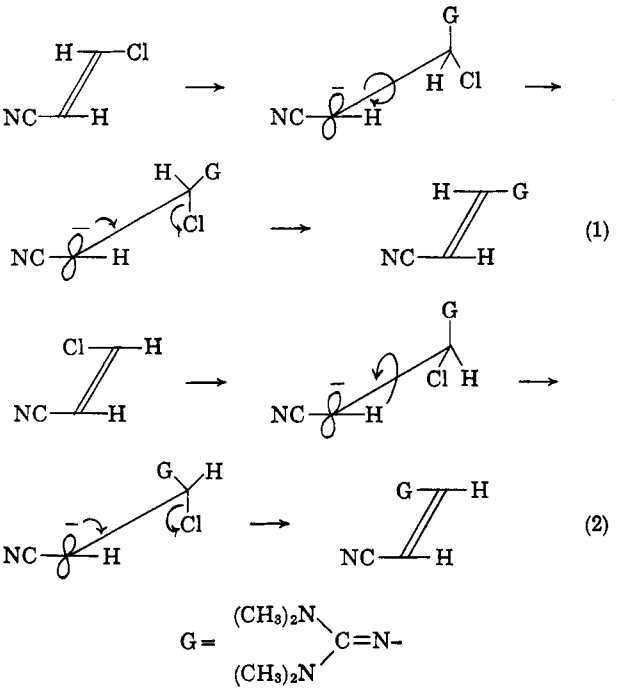
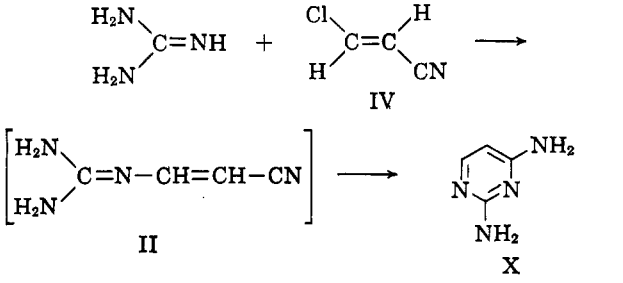


An attempt to synthesize the parent cyanovinylguanidine II from IV and guanidine was unsuccessful; the only product isolated was 2,4-diaminopyrimidine (X). Apparently addition–elimination occurred and was followed by cyclization to the aromatic system.



Experimental[6]

trans-2-(2-Cyanovinyl)-1,1,3,3-tetramethylguanidine (VII).—To a solution of 0.59 g. (5.0 mmoles) of 1,1,3,3-tetramethylguanidine in 5 ml. of benzene was slowly added 0.22 g. (2.5 mmoles) of *trans*-3-chloroacrylonitrile.[4] After 16 hr. at room temperature, the crystals, m.p. 202–205°, of tetramethylguanidine hydrochloride which separated were removed by filtration. The filtrate was concentrated under reduced pressure to a solid, which upon recrystallization from ether yielded 0.15 g. (37%) of an off-white solid, m.p. 89–90.5°. Two recrystallizations from ether afforded the analytical sample as long colorless prisms, m.p. 90–91°, λ_{max}^{KBr} 4.55 μ, and λ_{max}^{MeOH} 298 mμ (ϵ 26,600). The n.m.r. spectrum ($CDCl_3$) showed doublets at τ 2.48 and 5.27 (J = 14 c.p.s., one proton each) and a singlet at 7.07 (12 protons).

Anal. Calcd. for $C_8H_{14}N_4$: C, 57.80; H, 8.49; N, 33.71. Found: C, 57.44; H, 8.31; N, 33.44.

trans-2-(2-Cyanovinyl)-1,1,3,3-tetramethylguanidine Hydrochloride (IX).—An ethereal solution of 1.0 g. (6.0 mmoles) of *trans*-2-(2-cyanovinyl)-1,1,3,3-tetramethylguanidine was acidified with ethereal hydrogen chloride. The precipitate was collected and recrystallized from acetone to yield 0.53 g. (43%) of cream-colored crystals, m.p. 185–187°. An additional recrystallization afforded the analytical sample as long regular prisms, m.p. 187–188°, λ_{max}^{KBr} 4.50 μ, and λ_{max}^{MeOH} 258 mμ (ϵ 27,000). The n.m.r. spectrum (DMSO-d_6) showed doublets at τ 2.33 and 4.25 (J = 14 c.p.s., one proton each) and a singlet at 6.88 (12 protons).

