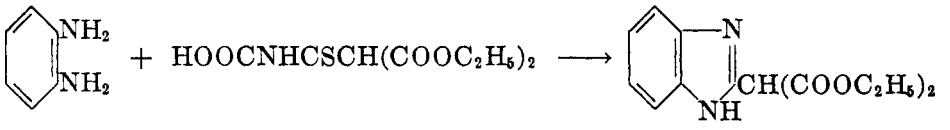


Benzimidazolethiol is obtained as a by-product in this reaction:

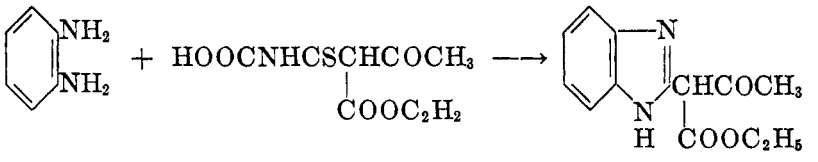


Similarly, α-dithionaphthoic acid gives a 71 per cent yield of 2-α-naphthylbenzimidazole and *p*-methyldithiobenzoic acid gives 2-*p*-tolylbenzimidazole in 60 per cent yield (767).

Ghosh (271, 272) has condensed *o*-phenylenediamine with thioacetylcarbonic acid derivatives to obtain 2-substituted benzimidazoles:



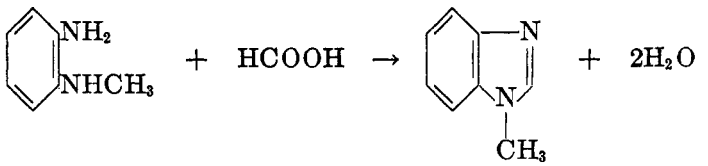
X



XI

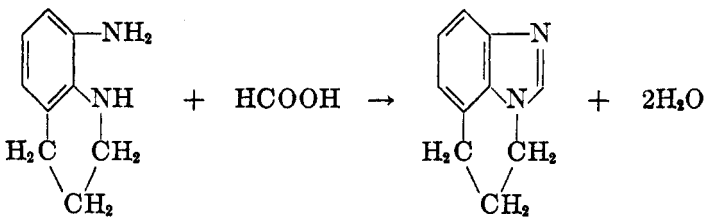
Both X and XI on heating with 15 per cent alcoholic potassium hydroxide solution give 2-methylbenzimidazole. Acid hydrolysis of XI with concentrated hydrochloric acid (272) gives the corresponding acid.

A wide variety of *o*-phenylenediamines have been used in this general reaction. *N*-Monosubstituted *o*-phenylenediamines lead to 1-substituted benzimidazoles. Treatment of *N*-methyl-*o*-phenylenediamine, for example, with formic acid gives 1-methylbenzimidazole (253):



N,*N*′-Disubstituted *o*-phenylenediamines give "pseudo bases" (*cf.* page 468).

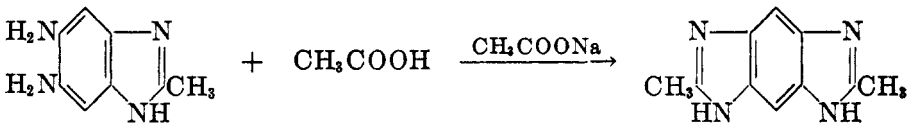
A large number of ring-substituted *o*-phenylenediamines have been used successfully. Among the substituent groups in the phenyl ring of the *o*-phenylenediamines that have been used are various alkyl, aryl, alkoxy, and aryloxy groups, halogens (chlorine, bromine, iodine), amino groups (primary, secondary, and tertiary), nitro (577), cyano (112), carboxylic acid (274, 279, 652), arsonic acid (64, 361, 576, 577), acetyl (113), carbalkoxy (183), sulfonamido (5), and alkylsulfonamido (6) groups. 1,2,3-Triaminobenzene gives 4(or 7)-aminobenzimidazoles (17, 329, 647, 726). 8-Aminotetrahydroquinoline and related compounds act as *N*-alkyl-*o*-phenylenediamines (55, 307, 377, 617), of which they may be considered as cyclic analogs. 8-Aminotetrahydroquinoline, for example, with formic acid gives 4-imidazo-(*ij*)-tetrahydroquinoline (307).



The corresponding compounds derived from indoline derivatives do not appear to have been prepared.

Diamines which are very easily oxidized may be converted to benzimidazoles by fission of the components at 180°C. with aqueous hydrochloric acid in an evacuated tube (615).

o-Diaminobenzimidazoles react with carboxylic acids to give benzobisimidazoles (442):

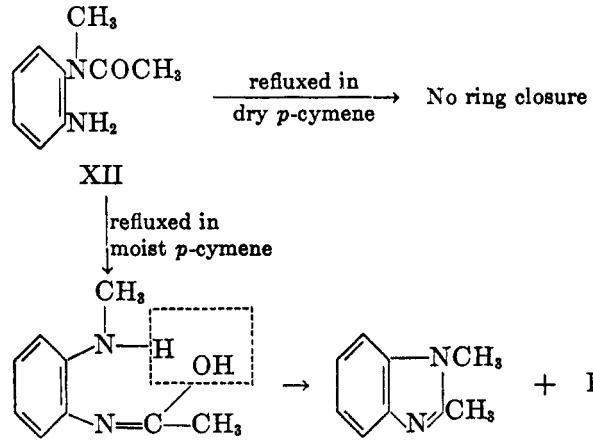


These compounds may be obtained also from tetraaminobenzenes by treatment with organic acids in the presence of dilute mineral acids (579).

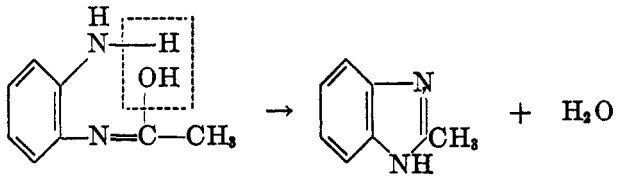
Phillips (572, 576, 577, 581) introduced an important modification in the reaction of *o*-phenylenediamines with organic acids to give benzimidazoles in the use of dilute mineral acid (usually about 4 *N* hydrochloric acid) in the reaction mixture. In some cases this permits the reaction to take place at a lower temperature and has permitted the preparations of compounds that were formed either not at all or in low yields when the components were heated together without the use of mineral acid. Good yields are obtained with aliphatic acids, while benzoic acid gives only a trace of 2-phenylbenzimidazole (572). Good yields may be obtained with aromatic acids, however, by carrying out the reaction in a sealed tube at about 180–185°C. (615, 616).

The mechanism of the reaction of organic acids with *o*-phenylenediamines has been studied (287, 486, 578, 633). Phillips (578) concluded that the monoacyl derivative was the necessary intermediate for the reaction. The monoacyl derivatives passed readily into the corresponding benzimidazoles on heating with dilute mineral acid. Since diacyl-*o*-phenylenediamines also gave benzimidazoles under the same conditions, it was concluded that the latter reaction involved as the first step the hydrolysis of the diacyl derivative to the monoacyl derivative. Phillips' conclusion concerning the monoacyl-*o*-phenylenediamine as the necessary intermediate in the reaction has been confirmed by Roeder and Day (633). These authors also showed that monoacyl-*o*-phenylenediamines do not yield benzimidazoles under anhydrous conditions unless there is at least one hydrogen on each of the two nitrogen atoms. They showed that *o*-amino-*N*-methylacetanilide (XII) did not undergo ring closure under anhydrous conditions, whereas benzimidazole formation occurred when water was present.

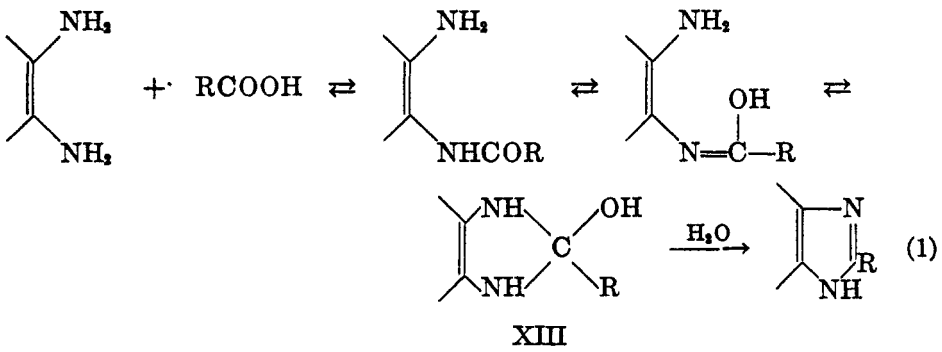
The reaction was explained as involving first the hydrolysis



of the acetyl group and then reacetylation on the other nitrogen atom and subsequent removal of water as indicated above. In contrast to the behavior of XII, the isomeric *N*-methyl-*N'*-acetyl-*o*-phenylenediamine underwent ring closure readily when refluxed in dry xylene. These and other experiments indicate that the reaction for the ring closure in general probably involves the splitting out of water by losing the oxygen of the acetyl group and one hydrogen from each of the two nitrogens (287, 633):



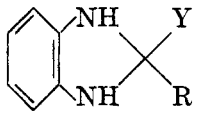
The complete reaction has been considered (172, 486) as probably proceeding according to equation 1.



XIII

McCoy and Day (486) have pointed out that other reactions leading to benzimidazoles may be considered as involving an intermediate of the type XIII which

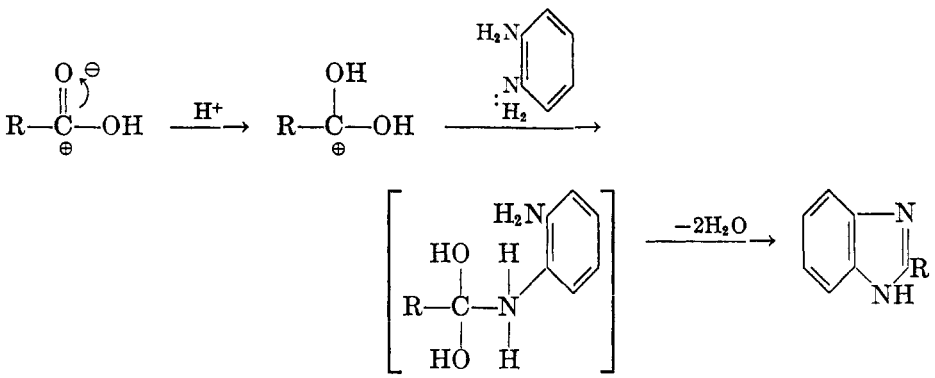
in the general case may be considered as in XIV. The final step in the reaction involves the removal of HY,



XIV

where Y = OH, NH_2, HNR, NR_2, H, etc.

The role of hydrochloric acid in the reaction has been studied (616), the reaction in this case being carried out in a sealed tube. The catalytic action of hydrochloric acid is explained as activation of the carboxyl group by addition of a proton to oxygen, forming a carbonium ion with electron deficiency at the carbon atom. The intermediate in the reaction is the addition product formed by the entry of the unshared electron pair of one nitrogen into the carbonium ion of the acid radical:

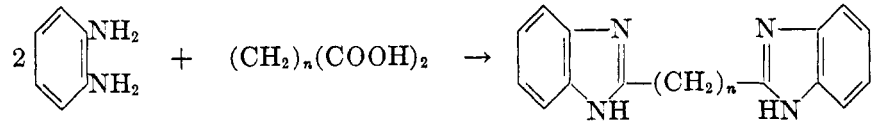


o-Phenylenediamine dihydrochloride gave no reaction with benzoic acid under anhydrous conditions. Addition of a small amount of water gave a 30 per cent yield of 2-phenylbenzimidazole. When the reaction was carried out with *o*-phenylenediamine as the free base, a 65 per cent yield of 2-phenylbenzimidazole was obtained. The conclusion was drawn, therefore (616), that the free diamine is responsible for the reaction and that the hydrochloride salt of the diamine will react only under conditions which permit its hydrolysis first to the free diamine. The concentration of hydrochloric acid in the reaction was also varied and the optimum concentration was found to be 25 per cent.

The conversion of aliphatic acids to benzimidazoles by reaction with *o*-phenylenediamines has been used as a method for characterizing aliphatic acids (127, 613, 661).

b. Dibasic acids

When dibasic acids are caused to react with *o*-phenylenediamines the products formed depend on the mole ratio of the reactants and the experimental conditions. When two or more moles of the *o*-phenylenediamine are heated with one mole of the dibasic acid, the products in most cases are bisbenzimidazoles (666).



The dibasic acids from which bisbenzimidazoles have been obtained are listed in table 3.

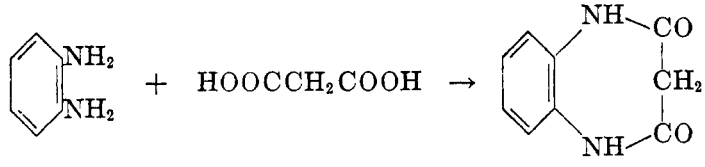
Oxalic acid gives 2,3-dihydroxyquinoxalines (573, 576, 666). Oxalic acid with *N*-substituted *o*-phenylenediamines is reported to give only starting material

TABLE 3

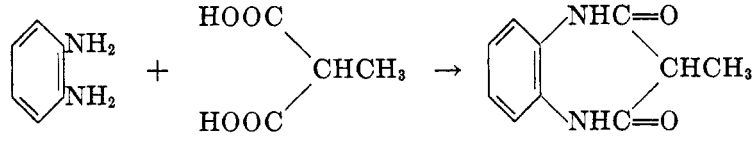
Dibasic acids from which bisbenzimidazoles have been obtained

ACID	YIELD	REFERENCES
	per cent	
Succinic	28	(152, 575, 583, 666, 695)
Glutaric	50, 30	(418, 666)
Adipic	46	(666)
Pimelic	62	(666)
Suberic	56	(666)
Azelaic	63	(666)
Sebacic	60	(666)
2,5-Furandicarboxylic		(149)
Maleic		(126)
Fumaric		(145, 148)

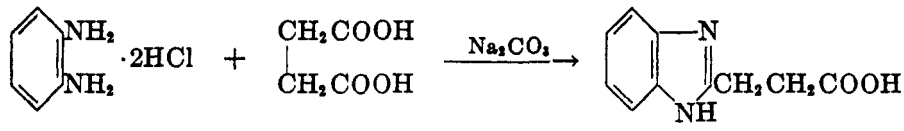
(577). Malonic acid with *o*-phenylenediamines gives *o*-phenylenemalonamides (504, 507, 574, 576, 585, 665, 666, 667) in good yield:



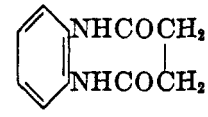
The same product is formed when equimolecular amounts of the two components are used (507). Isosuccinic acid gives the analogous product in poor yield (507):



When equimolecular amounts of *o*-phenylenediamines and dibasic acids are used, it is possible to obtain benzimidazole acids. β-(2-Benzimidazole)propionic acid may be obtained by heating equimolecular amounts of *o*-phenylenediamine dihydrochloride, succinic acid, and sodium carbonate to 180°C. (507).

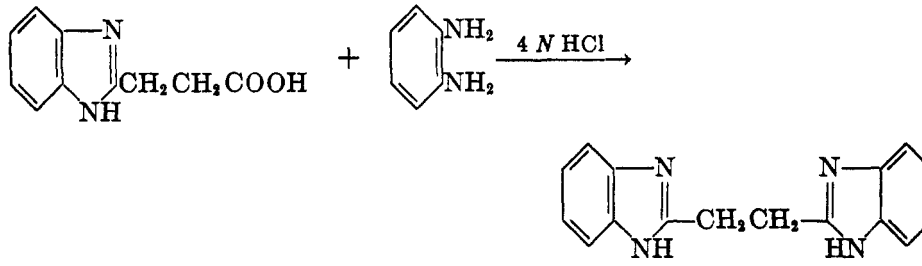


Equimolecular amounts of *o*-phenylenediamine and succinic acid when heated with 4 *N* hydrochloric acid are reported to give β-(2-benzimidazole)propionic acid and 2,2′-diaminosuccinanilide (XV) (574).



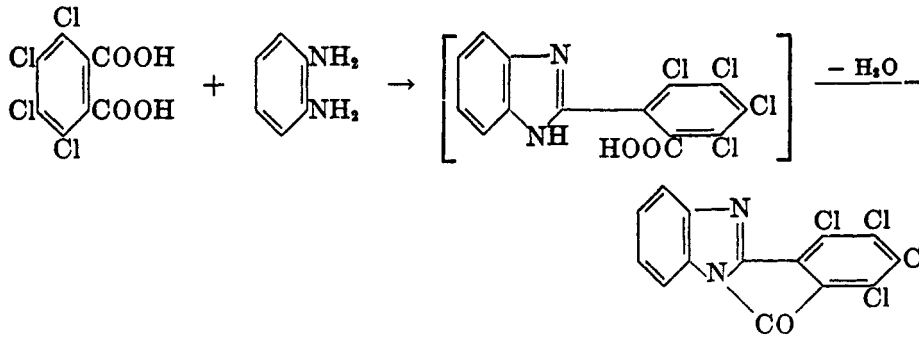
XV

β-(2-Benzimidazole)propionic acid on further condensation with *o*-phenylenediamine gives the bisbenzimidazole (575).



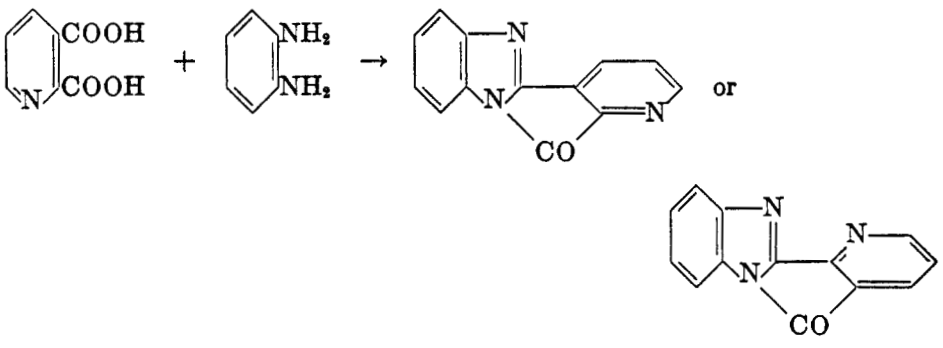
The same product has been obtained by treatment of XV with hot 4 *N* hydrochloric acid (575). Succinic acid with 3,4-diaminophenylarsenic acid is reported to give only starting material (576).

Equimolecular amounts of tetrachlorophthalic acid and *o*-phenylenediamine when heated gradually to 250°C. give a 60 per cent yield of (tetrachloro-*o*-benzoylene)-2,1-benzimidazole (89).



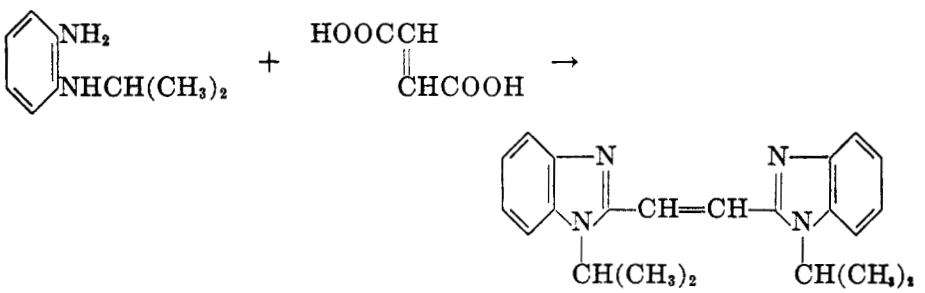
A 76 per cent yield may be obtained by carrying the reaction out in nitrobenzene as a solvent (89). Under the vigorous conditions of the reaction the benzimidazole acid first formed loses an additional mole of water.

From the reaction between quinolinic acid and *o*-phenylenediamine are obtained α,β-picolinoylene-2,1-benzimidazole and 2-(β-pyridyl)benzimidazole (90):



Dibasic acids containing one carboxylic acid group and one sulfonic acid group react with *o*-phenylenediamines to yield benzimidazolesulfonic acids. Dibasic acids of this type that have been used in the synthesis of benzimidazoles are listed in table 4.

N-Substituted *o*-phenylenediamines have been used also in the reaction with dicarboxylic acids. Using oxalic acid, Phillips (577) obtained only starting material with *N*-methyl- and *N*-phenyl-*o*-phenylenediamines. However, fumaric acid is reported to condense with *N*-isopropyl-*o*-phenylenediamine (148):



The reaction of acids containing three or more carboxyl groups with *o*-phenylenediamines does not appear to have been investigated.

2. By reaction with acid anhydrides

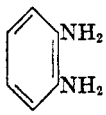
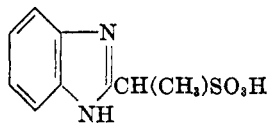
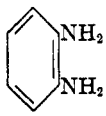
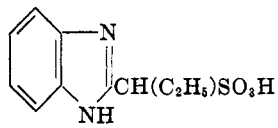
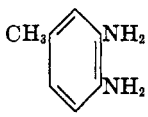
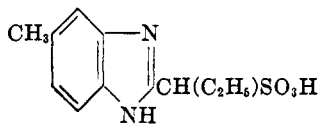
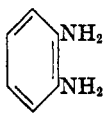
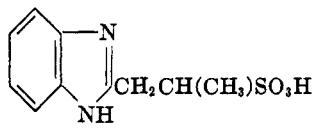
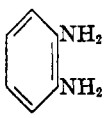
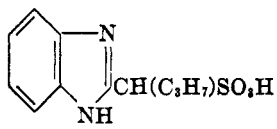
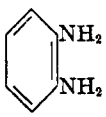
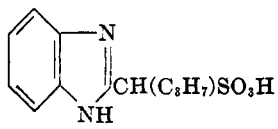
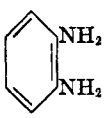
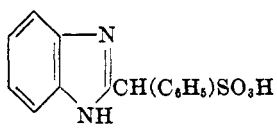
a. Anhydrides of monobasic acids

The reaction of acid anhydrides and *o*-phenylenediamines will lead to benzimidazoles or to *N*,*N'*-diacylphenylenediamines (510) depending on the conditions employed. It was formerly thought that *o*-phenylenediamines yield

benzimidazoles with acids and diacyl derivatives with acid anhydrides (510); however, this was shown (16) to be incorrect. Time appears to be a decisive

TABLE 4

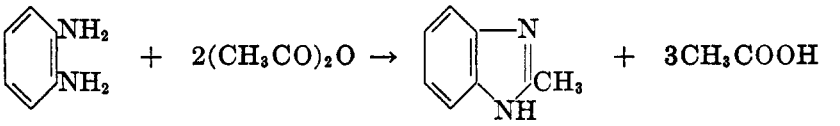
Benzimidazolesulfonic acids

ACID USED	*o*-PHENYLENE-DIAMINE USED	PRODUCT	REFERENCE
$HO_3SCH(CH_3)COOH$			(26)
$HO_3SCH(C_2H_5)COOH$			(28)
$HO_3SCH(C_2H_5)COOH$			(28)
$HO_3SCH(CH_3)CH_2COOH$			(27)
$HO_3SCH(C_3H_7)COOH$			(29)
$HO_3SCH(C_3H_7)COOH$ (*d*-form)		 (*l*-form)	(29)
$HO_3SCH(C_6H_5)COOH$			(130)

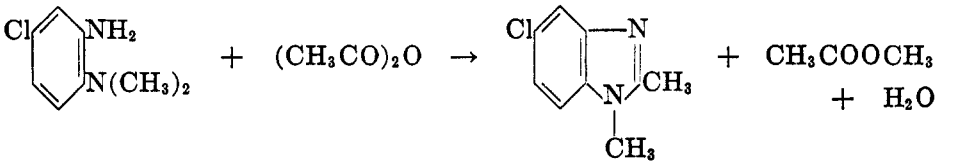
factor and if the refluxing is continued long enough benzimidazoles may be obtained, usually in good yield. Practically the only acid anhydride that has been used in the preparation of benzimidazoles has been acetic anhydride. How-

ever, the mixed formic–acetic anhydride (70) and benzoic anhydride (120, 735, 763) have also been used successfully.

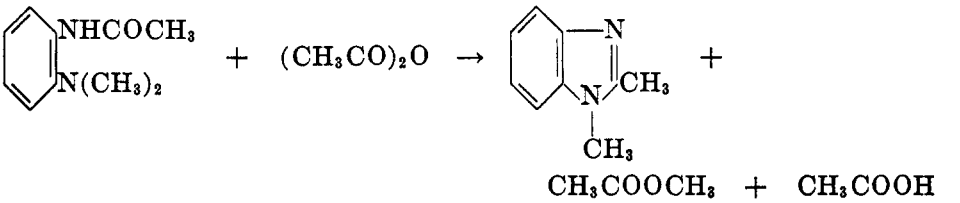
o-Phenylenediamine when heated under reflux for several hours with acetic anhydride is completely converted to 2-methylbenzimidazole (16):



A wide variety of *o*-phenylenediamines have been used in this reaction, the types being similar to those diamines mentioned previously in connection with the syntheses from carboxylic acids. *N*-Substituted *o*-phenylenediamines lead to 1-substituted benzimidazoles and *N*,*N*′-disubstituted *o*-phenylenediamines lead to "pseudo bases", discussed separately in a later section. *N*,*N*-Dimethyl-*o*-phenylenediamines when heated with acetic anhydride give 1,2-dimethylbenzimidazoles (590, 594, 601, 656). Thus, 4-chloro-2-aminodimethylaniline when heated with excess acetic anhydride at 145–160°C. gives 1,2-dimethyl-5-chlorobenzimidazole (594).



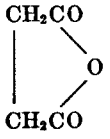
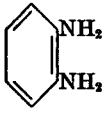
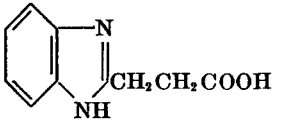
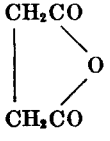
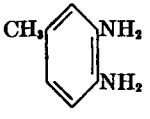
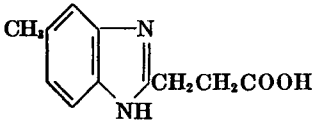
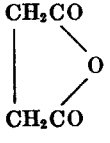
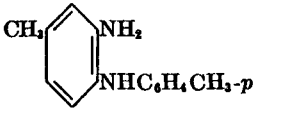
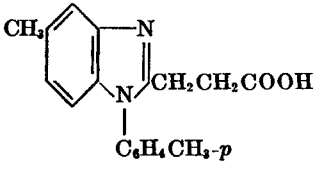
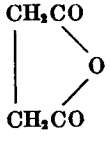
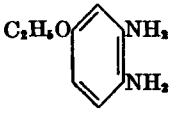
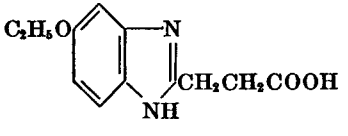
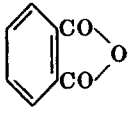
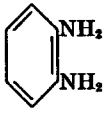
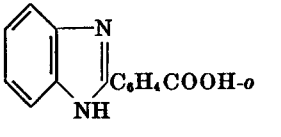
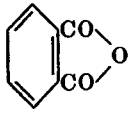
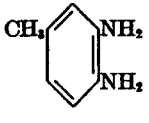
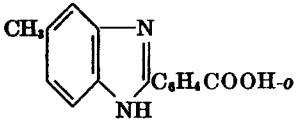
Similarly, *N*,*N*-dimethyl-1,2,4-triaminobenzene gives 5-acetamido-1,2-dimethylbenzimidazole, which on hydrolysis yields 5-amino-1,2-dimethylbenzimidazole (601, 656), and *m*-amino-*N*,*N*-dimethyl-*p*-toluidine gives 5-methyl-1,2-dimethylbenzimidazole with *m*-acetamido-*N*,*N*-dimethyl-*p*-toluidine as a by-product (590). *N*,*N*-Dimethyl-*N*′-acetyl-*o*-phenylenediamine with acetic anhydride also gives 1,2-dimethylbenzimidazole (595):



The reaction of *o*-phenylenediamines with acetic anhydride has been carried out with acetic anhydride alone or with acetic anhydride to which has been added sodium acetate (116, 469, 518, 553), mineral acids, or acetic acid (164). Excellent results have been obtained by employing the modification of Phillips (570, 577, 580, 583) involving the addition of dilute mineral acids (usually about 4 *N* hydrochloric acid) to the reaction mixture. Thus, 2-methylbenzimidazole may be obtained in 93.3 per cent yield from *o*-phenylenediamine and acetic anhydride on heating with 15 per cent hydrochloric acid (729). Good

TABLE 5

Benzimidazoles from anhydrides of dibasic acids

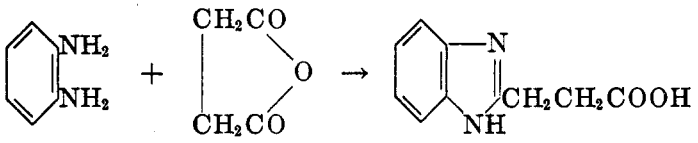
ANHYDRIDE	DIAMINE	PRODUCT	REFERENCES
			(11, 73, 144, 508)
			(10)
			(238)
			(144)
			(12, 509, 715)
			(143)

(238)
(73)
(143)
(143)

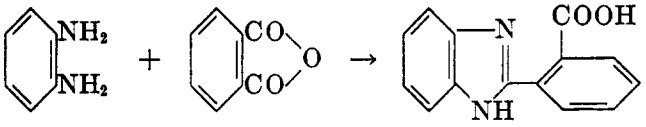
results have been obtained also with substituted *o*-phenylenediamines (577, 580, 583, 669).

b. Anhydrides of dibasic acids

The anhydrides of dibasic acids react as monobasic acids; for example, succinic anhydride with *o*-phenylenediamine gives β-(2-benzimidazole)propionic acid (XVI) and phthalic anhydride gives *o*-(2-benzimidazole)benzoic acid (XVII).



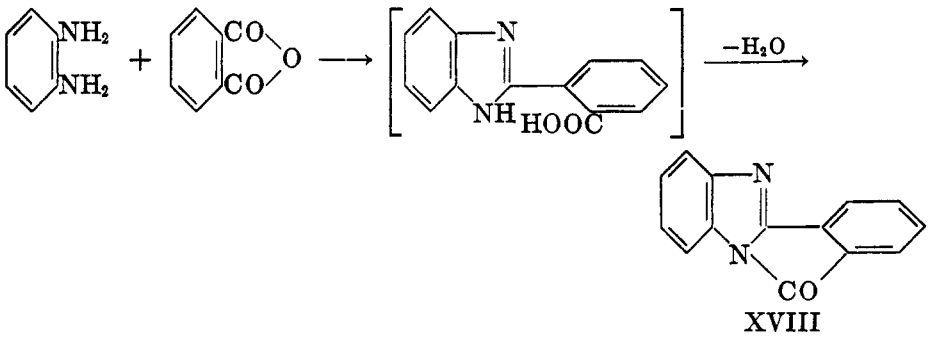
XVI



XVII

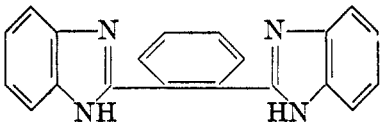
Anhydrides of dibasic acids that have been condensed with *o*-phenylenediamines to give benzimidazole acids of this type are listed in table 5. In several cases amides (11, 143, 508), or phthalanils (73, 509) have been obtained as by-products.

The reaction of *o*-phenylenediamines and phthalic anhydride has been investigated rather extensively under varying conditions. Heating the components in alcoholic solution gives the *o*-substituted benzoic acid (XVII) (143, 238). Direct heating of equimolecular amounts of *o*-phenylenediamine and phthalic anhydride to 140–150°C. gives *o*-benzoylene-2,1-benzimidazole (XVIII) (88).



XVIII

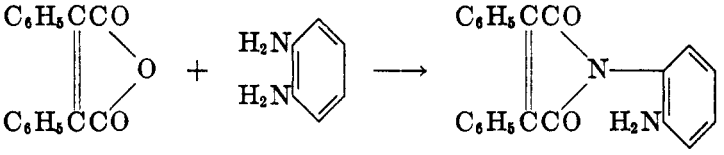
Tetrachlorophthalic anhydride behaves similarly (89). When *o*-phenylenediamine and phthalic anhydride are heated to 120–130°C. with prevention of the return of the evolved water, the products obtained are diphthaloyl-*o*-phenylenediamine, *o*-benzoylene-2,1-benzimidazole (XVIII), and phenylenedibenzimidazole (XIX) (614).



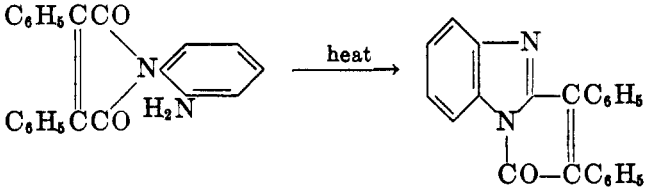
XIX

The latter product (XIX) may be obtained also from *o*-benzoylene-2,1-benzimidazole (XVIII) and *o*-phenylenediamine (614) and from *o*-phenylenediamine and phthalic anhydride by heating to 180°C. (736) or to 290°C. (467). Succinic anhydride and *o*-phenylenediamine at 180°C. behave similarly (736).

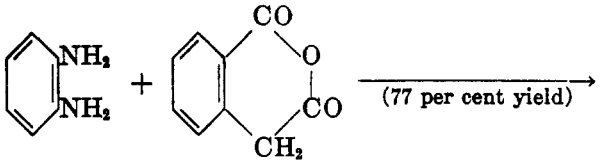
The action of *o*-phenylenediamine upon the anhydrides of diphenylmaleic, homophthalic, and diphenic acids has also been investigated. Equimolecular amounts of diphenylmaleic anhydride and *o*-phenylenediamine when heated under reflux in alcohol give an 85–90 per cent yield of *N*-(2-aminophenyl)diphenylmaleimide (83).

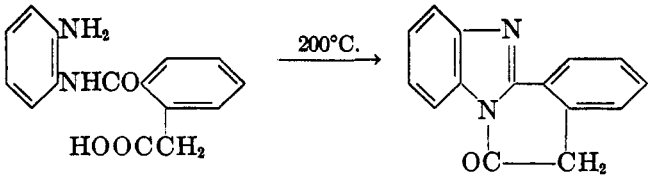


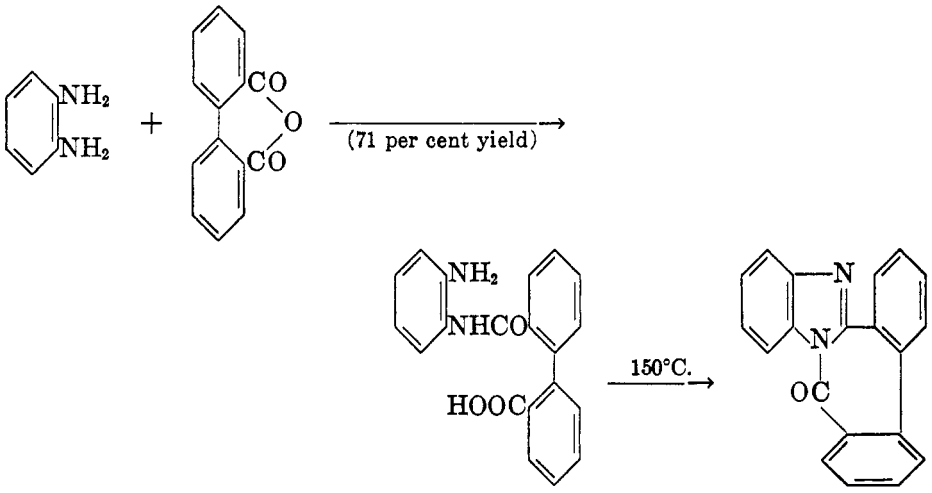
This substance cyclizes on heating:



Homophthalic acid anhydride and diphenic anhydride react somewhat analogously (82):



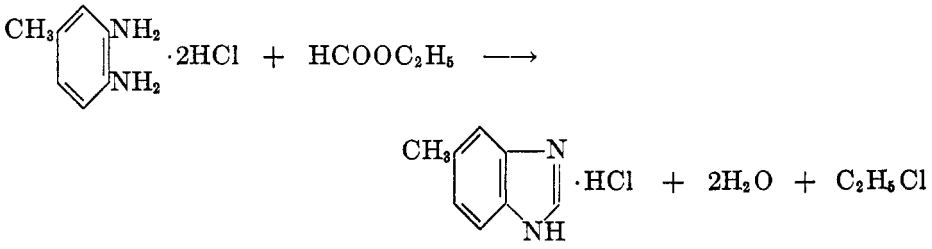




3. By reaction with esters

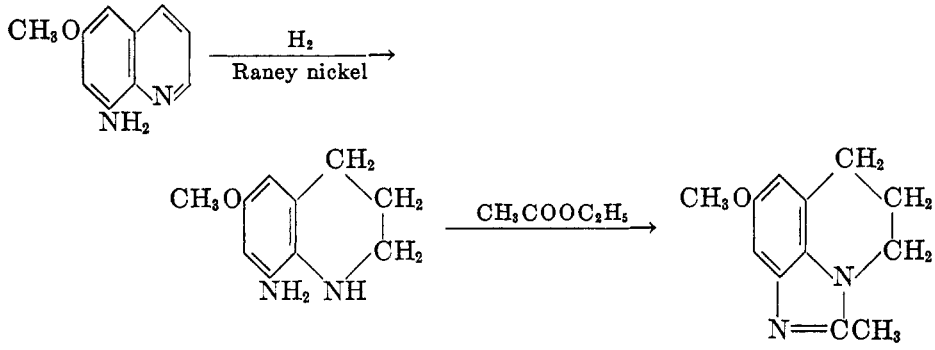
Reaction of *o*-phenylenediamines with esters also yields benzimidazoles; however, this method has not been used frequently.

von Niementowski (537) first investigated the reaction of esters and *o*-phenylenediamines to give benzimidazoles. Equimolecular amounts of 3,4-diaminotoluene dihydrochloride and ethyl formate when heated in a sealed tube for 3 hr. at 225°C. give 84 per cent of 5(or 6)-methylbenzimidazole hydrochloride (544).



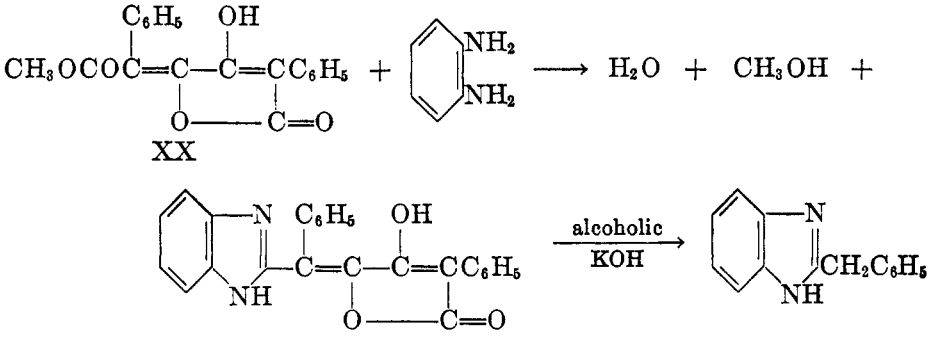
The product is not further alkylated by the ethyl chloride formed (538). Ethyl acetate under the same conditions gives only a poor yield of 2,5(or 2,6)-dimethylbenzimidazole, and poor yields of benzimidazoles would probably be obtained from esters of acids of higher molecular weight (544). A good yield of 2-methylbenzimidazole may be obtained by allowing a mixture of *o*-phenylenediamine and ethyl acetate to stand (378).

It has been reported (59) that high-pressure hydrogenation of 6-methoxy-8-aminoquinoline in ethyl acetate solution using 25 per cent Raney nickel gives, in addition to the expected 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline, a 40 per cent yield of 5-methoxy-2-methyl-1,7-trimethylenebenzimidazole:



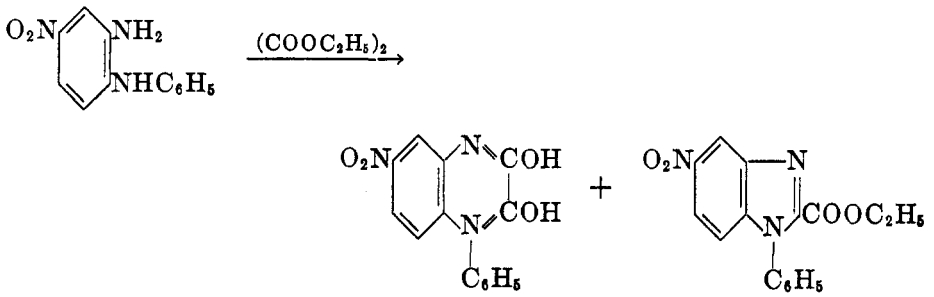
Ethyl cyanoacetate with *o*-phenylenediamine gives a 70 per cent yield of 2-cyanomethylbenzimidazole (166). Ethyl α-hydroxyisobutyrate gives a 93.3 per cent yield of 2-(2′-hydroxyisopropyl)benzimidazole and ethyl 3-ethoxypropionate gives an 82 per cent yield of β-ethoxyethylbenzimidazole (145). Ethyl and methyl methacrylate fail to react with *o*-phenylenediamine at reflux temperatures (24). Ethyl ω-diethylaminobutyrate is reported to undergo condensation with *o*-phenylenediamine in the presence of copper sulfate to give the copper salt of 2-(diethylaminopropyl)benzimidazole (364).

Vulpinic acid (XX) gives a benzimidazole with *o*-phenylenediamine. The benzimidazole formed is cleaved to 2-benzylbenzimidazole with alcoholic potassium hydroxide (654).

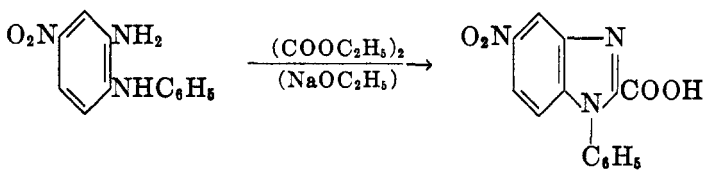


A number of patents have been issued for the preparation of 2-substituted benzimidazoles from *o*-phenylenediamines and various naturally occurring fats and oils, such as coco fat (284, 684, 693), coconut oil (685), fish oil (686), olive oil (284, 687), castor oil (284, 688), linseed oil (284, 689), and various other glycerides of saturated and unsaturated acids (284).

