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

The Associative Isomerism of 2,4(5)-Diphenylimidazole[1]

BY PAUL G. HAINES[2] AND E. C. WAGNER

The diphenylimidazole (I), m. p. 168°, obtained by Minovici[3] by action of ammonia upon 2,5-diphenyloxazole was designated as 2,5-diphenylimidazole. Kunckell[4] obtained an isomeric compound (II), m. p. 194°, by interaction of phenacyl bromide and benzamidine, and represented it to be 2,4-diphenylimidazole. In the study here reported there was obtained a third form (III), m. p. 179°, by treating either I or II with pyridine. This paper presents the results of experiments to examine into the nature of the relationships among these compounds.

Earlier evidence as to the isomerism of I and II is inconclusive. The unsupported claim of Weidenhagen and Hermann[5] that they are polymorphs cannot be reconciled with behaviors mentioned below. Burtles and Pyman[6] found that both I and II yield with each of several acids a common salt, and concluded tentatively that the two bases may be the isomers named above, *i. e.*, the compounds corresponding to the two tautomeric forms of the amidine system present. These however are mesohydric tautomers[7] which, because of associative hydrogen bonding, are probably no more separable than are the tautomeric forms of amidines or of imidazoles previously studied.[8] The other three possible tautomers of diphenylimidazole are hypothetical and, while one of them might be somewhat stabilized by conjugation more extended than that of the others, there is little or no reason to believe that I and II and the new third isomer III, all of which are isolable without difficulty, are desmotropes. It was observed also by Burtles and Pyman[6] that II is gradually convertible to I by hot alcohol and that in alcohol this change cannot be reversed by seeding with II. Of the three forms only I is thermally stable; a slow conversion of II or III to I occurs on fusion, and more slowly on heating below fusion temperatures. Compounds II and III have reproducible melting points, but melting is preceded by sintering, due probably to incipient conversion to I, and better values are obtained if melting points are taken rapidly.

The facts reviewed do not permit a decision as to the nature of the relationships among the three isomers. The present study provides an explanation in the characteristic associative effects which are induced in 2,4(5)-diphenylimidazole by contact with solvents. Which of the three forms is obtained in any case, regardless of the method of formation, was found to be determined by the identity of the solvent with which it was last in equilibrium. On this basis the solvents tested fall into four categories, *viz.*: (1) Solvents which yield form I (m. p. 168°): acetone, *n*-amylamine, anisole, carbon bisulfide, carbon tetrachloride, chlorobenzene, chloroform, cyclohexanol, diethyl ether, di-isopropyl ether, ethyl acetate, ethanol, mesitylene, methanol, 2-methylbutanol-2, naphthalene, nitrobenzene, 1-nitropropane, *n*-octane, pentanol-1, pentanone-2, 2-picoline, 3-picoline, propanol-2, toluene, 2,2,4-trimethylpentane; (2) solvents which yield form II (m. p. 194°): benzene, dioxane, thiophene; (3) solvents which yield mixtures of I and II: aniline, cyclohexene, piperidine, pyrrole; (4) solvent which yields form III (m. p. 179°): pyridine. In most of these solvents equilibrium is reached rapidly, but not in ethanol. Rapid crystallization of II from ethanol yields II unchanged, but crystallization after the solution is allowed to stand for a sufficient time yields pure I; intermediate intervals lead to a product with the melting point characteristics of a mixture. The deceptive structural implications of the methods used to prepare I and II are now explicable. Minovici crystallized his product from alcohol and obtained I. Kunckell treated his product with benzene (converting to II) and then crystallized rapidly from ethanol and recovered II.[9] Weidenhagen and Hermann (by synthesis using phenacyl alcohol, benzaldehyde and ammoniacal cupric acetate) crystallized the diphenylimidazole from benzene and obtained II. By proper selection of solvents the three forms are quantitatively interconvertible, and any method of preparation will serve to produce all three isomers.

A saturated solution of any form in one of the solvents of classes 1, 2 or 4, if seeded with a form not characteristic of that solvent, does not yield crystals of the form used for seeding. A melt of form I, if seeded with crystals of II or III at temperatures suitable for the solidification of these forms, is not converted to II or III but solidifies as I. As mentioned above form I is obtained by slow thermal conversion of II or III (as by fusion for several hours); this change

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[1] Paper constructed from the Ph.D. dissertation of Paul G. Haines, University of Pennsylvania, August, 1948. Presented in brief at the Miniature Meeting of the Philadelphia Section of the American Chemical Society, Philadelphia, January 20, 1949.