Anal. Calcd. for $C_8H_{15}ClN_4$: C, 47.41; H, 7.41; Cl, 17.53; N, 27.65. Found: C, 47.20; H, 7.41; Cl, 17.31; N, 27.15.

cis-2-(2-Cyanovinyl)-1,1,3,3-tetramethylguanidine (VIII). A.—To a cold, stirred solution of 14.7 g. (0.13 mole) of 1,1,3,3-tetramethylguanidine in 100 ml. of benzene was added dropwise under nitrogen a solution of 5.5 g. (0.065 mole) of *cis*-3-chloroacrylonitrile.[4] The mixture was stirred at room temperature for 16 hr., the tetramethylguanidine hydrochloride which separated was removed, and the solution was concentrated under reduced pressure to a brown, oily solid. Three recrystallizations from ether yielded 3.1 g. (29%) of regular prisms, m.p. 53–56°, λ_{max}^{KBr} 4.55 μ, and λ_{max}^{MeOH} 299 mμ (ϵ 23,400). The n.m.r. spectrum ($CDCl_3$) showed doublets at τ 2.88 and 5.78 (J = 7 c.p.s., one proton each) and a singlet at 7.10 (12 protons). The melting point was depressed to 48–53° upon admixture with the *trans* isomer VII.

Anal. Calcd. for $C_8H_{14}N_4$: C, 57.80; H, 8.49; N, 33.71. Found: C, 57.48; H, 8.57; N, 33.34.

B.—To a cold, stirred solution of 1.7 g. (0.033 mole) of propiolonitrile[7] in 40 ml. of benzene was added dropwise under nitrogen a solution of 3.8 g. (0.033 mole) of 1,1,3,3-tetramethylguanidine in 30 ml. of benzene. The mixture was stirred at room temperature for 16 hr. and filtered. The filtrate was concentrated under reduced pressure to a brown tar. Two recrystallizations from ether yielded 0.25 g. (4.5%) of long colorless prisms, m.p. 55–59°.

Anal. Calcd. for $C_8H_{14}N_4$: C, 57.80; H, 8.49; N, 33.71. Found: C, 57.80; H, 8.57; N, 33.93.

The n.m.r. spectrum of the compound was identical with that of the product of method A.

Isomerization of *cis*- to *trans*-2-(2-Cyanovinyl)-1,1,3,3-tetramethylguanidine.—A mixture of 0.12 g. of *cis*-2-(2-cyanovinyl)-1,1,3,3-tetramethylguanidine, 0.2 g. of activated alumina, and 50 ml. of ether was heated under reflux for 5 hr. and filtered. The filtrate was concentrated under reduced pressure to 0.12 g. of liquid which crystallized on standing to a pale yellow solid, m.p. 84–85°. The melting point was not depressed upon admixture with *trans*-2-(2-cyanovinyl)-1,1,3,3-tetramethylguanidine. The n.m.r. spectrum of the product was identical with that of VII prepared above.

2,4-Diaminopyrimidine (X).—To a cold, stirred suspension of 3.0 g. (0.05 mole) of guanidine[8] in 150 ml. of acetonitrile was added dropwise a solution of 2.2 g. (0.025 mole) of *trans*-3-chloroacrylonitrile in 60 ml. of acetonitrile. The brown mixture was stirred overnight at room temperature and filtered. The filtrate was concentrated under reduced pressure to 3.5 g. of a brown solid, which was extracted with chloroform. Concentration of the chloroform solution left 0.45 g. of a tan solid, m.p. 122–140°. Three recrystallizations from isopropyl alcohol–hexane afforded colorless microcrystals, m.p. 147–149° (lit.[9] m.p. 149–150°). The ultraviolet spectrum of the compound, λ_{max}^{MeOH} 284 mμ (ϵ 6400), was identical with that of authentic 2,4-diaminopyrimidine.