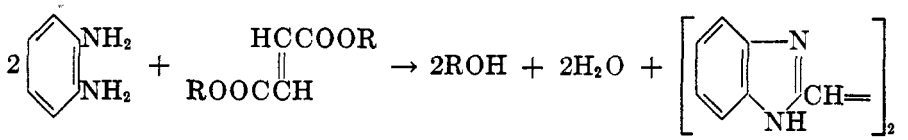
Diethyl oxalate reacts with *o*-phenylenediamine to yield quinoxalines; however, in several cases, benzimidazoles have been obtained. For example, 2-amino-4-nitrodiphenylamine, when heated under reflux with diethyl oxalate, gives the expected quinoxaline with 1-phenyl-2-carbethoxy-5-nitrobenzimidazole as a by-product (626).



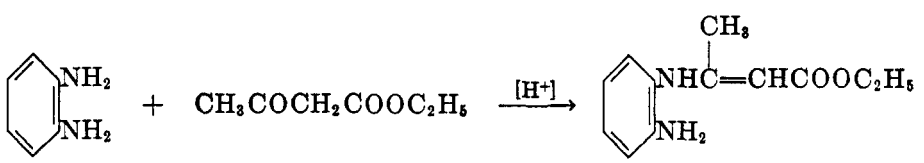
By treating the same diamine with diethyl oxalate and sodium ethoxide in alcoholic solution and allowing the reaction mixture to stand for several days, the corresponding acid may be obtained (627):



Esters of fumaric acid are reported to lead to the bisethylene compound (145):

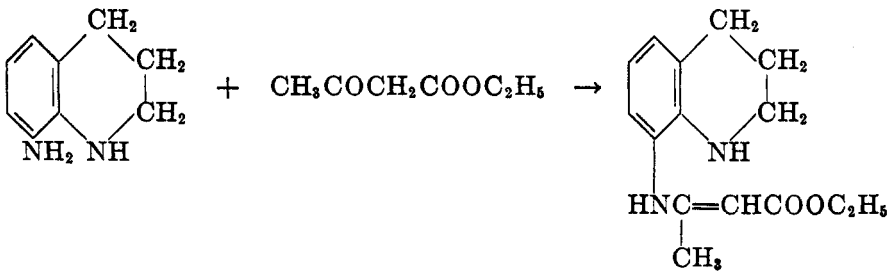


The reaction of ethyl acetoacetate with *o*-phenylenediamines can lead to several products, depending upon whether the reaction is carried out under acidic, neutral, or basic conditions. Under acidic conditions ethyl β-(2-aminoanilino)crotonate is formed (XXI) from ethyl acetoacetate and *o*-phenylenediamine (663). This substance is also obtained when equimolecular amounts of the reactants are shaken together (324); however, it has been pointed out (663)



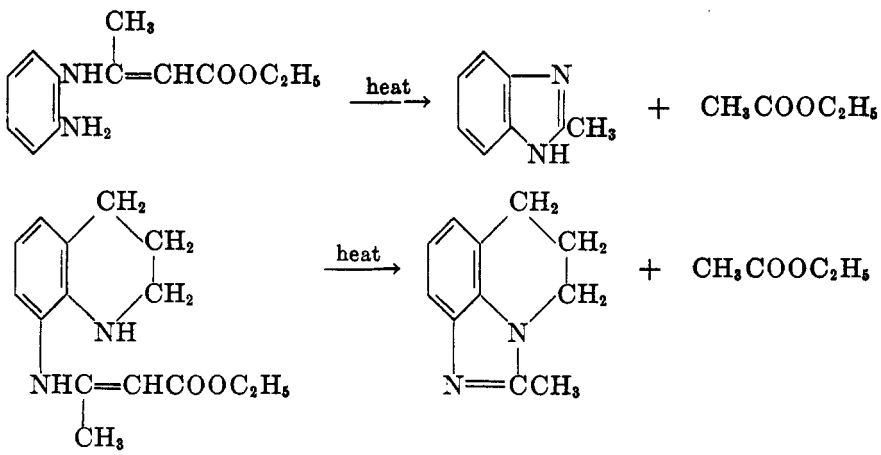
XXI

that this second reaction, apparently carried out under neutral conditions, probably was carried out in reality under acidic conditions, owing to the fact that impure ethyl acetoacetate was probably used. 8-Amino-1,2,3,4-tetrahydroquinoline reacts with ethyl acetoacetate under acidic conditions to give a product analogous to XXI (308):

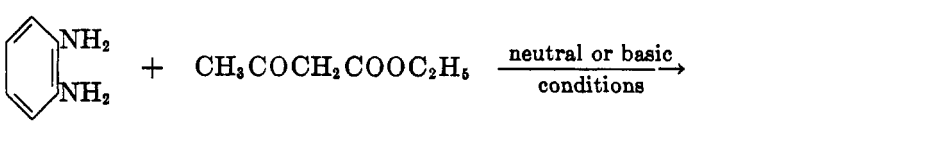


XXII

Both XXI and XXII on heating are converted to 2-methylbenzimidazoles (241, 308, 324, 663):



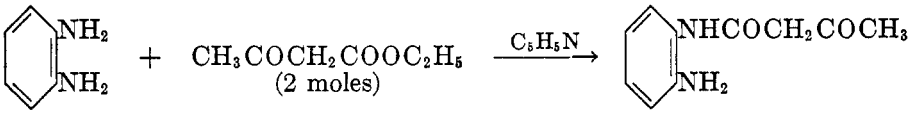
By carrying out the condensation of *o*-phenylenediamine and ethyl acetoacetate under neutral or basic conditions, Sexton (663) obtained a mixture of two other products:



XXIII XXIV

XXIII is the major product under neutral conditions (71–72 per cent) and XXIV is the major product under basic conditions (64 per cent). Monti (513), in

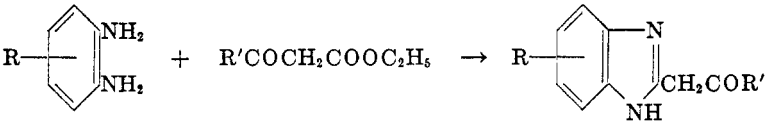
carrying out the reaction with two mole-equivalents of ethyl acetoacetate under basic conditions (a trace of pyridine), obtained 2-aminoacetylacetanilide (XXV),



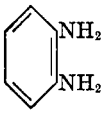
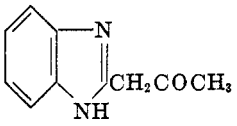
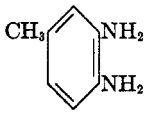
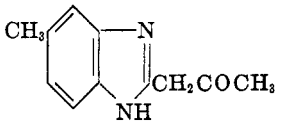
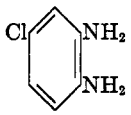
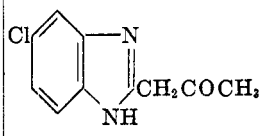
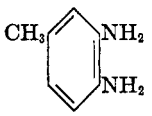
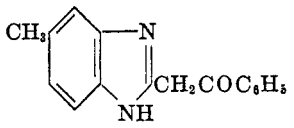
XXV

TABLE 6

2-Acylmethyl- and 2-aroylmethylbenzimidazoles

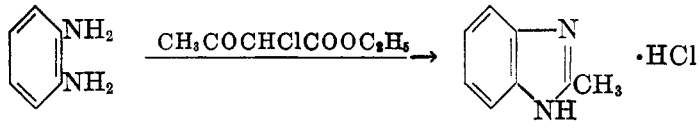


(R = H, CH_3, Cl)

DIAMINE	R'	PRODUCT
	CH_3	
	CH_3	
	CH_3	
	C_6H_5	

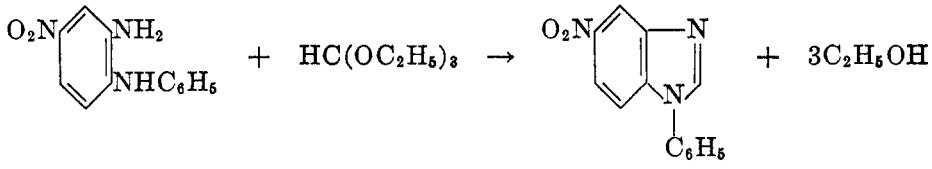
which is probably an intermediate in the formation of XXIII and XXIV. Both XXIII and XXV on treatment with strong acids are converted to 2-hydroxybenzimidazole and acetone (513, 663). By using other β-keto esters and *o*-phenylenediamines under basic conditions, other products analogous to 2-benzimidazoleacetone (XXIV) have been obtained (662). These products are listed in table 6.

Ethyl α-chloroacetoacetate and *o*-phenylenediamine, when heated under reflux in ethanol, give 2-methylbenzimidazole hydrochloride in high yield (65).

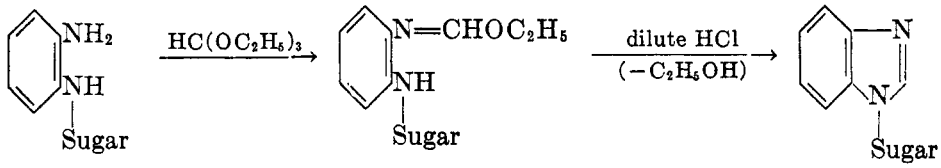


o-Toluylenediamine and ethyl α-chloroacetoacetate lead to 2,5(or 2,6)-dimethylbenzimidazole (13).

Ethyl orthoformate was first used for the preparation of benzimidazoles by von Walther and Kessler (732). These authors prepared 1-phenyl-5-nitrobenzimidazole by the reaction between ethyl orthoformate and 4-nitro-2-aminodiphenylamine.



Very recently, the use of ethyl orthoformate has been investigated more fully by Mamalis, Petrow, and Sturgeon (474, 475). These authors found that *o*-phenylenediamines or *N*-alkylated *o*-phenylenediamines may be converted to the corresponding benzimidazoles in almost quantitative yield by the use of an excess of ethyl orthoformate at an elevated temperature or in a solvent such as ethanol or ethyl acetate. This method was investigated because several of the diamines used by these authors were acid sensitive. Several *N*-tetracetyl-D-glucose)-*o*-phenylenediamines and *o*-phenylenediaminetriacetylpentosides were converted to 1-substituted benzimidazoles by this general method; however, in most cases the first product isolated was not the benzimidazole but rather the ethylisoformalide of the diamine.



The latter product, however, undergoes ring closure readily upon treatment with hot, very dilute hydrochloric acid.

Esters of chloroformic acid lead to 2(3*H*)-benzimidazolones (703, 705, 706); these reactions are discussed in Section II, A, 13.

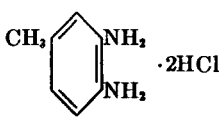
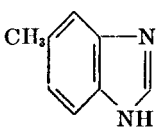
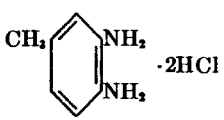
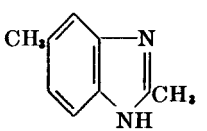
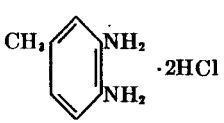
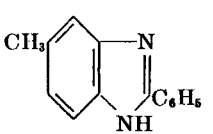
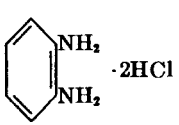
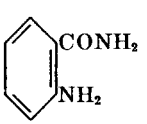
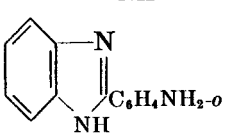
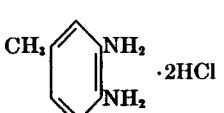
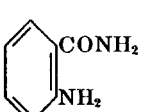
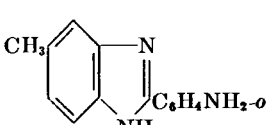
4. By reaction with amides

Relatively few amides have been used for the synthesis of benzimidazoles. However, good yields have been obtained in most cases. The amides that have been used are listed in table 7.

The reaction of *o*-phenylenediamines with urea and related compounds is discussed in Section II, A, 13.

TABLE 7

Benzimidazoles from amides

DIAMINE	AMIDE	PRODUCT	YIELD	REFERENCE
	$HCONH_2$		*per cent* "Almost theoretical"	(539)
	CH_3CONH_2		95	(539)
	$C_6H_5CONH_2$		70	(539)
			60	(541)
			55	(542)

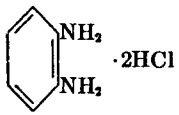
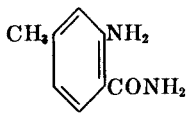
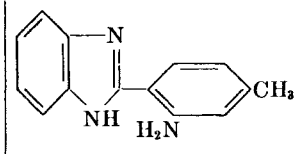
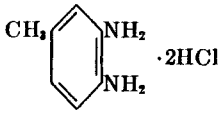
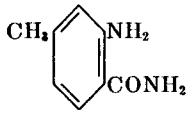
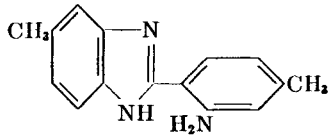
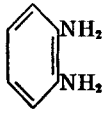
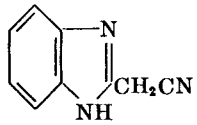
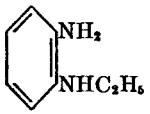
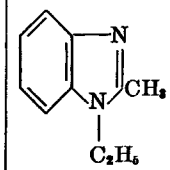
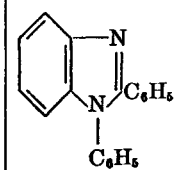
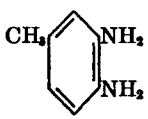
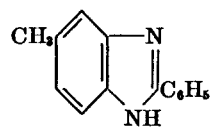
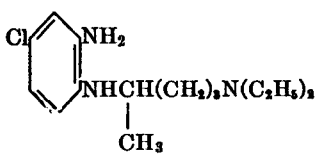
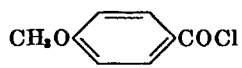
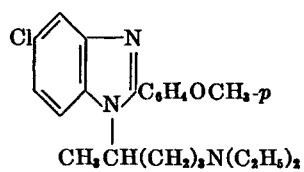
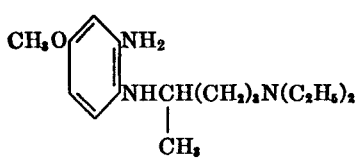
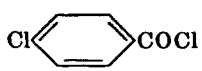
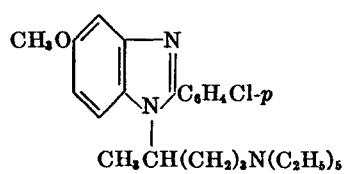
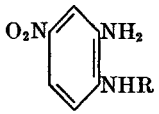
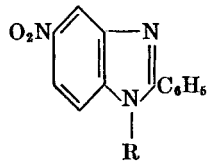
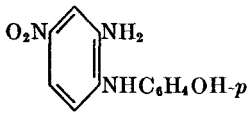
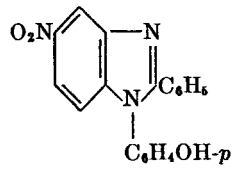
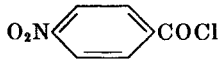
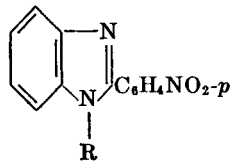
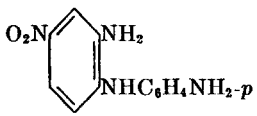
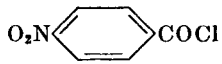
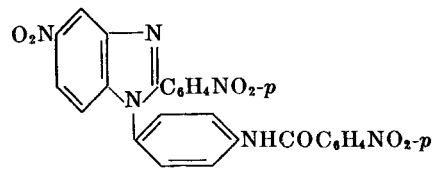
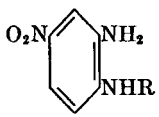
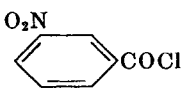
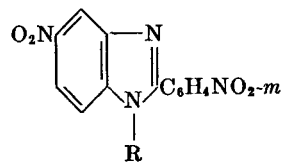
				(542)
				(543)
	NH_2COCH_2CN		63	(166)

TABLE 8

Benzimidazoles from acid chlorides and N-substituted o-phenylenediamines

DIAMINE	ACID CHLORIDE	PRODUCT	REFERENCES
	CH_3COCl		(313)
	C_6H_5COCl		(75)
	C_6H_5COCl		(288)
			(489)
			(488)

 R = CH_3, C_6H_5, *o*-tolyl, *p*-tolyl, *α*-naphthyl, *β*-naphthyl	C_6H_5COCl		(522)
	C_6H_5COCl		(479)
 R = C_6H_5, *p*-tolyl			(524, 655)
			(434)
 R = C_6H_5, *p*-tolyl			(525)

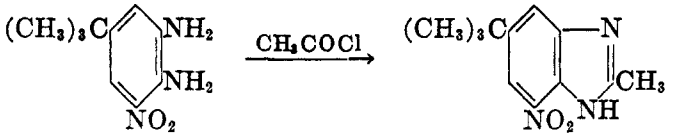
Equimolecular amounts of *o*-phenylenediamine dihydrochloride and thiobenzamide when heated to 240–250°C. give an almost quantitative yield of 2-phenylbenzimidazole (562).

5. By reaction with acid chlorides

The action of acid chlorides on *o*-phenylenediamines leads to benzimidazoles or monoacylated or diacylated *o*-phenylenediamines, depending upon experimental conditions. The Schotten–Baumann procedure leads to diacylated *o*-phenylenediamines; as a matter of fact, this is one of the methods for cleavage of the imidazole ring of benzimidazoles.

p-Toluoyl chloride with *o*-phenylenediamine in benzene solution is reported to give only a small yield of 2-tolylbenzimidazole (128, 344). Phthaloyl chloride on gentle warming gives 2-(benzimidazole-2′)benzoic acid and other products (485).

Acetyl chloride with 3,4-diaminotoluene in benzene solution yields 2,5(or 2,6)-dimethylbenzimidazole if the reaction is carried out without cooling and diacetyl-*o*-phenylenediamine when the reaction is cooled (80). Benzoyl chloride, phenylacetyl chloride, and benzenesulfonyl chloride when heated in benzene solution give only acylated *o*-phenylenediamines (80). 1-*tert*-Butyl-3,4-diamino-5-nitrobenzene heated with acetyl chloride on a water bath is reported to give 5(or 6)-*tert*-butyl-7(or 4)-nitro-2-methylbenzimidazole (395).



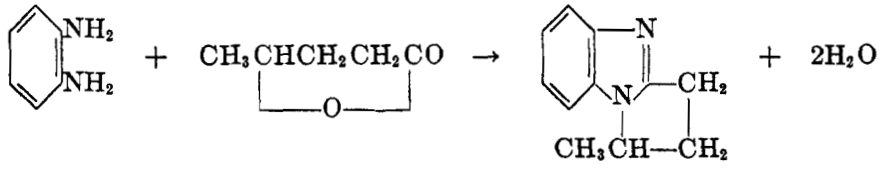
Most reactions between *o*-phenylenediamines and acid chlorides to give benzimidazoles have been carried out with aroyl chlorides. The reactions are carried out usually by heating the components together at about 200–220°C., by heating under reflux, or by heating on a steam bath in the presence of pyridine or a similar basic substance. Since benzimidazoles which possess no grouping in the 1-position may undergo acylation with acid chlorides, most reactions have been carried out with *N*-substituted *o*-phenylenediamines. Table 8 lists the compounds that have been prepared by the reaction of acid chlorides and *N*-substituted *o*-phenylenediamines.

The action of phosgene on *o*-phenylenediamines is discussed in Section II, A, 13.

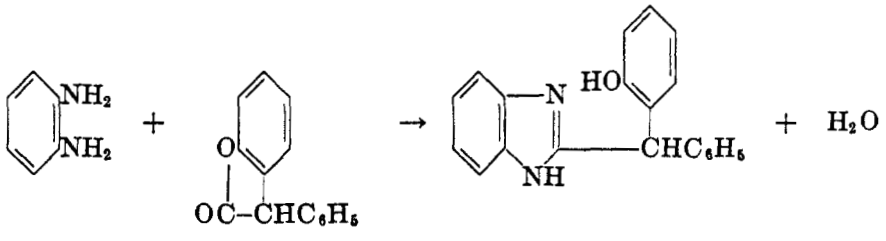
6. By reaction with lactones

The reaction of lactones with *o*-phenylenediamines was first studied by Bistrzycki and Schmutz (100), who investigated several γ-lactones of alcohol acids and phenol acids.

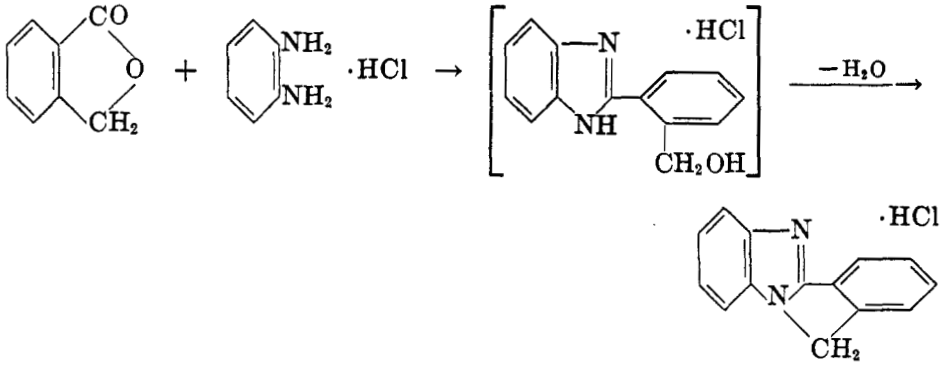
Valerolacetone when refluxed with *o*-phenylenediamines gives only a small yield of 1,2-(1′-methyltrimethylene)benzimidazole (103).



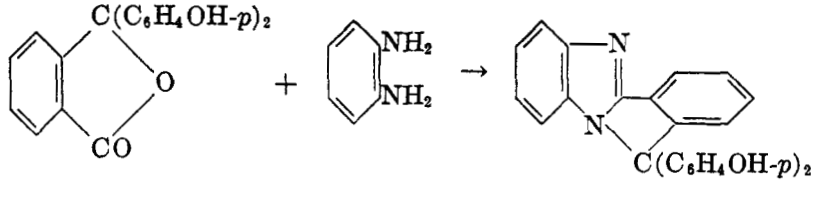
2-Hydroxydiphenylacetic acid lactone when heated at 120–130°C. with *o*-phenylenediamine gives a quantitative yield of 2-(2′-hydroxybenzhydryl)benzimidazole (104).



This lactone reacts analogously with 3,4-diaminophenetole (105). Phthalide with *o*-phenylenediamine hydrochloride is reported to give *o*-benzylene-2,1-benzimidazole hydrochloride in about 80 per cent yield; however, there is some doubt about the structure of this compound.

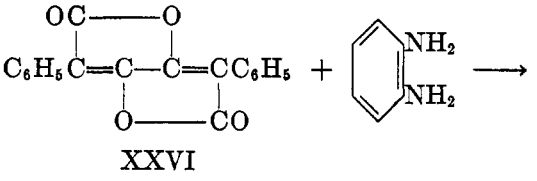


Phenolphthalein is reported to react in a somewhat analogous manner (102):

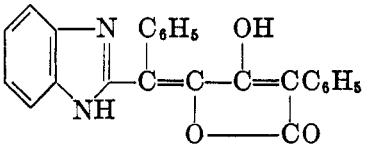


Biphthalyl and dihydrodiphthalyl with *o*-phenylenediamine at 280–290°C. in a sealed tube are reported to give phenylenedibenzimidazole (XIX) (467).

Pulvinic acid lactone (XXVI) and *p,p'*-dimethoxypulvinic acid lactone yield benzimidazoles (654):



XXVI



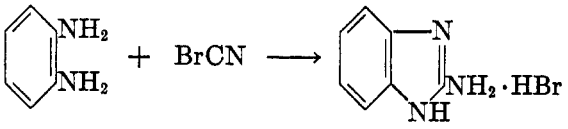
Phthalophenone and the lactone of 2-hydroxy-5-methyltriphenylacetic acid are reported not to undergo reaction with *o*-phenylenediamine (100).

Lactones of acids derived from sugars are discussed in Section II, F.

7. By reaction with nitriles

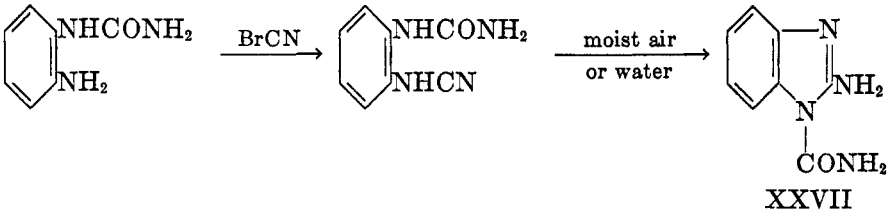
a. Reaction with cyanogen bromide

Cyanogen bromide will react with *o*-phenylenediamines to yield 2-aminobenzimidazoles in good yield; for example, 2-aminobenzimidazole may be prepared from cyanogen bromide and *o*-phenylenediamine:



The reaction is carried out by mixing equimolecular amounts of the reactants in aqueous suspension (466, 586).

Pellizzari (564) has obtained benzimidazole derivatives by treatment of *o*-aminophenylurea with cyanogen bromide:



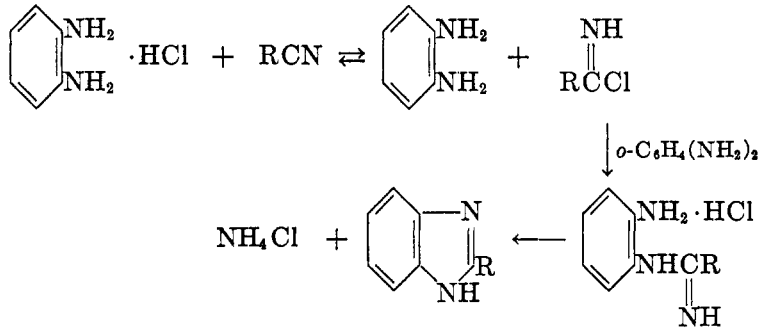
XXVII

o-Phenylene-α-guanylurea (XXVII) is unstable and tends to hydrolyze to 2-aminobenzimidazole.

Other methods for the synthesis of 2-aminobenzimidazoles are discussed in Section II, A, 15.

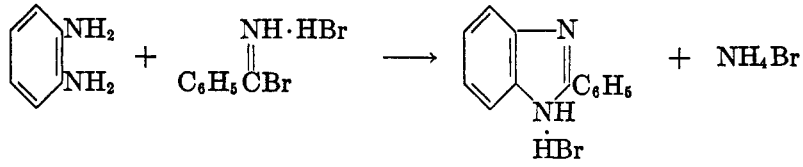
b. Reaction with other nitriles

Nitriles when heated with *o*-phenylenediamine hydrochloride give 2-substituted benzimidazoles. This reaction has been studied by Hölljes and Wagner (330), who find that the reaction proceeds under acid conditions and probably involves hydrogen-ion catalysis. The following mechanism for this reaction is suggested (330):

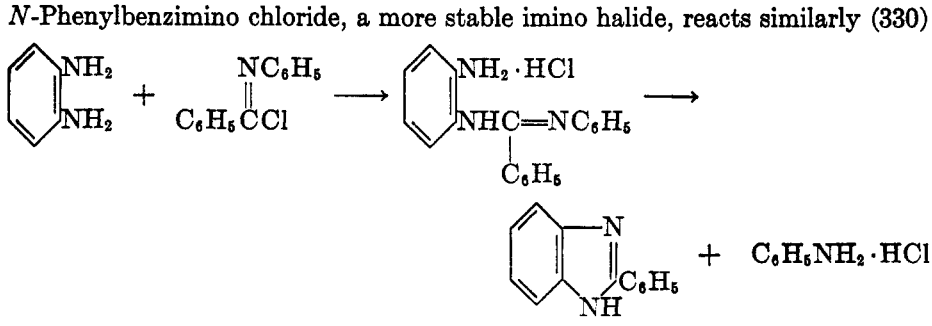


The reaction is carried out usually at about 200°C.; at this temperature ammonium chloride will undergo decomposition to regenerate additional hydrogen chloride and cause the reaction to proceed further. The reaction proceeds under anhydrous conditions and is therefore not due to the generation of acid or amide *in situ*. The first step in the reaction appears to be the rate-determining step.

In support of this mechanism Hölljes and Wagner (330) showed that benzimidazoles could be prepared also from imino halides of the type indicated as an intermediate in the proposed mechanism; for example, benziminobromide hydrobromide on brief warming with *o*-phenylenediamine gives 2-phenylbenzimidazole.



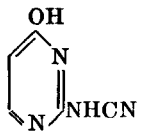
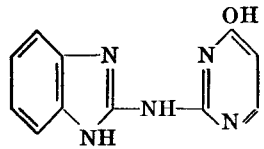
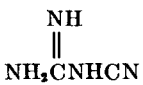
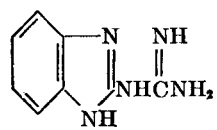
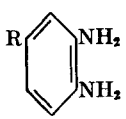
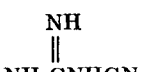
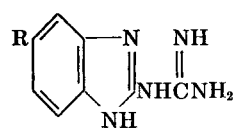
N-Phenylbenzimino chloride, a more stable imino halide, reacts similarly (330):

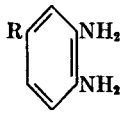
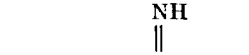
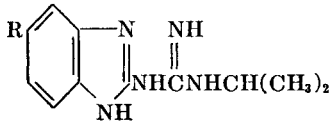
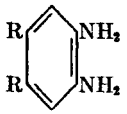
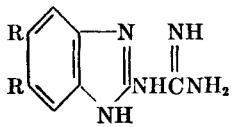
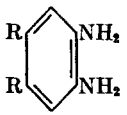
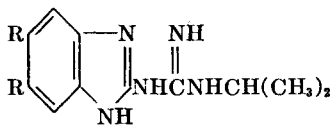


Hölljes and Wagner found that in the absence of acid no reaction takes place.

TABLE 9

Benzimidazoles from nitriles

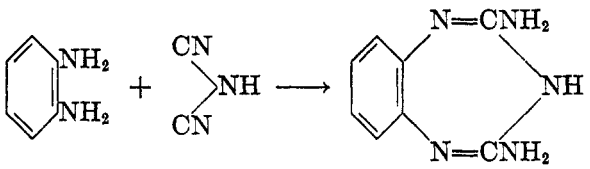
DIAMINE	NITRILE	PRODUCT	YIELD	REFERENCES
			per cent	
o-Phenylenediamine	HCN	Benzimidazole	5.9	(331)
o-Phenylenediamine	CH_3CN	2-Methylbenzimidazole	27.3	(331)
o-Phenylenediamine	C_2H_5CN	2-Ethylbenzimidazole	58.8	(331)
o-Phenylenediamine	*n*-C_3H_7CN	2-*n*-Propylbenzimidazole	71.0	(331)
o-Phenylenediamine	*n*-C_4H_9CN	2-*n*-Butylbenzimidazole	47.4	(331)
o-Phenylenediamine	*n*-$C_5H_{11}CN$	2-*n*-Amylbenzimidazole	50.0	(331)
o-Phenylenediamine	C_6H_5CN	2-Phenylbenzimidazole	72.4	(331)
o-Phenylenediamine	*p*-$CH_3C_6H_4CN$	2-*p*-Tolylbenzimidazole	70.9	(331)
o-Phenylenediamine	$C_6H_5CH_2CN$	2-Benzylbenzimidazole*	83	(764)
o-Phenylenediamine				(63)
o-Phenylenediamine	$HOCH_2CH_2CN$	2-(2′-Hydroxyethyl)benzimidazole	59	(24)
o-Phenylenediamine				(566)
 (R = Cl, CH_3O, CH_3)				(1,414)

 (R = H, Cl, CH_3O, CH_3)				(1, 414)
 (R = Cl, CH_3, CH_3O)				(414)
 (R = Cl, CH_3, CH_3O)				(414)

* This reaction was carried out by heating equimolecular amounts of *o*-phenylenediamine dihydrochloride and benzyl cyanide at 200°C. at atmospheric pressure for 5 hr.

Nitriles that have been used in the synthesis of benzimidazoles are listed in table 9.

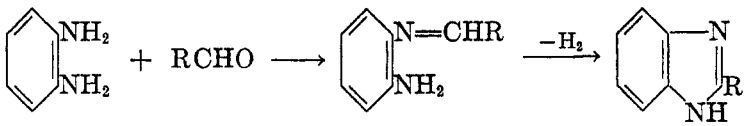
Dicyanimide with *o*-phenylenediamine gives a seven-membered ring compound, 2,4-diamino-1,3,5-triazabenzepine (XXVIII) (1), which possesses a structure comparable to that obtained from *o*-phenylenediamine and malonic acid.



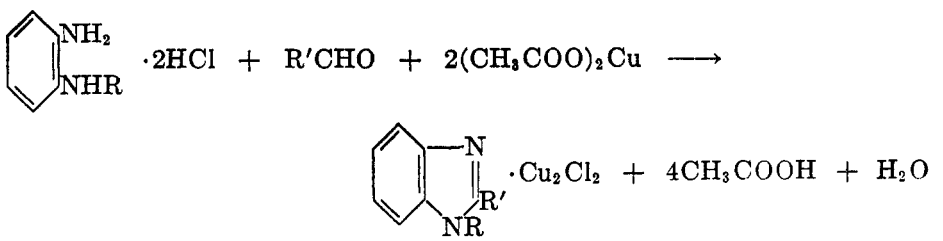
XXVIII

8. By reaction with aldehydes

Under the correct conditions aldehydes may react with *o*-phenylenediamines to yield 2-substituted benzimidazoles.

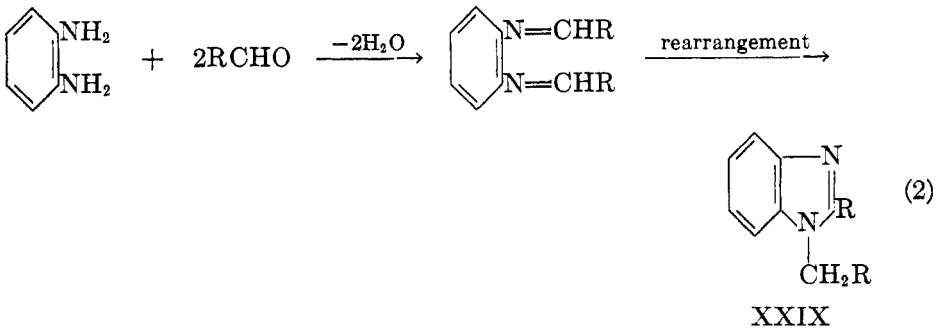


Since an oxidation is involved, the reaction is best carried out under oxidative conditions. This oxidation may be brought about by the air or, more conveniently, by the use of other oxidizing agents such as cupric acetate. This latter reagent was first introduced by Weidenhagen (741). Weidenhagen's method consists in reacting the diamine and aldehyde in water or alcoholic solution in the presence of cupric acetate or a similar cupric salt. The cuprous salt of the benzimidazole separates, and by means of hydrogen sulfide it may be readily decomposed to the free benzimidazole and cuprous sulfide. The sulfide may be removed readily by filtration. By means of Weidenhagen's method excellent yields of 2-substituted benzimidazoles may be obtained. A large number of alkyl, aryl, and heterocyclic aldehydes have been used with uniformly good results (375, 741, 743, 744). *N*-Alkylated *o*-phenylenediamines give very good yields of 1-substituted benzimidazoles (489, 743, 763). In the latter case, although no imide hydrogen is present, cuprous salts of the benzimidazoles are also formed first (743):



The cuprous salts formed can be decomposed with hydrogen sulfide in the usual way.

When the reaction between *o*-phenylenediamines and aldehydes is carried out in the absence of a specific oxidizing agent such as cupric acetate, the reaction may lead either to 2-substituted benzimidazoles or to "aldehydines" (equation 2):

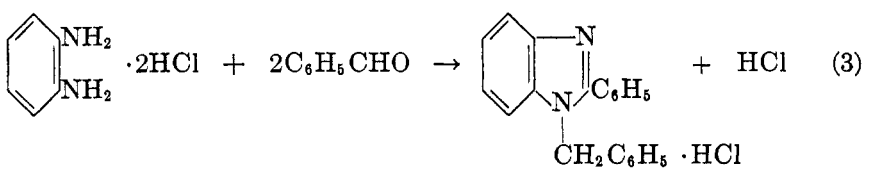


(2)

XXIX

In most cases the formation of "aldehydines" and 2-substituted benzimidazoles takes place simultaneously. In some cases "aldehydines" are the major product and in some cases 2-substituted benzimidazoles are the major product (320).

The reaction for the preparation of "aldehydines" was first discovered by Ladenburg (447, 448, 450) and the structure of the products elucidated by Hinsberg (316, 320). The reaction is usually carried out by heating the diamine with the aldehyde to 120–160°C., or the dry diamine dihydrochloride is heated with the aldehyde until the evolution of hydrogen chloride ceases (450).



(3)

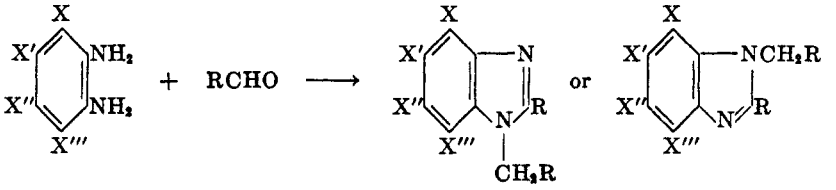
This latter reaction (equation 3) may be used to distinguish *o*-diamino dihydrochlorides from *m*- and *p*-diamine dihydrochlorides, since only the diamine dihydrochlorides of the ortho series evolve hydrogen chloride when heated for several minutes with a few drops of benzaldehyde (461).

Those "aldehydines" which have been prepared from *o*-phenylenediamines and aldehydes are listed in table 10. The best yields of "aldehydines" are obtained usually by carrying out the reaction under acidic conditions. 2-Substituted benzimidazoles are usually obtained along with the "aldehydine."

From the reaction between *o*-phenylenediamine dihydrochloride and phthalaldehyde, Thiele and Falk (714) obtained a product which they thought to be *o*-benzylene-2,1-benzimidazole. This was assumed to form in a manner analogous to the preparation of "aldehydines" (equation 4). However, Betrabet and Chakravarti (74) claim that the structure assigned by Thiele and Falk is er-

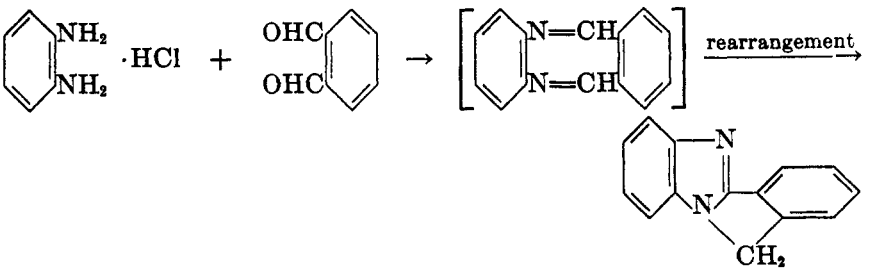
TABLE 10

Preparation of aldehydines



R	X	X′	X″	X‴	REFERENCES
H	H	H	H	H	(254)
CH_3	H	H	H	H	(322)
H	H	CH_3	H	H	(254)
C_2H_5	H	H	H	H	(322)
CH_3	H	CH_3	H	H	(320)
i-C_3H_7	H	CH_3	H	H	(320)
H	H	CH_3	Cl	H	(519)
C_6H_5	H	H	H	H	(451, 747)
C_6H_5	H	CH_3	H	H	(447, 448, 450)
C_6H_5	H	CH_3O	CH_3O	H	(520)
C_6H_5	H	NH_2	H	H	(323, 325)
C_6H_5	H	NO_2	H	H	(610)
p-$CH_3OC_6H_4$	H	H	H	H	(452)
p-$CH_3OC_6H_4$	H	CH_3	H	H	(452)
o-HOC_6H_4	H	CH_3	H	H	(448)
m-$O_2NC_6H_4$	H	H	H	H	(611)
m-$O_2NC_6H_4$	H	NO_2	H	H	(612)
p-$O_2NC_6H_4$	H	H	H	H	(322)
	H	H	H	H	(520)
	H	CH_3	H	H	(448, 452)

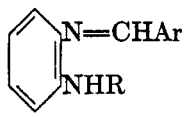
roneous and that their compound was instead the intermediary Schiff base shown in equation 4.



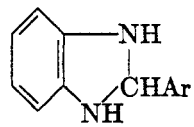
(4)

Aliphatic aldehydes in *neutral* solution with *o*-phenylenediamines may form substances which have the same empirical formulae as "aldehydines" but possess higher molecular weights and are probably dimers or polymers of "aldehydines" (323).

Aromatic aldehydes react with *o*-phenylenediamines which are monosubstituted at one nitrogen to form compounds which have been formulated as either azomethines (XXX) or 2,3-dihydrobenzimidazoles (XXXI).



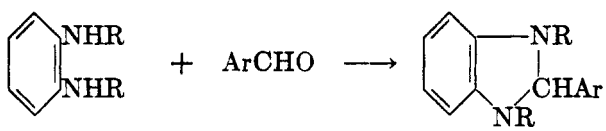
XXX



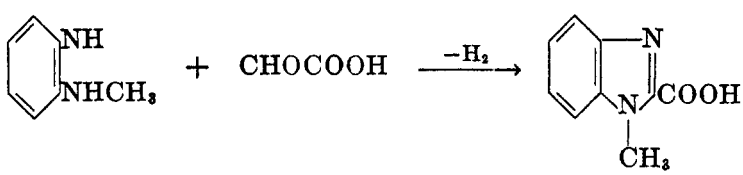
XXXI

1,2-Disubstituted benzimidazoles have been reported also as the product of this reaction (188, 210, 211, 215, 711). Fischer (210) obtained 1-methyl-2-phenylbenzimidazole by heating *N*-methyl-*o*-phenylenediamine and benzaldehyde in alcoholic solution; however, Weidenhagen, Train, Wegner, and Nördstrom (743) report that a different compound is obtained when the reaction is carried out with the use of cupric acetate according to Weidenhagen's method.