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[3] Minovici, *Ber.*, **29**, 2103 (1896).

[4] Kunckell, *ibid.*, **34**, 637 (1901).

[5] Weidenhagen and Hermann, *ibid.*, **68**, 1953 (1935).

[6] Burtles and Pyman, *J. Chem. Soc.*, 361 (1923).

[7] Hunter and Marriott, *ibid.*, 777 (1941); Hunter, *ibid.*, 806 (1945).

[8] The essentials of this matter are summarized by Runner, Kilpatrick and Wagner, THIS JOURNAL, **69**, 1406 (1947).

[9] Repetition of Kunckell's procedure with omission of the treatment with benzene and with crystallization from ethanol yielded I.

is not influenced by seeding with II or III. When any form is dissolved in, and allowed to attain equilibrium with, a solvent miscible with water and is then rapidly precipitated by addition of water, the isomer that separates is the one characteristic of the solvent, indicating that differences among I, II and III exist when the compounds are in solution, *i. e.*, that distinguishing characteristics are not instantly lost upon dissolution in a solvent (*e.g.*, ethanol). These facts appear to exclude polymorphism as an explanation for the existence of the three forms.

No consistent basis for the like effects of solvents in the same class with respect to compounds I, II and III is obvious. It appears that transformation of II or III to I occurs rapidly in solvents of relatively high dielectric constant (*e. g.*, nitrobenzene), less rapidly in solvents such as alcohols, and very slowly in solvents of low dielectric constant (*e. g.*, *n*- and iso-octane). The virtually instantaneous conversion of I to II by dioxane, and of I to III by pyridine, cannot be correlated with the structural, functional or polar characteristics of these solvents, for the other ethers tested, and also the esters, produced compound I, while pyridine is unique among the basic solvents tested. This matter rests for the present on an empirical basis.

Unsymmetrically substituted amidines in general, and the isomers of diphenylimidazole, lose their tautomeric character when combined with acids, and this has been assumed also for their salts with strong bases. To test the latter view compound II was treated with metallic potassium (in dioxane) and the solid salt was decomposed by water; the compound recovered was I. Final conversion to I was not a solvent effect but must have been due to presence, in the potassium salt, of the resonating diphenylimidazole anion (common to all three isomers), which in contact with water reverted to diphenylimidazole as the stable isomer I.

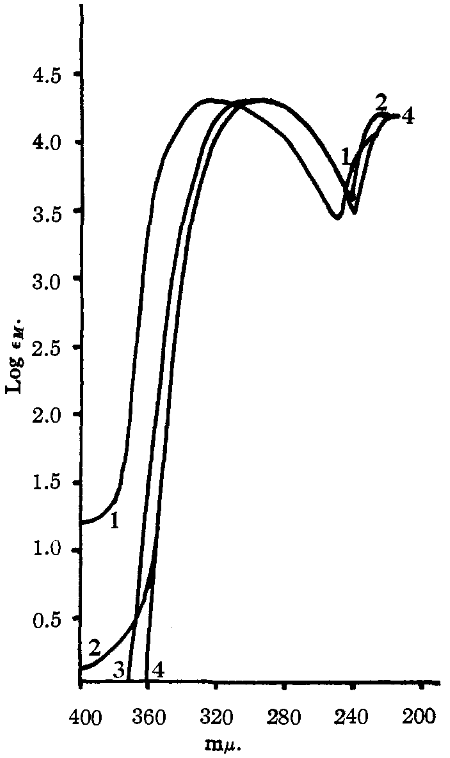

Fig. 1.—Ultraviolet absorption spectrum of 2,4(5)-diphenylimidazole in, (1) sodium ethylate-ethanol solution, (2) dioxane solution, (3) pyridine solution, (4) 95% ethanol solution.