(6) Melting points were determined in a Hershberg apparatus and are uncorrected. Microanalyses were performed by Mr. L. M. Brancone and staff. Ultraviolet and n.m.r. spectra were determined by Mr. W. Fulmor and staff.

(7) C. Moureu and J. C. Bongrand, *Ann. chim.* (Paris), [9] **14**, 47 (1920).

(8) W. Marckwald and F. Struwe, *Chem. Ber.*, **55**, 457 (1922).

(9) J. P. English and J. W. Clapp, U. S. Patent 2,416,617 (1947).

The Preparation of 2-Methyl-1-phenylbenzimidazole 3-Oxide

JOHN W. SCHULENBERG AND S. ARCHER

Sterling-Winthrop Research Institute, Rensselaer, New York

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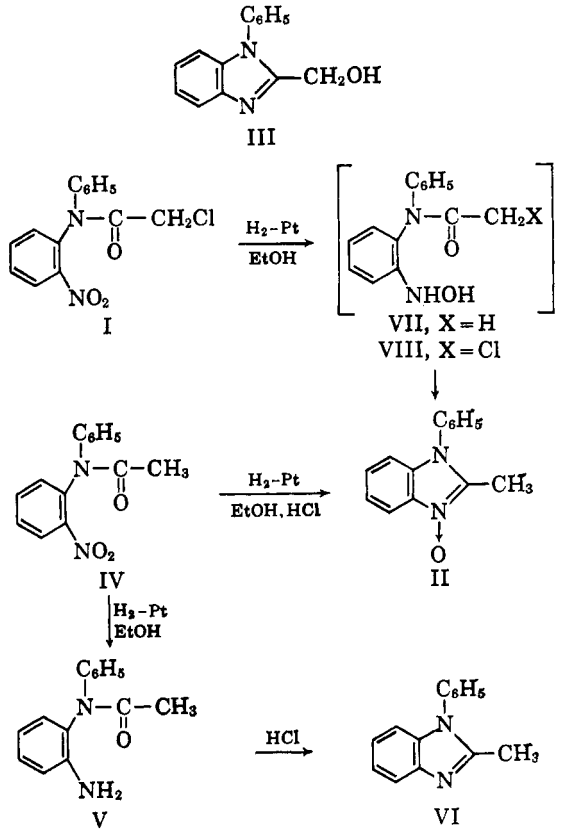
Several years ago we prepared 2-chloro-2′-nitro-N-phenylacetanilide (I) and hydrogenated it with platinum in ethanol. A hydrochloride was obtained in good yield. On the basis of analytical results, mechanistic considerations, and the absence of a carbonyl



band in the infrared spectrum, the structure 2-methyl-1-phenylbenzimidazole 3-oxide (II) was tentatively assigned. This could have resulted from reduction to the hydroxylamine stage, cyclization, dehydration to the N-oxide, and reductive dehalogenation (not necessarily in this order). One alternative structure, 1-phenylbenzimidazole-2-methanol (III), was eliminated by synthesis.

Recently, a series of benzimidazole N-oxides was synthesized by Takahashi and Kano by reduction of *o*-nitroanilides with hydrogen sulfide and ammonia.[1] Included in their report was the preparation of II from 2′-nitro-N-phenylacetanilide (IV). We repeated this reaction and obtained material identical with our hydrogenation product, confirming the postulated structure.

It was of interest to see if IV could be converted directly to the N-oxide II by catalytic hydrogenation. Under neutral conditions, IV has been reported to furnish the expected reduction product V.[1,2] It was claimed in one paper that hydrogenation of IV with platinum in 50% ethanol gave V but the same reaction in 95% ethanol afforded 2-methyl-1-phenylbenzimidazole (VI).[3] However, we have carried out this hydrogenation in 50% ethanol, 95% ethanol, absolute ethanol, and ethyl acetate and obtained V in good yield in all cases. The amide V can be converted to VI either by refluxing in xylene or by treatment with hydrochloric acid at room temperature.

