4. Methyl-*n*-butylphenacylsulfonium bromide has been shown to undergo decomposition in the presence of methyl alcohol and dimethyl-*n*-butylsulfonium bromide has been identified as the final product of this chemical change. An interpretation of the mechanism of this decomposition is noted.

5. Absolute methanol has been found to serve best as a solvent medium for these sulfonium reactions.

6. The dialkyl-*p*-phenylphenacylsulfonium bromides and nitrates are best suited as derivatives for the sulfides studied.

CHAPEL HILL, N. C. RECEIVED FEBRUARY 20, 1942

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

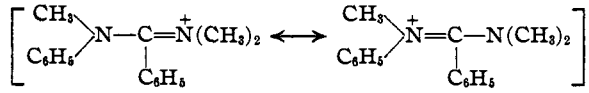
The Tautomeric Character of the Imidazole Ring

BY HARRY GREEN AND ALLAN R. DAY

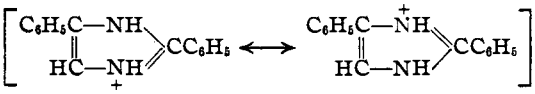
The active tautomerism of the open chain amidines has long been established. Evidence for this was obtained through the application of three methods, namely, symmetry, fission and substitution tests.[1-3] Confirmatory evidence was supplied by the observation that hydrolytic fission of a single amidine yielded two pairs of products, each pair being derived from one tautomeric form of the parent compound.

Evidence for the tautomerism of the imidazole ring (a cyclic amidine) was first presented by Kaiser.[4] He obtained only one imidazole from the reduction of 3-nitro-4-acetaminobenzoic acid and 4-nitro-3-acetaminobenzoic acid. Similar evidence was obtained by Gallinek.[5] Fischer and Romer[6] have shown that 2,5(6)-dimethylbenzimidazole reacts tautomerically with methyl iodide, the corresponding 1,2,5- and 1,2,6-trimethylbenzimidazoles being formed in almost equal quantities. Furthermore Fischer and Rigaud,[7] by removing methyl chloride from the hydrochlorides of these products, obtained only one dimethylbenzimidazole.

More recent work by Pyman[3] indicated that the tautomerism of the amidines might not be due to a prototropic change but rather to an electromerization of the cations of their salts. At the time of Pyman's investigations, there was only a single example of the existence of two isomeric forms of an amidine, namely, the occurrence of both 2,4- and 2,5-diphenylimidazole. Pyman showed that these two compounds were actually isomeric and not polymorphous forms, but they yielded identical salts with any given acid. Further investigation of certain open chain amidines, which contained no potentially mobile hydrogen atom, gave similar results. The isomeric methylphenylaminobenzenylmethylamidine and dimethylaminobenzenylphenylamidine yielded the same methiodide. Pyman recognized the fact that the two quaternary salts possessed the same common cation. His view may be expressed as follows



A similar scheme would apply to the cations of the salts of 2,4- and 2,5-diphenylimidazoles



More recently, Galimberti[8] has obtained two isomeric naphthimidazoles by treating alcoholic solutions of 1-nitro-β-benznaphthalide and 2-nitro-α-benznaphthalide with zinc and hydrochloric acid. This suggests the possibility that the isolation of the two forms might have been due to the immobilizing influence of the phenyl group and the phenylene group which is attached to the benzene ring of the 2-phenylbenzimidazole structure. When regarded in this light, there is a striking structural similarity between these compounds and the diphenylimidazoles studied by Pyman.

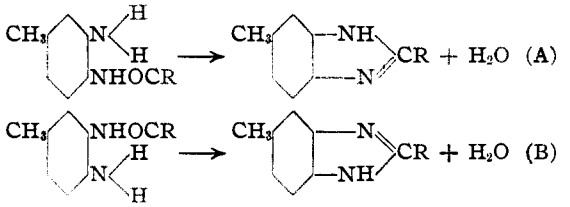
Thus there are really two problems which need to be clarified: (1) can the tautomerism of the

(1) Von Pechmann, *Ber.*, **28**, 1869, 2362 (1895); **30**, 1779 (1897).
(2) Marckwald, *Ann.*, **286**, 343 (1895); Cohen and Marshall, *J. Chem. Soc.*, **97**, 328 (1910).
(3) Pyman, *ibid.*, **123**, 367 (1923).
(4) Kaiser, *Ber.*, **18**, 2942 (1885).
(5) Gallinek, *ibid.*, **30**, 1912 (1897).
(6) Fischer and Romer, *J. prakt. Chem.*, [2] **73**, 424 (1906).
(7) Fischer and Rigaud, *Ber.*, **35**, 1258 (1902).
(8) Galimberti, *Gazz. chim. ital.*, **68**, 96 (1938).

imidazoles be explained on the basis of the resonance of the cations alone; and (2) what is the effect of immobilizing groups on the system. The two problems could not be studied simultaneously, for if two isomeric imidazoles were isolated, which contained a so-called immobilizing group, one could not say that the isolation was due to this influence or to the fact that the imidazoles were prepared without intermediate cation formation. An answer to the first problem must precede an attack on the second problem, and consequently the present work centers around the first, although a start was made on electronegative groups where the preparation of 2-phenyltolimidazole was studied.

