

reaction mixture was exposed to direct sunlight and stirred continuously throughout the course of the reaction. A deep red color appeared during the process but faded when the reaction was complete. After the mixture had cooled, crude succinimide was isolated by suction filtration and washed with carbon tetrachloride. The filtrate and washings were combined and shaken for 30 minutes with saturated sodium bicarbonate. The organic layer was separated, dried over anhydrous magnesium sulfate and the product distilled through a 10" packed column. The products were identified by the preparation of derivatives as follows.

The semicarbazone of α -bromoacetaldehyde was prepared from the acetal. Seven grams of the acetal was shaken with 20 ml. of hydrochloric acid for 48 hours and the product taken up in ether. The ether was allowed to evaporate, the residue dissolved in 20 ml. of ethanol and the semicarbazone prepared according to the directions of Shriner and Fuson.¹⁶ The product melted at 129.5–130°. A melting point of 128° has been reported.¹⁶

α -Bromopropionanilide was prepared from the product of bromination of propionaldehyde diethyl acetal. Six grams of the product was shaken with 20 ml. of hydrochloric acid for several days, the mixture extracted with ether and the ether extracts washed with saturated sodium bisulfite solution. Enough 10% sodium hydroxide was added to the bisulfite solution to make it alkaline and the aldehyde oxidized to the acid with potassium permanganate. The mixture was acidified, treated with sodium bisulfite and the acid extracted with ether. α -Bromopropionanilide, m.p. 97°, was prepared according to the directions of Shriner and Fuson.¹⁷ This corresponds to the melting point given in the literature¹⁸ for α -bromopropionanilide.

(15) R. L. Shriner and R. C. Fuson, "Identification of Organic Compounds," Second edition, John Wiley and Sons, Inc., New York, N. Y., 1940, p. 142.

(16) H. Hibbert and H. S. Hill, *THIS JOURNAL*, **45**, 734 (1923).

(17) R. L. Shriner and R. C. Fuson, *loc. cit.*, p. 132.

(18) C. A. Bischoff and P. Walden, *Ber.*, **27**, 2939 (1894).

α -Bromobutyraldehyde.—The acetal was hydrolyzed to the free aldehyde with hydrochloric acid as described earlier and isolated by means of its bisulfite addition complex. The aldehyde had n_D^{20} 1.4693 whereas 1.4683 had been reported¹⁹ for that compound.

α -Bromoisobutyric acid was prepared from the product of bromination of isobutyraldehyde diethyl acetal. Five and one-half grams of the acetal was converted to α -bromoisobutyric acid according to the directions given for the preparation of α -bromopropionic acid. The solid acid was isolated in a Buchner funnel and then recrystallized from hot water, m.p. 48–49°. A melting point of 49° is recorded for this acid.²⁰

Reaction of Benzaldehyde Diethyl Acetal with NBS.—Freshly distilled benzaldehyde diethyl acetal, 32.0 g. (0.195 mole), was caused to react with NBS under conditions identical with those described for the preparation of α -bromoacetaldehyde diethyl acetal. The product of this reaction, which gave an immediate and copious precipitate with alcoholic silver nitrate, was purified by distillation through a 10" electrically heated column packed with $3/16$ " glass helices, b.p. 40° (1.0 mm.); n_D^{20} 1.5058; d_4^{20} 1.07. The constants correspond to those of ethyl benzoate. Five ml. of this material was boiled under reflux with 40 ml. of 25% sodium hydroxide for 1 hour. This solution was subjected to distillation until 10 ml. of distillate had been collected and this distillate was saturated with potassium carbonate. The organic layer was separated and a 3,5-dinitrobenzoate prepared according to the directions of Shriner and Fuson.²¹ The ethyl 3,5-dinitrobenzoate melted at 92–93°. The residue in the still pot was made acid to litmus with dilute phosphoric acid, the precipitate isolated by filtration and recrystallized from hot water, m.p. 120–121°.

(19) A. Kirrmann, *Compt. rend.*, **184**, 525 (1927).

(20) W. Markownikoff, *Ann.*, **153**, 228 (1870).

(21) R. L. Shriner and R. C. Fuson, *ref. 16*, p. 138.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

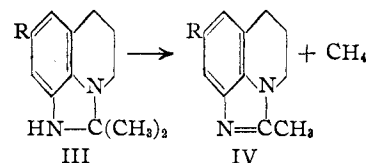
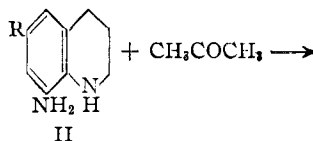
The Reaction of *o*-Phenylenediamines with Carbonyl Compounds. II. Aliphatic Ketones¹

BY ROBERT C. ELDERFIELD AND JOHN R. MCCARTHY

Reaction of *o*-phenylenediamine and its monoalkyl derivatives with ketones has been shown previously to yield benzimidazoles. This reaction, which involves cleavage of a carbon-carbon bond under relatively mild conditions has been studied further. Factors which apparently govern the elimination of alkyl groups from benzimidazolines with the production of benzimidazoles are discussed. The bearing of these observations on previously reported reactions of *o*-phenylenediamine with ketones is also discussed.

In a preceding paper² it was shown that direct heating of *o*-phenylenediamine (I), or a mono-N-alkyl derivative of *o*-phenylenediamine with aldehydes or ketones results in the formation of derivatives of benzimidazole which arise from degradation of an intermediate imidazoline as illustrated by II-IV.

Although the elimination of a fragment of a carbonyl compound by cleavage of a carbon-carbon bond to form an azomethine linkage is a fairly common reaction, factors which govern such degradations have, in general, been subordinated to over-all synthetic considerations. An example may be found in Riehm's synthesis of 2,4-dimethylquinoline³ from the reaction of aniline with acetone or



mesityl oxide. Methane is evolved during the course of the reaction. Knoevenagel and Bahr,⁴ Reddelien and Thurm,⁵ and Craig⁶ have advanced evidence that the reaction proceeds through 2,2,4-trimethyl-1,2-dihydroquinoline.

(4) Knoevenagel and Bahr, *ibid.*, **55**, 1916 (1922).

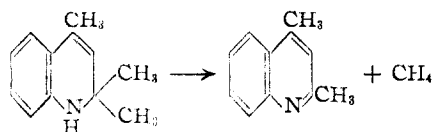
(5) Reddelien and Thurm, *ibid.*, **65**, 1511 (1932).

(6) Craig, *THIS JOURNAL*, **60**, 1458 (1938).

(1) This paper comprises a dissertation submitted by John R. McCarthy in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

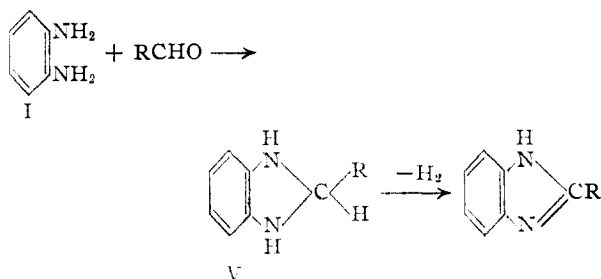
(2) Elderfield and Kreysa, *THIS JOURNAL*, **70**, 44 (1948).

(3) Engler and Riehm, *Ber.*, **18**, 2245 (1885).

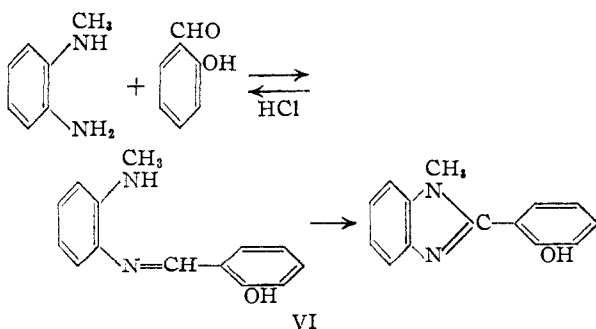


The only examples of this type of reaction known to us in which preferential rupture of a carbon-carbon bond occurs, if opportunity presents itself, are found in reactions involving cleavage of 2,2-disubstituted-1,2-dihydroquinolines. Thus, when the "anils" of methyl ethyl ketone and acetophenone are heated, substituted quinolines are formed by the loss of ethane and benzene, respectively.^{6,7}

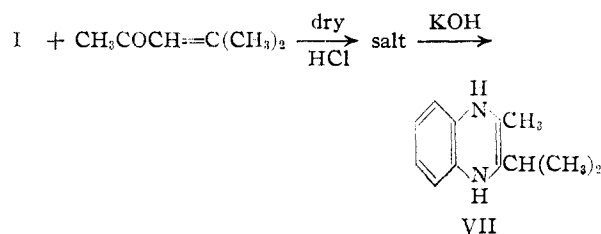
Many instances may be found in the literature in which an azomethine linkage is set up by loss of hydrogen. Ladenburg's^{8,9} synthesis of benzimidazoles from I and the suggested routes for this reaction are pertinent to the present discussion. Hinsberg¹⁰ considered that the reaction proceeded through an unstable benzimidazoline by an oxidative loss of hydrogen with reduction of a molecule of the aldehyde.