When the hydrogenation of IV was carried out in ethanol in the presence of 0.2 mole of hydrochloric acid and the product was then treated with excess acid, the hydrochloride of VI was obtained. On the other hand, when 1 mole or more of acid was present during the reduction, the hydrochloride of the N-oxide II resulted in good yield. Therefore, acid can catalyze cyclization of the intermediate hydroxylamine (VII) to the point where ring closure is faster than reduction to the primary amine.[4] In the hydrogenation of the chloroacetyl derivative I, the hydrogen chloride generated by reductive dehalogenation must catalyze ring closure of VII and VIII. This catalytic dechlorination probably can occur at several stages, since we have found that 2-chloro-N,N-diphenylacetamide and 2-(chloromethyl)benzimidazole can be hydrogenolyzed to N,N-diphenylacetamide and 2-methylbenzimidazole hydrochloride, respectively.

Experimental[5]

2-Chloro-2′-nitro-N-phenylacetanilide (I).—A mixture of 107 g. (0.5 mole) of *o*-nitrodiphenylamine, 75 ml. (113 g., 1 mole) of chloroacetyl chloride, and 150 ml. of toluene was refluxed 4.5 hr. The solvent was removed *in vacuo* and the dark red oil was crystallized from absolute ethanol to give an orange solid. Recrystallization from absolute ethanol afforded 100 g. (69%) of yellow prisms: m.p. 122–124°; λ_{max} 232 mμ (ϵ 16,300) and 300 mμ (ϵ 1600); and 5.91 μ.

Anal. Calcd. for $C_{14}H_{11}ClN_2O_3$: C, 57.84; H, 3.81; Cl, 12.20. Found: C, 57.72; H, 3.94; Cl, 12.21.

2′-Nitro-N-phenylacetanilide (IV).[6]—A mixture of 21.4 g. (0.1 mole) of *o*-nitrodiphenylamine, 15 ml. (16.5 g., 0.21 mole) of acetyl chloride, 0.5 g. of zinc chloride, and 20 ml. of ben ene was stirred and refluxed 3 hr. After careful addition of 75 ml. of absolute ethanol, the product crystallized as a yellow solid, m.p. 133–136.5°, yield 21.3 g. (83%). Recrystallization from absolute ethanol gave 18.6 g., m.p. 134.5–137° (lit.[6] m.p. 134–135°).

2′-Amino-N-phenylacetanilide (V).—A mixture of 5.12 g. (0.02 mole) of recrystallized 2′-nitro-N-phenylacetanilide (IV), 100 ml. of ethyl acetate, and 200 mg. of platinum oxide was shaken under hydrogen on a Parr hydrogenator for 30 min. Removal of catalyst and solvent left a yellow oil which was crystallized from benzene–hexane to give 3.70 g. (82%) of white solid, m.p. 112–115° (lit.[2,3] m.p. 115–116°). Recrystallization from benzene–hexane furnished the analytical sample: m.p. 112.5–116.5°; λ_{max} 296 mμ (ϵ 3300); 2.88, 2.96 and 6.00 μ; δ = 7.17–7.87 (aromatic), 4.45 (NH_2), and 2.55 p.p.m. (CH_3).

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.73; H, 6.40; N, 12.24.

Similar hydrogenations in absolute ethanol and 95% ethanol gave yields of 80–83% while a 71% yield was obtained when 50% ethanol was used. Melting points and spectra showed that V, rather than 2-methyl-1-phenylbenzimidazole (VI), was the product in each case.

In some runs, a lower-melting form of V resulted. The melting point, 105–108°, was unchanged on recrystallization from benzene–hexane. When recrystallized again from the same solvent pair, but seeding with the higher-melting form, colorless rods, m.p. 112.5–116°, resulted. The infrared spectra of the two forms differed when run as solids (KBr), but chloroform solutions gave identical curves. The n.m.r. spectra (deuteriochloroform) of the two solids were identical.

(1) S. Takahashi and H. Kano, *Chem. Pharm. Bull.* (Tokyo), **11**, 1375 (1963).

(2) E. J. Forbes and R. T. Wragg, *Tetrahedron*, **8**, 79 (1960).

(3) P. A. S. Smith, B. B. Brown, R. K. Putney, and R. F. Reinisch, *J. Am. Chem. Soc.*, **75**, 6335 (1953).