This work included a systematic attempt to prepare isomeric tolimidazoles under acid, neutral and basic conditions. The immobilizing influence of the methyl group, attached to the aromatic nucleus, may be considered negligible. The preparations in acid solution were not carried out with any hope of isolating isomeric compounds but merely to compare the results with the data obtained from the ring closures carried out under neutral and alkaline conditions.

Examination of equations (A) and (B) discloses the fact that, if it were possible to isolate

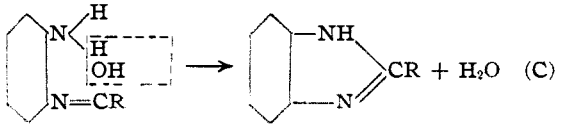


(A)

(B)

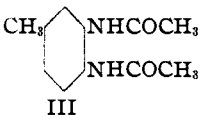
R = CH_3 or C_6H_5

two forms of the tolimidazole, then the manner in which water splits out would be a determining factor in the final structures of the two. Roeder and Day[9] have shown that the ring closure produced by the action of organic acids on *o*-phenylenediamine probably proceeds through the monoacyl derivatives. The latter products split out water by losing the oxygen atom of the acyl group and one hydrogen from each of the two adjacent nitrogen atoms (Eq. C).

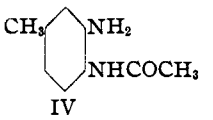


(C)

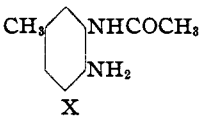
Even though this mechanism appeared to be reasonably well established, it seemed desirable to extend the generality of this mechanism to the ring closures produced by the action of organic acids on 3,4-diaminotoluene, since the preparations of tolimidazoles were to be used for a study of the tautomeric character of the imidazole nucleus. The starting compounds for this study were 3,4-diacetaminotoluene (III), 3-amino-4-acetaminotoluene (IV), and 4-amino-3-acetaminotoluene (X).



III



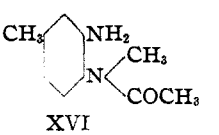
IV



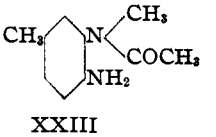
X

A sample of III after having been refluxed (176°) for four hours in dry cymene was recovered quantitatively, no 2,5(6)-dimethylbenzimidazole (I) being formed. When compounds IV and X were refluxed under similar conditions, quantitative yields of the dimethylbenzimidazole were obtained. Compound III can be cyclized (in the absence of water) to the imidazole (I) only by heating it above its melting point (>211°). In the fused state ring closure was effected by the splitting out of acetic acid. The fact that the diacyl compound required a more vigorous method to effect ring closure practically excludes it as an intermediate in the methods used in the experimental part for making the tolimidazoles.

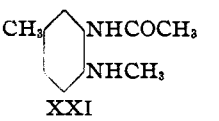
In order to study the mechanism for the splitting out of water from the monoacyl compounds, the following compounds were used: 3-amino-4-(N-methylacetamino)-toluene (XVI), 4-amino-3-(N-methylacetamino)-toluene (XXIII), 3-acetamino-4-methylaminotoluene (XXI) and 4-acetamino-3-methylaminotoluene (XXVIII).



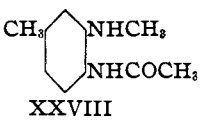
XVI



XXIII



XXI



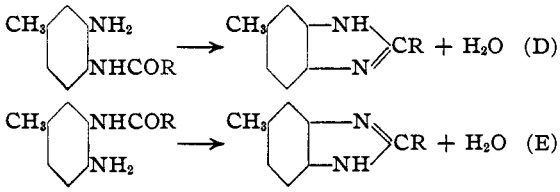
XXVIII

Compounds XVI and XXIII, respectively, were refluxed in dry cymene for four hours, but no trace of the corresponding imidazoles, 1,2,5- or 1,2,6-trimethylbenzimidazole, could be detected.

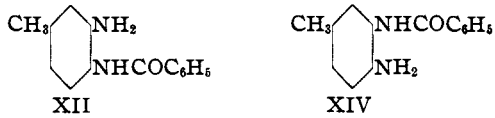
(9) Roeder and Day, *J. Org. Chem.*, **8**, 25 (1941).