O. Fischer¹¹ extended Ladenburg's method to include the preparation of 1,2-disubstituted benzimidazoles and suggested that the reaction proceeded through an intermediate Schiff base (VI) on the basis of the reconversion of the intermediate to its original components when it was refluxed with acid. Fischer's interpretation is also favored by Wiedenhagen.⁹

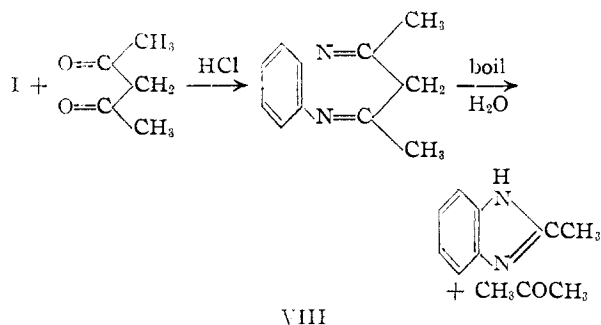


Only two references pertinent to the reaction of simple ketones with derivatives of I have been found. In neither has the formation of an imidazole been described. Ekeley and Wells¹² have reported the alleged preparation of 1,4-dihydroquinoxalines (VII) from I and acetone or mesityl oxide.



Barber and Wragg¹³ obtained the imidazoline, III, from acetone and 6-methoxy-8-amino-1,2,3,4-tetrahydroquinoline. The imidazoline structure was favored over the alternate Schiff base because of the failure of III to hydrogenate over platinum oxide. This conclusion is supported by ultraviolet absorption data.²

Benzimidazoles may be prepared from I and diketones by rupture of carbon-carbon bonds. Thiele and Steimmig¹⁴ obtained 2-methylbenzimidazole from I and acetylacetone, presumably through the seven-membered intermediate (VIII).



Brand and Wild¹⁵ obtained 1,2-diphenylbenzimidazole from *o*-aminodiphenylamine and benzil. Several instances of the formation of benzimidazoles from *o*-phenylenediamine derivatives and acetoacetic esters may be found.^{16,17,18} Sexton¹⁷ suggests a seven-membered intermediate analogous to that of Thiele and Steimmig.¹⁴

In the present paper we present the results of a study of the effect of varying the structure of the ketone and of the aromatic *o*-diamine on the course of the reaction by which benzimidazoles are formed from these reactants.

The reaction of an *o*-phenylenediamine derivative with a lower aliphatic ketone can be studied under conditions which permit good correlation of the effects of structural changes of the reactants on its course. When the over-all reaction is formulated as follows, the intermediate imidazoline (IX) can be isolated. Thermal decomposition of IX results in the elimination of either R' or R'' as hydrocarbon, and, since R'H or R''H are gases when lower ketones are used, a convenient eudiometric method for determining both the minimum temperature at which evolution of hydrocarbon occurs and the rate at which such evolution takes place is at hand. Further, by analysis of the evolved gases

(7) German Patent 363,582 [Friedländer, 14, 520].

(8) Ladenburg, *Ber.*, 11, 1648 (1878).

(9) Wiedenhagen, *ibid.*, 69, 2263 (1936).

(10) Hinsberg, *ibid.*, 20, 1585 (1887).

(11) O. Fischer, *ibid.*, 25, 2826 (1892).

(12) Ekeley and Wells, *ibid.*, 38, 2259 (1905); 39, 1646 (1906).

(13) Barber and Wragg, *J. Chem. Soc.*, 610 (1946).

(14) Thiele and Steimmig, *Ber.*, 40, 955 (1907).

(15) Brand and Wild, *ibid.*, 56, 105 (1923).

(16) Hazlewood, Hughes and Lions, *J. Proc. Roy. Soc. N. S. Wales*, 71, 467 (1937-1938) [C.A., 33, 610 (1939)].

(17) Sexton, *J. Chem. Soc.*, 303 (1942).

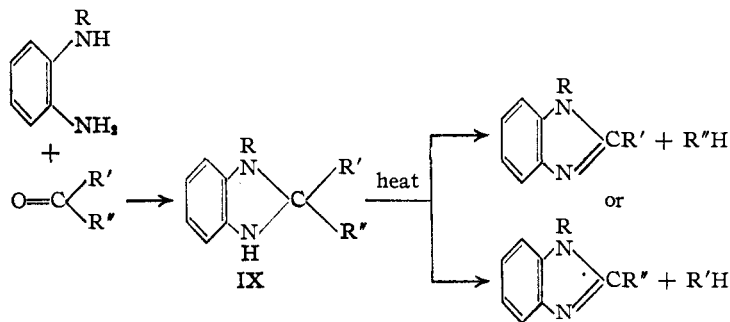
(18) Baxter and Spring, *ibid.*, 229 (1945).

TABLE I
THE REACTION OF *o*-PHENYLENEDIAMINE AND ITS DERIVATIVES WITH KETONES

Diamine	Ketone	2-Substituent of resulting benzimidazole	Hydrocarbon liberated	Init. gas evolution temp. (°C. ± 8°)	
<i>o</i> -Phenylene-	Acetone	Methyl	Methane	260	
	Mesityl oxide	Methyl	Methane	195	
	Methyl ethyl	Methyl	Ethane	235	
	<i>n</i> -Propyl isopropyl	<i>n</i> -Propyl	Gas not detmd.	200	
	Di- <i>n</i> -propyl	<i>n</i> -Propyl	Propane	235	
	Methyl <i>n</i> -propyl	Methyl + propyl	Propane	230	
	Methyl isopropyl	Methyl	Propane	205	
	Methyl <i>t</i> -butyl	Methyl	Isobutane	185	
	Methyl isobutyl	Methyl	Isobutane	225	
	Methyl cyclopropyl	Cyclopropyl	Methane	245	
	Methyl vinyl	Not determined	Methane	265	
	Dibenzyl	Benzyl	Toluene	250	
	Methyl benzyl	Methyl + benzyl ^a	Methane + toluene	225	
	Benzophenone	Phenyl	Not detmd.	190	
	N-Monomethyl- <i>o</i> -phenylene-	Acetone	Methyl	Methane	245
		Di- <i>n</i> -propyl	<i>n</i> -Propyl	Propane	150
		Methyl <i>n</i> -propyl	Methyl	Propane	145
Methyl isopropyl		Methyl	Propane	110	
N-Monophenyl- <i>o</i> -phenylene-	Methyl ethyl	Methyl	Isobutane	100	
	Methyl <i>n</i> -propyl	Methyl	Gas not detmd.	245	
N,N'-Dimethyl- <i>o</i> -phenylene-	Methyl isopropyl	Not obtd.	None	...	

^a 2-Benzylbenzimidazole was reported in a preceding paper² to be the chief product of this reaction. However, when the reaction was carried out at a lower temperature in the present work, slightly more toluene than methane was eliminated.

in the mass spectrometer, an accurate determination of the amounts of R'H and R"H in the evolved gases becomes possible. Although the intermediate imidazoline was not isolated in all cases, the assumption of its formation in those instances in which it was not isolated appears to be justified.



The results of a series of such studies insofar as the nature of the hydrocarbon evolved is concerned are given in Table I. The initial gas evolution temperature given in Table I is defined as that temperature at which the intermediate imidazoline (IX) decomposes with evolution of gaseous hydrocarbon at a conveniently ascertainable minimum rate. It is reproducible to ± 8°.

The results with three ketones shown in Table I are contrary to the earlier opinion¹⁹ that the relative mass of the substituents plays a role in determining which of the two substituents in the 2 position of a 1,2-dihydro nitrogen-carbon grouping in a heterocycle is eliminated with the formation of an

azomethine linkage. Methane comprised ninety per cent. or more of the gas evolved in the reactions of methyl cyclopropyl ketone, methyl vinyl ketone, and mesityl oxide with I. In all other cases the heavier substituents appear to have been cleaved preferentially. Furthermore, the suggestion² that

the degree of substitution on one of the nitrogen atoms of the diamine might be a directing factor now appears to lack sufficient support. With all unsymmetrical ketones studied, substitution of either an alkyl or aryl group on one of the nitrogens of *o*-phenylenediamine resulted in no change in the substituent appearing in the 2-position of the resulting benzimidazoles as compared to the benzimidazoles arising from *o*-phenylenediamine. A more attractive generalization is that the carbon-carbon

bond which is broken is the one proceeding from the carbon atom having the greater degree of substitution.