Chemical tests which might show functional differences if the three forms of diphenylimidazole are any of the five possible single tautomers failed to reveal any such differences. (1) A color reaction by which II can be distinguished from I and III, but which throws no light on the problem, is described in the experimental section. (2) Benzene diazonium chloride coupled with each of the isomers (in suitable solvents) to yield in each case the single azo-dye 2,4(5)-diphenyl-5(4)-benzeneazoimidazole. This reaction[10] therefore lacks diagnostic significance, nor does the identity of the product reveal the structure of diphenylimidazole at the moment of coupling for, as is usual in such systems, it cannot be stated whether coupling occurs directly on carbon or initially on nitrogen followed by rearrangement. (3) Methylmagnesium iodide reacted quantitatively with I, II and III in suitable solvents, to liberate one equivalent of methane from each, indicating presence of —NH— in each, since 1-methyl-2,4-diphenylimidazole (made from the potassium salt by methylation) yielded no gas with the Grignard reagent. The coupled dye mentioned above reacted with methylmagnesium iodide to yield one equivalent of methane, a result which shows the presence of —NH— and hence attachment of the azo group to carbon.

The **ultraviolet spectra** of I, II and III in appropriate solvents reveal no significant differences (Fig. 1). In alkaline environment (in which a common anion may be present) the absorption, compared with the absorptions of I, II and III in absence of alkali, showed only an appreciable bathochromic effect but no other pronounced difference. In acid environment the spectral curve of the common cation is nearly the same as the curves for the single isomers. It appears that the differences among I, II and III are such as to produce no recognizable ultraviolet absorption effects.

The **infrared spectra** of compounds I, II and III (in solid form suspended in "Nujol") appear in Figs. 2 and 3. The curves for II and III resemble one another more than either resembles the curve for I, though all are similar at most points. The N—H stretching band at about 3100 cm.$^{-1}$ is fairly sharp for I but is considerably

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(10) Fargher and Pyman, *J. Chem. Soc.*, 217, 1015 (1919).

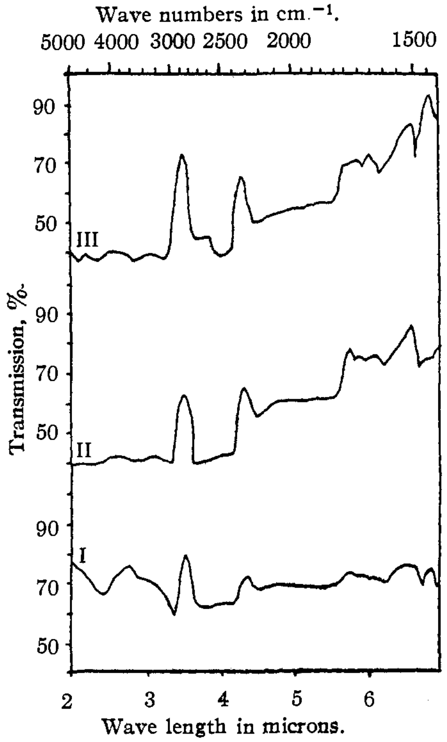


Fig. 2.—Infrared absorption spectra of compounds I, II and III in Nujol suspension.

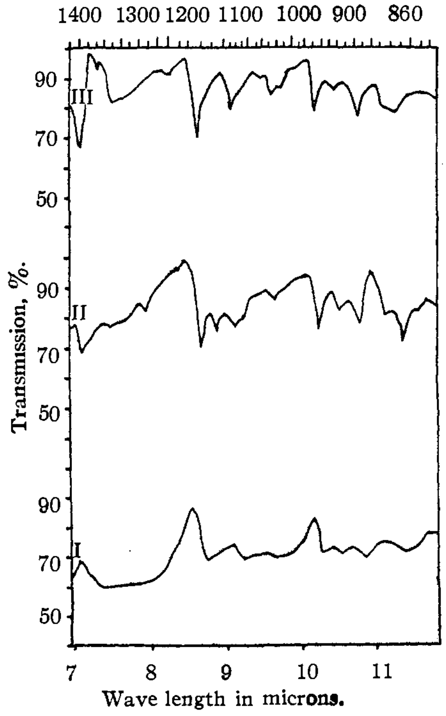
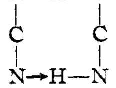


Fig. 3.—Infrared absorption spectra of compounds I, II and III in Nujol suspension.

flattened for II and III, a result thought to be consistent with conclusions as to the state of aggregation of each compound, drawn from molecular weight data discussed below. The NH absorption at 3100 cm.$^{-1}$ is not entirely distinct from the CH absorption of the benzene rings. The C=N absorption, to be expected at about 1640 cm.$^{-1}$, appears to be partially merged with the absorption at 1600 cm.$^{-1}$ due to aromatic C=C. Whether or not C=N absorption should appear is uncertain, for the Raman spectrum (in general closely related to the infrared spectrum) of imidazole was found by Shigorin and Syrkin[11] to show no frequency corresponding to C=N, though it was found in the Raman spectrum of N,N′-diphenylacetamidine.