N,*N*'-Disubstituted *o*-phenylenediamines with aromatic aldehydes give compounds which have been formulated as 2,3-dihydrobenzimidazoles:



Aldehydo acids react preferentially at the aldehydo grouping. Glycolic acid, for example, gives 2-benzimidazolecarboxylic acid (722).



Calcium glycolate reacts similarly (315, 318). Phthalic aldehydo acids (78, 668) and derivatives thereof (79, 81) react at the aldehyde grouping to give (benzimidazole-2)benzoic acids.

Terephthalaldehyde gives a bisbenzimidazole:

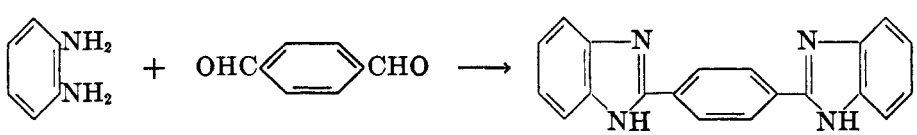
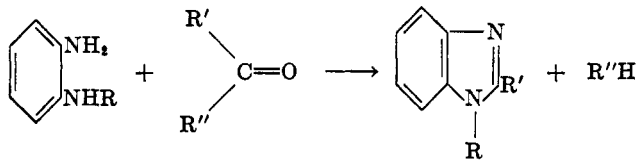
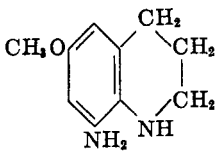
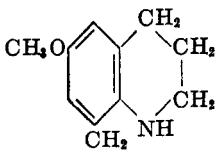
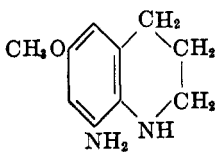
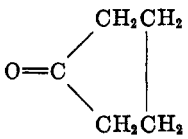
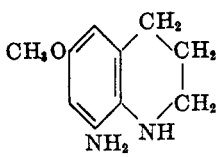
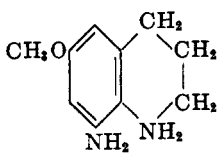
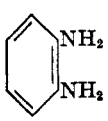
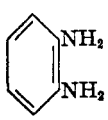


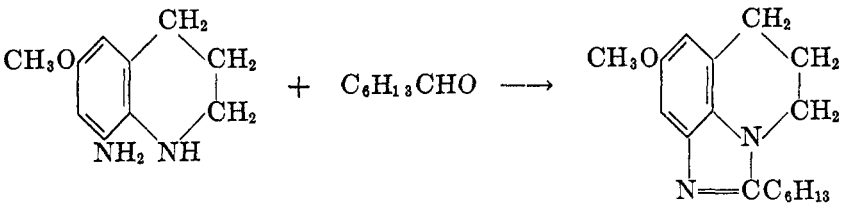
TABLE 11

The reaction of o-phenylenediamines with ketones



DIAMINE	KETONE (R'COR'')	R'
	CH_3COCH_3	CH_3
	$CH_3CO(CH_2)_5CH_3$	CH_3
		n-C_4H_9
	$CH_3CO(CH_2)_3N(C_2H_5)_2$	CH_3
	$CH_3COCH_2C_6H_5$	CH_3
	$CH_3CO(CH_2)_3N(C_2H_5)_2$	(Product not isolated)
	$CH_3COCH_2C_6H_5$	CH_3 and $C_6H_5CH_2$

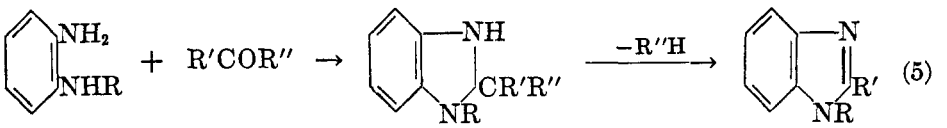
6-Methoxy-8-amino-1,2,3,4-tetrahydroquinoline reacts with heptaldehyde to give a 2-hexylimidazole (188):



9. By reaction with ketones[2]

a. Ketones containing one carbonyl group

The reaction of *o*-phenylenediamines with a number of ketones has been investigated by Elderfield and Kreysa (188). The reaction occurs as indicated in equation 5 (188).



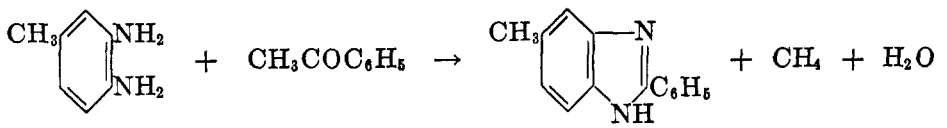
(5)

R=H or alkyl. XXXII

In several cases the product represented by R″H was isolated and identified. The results obtained by these workers are summarized in table 11 (188).

From the results summarized in table 11 it appears that in the reaction of 6-methoxy-8-aminotetrahydroquinoline (and possibly other *N*-substituted *o*-phenylenediamines) with methyl ketones the larger alkyl group of the ketone is lost rather than the methyl group, whereas in the reaction of *o*-phenylenediamine with methyl benzyl ketone and, presumably, with 1-diethylamino-4-pentanone, elimination of the methyl group occurs to a major extent. The direct elimination of the alkyl group and of hydrogen (as R″H) from the intermediate benzimidazolines (XXXII) may be assumed to be due to the gain in resonance stabilization on conversion to the benzimidazole (188).

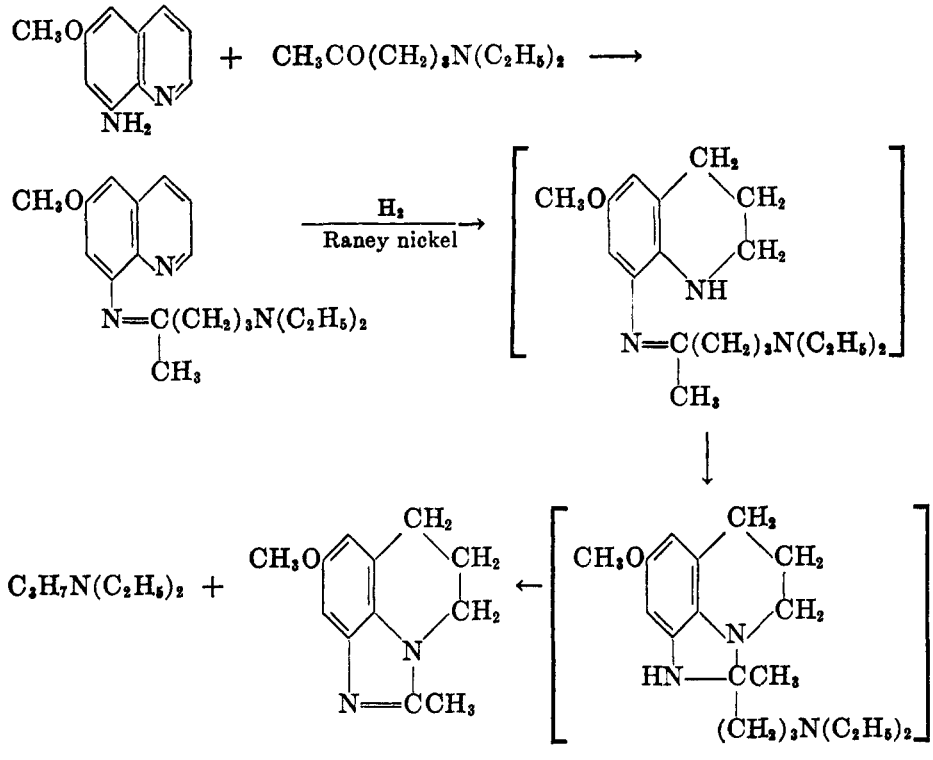
Ladenburg and Rügheimer (453) obtained 2-phenyl-5(or 6)-methylbenzimidazole by heating 3,4-diaminotoluene with acetophenone at 180°C. for some time. Here again the methyl group is the one that is eliminated preferentially:



2-Phenylbenzimidazole may be obtained also from benzoin and *o*-phenylenediamine dihydrochloride (394). If *o*-phenylenediamine is used as the free base, the product is 2,3-diphenylquinoxaline (394).

[2] *Note added in proof:* The reaction of *o*-phenylenediamines with ketones has recently been studied more fully by Elderfield and McCarthy (J. Am. Chem. Soc. **73**, 975 (1951)).

Elderfield, Kreysa, Dunn, and Humphreys (189) obtained 2-methyl-8-methoxy-5,6-dihydro-4-imidazo-(*ij*)-quinoline as the major product from a reductive-amination reaction involving 6-methoxy-8-aminoquinoline and 1-diethylamino-4-pentanone. In this reaction it appears that the pyridine ring is reduced before the azomethine grouping and the resulting reduced product rearranges to a benzimidazoline-type intermediate, the type formed in the reaction of *o*-diamines with ketones (XXXII), which yields an imidazole by rupture of a carbon–carbon bond (189):

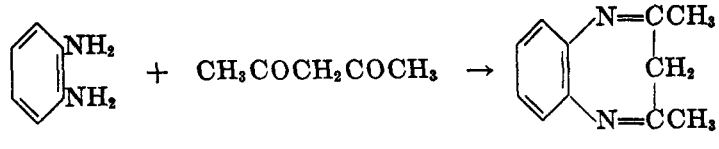


N,*N*-Diethyl-*n*-propylamine was detected in the reaction product.

The reaction of ethyl acetoacetate and other β-keto esters with *o*-phenylenediamines is discussed in Section II, A, 3.

b. Ketones containing two or more carbonyl groups

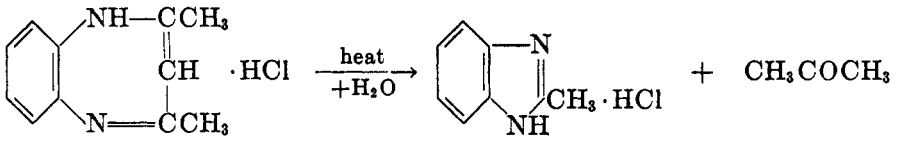
o-Phenylenediamine and acetylacetone on gentle warming in alcohol or acetic acid solution react as indicated in equation 6.



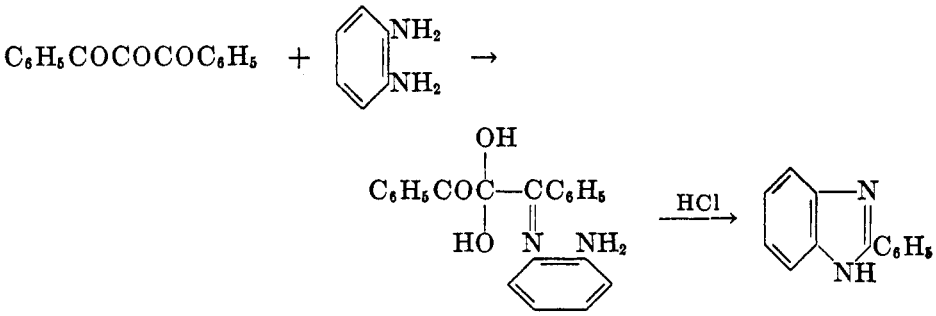
(6)

XXXIII

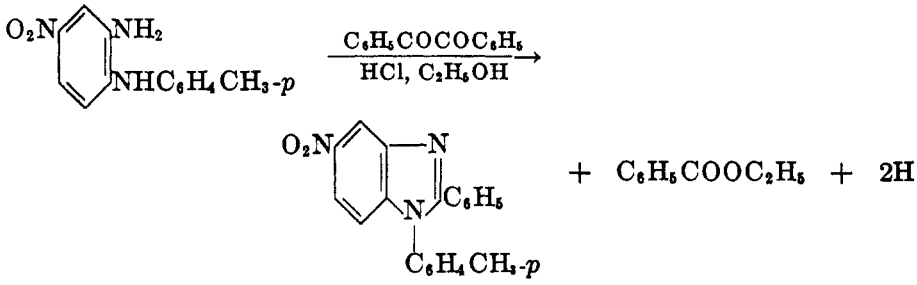
Heating an aqueous solution of the hydrochloride of XXXIII under reflux gives 2-methylbenzimidazole and acetone (717).



Benzoylacetone reacts in an analogous manner (717), the intermediate compound of type XXXIII decomposing simultaneously to a mixture of 2-methylbenzimidazole, acetophenone, 2-phenylbenzimidazole, and acetone. Dibenzoylmethane and *o*-phenylenediamine give 2-phenylbenzimidazole (261). The same product may be obtained also from diphenyltriketone (261).



Dibenzoylphenylmethane and tribenzoylphenylmethane when heated with *o*-phenylenediamine in the presence of hydrochloric acid also give 2-phenylbenzimidazole (747). Dibenzil when heated with an equimolecular amount of 4-nitro-2-amino-4′-methyldiphenylamine in an alcoholic solution containing slightly more than an equivalent amount of hydrogen chloride is reported to give 1-tolyl-5-nitro-2-phenylbenzimidazole (120).



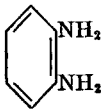
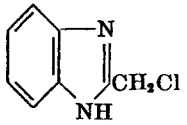
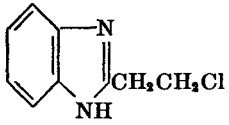
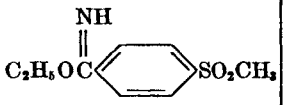
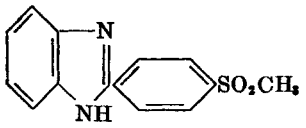
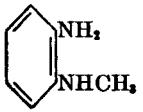
2-Amino-4-nitrodiphenylamine behaves similarly, but 2-amino-4-chlorodiphenylamine gives only a stilbazonium compound and no benzimidazole derivative (120).

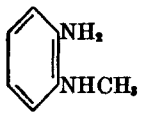
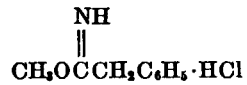
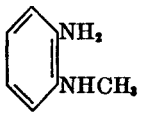
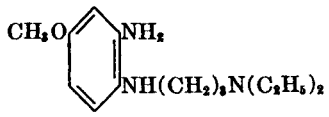
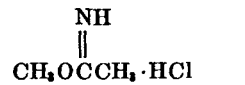
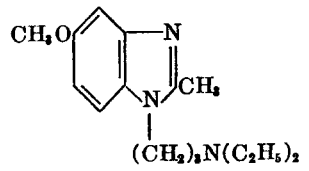
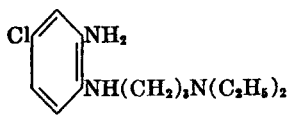
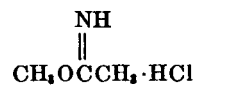
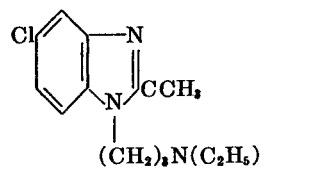
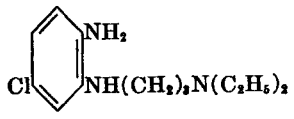
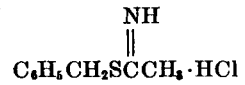
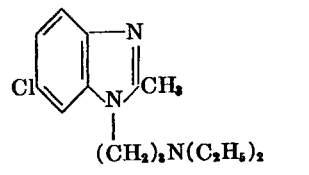
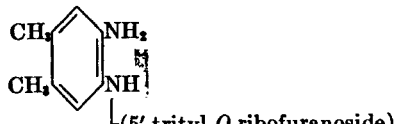
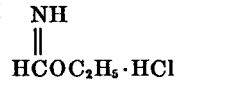
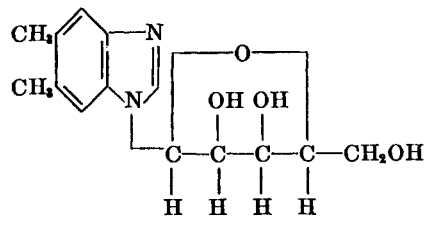
10. By reaction with potassium hydroxide and chloroform

Grassi-Cristaldi and Lambarbi (286, 727) report the preparation of benzimidazole by heating *o*-phenylenediamine with chloroform and potassium hy-

TABLE 12

Benzimidazoles from o-phenylenediamines and imino-ethers and imino-thioethers

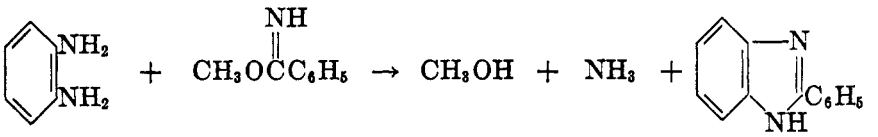
DIAMINE	IMINO-ETHER	PRODUCT	YIELD	REFERENCE
			per cent	
o-Phenylenediamine	$CH_3OC(=NH)CH_3 \cdot HCl$	2-Methylbenzimidazole	91	(413)
o-Phenylenediamine	$CH_3OC(=NH)C_6H_5 \cdot HCl$	2-Phenylbenzimidazole		(748)
o-Phenylenediamine	$CH_3OC(=NH)CH_2C_6H_5 \cdot HCl$	2-Benzylbenzimidazole	84	(413)
	$C_2H_5OC(=NH)CH_2Cl \cdot HCl$		70	(415)
	$C_2H_5OC(=NH)CH_2CH_2Cl \cdot HCl$			(415)
				(136)
o-Phenylenediamine	$CH_3SC(=NH)CH_2C_6H_5 \cdot HCl$	2-Benzylbenzimidazole	72	(413)
	$CH_3OC(=NH)CH_3 \cdot HCl$	1,2-Dimethylbenzimidazole	60	(413)

		1-Methyl-2-benzylbenzimidazole		(413)
		1-Methyl-2-benzylbenzimidazole	66	(413)
				(413)
			"Small"	(413)
				(413)
		 (after acid hydrolysis)		(121)

droxide (dissolved in ethanol). This convenient method for the preparation of benzimidazole is related to the method involving the use of ethyl orthoformate (Section II, A, 3).

11. By reaction with imino-ethers and imino-thioethers

The synthesis of benzimidazoles from imino-ethers or imino-thioethers and *o*-phenylenediamines has been investigated by King and Acheson (413). This reaction may be illustrated by the preparation of 2-phenylbenzimidazole from *o*-phenylenediamine and benzimino methyl ether (equation 7) (748). When the



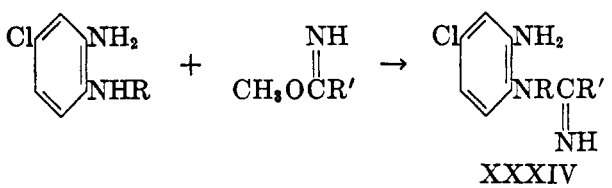
(7)

reaction of *o*-phenylenediamines with imino-ethers is carried out in the absence of acid relatively high temperatures (about 130°C.) are required; on the other hand, very good yields may be obtained at much lower temperatures if one equivalent of acid is present. If three equivalents of acid are present, lower yields are obtained (413).

Good yields of 1,2-disubstituted benzimidazoles may be obtained by using *N*-substituted *o*-phenylenediamines (413).

Benzimidazoles that have been obtained from *o*-phenylenediamines and imino-ethers or imino-thioethers are listed in table 12.

A side reaction leading to amidines (equation 8) limits the preparation of

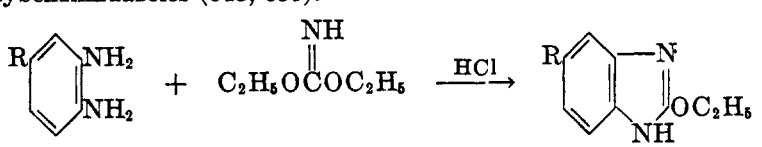


(8)

XXXIV

5-chlorobenzimidazoles by this method. However, the resulting amidines (XXXIV) on treatment with acetyl chloride are converted readily to the corresponding benzimidazoles (413).

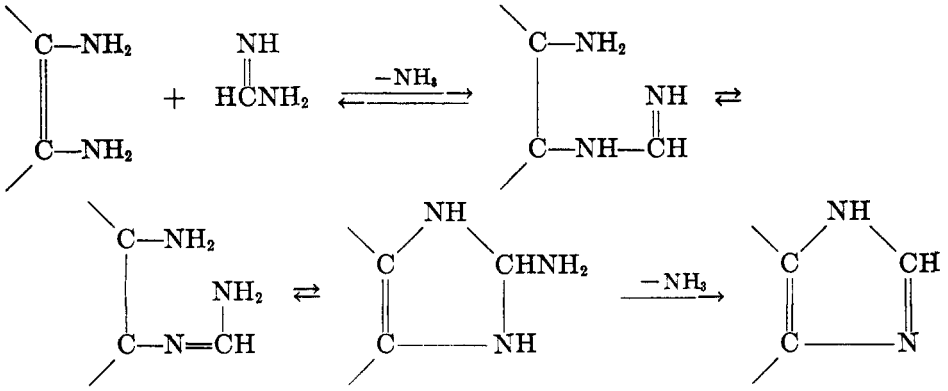
o-Phenylenediamines and diethyl iminocarbonate in the presence of acid yield 2-ethoxybenzimidazoles (648, 650).



R = H or CH_3.

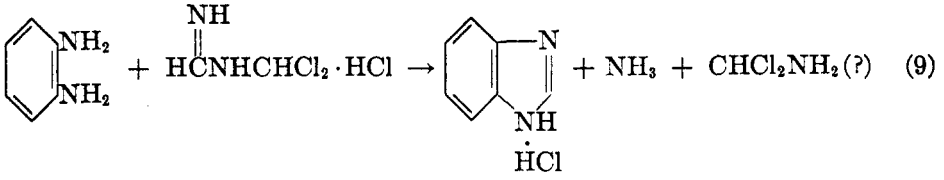
12. By reaction with amidines and guanidines

Amidines will react with *o*-phenylenediamines to yield benzimidazoles. The following mechanism for this reaction, as applied to formamidines, has been suggested (486):



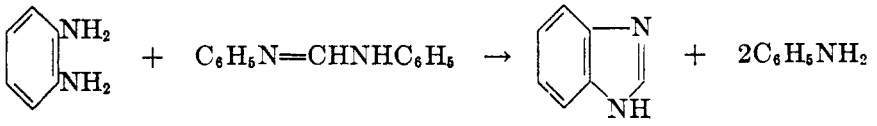
The work of Hölljis and Wagner (330) would indicate that the reaction of amidines with *o*-phenylenediamines is acid catalyzed, although additional evidence is needed on this point.

Dains (171) obtained benzimidazole in about 80 per cent yield by heating dichloromethylformamidine hydrochloride and *o*-phenylenediamine in benzene (equation 9).



(9)

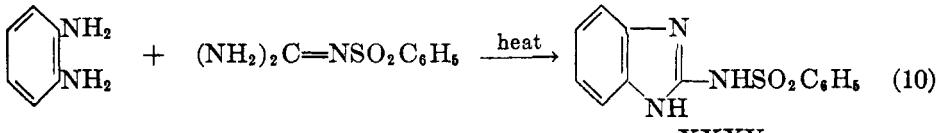
Diphenylformamidine gives an 85.3 per cent yield of benzimidazole when heated at about 125°C. with *o*-phenylenediamine (729):



Di(*p*-tolyl)formamidine reacts similarly with the liberation of two moles of *p*-toluidine. Phenyl *o*-tolylacetamidine gives a 63.6 per cent yield of 2-methylbenzimidazole when heated with *o*-phenylenediamine at 180°C. (729).

Diphenylbenzamidine with *o*-phenylenediamine dihydrochloride gives a 46 per cent yield of 2-phenylbenzimidazole. In the absence of acid no 2-phenylbenzimidazole is formed (332).

Price and Reitsema (618) have reported the condensation of benzenesulfonamidoguanidines with *o*-phenylenediamine to give 2-(benzenesulfonamido)benzimidazoles (equation 10). 2-(Benzenesulfonamido)benzimidazole (XXXV) may



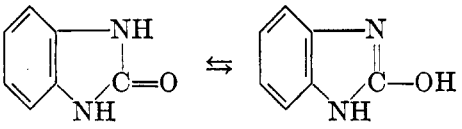
(10)

XXXV

be obtained in this way in 56 per cent yield. *m*-Nitro- and *p*-aminobenzenesulfonamidobenzimidazoles may be prepared analogously from the corresponding substituted benzenesulfonamidoguanidines (618).

13. Preparation of 2(3H)-benzimidazolones

2(3*H*)-Benzimidazolone (XXXVI) and 2-hydroxybenzimidazole (or 2-benzimidazolol) (XXXVII) are tautomeric substances.

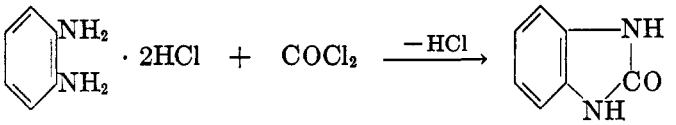


XXXVI XXXVII

In certain reactions the oxygenated function in the 2-position behaves as though it were in the keto form, while in other reactions it behaves as a hydroxyl group.

a. Synthesis by the reaction of *o*-phenylenediamines with phosgene

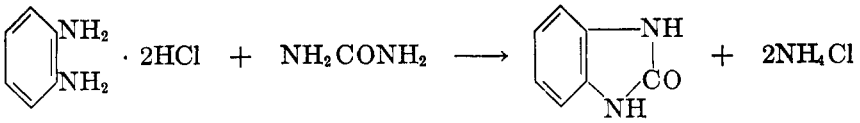
Phosgene with *o*-phenylenediamines gives 2(3*H*)-benzimidazones, often in excellent yield. The reaction is carried out usually in an organic solvent such as benzene, toluene, or chloroform or an aqueous solution of the dihydrochloride salt of the diamine may be used. Phosgene is usually used in excess. This method was first used by Hartmann (303), who prepared 2(3*H*)-benzimidazolone in this way.



A rather wide variety of *o*-diamines have been used successfully in this reaction, including those which contain alkyl (303), alkoxy (157), halogen (243, 303), carboxy (155, 192, 193), carbalkoxy (397), arsonic acid (421), and stibinic acid (360, 704, 706) groups on the benzene ring. *N*-Monosubstituted *o*-phenylenediamines lead to 1-substituted benzimidazolones (421, 608).

b. From *o*-phenylenediamines and urea

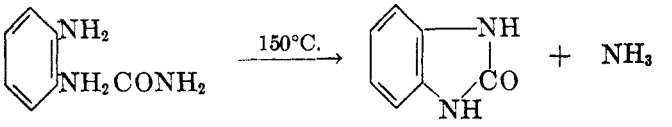
o-Phenylenediamine dihydrochloride when heated with urea at 130°C. gives 2(3*H*)-benzimidazolone (435).



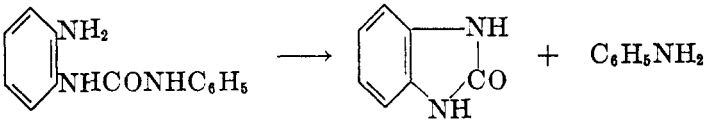
This general method has been used also for the preparation of substituted benzimidazolones (444, 649). By heating *o*-phenylenediamine and urea under

reflux in amyl alcohol solution until the evolution of ammonia ceased, Mistry and Guha (512) obtained a 95 per cent yield of 2(3*H*)-benzimidazolone.

2(3*H*)-Benzimidalones may be prepared also from *o*-aminophenylureas. These latter compounds are undoubtedly intermediates in the preparation of 2(3*H*)-benzimidazolones from *o*-phenylenediamines and urea. The cyclization may be brought about by heating the reactants to about 150°C. or above the melting point or the *o*-aminophenylurea may be heated with mineral acids (290, 769). Pellizzari, for example, obtained 2(3*H*)-benzimidazolone by heating *o*-aminophenylurea at 150°C. for some time (564).

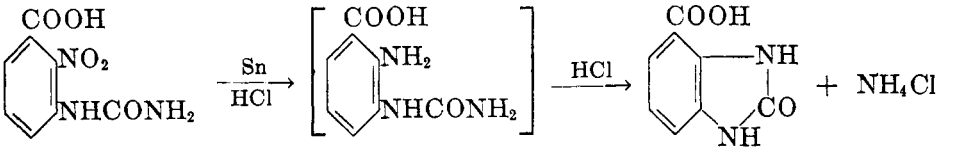


The same compound may be obtained by heating *N*-phenyl-*N'*-*o*-aminophenylurea at about 183°C. (307).



N,*N*-Diphenyl-*N'*-*o*-aminophenylureas also give 2(3*H*)-benzimidazolones on heating, with the liberation of two moles of aniline (462).

2(3*H*)-Benzimidazolones have been obtained also from *o*-nitrophenylureas (290). Griess (290), for example, obtained 2(3*H*)-benzimidazolone-4-carboxylic acid from *N*-(2-nitro-3-carboxyphenyl)urea on reduction with tin and hydrochloric acid.

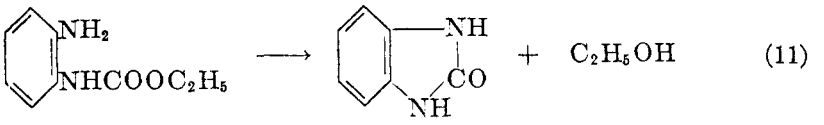


XXXVIII

The intermediary *o*-aminophenylurea is cyclized under the acidic condition employed in the reduction.

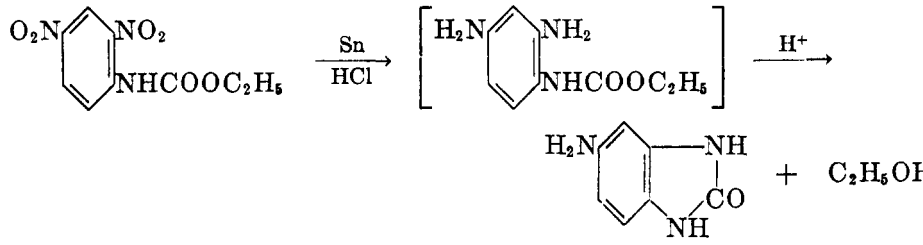
C. FROM PHENYLURETHANS

2(3*H*)-Benzimidazolone was prepared by Rudolph (638) by heating *o*-aminophenylurethan above its melting point (equation 11):

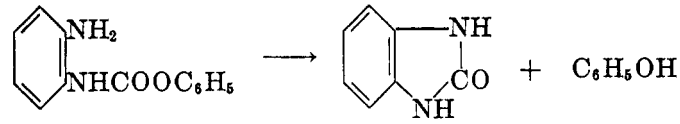


(11)

Hager (300) obtained 5-amino-2(3*H*)-benzimidazolone by reducing 2,4-dinitrophenylurethan with tin and hydrochloric acid:

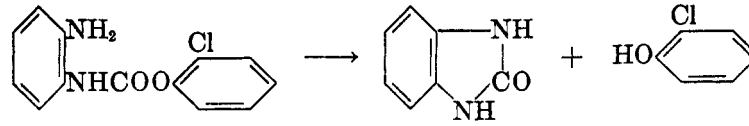


2(3*H*)-benzimidazolone may be prepared also from *N*-carbophenoxy-*o*-phenylenediamine (XXXIX) (620, 621):



XXXIX

This material is soluble in potassium hydroxide solution, and cyclization to 2(3*H*)-benzimidazolone may be brought about by acidification of the potassium hydroxide solution with dilute mineral acids. The cyclization may be brought about also by heating the solution. *N*-[Carbo-*o'*-chlorophenoxy]-*o*-phenylenediamine (XL) behaves analogously (620, 621):



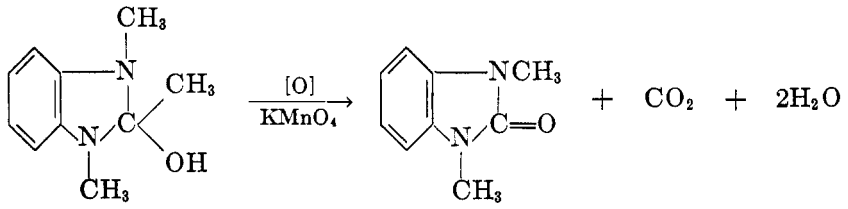
XL

The cyclization in this case takes place on attempted recrystallization of the substituted diamine (XL) from alcohol.

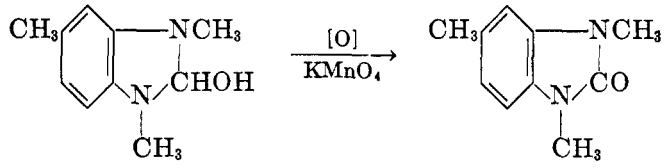
Several patents have been issued for the preparation of 5(or 6)-arsenic acid (359, 703) or 5(or 6)-stibinic acid (705, 706) derivatives of 2(3*H*)-benzimidazolones. These compounds may be prepared by treating 3,4-diaminophenylarsenic acid or 3,4-diaminostibinic acid with enough chloroformic ester to react with one of the amino groups, followed by cyclization of the resulting urethans by heating with dilute mineral acids or by heating with the material itself. *N*-Monosubstituted-3,4-diaminobenzenearsenic or stibinic acids lead to 1-substituted 2(3*H*)-benzimidazolones (359, 703, 706).

d. By the oxidation of "pseudo bases"

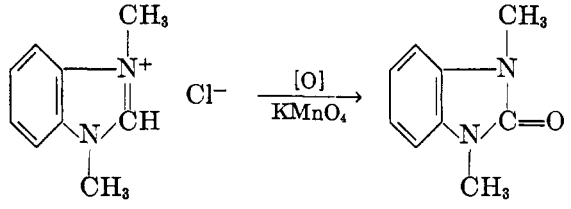
1,3-Disubstituted 2(3*H*)-benzimidazolones may be prepared conveniently by oxidation of "pseudo bases" or the quaternary salts derived therefrom. Potassium permanganate is usually used as the oxidizing agent. 1,2,3-Trimethylbenzimidazolium hydroxide, for example, on oxidation with potassium permanganate in the cold is converted to 1,3-dimethyl-2(3*H*)-benzimidazolone (230).



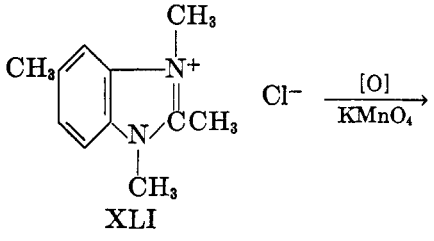
Conversion to the 2(3*H*)-benzimidazolone may be brought about also by simply subjecting the pseudo base to distillation (230). 1,3,5-Trimethylbenzimidazolium hydroxide on oxidation with potassium permanganate gives 1,3,5-trimethyl-2(3*H*)-benzimidazolone (250).



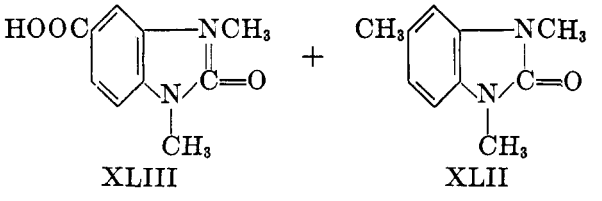
1,3-Disubstituted benzimidazolium halides also yield 2(3*H*)-benzimidazolones under vigorous conditions of oxidation. Pinnow and Sämann, for example, obtained 1,3-dimethyl-2(3*H*)-benzimidazolone by oxidizing 1,3-dimethylbenzimidiazolium chloride with potassium permanganate (602).



If the phenyl ring of the benzimidazolium halide contains a methyl or other alkyl group, this may be oxidized under the conditions of the reaction to a carboxy group (598, 603, 606). Thus, from 1,2,3,5-tetramethylbenzimidazolium chloride (XLI), Pinnow and Sämann (603) obtained a mixture of the expected product (XLII) and the corresponding acid (XLIII).



XLI



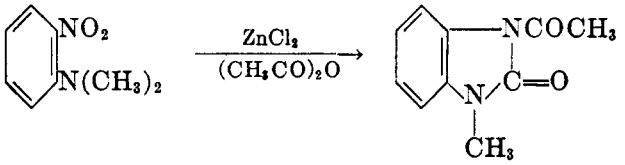
XLIII XLII

Silver oxide has been used also as an oxidizing agent in reactions of this type (249).

e. By treatment of *o*-nitro-*N*,*N*-dimethylanilines with acetic anhydride and zinc chloride

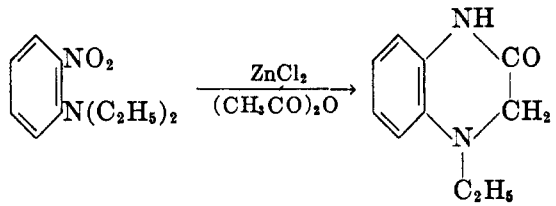
This reaction has been investigated by van Romburgh and Huyser (635, 636).

o-Nitro-*N*,*N*-dimethylaniline, when heated under reflux for several hours with zinc chloride (0.5 part) and acetic anhydride (2 parts), is converted to 1-methyl-3-acetyl-2(3*H*)-benzimidazolone.



This reaction has been carried out also, in good yields, with 2,4-dinitro-, 3,6-dinitro-, and 3,4,6-trinitro-*N*,*N*-dimethylanilines to give the corresponding nitro-2(3*H*)-benzimidazolones. In the case of the 3,4,6-trinitro-*N*,*N*-dimethylaniline, the product was not the 3-acetyl derivative, but rather the nonacetylated product having hydrogen in the 3-position. The acetyl group present in the other 2(3*H*)-benzimidazolones prepared may be conveniently removed by hydrolysis with dilute sodium hydroxide solution, by treatment with chromic acid in acetic acid solution, or by the use of iron and hydrochloric acid (635, 636).

When the above reaction is carried out with *o*-nitro-*N*,*N*-*diethyl*anilines, the products are not 2(3*H*)-benzimidazolones, but rather 1,2,3,4-tetrahydro-3-keto-1-ethylquinoxalines (635, 636).



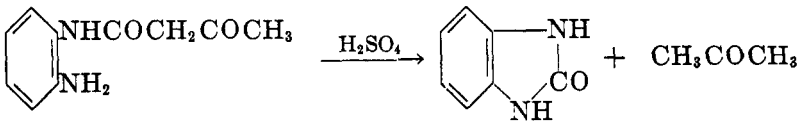
f. Miscellaneous methods

2(3*H*)-Benzimidazolone has been prepared also by the isomerization of 1-hydroxybenzimidazolone by means of benzoyl chloride in cold sodium hydroxide solution, by heating with water in a sealed tube, or by heating with zinc dust (549, 550).

2(3*H*)-Benzimidazolones have been obtained in addition by treatment of 2-chlorobenzimidazoles or 2-ethoxybenzimidazoles (648, 650) with concentrated hydrochloric acid (443, 650) or by treatment of 2-aminobenzimidazoles with barium hydroxide solution in a sealed tube or with nitrous acid (587).

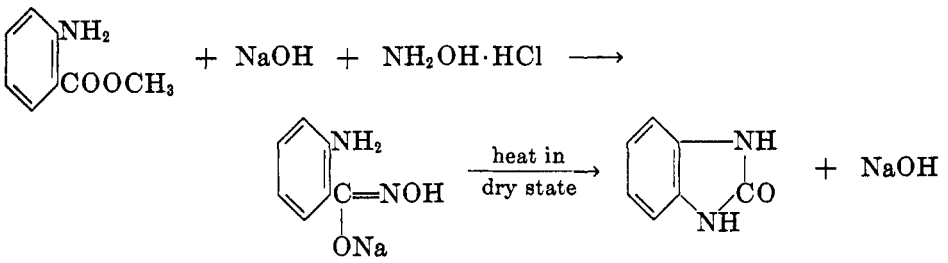
Manuelli and Recchi (478) obtained 2(3*H*)-benzimidazolone by heating *o*-

phenylenediamine dihydrochloride with urethan in the presence of molten sodium acetate. Monoacetylacetanilide yields 2(3*H*)-benzimidazolone, also, on cleavage with strong acids (513):



Elbs (186) obtained 5-methyl-2(3*H*)-benzimidazolone by the electrolytic reduction of *o*-nitro-*p*-methyllactanilide in acid solution.

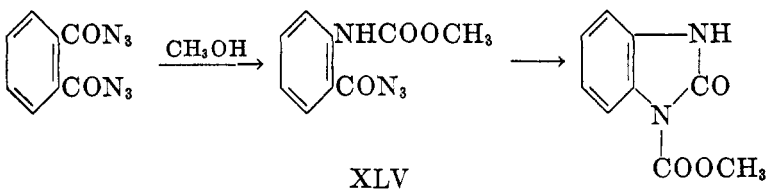
2(3*H*)-Benzimidazolone has been obtained by the rearrangement of the sodium salt of 2-aminobenzhydroxamic acid (XLIV) (660):



XLIV

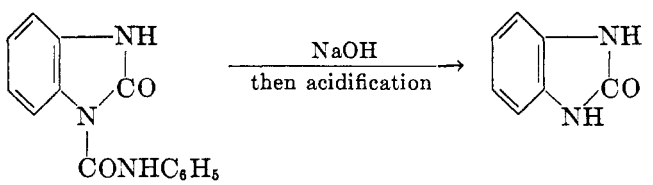
The potassium salt of the dibenzoyl derivative also rearranges to 2(3*H*)-benzimidazolone.

2-(Carbomethoxyamino)benzoyl azide (XLV), obtainable from phthalyl diazide and methyl alcohol, on heating in toluene yields 1-carbomethoxy-2(3*H*)-benzimidazolone (468):



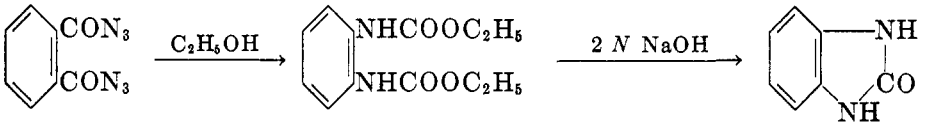
XLV

The analogous 1-carbethoxy derivative may be obtained in the same manner. From XLV, by treatment with aniline followed by heating of the resulting 2-(carboanilidoamino)benzoyl azide in toluene, may be obtained 1-carboanilido-2(3*H*)-benzimidazolone (XLVI), which readily undergoes hydrolysis to 2(3*H*)-benzimidazolone (468).