Clearly such a generalization holds for all the unsymmetrical ketones investigated with the questionable exception of methyl cyclopropyl ketone. It may be argued that the cyclopropyl group is analogous to the vinyl group insofar as degree of substitution is concerned. Chemically, there is a close resemblance of cyclopropyl derivatives to olefins.²⁰ Although the pyrolysis residue of the reaction involving methyl vinyl ketone was an unworkable tar, the concurrent and exclusive evolution of methane probably warrants classifying both methyl

(19) Hollins, "Synthesis of Nitrogen Ring Compounds," D. Van Nostrand Co., New York, N. Y., 1924, p. 264.

(20) Gilman, "Organic Chemistry," Vol. I, John Wiley and Sons, Inc., 2nd ed., New York, N. Y., 1943, p. 101.

vinyl and methyl cyclopropyl ketones in the same category as possessing a low degree of substitution on an alpha carbon atom. In summary, one might expect the ease of elimination of a branch of an unsymmetrical ketone to decrease in the following order: *t*-butyl > isopropyl > benzyl, isobutyl, *n*-propyl, ethyl > methyl > cyclopropyl, vinyl.

The chemical evidence discussed above and presented in Table I, involving the effect of structure on the direction the reaction may follow, receives support from semi-quantitative physical measurements on the ease of reaction. The last column of Table I is presented as an indication of the facility with which a benzimidazoline degrades to a benzimidazole and a hydrocarbon. The initial gas evolution temperature apparently reflects the energy level at which the desired fission of a carbon-carbon bond occurs. Since non-reversible reactions usually follow a path requiring the least amount of energy, it seems probable that a correlation should exist between the "degree-of-substitution" arrangement of the series of radicals given above and a series based on initial gas evolution temperatures. Seemingly, this is the case, within the limit of error. Thus, in the reaction of *n*-propyl isopropyl ketone with I the isopropyl group should be ejected inasmuch as methyl *n*-propyl ketone has an initial gas evolution temperature of 230° compared to only 205° for methyl isopropyl ketone. Indeed, only 2-*n*-propylbenzimidazole was found to be produced in this reaction; an inflammable gas, presumably propane, was evolved at 200°.

The effect of substitution on one of the nitrogen atoms of the diamine does not alter the proportions of R'H or R''H which are eliminated. Introduction of a methyl group into the diamine facilitates the

elimination of hydrocarbon as evidenced by a consistent lowering of the initial gas evolution temperatures in those experiments in which *N*-methyl-*o*-phenylenediamine was used. The effect of each ketone on the ease and course of the degradation, according to the degree of substitution on the alpha carbon atom, is added to the accelerating effect of the *N*-methyl substituent. In the few instances investigated, an *N*-aryl substituent exerts no effect on the reaction and an *N,N'*-dialkyldiamine fails to undergo the reaction.

Although the relationship between initial gas evolution temperature and reaction rate is implied in the familiar van't Hoff form of the Arrhenius equation²¹ it was thought advisable to substantiate the reliance on initial gas evolution temperatures by a study of reaction rates in a few typical cases. By the use of an inert diluent, it was possible to maintain the reaction temperature during the evolution of hydrocarbon at about $\pm 1^\circ$ and the data on the rates of hydrocarbon evolution from several imidazolines are shown in Fig. 1. In Fig. 1 the concentration to which the ordinates refer represents the ratio $V - V_t/V$, where V is the total volume of gas evolved and V_t is the volume of gas liberated at any time, t . The reactions were followed to 50-75% of completion based on the amount of diamine taken. The greater slope of the curves with *N*-methyl-*o*-phenylenediamine (A,B) compared to those with *o*-phenylenediamine (C,F), despite the lower temperature of the former, is in keeping with the differences noted in initial gas evolution temperatures. Furthermore, the close proximity in slope between the *N*-phenyl-*o*-phenylenediamine (E) and *o*-phenylenediamine (F) curves is in agreement with rates deducible from their common value for the initial evolution temperature. The slightly greater slope of E is attributable to the higher temperature prevailing. Finally, the effect of substitution on the alpha carbon atom of the starting ketone again exerts an influence on reaction rate which may be inferred from consideration of the corresponding initial gas evolution temperatures (C,D,F for the unsubstituted diamine and A,B for the substituted).

The reaction of I with methyl propyl ketone was studied at two temperatures, in order to get some idea of the temperature dependence of the rates discussed above. Curves F and G of Fig. 2 show the effect of a 25° temperature difference on the rates. It therefore appears that there is little need for rigorous quantitative study to strengthen the argument.²²

The reaction under discussion is catalyzed by bases such as sodium alkoxide. No effect on the elimination of hydrocarbon other than acceleration of the reaction rate was noted when the reaction be-

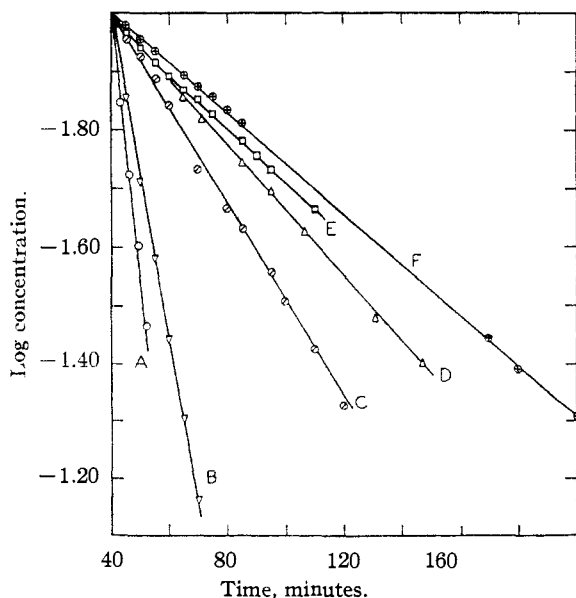


Fig. 1.—A, *N*-Methyl-*o*-phenylenediamine + methyl isopropyl ketone at 173°; B, *N*-methyl-*o*-phenylenediamine + methyl propyl ketone at 175°; C, *o*-phenylenediamine + methyl isopropyl ketone at 260°; D, *o*-phenylenediamine + methyl isobutyl ketone at 258°; E, *N*-phenyl-*o*-phenylenediamine + methyl propyl ketone at 269°; F, *o*-phenylenediamine + methyl propyl ketone at 258°.

(21) Amis, "Kinetics of Chemical Change in Solution," The Macmillan Co., New York, N. Y., 1949, p. 17.

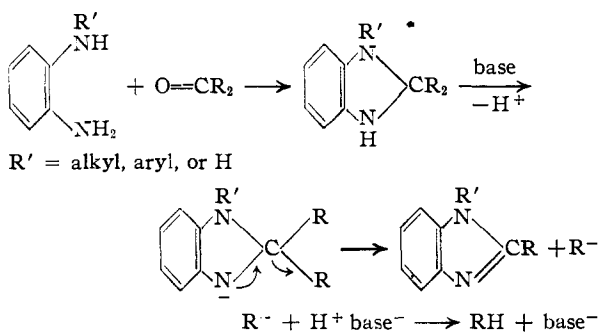
(22) The data represented in Fig. 2 lead directly to calculation of first order reaction constants. Although accurate determination of the energy of activation involved awaits more precise experimentation, the constants obtained from curves F and G of Fig. 2 are 0.010 min.⁻¹ and 0.027 min.⁻¹, respectively. From these figures an approximate value for the energy of activation in the range of 24 kcal. can be arrived at. Although this figure is at best an approximation, its low value suggests that a good portion of the driving force required for the reaction arises from the increased resonance stabilization of the amidine structure produced in the final benzimidazole.

tween equivalent amounts of *o*-phenylenediamine and methyl ethyl ketone was carried out in the presence of an equivalent amount of sodium *n*-hexylate. Curves H and J of Fig. 2 indicate the great degree of positive catalysis brought about by base despite a drop of about 100° in reaction temperature. Base catalysis by sodium alkoxides and hydroxide has been investigated on a limited scale with other reactants with resultant lowering of initial gas evolution temperatures. However, a weak base, such as dimethylaniline was without effect. A similar catalysis of the decomposition of 2,2,4-trimethyl-1,2-dihydroquinoline by sodamide has been noted by Craig.⁶

The question as to whether acid catalysis is operative in the conversion of a dihydride to an azomethine linkage cannot be answered unequivocally at this time. In the present work the reaction was not catalyzed either positively or negatively by *p*-toluenesulfonic acid. Barber and Wragg¹³ report that the imidazoline III reverted to the original ketone and diamine when attempts were made to prepare either the hydrochloride or picrate. Reddellien and Thurm⁵ state that the true anil of aniline and mesityl oxide is readily cleaved by acid into its components. On the other hand they report that 2,2,4-trimethyl-1,2-dihydroquinoline, which is analogous to the benzimidazoles here under consideration, is stable to acids. Similar "anils" have been found to degrade under acid conditions to heterocycles containing an azomethine linkage.^{4,6,23} Inasmuch as Schiff bases vary in their degree of stability to acid²⁴ it is not surprising that benzimidazoles should also exhibit variable tendencies to revert to their components. This analogy seems justified if the assumption may be made that both benzimidazoles and Schiff bases cleave in acid by similar mechanisms.