Contrary to this reluctance of ring closure, compounds XXI and XXVIII were easily converted into the corresponding trimethylbenzimidazoles, when refluxed in dry benzene and dry toluene. This ease of ring closure was also noted in the melting points of XXI and XXVIII, for they melted over a wide range, approaching the melting points of the corresponding imidazoles.

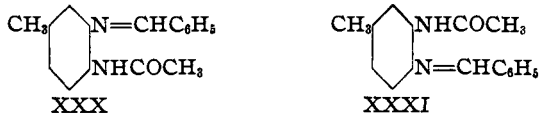
These results indicated that in the formation of the benzimidazoles studied, the monoacyl derivatives were the probable intermediates, and when water split out to form the imidazole, the two hydrogen atoms were furnished by the two adjacent nitrogen atoms. From this one could predict the initial position of the —NH— group relative to the aromatic ring (Eqs. D and E).



For the preparation of tolimidazoles in neutral and acid media, the following compounds were used: 3-amino-4-acetaminotoluene (IV), 4-amino-3-acetaminotoluene (X), 3-amino-4-benzoylaminotoluene (XII), and 4-amino-3-benzoylaminotoluene (XIV).



For ring closures in basic medium, 3-benzalamino-4-acetaminotoluene (XXX) and the isomeric 4-benzalamino-3-acetaminotoluene (XXXI) were used.

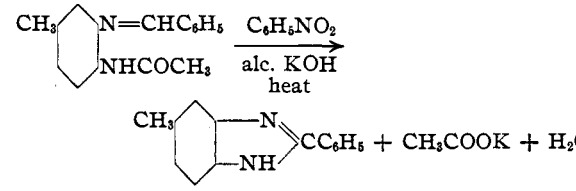


The same benzimidazole, 2,5(6)-dimethylbenzimidazole (I), was obtained when IV and X, respectively, were refluxed in dry cymene and when they were heated just above their melting points in a nitrogen atmosphere. The same benzimidazole (I) was also obtained when IV and X, respectively, were refluxed in 4 *N* hydrochloric acid.[10]

The expression "the same benzimidazole" may be somewhat misleading. Actually what is meant is that either the same mixture of tautomers or possibly a resonance hybrid of two formal isomers was obtained in both cases.

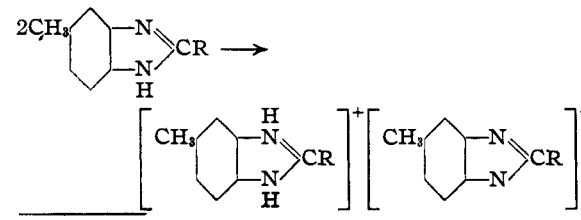
The same imidazole, 2-phenyl-5(6)-methylbenzimidazole (II), was obtained when XII and XIV, respectively, were refluxed in dry cymene, fused in an atmosphere of nitrogen or when refluxed in 4 *N* hydrochloric acid.

Traube[11] has shown that by using anhydrous ferric chloride the oxidative ring closure of 1,3-dimethyl-4-amino-5-benzalaminouracil to the corresponding imidazole could be accomplished. This procedure was modified and applied to 3-benzalamino-4-acetaminotoluene (XXX) and 4-benzalamino-3-acetaminotoluene (XXXI). These compounds, XXX and XXXI, respectively, were simultaneously hydrolyzed and oxidized by the action of nitrobenzene and alcoholic potassium hydroxide, *i. e.*,



In both cases the same imidazole, 2-phenyl-5(6)-methylbenzimidazole was obtained.

It was impossible to isolate two isomeric tolimidazoles from acid, neutral or basic media Definite conclusions from this work probably are dangerous to make but certain facts are indicated. The starting compounds, in the preparation of the tolimidazoles, were so selected that they would give, initially at least, a definite orientation to the resulting tolimidazole molecules. The fact that isomeric forms were not isolated suggests anion formation in alkaline solution and cation formation in acid solution, which is followed at once in both cases by electromerization. In cymene solution the possibility of both exists, but it must be remembered that this does not exclude the possibility of prototropy. In neutral solution, collision of two molecules of the imidazole can supply a proton and remove a proton from a combined cationic–anionic change, *i. e.*,



(10) Phillips, *J. Chem. Soc.*, 172, 2393 (1928).

(11) Traube, *Ber.*, 39, 229 (1906).

The tautomerism of the imidazoles cannot be explained by either theory alone and it is possible that it involves both prototropy and electromerism depending upon the conditions.[12]

This work is being continued along two lines: (1) the resonance hybrid, mentioned by Hunter and Marriott, might explain the whole nature of the so-called tautomeric triad system in the cyclic amidines and it is hoped that further studies may shed more light on this possibility; (2) the fact that Galimberti isolated two forms of 2-phenylnaphthimidazole must mean that the system, whatever its nature, has been immobilized. The effects of immobilizing groups are now being studied.