XLVI

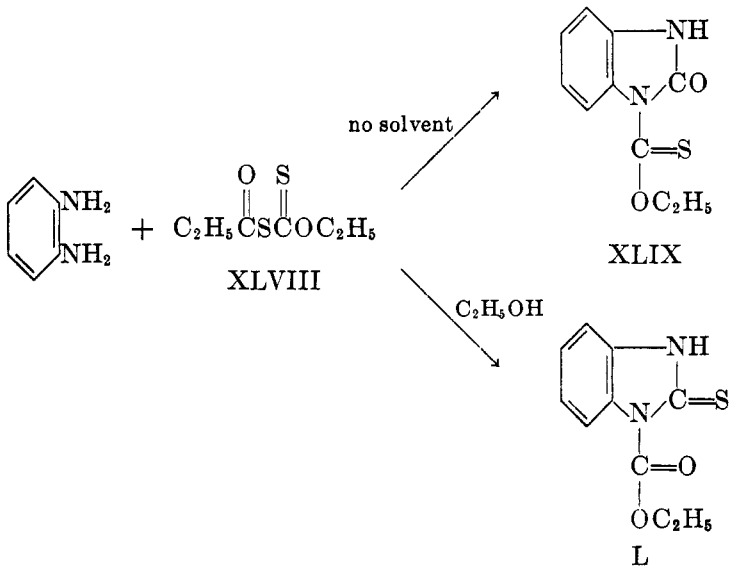
Phthalyl azide reacts with two moles of ethanol to give *o*-phenylenediurethan (XLVII), which on treatment with 2 *N* sodium hydroxide solution gives 2(3*H*)-benzimidazolone (176).



XLVII

2(3*H*)-Benzimidazolones have been obtained also as by-products from the reaction of phthalyl anhydrides and sodium azide in the presence of sulfuric acid (141, 142).

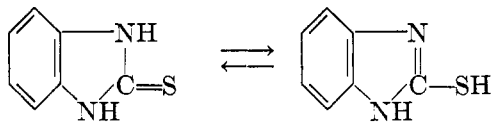
Guha and Dutra have investigated the reaction between *o*-phenylenediamine and ethyl xanthoformate (XLVIII). 1-Thiocarbethoxy-2(3*H*)-benzimidazolone (XLIX) is obtained when the reaction is carried out without solvent at room temperature and 1-carbethoxy-2(3*H*)-benzimidazolethione (L) is obtained in ethanolic solution.



XLVIII XLIX L

14. Preparation of 2(3H)-benzimidazolethiones

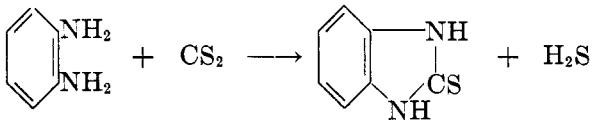
2(3*H*)-Benzimidazolethione[3] and 2-mercaptobenzimidazole are tautomeric substances, analogous to 2(3*H*)-benzimidazolone and 2-hydroxybenzimidazole.



[3] Before 1937 the name in *Chemical Abstracts* was 2-benzimidazolemercaptan. Other names found in the literature are *o*-phenylenethiourea, 2-benzimidazolethiol, 2-thiobenzimidazolone, and *o*-phenylenethiocarbamide.

a. Synthesis from *o*-phenylenediamines and carbon disulfide

2(3*H*)-Benzimidazolethiones, in general, may be prepared very conveniently by this method. The reaction is carried out usually by heating the reactants in alcoholic solution with or without the addition of alkali to the reaction mixture. 2(3*H*)-Benzimidazolethione, itself, has been prepared by this method (139, 294, 405).



In many cases the reaction has been carried out on *N*-aryl-*o*-phenylenediamines, so that the products of the reactions are 1-aryl-2(3*H*)-benzimidazolethiones (179, 215, 252, 292, 380, 381, 382, 383). However, 2(3*H*)-benzimidazolethiones containing hydrogen (5, 6, 176, 242, 358), an alkyl (213), or a dialkylaminoalkyl (489) group in the 1-position have been prepared also by this method. *o*-Phenylenediamines containing substituent groups in the phenyl ring have been used, including those containing alkyl (139, 380, 382, 383), halogen (139, 242, 381, 489), phenyl (179), anilino (215), sulfonamido and *N*-substituted sulfonamido (6, 29) groups and sodium 3,4-diaminosulfonate (358).

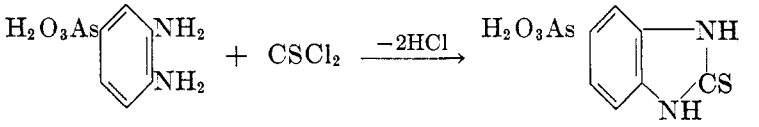
3,4-Diaminophenylarsenic acid and carbon disulfide give 2(3*H*)-benzimidazolethione-5-arsenic disulfide and arsenious sulfide (197).

b. From *o*-phenylenediamines and thiourea

This reaction is analogous to the preparation of 2(3*H*)-benzimidazolones from *o*-phenylenediamines and urea. 2(3*H*)-Benzimidazolethione may be prepared by this method by heating *o*-phenylenediamine dihydrochloride and thiourea to 170–180°C. (436). Excellent yields have been obtained by carrying out the reaction in amyl alcohol and heating under reflux until the evolution of ammonia becomes negligible (512). 2(3*H*)-Benzimidazolethiones that have been prepared from *o*-phenylenediamines and thiourea are listed in table 13.

c. From *o*-phenylenediamines and thiophosgene

Billeter and Steiner (76) obtained 2(3*H*)-benzimidazolethione and 5-methyl-2(3*H*)-benzimidazolethione by the action of thiophosgene on *o*-phenylenediamine and 3,4-diaminotoluene, respectively. 3,4-Diaminobenzenearsonic acid and thiophosgene gave a 78 per cent yield of 2(3*H*)-benzimidazolethione-5-arsonic acid (195).



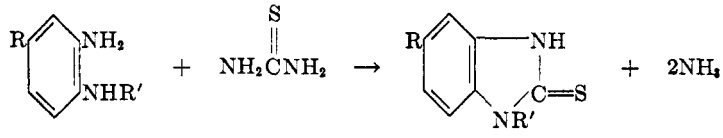
d. From hydrazo compounds and carbon disulfide

2(3*H*)-Benzimidazolethiones may be prepared also by heating hydrazo compounds with carbon disulfide at about 150°C. or, in some cases, at lower temperatures when heated for longer periods of time. This reaction has been studied by Jacobson and Hugershoff (384). The reaction apparently involves rearrangement

of the hydrazo compound to an *o*-aminodiarylamine under the conditions of the reaction and the reaction of the resulting diamine with carbon disulfide in the normal manner. This reaction, however, is not a general reaction (384).

TABLE 13

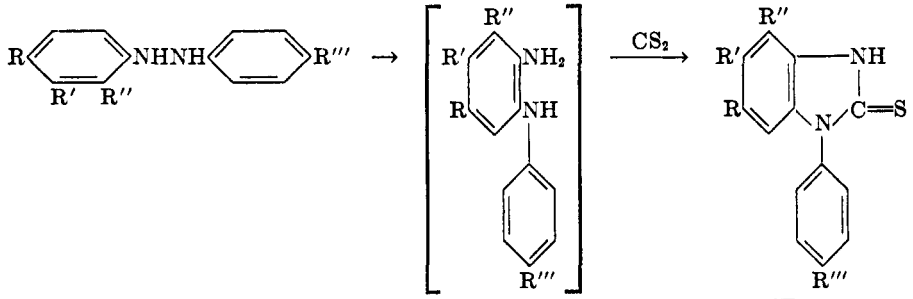
2(3H)-Benzimidazolethiones from o-phenylenediamines and thiourea



R	R′	YIELD	REFERENCES
		per cent	
H	H	——	(436)
		"Excellent"	(512)
		67.4	(139)
H	CH_3	15.2	(139)
H	*n*-C_4H_9	7.2	(139)
CH_3	H	20.0	(139)
CH_3O	H	25.2	(139)
C_2H_5O	H	22.0	(139)
Cl	H	48.0	(139)

TABLE 14

2(3H)-Benzimidazolethiones from hydrazo compounds and carbon disulfide



R	R′	R″	R‴	REFERENCE
C_2H_5O	H	H	H	(385)
C_2H_5O	H	CH_3	H	(389)
C_2H_5O	H	H	CH_3	(387)
C_2H_5O	CH_3	H	CH_3	(391)
C_2H_5O	H	CH_3	CH_3	(390)

The 2(3*H*)-benzimidazolethiones that have been prepared by this method are listed in table 14.

e. Miscellaneous methods

2(3*H*)-Benzimidazolethione may be prepared in 84–86.5 per cent yield by the action of potassium ethyl xanthate on *o*-phenylenediamine. This is the method given in *Organic Syntheses* (165) for the preparation of this compound. 2(3*H*)-

Benzimidazolethione-5-arsonic acid may be prepared by the same general method (198) from 3,4-diaminobenzenearsonic acid.

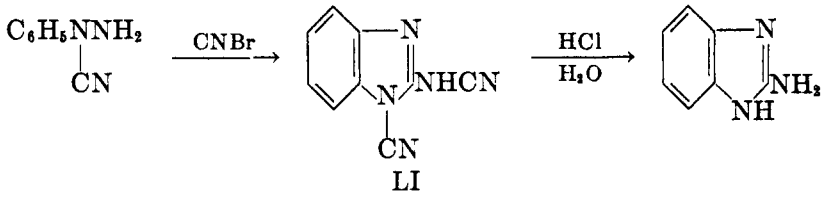
2(3*H*)-Benzimidazolethiones have been prepared also from *o*-phenylenediamine dihydrochlorides and ammonium thiocyanate. A solution of the two substances is usually evaporated to dryness on a steam bath and then heated for a short time. By this general method 2(3*H*)-benzimidazolethione (242, 259) and the 5-chloro (242), 4-methyl (459), and 5-methyl (458) derivatives of 2(3*H*)-benzimidazolethione have been prepared.

The preparation of 1-carbethoxy-2(3*H*)-benzimidazolethione (292), using ethyl xanthoformate, has been mentioned previously in Section II, A, 13, f.

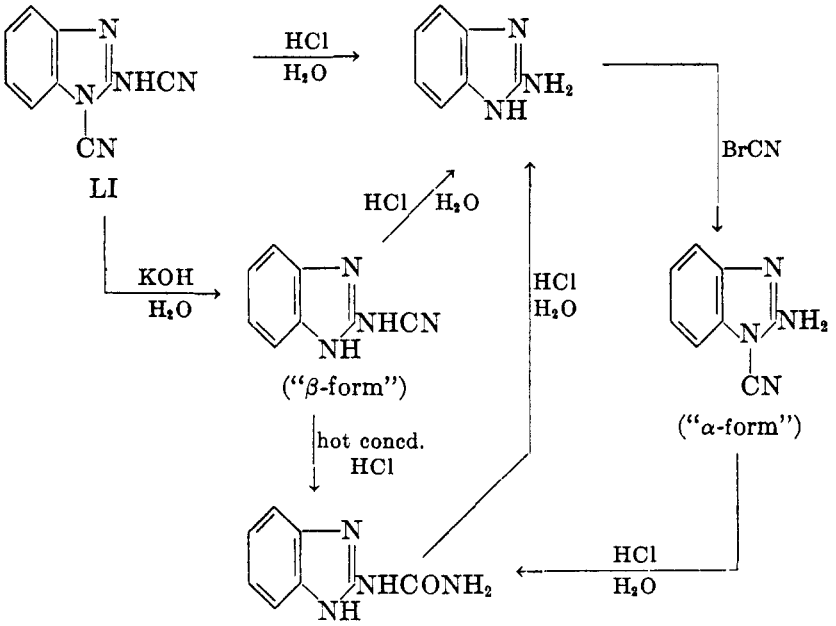
15. Preparation of 2-aminobenzimidazoles

The preparation of 2-aminobenzimidazoles by the action of cyanogen bromide on *o*-phenylenediamines (466, 586) has been mentioned previously (Section II, A, 7, a). 2-Aminobenzimidazoles may be prepared also by the action of cyanogen bromide (or cyanogen chloride) on phenylhydrazines (569):

$C_6H_5NHNH_2 + CNBr \rightarrow$



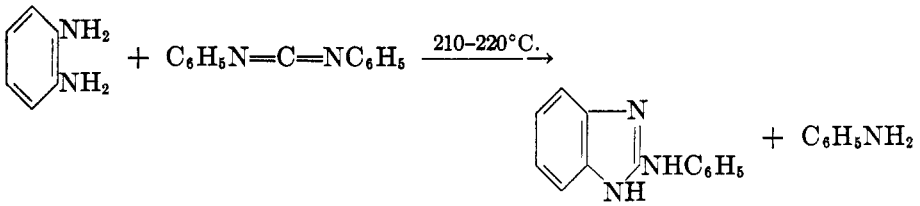
A number of interesting products can be prepared from 2-aminobenzimidazole and its precursor (LI) in this latter reaction. Some of these transformations are indicated below:



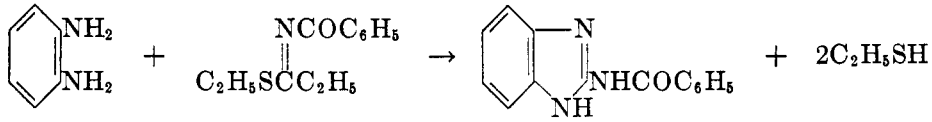
The dicyano derivative (LI) reacts also with amines (ammonia, aniline, and hydrazine) to form tricyclic derivatives containing a melamine ring. These and other transformations in this series have been studied extensively by Pellizzari (565, 566, 567, 568, 569).

2-Aminobenzimidazoles may be prepared also by the action of ammonia on 2-chloro-5(or 6)-nitrobenzimidazole (443) or 2-benzimidazolesulfuric acid (370). Aniline has been used instead of ammonia with 2-chloro-5(or 6)-nitrobenzimidazole to yield 2-anilino-5(or 6)-nitrobenzimidazole (443). Other primary and secondary amines (370) and hydrazine (368, 372) or substituted hydrazines have been used in place of ammonia with 2-benzimidazolesulfuric acid.

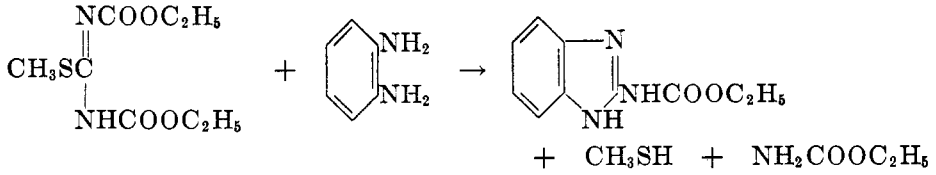
2-Arylaminobenzimidazoles may be prepared by the action of diarylcarbodiimides on *o*-phenylenediamines (406, 408, 410, 411):



2-(Benzoylamino)benzimidazole and 2-(cinnamoylamino)benzimidazole have been prepared by the action of benzoyl cyanamide (588) and cinnamoyl cyanamide (589), respectively, on *o*-phenylenediamine dihydrochloride. The two benzimidazoles on hydrolysis with potassium hydroxide solution yield 2-aminobenzimidazole. 2-Benzoylaminobenzimidazole has been prepared also by the action of the diethyl ester of benzoylimidedithiocarbonic acid on *o*-phenylenediamine (749):



2-Carbethoxyaminobenzimidazole may be prepared in 97 per cent yield by heating molar quantities of *o*-phenylenediamine and the methyl ether of thiocarbonyldiurethan in alcoholic solution (521):



B. FROM MONOACYL- AND DIACYL-*o*-PHENYLENEDIAMINES

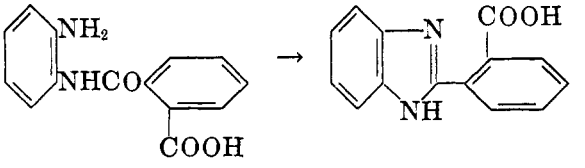
As mentioned previously, monoacyl-*o*-phenylenes are probably involved as intermediates in the synthesis of benzimidazoles from *o*-phenylenediamines and organic acids (578, 633) and related compounds.

Benzimidazoles may be prepared from monoacyl-*o*-phenylenediamines directly. Ring closure to benzimidazoles may be effected by heating the material itself, by distillation, by heating in the presence of mineral acid or acetic acid, or by heating under reflux an alkaline alcoholic solution of the monoacyl derivative. Acetic anhydride has also been used to effect ring closure.

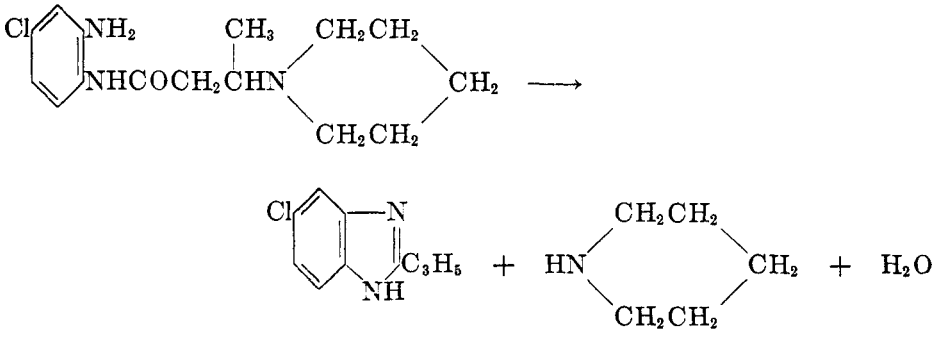
Diacyl derivatives, in general, are transformed into benzimidazoles by heating at a relatively high temperature (137), by keeping the material in the fused state for some time (42, 106), or by distillation (80, 641); by heating with acids either under pressure at a relatively high temperature (137, 344, 477, 736), or by heating under reflux with dilute mineral acids or acetic acid. Alkaline conditions have been used also (379, 578).

A relatively large number of monoacyl- and diacyl-*o*-phenylenediamines have been converted to benzimidazoles by the general method of Phillips, employing the use of dilute (about 4 *N*) hydrochloric acid (62, 570, 571, 576, 577, 578, 581).

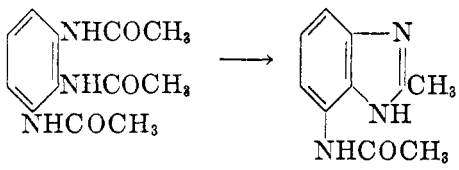
A relatively large number of 2-substituted alkyl- and aryl-benzimidazoles have been prepared by utilizing the various methods outlined above. 2-Cinnamylbenzimidazoles may be prepared from dicinnamoyl-*o*-phenylenediamines (437). *N*-(*o*-Carboxybenzoyl)-*o*-phenylenediamine when heated under reflux in an alcoholic alkaline solution gives *o*-(2-benzimidazole)benzoic acid:



2-Dialkylaminomethylbenzimidazoles may be prepared from the corresponding monacyl-*o*-phenylenediamines (3, 182). In attempts to prepare the corresponding 2-(dialkylaminoethyl)benzimidazoles in an analogous way, the only products obtained are benzimidazoles with an unsaturated group in the 2-position, formed by the splitting out of a dialkylamine residue (3, 301); thus, Hall and Turner (301) obtained 5(or 6)-chloro-2-propenylbenzimidazole in an attempted cyclization of *p*-chloro-*o*-amino-β-piperidinobutyranilide:



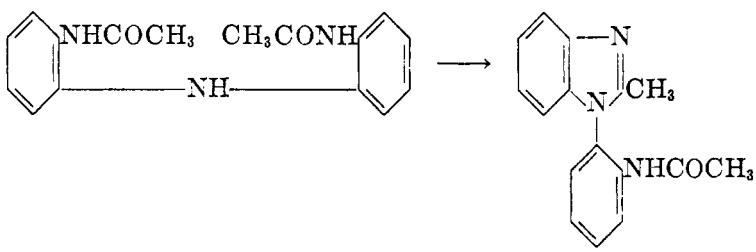
1,2,3-Triacetylaminobenzene on ring closure gives 2-methyl-4(or 7)-acetylaminobenzimidazole (15):



LII

Further cyclization of the resulting compound (LII) to form a tricyclic structure with two imidazole rings does not appear to take place.

2,2′-Diacetylaminodiphenylamines on ring closure give 1-(2′-acetylaminophenyl)-2-methylbenzimidazoles (721).



Reference has already been made to the studies of Roeder and Day (634) and Green and Day (287) on the mechanism of the formation of benzimidazoles from monoacyl- and diacyl-*o*-phenylenediamines. The studies of these workers indicate that in the removal of water from monoacyl-*o*-phenylenediamines to yield benzimidazoles one atom of hydrogen must come from each of the two nitrogen atoms. Under anhydrous conditions no benzimidazole is formed unless one hydrogen is available on each nitrogen atom.

C. BY REDUCTION OF ACYLATED *o*-NITROANILINES

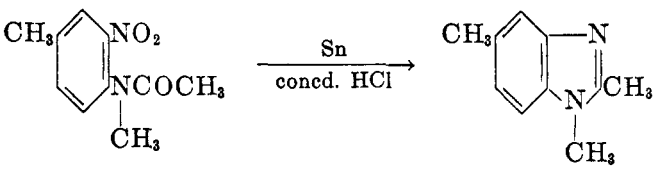
Acylated *o*-nitroanilines when reduced with tin and hydrochloric acid or similar reducing agents yield monoacyl-*o*-phenylenediamines by reduction of the nitro group in the normal manner; however, under the conditions of the reduction the resulting diamine immediately undergoes cyclization to the benzimidazole (327, 335, 339, 343).

This method has been used extensively for the preparation of benzimidazoles and, together with the method involving the action of carboxylic acids of *o*-phenylenediamines, probably constitutes one of the methods that have been most used. This general method has been used frequently for the preparation of 2-arylbenzimidazoles, especially.

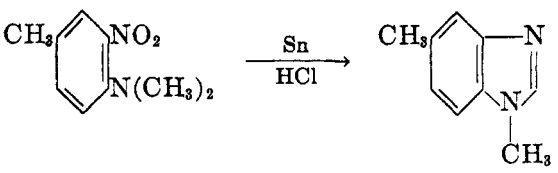
The reducing agents generally employed are tin and hydrochloric or acetic acid, and stannous chloride and hydrochloric acid. Other means that have been

used satisfactorily include electrolytic reduction in acidic solution (118), zinc dust and aqueous acetic acid (581), iron and dilute hydrochloric acid (31), and catalytic reduction with palladium catalyst in acetic acid solution (432), or platinum oxide in ether solution under acidic conditions (2). The use of oxygen acceptors, such as ferrous oxalate, is also reported (740).

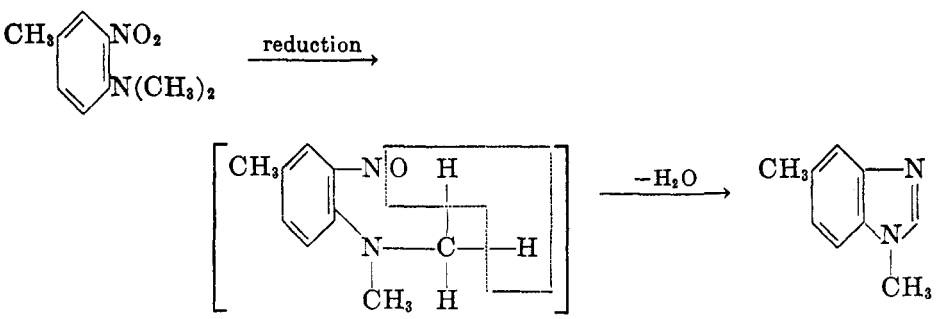
N-Substituted acylated *o*-nitroanilines lead to 1-substituted benzimidazoles. For example, *N*-methyl-2-nitro-4-methylacetanilide on reduction yields 1,2,5-trimethylbenzimidazole (2, 529):



1-Substituted derivatives have been observed also by von Pinnow (591, 592, 593, 594, 597, 600, 605) among the products of the reduction of *o*-nitrodimethylanilines. Thus, 3-nitro-4-dimethylaminotoluene on reduction with tin and dilute hydrochloric acid gives some 1,5-dimethylbenzimidazole:



This reaction may be brought about also with sodium sulfite (18 per cent yield) (472). It appears to involve first the reduction of the nitro group to a nitroso group followed by the removal of water (472).

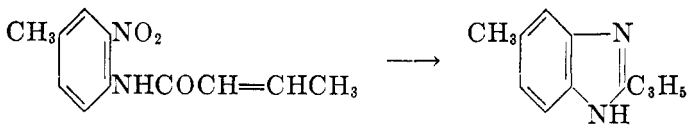


A competing reaction involves the further reduction of the nitroso group, which accounts for the low yields of benzimidazoles usually obtained.

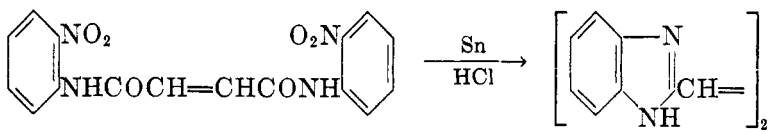
If the acylated *o*-nitroaniline contains an additional nitro group, the second nitro group is reduced to an amino group during the reaction (345, 433, 463, 464, 526, 733). Carboxy (400), carbalkoxy (184, 185), halogen (30, 31, 185, 593), and cyanomethyl (66) groups remain intact.

Trichloroacetyl-4-methyl-2-nitroaniline with tin and hydrochloric acid undergoes hydrolysis (340) to 3,4-diaminotoluene dihydrochloride and trichloroacetic acid. Salicyloyl-*o*-nitroaniline is converted readily to 2-(*o*-hydroxyphenyl)-benzimidazole (347).

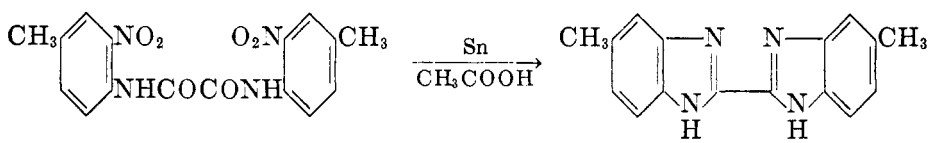
4-Crotonoylamino-3-nitrotoluene yields 3-propenyl-5(or 6)-methylbenzimidazole. The double bond is not reduced in the reaction.



The maleoyl derivative of *o*-nitroaniline on reduction with tin and hydrochloric acid gives 1,2-dibenzimidazolylethylene (147).



2,2′-Dibenzimidazoles (LIII) may be obtained from the substituted oxamide derivatives (341, 352):

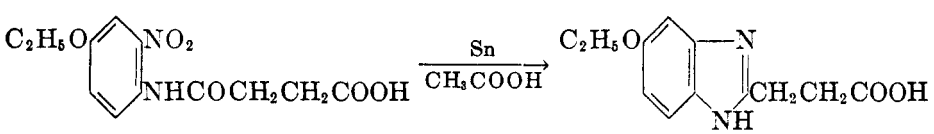


LIII

Dialkylaminoacetyl derivatives of *o*-nitroaniline on warming with tin and hydrochloric acid are converted to 2-(dialkylaminomethyl)benzimidazoles (184, 185).

Aroylacetyl- or acylacetyl-*o*-nitroanilines on reduction under acidic conditions yield 2-aroylmethyl- and 2-acylmethylbenzimidazoles, respectively (662, 663).

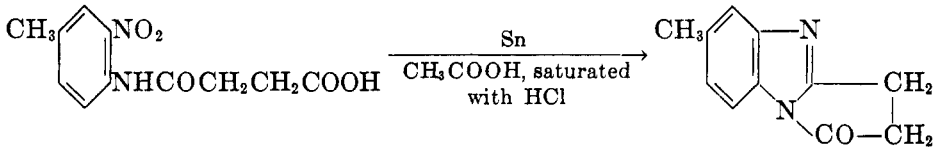
2-Nitro-4-ethoxysuccinanilic acid (LIV) on reduction with tin and acetic acid gives only a very poor yield of 5(or 6)-ethoxybenzimidazole-2-propionic acid (144).



LIV

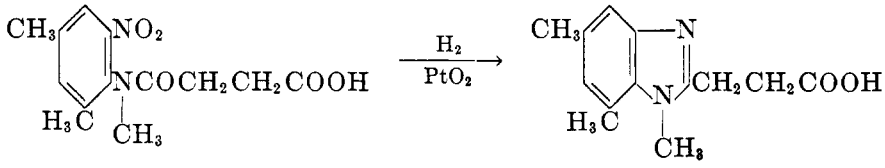
2-Nitro-4-methylsuccinanilic acid (LV) on reduction under anhydrous conditions

employing tin and acetic acid saturated with hydrogen chloride gives a tricyclic compound through the loss of two moles of water (342):



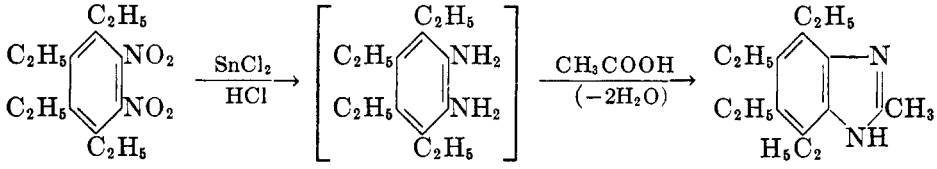
LV

Catalytic reduction of *d*-*N*-succinoyl-1-methylamino-2,4-dimethyl-6-nitrobenzene (LVI) is reported to give β-(1,5,7-trimethyl-2-benzimidazole)propionic acid (2):

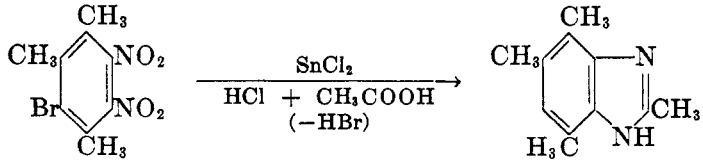


LVI

Several examples occur in the literature in which *o*-dinitrobenzenes have been used as starting materials for the synthesis of benzimidazoles. These substances on reduction with stannous chloride and hydrochloric acid in the presence of acetic acid give 2-methylbenzimidazoles (676, 678, 679, 680). Thus, 2-methyl-4,5,6,7-tetraethylbenzimidazole may be prepared from 1,2-dinitro-3,4,5,6-tetraethylbenzene by heating the latter under reflux with a solution of stannous chloride in a mixture of hydrochloric and acetic acids (676):

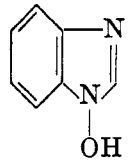


When this reaction is carried out with 1,2-dinitro-4-bromo-3,5,6-trimethylbenzene the bromine is removed and 2,4,5,7(or 2,4,6,7)-tetramethylbenzimidazole is obtained (679):

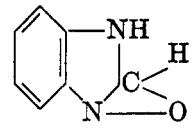


von Niementowski (30, 528, 530, 533, 536, 548) first showed that among the

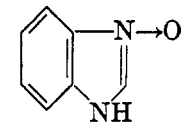
reduction products of acylated *o*-nitroanilines are found, sometimes, compounds which contain an oxygen atom. These compounds have been called "oxbenzimidazoles" and for the simplest case correspond to either of the following structures (LVII, LVIII, LVIX):



LVII



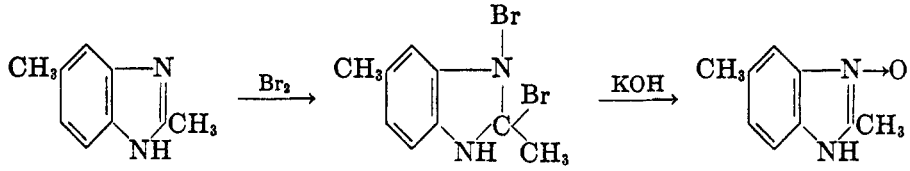
LVIII



LVIX

When an alcoholic ammonium sulfide solution is used as the reducing agent, yields of "oxbenzimidazoles" as high as 60–70 per cent may be obtained (57, 58, 548).

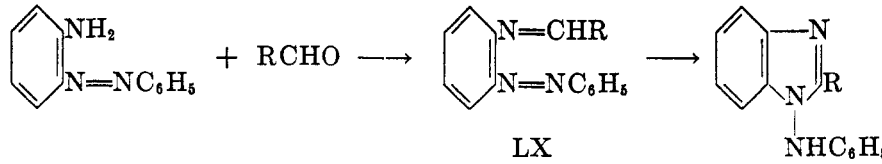
von Niementowski (533) obtained "oxbenzimidazoles" also in the following manner:



"Oxbenzimidazoles" are converted to the corresponding benzimidazoles by treatment with acetic anhydride, distillation with zinc dust or soda lime, or treatment with potassium permanganate in warm sulfuric acid solution or with ferrous sulfate in ammonium hydroxide solution. As mentioned previously, "oxbenzimidazoles" may be isomerized readily to 2(3*H*)-benzimidazolones.

D. FROM *o*-AMINOAZO COMPOUNDS: THE PREPARATION OF *N*-(ARYLAMINO)BENZIMIDAZOLES

o-Aminoazo compounds react with aldehydes to form Schiff bases in the normal manner.



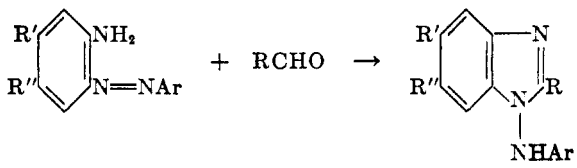
LX

The resulting Schiff bases (LX), however, readily isomerize (e.g., in boiling acetic acid) with the shifting of a hydrogen atom to form *N*-arylaminobenzimidazoles. This isomerization is analogous to that involved in the preparation of "aldehydines." The correct structure of the products was first elucidated by Fischer (226, 227).

The reaction is carried out usually by heating the *o*-aminoazo compound and aldehyde in acetic acid, formic acid, alcoholic hydrogen chloride, pyridine, or alcoholic solution. The *N*-(arylamino)benzimidazoles that have been prepared by this general method are listed in table 15.

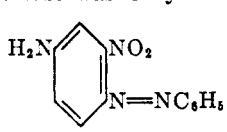
TABLE 15

N-(Arylamino)benzimidazoles



R	Ar	R′	R″	REFERENCES
H	C_6H_5	H	H	(754)
H	*p*-$CH_3C_6H_4$	H	CH_3	(275)
C_2H_5	*p*-$CH_3C_6H_4$	H	CH_3	(276)
n-C_5H_{11}	*p*-$CH_3C_6H_4$	H	CH_3	(277)
C_6H_5	C_6H_5	H	H	(755)
C_6H_5	*p*-$CH_3C_6H_4$	H	CH_3	(133, 226, 228, 278)
C_6H_5	C_6H_5	NH_2	H	(227)*
C_6H_5	C_6H_5	$C_6H_5C{=}N-$	H	(227)*
o-HOC_6H_4	C_6H_5	*o*-$HOC_6H_4C{=}N-$	H	(225)*
o-HOC_6H_4	*p*-$CH_3C_6H_4$	H	CH_3	(223)
o-ClC_6H_4	*p*-$CH_3C_6H_4$	H	CH_3	(228)
o-$O_2NC_6H_4$	*p*-$CH_3C_6H_4$	H	CH_3	(226, 227, 552)
m-$O_2NC_6H_4$	*p*-$CH_3C_6H_4$	H	CH_3	(226, 227, 552)
p-$O_2NC_6H_4$	*p*-$CH_3C_6H_4$	H	CH_3	(226, 227, 552)
p-$(CH_3)_2NC_6H_4$	*p*-$CH_3C_6H_4$	H	CH_3	(224)
	*p*$CH_3C_6H_4$	H	CH_3	(226)

* The starting material in this case was Chrysoidine:



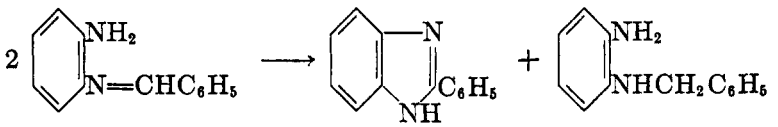
Reduction of these compounds with hydriodic acid or zinc and hydrochloric acid leads to benzimidazoles by the removal of the arylamino residue in the 1-position (227).

N-Arylaminobenzimidazoles may be prepared also by treating 1-chlorobenzimidazoles with arylamines (226).

E. FROM SCHIFF BASES

The preparation of benzimidazoles and aldehydines from Schiff bases of *o*-phenylenediamines has been discussed previously in Section II, A, 8. The Schiff bases are undoubtedly intermediates in this latter reaction.

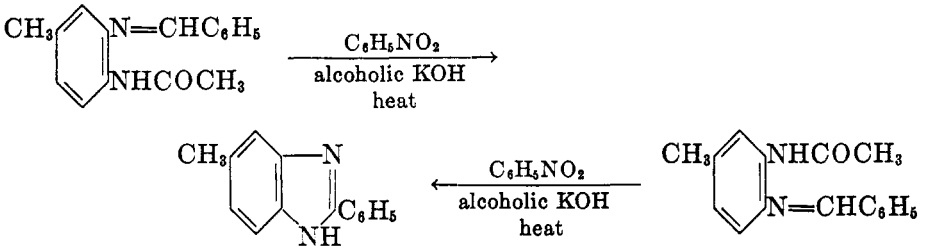
The conversion of monoalkylidene Schiff bases to benzimidazoles involves oxidation and the reaction can be brought about, for example, by prolonged standing of a solution in the air, or by heating under reflux an alcoholic or ethereal solution of the Schiff base. The oxidation involved has been attributed to the presence of air (323). However, this conversion takes place in an inert atmosphere, as shown by Crippa and Moffei (169), who have studied this reaction in detail. These authors suggest that in an inert atmosphere the formation of benzimidazoles may occur as indicated in equation 11.



(11)

The conversion of monoalkylidene-*o*-phenylenediamines to benzimidazoles may be brought about also with chemical oxidizing agents such as mercuric oxide (117, 214, 392), cupric acetate, and lead tetraacetate. The use of the latter two reagents has been investigated by Stevens and Bower (700, 701). The use of lead tetraacetate in benzene or acetic acid solution gives benzimidazoles in excellent yield.

Green and Day (289) obtained 2-phenyl-5(or 6)-methylbenzimidazole in about 80 per cent yield from 3-benzalamino-4-acetaminotoluene and from 4-benzalamino-3-acetaminotoluene by heating with nitrobenzene and alcoholic potassium hydroxide solution:



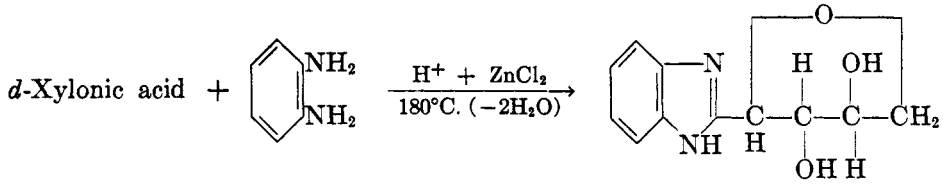
F. BENZIMIDAZOLE DERIVATIVES OF SUGARS

1. Benzimidazoles containing a sugar residue in the 2-position

The preparation of benzimidazoles from various sugars and *o*-phenylenediamines was first investigated by Griess and Harrow (291, 292, 293). Their method consists in the evaporation of an aqueous solution of an aldose and an *o*-phenylenediamine. The correct structure for the products obtained was deter-

mined later (321, 559, 651). This reaction has been investigated by several other investigators (319, 321, 425, 558, 651); however, the yields obtained are poor and in many cases quinoxalines are obtained as by-products.

Haskins and Hudson (306) and Moore and Link (516, 517) carried out this reaction by first oxidizing the aldose to an aldonic acid and treating the resulting acid with an *o*-phenylenediamine. In this way, good yields of benzimidazoles may be obtained. This general method has been used rather extensively to prepare benzimidazole derivatives substituted in the 2-position with a sugar residue (60, 71, 72, 298, 302, 353, 501, 517, 630, 631, 671). The reaction is carried out usually by heating the aldonic acid and *o*-phenylenediamine in the presence of a mineral acid, such as a mixture of hydrochloric and phosphoric acids (517). When the reaction is carried out at 180°C. in the presence of zinc chloride and hydrochloric acid the products are "anhydro" derivatives formed by the loss of an additional mole of water in the sugar portion of the 2-sugar-substituted benzimidazole (353). Thus, xylonic acid reacts with *o*-phenylenediamine in the presence of zinc chloride and hydrochloric acid to give *anhydro-d*-xylobenzimidazole (354, 518):



Epimerization appears to be possible at higher temperatures (517). Epimerization depends also on the concentration of mineral acid used in the reaction (61).

The general procedure mentioned above is applicable to saccharic acids, the products in these cases being dibenzimidazoles (471). Uronic acids can be converted to saccharic acids (e.g., with hydrogen bromide and bromine) and identified as the dibenzimidazoles (471).

Aldoses may be condensed directly with *o*-phenylenediamine to give benzimidazoles, occasionally in good yield (175, 517), by employing the use of cupric acetate as an oxidizing agent, according to the method of Weidenhagen (741).

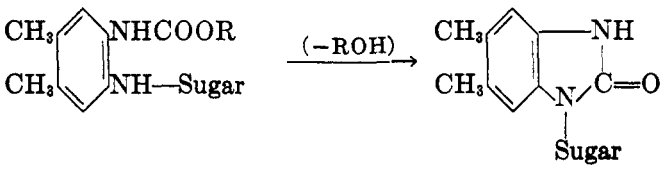
For the characterization of sugars, benzimidazole derivatives have been reported to be superior to hydrazones and osazones (516). They form hydrochlorides and picrates readily and may be precipitated from solution as the copper salt (516). Richtmeyer and Hudson (631) have enunciated the so-called "benzimidazole rule," which relates the stereochemical configuration of the hydroxyl group in the 2(or α)-position of the aldonic acid with the optical rotation of the derived benzimidazole.

Benzimidazoles containing sugar residues in the 2-position have been used as a means of resolving racemic tartaric acid (306, 709) and potassium acid tartrate (709).

2. Benzimidazoles containing a sugar residue in the 1-position

These may be prepared from *N*-monosubstituted-*o*-phenylenediamines in which the substituent is a sugar moiety. These *o*-diamines may be caused to undergo ring closure by one of the conventional methods for the preparation of benzimidazoles (121, 401).