Finally, the possibility of a peroxide-catalyzed free radical decomposition²⁵ has been considered although the absence of a variety of components in the evolved gases appears to argue against such a mechanism. Addition of benzoyl peroxide to the reaction of *o*-phenylenediamine and methyl ethyl ketone produced no observable effect. We therefore reject a free radical mechanism.

Pending the accumulation of further evidence, we suggest the following sequence as offering a reasonable basis for the observed facts regarding the reaction



(23) Hinsberg and Koller, *Ber.*, **29**, 1502 (1896).

(24) Sprung, *Chem. Revs.*, **26**, 297 (1940).

(25) Waters, "The Chemistry of Free Radicals," Clarendon Press, Oxford, 1946, p. 180 ff.

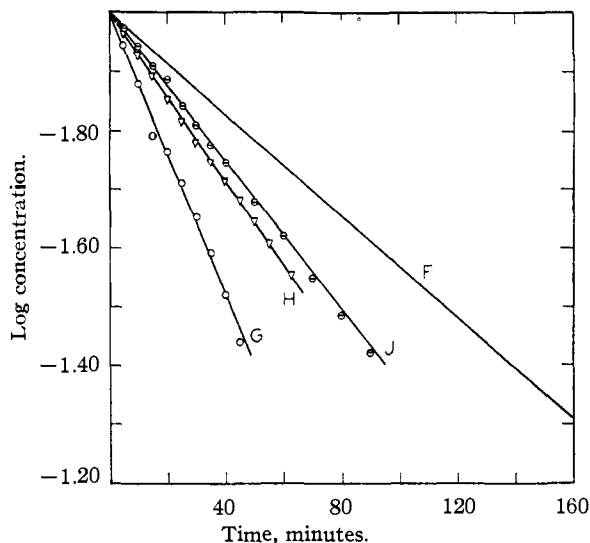


Fig. 2.—F, *o*-Phenylenediamine + methyl propyl ketone at 258° (see Fig. 1); G, same as F, at 282.5°; H, *o*-phenylenediamine + methyl ethyl ketone + base at 164°; J, same as H, at 262.5° (with base omitted).

The role of added base is obvious. In the uncatalyzed reaction, the imidazoline serves as base.

We have also studied the properties of the intermediates involved in certain of these reactions. Available evidence supports the formulation of these intermediates as imidazolines, at least in the reactions involving *o*-phenylenediamine. Ultraviolet absorption curves²⁶ for the intermediates arising from the condensation of I with mesityl oxide and methyl *n*-propyl ketone and from *N*-methyl-*o*-phenylenediamine with acetone are shown in Fig. 3. The ordinates are specific extinction coefficients rather than their conventional logarithms in order to bring out differences more sharply. The curves for all three intermediates (L, M, N) have a minimum near 292 $m\mu$ and a maximum at about 315 $m\mu$. Except for an unexplained bathochromic shift of about 20 $m\mu$, these portions of curves L, M and N parallel the minimum, maximum and drop observed in the reference curve for *o*-phenylenediamine (K). The peak near 265 $m\mu$ in curve N may be due to the fact that this intermediate is, indeed, a Schiff base.

When *o*-phenylenediamine was condensed with excess methyl *n*-propyl ketone, it was noted that more than one equivalent of water was formed. The resulting intermediate furnished analytical figures corresponding to $\text{C}_{14}\text{H}_{24}\text{N}_2$. Reduction of the intermediate over platinum oxide resulted in the uptake of one mole of hydrogen. When the intermediate was heated, the evolved gas consisted mainly of propane together with some methane and 2-methylpentene-1. The residue from the pyrolysis, after fractional recrystallization from water, yielded chiefly 2-methylbenzimidazole together with a smaller amount of 2-propylbenzimidazole. Further, methyl propyl ketone was found in the distillate after steam distillation of the pyrolysis residue. This evidence indicates that the methyl *n*-propyl ketone underwent an aldol condensation to an un-

(26) We wish to acknowledge the kind assistance of Mrs. Bella Z. Berson of these laboratories in obtaining the spectra here reported.

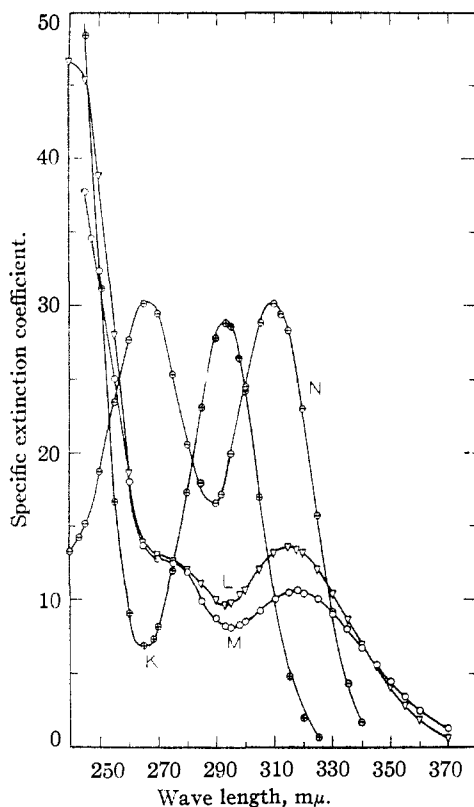
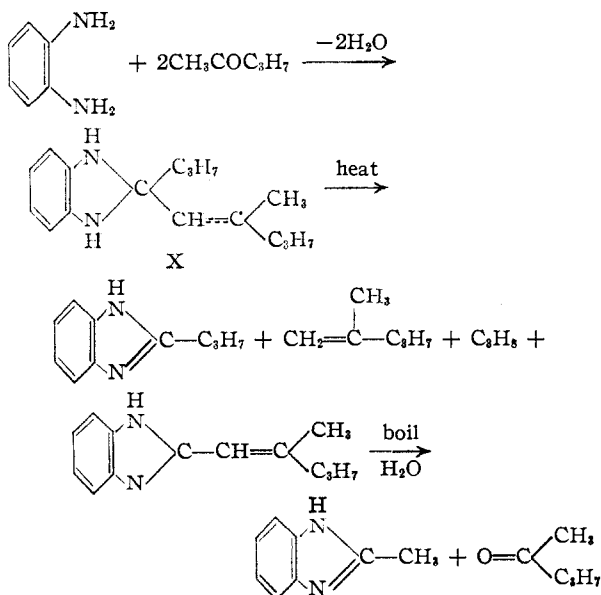


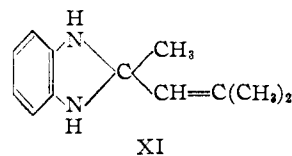
Fig. 3.—K, *o*-Phenylenediamine; L, *o*-phenylenediamine and mesityl oxide intermediate; M, *o*-phenylenediamine and methyl propyl ketone intermediate; N, N-methyl-*o*-phenylenediamine and acetone intermediate; solvent, 95% ethanol.

saturated ketone, prior to reaction with *o*-phenylenediamine. In accordance with the generalization given above relating the degree of substitution on the carbon atom attached to the 2 carbon atom of the intermediate benzimidazoline to the direction of cleavage, pyrolysis of this intermediate gave the expected degradation products. These changes may be represented as



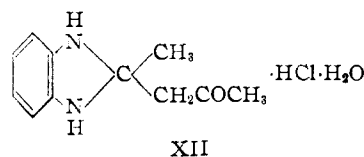
The formation of 2-methylbenzimidazole resulted from a reversed aldol condensation during the boiling of the crude pyrolysis residue with water. The somewhat resinous pyrolysis residue was recrystallized directly from water to 2-alkylbenzimidazoles without isolation of any 2-alkenylbenzimidazoles. The presence of methane in the evolved gas is probably due to the presence of an isomeric α,β -unsaturated ketone as an impurity.