Association Studies.—Determination of the molecular weights of compounds I, II and III at increasing concentrations furnished data for the association curves plotted in Fig. 4. These results reveal distinctive differences in the states of aggregation of the three compounds. Compound II is undeviatingly dimeric (in boiling dioxane), and compound III is definitely monomeric (in boiling pyridine), within the ranges of concentration tested. Compound II is provisionally postulated to be (in dioxane) a cyclic dimer with the units joined through hydrogen bonds, and representable by the condensed formula



$$\begin{array}{ccc} N & —H\leftarrow & N \\ | & & | \\ C & & C \\ | & & | \\ N & \rightarrow H— & N \end{array}$$

in which N—C—N represents

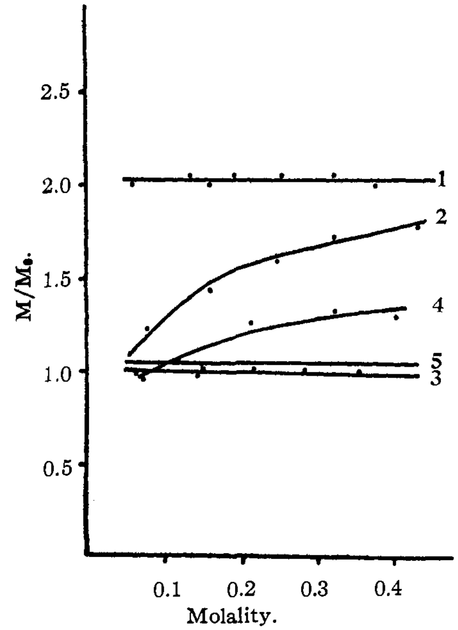


Fig. 4.—Association of 2,4(5)-diphenylimidazole in certain solvents. Curve 1 is form II in 1,4-dioxane; 2 is I in pentanone-2; 3 is III in pyridine; 4 is I in 2-picoline; 5 is naphthalene in each of the above solvents;

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(11) Shigorin and Syrkin, *Bull. acad. sci. U. R. S. S., Ser. phys.*, **9**, 225 (1945); *Chem. Abstracts*, **40**, 1831 (1946).

the diphenylimidazole unit.[12] Compound III must be wholly unassociated, or fully solvated, in order to exist in pyridine as the monomer. Solvation alone may be inadequate to account for this result, since triethylamine, amylamine, and α- and β-picolines produce form I, but it may be significant that solid III stubbornly retains traces of pyridine. Two isomeric forms of 5 - (2,4 - dinitroanilino) - 2 - methyl - benzimidazole studied by Stauble[13] were stated to be monomer and dimer, respectively, the latter being postulated as a bimolecular salt involving the aci-form of a nitro group. These conclusions appear to be supported by no molecular weight results, but some behaviors of the two isomers resemble those of the diphenylimidazoles, for both isomers yield identical salts with acids and are interconvertible by solvent. Compound I (in boiling pentanone-2) is a molecular aggregate the degree of association of which increases with concentration. This continued ability to associate is suggestive of an indefinite linear aggregate or polymer having at each concentration the average molecular weight shown in Fig. 4, and representable by the formula ·····N—C—N—H·····N—C—N—H·····N—C—N······ Similar results have been obtained, and similar conclusions drawn, for imidazole itself.[7,14] These or analogous differences among compounds I, II and III when in solution may exist in the solid substances, since these have reproducible melting points, though the manner of aggregation may be modified when the influence of the solvent is withdrawn. Differences persist also in the molten state, as indicated by the failure to effect interconversion by seeding.

Experimental

Preparation of 2,4(5)-Diphenylimidazole.—The method of Kunckell,[4] using benzamidine[15] and phenacyl bromide, with modifications in the isolation procedure, served for preparation of I, II and III. The reaction mixture was freed of chloroform by evaporation, and the brown residue was treated with warm dilute ammonia water to induce separation of crystals, which were separated and warmed with aqueous sodium carbonate for an hour with stirring. The crude product was washed with water, then dissolved in benzene containing a little dioxane and decolorized with charcoal. The crystallized product (compound II) was colorless and melted at 194-196°,[16] after sintering; the yield was 66%. To obtain compound I a solution of II in ethanol was slowly evaporated to dryness, preferably overnight. The residue melted at 167-168°. To obtain compound III either of the other forms was dissolved in pyridine and the solute was isolated either by crystallization or by evaporation to dryness. The compound so recovered melted at 177-179° after slight sintering. It strongly retained the odor of pyridine, eliminated by pulverizing the compound and heating at 100° and 2 mm. pressure over sulfuric acid in an Abderhalden drier.