(4) Catalytic hydrogenation of *o*-nitrophenylalanine has recently been reported to give similar results. The free base yields *o*-aminophenylalanine while the hydrochloride gives 3-amino-3,4-dihydro-1-hydroxycarbostyril: A. L. Davis, O. H. P. Choun, D. E. Cook, and T. J. McCord, *J. Med. Chem.*, **7**, 632 (1964).

(5) All melting points were determined in capillaries and are corrected. Ultraviolet spectra were run in 95% ethanol (Cary spectrophotometer), infrared spectra in potassium bromide disks (Perkin-Elmer 21), and n.m.r. spectra in deuteriochloroform using tetramethylsilane as the external standard (Varian A-60). We thank Dr. F. C. Nachod, Dr. R. K. Kullnig, Miss C. Martini, and Mr. M. Priznar for spectral determinations and Mr. K. D. Fleischer and staff for analytical results.

(6) F. Kehrmann and E. Baumgartner, *Helv. Chim. Acta*, **9**, 673 (1926). The literature procedure uses acetic anhydride.

2-Methyl-1-phenylbenzimidazole (VI).[7]—A solution of 2.26 g. (0.01 mole) of 2'-amino-N-phenylacetanilide (V) in 10 ml. of dry xylene was refluxed for 16 hr.[11,12] Solvent removal left a yellow oil which was crystallized from benzene–hexane to give 1.36 g. (65%) of pale tan crystals: m.p. 70.5–72.5°, lit.[8] m.p. 72–73°; δ = 7.50–8.33 (aromatic) and 2.87 p.p.m. (CH_3).

Hydrochloride. A.—A portion of the above base VI was dissolved in 2-propanol and treated with excess ethanolic HCl to give a white solid, m.p. 220–223°. Recrystallization from 2-propanol gave the analytical sample, m.p. 222–225°.

Anal. Calcd. for $C_{14}H_{13}ClN_2$: C, 68.71; H, 5.35; N, 11.45. Found: C, 68.77; H, 5.13; N, 11.28.

B.—A solution of 0.9 g. (0.004 mole) of 2'-amino-N-phenylacetanilide in acetone–ether was treated with 0.008 mole of ethanolic HCl and kept overnight at room temperature.[13] White needles began to crystallize about 1 hr. after the HCl was added. The product, 0.6 g. (60%), m.p. 220.5–223.5°, was shown by infrared spectrum and mixture melting point to be identical with material obtained by procedure A.[14] The reaction could be carried out, with comparable results, on crude V obtained directly from hydrogenation of IV.

2-Methyl-1-phenylbenzimidazole 3-Oxide Hydrochloride (II·HCl). A.—In a typical run, a mixture of 14.55 g. (0.05 mole) of 2-chloro-2'-nitro-N-phenylacetanilide (I), 200 mg. of platinum oxide, and 200 ml. of absolute ethanol was shaken under hydrogen on a Parr hydrogenator for 30–60 min. The hydrogen uptake was about 0.16–0.17 mole. The catalyst and solvent were removed and the resulting reddish brown gum or solid was crystallized from acetone–ether to give, in one case, 9.0 g. (69%) of off-white solid, m.p. 204–209° dec. Recrystallization from acetone gave white prisms, m.p. 205–210° dec.

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: C, 64.49; H, 5.02; N, 10.75. Found: C, 64.52; H, 5.12; N, 10.96.

Authentic hydrochloride was prepared from II (made by the literature procedure)[1] and found to melt at 202–207° dec. Infrared comparison and mixture melting point showed that the samples were identical.

In other runs, yields of 51–75% were obtained. In some runs, lower melting points (around 192–204°) resulted and the product was more difficult to purify. Carrying out the hydrogenation with added ethanolic HCl had little effect except that the yields were slightly lower and the products were somewhat darker. The product could also be obtained by carrying out the hydrogenation with platinum in ethyl acetate or palladium on carbon in ethanol. The product deteriorates slowly on long standing (several years) at room temperature.