These observations may offer a satisfactory explanation for the observations of Ekeley and Wells¹² who preferred a 1,4-dihydroquinoxaline structure (VII) rather than that of an imidazoline (XI) for the product resulting from the condensation of *o*-phenylenediamine with mesityl oxide



We have succeeded in degrading thermally the Ekeley and Wells intermediate to methane and a pyrolysis residue which, after recrystallization from boiling water, was identified as 2-methylbenzimidazole. No other examples of 1,4-dihydroquinoxalines have been reported, but it is likely that, through tautomerization, they would behave analogously to 1,2-dihydroquinoxalines, which have been shown to yield quinoxalines rather than benzimidazoles.²⁷

Although we have not investigated the proposed seven membered ring intermediate of Thiele and Steimmig,¹⁴ it would seem that the alternate structure (XII) should receive consideration.



Thiele and Steimmig reported the isolation of 2-methylbenzimidazole and acetone when their intermediate was heated with water.

Experimental^{28,29}

General Procedure.—The apparatus in which the preparation of the imidazolines and subsequent pyrolyses were carried out is shown in Fig. 4. The reaction vessel was a 100-ml. flask provided with a thermometer well and a gas inlet tube for introduction of the sweep gas. A Claisen adapter to which was sealed a graduated tube for measuring the amount of water removed azeotropically was attached to the flask. The center arm of the adapter was closed either with a stopper or connected with vacuum as was desired. The side arm of the adapter was connected with a reflux condenser. The exit tube at the top of the condenser led to a solid carbon dioxide (or ice) trap and thence to a 1500-ml. eudiometer provided with a leveling bulb. The eudiometer was calibrated to ≈ 1 ml. At the top of the eudiometer a capillary tube with stopcock was sealed for the removal of gas samples. The bottom of the eudiometer was provided with a mercury reservoir seal. The reaction flask was heated by a Glas-col 100-ml. mantle packed with glass wool to aid in the heat transfer (see below).

(27) Fischer, *Ber.*, **24**, 719 (1891); **26**, 192 (1893).

(28) All melting points and initial gas evolution temperatures have been corrected for stem exposure except as noted otherwise.

(29) The microanalyses were done by the Clark Microanalytical Laboratories, Urbana, Ill.

To one molecular proportion of diamine placed in the reaction flask were added three molecular proportions of ketone. The reservoir of the liquid separator was filled with ketone (11 ml.) in order to aid in azeotropic removal of water. When the ketone did not form a separable azeotrope with water, 20 ml. of benzene or a homolog thereof was substituted for the extra 11 ml. of ketone.

After sealing the system by filling the eudiometer with water approximately one liter of carbon dioxide was passed through the system through the gas sweep tube with the center arm of the Claisen adapter closed by a stopper. Sufficient heat was applied to produce gentle refluxing of the contents of the reaction flask and refluxing was continued until no more water was collected in the separator attached to the Claisen adapter—usually 5 hours. The contents of the reaction flask were cooled, the stopper of the middle neck of the Claisen adapter was removed and the system was evacuated at 1 mm. pressure until all excess ketone, or other azeotroping agent, was removed. After replacing the stopper of the Claisen adapter, the flask containing the crude intermediate was again swept with carbon dioxide, the eudiometer was refilled with water and gentle heating of the reaction flask was started, during which a slow stream of carbon dioxide was passed through the system. The volume increments of the thermally expanded gas collected in the eudiometer were plotted roughly against the temperature of the contents of the reaction flask, readings being taken at regular, frequent intervals. The temperature was increased at approximately two degrees per minute. That temperature at which a marked increase in rate of evolution of gas occurred represented the initial gas evolution temperature.

When kinetic measurements of the rate of gas evolution were desired, the above process was repeated with the addition of 20 ml. of an inert diluent to the isolated intermediate imidazoline. The diluent was chosen so that the boiling point enabled maintenance of a constant temperature convenient for a measurable rate of gas evolution. When a reasonably constant temperature had been attained, the volume of the gas evolved was plotted against time. The decomposition was continued until the rate of gas evolution became negligible. Approximately 250 ml. of carbon dioxide was then swept through the system.

The collected gas was displaced through the top of the eudiometer into a 200-ml. Hempel double bulb pipet which contained a 40% solution of potassium hydroxide. The first portions of the gas were used for flushing residual air from the connecting tubes and were discarded. After standing for 24 hours over potassium hydroxide solution to remove traces of the sweep gas, carbon dioxide, the gas was displaced from the Hempel bulbs into a 125-ml. gas sample flask, which had been previously completely evacuated except for a few grams of phosphorus pentoxide. The dried gas was allowed to expand either into a well-evacuated mass spectrometer analysis bulb or into a 100-ml. infrared cell. The gas analyses were made using either a mass spectrometer^{30,31} of the Nier type having a 60° arc with a constant magnetic field and variable voltage or a Perkin-Elmer infrared spectrometer.

The pyrolysis residue which remained in the reaction flask was chilled and usually triturated with cold absolute ether (sometimes in a solid carbon dioxide bath) to remove diluent and decomposition tars. The semi-crude residue was then recrystallized from water or from dilute alcohol using decolorizing carbon. Identification of solid products was usually made by mixture melting points with benzimidazoles synthesized for the purpose.

Since the possibility exists that faulty heat transfer from the Glas-col heating mantle to the reaction mixture may provide misleading initial decomposition temperatures, the following experiment was performed as a control.

The isolated crude intermediate benzimidazoline from the reaction of *o*-phenylenediamine with methyl *n*-propyl ketone was heated in a reaction flask in a Woods metal-bath with manual stirring of the reaction mixture. The temperature difference between the bath and the reaction mixture was about 10°. The initial gas evolution temperature was determined as described above. The results were as follows:

(30) Washburn, Wiley and Rock, *Ind. Eng. Chem., Anal. Ed.*, **15**, 541 (1943).

(31) We wish to express our indebtedness to Professor T. I. Taylor, of this department, for assistance in both the mass spectrographic and infrared analyses here reported.

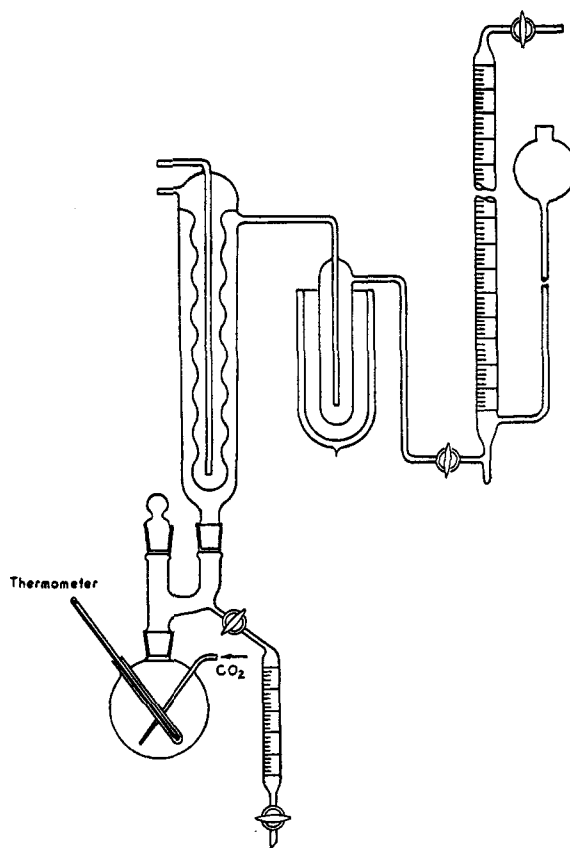


Fig. 4.—Apparatus.

with a Wood's metal bath: bath temp. 232°; initial gas evolution temp. 224°; with a Glas-col mantle: initial gas evolution temp. 230°. With methyl *t*-butyl ketone, the results were: with a Woods metal-bath: bath temp. 181°; initial gas evolution temp. 176°; with a Glas-col mantle: initial gas evolution temp. 185°.

It is therefore believed that the reported initial gas evolution temperatures reflect true values.