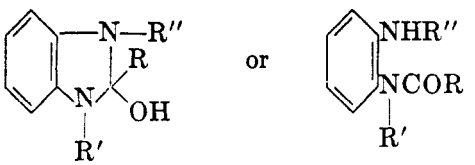
Several 1-sugar-substituted 2-hydroxybenzimidazoles have been obtained as by-products in the synthesis of flavins. These compounds were obtained by ring closure of *N*-sugar-substituted *N'*-carbalkoxy-*o*-phenylenediamines (194, 402, 403, 404).



G. "PSEUDO BASES"

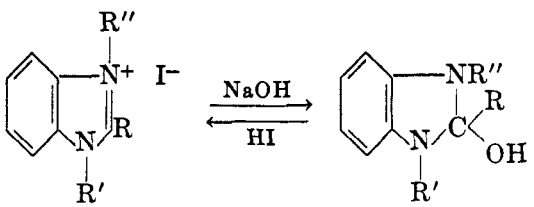
1. Structure

"Pseudo bases" possess either the structure LXI or the structure LXII.



LXI LXII

Until recently the evidence was very much in favor of the 2,3-dihydrobenzimidazolol (LXI) structure; consequently, "pseudo bases" in the literature have been assigned this structure. The arguments for the carbinol structure (LXI) appear to have been developed on the following assumptions: "Pseudo bases" may be synthesized from benzimidazolium iodides by reaction with sodium hydroxide.

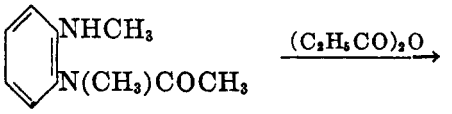


LXI

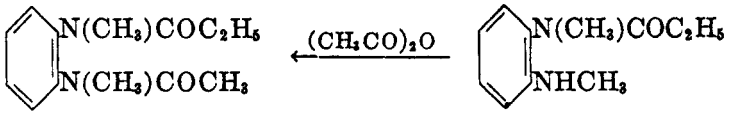
The reaction may be reversed by treatment in the cold with acid. The resulting "pseudo base" is not strongly basic, is volatile in steam, and is soluble in ether; hence the product could not be the benzimidazolium hydroxide and it was assumed (251, 532) that it must possess the carbinol structure (LXI). The amide

structure (LXII) was considered, but it appeared to be less likely because of the ease with which the product may be converted to the benzimidazolium halide by treatment with acid.

Very recently, Smith, Rasmussen, and Ballard (674) investigated the infrared spectra of these compounds. These spectra indicate the presence of an amide linkage, which would indicate structure LXII rather than LXI. The authors present, in addition, chemical evidence which would also indicate the amide structure; for example, these authors showed that LXIV on treatment with propionic anhydride and LXV on treatment with acetic anhydride gave the same compound (LXXIII).

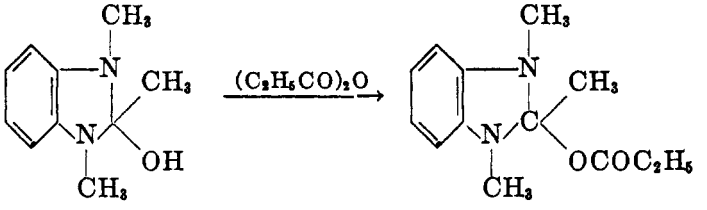


LXIV

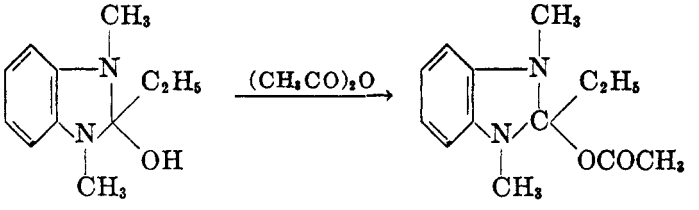


LXXIII LXV

If the compounds had possessed the 2,3-dihydrobenzimidazolol structures (LIVa and LXVa), different products would have been obtained:



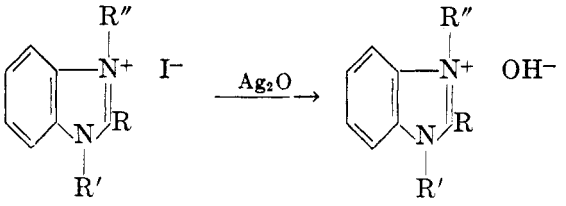
LXIVa



LXVa

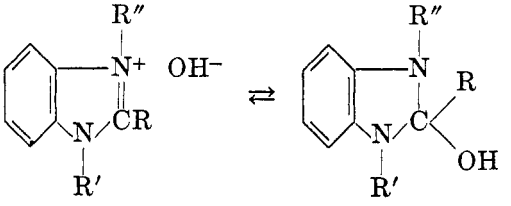
In view of this recent work it would appear that the evidence was in favor of the amide structure (XLII) for these compounds. However, in order to avoid confusion with the literature, the carbinol structure (LXI) is used throughout the present review.

When benzimidazolium halides are heated with freshly precipitated silver oxide the products obtained are insoluble in ether and are, accordingly, the corresponding benzimidazolium hydroxides:



These substances are transformed into "pseudo bases" by treatment with alkali.

Tinkler (718) reports that neutral "pseudo bases" on standing for some time become strongly alkaline. On the basis of this fact and of ultraviolet spectral studies and electrical conductivity measurements it appears that benzimidazolium hydroxides and "pseudo bases" are in equilibrium:

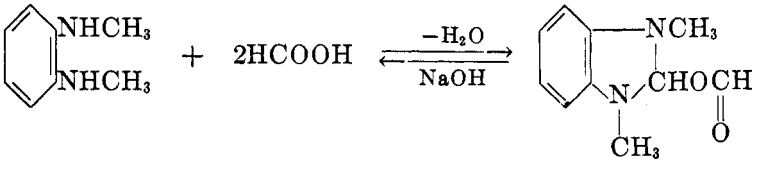


In contradistinction to this it has been reported recently (674) that benzimidazolium hydroxides in the absence of *excess* soluble alkali are quite stable and are not transformed into pseudo bases as reported by Tinkler.

2. Preparation

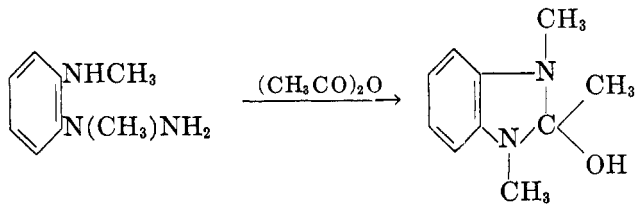
As mentioned previously, "pseudo bases" may be prepared by treatment of benzimidazolium halides with alkali (241, 249, 532, 581, 609, 665).

They may be obtained also by treatment of *N*,*N'*-disubstituted *o*-phenylenediamines with aliphatic acids (229, 299, 584) or acetic anhydride (229, 551, 734). Thus, *N*,*N'*-dimethyl-*o*-phenylenediamine when heated at 140°C. with formic acid gives the formate of 1,3-dimethyl-2,3-dihydrobenzimidazolol (229):

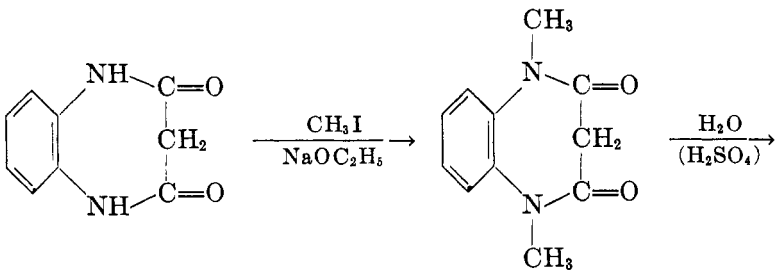


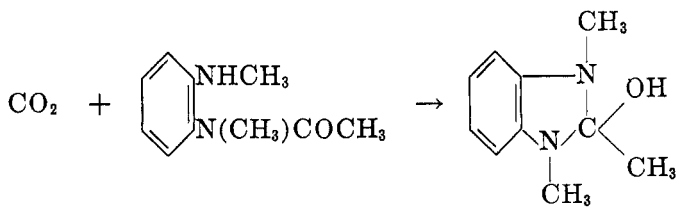
The preparation from *N*,*N'*-disubstituted *o*-phenylenediamines and aliphatic acids is a reversible reaction since the product, in some cases, may be cleaved by vigorous treatment with alkalis to regenerate the diamine and aliphatic acid.

o-Methylamino-α-methylphenylhydrazine on treatment with acetic anhydride also gives 1,2,3-trimethyl-2-hydroxy-2,3-dihydrobenzimidazole (424).

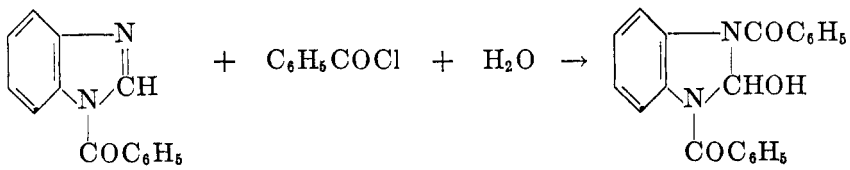


Shriner and Boermans (665) obtained the same compound from phenylenemalonamide:



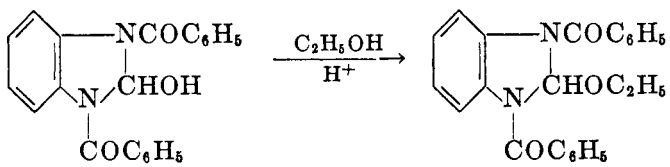


1-Benzoylbenzimidazole on treatment with one mole of benzoyl chloride and 0.5–0.1 mole of water in a benzene–ether mixture gives 1,3-dibenzoyl-2-hydroxy-2,3-dihydrobenzimidazole (267).

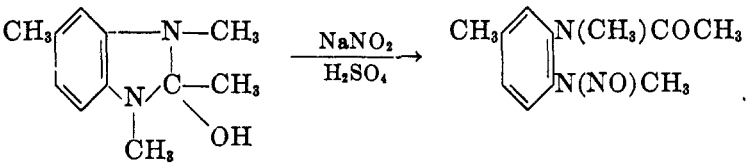


LXVI

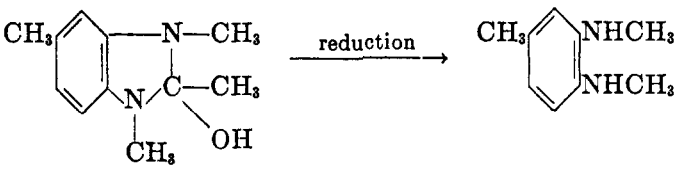
LXVI on treatment with ethanol and hydrochloric acid is reported to give the corresponding 2-ethoxy analog (268):



Fischer (251) reports that 1,2,3,5-tetramethyl-2-hydroxy-2,3-dihydrobenzimidazole shows Liebermann's reaction and reacts with sodium nitrite and sulfuric acid with cleavage of the imidazoline ring:



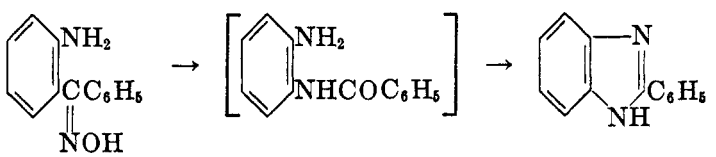
This reaction is explained readily if the amide structure (LXII) for the "pseudo base" is assumed. Reduction with sodium in absolute ethanol or zinc dust in alkaline solution also cleaves the imidazoline ring (251):



Distillation of 1,3-dimethyl-2-hydroxy-2,3-dihydrobenzimidazole is reported (230) to give mostly 1-methylbenzimidazole with 1,3-dimethyl-2(3*H*)-benzimidazolone among the by-products. As mentioned previously, 2(3*H*)-benzimidazolones may also be obtained by oxidation of "pseudo bases".

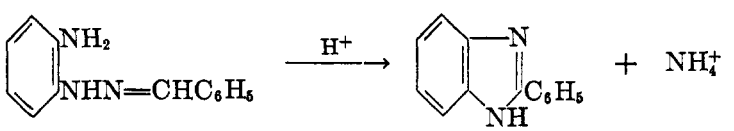
H. MISCELLANEOUS SYNTHESES

2-Phenylbenzimidazole has been obtained by the rearrangement of *o*-aminobenzophenone oxime:



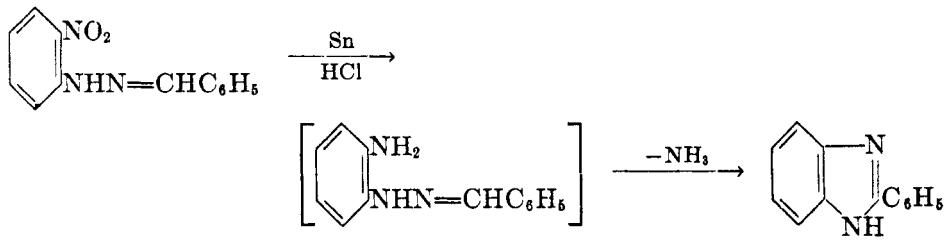
This reaction may be carried out by heating *o*-aminobenzophenone and hydroxylamine hydrochloride in alcoholic solution at 130–140°C. in a sealed tube (20).

Benzylidine-*o*-aminophenylhydrazone (LXVII) gives 2-phenylbenzimidazole in quantitative yield when warmed with dilute mineral acids (255, 256):

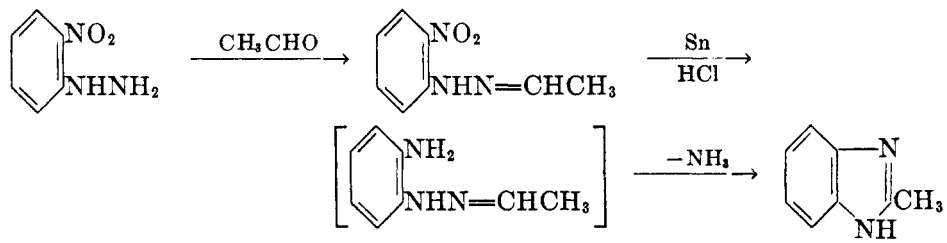


LXVII

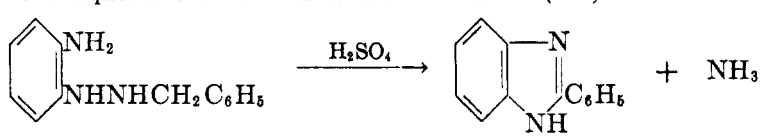
Guha and Ray (297) obtained 2-phenylbenzimidazole in a similar manner from the corresponding *o*-nitro analog:



2-Methylbenzimidazole may be prepared in the same way (295):

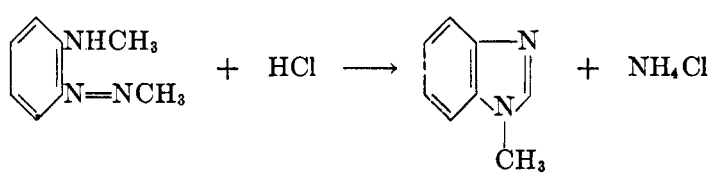


2-Phenylbenzimidazole may be obtained by heating β-(2-aminophenyl)benzylhydrazine in aqueous alcoholic sulfuric acid solution (257):



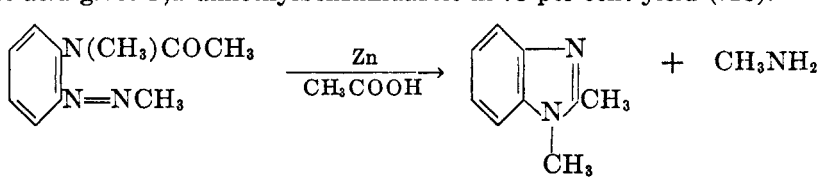
Analogs containing an α-sulfonic acid group also yield 2-phenylbenzimidazole (258).

1-Methylbenzimidazole has been prepared from *o*-(methylazo)methylaniline (422):

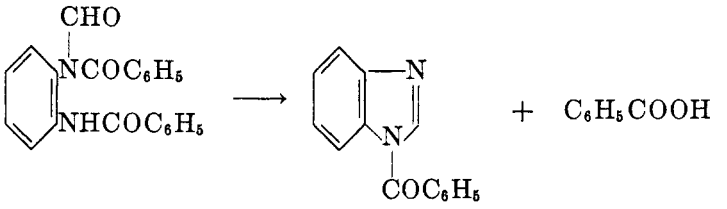


LXVIII

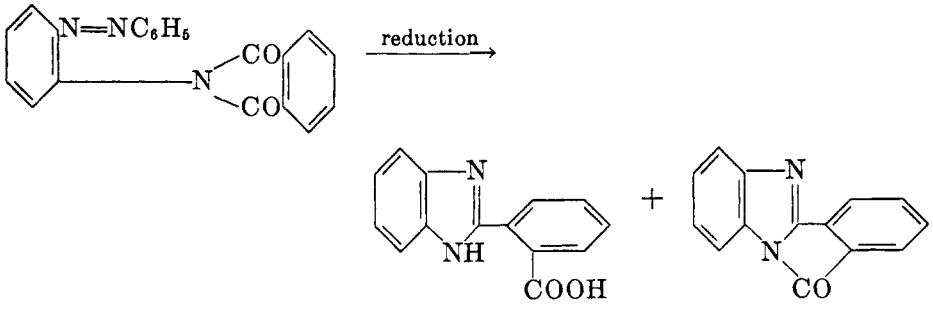
1-Methylbenzimidazole has been obtained also from the acetyl derivative of LXVIII (423). Reduction of the acetyl derivative of LXVIII with zinc dust and acetic acid gives 1,2-dimethylbenzimidazole in 73 per cent yield (423).



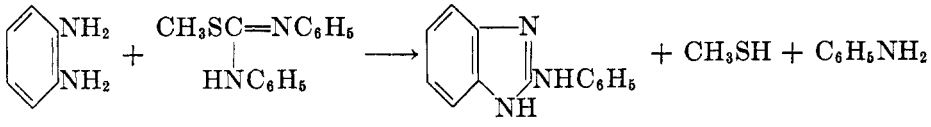
N-Formyl-*N*,*N'*-dibenzoyl-*o*-phenylenediamine when heated at 180–200°C. gives 1-benzoylbenzimidazole in addition to other products (759):



o-Phthalimidoazo derivatives on reduction give a mixture of 2-benzimidazole-*o*-benzoic acids and benzoylenebenzimidazoles (167):

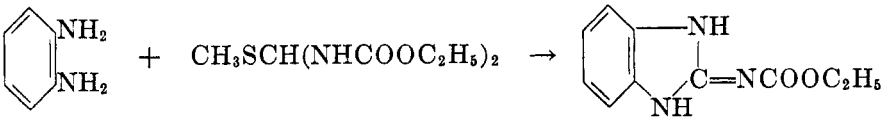


o-Phenylenediamine reacts smoothly with methyldiphenylisothiourea at 140°C. to give 2-anilinobenzimidazole (173):



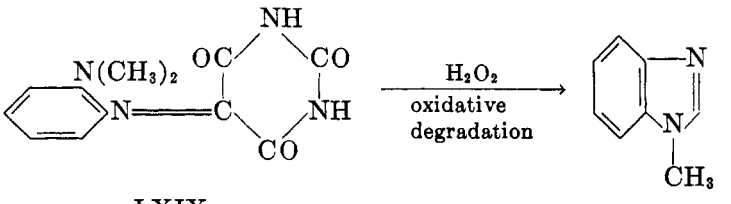
2-*p*-Tolylamino- and 2-*o*-tolylaminobenzimidazoles may be prepared in an analogous manner (173).

o-Phenylenediamine when heated in alcoholic solution with a molecular amount of the methyl ether of thiocarbonyldiurethan gives 2-carbethoxyimino-2,3-dihydrobenzimidazole (521).



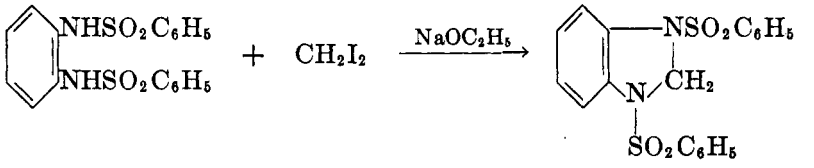
The preparation of 2-phenyl-5(or 6)-chlorobenzimidazole by heating 2,4-diphenyl-2,3-oxo-6-chloroquinazoline in a sealed tube at 150°C. with concentrated hydrochloric acid and ethanol has been reported (178).

Rudy and Cramer (639) report that alloxan 2-dimethylaminoanil (LXIX) on oxidative degradation with hydrogen peroxide is converted to 1-methylbenzimidazole. The whole alloxan residue is oxidized away in the process.



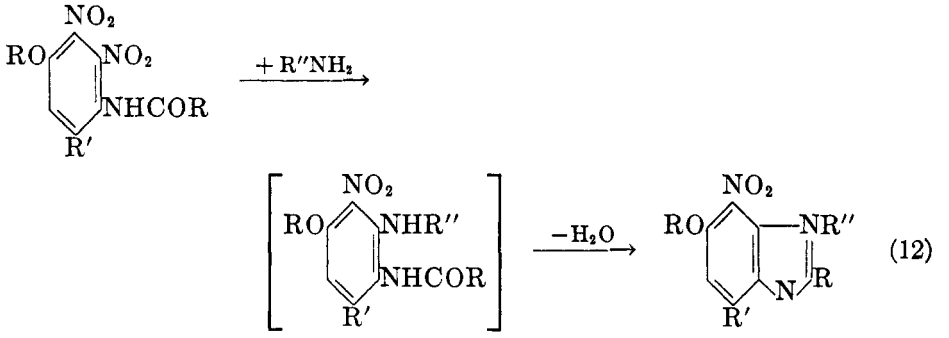
LXIX

N,*N*′-Dibenzenesulfonyl-*o*-phenylenediamine (LXX) when treated with methylene iodide in the presence of sodium ethoxide is reported to give 1,3-dibenzenesulfonylbenzimidazoline (326) (LXXI):



LXX LXXI

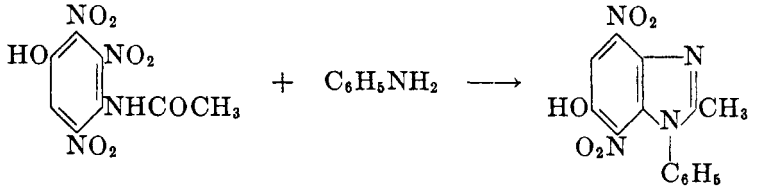
Meldola in a series of papers (491, 492, 493, 494, 497, 498, 499, 500) has studied the preparation of 1,2-disubstituted benzimidazoles by means of the reaction between primary amines and acylated *o*-nitroanilines in which the nitro group is labilized by the presence of other groups in the benzene ring. The general reaction is illustrated in equation 12:



(12)

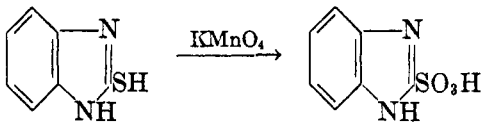
R = H, CH_3, or C_2H_5; R′ = NO_2 or H.

R″ in most of the cases studied was an aryl group. By means of this general reaction a large number of benzimidazoles have been prepared, in many cases in good yield; for example, 1-phenyl-2-methyl-4,7-dinitro-6-hydroxybenzimidazole may be prepared in this way in yields of 84–91 per cent (495):

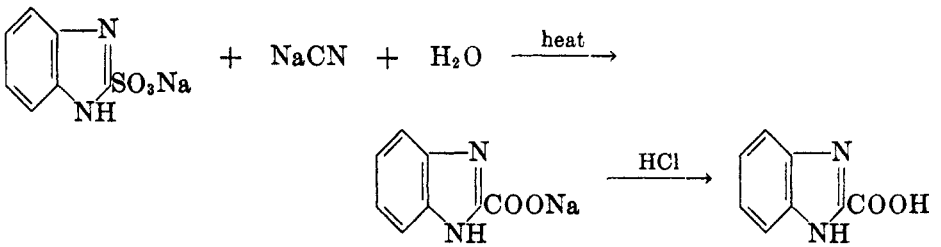


I. SYNTHESES FROM OTHER BENZIMIDAZOLES

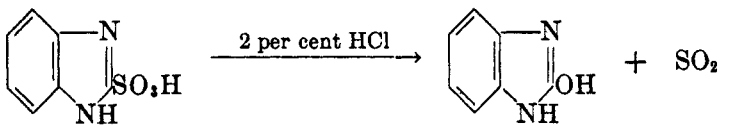
Several patents have been issued describing the preparation of various 2-substituted benzimidazoles from benzimidazole-2-sulfonic acids. These acids may be obtained in yields as high as 90 per cent from 2-mercaptobenzimidazoles by oxidation with potassium permanganate in dilute alkaline solution (200):



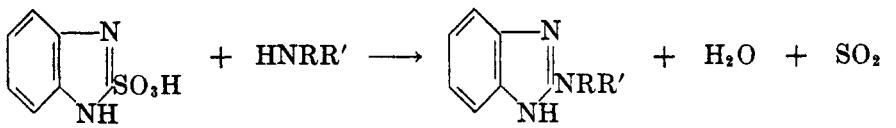
Treatment of these sulfonic acids with alkali cyanides and water by heating at 150°C. for several hours gives 2-benzimidazolecarboxylic acids (367).



2(3*H*)-Benzimidazolones may be prepared also from 2-benzimidazolesulfonic acids (366, 369); for example, 2-benzimidazolesulfonic acid on treatment with 2 per cent hydrochloric acid at 150°C. gives 2-hydroxybenzimidazole.



Treatment of 2-benzimidazolesulfonic acid with ammonia or primary or secondary amines yields 2-aminobenzimidazoles (370):



2-Aminobenzimidazole may be prepared in this way in good yield by using ammonia and heating the reactants for 2 hr. at 120–130°C. 2-Hydrazinobenzimidazoles may be obtained in an analogous way (368, 372) by using hydrazine or a substituted hydrazine (e.g., phenylhydrazine).

The patents cited above (366, 367, 369, 370, 372) claim also that these reactions may be carried out with 1-substituted 2-benzimidazolesulfonic acids.

It is claimed that 2-hydrazinobenzimidazoles may be obtained also from hydrazines and 2(3*H*)-benzimidazolones or 2-halogen-substituted benzimidazoles in a manner analogous to the method from 2-benzimidazolesulfonic acid (368, 372).

A large number of benzimidazolecarboxylic acids have been prepared by the oxidation of substituted groups of benzimidazoles.

III. Physical Properties of Benzimidazoles

The melting points of a number of the simpler benzimidazoles are listed in table 16. From this table it will be noted that the introduction of a substituent into the 1-position in general lowers the melting point. This appears to be due to the fact that benzimidazoles containing hydrogen in the 1-position are associated.

Benzimidazoles with the imide nitrogen (i.e., hydrogen in the 1-position) are usually more soluble in polar solvents and less soluble in organic solvents. Benzimidazole, for example, is soluble in hot water but difficultly soluble in ether and insoluble in benzene and ligroin. With the introduction of other nonpolar substituents in various positions of the benzimidazole ring, the solubility in nonpolar solvents is increased; 2-methylbenzimidazole, for example, is easily soluble in ether. Conversely, the introduction of polar groupings into the molecule increases solubility in polar solvents; thus, 2-aminobenzimidazole is soluble in water.

TABLE 16
Melting points of benzimidazoles

BENZIMIDAZOLE	MELTING POINT	BENZIMIDAZOLE	MELTING POINT
	°C.		°C.
Benzimidazole	170	2,5(or 2,6)-Dimethylbenzimidazole	203
1-Methylbenzimidazole	61	2-Phenyl-5(or 6)-methylbenzimidazole	239
2-Methylbenzimidazole	176	2(3*H*)-Benzimidazolone	308
2-Phenylbenzimidazole	294	2(3*H*)-Benzimidazolethione	292–293
1,2-Diphenylbenzimidazole	112		

Benzimidazoles are also distillable. Benzimidazole distills unchanged above 300°C.

Benzimidazoles are weakly basic, being somewhat less basic than the imidazoles. Accordingly, they are in general soluble in dilute acids. The pK_a values have been determined for benzimidazole (4, 398, 658, 712) (pK'_{a_1} = 5.30; pK'_{a_2} = 12.3),[4] 2-methylbenzimidazole (658), and 2-aminobenzimidazole (4). The relative basicity of the benzimidazole ring has been determined also by an indirect qualitative method involving comparison of the spectrum of a cyanine dye containing the benzimidazole ring as a constituent with cyanine dyes derived from other basic substances. The method involves a measurement of the deviation in $\lambda_{max.}$ which is assumed to be due to the basicity of the heterocyclic structure.

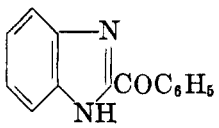
Benzimidazoles are also sufficiently acidic to be generally soluble in aqueous alkali and form *N*-metallic compounds. The acidic properties of the benzimidazoles, like those of the imidazoles (629), seem to be due to stabilization of the ion by resonance.

[4] Reference 712.

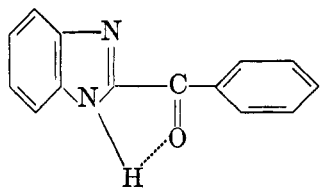
The solubility of benzimidazoles in alkaline solutions depends on the particular compound in question. The more acidic benzimidazoles may be soluble in less basic solutions, such as potassium carbonate solution.

2(3*H*)-Benzimidazolone is difficultly soluble in dilute sodium hydroxide solution. It is insoluble in dilute hydrochloric acid but is readily soluble in slightly warmed concentrated hydrochloric acid. 2-Benzimidazolecarboxylic acids are easily soluble in dilute acids.

Hunter and Marriott (357) determined the molecular weight of a number of benzimidazoles from freezing-point data in naphthalene solution over a range of concentrations. Evidence was obtained indicating molecular association through N—H—N bonds in those compounds possessing an unsubstituted NH grouping. The strength of this bond is evidently enhanced by resonance of the benzimidazole nucleus. Those substances which are substituted in the 1-position by an alkyl, aryl, acyl, carbalkoxy, or amino group are not highly associated. Substances such as 2-benzoylbenzimidazole (LXXII) occupy an intermediate position, being less highly associated than other benzimidazoles unsubstituted in the 1-position. It would appear that a majority of the molecules possess the internal chelate structure (LXXIII).



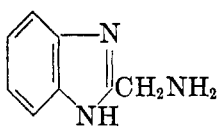
LXXII



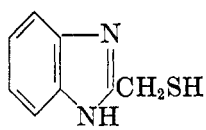
LXXIII

Such internal chelation is possible in a number of 2-substituted benzimidazoles. Evidence for such internal chelation has been obtained also from ultraviolet absorption data (752).

Hughes and Lions (356) found that 2-aminomethylbenzimidazole (LXXIV) and benzimidazole-2-methylmercaptan (LXXV) coördinate with copper and other metals to give complexes of the type shown in formula LXXX (page 483).



LXXIV



LXXV

The ultraviolet absorption spectra of several benzimidazoles have been determined (69, 121, 191, 273, 353, 698, 726, 750, 751). The infrared spectra of "pseudo bases" have been studied (674). These spectra indicate the presence of an amide linkage in these substances. The Raman spectra of benzimidazole, 1-methylbenzimidazole, and 2-methylbenzimidazole have been studied (420).

The dipole moment of benzimidazole has been determined, the values that have been obtained being 3.93 D (in dioxane) (396) and 4.08 D (710).

IV. Chemical Properties of Benzimidazoles

A. Reactions of the Benzimidazole Ring

The benzimidazole ring possesses a high degree of stability. Benzimidazole, for example, is not affected by concentrated sulfuric acid when heated under pressure to 270°C. (208), nor by vigorous treatment with hot hydrochloric acid or with alkalis. Oxidation cleaves the benzene ring of benzimidazole only under vigorous conditions. The benzimidazole ring is also quite resistant to reduction; however, tetrahydro- and hexahydrobenzimidazoles in which the benzene ring is reduced may be prepared by catalytic reduction under certain conditions.

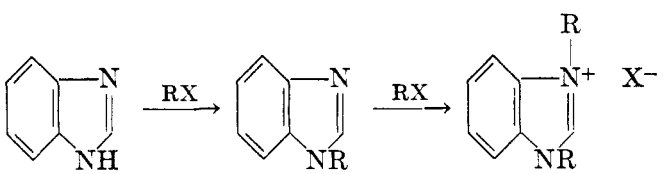
Benzimidazole gives a negative test with sodium nitroprusside and alkali. 2(3*H*)-Benzimidazolethione gives a red color with these reagents (561). Benzimidazole does not couple to indazole in the presence of alkaline benzene diazotate.

1. Reactions involving the nitrogens at the 1- and 3-positions

Benzimidazoles form salts with acids readily. Thus, benzimidazole readily forms a monohydrochloride, monopicrate, mononitrate, monoacetate, etc. Benzimidazole also forms a salt with 2-nitro-1,3-indanedione (724) and with copper azide (154).

a. Alkylation

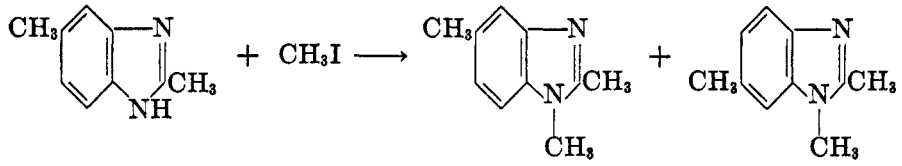
Benzimidazoles, upon alkylation with alkyl halides, yield 1-alkylbenzimidazoles and, under more vigorous conditions, 1,3-dialkylbenzimidazolium halides.



The alkylation of benzimidazoles has been studied quite extensively (49, 212, 217, 218, 219, 220, 222, 231, 239, 245, 248, 313, 334, 349, 499, 500, 592, 599, 602, 645, 718), especially by O. Fischer. The alkylation has been carried out with various alkyl and aralkyl groups. For the preparation of benzimidazolium halides the reaction is carried out usually by heating the benzimidazole (or *N*-substituted benzimidazole) with an excess of alkyl halide in methanol under pressure at a temperature of about 110–150°C. Alkyl iodides are usually used and, in some cases, periodides are obtained as by-products or as the exclusive product. The periodides, however, may be converted conveniently to benzimidazolium iodides with lead hydroxide.

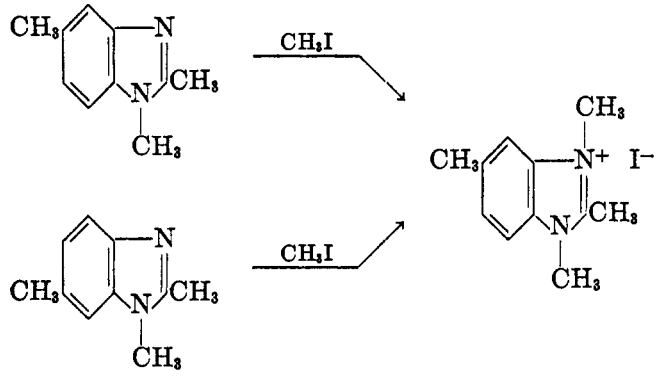
When the alkylation reaction is carried out at a lower temperature with one equivalent of alkyl halide, 1-alkylbenzimidazoles may be the main product; thus, equimolecular amounts of benzimidazole and methyl iodide in methanol at 90–100°C. give mostly 1-methylbenzimidazole hydroiodide (217). When the benzimidazole contains a substituent group, a mixture of isomers may be ob-

tained; for example, 2,5(or 2,6)-dimethylbenzimidazole on prolonged treatment with methyl iodide at room temperature gives a mixture of 1,2,5-trimethylbenzimidazole (LXXVI) and 1,2,6-trimethylbenzimidazole (LXXVII) (220).



LXXVI LXXVII

Both LXXVI and LXXVII on further treatment give the same compound (m.p. 221°C.): namely, 1,2,3,5(or 1,2,3,6)-tetramethylbenzimidazolium iodide (221).

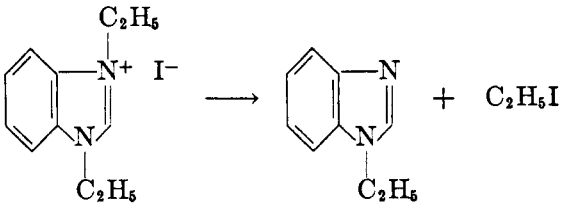


Fischer (221) has postulated that in the preparation of benzimidazolium iodides methyl iodide adds first to the double bond of the imidazole ring to give a 2-iodo-3-methyl derivative, which then undergoes rearrangement to the stable benzimidazolium iodide.

1,2,5-Trimethylbenzimidazole (LXXVI) and 1,2,6-trimethylbenzimidazole (LXXVII) (as the hydrochloride salts) on vigorous heating split out methyl chloride to give the same compound: namely, 2,5(or 2,6)-dimethylbenzimidazole (249). The fact that the same compound is obtained indicates the tautomeric state of the benzimidazole ring system. The corresponding *N*-ethyl compounds behave analogously, losing ethyl chloride to give 2,5(or 2,6)-dimethylbenzimidazole (247).

2,4,5,7(or 2,4,6,7)-Tetramethylbenzimidazole when heated under reflux with methyl iodide in benzene solution gives the methiodide (111). When the reaction is carried out in xylene with the addition of metallic sodium, 1,2,3,-4,5,7(or 1,2,3,4,6,7)-hexamethylbenzimidazolium iodide is obtained.

1,3-Dialkylbenzimidazolium iodides on heating under diminished pressure lose the elements of alkyl iodide to give 1-alkylbenzimidazoles. Thus, 1,3-diethylbenzimidazolium iodide loses ethyl iodide to yield 1-ethylbenzimidazole (19) in 80 per cent yield.

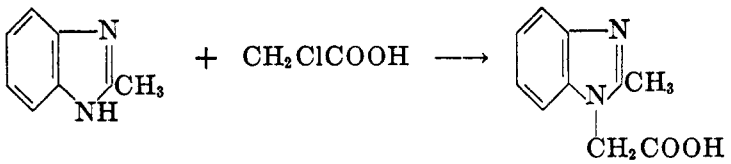


This reaction has been studied by von Auwers and Mauss (18). With mixed benzimidazoles (i.e., with those containing different groups at N-1 and N-3) the reaction proceeds less readily.

Methyl sulfate with or without the addition of alkali yields 1-methylbenzimidazoles (356, 581, 673, 677).

Phillips (581) studied the alkylation of benzimidazoles containing methyl, bromo, or nitro groups in the 5(or 6)-position and found that with methyl sulfate or methyl iodide as the methylating agent the formation of the 1,6-isomeride is favored. With methyl sulfate in the presence of aqueous alkali the proportion of the 1,6-isomeride is reduced.

Chloroacetic acid and chloroacetamide with benzimidazoles give (benzimidazole-1)acetic acid derivatives (203, 625):



2,5-Dimethylbenzimidazole reacts analogously with ethyl chloroacetate in the presence of sodium ethoxide solution (52). Ethyl chloroformate in ether solution yields 1-carbethoxybenzimidazoles (328).

Benzimidazole with ethylene chlorohydrin in sodium hydroxide solution gives a 33 per cent yield of 1-β-hydroxyethylbenzimidazole (490). In toluene solution without the addition of sodium hydroxide, a 60–65 per cent yield is obtained. The same product may be obtained from benzimidazole and ethylene oxide (490). Treatment of benzimidazole with dichloroethylene or dibromoethylene gives a polymeric benzimidazolium halide.

Benzimidazoles have been alkylated in the 1-position also with dialkylaminoalkyl halides, either with or without the addition of a basic material such as sodium ethoxide (554, 669). The silver salt of benzimidazole has been alkylated with *N*-(β-bromoethyl)phthalimide (473).

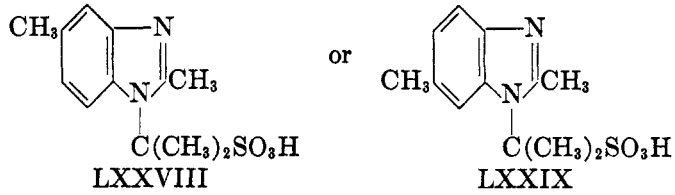
Benzimidazoles containing a sugar residue in the 2-position have also been alkylated in the 1-position (353).

Aryl isocyanates react with benzimidazoles in the 1-position (314). Prolonged treatment with excess ethereal diazomethane fails to methylate either 2-benzyl- or 2-phenylbenzimidazole.

2,5(or 2,6)-Dimethylbenzimidazole with benzyl chloride in ethanolic sodium ethoxide solution yields 1-benzyl-2,5(or 2,6)-dimethylbenzimidazole (51). Benzimidazole and 2-methylbenzimidazole have been alkylated with esters of lauryl

and cetyl alcohols (692). 1-Dodecyl-2-methylbenzimidazole has been obtained in 58 per cent yield by the reaction between two moles of 2-methylbenzimidazole and one mole of dodecyl chloride (445).

Chloral when heated in a flask with benzimidazole gives 1-[β,β,β-trichloro-α-hydroxyethyl]benzimidazole (32). 2,5(or 2,6)-Dimethylbenzimidazole reacts analogously (44). When 2,5(or 2,6)-dimethylbenzimidazole is added to acetone saturated with sulfur dioxide a product is obtained which has been assigned (333) the structure indicated by LXXVIII or LXXIX.