Experimental

All of the melting points recorded are corrected values. Starred compounds represent known compounds and the melting points checked the literature values unless otherwise stated.

Reduction.—All reductions were carried out at atmosphere pressure and room temperature, in the presence of 10% palladium charcoal catalyst.[13] The apparatus used was essentially that employed by Schaefer.[14]

2,5(6)-Dimethylbenzimidazole (I)*.—This compound was prepared from 3,4-diaminotoluene by Phillips' method,[10] m. p. 203–204°.

Anal. Calcd. for $C_9H_{10}N_2$: N, 19.16. Found: N, 19.10.

2-Phenyl-5(6)-methylbenzimidazole (II)*.—It was prepared by refluxing a pyridine solution of 3,4-diaminotoluene dihydrochloride and an equivalent of benzoyl chloride for three hours, then pouring into water. The crude product was recrystallized from benzene as colorless needles, m. p. 249–250°.[15]

Anal. Calcd. for $C_{14}H_{12}N_2$: N, 13.46. Found: N, 13.38.

3,4-Diacetaminotoluene (III)*.—This compound was prepared by the method of Lumière and Barbier as outlined by Fieser,[16] yield 86%, m. p. 211–211.3°.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: N, 13.59. Found: N, 13.57.

3-Amino-4-acetaminotoluene (IV)*.—3-Nitro-4-aminotoluene was refluxed with excess acetic anhydride for two to three hours, cooled and poured into cold water. Recrystallization from petroleum ether gave light yellow needles of 3-nitro-4-acetaminotoluene (V)*; yield, 93%. Recrystallized from water the yellow needles melted at 93–93.4°. Thirty grams of V was dissolved in 250 cc. of dry alcohol and reduced catalytically at 20°. The reduced product was isolated as its hydrochloride (VI); yield, 21 g. (70%); m. p, 228–230°.

Anal. Calcd. for $C_9H_{13}N_2OCl$: N, 13.96. Found: N, 13.86.

The base (IV) was obtained by treating the hydrochloride with aqueous sodium bicarbonate and recrystallizing the dry product from benzene; m. p. 132.6–133°.

4-Nitro-3-aminotoluene (VII)*.—The method of McGookin and Swift[17] failed to give any appreciable quantity of 4-nitro-3-aminotoluene. The 6-nitro isomer (VIII) was formed in excellent yield.

The desired compound finally was prepared by a modification of the method of Witt and Uterman.[18] Eighty-one grams (0.54 mole) of acet-*m*-toluide (IX) was dissolved in 136 cc. of glacial acetic acid and 28 cc. of acetic anhydride. The temperature was kept below 10° throughout the rest of the experiment. A solution of 30.4 cc. (0.65 mole) of fuming nitric acid (sp. gr. 1.50) in 120 cc. of acetic anhydride was slowly added to the well stirred solution. After the addition (two and one-half hours) the solution was stirred for one and one-half hours. The solution was then poured into 2 liters of ice water. The crude product was dissolved in cold concentrated sulfuric acid and diluted with an equal volume of water. The solution was heated on a steam-bath for five hours, cooled and diluted with water until no more precipitate formed. The brownish-orange prisms of the 4-nitro isomer were removed and recrystallized from alcohol; m. p. 110–110.5°; yield 30 g. (36%). The filtrate from above on neutralization with ammonium hydroxide yielded the 6-nitro isomer.

4-Amino-3-acetaminotoluene (X)*.—Twenty-six grams (0.17 mole) of VII was acetylated in the usual manner with acetic anhydride. The crude 4-nitro-3-acetaminotoluene (XI)* was recrystallized from petroleum ether; m. p. 84.9–85.5°; yield, 29.5 g. (89%).

Twenty-seven grams (0.14 mole) of the above compound (XI) was dissolved in 300 cc. of dry alcohol and reduced at 20°. The filtrate from the catalyst, was evaporated to dryness at room temperature, in order to avoid ring closure. Recrystallization from benzene gave lustrous plates, which became opaque on drying; yield 20 g. (88%); m. p. 144–145°.

Anal. Calcd. for $C_9H_{12}N_2O$: N, 17.07. Found: N, 16.98.

(12) Since the completion of this work, Hunter and Marriott, *J. Chem. Soc.*, 777 (1941), have published their results on the molecular weight determinations of a series of benzimidazoles in naphthalene solution, over a range of concentrations. They found that benzimidazoles, unsubstituted in position one, were all highly associated, but association was completely checked by replacement of the imino hydrogen. They state this indicates molecular association through N–H–N bonds in the case of those benzimidazoles which possess the unsubstituted imino group. The bond is believed to involve a bridge between the imino group of one molecule and the tertiary nitrogen atom of another. The large factors of association support this. They further state, "whatever the form, the molecular association takes, it appears likely that the virtual tautomerism is closely connected with it, *i. e.*, the alternative attachment of the tautomeric hydrogen atom to one nitrogen atom or the other gives rise to a resonance hybrid, showing all the properties of the virtually tautomeric mixture."