Reactions of *o*-Phenylenediamine (I) with Ketones.
(a) With Acetone.—Commercially available I was successively recrystallized from heptane, using decolorizing carbon, and then from water, to give white plates melting at 103–103.5°. The acetone used was distilled at 56.3–56.4° through a 15-plate Fenske column packed with glass helices. Five and four-tenths grams of the diamine, 29 g. of acetone and 20 ml. of dry benzene were heated for 48 hours as described in the above general procedure. The initial gas evolution temperature was 260°. Since a kinetic measurement of the rate of degradation was not desired, no diluent was used. Heating was carried out at 270–280° for 2 hours, during which time approximately 600 ml. of gas was evolved. Infrared analysis of the treated gas (potassium hydroxide removal of carbon dioxide followed by drying over phosphorus pentoxide) gave absorption peaks approximately at the following wave numbers: 4250, 3000, 1350 and 1290 cm^{-1} . The mass spectrogram obtained was in very close agreement with that published for pure methane.³² Successive recrystallizations from water of the heated residue gave 1.5 g. of white leaflets melting at 174.5–175.5°. Mixture melting points with authentic 2-methylbenzimidazole gave no depression.

Procedure B.—Ten and eight-tenths grams of I was refluxed for 6 hours with 125 ml. of acetone and the condensate was passed through a Soxhlet extractor containing C.P. granular anhydrous calcium chloride in a parchment thimble. After standing for one day in an ice-box, 8.5 g. of brown solid separated from the reaction mixture. Recrystallization of the brown crude reaction mixture from ligroin with decolorizing carbon yielded white crystals, m.p. 124.5–125°, which

(32) National Bureau of Standards, A. P. I. Research Project 44, Washington, Serial No. 528 (1946).

gave analytical figures corresponding to those demanded by 2-methyl-2-isobutenylbenzimidazoline.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 76.5; H, 8.5; N, 14.9. Found: C, 76.2; H, 8.2; N, 14.8.

b. With Mesityl Oxide. Procedure A.—The mesityl oxide was distilled through a 6-plate Fenske column packed with glass helices and collected over the range 127.0–127.3°. After refluxing a mixture of 10.8 g. of I and 29.4 g. of mesityl oxide for 4 hours, approximately 1.5 g. of water was azeotropically removed. The intermediate was isolated after the reaction mixture remained overnight in an ice-box. Recrystallization from ligroin with decolorizing carbon gave white crystals, m.p. 124.5–125°. The substance was identified by mixture melting points with the compound $C_{12}H_{16}N_2$ obtained from the preceding condensation of I with acetone. On pyrolysis of this imidazoline, the initial evolution temperature was 195°. Continued heating to 280° caused evolution of a gas which gave the same infrared spectrogram as methane.³² Analysis of the gas by the mass spectrometer confirmed the presence of slightly more than 90% of methane. Recrystallization of the pyrolysis residue from water gave 4.3 g. of white crystals, m.p., 174–175°. Mixture melting points with authentic 2-methylbenzimidazole³³ showed no depression.

Procedure B.—The procedure of Ekeley and Wells¹² was followed. The free base obtained melted at 124–124.5°. Mixture m.p.'s of this base with the benzimidazoline of m.p. 125° obtained in the above Procedure A showed no depression. Pyrolysis of Ekeley and Wells' base gave the same products obtained in Procedure A.

c. With Methyl Ethyl Ketone.—Five and four-tenths grams of I, 14.5 g. of methyl ethyl ketone (distilled at 79–79.5°), and 11 ml. of benzene were refluxed for 5 hours during which the water formed was removed azeotropically. The general procedure was followed. The initial gas evolution temperature was 235°. Diphenyl ether was used as a diluent for a kinetic investigation of the rate of thermal degradation at 262.5° ($\pm 0.8^\circ$). The results are recorded by curve J, Fig. 2. Approximately 600 ml. of gas was evolved which, on analysis by the mass spectrometer, consisted of approximately 95% ethane and less than 5% methane. On working up the contents of the pyrolysis flask, 0.6 g. of white needles was obtained from hot water. The compound, m.p. 175–176°, was identified by mixture m.p.'s with authentic 2-methylbenzimidazole. It is reported that 2-ethylbenzimidazole, m.p. 174.5°, may depress the m.p. of 2-methylbenzimidazole to a temperature as low as 157–158°.³⁴

Base catalysis was noted on repetition of the above procedure when a solution of 1.2 g. of sodium dissolved in 25 ml. of *n*-hexyl alcohol was added to the intermediate prior to pyrolysis. No diluent other than the hexyl alcohol was used. A kinetic study of the rate of degradation was carried out at 164° ($\pm 0.2^\circ$). The results are shown by curve H, Fig. 2. The pyrolysis residue, on trituration with ether and recrystallization from water, gave 0.2 g. of 2-methylbenzimidazole as shown by mixture m.p.'s.

d. With Methyl *n*-Propyl Ketone.—A mixture of 16.2 g. of I, 26 g. of methyl *n*-propyl ketone and 11 ml. of dry benzene was refluxed for 18 hours as described in the gen-

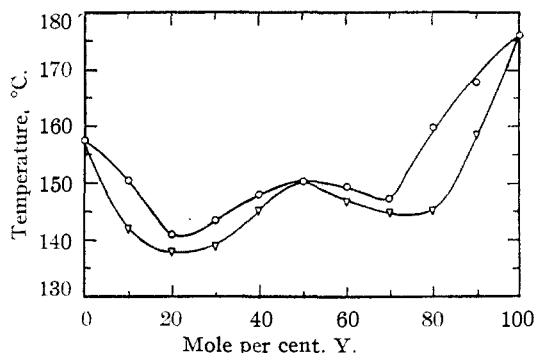


Fig. 5.—X, 2-*n*-Propylbenzimidazole; Y, 2-methylbenzimidazole.

(33) Ladenburg, *Ber.*, **8**, 677 (1875).

(34) Pool, Harwood and Ralston, *THIS JOURNAL*, **59**, 178 (1937).

eral procedure during which approximately 5 g. of water was removed. Volatile material was removed at water-pump pressure below 190°. The residual oily intermediate benzimidazoline was distilled three times through a Vigreux column yielding 16 g. of light yellow oil, b.p. 141–142° at 0.6 mm.; n_D^{25} 1.5550. A duplicate run gave an oil, b.p. 161–162° at 2 mm. with the same index of refraction. Both samples were submitted for analysis. The analytical figures agree with the structure, X, assigned to this product.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 78.6; H, 9.9; N, 11.5. Found: C, 78.6, 78.7; H, 9.9, 9.6; N, 11.8, 11.8.

The presence of one double bond in X was demonstrated by absorption of one equivalent of hydrogen in 20 minutes when X was reduced catalytically in alcohol over platinum oxide.

Pyrolysis of 10 g. of the isolated intermediate evolved over 300 ml. of gas which was analyzed by the infrared spectrometer. Peaks observed at approximately the following wave numbers were found: 4400, 4200, 3900, 3000, 1470, 1390, 1160, 1060, 930, 910 and 750 cm^{-1} . These are in good agreement with the published spectrogram for propane.³⁵ The gas liberated by pyrolysis of the semi-purified intermediate benzimidazoline obtained in a similar manner was analyzed by the mass spectrometer and consisted of 80% propane, 5% methane and presumably air.

In several repetitions of the above procedure, the initial gas evolution temperature varied between 225–240° with the average being 230°. The rate of gas evolution was measured at 258° ($\pm 0.7^\circ$) by use of 20 ml. of diphenyl ether as diluent and at 282.5° ($\pm 0.5^\circ$) by use of 20 ml. of ethyl α -naphthyl ether (b.p. 152–154° at 18 mm.). These data are shown by curves F and G of Fig. 2.

The tarry residue from a typical experiment was triturated with ether for removal of the diluent and some decomposition products. Recrystallization of the waxy ether insoluble material from water with charcoal gave 8 g. of white solid (based on 10.8 g. of *o*-phenylenediamine). Fractional crystallization of this from water gave 1.4 g. of 2-methylbenzimidazole, m.p. 175–176° and 0.2 g. of 2-*n*-propylbenzimidazole, m.p. 156–157°. The substances were identified by mixture m.p.'s with authentic samples.³⁴

During the above fractional crystallization a small portion of material m.p. 149.5–150° was obtained. When this was mixed with a synthetic mixture of equimolar quantities of the two benzimidazoles no depression of m.p. was noted. In view of the formation of this compound, no further use was made of the melting point diagram of the two benzimidazoles (Fig. 5) for analytical purposes. Rather reliance was placed on analyses of the evolved gases for estimating the relative amounts of the benzimidazoles formed.