Anal. of Compound III.[17] Calcd. for $C_{15}H_{12}N_2$: C, 81.82; H, 5.45; N, 12.73. Found: C, 81.85; H, 5.38; N, 12.80.

Solvent Tests.—About 0.05 g. of I, II or III was dissolved in the selected solvent, and after refluxing for thirty minutes the solution was taken to dryness under reduced pressure and the product was identified by melting point. When transformation was incomplete within thirty minutes the period of heating was extended. The results of these tests are summarized above. The rapidity of the transformation in dioxane was demonstrated by dissolving I rapidly (within 45 seconds) in dry dioxane (0.5 g. in 30 ml.) and immediately adding 250 ml. of water. The precipitated base was II, m. p. 193-196° with sintering. A similar experiment with pyridine as solvent showed equally rapid conversion of I to III.

Seeding Experiments.—(1) In a small test-tube immersed in an oil-bath maintained at 173° compound I (m. p. 168°) was fused and the melt was seeded with crystals of II (m. p. 194°). After ten minutes, during which no crystallization occurred, crystals of III (m. p. 179°) was introduced. Initially the seed crystals slowly dissolved in small part, and a small quantity of new crystals formed at the surface of the remaining crystals, but did not increase. After an hour the test-tube was withdrawn and allowed to cool gradually. The melting point of the solidified material (care being taken not to include any of the seed crystals) was found to be 167-168°, and the melting point of a mixture of I was 167-168°. (2) In a similar experiment compound II was melted in a test-tube at 200°, after which the temperature was lowered to 195° and kept at this point for two hours. The temperature was then reduced to 173° and at this temperature the melt was seeded first with crystals of II and then with crystals of III. A few crystals formed at the surfaces of the seed crystals after about ten minutes, but the amount did not increase in the course of two hours at 173°. The melt was allowed to cool to room temperature. The melting point of the solid was 165-167°; that of a mixture with I was 166-168°. In this case thermal conversion of II to I occurred, a change not attributable to seeding and indicative of the greater thermal stability of compound I.

Transformation via the Potassium Salt.—Compound II (0.5 g., 0.0023 mole) in anhydrous dioxane was treated with potassium (0.1 g., 0.0025 mole), and the mixture was heated at reflux for two hours with a calcium chloride tube attached to the condenser. The dioxane was decanted from the brown solid residue, which was washed

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[12] A similar aggregation of amidines by hydrogen bonding or by bimolecular salt-formation has been suggested [Shriner and Neumann, *Chem. Rev.*, **35**, 380 (1944)].

The structure suggested for compound II may well be considered doubtful on steric grounds, since it assumes that the two units exist planar and parallel, *i. e.*, that rotation of the phenyl groups about the C_6H_5-C axes is restricted or inhibited. At intervals during the rotation of the phenyl groups the two molecules may be fully planar, except with respect to the N-H bond, the angle of which with the plane of the molecule would perhaps be favorable to establishment of intermolecular hydrogen bonds. The strains operating to disrupt this dimeric configuration, leading to a linear aggregation, are perhaps represented by the relative instability of II which on heating is converted to the thermostable and linear form I. The only alternative apparent is that compound II is a linear aggregate which in dioxane (benzene, thiophene) is either limited to two molecular units or has an average molecular weight double the formula weight.

The interesting possibility was proposed by a referee that II is formed by reversible Diels-Alder condensation. This view can be reconciled with the chemical properties of II and especially with its strictly dimeric character, though it suggests differences between II and the other two isomers greater than those observed. If II is a full structural dimer at 100° (in dioxane) its rapid conversion to I in acetone, carbon disulfide and ether, *i. e.*, at much lower temperature, is explicable only by *ad hoc* assumptions with respect to the effects of solvents on this Diels-Alder adduct. Since there is no evidence available as to the structure of II beyond the fact that it is dimeric in boiling dioxane, the tentative structure suggested, together with the comments just added, represent the limits of speculation we prefer not to exceed at this time.