As convincing as this evidence is for the benzimidazole series, it does not appear to offer an explanation for Galimberti's isolation of two isomeric naphthimidazoles.

(13) Hartung, THIS JOURNAL, **50**, 3370 (1928).

(14) Schaefer, *Ind. Eng. Chem., Anal. Ed.*, **2**, 115 (1930).

(15) Fischer [*J. prakt. Chem.*, [2] **107**, 22 (1924)] reported m. p. 240°.

(16) Fieser, "Experiments in Organic Chemistry," Heath and Co., Boston, Mass., 1935, p. 165.

(17) McGookin and Swift, *J. Soc. Chem. Ind.*, **58**, 152 (1939).

(18) Witt and Uterman, *Ber.*, **39**, 3901 (1906).

This compound gave the qualitative tests for a primary aromatic amine.[19]

3-Amino-4-benzoylaminotoluene (XII)*.—To a solution of 15.2 g. (0.1 mole) of 3-nitro-4-aminotoluene in 27 cc. of pyridine was added 14.05 g. (0.1 mole) of benzoyl chloride, the solution refluxed for 3 hours and poured slowly into water. Pure 3-nitro-4-benzoylaminotoluene (XIII) was obtained by recrystallization of the crude product from benzene; yield, 20 g. (78%); m. p. 146–148°.

Eighteen grams (0.07 mole) of XIII was dissolved in 200 cc. of dioxane and hydrogenated at 20°. Water was added to the filtrate from the catalyst to precipitate the reduction product. The latter on recrystallization from ethyl alcohol gave colorless needles of 3-amino-4-benzoylaminotoluene (XII); yield, 13 g. (81%); m. p. 198–198.5°.[20]

Anal. Calcd. for $C_{14}H_{14}N_2O$: N, 13.39. Found: N, 13.30.

4-Amino-3-benzoylaminotoluene (XIV)*.—4-Nitro-3-aminotoluene was benzoylated by the method used for 3-nitro-4-aminotoluene. Recrystallization from benzene gave yellow prisms of 4-nitro-3-benzoylaminotoluene (XV)*; m. p. 97–98°; Morgan[19] gave m. p. 83°.

Anal. Calcd. for $C_{14}H_{12}N_2O_3$: N, 10.94. Found: N, 10.85.

The nitro compound (XV) was reduced and isolated in the same manner as XI; yield of XIV, 72%; m. p. 158°.

3-Amino-4-(N-methylacetamino)-toluene (XVI)*.—This compound was prepared from 3-nitro-4-aminotoluene by the method used by Roeder and Day[9] to prepare *o*-amino-N-methylacetanilide. 3-Nitro-4-aminotoluene → 3-nitro-4-(*p*-toluenesulfonamido)-toluene (XVII*, yield 83%, m. p. 101.5–102.5°) → 3-nitro-4-(N-methyl-*p*-toluenesulfonamido)-toluene (XVIII*, yield 95%, m. p. 123.5–124.5°) → 3-nitro-4-methylaminotoluene (XIX*, yield 94%, m. p. 185.2–185.5°). Compounds XVII, XVIII and XIX were purified by recrystallization from methyl alcohol.

3-Nitro-4-(N-methylacetamino)-toluene (XX)* was prepared by heating 20 g. (0.12 mole) of XIX with 36 cc. of acetic anhydride until solution was complete. The cooled solution was poured into water, neutralized with ammonium hydroxide and extracted with benzene. The benzene was evaporated and the residue recrystallized from ether; light yellow plates; yield, 20 g. (80%); m. p. 64.1–64.5°. Nineteen grams (0.092 mole) of the above nitro compound was reduced and isolated in the same manner as XI. Colorless needles of XVI were obtained; yield, 14 g. (88%); m. p. 167–167.5°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.86; N, 15.73. Found: C, 67.50; H, 8.06; N, 15.61.

3-Acetamino-4-methylaminotoluene (XXI)*.—Forty grams (0.24 mole) of 3-nitro-4-methylaminotoluene (XIX) was dissolved in 250 cc. of dry ethyl alcohol and hydrogenated at 20°. The filtrate from the catalyst, which darkened rapidly if allowed to stand, was immediately saturated with dry hydrogen chloride and ether added. The dihydrochloride (XXII)* was recrystallized from dry alcohol and dried *in vacuo* as colorless prisms, m. p. 147° (softens at 80°); Morgan[19] gave 175–185° with decomposition.

Anal. Calcd. for $C_8H_{14}N_2Cl_2$: N, 13.39. Found: N, 13.35.

All attempts to prepare the free base failed, as it darkened so rapidly in air that a good melting point and analysis were impossible.