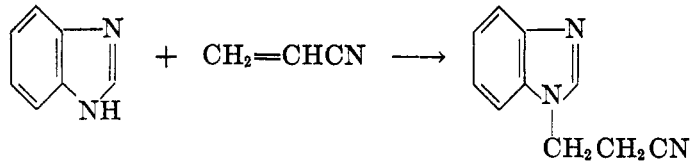


LXXVIII LXXIX

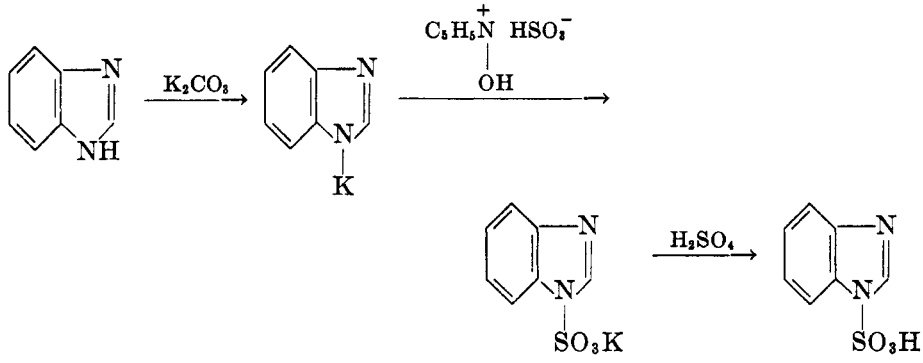
2-Phenylbenzimidazole, when heated with excess cyanogen iodide, is reported (333) to give 1-cyano-2-phenylbenzimidazole among other products.

Several patents (283, 691) describe the preparation of 1,3-dialkylbenzimidazolium chlorides by heating 1-alkylbenzimidazole hydrochlorides in alcoholic solution. The alkyl group introduced into the 3-position is that of the alcohol used.

Benzimidazole undergoes cyanoethylation in the 1-position in very good yield (371, 373, 374):



(1-Benzimidazole)sulfonic acid may be prepared in 69 per cent yield by the alkylation of the potassium salt of benzimidazole with pyridinium-*N*-sulfonic acid (742):



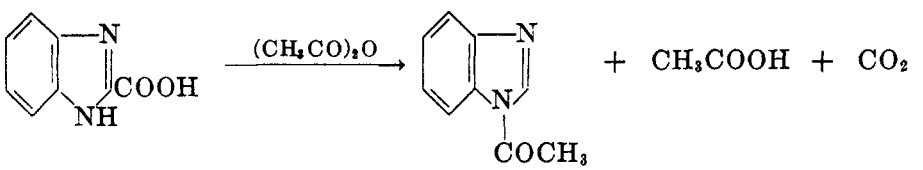
Benzimidazole reacts with formaldehyde to give 1-hydroxymethylbenzimidazole in very good yield (25).

b. Acylation

N-Acylbenzimidazoles may be prepared by the action of acid chlorides or anhydrides on benzimidazoles. The reaction is usually carried out in the absence of water. In the presence of water and especially in alkaline solution (Schotten–Baumann procedure) cleavage of the imidazole ring may occur.

1-Benzoylbenzimidazole and 1-acetylbenzimidazole may be prepared by the action of benzoyl chloride and acetyl chloride, respectively, on benzimidazole (43, 264, 265, 269, 309). 1-Benzoyl and 1-acetyl derivatives have been prepared also by the action of these acid chlorides on the silver salts of benzimidazoles (53). *N*-Acylbenzimidazoles are generally relatively unstable when heated with aqueous solutions and tend to hydrolyze to benzimidazoles (43, 95, 264, 555).

1-Acetylbenzimidazole has been prepared also by heating 2-benzimidazolecarboxylic acid with acetic anhydride (95), decarboxylation occurring at the same time:



N-Formyl-*N*,*N*′-dibenzoyl-*o*-phenylenediamine on heating to 180–200°C. is reported (759) to give 1-benzoylbenzimidazole in addition to other products.

2-Methylbenzimidazole when heated with acetic anhydride gives 1-acetyl-2-methylbenzimidazole (96). 1-Benzoyl-2-methylbenzimidazole has been obtained (760) from the reaction between 2-methylbenzimidazole and benzoyl chloride in the presence of sodium hydroxide solution.

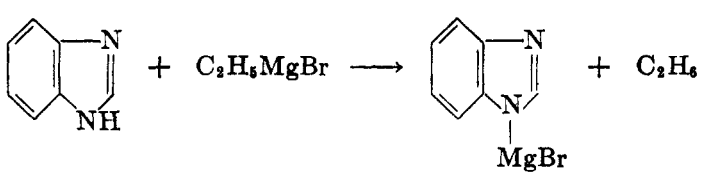
4,5,6,7-Tetrahydrobenzimidazoles may be smoothly benzoylated with benzoyl chloride in pyridine (745).

Oddo and Raffa (556, 557) have studied the reaction of acid anhydrides with benzimidazole under various conditions. If the excess acid anhydride is removed before the reaction product is poured into water, yields of *N*-acylbenzimidazole as high as 100 per cent may be obtained. Under other conditions, when the excess of acid anhydride is not removed, *N*,*N*′-diacyl-*o*-phenylenediamines are obtained.

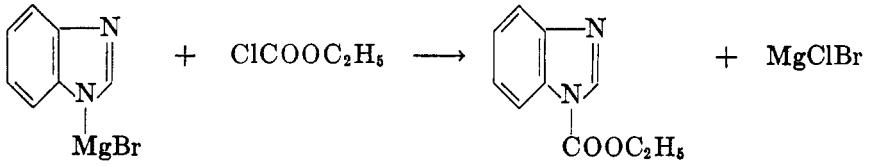
It is reported that 2-phenylbenzimidazole is unaffected by benzoyl chloride at 160°C. (337).

c. The action of Grignard reagents on benzimidazoles

Grignard reagents react with the active hydrogen in the 1-position of benzimidazole (555):



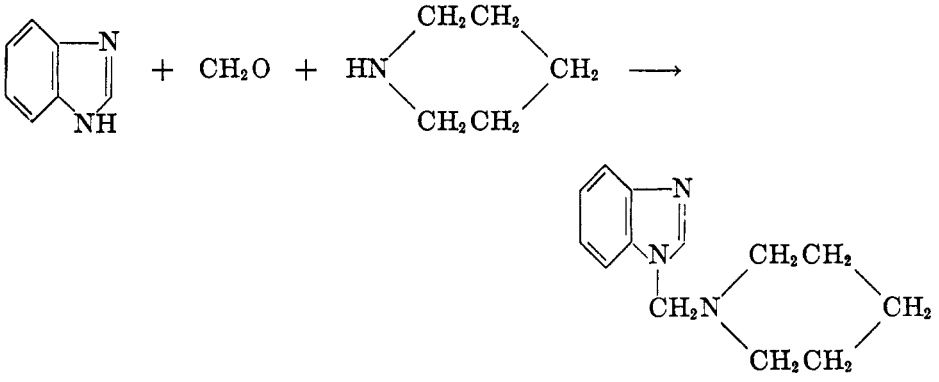
Benzimidazole-1-magnesium bromide ("magnesylbenzimidazole") reacts with aliphatic acid chlorides or anhydrides to yield 1-acylbenzimidazoles (555, 556, 557). With ethyl chloroformate, 1-carbethoxybenzimidazole is obtained (555, 556):



Benzoyl chloride gives 1-benzoylbenzimidazole as a by-product, the main product being *N*,*N'*-dibenzoyl-*o*-phenylenediamine (555).

d. Benzimidazoles in the Mannich reaction

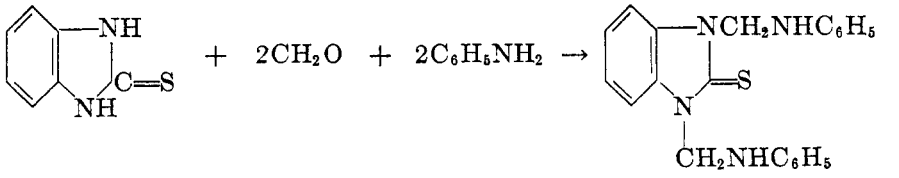
Bachman and Heisey (25) have studied benzimidazoles in the Mannich reaction. Equimolecular amounts of benzimidazole, formaldehyde, and piperidine give a 97 per cent yield of 1-(piperidinomethyl)benzimidazole.



Morpholine gives a 97 per cent yield and diethylamine a 74 per cent yield of the corresponding Mannich base in the same reaction. 2-Ethylbenzimidazole and 1-phenylbenzimidazole do not react; however, reaction with 2-alkylbenzimidazoles might occur at higher temperatures (25). Attempts to use primary amines or higher aldehydes in place of formaldehyde in the reaction were unsuccessful.

Benzimidazole when used as the amine component with formaldehyde and 2-nitropropane or pyrrole reacts abnormally to give a 95 per cent yield of 1-hydroxymethylbenzimidazole. 2-Ethylbenzimidazole is less reactive and apparently does not react with formaldehyde in this manner (25).

2(3*H*)-Benzimidazolethione with formaldehyde and aniline is reported (362) to give 1,3-bis(anilinomethyl)benzimidazole-2-thione.

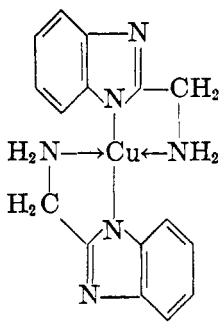


e. Metal derivatives of benzimidazole

The hydrogen in the 1-position of benzimidazoles is sufficiently acidic to be replaced by metals and give *N*-metal benzimidazoles. This was first shown by Bamberger and Lorenzen (48). 2,5(or 2,6)-Dimethylbenzimidazole, for example, when treated in alcoholic solution with an ammoniacal silver nitrate solution yields the *N*-silver salt, insoluble in water and in most organic solvents. The corresponding *N*-sodium salt may be prepared by adding an equivalent amount of sodium ethoxide, and then adding ether. The *N*-sodium salt thus obtained is hydrolyzed with water to regenerate 2,5(or 2,6)-dimethylbenzimidazole. Other benzimidazoles, however, such as 2-methylbenzimidazole and 2-phenylbenzimidazole, dissolve readily in aqueous sodium hydroxide solution (48).

A rather wide variety of metals form salts with benzimidazoles. The silver (48), copper, nickel, cobalt, cadmium, mercury (mercurous chloride salt), and zinc salts of benzimidazole, for example, have been prepared (205, 672). However, other benzimidazoles may not form metal salts with all of the metals listed above. 2-Phenylbenzimidazole and 2-methylbenzimidazole form silver and mercury salts but no salts with copper, cadmium, cobalt, or zinc (205). 1-Benzylbenzimidazole, 1-phenylbenzimidazole, and 1,6-dimethylbenzimidazole, containing no hydrogen in the 1-position, are reported (205) not to form metal salts with copper, cadmium, cobalt, zinc, and silver; however, mercurous chloride salts of 1-phenylbenzimidazole and 1-*p*-tolylbenzimidazole have been reported (46, 393). 2-Phenoxymethyl-, 2-ethoxymethyl-, and 2-methoxymethylbenzimidazoles give silver and mercury salts. 2(3*H*)-Benzimidazolone and 2-chlorobenzimidazole yield no metal derivatives. The salt-forming ability of 2-α-pyridyl- and 2-β-pyridylbenzimidazoles with metals has been investigated (455, 456). 2(3*H*)-Benzimidazolethiones form *S*-metal salts. The ability of various benzimidazoles to form metal salts has been studied extensively by Feigl and Gleich (205). A number of silver, gold, and copper salts of various benzimidazoles are described (363) and are claimed to be of value as therapeutic agents.

2-Aminomethylbenzimidazole coördinates with metals such as copper to give a complex of the following type (356):



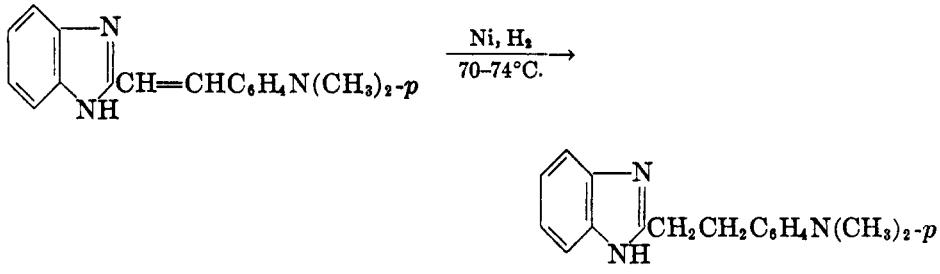
LXXX

(Benzimidazole-2)methylmercaptan coördinates with metals in an analogous way (356).

2. Reduction of benzimidazoles; hydrogenated benzimidazoles; dehydrogenation of reduced benzimidazoles

Until very recently it was thought that the benzimidazole ring was stable to reduction. Treatment of benzimidazole, 2-methylbenzimidazole, or 2,5(or 2,6)-dimethylbenzimidazole with red phosphorus and hydriodic acid even to 300°C. gives no reduced product (47, 208). Red phosphorus and hydriodic acid have been used, in fact, to cleave arylamino groups from benzimidazoles without affecting the benzimidazole ring in the process (227). Sodium in refluxing absolute alcohol also causes no reduction of the benzimidazole ring (108).

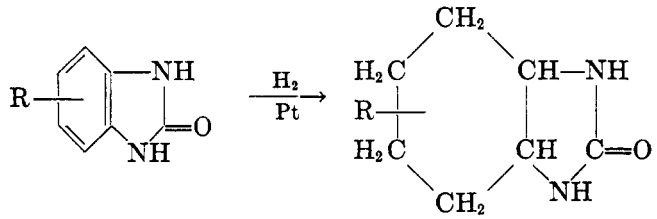
Catalytic reduction of benzimidazole (305, 739, 746) even under high pressure with nickel as the catalyst (305, 746) is reported to give negative results. 2-Phenylbenzimidazole gives only 2-cyclohexylbenzimidazole. Hydrogenation of 2-(*p*-dimethylaminostyryl)benzimidazole with nickel at atmospheric pressure saturates only the olefinic linkage in the 2-position (640):



Other benzimidazoles possessing an unsaturated side chain have been hydrogenated with nickel and hydrogen under high pressure to effect hydrogenation only in the side chain (285).

Hartmann and Panizzon (305), however, first showed that certain benzimidazoles could be reduced to 4,5,6,7-tetrahydrobenzimidazoles in good yield with platinum (Adam's catalyst) in acetic acid solution at atmospheric pressure. The reduction is successful only with those benzimidazoles which contain a substituent in the 2-position. Thus, 2-methyl-, 2-ethyl-, and 1,2-dimethylbenzimidazoles give the corresponding tetrahydrobenzimidazoles, and 2-phenylbenzimidazole yields 2-cyclohexyltetrahydrobenzimidazole. Benzimidazole and those benzimidazoles containing a substituent in the 1-position (but not in the 2-position) could not be reduced with platinum according to this method. The presence of a substituent in the benzene ring of the benzimidazole hinders hydrogenation also, even for those compounds which also contain a substituent in the 2-position. 5(or 6)-Ethoxy-2-methylbenzimidazole yields 2-methyltetrahydrobenzimidazole, the ethoxy group undergoing cleavage.

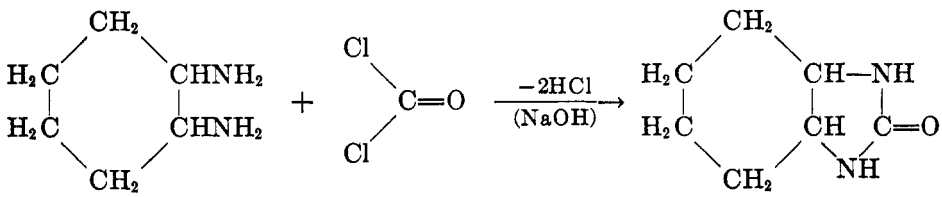
A number of 2(3*H*)-benzimidazolones containing substituents on the benzene ring have been reduced catalytically to hexahydrobenzimidazoles, in good yield, with platinum in acetic acid solution at several atmospheres pressure (155, 193, 751).



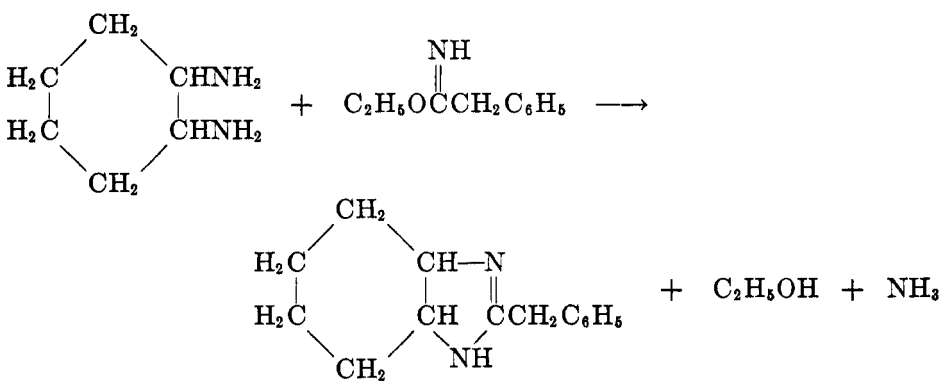
R = $-(CH_2)_nCOOH$ (where n = 0, 3, 4).

Hexahydro-2(3*H*)-benzimidazolone may be obtained from 2(3*H*)-benzimidazole by this general method in 38 per cent yield (192).

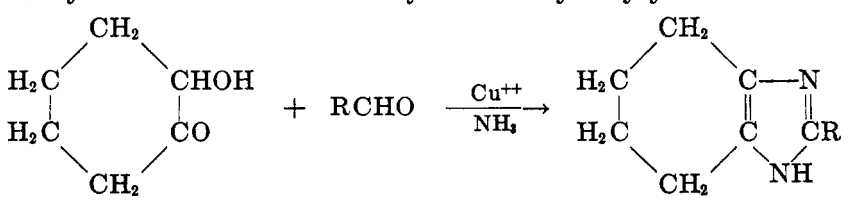
A number of hydrogenated benzimidazoles have been prepared also by chemical methods. Hexahydro-2(3*H*)-benzimidazolone may be obtained by the reaction between hexahydro-*o*-phenylenediamine and phosgene in sodium hydroxide solution (181).



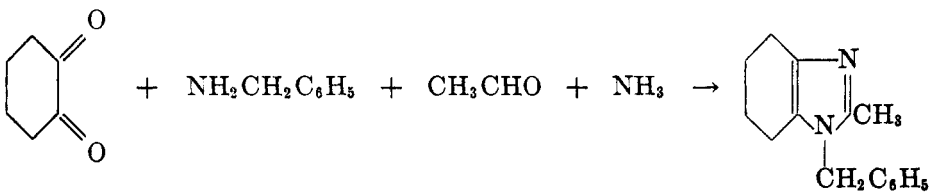
2-Benzylhexahydrobenzimidazole may be prepared by treatment of the same diamine with an imino-ether (694):



Tetrahydrobenzimidazoles may be prepared also by chemical methods. Weidenhagen and Wegner (745) prepared a series of 2-substituted tetrahydrobenzimidazoles by the reaction between aldehydes and 2-hydroxycyclohexanone.



This procedure is analogous to a method for the synthesis of imidazoles from aldehydes and acyloins. By using 4-methyl-2-hydroxycyclohexanone the corresponding 5(or 6)-methyltetrahydrobenzimidazoles may be obtained (745). Tetrahydrobenzimidazoles may be prepared also from 1,2-cyclohexanedione. This compound when treated with benzylamine, acetaldehyde, and ammonia in ethanol yields 38 per cent of 1-benzyl-2-methyltetrahydrobenzimidazole.

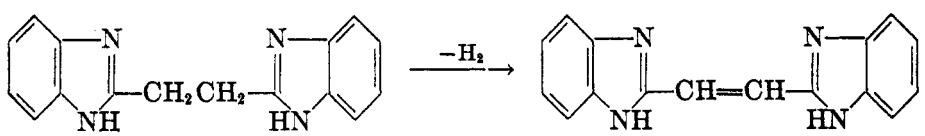


2-Methyltetrahydrobenzimidazole may be prepared in an analogous way by using an excess of ammonia (470).

In general, tetrahydrobenzimidazoles melt higher than the corresponding benzimidazoles and possess greater basicity. Potassium permanganate completely destroys the molecule. The imidazole ring may be cleaved in poor yield with benzoyl chloride and sodium hydroxide solution.

Attempted dehydrogenation of tetrahydrobenzimidazoles with palladium sponge does not give the corresponding benzimidazole but instead a compound of high molecular weight (745).

Several patents (152, 695) describe the dehydrogenation of a number of 1,2-di(2-benzimidazolyl)ethanes to the corresponding ethylenes at elevated temperatures in the presence of a mild oxidizing agent such as ferric sulfate or mercuric acetate.



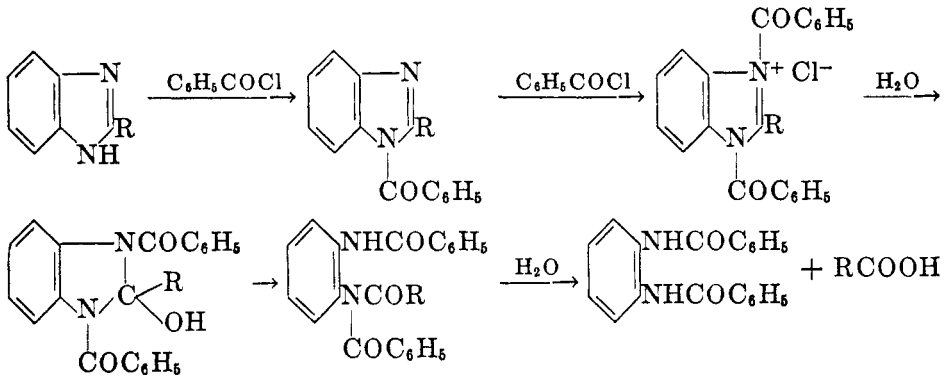
The benzimidazoline or 2,3-dihydrobenzimidazole structure does not appear to have been established with certainty.

3. Cleavage of the imidazole ring

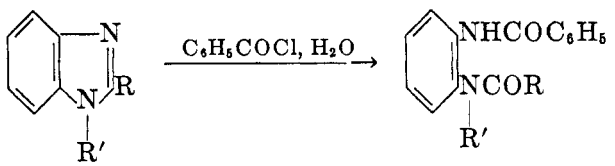
The imidazole ring of benzimidazoles may be readily cleaved by one of several methods:

a. Aroyl halides in the presence of water

Benzimidazoles when treated with benzoyl chloride yield first *N*-benzoylbenzimidazoles. In the presence of additional acid chloride and in the presence of water further reaction may occur and *N*,*N*′-dibenzoyl-*o*-phenylenediamines are obtained. This transformation has been postulated (266, 757) as occurring as follows:



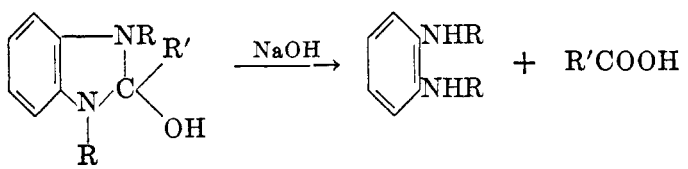
The benzoyl chloride addition product is hypothetical; however, the other products have been isolated. Benzimidazoles which have a substituent group in the 1-position are cleaved in a similar manner (757):



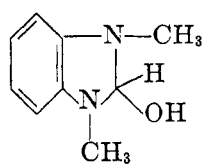
These reactions may be carried out conveniently in alkaline solution; consequently, benzoylation according to the Schotten–Baumann procedure (benzoyl chloride in aqueous alkali) readily cleaves the imidazole ring (41, 122, 757). In addition to *N*,*N*′-dibenzoyl-*o*-phenylenediamines there may be formed as by-products 1-benzoylbenzimidazoles and *N*,*N*′-dibenzoyl-*N*-aryl-*o*-phenylenediamines (266, 757).

b. By reactions involving "pseudo bases"

Pseudo bases on vigorous treatment with alkaline reagents may be cleaved to *N*,*N*′-dialkyl-*o*-phenylenediamines (558, 696, 697, 698, 699):

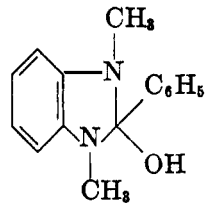


This reaction, however, is not a general one and in certain cases it proceeds with difficulty or not at all. With 1,3-dimethyl-2-hydroxy-2,3-dihydrobenzimidazole (LXXXI) cleavage occurs readily on refluxing with aqueous alkali.



LXXXI

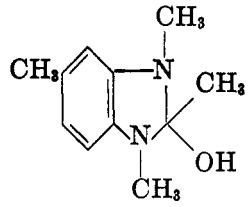
The presence of a nitro or bromo group in the 5-position facilitates cleavage, whereas an alkyl group on the benzene ring has a hindering affect (251, 582). In the latter cases temperatures to 150°C. are required to effect cleavage. In general, the presence of groups larger than hydrogen in the 2-position also hinders cleavage. 1,3-Dimethyl-2-phenyl-2-hydroxy-2,3-dihydrobenzimidazole (LXXXII) may be cleaved by refluxing with aqueous-alcoholic potassium hydroxide solution (251).



LXXXII

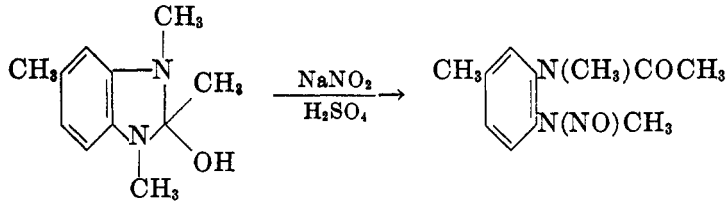
Other pseudo bases containing a 2-aryl group have been cleaved in a similar manner.

2-Hydroxy-1,2,3,5-tetramethyl-2,3-dihydrobenzimidazole (LXXXIII) has been cleaved also by treatment with sodium and alcohol or with zinc dust in alkaline solution (251). Treatment of LXXXIII with sodium nitrite in dilute

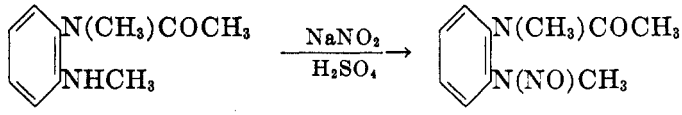


LXXXIII

sulfuric acid gives 3-acetylmethylamino-4-methylnitrosoaminotoluene (251).

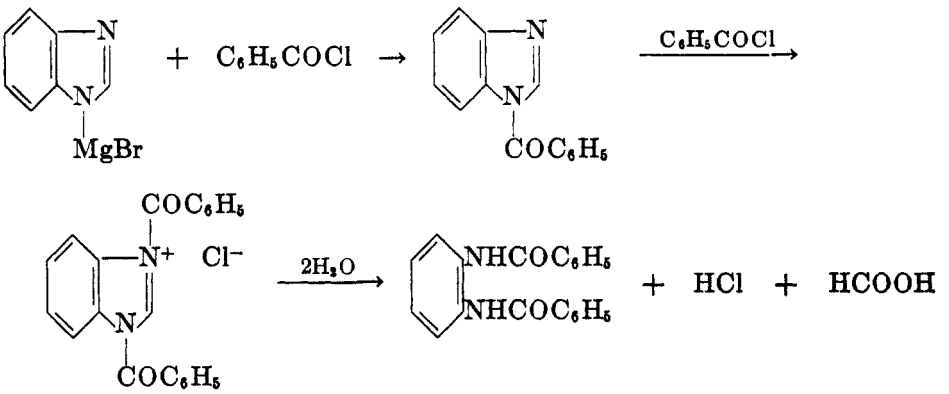


This latter reaction is best explained if the psuedo base is considered as being in the amide form (*cf.* page 467):



c. By treatment of 1-benzimidazoylmagnesium halides with aroyl chlorides

Whereas acyl halides react with 1-benzimidazoylmagnesium halides to form 1-acylbenzimidazoles, aroyl halides react to form chiefly an open-chain diamine through rupture of the imidazole ring. Thus, 1-benzimidazoylmagnesium bromide when treated with benzoyl chloride in ether solution gives mostly *N*,*N*′-dibenzoyl-*o*-phenylenediamine, with 1-benzoylbenzimidazole and benzimidazole as side-products (555). The rupture of the imidazole ring has been postulated (555) as occurring as follows:

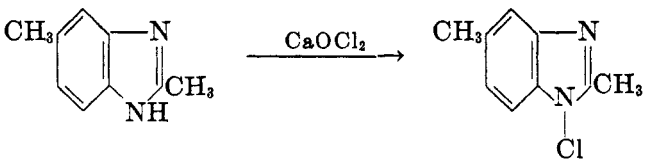


d. By treatment with acid anhydrides

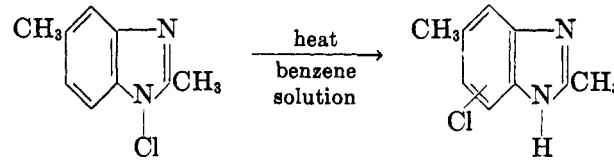
Oddo and Raffa (556, 557) have studied the action of acid anhydrides on benzimidazoles under a variety of conditions. When benzimidazole is heated with an excess of acetic anhydride and the reaction product poured into boiling water without first removing the excess anhydride the product is *N*,*N*′-diacetyl-*o*-phenylenediamine (556). Propionic anhydride and butyric anhydride react analogously (557). Benzimidazole is also cleaved to *N*,*N*′-diacetyl-*o*-phenylenediamine by the action of acetic anhydride and sodium acetate at reflux temperatures (312).

4. Halogenation

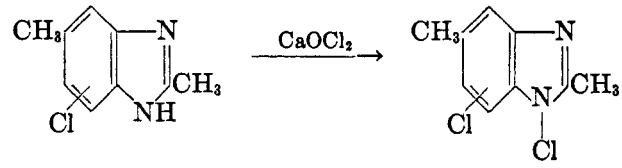
When 2,5(or 2,6)-dimethylbenzimidazole in an aqueous acid solution is treated with a saturated solution of bleaching powder at 0–5°C. 1-chloro-2,5(or 2,6)-dimethylbenzimidazole is obtained:



The *N*-chloro compound loses chlorine quite readily, even at relatively low temperatures. When heated under reflux in benzene solution a rearrangement of the chlorine atom to the benzene ring takes place:



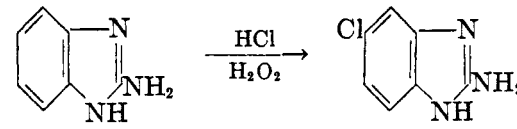
The *N*-chloro derivative of this compound may then be prepared by treatment again with bleaching powder:



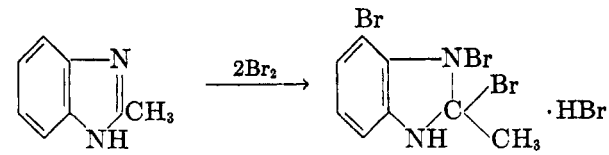
Treatment of the latter compound by refluxing in benzene solution rearranges the *N*-chlorine atom again into the ring. This process may be repeated until the totally chlorinated compound (1,4,5,6-tetrachloro-2,5-dimethylbenzimidazole) is obtained (50).

A number of 5-hydroxybenzimidazoles and 5-aminobenzimidazoles have been chlorinated with chlorine in acetic acid solution (260). The chlorinated products obtained in each case are listed in table 17.

2-Aminobenzimidazole may be chlorinated in the 5(or 6)-position in 95 per cent yield by treatment with hydrochloric acid and hydrogen peroxide (466).



The bromination of 2-methylbenzimidazole has been studied by Baczynski and von Niementowski (30). The addition of two moles of bromine to a cold acetic acid solution of 2-methylbenzimidazole gives a tetrabromo derivative:



2-Methyl-6-bromobenzimidazole and 2-methyl-4-bromobenzimidazole under the same conditions give 2-methyl-2,3,4,6-tetrabromobenzimidazoline hydrobromide. 2-Methyl-4,6,?-tribromobenzimidazole at steam-bath temperature adds bromine across the 2,3-double bond. The bromine atoms at the 2- and 3-positions of the brominated products mentioned above may be removed by heating with

TABLE 17

Chlorination of 5-hydroxy- and 5-aminobenzimidazoles

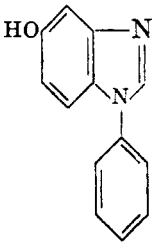
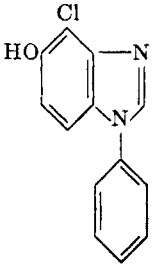
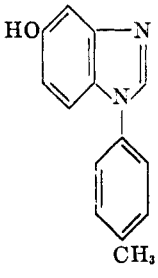
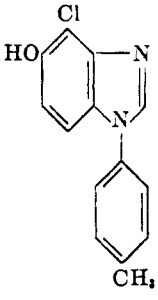
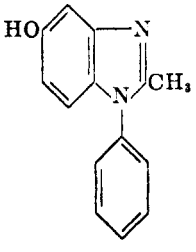
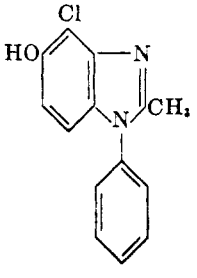
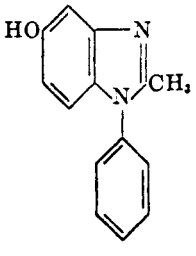
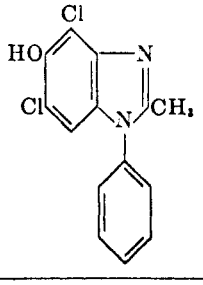
STARTING BENZIMIDAZOLE	CHLORINATING CONDITIONS	PRODUCT
	Calculated amount of chlorine	
	Calculated amount of chlorine	
	Calculated amount of chlorine	
	Excess chlorine	

TABLE 17—*Continued*

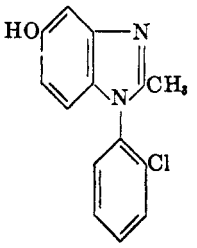
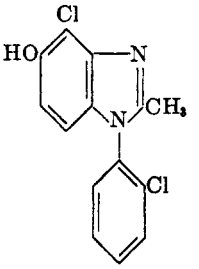
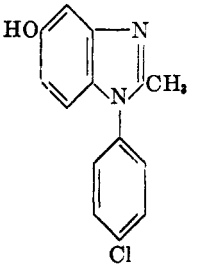
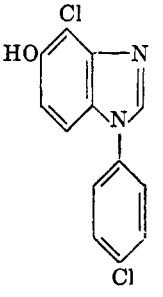
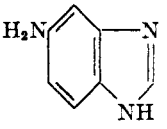
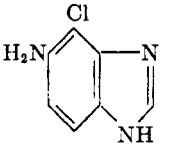
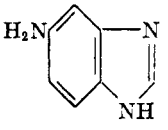
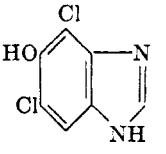
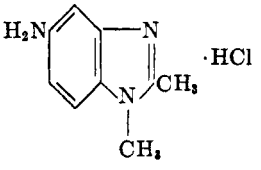
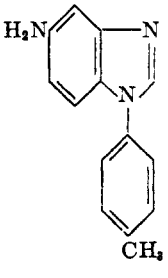
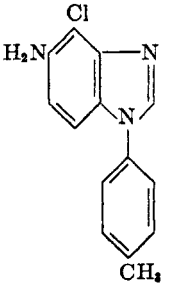
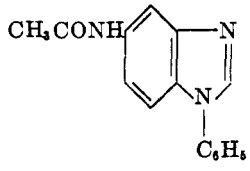
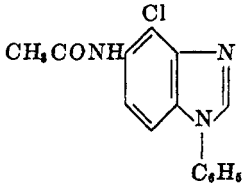
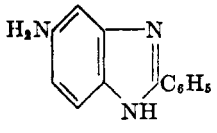
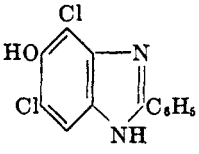
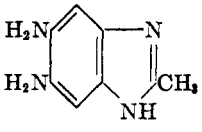
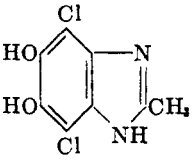
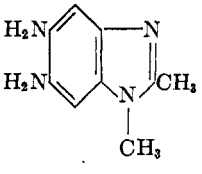
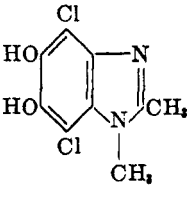
STARTING BENZIMIDAZOLE	CHLORINATING CONDITIONS	PRODUCT
	Calculated amount of chlorine	
	Calculated amount of chlorine	
		
	Saturated with chlorine, followed by reduction of the keto chloride	
	Saturated with chlorine	Mixture of dichlorinated and trichlorinated products
		

TABLE 17—*Concluded*

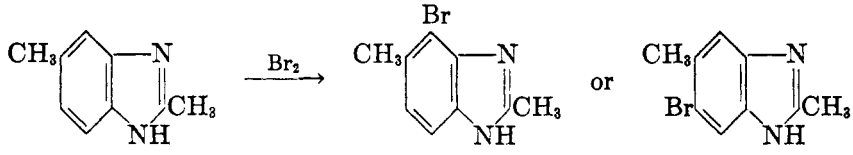
STARTING BENZIMIDAZOLE	CHLORINATING CONDITIONS	PRODUCT
		
	Saturated with chlorine, followed by reduction of the keto chloride	
	Saturated with chlorine, followed by reduction of the keto chloride	
	Saturated with chlorine, followed by reduction of the keto chloride	

benzene, aniline, or aqueous potassium iodide solution to give brominated products containing bromine only in the benzene ring. Treatment with water in some cases removes the bromine atoms at the 2-and 3-positions but the second bromine removed enters the benzene ring; thus, 2,3,4-tribromo-2-methylbenzimidazoline on treatment with water gives 4,6(or 5,7)-dibromo-2-methylbenzimidazole.

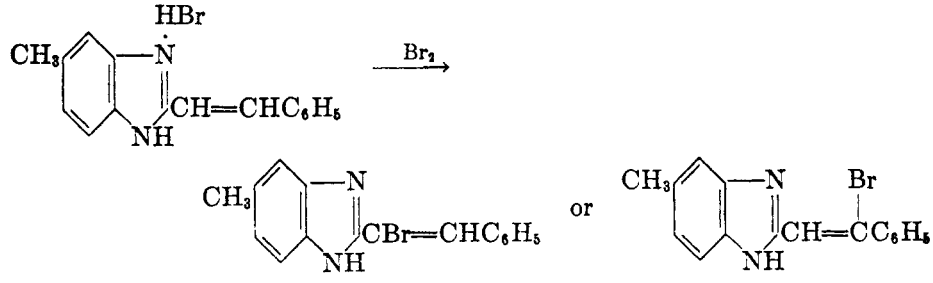
2-Methylbenzimidazole on long standing with one mole of bromine in acetic acid solution gives 2-methyl-4(or 7)-bromobenzimidazole. Bromination with two moles of bromine in cold alkaline solution gives 2-methyl-4,6(or 5,7)-dibromobenzimidazole. Bromination of the latter product with one mole of bromine in alkaline solution gives a tribromo derivative (2-methyl-4,6,?-tribromobenzimidazole). Exhaustive bromination of 2-methylbenzimidazole or any of its brominated products in alcoholic solution gives 2-methyl-4,5,6,7-tetrabromobenzimidazole. Bromination in all of these cases does not take place on the 2-methyl group, since this grouping in the brominated products still shows all the characteristic reactions of the 2-methyl group of benzimidazoles (30).

2-Ethylbenzimidazole on treatment with bromine water gives a mixture of di- and tribrominated 2-ethylbenzimidazoles (675).

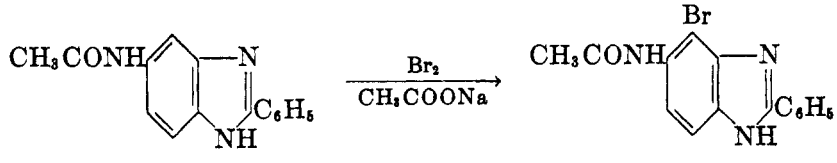
Treatment of 2,5(or 2,6)-dimethylbenzimidazole with bromine in acetic acid or carbon disulfide (534) or in chloroform (45) leads to either 4(or 7)-bromo-2,5(or 2,6)-dimethylbenzimidazole or 6(or 5)-bromo-2,5(or 2,6)-dimethylbenzimidazole.



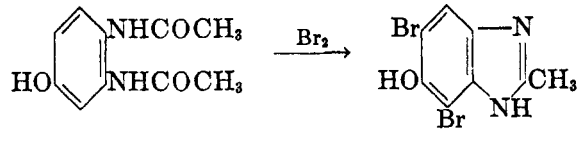
5(or 6)-Methyl-2-styrylbenzimidazole hydrobromide on treatment with bromine in chloroform gives a perbromide which on refluxing in alcohol yields a product brominated in the side chain (206).



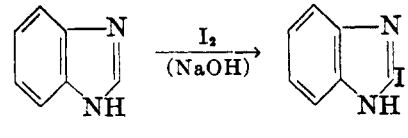
2-Methyl-1-phenyl-5-hydroxybenzimidazole on bromination in aqueous acetic acid solution leads to 2-methyl-1-phenyl-5-hydroxy-4-bromobenzimidazole. The 4,6-dibromo analog may be obtained by bromination in acetic acid solution. Bromination of 2-phenyl-5-acetylaminobenzimidazole in the presence of sodium acetate gives 2-phenyl-4-bromo-5-acetylaminobenzimidazole (260):



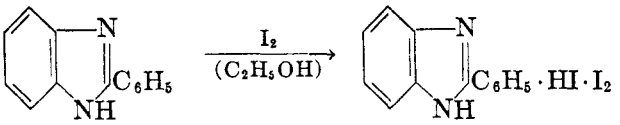
It is reported (311) that 3,4-diacetylaminophenol when treated with excess bromine gives 2-methyl-5,7(or 4,6)-dibromo-6(or 5)-hydroxybenzimidazole:



Treatment of benzimidazole in aqueous solution with the theoretical amount of iodine (*N*/10 solution) in the presence of sodium hydroxide gives a quantitative yield of 2-iodobenzimidazole (560).



2-Phenylbenzimidazole on heating with six moles of iodine in an alcoholic solution is reported (348) to give a triiodide:



This substance on heating under reflux in aqueous solution yields 2-phenylbenzimidazole hydroiodide. 2-Benzylbenzimidazole gives the corresponding triiodide under comparable conditions (736).

5. Nitration

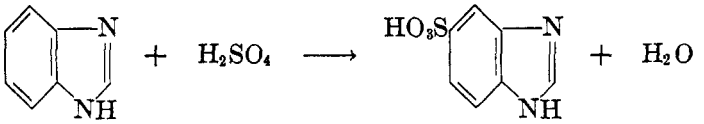
The nitration of benzimidazoles proceeds readily. In most cases nitration appears to take place preferentially at the 5- or 6-position. However, the nitro group may also enter the 4- or 7-position, especially if the 5- or 6-position is blocked.