[13] Stauble, *Helv. Chim. Acta*, **30**, 224 (1947).

[14] Hückel, Datow and Simmersback, *Z. physik. Chem.*, **A186**, 129 (1940).

[15] Ronzio and Ekeley, *Org. Syntheses*, Coll. Vol. I, 2nd ed., 1941 p. 6.

[16] All melting points reported are corrected values.

[17] As a precaution compounds I and II were reanalyzed and yielded results consistent with the formula.

with several 30-ml. portions of dry ether, the last traces of which were removed under reduced pressure. The residual dry powder was treated with 250 ml. of water, and the mixture was shaken for twenty minutes and then filtered. The product melted at 155-165°; a mixture with I melted at 160-165°. Since no solvent capable of transforming II to I was used, the conversion must have involved the common anion present in the salt, which by hydrolysis yielded the stable form, I.

Color Reaction.—(1) To 0.2 g. of dextrose in each of four test-tubes was added 2 ml. of concentrated sulfuric acid. After twenty minutes 100 mg. each of I, II and III was added to each of three tubes (the fourth serving as control), and all were agitated to effect rapid solution. At the end of thirty minutes the colors, observed by transmitted light, were bright and transparent red for I and III, dark and nearly opaque brown for II, while the control was light brown. (2) In tests similarly conducted (3 ml. sulfuric acid, 0.1 g. dextrose), I, II and III were introduced as freshly prepared solutions in chloroform[18] (0.1 g. base in 22 ml. of solvent), followed by rapid mixing to dissolve the base in the acid layer. The chloroform was decanted and the acid liquids were transferred to test-tubes and examined for color after thirty minutes. In this experiment the colors developed at about equal rates and were all clear red of about equal intensities. The distinction between II and the other isomers in the first test is probably due to differences in rates of solubility in sulfuric acid.

Coupling Reaction.—A chilled solution of benzene diazonium chloride (aniline, 0.31 g., 0.8 *N* hydrochloric acid, 30 ml., $NaNO_2$ 0.23 g.) was neutralized by sodium bicarbonate and divided into three equal parts, to which were added respectively 0.22 g. each of I in 95% ethanol, II in dioxane, and III in pyridine (28 ml. of solvent in each case). An orange precipitate separated from the alcoholic solution; after crystallization from 85% ethanol it weighed 0.2 g. and melted at 205-206° with sintering. The dioxane and pyridine solutions yielded a similar precipitate upon addition of water (20 ml. and 45 ml., respectively). Melting points and mixed melting points showed the three products to be identical.

Anal. Calcd. for $C_{21}H_{16}N_4$: C, 77.77; H, 4.94; N, 17.28. Found: C, 77.65; H, 4.72; N, 17.49.

This compound in anisole, when treated with methylmagnesium iodide, yielded 1.01 equivalent of methane, confirming its identity as 2,4(5)-diphenyl-5(4)-benzeneazoimidazole (or the tautomeric phenylhydrazone).

Determination of Reactive Hydrogen.—In an apparatus comprising a reaction and evolution bottle with spill-cup, a gas buret and a leveling tube, and previously flooded with dry nitrogen, compounds I, II and III in dry anisole, dioxane and pyridine, respectively, were treated with methylmagnesium iodide in the same solvents.[19] The amounts of methane, expressed in equivalents based on one reactive hydrogen, were 1.07, 1.01 and 1.05.

Methylation of 2,4(5)-Diphenylimidazole.—A mixture of 4.4 g. (0.02 mole) of II in 100 ml. of anhydrous dioxane and 0.8 g. (0.02 g. at.) of potassium was heated at reflux for three hours, with a calcium chloride tube attached to the condenser outlet. The partly cooled mixture was treated with 3.6 g. (0.025 mole) of methyl iodide, warmed for thirty minutes and then refluxed for two hours. The cooled mixture was filtered and the precipitate was washed sparingly with dioxane. The combined liquids were evaporated to dryness and the brown residue was dissolved in hot *n*-hexane, decolorized by charcoal, and crystallized. The colorless crystals weighed 1.3 g. and melted at 112-117°. Further crystallizations raised the melting point to 117.0-117.6°.

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 82.05; H, 5.98. Found: C, 82.04; H, 6.14.