The acetylated product (XXI) was prepared as follows. Ten and one-half grams of XXII was treated with an equivalent quantity of dilute sodium hydroxide and extracted with ether. To the dried ether solution was added an equivalent of sodium bicarbonate and an equivalent of acetic anhydride in 10 cc. of dry ether. After two hours, the solution was filtered and the filtrate treated with dry hydrogen chloride. The precipitated hydrochloride was dissolved in water and neutralized with dilute ammonium hydroxide. The almost colorless crystals were dried *in vacuo;* yield, 3 g. (35%); m. p. 135° (softened at 75°).

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.86; N, 15.73. Found: C, 67.51; H, 8.00; N, 15.60.

4-Amino-3-(N-methylacetamino)-toluene (XXIII).—This compound was prepared from 4-nitro-3-aminotoluene by the same series of reactions used for preparing 3-amino-4-(N-methylacetamino)-toluene.

4-Nitro-3-(*p*-toluenesulfonamido)-toluene (XXIV), yellow needles, yield 90%, m. p. 136–137°.

Anal. Calcd. for $C_{14}H_{14}N_2O_4S$: N, 9.15. Found: N, 9.03.

4-Nitro-3-(N-methyl-*p*-toluenesulfonamido)-toluene (XXV), yellow cubes, yield 92%, m. p. 89.3–90.3°.

Anal. Calcd. for $C_{15}H_{16}N_2O_4S$: N, 8.75. Found: N, 8.65.

4-Nitro-3-methylaminotoluene (XXVI)*, orange needles, yield 90%, m. p. 81–82°.

4-Nitro-3-(N-methylacetamino)-toluene (XXVII) was prepared by heating 5 g. (0.03 mole) of XXVI with 9 cc. of acetic anhydride and 0.2 cc. of concentrated sulfuric acid at 100° for two hours. The cold solution was poured into water, neutralized with ammonium hydroxide and extracted with benzene. The benzene solution was dried and evaporated. The oil which resulted could not be solidified.

The 4-amino-3-(N-methylacetamino)-toluene was prepared by hydrogenating a dry alcohol solution of the above oil by the same procedure used for XI; colorless needles; yield, 57%; m. p. 142–142.5°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.86; N, 15.73. Found: C, 67.39; H, 8.00; N, 15,68.

3-Methylamino-4-acetaminotoluene (XXVIII).—Ten grams (0.09 mole) of 4-nitro-3-methylaminotoluene (XXVI) was hydrogenated in dry alcohol solution. The filtrate from the catalyst was saturated immediately with dry hydrogen chloride; colorless needles of the dihydrochloride (XXIX) were obtained; yield, 8 g. (64%); m. p., decomposed at 190°.

Anal. Calcd. for $C_8H_{14}N_2Cl_2$: N, 13.39. Found: N, 13.36.

Attempts to prepare the free base yielded a product

(19) Morgan [*J. Chem. Soc.*, **103**, 1400 (1913)] noted that recrystallization of the product from benzene gave a compound, m. p. 145–150°, which he believed to be the corresponding imidazole, although he did not report any analyses.

(20) Harris [*Ber.*, **26**, 194 (1893)] reported m. p. 193–194°.

which darkened so rapidly that a good melting point and analysis were impossible.

The acetylated product (XXVIII) was prepared from the above dihydrochloride by the procedure used for XXI. To obtain a colorless product, it was necessary to have present a small amount of sodium hydrosulfite throughout the preparation. The free base so obtained contained some water which could not be removed easily without effecting ring closure. The product was dissolved in dry ether, dried over sodium sulfate and the compound isolated by evaporating the ether. After drying *in vacuo*, it melted at 74–78°.

Anal. Calcd. for $C_{10}H_{14}N_2O$: C, 67.41; H, 7.87; N, 15.73. Found: C, 67.80; H, 7.88; N, 15.36.

3-Benzalamino-4-acetaminotoluene (XXX).—To a suspension of 3-amino-4-acetaminotoluene in dry alcohol, was added an equivalent amount of freshly distilled benzaldehyde. After a few minutes of shaking, the compound was completely dissolved. After two hours the solution was evaporated to dryness on the steam-bath and the residue recrystallized from petroleum ether; yellow prisms; yield 78%; m. p. 88–90°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.34; N, 11.11. Found: C, 76.23; H, 6.36; N, 11.17.

4-Benzalamino-3-acetaminotoluene (XXXI).—This compound was prepared from 4-amino-3-acetaminotoluene by the method described for XXX; yellow prisms; yield, 84%; m. p. 122–123°.

Anal. Calcd. for $C_{16}H_{16}N_2O$: C, 76.19; H, 6.34; N, 11.11. Found: C, 76.10; H, 6.53; N, 11.13.