Nitrobenzimidazoles that have been obtained by the nitration of benzimidazoles are listed in table 18.

6. Miscellaneous reactions

2(3*H*)-Benzimidazolone reacts with succinic anhydride and glutaric anhydride in the presence of aluminum chloride to give β-(benzimidazoyl-5)propionic acid (13 per cent yield) and γ-(benzimidazoyl-5)butyric acid (5 per cent yield), respectively (155, 312).

A number of patents describe "sulfonated benzimidazoles" obtained by the sulfonation of benzimidazoles with either sulfuric acid (150, 283, 363, 655, 683) or chlorosulfonic acid (682, 690). Treatment of benzimidazole with concentrated sulfuric acid gives 5-benzimidazolesulfonic acid (363).



The benzimidazole nucleus is very stable to oxidation in that it is possible to carry out the oxidation of substituent groups without affecting the nucleus. Vigorous oxidation with a hot alkaline solution of potassium permanganate gives a small amount of 4,5-imidazoledicarboxylic acid (40).

Fries (260) has investigated the benzenoid and naphthenoid characteristics of benzimidazoles. Benzimidazoles are mainly benzenoid in their reactions, although some analogies to naphthalene are apparent. For example, halogenation of 5-hydroxybenzimidazole takes place preferentially at the 4-position, although halogenation may occur also on the opposite side of the hydroxyl group (6-position). In the Skraup reaction on 5-aminobenzimidazoles ring closure occurs preferentially on the 4-position; however, ring closure may occur also on the 6-position if the 4-position is blocked. 5-Aminobenzimidazoles form diazoamino compounds with aryldiazonium salts. Nitration and halogenation may take

TABLE 18

Nitration of benzimidazoles

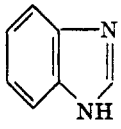
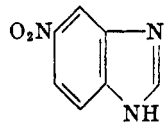
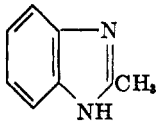
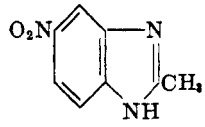
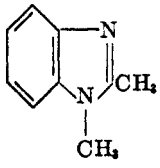
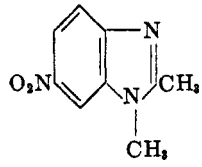
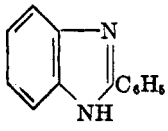
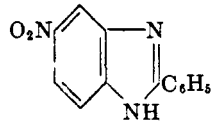
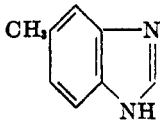
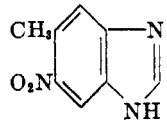
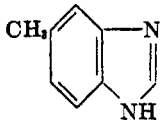
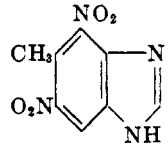
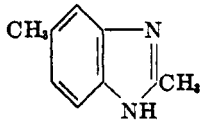
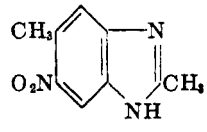
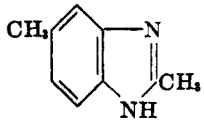
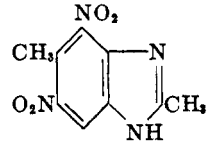
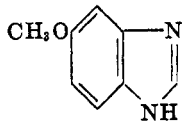
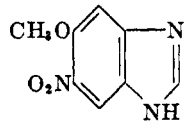
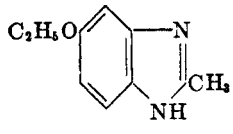
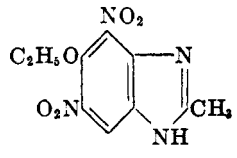
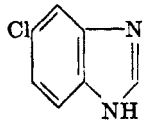
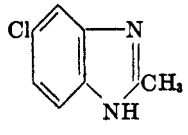
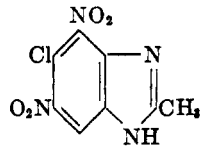
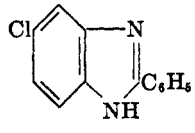
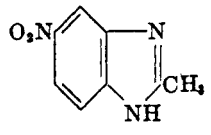
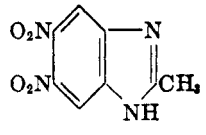
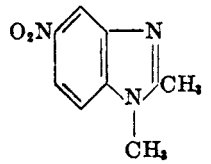
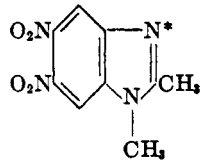
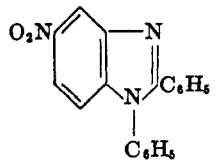
STARTING BENZIMIDAZOLE	NITRATING CONDITIONS	PRODUCT	REFERENCES
	$HNO_3 + H_2SO_4$		(33, 233, 726, 762)
	$HNO_3 + H_2SO_4$		(234)
	$HNO_3 + H_2SO_4$		(696)
	Fuming HNO_3		(338)
	Fuming HNO_3		(235)
	Concentrated $H_2SO_4 + KNO_3$; warm on steam bath		(480)
	HNO_3		(236, 527)
	$H_2SO_4 + KNO_3$; warm on steam bath		(480)

TABLE 18—*Continued*

STARTING BENZIMIDAZOLE	NITRATING CONDITIONS	PRODUCT	REFERENCES
	$HNO_3 + H_2SO_4$		(554)
	$KNO_3 + H_2SO_4$; 80–90°C.		(480)
	$HNO_3 + H_2SO_4$	5(or 6)-Chloro-?-nitrobenzimidazole	(244)
	$H_2SO_4 + KNO_3$; heat on steam bath		(480)
	HNO_3	5(or 6)-Chloro-?-nitro-2-phenylbenzimidazole	(240)
	$HNO_3 + H_2SO_4$		(441)
	H_2SO_4 + fuming HNO_3		(260)
	Fuming HNO_3	5, ?-Dinitro-1,2-diphenylbenzimidazole	(523)

* The 4,5-dinitro isomer was obtained as a by-product in 5 per cent yield.

TABLE 18—*Continued*

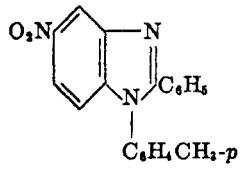
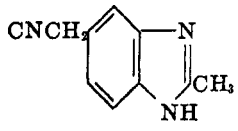
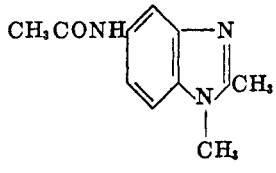
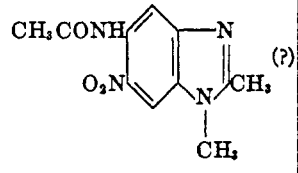
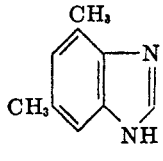
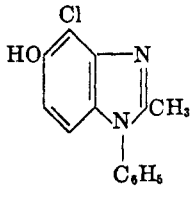
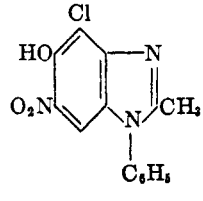
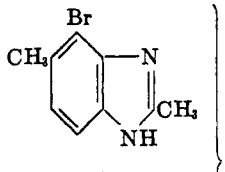
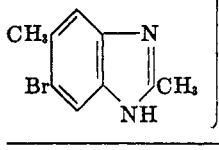
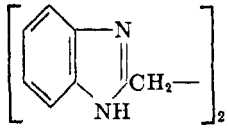
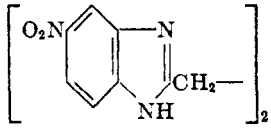
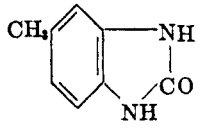
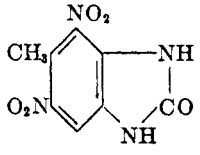
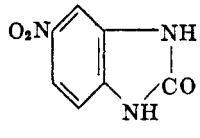
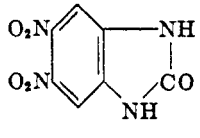
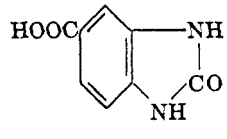
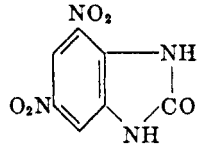
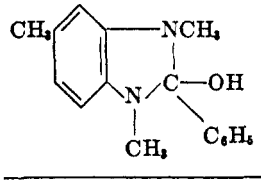
STARTING BENZIMIDAZOLE	NITRATING CONDITIONS	PRODUCT	REFERENCES
	Fuming HNO_3	5,?-Dinitro-1-*p*-tolyl-2-phenylbenzimidazole	(523)
	Fuming HNO_3; −5° to −10°C.	"?-Nitro derivative"	(482)
	HNO_3		(657)
	HNO_3 + H_2SO_4	"5- or 7-nitro derivative"	(237)
	HNO_3 + CH_3COOH		(260)
 or 	Fuming HNO_3	"?-Nitro derivative"	(535)

TABLE 18—*Concluded*

STARTING BENZIMIDAZOLE	NITRATING CONDITIONS	PRODUCT	REFERENCES
			(151)
	$KNO_3 + H_2SO_4$; 80–90°C.		(480)
	Dissolve in fuming HNO_3		(440)
	$H_2SO_4 + HNO_3$ at low temperature (or) reflux with HNO_3		(604)
	Nitrous oxide (or) cold HNO_3	"?-Nitro derivative"	(350)

place preferentially on the 5-position (corresponding to the β-position of naphthalene). Chlorides of hydroxybenzimidazoles may lead to keto chlorides or an ortho-quinone (analogy to naphthalene).

Benzimidazoles are unaffected by hydroxylamine.

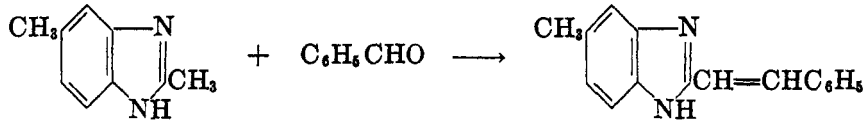
B. REACTIONS INVOLVING SUBSTITUENT GROUPS

A number of reactions of benzimidazoles involve commonplace transformations, such as the conversion of an acid to its ester, etc. Such reactions will not be considered in the following discussion but rather only these reactions which are characteristic of benzimidazoles.

1. Reactions involving the 2-methyl or methylene group

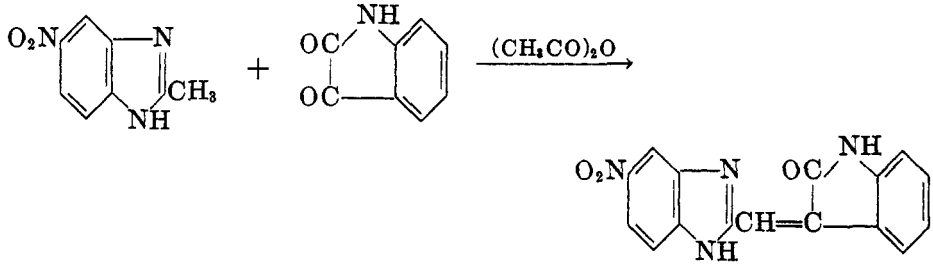
The methyl group of 2-methylbenzimidazoles is comparable in its activity to the methyl group of α-picoline, quinaldine, or methyl ketones and shows

most of the same reactions of these compounds. The benzimidazole ring, like the pyridine and quinoline ring, because of its electron-attracting nature imparts a positive character to the carbon atom of the 2-methyl group. 2-Methylbenzimidazoles, for example, react with aromatic aldehydes in aldol-type condensations in a manner analogous to α-picoline and quinaldine (35).

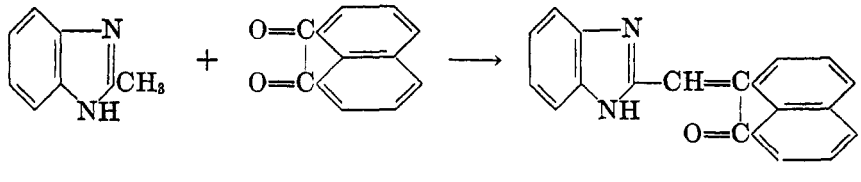


The above reaction may be carried out by heating the two reactants together at 200°C. for 2 hr. A rather large variety of aromatic aldehydes and 2-methylbenzimidazoles have been condensed in this manner. In addition to 2-methylbenzimidazoles other benzimidazoles having a 2-alkyl or 2-aralkyl group have been used.

Phenanthraquinone condenses with 2-methyl-5(or 6)-nitrobenzimidazole in boiling acetic anhydride to form an abnormal product (439). Isatin gives a normal condensation product (438):

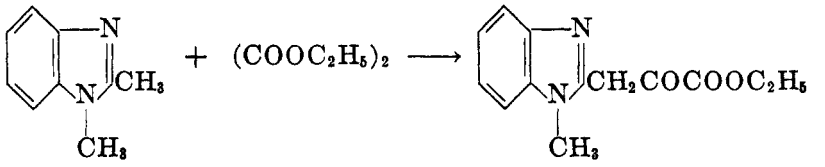


Isatin condenses similarly with 2-methylbenzimidazole and 2-benzylbenzimidazole (8). Acenapthenequinone condenses in an analogous manner with 2-methylbenzimidazole (9):



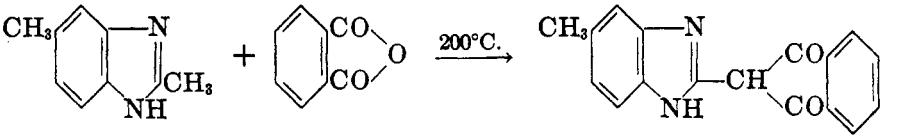
Negative results are reported with benzil, quinone, *p*-dimethylaminobenzaldehyde, and alloxan (the alloxan is decomposed) (9).

1,2-Dimethylbenzimidazole when allowed to stand for 1 week with diethyl oxalate gives a small yield of condensed product (114):

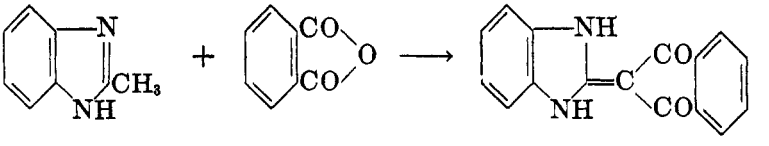


1-Phenyl-2-methylbenzimidazole gives a poor yield of the corresponding condensation product after 4 days (115).

2-Methylbenzimidazoles like quinaldine react with phthalic anhydride at an elevated temperature to yield phthalones (36):



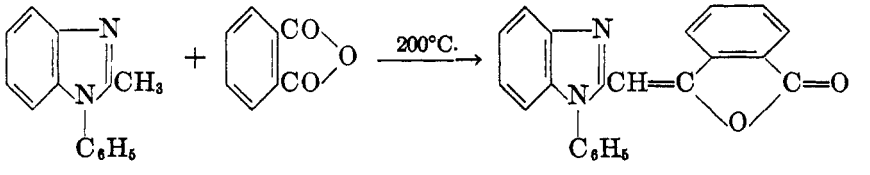
Phthalones from a number of 2-methylbenzimidazoles have been prepared in this way. van Alphen (7) prepared the phthalone from 2-methylbenzimidazole; however, he assigns this compound a somewhat different structure (LXXXIV):



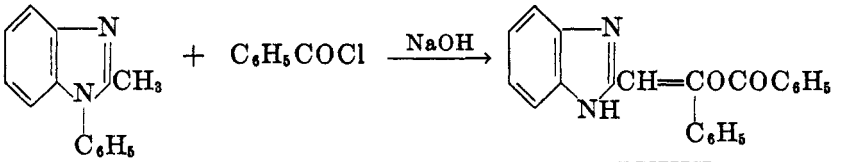
LXXXIV

The evidence for this structure is based on the fact that 2-methylbenzimidazole yields a phthalone, whereas 2-ethyl- and 2-benzylbenzimidazoles do not. The compound LXXXIV possesses a yellow color and is isomeric with indigo, the keto and imino groups on the latter compound having been interchanged.

Borsche and Doeller (115) have prepared the phthalone from 1-phenyl-2-methylbenzimidazole; however, they assign their product the *isophthalone* structure:



2-Methyl-1-phenylbenzimidazole on shaking with benzoyl chloride and sodium hydroxide solution reacts at the 2-methyl group (761):



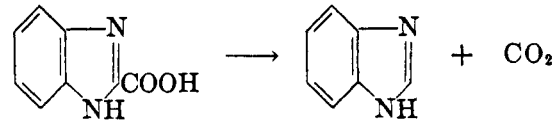
LXXXV

1-Phenyl-2-phenacylbenzimidazole also gives LXXXV under the same conditions. The product (LXXXV), on treatment with alcohol or on heating with 20 per cent hydrochloric acid, reverts to 1-phenyl-2-phenacylbenzimidazole (761).

The replacement of one of the active hydrogens of the methyl group of 2-methylbenzimidazoles by lithium or sodium, analogous to the corresponding reactions in the α-picoline series, apparently has not been studied. In such a case replacement of the hydrogen in the 1-position might be expected first; however, with 1-substituted benzimidazoles such substitution on the 2-methyl group might be possible.

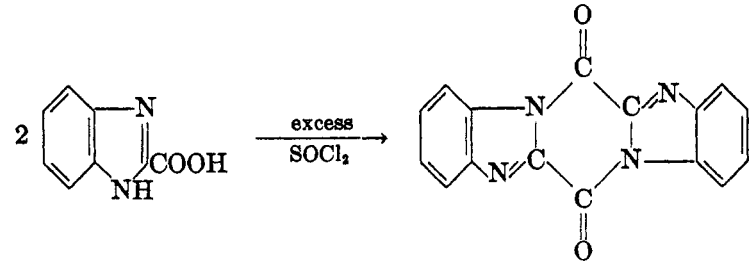
2. Reactions of 2-benzimidazolecarboxylic acids

Benzimidazoles containing a carboxyl group in the 2-position readily undergo decarboxylation on heating. 2-Benzimidazolecarboxylic acid on heating above its melting point, for example, yields benzimidazole (94):

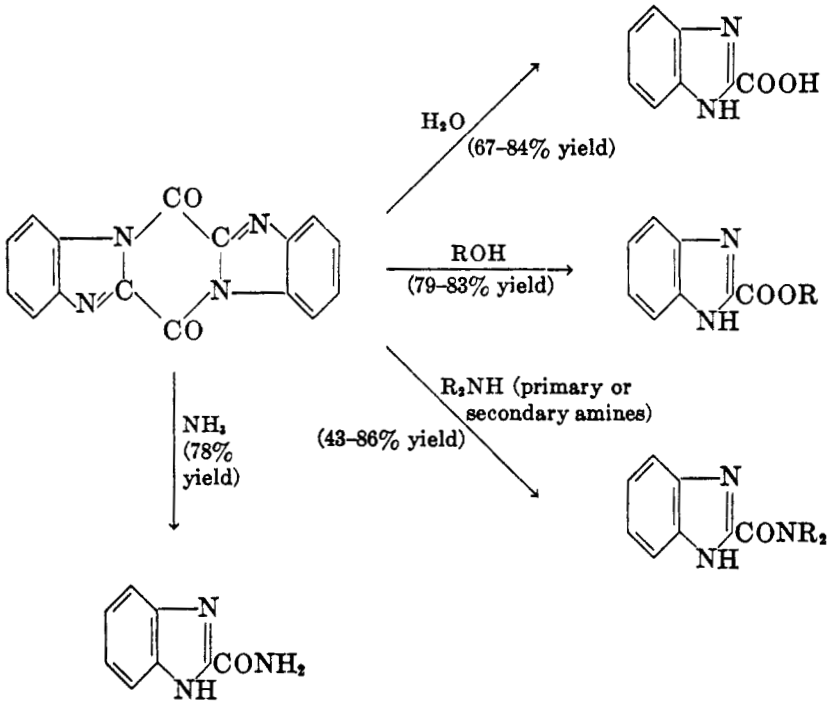


5(or 6)-Methyl-2-benzimidazolecarboxylic acid is decarboxylated in a similar manner by melting or by boiling the acid in acetic acid (39). 1-Phenyl-5-nitro-2-benzimidazolecarboxylic acid and the corresponding ethyl ester may be decarboxylated by heating with concentrated hydrochloric acid in a sealed tube at 150°C. (628).

2-Benzimidazolecarboxylic acid may not be converted to its acid chloride with phosphorus chlorides or thionyl chlorides (166). With excess thionyl chloride a yellow cyclic diamide containing no chlorine is obtained in 86 per cent yield:

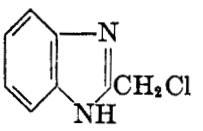


Acidic or basic hydrolysis of this substance regenerates 2-benzimidazolecarboxylic acid. Alcoholysis leads to 2-benzimidazolecarboxylic esters and treatment with ammonia or amines (primary or secondary) yields amides (166):



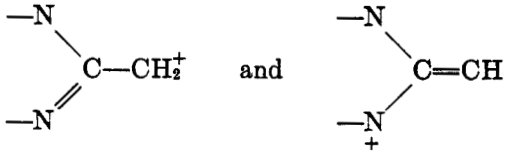
3. *Reactions of 2-(α-haloalkyl)benzimidazoles*

2-Chloromethylbenzimidazole (LXXXVI) and other 2-(α-haloalkyl)benzimi-



LXXXVI

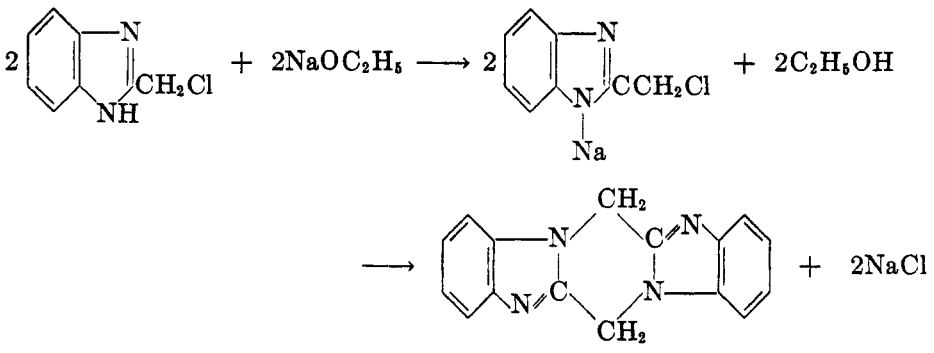
dazoles are highly reactive. Structurally, they are related to allyl and benzyl halides, since they possess the same $=CCH_2Cl$ grouping. The reactivity of these benzimidazoles is probably due to the existence of such resonating structures as:



The chemical reactivity of these substances has been investigated by Skolnick, Day, and Miller (670, 671), who find that these halides are more active than allyl and benzyl halides. 2-Chloromethylbenzimidazole is quantitatively hydrolyzed with boiling water in 30–60 min. Other 2-α-chloroalkylbenzimida-

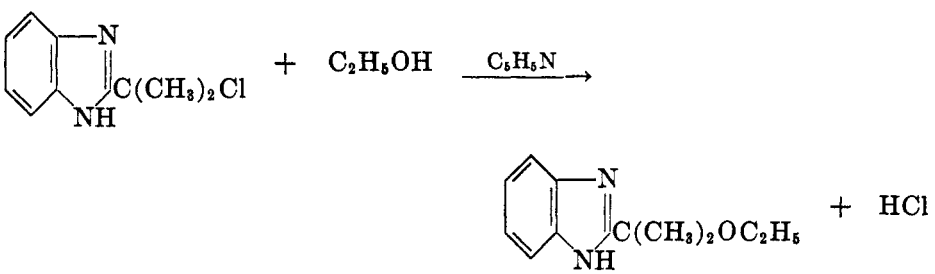
zoles that were studied are hydrolyzed in a somewhat shorter time and the 2-(α-chloroisopropyl) derivative is completely hydrolyzed by water at room temperature.

The Williamson reaction of 2-chloromethylbenzimidazole with sodium ethoxide leads not to 2-ethoxymethylbenzimidazole but rather to a product containing no oxygen, presumably LXXXVII (671).



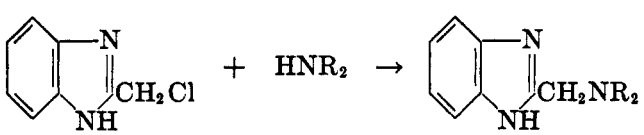
LXXXVII

2-(α-Chloroisopropyl)benzimidazole when refluxed in dry alcoholic solution in the presence of pyridine gives a good yield of 2-(α-ethoxyisopropyl)benzimidazole and hence reacts in a manner analogous to trityl chloride (triphenylmethyl chloride).

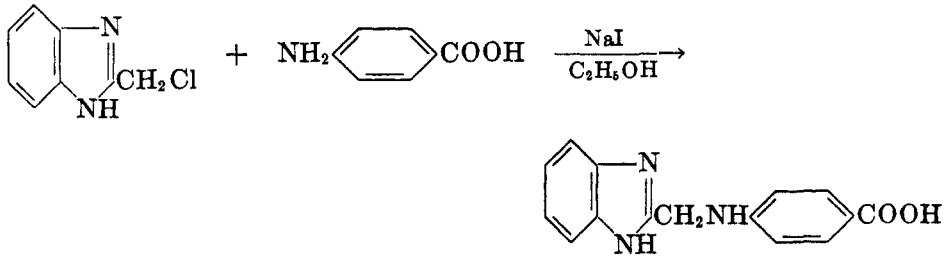


2-(α-Chloroalkyl)benzimidazoles react also with potassium iodide in acetone solution to yield the corresponding 2-(α-iodoalkyl)benzimidazoles. The reaction rates of several 2-(α-chloroalkyl)benzimidazoles in this reaction have been determined (670).

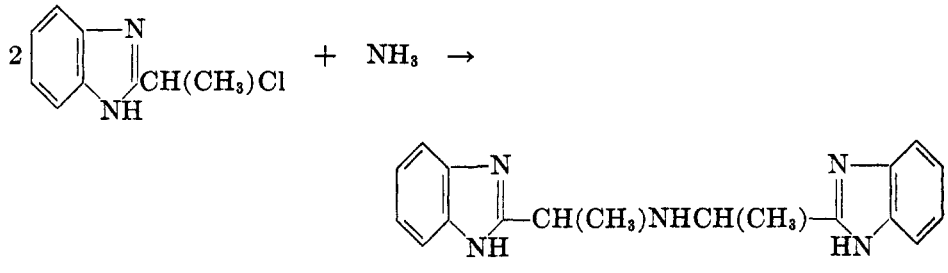
2-(α-Chloroalkyl)benzimidazoles react with primary and secondary amines to give 2-(α-aminoalkyl)benzimidazoles (109, 356, 415, 634, 698):



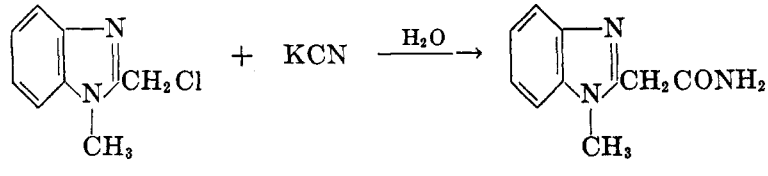
2-(α-Chloromethyl)benzimidazole reacts with *p*-aminobenzoic acid or its ethyl ester in alcoholic solution in the presence of a small amount of sodium iodide (415):



Various attempts to replace the chlorine of 2-(α-chloromethyl)benzimidazole by an amino group by reaction with ammonia are reported to give a mixture of products, with no 2-aminomethylbenzimidazole isolatable (356). 2-(α-Chloroethyl)benzimidazole with ammonia gives a 36–42 per cent yield of di(α-benzimidazolylethyl)amine (634):



1-Methyl-2-chloromethylbenzimidazole on treatment with potassium cyanide in acetone–water solution gives an 80 per cent yield of 1-methyl-2-benzimidazoleacetamide (671):



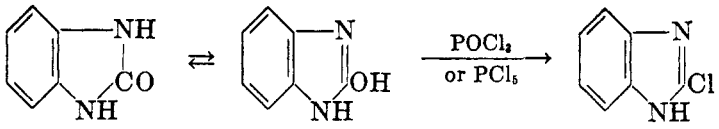
From the reaction between 2-α-chloromethylbenzimidazole and phenylmagnesium bromide, no product could be isolated (671).

4. Reactions of 2-(3H)-benzimidazolones

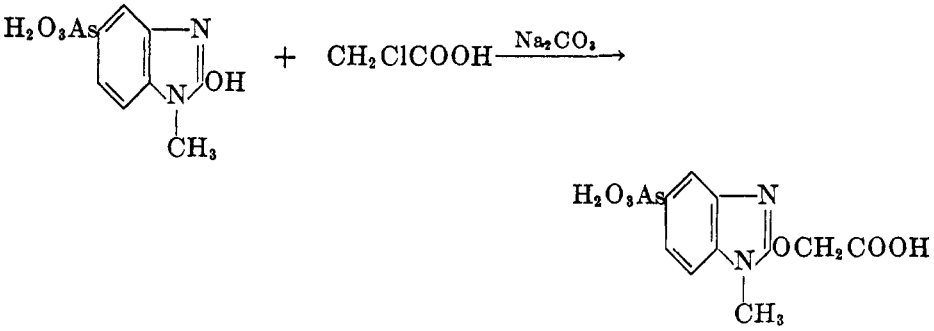
2(3*H*)-Benzimidazolones (or 2-hydroxybenzimidazoles) are extremely stable substances. 2(3*H*)-Benzimidazolone is not split by treatment with benzoyl chloride in alkaline solution.

2(3*H*)-Benzimidazolones show many of the reactions of 2-hydroxypyridines and 2-hydroxyquinolines; for example, treatment of 2(3*H*)-benzimidazolone

with phosphorus oxychloride or phosphorus pentachloride yields the 2-chloro derivative (478):



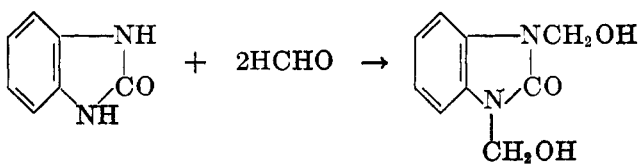
2-Hydroxybenzimidazoles have been alkylated on the oxygen in good yields by treatment with chloroacetic acid in sodium carbonate solution (707):



Heating of 2-ethoxybenzimidazoles with concentrated hydrochloric acid in a sealed tube cleaves the ether linkage to yield ethyl chloride and 2(3*H*)-benzimidazolone.

5-Ethoxy-2(3*H*)-benzimidazolone on refluxing with acetic anhydride is converted to the 1,3-diacetyl derivative (187). 2(3*H*)-Benzimidazolone is converted to the 1,3-disodium salt with dilute sodium hydroxide solution. Treatment of the resulting disodium salt with benzoyl chloride yields 1,3-dibenzoyl-2(3*H*)-benzimidazolone. 2(3*H*)-Benzimidazolone with ethanolic sodium hydroxide solution gives a monosodium salt which dissociates on warming with water. Treatment of the monosodium salt with benzoyl chloride gives a mixture of 2(3*H*)-benzimidazolone and 1,3-dibenzoyl-2(3*H*)-benzimidazolone. 2(3*H*)-Benzimidazolone also yields a silver salt, which on treatment with benzoyl chloride and acetyl chloride gives the *O*-benzoyl and *O*-acetyl derivatives of 2-hydroxybenzimidazole, respectively. Direct acetylation of 2(3*H*)-benzimidazolone gives 1,3-diacetyl-2(3*H*)-benzimidazolone (310).

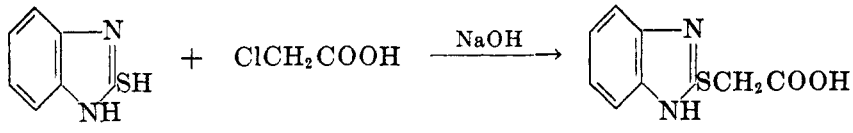
2-(3*H*)-Benzimidazolone is reported (514) to give 1-xanthyl-2(3*H*)-benzimidazolone with one mole of xanthydrol and the corresponding 1,3-dixanthyl derivative with two moles of xanthydrol. 2(3*H*)-Benzimidazolone on heating with an aqueous formaldehyde solution yields the corresponding 1,3-di(hydroxymethyl) derivative (515):



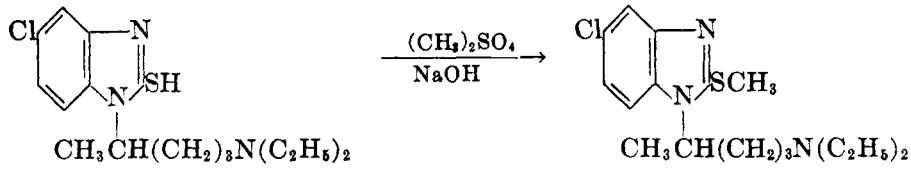
5. 2(3H)-Benzimidazolethiones

2(3*H*)-Benzimidazolethiones (or 2-mercaptobenzimidazoles) are generally stable substances and are soluble in dilute alkali.

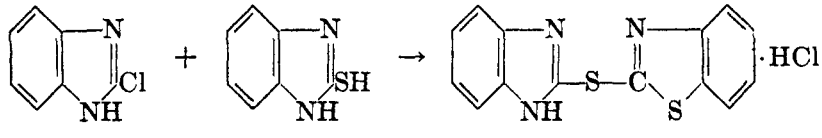
Alkylation occurs readily with replacement of the mercapto hydrogen to yield *S*-alkylated derivatives, and a number of these derivatives have been prepared (199, 201, 519, 651). 2(3*H*)-Benzimidazolethione, for example, may be alkylated with chloroacetic acid by refluxing in 2 *N* sodium hydroxide solution (202):



Methylation may be brought out by the use of dimethyl sulfate in alkaline solution (489):

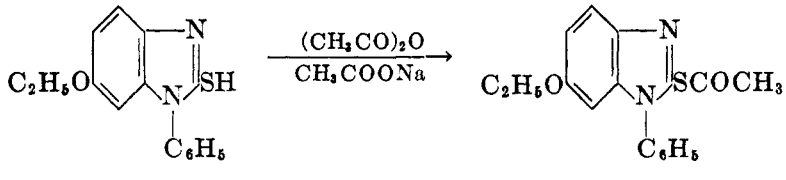


2-Chlorobenzothiazole when refluxed in an alcoholic solution with 2(3*H*)-benzimidazolethione yields 2-(benzothiazole-2′-mercapto)benzimidazole hydrochloride in 86 per cent yield (659).



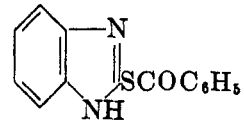
Like 2(3*H*)-benzimidazolone, 2(3*H*)-benzimidazolethione is reported (514) to give 1-xanthyl-2(3*H*)-benzimidazolethione with one mole of xanthydrol and the corresponding 1,3-dixanthyl derivative with two moles of xanthydrol.

Acetylation of 1-phenyl-6-ethoxy-2(3*H*)-benzimidazolethione by heating with acetic anhydride in the presence of molten sodium acetate gives the corresponding 2-thioacetyl derivative (386).



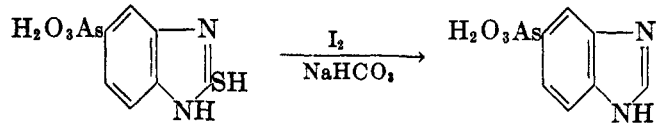
The corresponding 1-*p*-tolyl analog reacts analogously (388). 2(3*H*)-Benzimidazolethione is reported (270) to give only a monobenzoyl derivative (LXXXVIII),

in contradistinction to 2(3*H*)-benzimidazolone, which gives also a 1,3-dibenzoyl derivative.

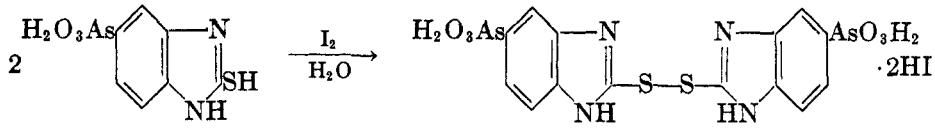


LXXXVIII

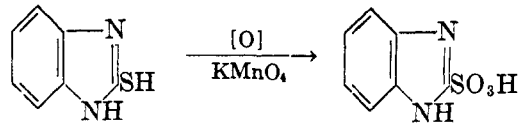
2(3*H*)-Benzimidazolethione is not desulfurized on treatment with hot alkaline lead solutions (460). The mercapto group of 2-mercaptobenzimidazoles may be removed by treatment with iodine (0.5 *N*) solution and sodium bicarbonate (196):



Aqueous iodine solution (1 *N*) yields the disulfide (199):

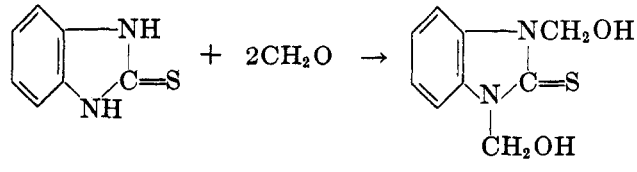


The mercapto group may be oxidized to the sulfonic acid group with alkaline potassium permanganate solution in good yields:



The resulting 2-benzimidazolesulfonic acid may be cleaved to benzimidazole with hydrochloric acid at 170°C. (199). 2-Benzimidazolesulfonyl chloride has been prepared by an oxidative chlorination of 2(3*H*)-benzimidazolethione (632).

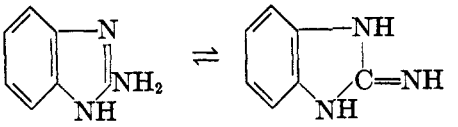
2(3*H*)-Benzimidazolethione, like 2(3*H*)-benzimidazolone, gives a 1,3-dihydroxymethyl derivative on heating with an aqueous formaldehyde solution (515):



2(3*H*)-Benzimidazolethione reacts with a number of cations to form metal derivatives (177, 201, 426, 427, 428, 429, 430, 431). A number of cations are precipitated quantitatively in this way and this reaction has been used as a basis for their quantitative estimation.

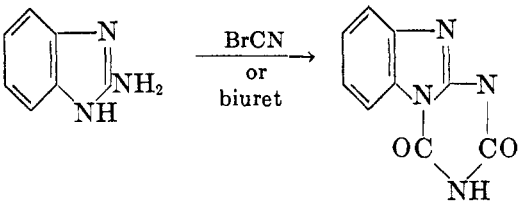
6. *2-Aminobenzimidazoles*

2-Aminobenzimidazoles may exist also in the imide form:

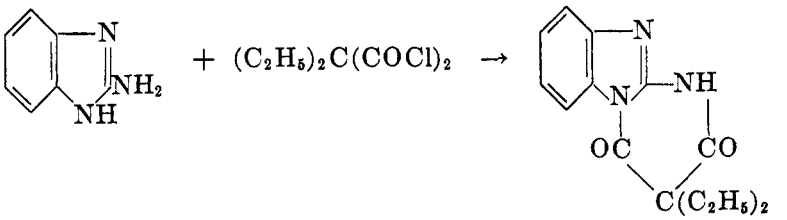


2-Aminobenzimidazole is soluble in water and soluble in alkali.

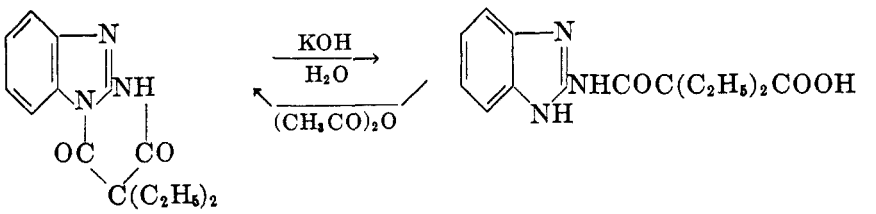
2-Aminobenzimidazole is converted to 2(3*H*)-benzimidazolone upon heating with barium hydroxide and a little water to 180–190°C. or by treatment with nitrous acid (587). Hypochlorous or hypobromous acid causes a series of color changes to take place (569). Treatment with two moles of cyanogen bromide in the presence of water and potassium bicarbonate or treatment with biuret at 180°C. yields a tricyclic compound (586):



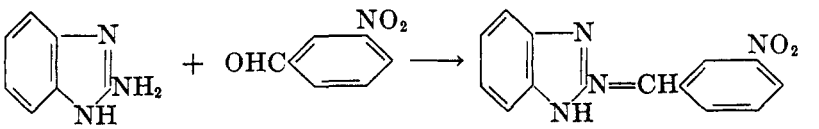
A tricyclic product is formed also by reaction with diethylmalonyl chloride in the presence of pyridine (170):



The ring in the latter compound may be opened with aqueous potassium hydroxide solution (170):

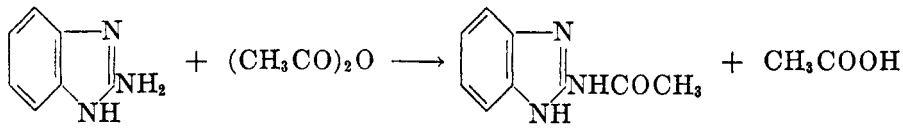


2-Aminobenzimidazole is reported (569) to condense with *m*-nitrobenzaldehyde to form a Schiff base:



However, benzaldehyde is reported not to give the normal Schiff base product. The condensation with formaldehyde is also complicated (170).

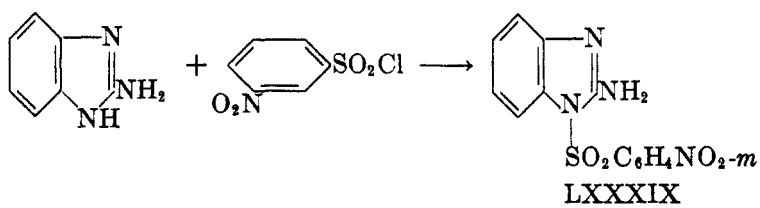
2-Aminobenzimidazole with acetic anhydride gives 2-acetylaminobenzimidazole (569):



Acetylation of 2-phenylaminobenzimidazoles with acetic anhydride takes place either in the 1-position or on the side-chain nitrogen in the 2-position. Treatment with several times the necessary amount of benzoic acid anhydride at 120–140°C. yields a dibenzoyl derivative (407).