This compound in anisole yielded no methane when treated with methylmagnesium iodide, indicating attachment of methyl to nitrogen. The conclusion that the compound is 1-methyl-2,4-diphenylimidazole is strengthened by the similarity of its ultraviolet spectrum with that of 2,4-diphenyloxazole, and especially by the nearly identical positions of the longest wave-length maxima. Curves for both appear in Fig. 5.

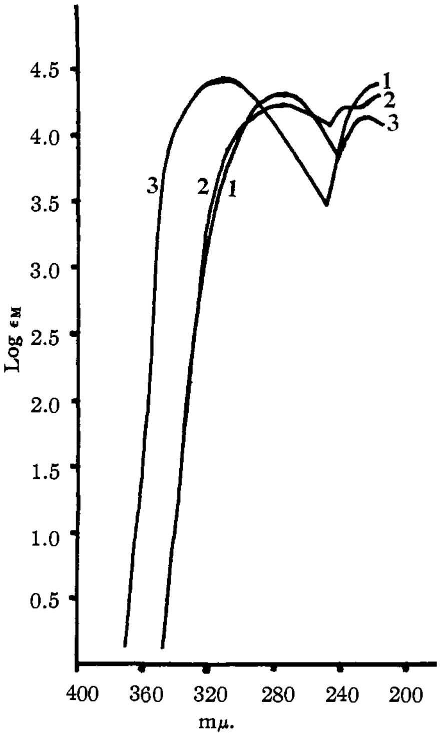

Fig. 5.—Ultraviolet absorption spectrum of methyldiphenylimidazole (curve 1), of 2,4-diphenyloxazole (curve 2), of 2,5-diphenyloxazole (curve 3). Solvent was 95% ethanol.

Preparation of 2,4-Diphenyloxazole.—The method of Fischer[20] yielded a mixture from which only N-benzalmandelamide (m. p. 195°) was isolated by crystallization. It was found that this by-product could be removed by alkaline hydrolysis. In the procedure thus modified a solution of 93 ml. of wet mandelonitrile[21] in 100 ml. of dry ethanol-free ether, was dried for an hour using anhydrous magnesium sulfate. The filtered solution was added to 53 g. of freshly distilled benzaldehyde, and dry hydrogen chloride was bubbled into the liquid, chilled in an ice-bath, during four and one-half hours. Gradual addition of 200 ml. of *n*-hexane caused separation of an oil, which soon solidified. This material (99 g., melting range 110-145°) was freed of the by-product named above by refluxing with a solution of 240 g. of potassium hydroxide in 2 l. of water for five hours, with a rapid stream of air passing to remove ammonia. The insoluble material (first an oil, later solidifying), after washing with water and drying in an evacuated desiccator, weighed 17.3 g. (from 61 g. of the first product) and melted at 69-71°. After crystallization from *n*-hexane, with decolorization by charcoal, the yield was 11.9 g. and the melting point 71-72°. Further purification, by treatment with absolute

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[18] Chloroform was used because in it the rate of change of II and III to I is so slow that the identities of II and III are retained during the brief period of exposure.

[19] For the experiment with I the Grignard reagent was prepared in anisole. For testing II and III the Grignard reagent was prepared in dry ether, which was then removed under reduced pressure by warming and was replaced by dioxane or pyridine.

[20] Fischer, *Ber.*, **29**, 205 (1896).

[21] Corson, *et al.*, "Organic Syntheses," Coll. Vol. I, 2nd ed., 1941, p. 336.

ethanol containing hydrogen chloride, dissolving the separated hydrochloride (m. p. 163–165°) in warm 95% ethanol and pouring the solution slowly into cold water, yielded the pure base of m. p. 72–73°.

Ultraviolet Spectra.—The apparatus used was a Beckman Model DU Quartz Spectrophotometer. The solvents were: for I, 95% ethanol; for II purified dioxane[22] finally redistilled through a 15-ball Snyder column with rejection of the fore-run; for III, pyridine dried over solid potassium hydroxide and distilled, only the middle fraction being used. The samples were purified as follows. Compound I was obtained from the hydrochloride (crystallized from 1 *N* hydrochloric acid) by action of warm aqueous ammonium hydroxide, and was then crystallized from 50% ethanol. Compound II was obtained pure from I by twice crystallizing from anhydrous dioxane. Compound III was obtained from I by two crystallizations from pyridine, and was freed of adhering solvent as described above. The ultraviolet spectra are shown in Fig. 1.