Ring Closures

One gram of 3,4-diacetaminotoluene (III) was heated in dry nitrogen at 180–190° for nine hours. The starting compound was quantitatively recovered: m. p. of sublimate, 211–211.5°; m. p. of unsublimed product, 211–211.5°; mixed m. p. with III, 211–211.6°.

One gram of III was heated in an atmosphere of dry nitrogen at 211–213° for two hours. Acetic acid was given off. The product was recrystallized from benzene and colorless crystals of 2,5(6)-dimethylbenzimidazole (I) were obtained; m. p. of sublimate and unsublimed product, 203–204°. The conversion was quantitative.

One gram of III was refluxed in 40 cc. of dry cymene for four hours. The starting compound was quantitatively recovered; m. p. 211–212°.

One and one-half grams of 3-amino-4-acetaminotoluene (IV) was heated just above its m. p. (133°) in dry nitrogen. After about fifteen minutes the liquid solidified. Recrystallization of the product from acetone gave 2,5(6)-dimethylbenzimidazole (I); m. p. of sublimate and unsublimed product, 203–204°. The conversion was quantitative.

Three grams of IV was refluxed in 50 cc. of dry xylene for four hours; weight of recovered product, 2.7 g. Most of the product melted at 116° and the small amount that remained was completely liquid at 198°. It was probably a mixture of the starting compound and the corresponding benzimidazole (I).

Two grams of IV was refluxed in 50 cc. of dry cymene for four hours. The 2,5(6)-dimethylbenzimidazole which separated from the solution on cooling was recrystallized from acetone; m. p. 203–204°; mixed m. p. with (I), 203–204°. The conversion was quantitative.

Eleven and one-half grams (0.07 mole) of IV was dissolved in 70 cc. of 4 *N* hydrochloric acid and the solution refluxed for one and one-half hours. The cooled solution was neutralized with sodium bicarbonate, and the precipitate recrystallized from acetone to yield colorless plates of the 2,5(6)-dimethylbenzimidazole (I); m. p. 203–204°; yield, 7 g. (68%).

Two grams of 4-amino-3-acetaminotoluene (X) was refluxed in 30 cc. of dry xylene for two hours. The starting compound was recovered quantitatively.

When X was heated just above its melting point in dry nitrogen, refluxed in dry cymene or refluxed with 4 *N* hydrochloric acid, the same 2,5(6)-dimethylbenzimidazole, m. p. 203–204° was obtained as was obtained under similar conditions from IV.

One and one-half grams of XII was refluxed in 50 cc. of dry xylene for four hours. The starting compound was quantitatively recovered; m. p. 198–199°; mixed m. p. with XII, 198–199°.

One gram of 3-amino-4-benzoylaminotoluene (XII) was heated at its m. p. 198°, in dry nitrogen. After two hours the liquid solidified. The crude product was recrystallized from benzene and colorless needles of 2-phenyl-5(6)-methylbenzimidazole (II) were obtained in quantitative yields; m. p. 249–250°.

One and one-half grams of XII was refluxed in 50 cc. of dry cymene for four hours. The recovered product on recrystallization from benzene gave colorless needles of II. The conversion was quantitative; m. p. 249–250°.

Four grams (0.018 mole) of XII was suspended in 20 cc. of 4 *N* hydrochloric acid and the mixture was boiled gently. Thirty cc. more of the acid was added together with 10 cc. of dioxane and 10 cc. of ethyl alcohol. However, complete solution was not effected. The mixture was refluxed for three hours, cooled and filtered. The product was suspended in water and neutralized with 3 *N* ammonium hydroxide. Recrystallization of the precipitate from benzene gave colorless needles of II; yield 3 g. (79%); m. p. 249–250°.

When 4-amino-3-benzoylaminotoluene (XIV) was heated just above its m. p. in dry nitrogen, refluxed in dry cymene or refluxed with 4 *N* hydrochloric acid, the same 2-phenyl-5(6)-methylbenzimidazole, m. p. 249–250°, was obtained as was obtained from XII under similar conditions.

One-half gram of 3-amino-4-(N-methylacetamino)-toluene (XVI) was refluxed in 10 cc. of dry cymene for four hours. Recrystallization from benzene gave quantitative recovery of the starting material, m. p. 166–167°, indicating ring closure had not occurred, mixed m. p. with XVI, 166–167°. Similar results were obtained with 4-amino-3-(N-methylacetamino)-toluene (XXIII).

One-half gram of 3-acetamino-4-methylaminotoluene (XXI) was refluxed in 10 cc. of dry benzene for four hours. The recovered product was recrystallized from petroleum ether; m. p. 141–142°. This corresponded to the m. p. of 1,2,5-trimethylbenzimidazole*, indicating ring closure had occurred. The conversion was quantitative.