In another experiment 10 g. of the benzimidazoline (X) was pyrolyzed. In the side arm of the Claisen adapter of the apparatus, 0.7 g. of a liquid, b.p. 59.5–61.5°, n_D^{25} 1.3920 collected. Schmitt and Boord³⁶ report b.p. 61.5–62° and n_D^{25} 1.3921 for 2-methylpentene-1. The substance readily absorbed bromine and decolorized permanganate solution. The pyrolysis residue was refluxed with water for 20 minutes and then steam distilled. From the distillate 0.1 g. of the 2,4-dinitrophenylhydrazone of methyl *n*-propyl ketone, m.p. 141–142°, was isolated and identified by mixture m.p.'s.

When the benzimidazoline (X) from 5.4 g. of I was pyrolyzed at 255° in the presence of 0.3 g. of dry *p*-toluenesulfonic acid no appreciable gas evolution occurred. From the black pyrolysis residue only 1 g. of *o*-phenylenediamine was recovered.

e. With Methyl Isopropyl Ketone.—Pyrolysis of the benzimidazoline prepared by refluxing 5.4 g. of I and 17 g. of methyl isopropyl ketone (b.p. 94.5–95°) for 14 hours gave an initial gas evolution temperature between 195 and 210° (average 205°) in three experiments. Analysis of the evolved gas (800 ml.) by the mass spectrometer showed it to be 99% propane. The rate of gas evolution at 260° ($\pm 0.8^\circ$) using diphenyl ether as a diluent is shown in curve C, Fig. 1. From the pyrolysis residue 2 g. of 2-methylbenzimidazole, m.p. 173–174°, was obtained after recrystallization from water.

f. With Methyl *t*-Butyl Ketone.—A mixture of 5.4 g. of I and 15 g. of methyl *t*-butyl ketone, b.p. 105.5–106°, was

(35) National Bureau of Standards, A. P. I. Research Project 44, Washington, Serial No. 529 (1946).

(36) Schmitt and Boord, *THIS JOURNAL*, **54**, 754 (1932).

refluxed for 4 hours during which 1 g. of water was removed. Pyrolysis of the residue gave 600 ml. of gas identified as 95% isobutane by the mass spectrometer and 3 g. of pure 2-methylbenzimidazole.

g. **With Methyl Isobutyl Ketone.**—When 5.4 g. of I and 20 g. of methyl isobutyl ketone (b.p. 117.5–118°) was refluxed for 20 hours, 2 g. of water was removed. Pyrolysis of the residue gave 350 ml. of gas consisting of 95% isobutane and 4% methane by the mass spectrometer. The rate of gas evolution at 258° ($\pm 0.5^\circ$) using diphenyl ether as diluent is shown in curve D, Fig. 1. From the residue, 2.1 g. of 2-methylbenzimidazole was isolated.

h. **With Methyl Cyclopropyl Ketone.**—A mixture of 10.8 g. of I, 21 g. of methyl cyclopropyl ketone (U. S. I. Chem., redistilled at 111–112°), and 20 ml. of dry toluene was refluxed for 12 hours. Initial evolution of gas (approx. 450 ml.) occurred at 245°. Analysis of the gas by the mass spectrometer indicated the presence of 95% methane. Recrystallization from water of the pyrolysis residue yielded 2 g. of white crystals melting at 227–228°.

Anal. Calcd. for $C_{10}H_{10}N_2$: C, 75.9; H, 6.4; N, 17.7. Found: C, 76.0; H, 6.3; N, 18.0.

The product did not give a positive unsaturation test with either dilute potassium permanganate or with bromine in carbon tetrachloride. No depression of melting points was observed when the above compound was mixed with the product obtained from the reaction of *o*-phenylenediamine and cyclopropylcarboxylic acid (*cf.* preparation below).

i. **With Cyclopropylcarboxylic Acid.**—Cyclopropylcarboxylic acid was prepared by treating 42 g. of methyl cyclopropyl ketone with a cold, freshly prepared solution of sodium hypobromite made by adding 160 g. of bromine to 150 ml. of 12 *N* sodium hydroxide. The yield of colorless oil, b.p. 180–183°, was 33 g. (78%). This acid has also been prepared by hydrolysis of cyclopropyl cyanide.³⁷ From 10.8 g. of I and 12.9 g. of the acid³⁴ 9.5 g. of the benzimidazole, m.p. 227–228°, after recrystallization from benzene and water, was obtained. The substance is presumably 2-cyclopropylbenzimidazole.

j. **With Methyl Vinyl Ketone.**—A mixture of 5.4 g. of I, 16.5 ml. of methyl vinyl ketone azeotrope (du Pont), and 20 ml. of benzene was refluxed for 15 hours. Following the general procedure, the evolution of gas started at 265°. Approximately 150 ml. of gas was collected during the pyrolysis to 300°. Analysis of the gas by the infrared spectrometer gave a spectrogram which was in good agreement with that reported for methane.³² The tarry pyrolysis residue was not workable and was discarded.

k. **With Di-*n*-propyl Ketone.**—Following the standard procedure, the gas evolved was 95% propane and 1.3 g. of 2-*n*-propylbenzimidazole, m.p. 157–157.5°, was obtained.

l. **With *n*-Propyl Isopropyl Ketone.**—On refluxing 10.8 g. of *o*-phenylenediamine with 34 g. of the ketone³⁸ 2 g. of water was removed in 3 hours. From the pyrolysis residue 2 g. of 2-*n*-propylbenzimidazole, m.p. 156–157°, was obtained. Wiedenhagen⁹ reports 2-isopropylbenzimidazole as melting at 228°.

m. **With Dibenzyl Ketone.**—A mixture of 10.8 g. of I and 42 g. of dibenzyl ketone³⁹ (b.p. 159–160° at 2 mm.) was heated at 170–250° for 21 hours during which 2 g. of water was removed along with 7.2 g. of toluene, identified by b.p., refractive index and oxidation to benzoic acid. From the residue 6 g. of 2-benzylbenzimidazole, m.p. 186.5–187°,² was obtained.

n. **With Benzophenone.**—After heating a mixture of 10.8 g. of I, 18.2 g. of benzophenone and 20 ml. of pseudocumene at 180–190° for 12 hours, the residue was recrystallized from 50% methanol with charcoal to give 4 g. of glistening white needles, m.p. 280–281° (uncor.). 2-Phenylbenzimidazole is reported to melt at 290°.⁴⁰

Reactions of *N*-Methyl-*o*-phenylenediamine with Ketones. a. **With Acetone.**—The *N*-methyl-*o*-phenylenediamine used was prepared in 33% over-all yield from *o*-nitroaniline.^{41,42} Immediately before use the substance was distilled under nitrogen through a Vigreux column;

the fraction, b.p. 136–139° at 16 mm., was collected. A mixture of 12.2 g. of *N*-methyl-*o*-phenylenediamine and 11.7 g. of acetone was refluxed for 8 hours. Long needles of an intermediate compound separated when the reaction mixture was chilled in a carbon dioxide-bath. After recrystallization from an equal weight of acetone the substance melted at 66–66.5°. This benzimidazoline turned pink on standing in air.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.0; H, 8.7; N, 17.3. Found: C, 73.6; H, 8.5; N, 17.0.

The ultraviolet absorption spectrum of the above compound in 95% ethanol is shown in curve N, Fig. 3.

The remainder of the dried intermediate was pyrolyzed with an initial gas evolution temperature of 245°. Over 500 ml. of gas was liberated which was pure methane by infrared analysis.³² After successive recrystallization from ethyl acetate and water the pyrolysis residue gave 0.7 g. of silky, white needles, m.p., 110–111°. Mixture m.p.'s with authentic 1,2-dimethylbenzimidazole showed no depression.

When the above procedure was repeated with the addition of a solution of one equivalent of sodium dissolved in 25 ml. of *n*-hexyl alcohol, the initial gas evolution temperature was lowered to 165°.

b. **With Methyl Isopropyl Ketone.**—Six and two-tenths grams of *N*-methyl-*o*-phenylenediamine was refluxed with 13 g. of methyl isopropyl ketone as described in the general procedure. During the first 45 minutes of refluxing, approximately 0.5 g. of water was removed and about 200 ml. of gas liberated. The initial gas evolution temperature was 110°. By gradual removal of excess ketone through the Claisen separator, the reaction temperature was raised to 173° ($\pm 1^\circ$) where rate measurements were made over a necessarily short period. The results are shown in curve A, Fig. 1. A total volume of approximately 1 l. of gas was given off. Analysis of the gas by the mass spectrometer indicated the presence of 92% propane. On recrystallization from water, the pyrolysis residue gave 1 g. of white needles melting at 110–111° which were identified by mixture m.p.'s with authentic 1,2-dimethylbenzimidazole.

c. **With Di-*n*-propyl Ketone.**—On refluxing 6.1 g. of *N*-methyl-*o*-phenylenediamine with 17 g. of di-*n*-propyl ketone, gas evolution occurred without resorting to subsequent pyrolysis. Initial evolution was noted at 150°. Almost 500 ml. of gas was collected. Analysis of the gas by the mass spectrometer showed the presence of 95% propane. On recrystallization from water, the contents of the flask gave 3.8 g. of a flocculent, white solid melting at 59–60°. An analytical sample prepared by further recrystallization from water melted at 64.5–65°.