Infrared Spectra.—Samples of I, II and III, purified as outlined, were suspended in "Nujol" and examined in a double-beam infrared spectrophotometer.[23] The plotted results appear in Figs. 2 and 3.

Molecular Weight Determinations.—The Cottrell ebulliometer,[24] enclosed to exclude drafts, was swept out with dry nitrogen before each determination. About 65 ml. of solvent (dried and fractionally distilled) was used, and in each case several values were obtained at increasing concentrations. At higher concentrations some difficulty was encountered owing to irregular splashing and foaming. The results, calculated in terms of extents of association, are shown graphically in Fig. 4.

Acknowledgment is made to Dr. John G. Miller for helpful discussions, and to Sarah M. Woods who performed the analyses.

Summary

Study of the two previously known forms of 2,4(5)-diphenylimidazole and of a third form discovered during the work showed that each is obtained by bringing any one of the three into equilibrium with certain solvents, and that by proper choice of solvents the compounds are freely interconvertible. They are chemical individuals with respect to melting points, and are not interconvertible by seeding, either in solution or in the fused state, but the two higher-melting forms are slowly convertible to the stable low-melting form by heat. The three compounds are identical with respect to certain chemical reactions which might disclose structural differences, and they yielded ultraviolet and infrared spectra which showed no sharply distinctive characteristics for any one form. Determination of molecular weights at several concentrations disclosed that in appropriate solvents one form is monomeric, one form is dimeric, and the stable form is increasingly aggregated as concentration increases. It is concluded that the three diphenylimidazoles are not desmotropes, but that they represent three distinct and relatively permanent states of molecular aggregation responsive to the influence of solvent environment. States above the monomeric are attributed to hydrogen bonding.

RECEIVED JANUARY 26, 1949

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[22] Fieser, "Experiments in Organic Chemistry," D. C. Heath and Co., N. Y., 2nd ed., 1941, p. 369.

[23] The spectra were determined by Samuel Sadtler and Son, Analytic and Consulting Chemists, Philadelphia, using an instrument made by Baird Associates, Inc.

[24] The low solubilities of the compounds in permissible solvents near their freezing points made the freezing point method inapplicable.

[CONTRIBUTION FROM THE RESEARCH LABORATORY, MEAD JOHNSON AND COMPANY]

Pyrazine Chemistry. IV. Bromination of 2-Amino-3-carbomethoxypyrazine[1]

BY R. C. ELLINGSON AND R. L. HENRY

In search of methods for the preparation of brominated aminopyrazine derivatives the method used for the bromination of α-aminopyridine[2] was tried. Bromination of aminopyrazine by this method was unsuccessful. However, the bromination of 2-amino-3-carbomethoxypyrazine proceeds readily and forms a single monobrominated pyrazine derivative in 90% yield.

Since this compound was used in the synthesis of several pyrazine derivatives, its structure was studied. According to the rules of substitution in the benzene series one might expect substitution in position 5.

The determination of the position of the bromine atom proved to be more difficult than was anticipated. The first two methods we attempted failed. Since they are the obvious procedures, we shall briefly describe them and point out where they failed.

The first method is based on well established reactions in the pyrazine series, namely, the hydrolysis and decarboxylation of pyrazine esters, the replacement of pyrazine-ring halogen atoms by the NH_2 group,[3] and the conversion of the pyrazine carboxyl group to NH_2 by way of the amide and the Hofmann reaction.[4] Thereby we had hoped to convert the compound into a diaminopyrazine in which the amino groups would be in the 2,5- or 2,6-positions depending on the location of the bromine atom. We also proposed to degrade the known 2,5-dicarboxypyrazine[5] into 2,5-diaminopyrazine and to compare the latter with the diaminopyrazine obtained from the bromopyrazine.

The brominated ester readily underwent hydrolysis and decarboxylation, but attempts to

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[1] Presented before the Organic Division of The American Chemical Society at its 109th meeting held at Atlantic City, N. J., April 1946.

[2] Chichibabin and Tyazhelova, *J. Russ. Phys.-Chem. Soc.*, **50**, 483 (1918).

[3] Ellingson and Henry, THIS JOURNAL, **70**, 1257 (1948).

[4] Hall and Spoerri, *ibid.*, **62**, 664 (1940).

[5] Stoehr, *J. prakt. Chem.*, [2] **47**, 487 (1893).