One-half gram of 4-acetamino-3-methylaminotoluene (XXVIII) was refluxed in 10 cc. of dry benzene for two

hours. The starting material was quantitatively recovered.

One-half gram of XXVIII was refluxed in 10 cc. of dry toluene for four hours. The solution was cooled and evaporated under reduced pressure. The residue was recrystallized from petroleum ether and colorless prisms were obtained; m. p. 122–123°. This corresponded to the m. p. of 1,2,6-trimethylbenzimadazole*, indicating ring closure had occurred.

All attempts to hydrolyze 3-benzalamino-4-acetaminotoluene (XXX) and 4-benzalamino-3-acetaminotoluene (XXXI) with alcoholic potassium hydroxide, or to oxidize them directly with nitrobenzene failed to give a crystalline product. The tolimidazoles were successfully obtained by carrying out the oxidation and hydrolysis in the same reaction mixture. Three grams (0.012 mole) of XXX was dissolved in 6 cc. of freshly distilled nitrobenzene. To this solution was added a solution of 0.76 g. (0.014 mole) of potassium hydroxide in 40 cc. of hot dry ethyl alcohol, and the reaction mixture heated on a steam-bath for four and one-half hours. The solution was cooled overnight and filtered. The filtrate was evaporated under reduced pressure and the residue thoroughly washed with petroleum ether. This product was the potassium salt of the imidazole, which may be obtained in quantitative yields. Subsequent washing with water converted the potassium salt into the imidazole. Recrystallization from benzene gave colorless needles of the 2-phenyl-5(6)-methylbenzimidazole (II); m. p. 249–250°; yield, 2 g. (80%).

Three grams of XXXI was hydrolyzed and oxidized in the same manner as in the above experiment; yield, 1.8 g. (78%); m. p. 249–250°. Mixed m. p. with product obtained in the above experiment was 249–250°. Therefore, the same imidazole was obtained in both experiments.

Summary

1. The monoacyl derivatives have been shown to be the probable intermediates in the formation of the tolimidazoles from 3,4-diaminotoluene and organic acids.

2. Roeder and Day's mechanism for the splitting out of water in the formation of benzimidazoles has been extended to the tolimidazoles.

3. It has been shown that the tautomerism of the imidazoles probably cannot be explained by any one theory alone and it is possible that it involves both prototropy and electromerism depending upon the conditions.

4. Changing the radical in position 2 from a methyl to a phenyl group was shown to have no apparent immobilizing effect upon the orientation of the imidazole ring relative to the aromatic nucleus.

5. An improved method for the preparation of 4-nitro-3-amino-toluene is reported.

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Pro-γ-carotene

BY L. ZECHMEISTER AND W. A. SCHROEDER

A remarkable class of naturally occurring polyene pigments is composed of those C_{40}-carotenoids which contain several *cis*-double bonds in their chromophores. Such a configuration manifests itself in a lower melting point, higher solubility and especially by a spectrum in which the bands have been shifted to much shorter wave lengths than those present in the spectrum of the corresponding all-*trans*-carotenoid. These new pigments crystallize well and are then fairly heat resistant in this form. Their solutions, however, undergo isomerization, slowly when heated and very rapidly when treated with iodine or other suitable catalysts[1] *e. g.*, hydrochloric acid. Melting of crystals also causes isomerization. A complicated mixture of stereoisomers is thus formed in which large amounts of the corresponding ordinary carotenoid occur. The latter forms the top zone in a chromatogram of the mixture while the unchanged fraction of the starting material forms the lowest zone (or one near the lowest).

It has been suggested[2] that the prefix "pro" be attached to the current name of the all-*trans* carotenoid in order to designate the compounds belonging to the class under consideration. Such a nomenclature does not point to any essential difference in structure from the so-called "neo"-carotenoids which have been detected as artificial products. The absorption maxima of the latter are only moderately lower than those of the start-

(1) L. Zechmeister and P. Tuzson, *Biochem. J.*, **32**, 1305 (1938); *Ber.*, **72**, 1340 (1939); L. Zechmeister, L. Cholnoky and A. Polgár, *ibid.*, **72**, 1678 and 2039 (1939); G. Ph. Carter and A. E. Gillam, *Biochem. J.*, **33**, 1325 (1939); H. H. Strain, "Leaf Xanthophylls," Carnegie Institute of Washington Publ. No. 490, 1938, and THIS JOURNAL, **63**, 3448 (1941). For bixin and crocetin see P. Karrer, A. Helfenstein, R. Widmer and Th. B. van Itallie, *Helv. Chim. Acta*, **12**, 741 (1929), and R. Kuhn and A. Winterstein, *Ber.*, **66**, 209 (1933), and **67**, 344 (1934).

(2) L. Zechmeister, A. L. LeRosen, F. W. Went and L. Pauling, *Proc. Nat. Acad. Sci.*, **27**, 468 (1941).