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.8; H, 8.1; N, 16.1. Found: C, 75.6; H, 8.0; N, 16.3.

Mixture melting points of the above compound with a sample of 1-methyl-2-propylbenzimidazole prepared according to the method of Phillips⁴¹ showed no depression. The picrate of the above compound on crystallization from ethanol, melted at 229–230°.

d. **With Methyl Propyl Ketone.**—Twelve and two-tenths grams of *N*-methyl-*o*-phenylenediamine was refluxed as usual with 26 g. of methyl *n*-propyl ketone (redistilled through a Vigreux column at 101–102°) for 3 hours. On pyrolysis of the intermediate an initial evolution temperature of 145° was noted. A rate study of the decomposition was carried out at 175° ($\pm 0.3^\circ$) using redistilled (153.5–155°) anisole as the diluent. The results are shown in curve B, Fig. 2. Approximately 900 ml. of gas was liberated. Analysis by the mass spectrometer indicated the presence of 80% propane, 5% methane and air. The residue from the pyrolysis was recrystallized from water yielding 1.5 g. of 1,2-dimethylbenzimidazole as silky white needles, m.p. 111–111.5°. Fischer⁴³ reports the substance as melting at 111°.

Anal. Calcd. for $C_9H_{10}N_2$: C, 74.0; H, 6.8. Found: C, 73.9; H, 6.7.

Reaction of *N*-Phenyl-*o*-phenylenediamine with Ketones. a. **With Methyl Propyl Ketone.**—*N*-Phenyl-*o*-phenylenediamine was prepared from *o*-chloronitrobenzene as described by Kehrman and Havas⁴⁴ except for reduction of the intermediate *o*-nitrodiphenylamine which was reduced catalytically in 60% yield in ethanol over Raney nickel at

(43) Fischer and Woldenburg, *Ber.*, **25**, 2838 (1892).

(44) Kehrman and Havas, *ibid.*, **46**, 341 (1913).

(37) McCloskey and Coleman, *Org. Syntheses*, **24**, 36 (1944).

(38) Gilman and Nelson, *Rec. trav. chim.*, **55**, 518 (1936); Cason and Prout, *Org. Syntheses*, **28**, 75 (1948).

(39) Hurd and Thomas, *This Journal*, **68**, 1240 (1936).

(40) Hunter and Marriott, *J. Chem. Soc.*, 777 (1941).

(41) Phillips, *ibid.*, 2824 (1929).

(42) Usherwood and Whiteley, *ibid.*, 1084 (1923).

700 lb. pressure. After recrystallization from heptane the substance melted at 79–80°.

Nine and two-tenths grams of *N*-phenyl-*o*-phenylenediamine was refluxed with 12.9 g. of methyl propyl ketone for 18 hours as described in the general procedure. On pyrolysis the initial gas evolution temperature was 230°. A rate study of the decomposition was made at 269° ($\pm 0.8^\circ$) using 20 ml. of diphenyl ether as a diluent. The results are shown in curve E, Fig. 1. Approximately 400 ml. of an inflammable gas was liberated which was not otherwise investigated. Trituration of the pyrolysis residue with ether and recrystallization from water gave 0.2 g. of 1-phenyl-2-methylbenzimidazole, m.p. 70.5–71.5°, which was identified by mixture m.p.'s with an authentic sample prepared from *N*-phenyl-*o*-phenylenediamine and acetic acid. Wolff⁴⁵ reports m.p. 72–73°.

b. With Methyl Ethyl Ketone.—After refluxing 9.2 g. of *N*-phenyl-*o*-phenylenediamine and 18 g. of methyl ethyl

ketone for 8 hours, pyrolysis gave 350 ml. of an inflammable gas which was not investigated further and 0.7 g. of 1-phenyl-2-methylbenzimidazole, m.p. 70–71°.

Attempted Benzoyl Peroxide Catalysis of the Degradation Reaction.—To the intermediate obtained from the previously described reaction of I with methyl ethyl ketone, there was added 0.05 of an equivalent of benzoyl peroxide. Heating was carried out at 180–220° (below the previously determined initial evolution temperature of 235°). Other than periodic minor explosive-like evolutions of gas, only a negligible amount was liberated.

Attempted Reaction of *N,N'*-Dimethyl-*o*-phenylenediamine with Methyl Isopropyl Ketone.—Seven grams of the diamine⁴⁶ (m.p., 23–25°) and 13 g. of methyl isopropyl ketone were refluxed as described in the general procedure. No water was azeotropically removed. Almost all of the ketone was recovered unchanged.

(46) Fischer and Fussenegger, *Ber.*, **34**, 936 (1901).

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(45) Wolff, *Ann.*, **394**, 59 (1912).

[CONTRIBUTION FROM THE RADIATION LABORATORY, UNIVERSITY OF CALIFORNIA]

Synthesis of Potential Purine Antagonists. I. 2,6-Diamino [3',2'-h]-thiazolinopurines

BY MAXWELL GORDON¹

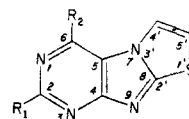
The synthesis of 2,6-diamino-4'-methyl[3',2'-h]thiazolinopurine is described and a route to 2,6-diamino[3',2'-h]thiazolinopurine is indicated. In addition, the following new derivatives of 2,6-diaminopurine have been prepared: 8-mercapto-, 8-acetylmercapto-, 8-carboxymethylmercapto- and 8-carbomethoxymethylmercapto-2,6-diaminopurine. Ultraviolet spectra of the above compounds have been measured in acid, neutral and alkaline solutions.

Various investigators have reported² that the concentration of nucleic acids in tumor-bearing animals is greater than in normal animals. From these results it has been postulated that adenine and guanine inhibitors could be found which would retard tumor growth. Hitchings³ has demonstrated adenine inhibition by 2,6-diaminopurine, and Burchenal⁴ has reported the activity of this inhibitor against leukemia. Roblin⁵ and Kidder⁶ have shown purine inhibition by 8-azaguanine, and the latter has extended the investigation of this compound to include demonstration of inhibition of mouse leukemia.⁷

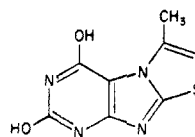
In our work it was thought to be of interest to prepare a series of purine analogs in which riboside formation at the 7- and 9-positions is blocked, and in which riboside formation might take place at other points in the molecule, in order to find compounds of greater cancer-inhibiting action than those described above. An investigation of the literature showed that considerable demethylation of alkyl purines probably occurs in the metabolism of caffeine and other alkyl xanthines,⁸ so the use of purines for this study in which the 7- or 9-position was blocked by an alkyl group was ruled out.

It appeared probable that blocking could be

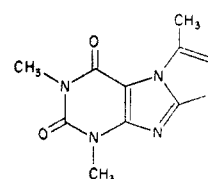
more effectively accomplished by use of a fused ring system, and the [3',2'-h]thiazolinopurines (I) hitherto prepared only by Todd,⁹ who synthesized a xanthine homolog (II), and by Ochiai,¹⁰ who prepared a [3',2'-h]thiazolinophylline (III), were thought to offer possibilities. Accordingly, a program was undertaken directed toward the synthesis of some thiazolino derivatives of 2,6-diaminopurine (I) ($R_1, R_2 = NH_2$). The results are recorded in this paper.



I



II



III

The thiazolino derivatives of adenine (I) ($R_1 = H$; $R_2 = NH_2$), guanine ($R_1 = NH_2$; $R_2 = OH$), and isoguanine ($R_1 = OH$; $R_2 = NH_2$) are also being synthesized in this Laboratory and will be made the subject of later communications.

The syntheses recorded in this paper were carried out according to the scheme recorded below. All purines shown are believed to be hitherto unreported in the chemical literature.

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(1) Atomic Energy Commission Postdoctorate Research Fellow in the Physical Sciences of the National Research Council 1949–1950. The work described in this paper was sponsored by the Atomic Energy Commission. Present address: Organic Chemistry Department, Imperial College of Science and Technology, London, S. W. 7, England.

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(3) Hitchings, *et al.*, *J. Biol. Chem.*, **174**, 765 (1948).

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