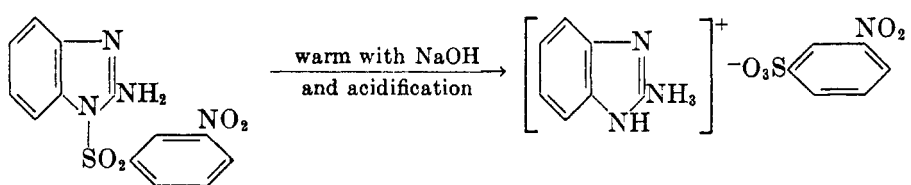
2-*p*-Tolylaminobenzimidazoles with nitrous acid give nitroso derivatives, the nitroso group being either in the 1-position or on the side-chain nitrogen atom (409).

2-Aminobenzimidazole reacts with sulfonyl chlorides at the ring nitrogen to give 1-sulfonylbenzimidazoles (618):



LXXXIX

It was thought formerly that reaction with sulfonyl chlorides occurred on the amino group in the 2-position; thus, 2-aminobenzimidazole is erroneously reported to give 2-sulfanilamidobenzimidazole on treatment with *p*-acetylaminobenzenesulfonyl chloride followed by hydrolysis of the acetyl group. Price and Reitsema (618) have shown that LXXXIX on warming with alkali and acidification yields 2-aminobenzimidazole *m*-nitrobenzenesulfonate (XC):



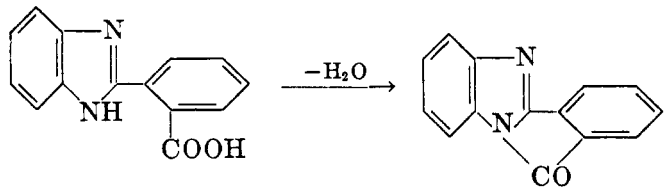
XC

On this basis, a salt structure analogous to that of XC is suggested (618) for the compound previously reported (622) as 2-sulfanilamidobenzimidazole; in fact, it has been shown (466) that 2-aminobenzimidazole on direct combination with sulfanilic acid gives a sulfonate salt corresponding in physical properties to the above-mentioned 2-sulfanilamidobenzimidazole or "sulfabenzimidazole."

2-Aminobenzimidazole is chlorinated in the 5-position in 95 per cent yield to give 2-amino-5(or 6)-chlorobenzimidazole (466).

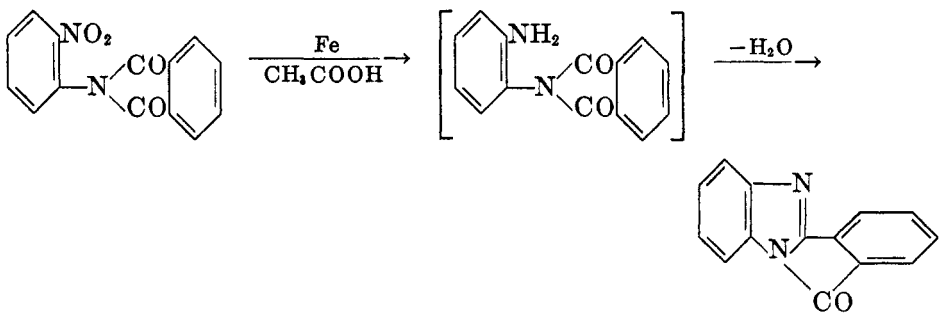
7. *o-Benzoylene-2,1-benzimidazole*[5] *and related compounds*

If the side chain in the 2-position of a benzimidazole contains a reactive group, this grouping may react at the nitrogen in the 1-position to yield a tricyclic compound. For example, *o*-(2-benzimidazole)benzoic acid on heating to 280°C. or on refluxing with acetic anhydride gives *o*-benzoylene-2,1-benzimidazole through lactam formation (88, 614, 644, 713):

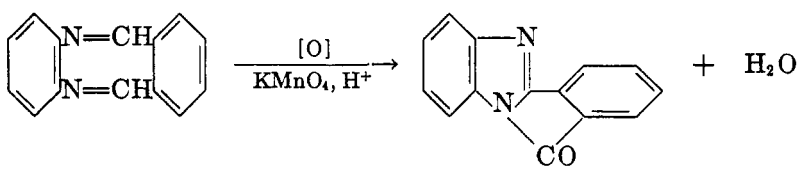


o-Benzoylene-2,1-benzimidazole possesses chromophoric character, being yellow in color.

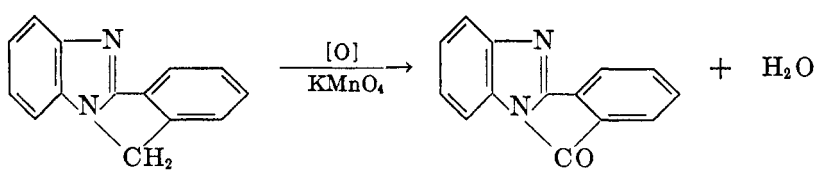
This substance may be obtained also by the reduction of *N*-(2-nitrophenyl)-phthalimide with iron and refluxing acetic acid (643), or sodium hydrosulfite and acetic acid, or by the reduction of *o*-phthalimidoazo derivatives (167).



It may be obtained also by the oxidation of the Schiff base XCI (74, 637, 714),



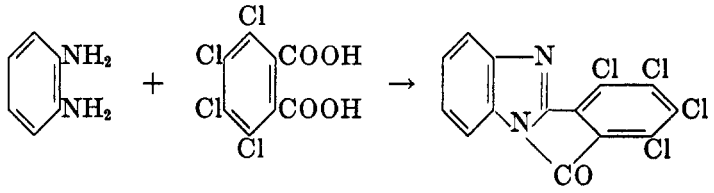
or by the oxidation of *o*-benzylene-1,2-benzimidazole (74).



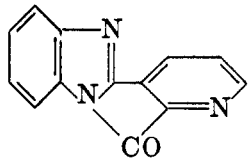
[5] According to *Chemical Abstracts* nomenclature *o*-benzoylene-2,1-benzimidazole is known as 11-isoindolo-[2,1-]benzimidazol-11-one. However, since the former name has been used almost exclusively in the literature, it is used also here.

In addition to *o*-benzoylene-2,1-benzimidazole, 5-methyl-*o*-benzoylene-2,1-benzimidazole (143) and 5-chloro-*o*-benzoylene-2,1-benzimidazole (637) are known.

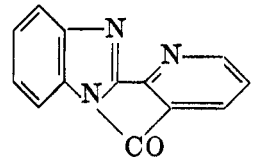
o-Phenylenediamine and tetrachlorophthalic acid when heated gradually to 250°C. give a good yield of a tetrachloro-*o*-benzoylene-2,1-benzimidazole (89).



Quinolinic acid and *o*-phenylenediamine give XCII (or XCIII) (90):

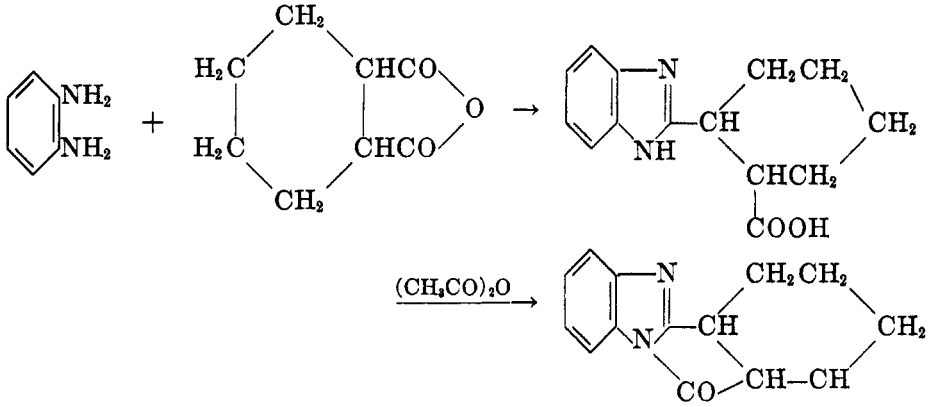


XCII

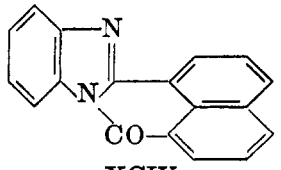


XCIII

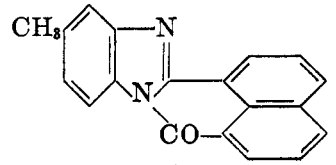
Hexahydrophthalic anhydride and *o*-phenylenediamine give *o*-(benzimidazole-2)-hexahydrobenzoic acid, which on cyclization with acetic anhydride yields hexahydro-*o*-benzoylene-2,1-benzimidazole (73):



The 5-methyl analog has also been prepared (73). By the use of 1,8-naphthoic anhydride, 1′,8′-naphthalene-2,1-benzimidazole (XCIV) and the corresponding 5-methyl analog (XCV) may be obtained (143) from *o*-phenylenediamine and 3,4-diaminotoluene, respectively.

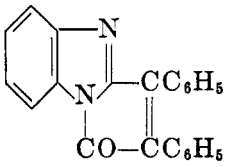


XCIV

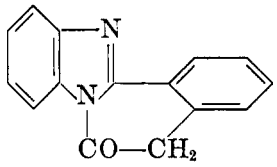


XCV

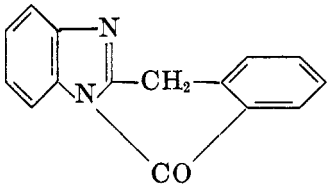
By the use of diphenylmaleic anhydride (84), homophthalic acid anhydride (85), and diphenic anhydride (86) the corresponding compounds XCVI, XCVII (or XCVIIa), and XCVIII, respectively, may be prepared.



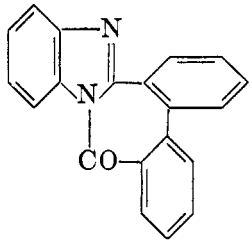
XCVI



XCVII

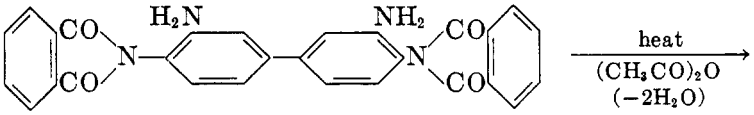


XCVIIa

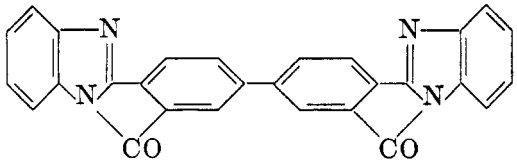


XCVIII

By heating the diphthalimide XCIX with acetic anhydride Crippa and Galimerti (168) have prepared the diphenyl derivative (C):

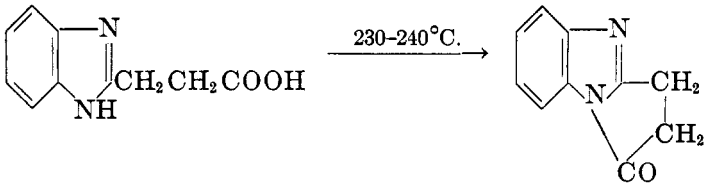


XCIX



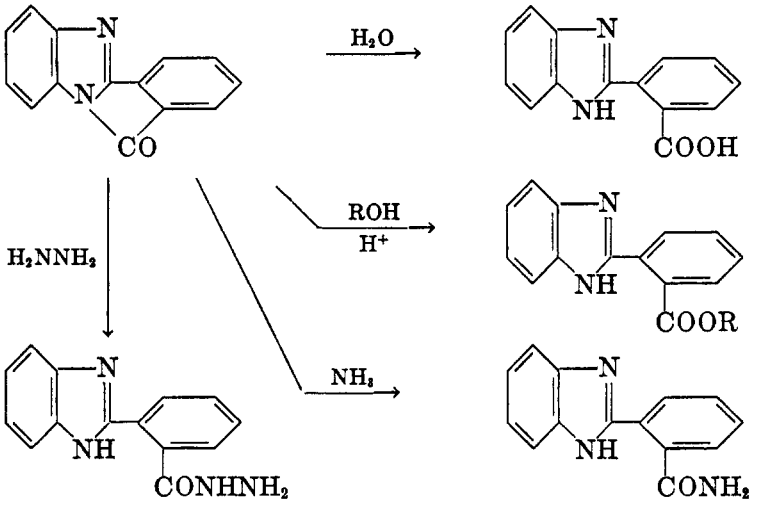
C

β-(2-Benzimidazole)propionic acid also undergoes lactam formation readily [e.g., by heating to 230–240°C. (503)] to give *o*-propionylene-1,2-benzimidazole:

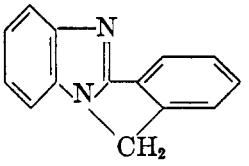


o-Benzoylene-2,1-benzimidazole and its derivatives and the compounds discussed above which are structurally related to *o*-benzoylene-2,1-benzimidazole

possess the normal reactions of a lactam ring. The amide linkage may be hydrolyzed with either alkali or acid. Alcoholysis leads to esters through cleavage of the lactam ring and treatment with ammonia, amines, and hydrazines leads to amides and hydrazides (83, 87, 503, 642, 713).

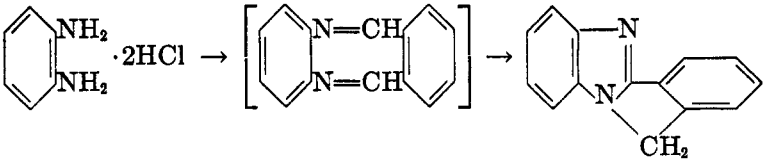


o-Benzylene-2,1-benzimidazole possesses the structure indicated by CI:

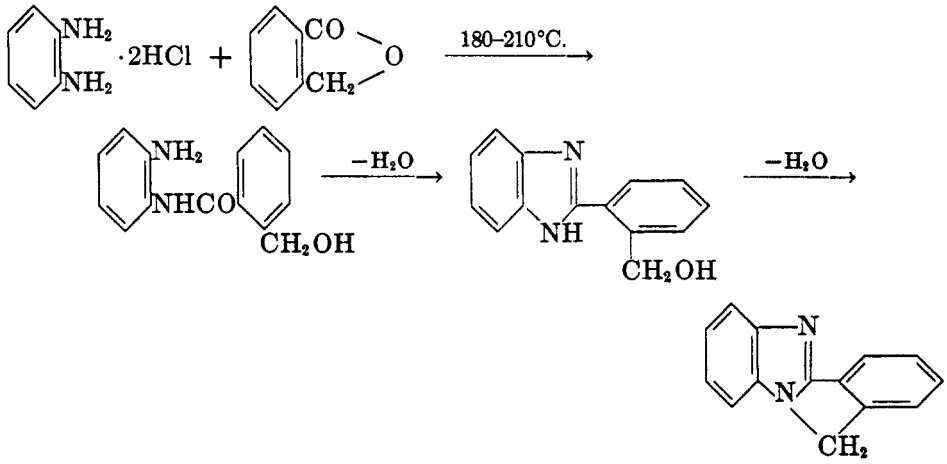


CI

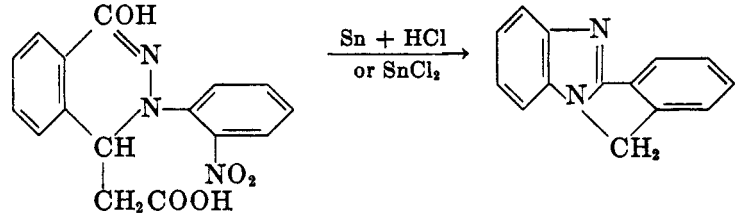
The synthesis of this compound was first reported by Thiele and Falk (714) from the reaction between *o*-phenylenediamine dihydrochloride and phthalaldehyde:



o-Benzylene-2,1-benzimidazole was reported to be a colorless compound melting at 210°C. (714). The reaction of phthalide and *o*-phenylenediamine hydrochloride also gives the same compound in about 80 per cent yield (101), the melting point of this compound checking that reported by Thiele and Falk:

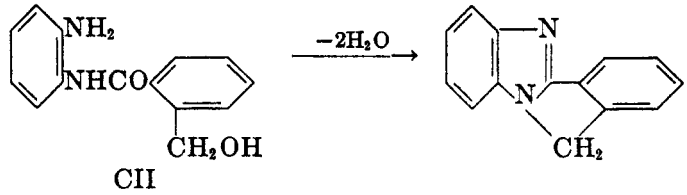


The preparation of *o*-benzylene-1,2-benzimidazole (and its 5-chloro derivative) is reported also from a dihydrophthalazine derivative (637):



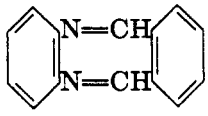
The melting point for this preparation also checks that reported by Thiele and Falk.

However, Betrabet and Chakravarti (74) have synthesized a compound which they claim to be *o*-benzylenebenzimidazole. These authors condensed phthalide and *o*-phenylenediamine in cold absolute ethanol and obtained *o*-hydroxymethyl-*o'*-aminobenzanilide (CII). Dehydration of this compound with acetic anhydride or by fusion gave a compound which these authors claim melts at 185°C.



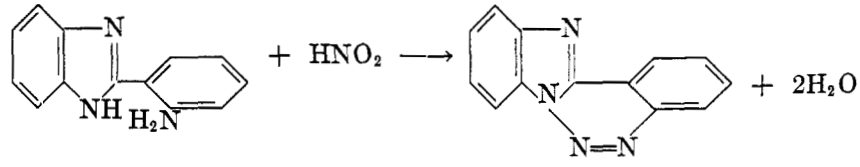
CII

These authors claim that the compound obtained by Thiele and Falk was in reality the Schiff base.



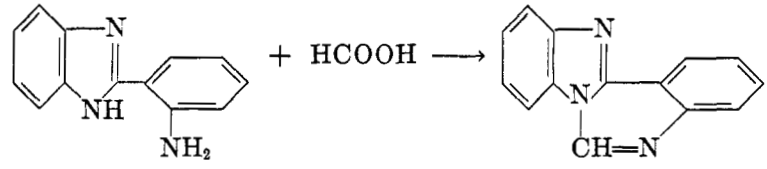
In *Beilstein* the compound prepared by Thiele and Falk is indeed represented as the Schiff base and for the sake of consistency it is represented as such throughout the present review. However, it would appear that the evidence is strong also for the *o*-benzylene-2,1-benzimidazole structure for Thiele and Falk's compound. The issue might be settled by the reduction of *o*-benzoylene-2,1-benzimidazole to *o*-benzylene-2,1-benzimidazole, possibly through the use of lithium aluminum hydride.

2-(*o*-Aminophenyl)benzimidazole on treatment with sodium nitrite and hydrochloric acid gives a quantitative yield of a tetra cyclic compound (545):

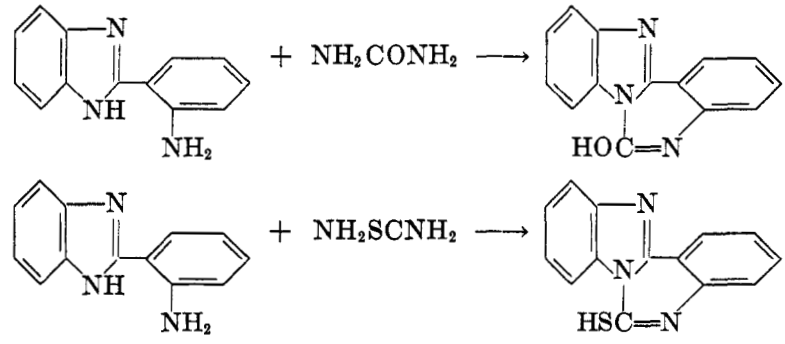


Amyl nitrite in neutral solution gives the same product.

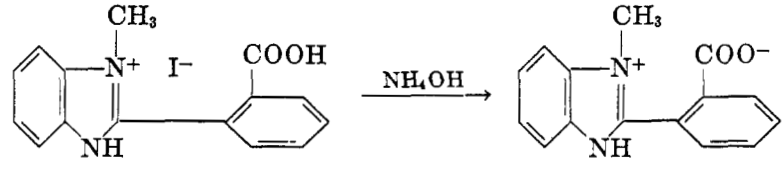
2-(*o*-Aminophenyl)benzimidazole reacts also with formic acid or formamide to give a tetracyclic compound (546):



2-(*o*-Aminophenyl)benzimidazole on treatment with urea and thiourea gives tetracyclic compounds (547):

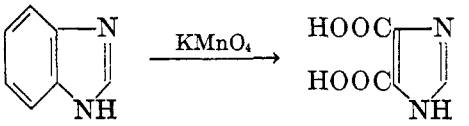


Treatment of *o*-(2-benzimidazole)benzoic acid methiodide with ammonium hydroxide or sodium acetate solution yields a betaine (646):



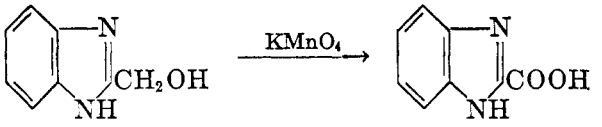
8. Oxidation

Benzimidazoles are stable to oxidation (34). By very vigorous conditions of oxidation (potassium permanganate in hot alkaline solution) it is possible to partially oxidize benzimidazole to obtain a small amount of imidazoledicarboxylic acid (40).



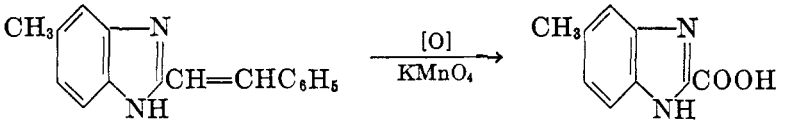
Because of the stability of the benzimidazole ring to oxidation it is possible to oxidize substituent groups without affecting the ring. By the oxidation of substituent groups a variety of benzimidazolecarboxylic acids have been prepared.

2-Benzimidazolecarboxylic acid may be conveniently prepared in good yield by the oxidation of 2-hydroxymethylbenzimidazole (166), which may be prepared by the action of glycolic acid on *o*-phenylenediamine.

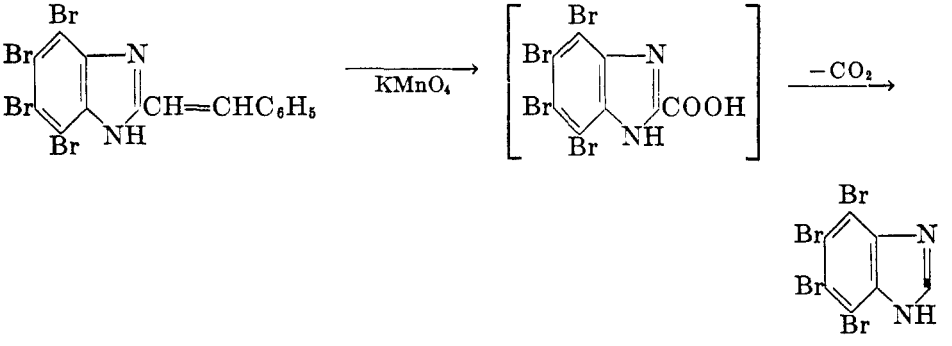


5(or 6)-Methyl-2-benzimidazolecarboxylic acid has been prepared in an analogous manner from 5(or 6)-methyl-2-hydroxymethylbenzimidazole (97).

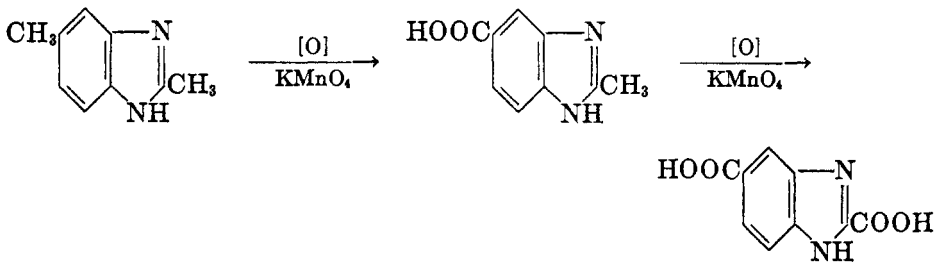
2-Benzimidazolecarboxylic acids may be obtained also by the oxidation of 2-styrylbenzimidazoles with potassium permanganate in the cold (38):



In some cases the acid obtained may immediately undergo decarboxylation under the conditions of the reaction so that the final product obtained is the benzimidazole (30):

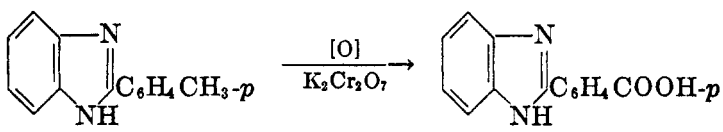


2-Methylbenzimidazoles and benzimidazoles containing a sugar residue in the 2-position (353) may be oxidized to 2-benzimidazolecarboxylic acids. 2,5(or 2,6)-Dimethylbenzimidazole is oxidized first at the 5(or 6)-methyl group and finally at the 2-methyl group to give 2,5(or 2,6)-benzimidazoledicarboxylic acid (37):

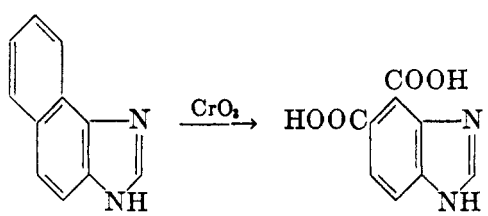


5(or 6)-Methylbenzimidazole gives 5(or 6)-benzimidazolecarboxylic acid on oxidation. 5(or 6)-Methyl-1-benzyl-2-phenylbenzimidazole is readily oxidized to 1-benzyl-2-phenyl-5(or 6)-benzimidazolecarboxylic acid (449).

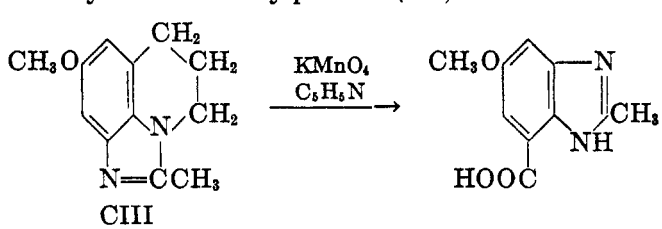
2-*p*-Tolylbenzimidazole on heating with potassium dichromate in a mixture of acetic acid and sulfuric acid is oxidized at the methyl group (128, 346, 351, 702):



Oxidation of naphthimidazole with chromic acid in acetic acid gives 4,5-benzimidazoledicarboxylic acid (206):

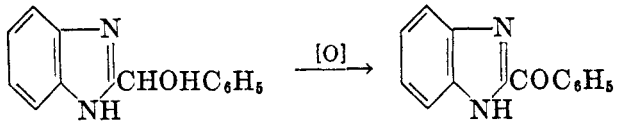


Oxidation of the imidazole CIII gives 2-methyl-5-methoxy-7-benzimidazolecarboxylic acid in 70 per cent yield with a small amount of 5-methoxy-2,7-benzimidazoledicarboxylic acid as a by-product (189).



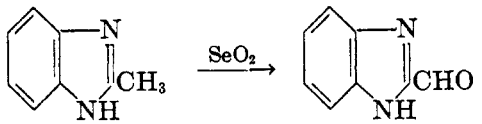
2,5(or 2,6)-Benzimidazoledicarboxylic acid has been prepared by treatment of a mixture of 2,3-diaminobenzoic acid and maltose (or lactose) with potassium permanganate (653).

2-Benzoylbenzimidazole may be prepared by the oxidation of 2-(α-hydroxybenzyl)benzimidazole with chromic acid in refluxing acetic acid (97):



5(or 6)-Methyl-2-benzoylbenzimidazole has been prepared in an analogous manner (98).

2-Benzimidazolealdehyde may be prepared by treatment of 2-methylbenzimidazole with selenium dioxide (376):

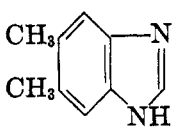


This procedure is applicable also to the preparation of 1-substituted 2-benzimidazolealdehydes (376). 2-Benzimidazolealdehyde has been prepared also by treatment with periodic acid of benzimidazoles substituted in the 2-position with a sugar residue. A 70 per cent yield of 2-benzimidazolealdehyde has been obtained in this manner from 2-(*d*-arabo)benzimidazole (353).

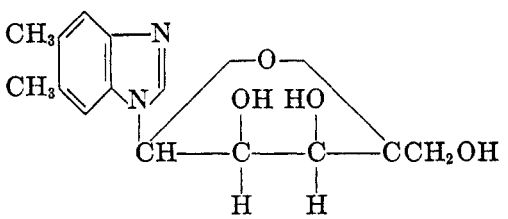
V. Natural Products Containing the Benzimidazole Nucleus

The benzimidazole nucleus does not appear to occur very widespread in nature. However, very recently the 5,6-dimethylbenzimidazole moiety has been shown to be part of the structure of vitamin B_{12}.

Vitamin B_{12} on acid hydrolysis leads to the formation of three closely related substances designated *components* α, β, and γ (68, 131, 132). *Component* γ is 5,6-dimethylbenzimidazole (CIV) (122, 123). *Component* β is 5,6-dimethylbenzimidazole-1-α-D-ribofuranoside (CV) (121).



CIV

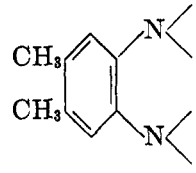


CV

The *α-component* is probably a phosphorylated derivative of CV, since the *α-component* on acid hydrolysis yields the *β-component* and phosphate (164). The phosphate moiety is undoubtedly attached to either C_2 or C_3 in the sugar residue

(131). A "ninhydrin-reacting" fragment is also released from vitamin B_{12} during hydrolysis (190). This has been identified as 1-amino-2-propanol (613, 756).

Of interest is the fact that the 1,2-diamino-4,5-dimethylbenzene moiety,

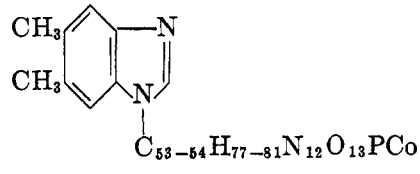


appears in riboflavin as well as in 5,6-dimethylbenzimidazole and vitamin B_{12}.

Vitamin B_{12} contains also one cyano group bound coördinatively to the cobalt atom present (125). Vitamin B_{12a} does not contain this cyano group. However, addition of cyanide ions to a solution of vitamin B_{12a} yields vitamin B_{12} (399).

Vitamin B_{12b}[6] (126) and vitamin B_{12c} (131, 132) are also closely related structurally to vitamin B_{12}. Vitamin B_{12c} on acid hydrolysis yields the same components (α-, β-, and γ-components) obtained from vitamin B_{12} (131, 132).

On the basis of available evidence, vitamin B_{12} has been assigned (123) the partial formula:



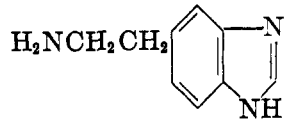
$$C_{53-54}H_{77-81}N_{12}O_{13}PCo$$

VI. Biological Action of Benzimidazoles

Benzimidazole and a number of derivatives of benzimidazole possess a variety of biological actions.

Benzimidazole, 2-methylbenzimidazole, and 2-phenylbenzimidazole have been studied pharmacologically by Auverman (14). Benzimidazole is relatively nontoxic and has little effect on the blood pressure.

Because of their relation to histamine, a number of β-aminoethyl derivatives of benzimidazole have been studied. 5(or 6)-β-Aminoethylbenzimidazole



and 2-methyl-5(or 6)-β-aminoethylbenzimidazole are said to cause a rise in blood pressure (481). 2-β-Aminoethylbenzimidazole dihydrochloride is stated to exhibit no pressor action even in high doses (144) and has no histamine-like activity on the isolated guinea-pig ileum (454).

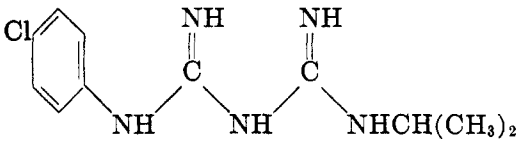
A large number of benzimidazole derivatives are reported to possess trypanosomicidal and spirocheticidal action and are active against diseases caused by

[6] *Note added in proof:* It has recently been shown (Kaczka, E. A., *et al.*: J. Am. Chem. Soc. **73**, 335 (1951)) that vitamin B_{12b} is identical with vitamin B_{12a}.

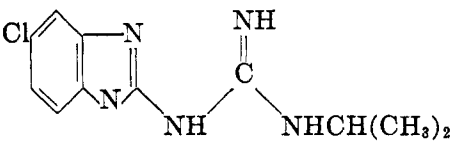
protozoa. These compounds in most cases are derivatives of 2(3*H*)-benzimidazolethione or 2(3*H*)-benzimidazolone containing an arseno, arsonic acid, or arsine oxide grouping on the benzene portion of the benzimidazole ring. 2(3*H*)-Benzimidazolonestibonic acid derivatives are also reported to be useful for the treatment of diseases caused by protozoa.

A number of benzimidazoles have been prepared and tested as antimalarials. In large part these have been benzimidazoles containing a diethylaminoalkyl grouping in the 1-position with other substituent groups in other positions of the benzimidazole ring (156, 416, 488, 489, 554, 669). Almost without exception, these compounds are without antimalarial activity. 2-Diethylaminomethyl-5(or 6)-chlorobenzimidazole and 2-piperidinomethyl-5(or 6)-chlorobenzimidazole also possess no antimalarial activity (301).

A number of benzimidazoles related to the active antimalarial Paludrine (CVI) have been prepared (1, 414). These may be looked upon as closed-ring analogs of Paludrine.

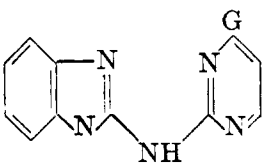


CVI



CVII

The closed-ring analog (CVII) of Paludrine itself as well as other compounds of this general type are without activity or possess only slight activity. A number of compounds closely related to CVII and possessing the general structure



(where G = dialkylaminoalkyl group) have been prepared (134, 135), and are claimed to be useful as antimalarials.

β-Benzimidazolylethylamine, 2-benzimidazolepropionic acid, 5-ethoxybenzimidazole-2-propionic acid, and 5-ethoxybenzimidazolylethylamine have been prepared also for testing for antimalarial activity (144).

A number of benzimidazoles have been prepared and tested as local anesthetics. 2-Methyl-5(or 6)-ethoxybenzimidazole is reported to have no local anesthetic activity (158). A number of 2-alkylaminomethylbenzimidazoles (109) and 2-(α-alkylaminoethyl)benzimidazoles (634) have been prepared, also. 2-

Diethylaminopropyl-5(or 6)-phenoxybenzimidazole is reported to be a local anesthetic (619).

2-Ethoxymethylbenzimidazole, 5-ethoxy-2-ethoxymethylbenzimidazole, 2-phenoxymethylbenzimidazole, and 5-ethoxy-2-phenoxymethylbenzimidazole have antipyretic activity (67).

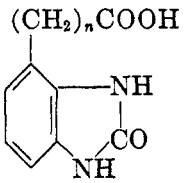
1-Dimethylaminoethylbenzimidazole and several related compounds containing substituent groups in the 2-position of the benzimidazole ring were found to possess only slight antihistaminic activity (763).

Benzimidazole shows anticonvulsant activity when administered in rather large doses (138, 720). *N*-Benzoylbenzimidazole shows only a trace of anticonvulsant activity, while 2-aminobenzimidazole is devoid of activity (138).

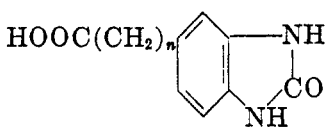
A number of 5-benzimidazolesulfonamides have been prepared (5, 6). No mention of activity is made with respect to these compounds. 2-(Benzenesulfonamido)benzimidazole, 2-(*m*-nitrobenzenesulfonamido)benzimidazole, 2-(*m*-aminobenzenesulfonamido)benzimidazole, and 2-(*p*-aminobenzenesulfonamido)-benzimidazole have been prepared (618). *N*-Sulfanilyl-4-aminobenzimidazole has antibacterial activity against *Pseudomonas aeruginosa* (484). 2-Benzimidazolesulfonamide is a carbonic anhydrase inhibitor (900, 901).

A number of benzimidazoles have been tested for goitrogenic activity (140, 487, 624, 697, 753). In the main, these compounds are derivatives of 2(3*H*)-benzimidazolethione. 2(3*H*)-Benzimidazolethione itself is markedly goitrogenic.

2(3*H*)-Benzimidazolonecarboxylic acids of the type of CVIII and CIX,

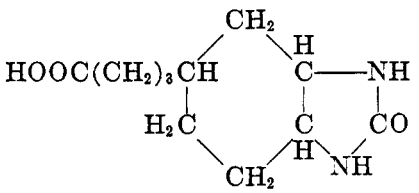


CVIII



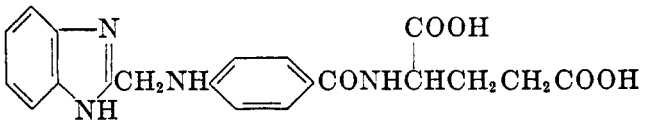
CIX

(where $n = 0, 3, 4$), as well as the corresponding hexahydro derivatives obtained by reduction of the benzene nucleus in these compounds, have been investigated for antibiotic activity (21, 22, 23, 129, 155, 191, 193, 765). A number of these compounds are reported to have bacteriostatic properties (155). Octahydro-2-oxo-5-benzimidazolebutyric acid inhibits the stimulating effect of *dl*-oxybiotin in *Lactobacillus arabinosus*



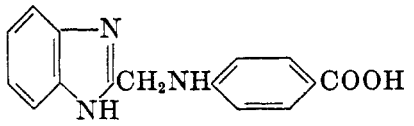
whereas stimulation due to *d*-biotin is virtually unaffected (21). This compound and several other compounds in this series possess an affinity for Avidin (765).

Several benzimidazole analogs of pteroylglutamic acid (folic acid) have been prepared in which the pterine ring is replaced by a benzimidazole ring. The compound CX,



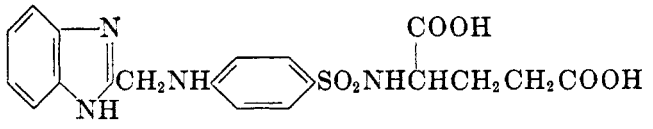
CX

which is the benzimidazole analog of pteroylglutamic acid, and CXI,



CXI

the benzimidazole analog of pteroic acid, have been prepared (180, 415, 417). CX has a low order of inhibitory activity against *Streptococcus faecalis* R. and *Lactobacillus casei*. The 5-chloro analog of CX has also been prepared (415). Its inhibitory power against *L. casei* is somewhat greater than that of CX (417). However, it has also been reported that CX in larger concentrations may replace folic acid as a growth factor (180). Compound CXII,



CXII

differing from CX only in the substitution of a sulfonyl group for a carbonyl group in the *p*-aminobenzoic acid moiety, has also been prepared. This compound was found to be a metabolite antagonist of pteroylglutamic acid (180). CXI when tested against *Streptococcus faecalis* R. was found to be inhibitory but less so than CX (417).

A number of 5-(2-benzimidazolylmethyl)barbituric acid derivatives have been prepared (483).

2-[Benzyl(2-chloroethyl)aminomethyl]benzimidazole has been screened against *sarcoma 180* (664).

Benzimidazole is reported to reduce skeletal muscle tone by acting on the central nervous system (281, 282), and hence is similar in its action to Myanesin. Benzimidazole is also reported (208) to have satisfactory fungicidal properties.

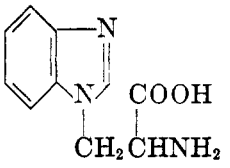
Benzimidazole inhibits the growth of several yeasts and bacteria. This action can be reversed by certain purines (762), and yeast nucleic acid (419). Benzimidazole also inhibits the production of vaccinia virus (719).

The physiological actions of 2-guanidobenzimidazole (77) and of a number of tetrahydrobenzimidazoles (305) and 1,2-disubstituted benzimidazoles (743) have

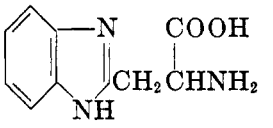
been studied. 2-Benzylhexahydrobenzimidazole has been studied for blood pressure action (304).

2-Alkylmercurimercaptobenzimidazole derivatives are claimed to be active as disinfectants (708). 4-Aminobenzimidazole is claimed as a "pharmaceutical" (329). 5,6-Dimethylbenzimidazole and salts thereof are claimed to be of value as growth-stimulating agents (124).

Mamalis, Petrom, and Sturgeon (476) have prepared several benzimidazole analogs of tryptophan of the general type:



and



These compounds show no biological activity against a variety of organisms.

VII. Uses of Benzimidazoles

A large number of patents describe benzimidazole derivatives of use in the textile industry as wetting, emulsifying, foaming, or softening agents or as dispersants for use in dyeing. In the main, these compounds are sulfonated benzimidazoles. Another use is in the treatment of fibers to improve whiteness of the undyed material or as an optical bleach.

A number of aminobenzimidazoles have been used for the preparation of sulfur and azo dyes of use in the textile industry.

Another use has been in the preparation of fluorescent dyes for use in such preparations as inks for marking clothes to be dry-cleaned. The mark becomes visible under ultraviolet light.

2-Mercaptobenzimidazole [2(3*H*)-benzimidazolethione] and several other benzimidazoles have found use in the photographing industry. These compounds reduce photographic "fog" and increase contrast and speed and hence have found use in photographic developing and fixing solutions.

2-Mercaptobenzimidazole has been found to be of value, too, as an antioxidant for rubber. This compound has been used also as a specific reagent for the detection of various metals.

Several benzimidazole derivatives have found use in the preparation of sunburn preventatives. These compounds protect the skin by absorbing ultraviolet rays.

5-Methylbenzimidazole has been used as a camphor substitute. 2-Methylbenzimidazole is said to be of value as a polymerization inhibitor and initiator in isoprene. 1-Piperidinomethylbenzimidazole has been claimed to be of value as a booster compound for use with antioxidants in rubber. A number of salts of benzimidazolesulfonic acid are said to be of value in preparations for the care of the mouth and teeth.

VIII. References

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