B.—A mixture of 7.68 g. (0.03 mole) of 2'-nitro-N-phenylacetanilide (IV), 200 mg. of platinum oxide, 30 ml. of ethanolic HCl (0.065 mole), and absolute ethanol (total volume 200 ml.) was hydrogenated on the Parr apparatus for 30 min. About 10% more than the theoretical amount of hydrogen was absorbed. Removal of catalyst and solvent and crystallization of the residue from acetone–ether gave 4.45 g. (57%) of pale pink solid, m.p. 204–210°. The material was shown to be identical with the product obtained from I (procedure A, above) by infrared comparison and mixture melting point. When the hydrogenation was carried out using equimolar amounts of IV and HCl, a 62% yield of white solid, m.p. 200–205°, resulted.

When the hydrogenation was carried out with 0.02 mole of IV and 0.004 mole of HCl, the crude product then being treated at room temperature with excess ethanolic HCl in acetone, 2-methyl-1-phenylbenzimidazole hydrochloride (VI·HCl), m.p. 218.5–224.5°, was obtained in 48% yield. This product depressed the melting point of the N-oxide hydrochloride (II·HCl), but not that of authentic VI·HCl (above). Infrared comparison confirmed the assigned structure.

2-Methyl-1-phenylbenzimidazole 3-Oxide (II).—The hydrochloride of II (obtained by procedure A) was treated with aqueous potassium carbonate and the freed base was extracted with chloroform. A yellow solid was obtained and recrystallized from ethyl acetate to furnish almost white prisms (79%), m.p. 161–167° dec. Another recrystallization from ethyl acetate, followed by drying *in vacuo* at 100° (darkened) gave the analytical sample: m.p. 165–170° dec., lit.[1] m.p. 164–165°; λ_{max} 283 mμ (ϵ 8000); δ = 7.75–8.75 (aromatic) and 3.17 p.p.m. (CH_3). The product was compared with authentic material prepared by the literature procedure.[1] The two samples had identical infrared and ultraviolet spectra and a mixture of the two gave no depression in melting point.

Anal. Calcd. for $C_{14}H_{12}N_2O$: C, 74.99; H, 5.38; N, 12.49. Found: C, 75.42; H, 5.14; N, 12.39.

In one run, the product, after drying at only 75°, melted at 127–130° dec. The analyses suggested the formula $C_{14}H_{12}N_2O \cdot 0.75H_2O$, but this hydrate has been reported to melt at 97–100°.[1]

2'-Anilino-2-hydroxyacetanilide.—To a solution of 1.5 g. (0.02 mole) of glycolic acid in 10 ml. of methanol was added 3.7 g. (0.02 mole) of N-phenyl-*o*-phenylenediamine in 10 ml. of chloroform. Next, 4.5 g. (0.022 mole) of dicyclohexylcarbodiimide in 5 ml. of chloroform was added. After standing overnight at room temperature, the precipitated dicyclohexylurea was filtered off and the solvent was removed from the reddish purple filtrate. The residual gum was taken up in 2-propanol, additional dicyclohexylurea was filtered off (total 80%), and the filtrate was diluted with hexane to give 1.6 g. (33%) of light brown product, m.p. 144–149.5°. This was recrystallized from ethyl acetate to give an almost white solid: m.p. 148–151°; λ_{max} 282 mμ (ϵ 13,300); and 3.02 and 6.03 μ.

Anal. Calcd. for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.83; N, 11.56. Found: C, 69.55; H, 5.96; N, 11.89.

1-Phenylbenzimidazole-2-methanol (III).—A mixture of 5.9 g. (0.024 mole) of 2'-anilino-2-hydroxyacetanilide (m.p. 143–150°), 5 g. (0.026 mole) of *p*-toluenesulfonic acid hydrate, and 250 ml. of toluene was slowly distilled over a 3-hr. period. After cooling, aqueous sodium hydroxide was added and the freed base was extracted with ether. Solvent removal left a brown solid which was recrystallized from benzene to give 4.3 g. (80%) of white product, m.p. 131–133°.

Anal. Calcd. for $C_{14}H_{12}N_2O$: N, 12.49; N_{AP}, 6.25.[15] Found: N, 12.38; N_{AP}, 6.17.

The hydrochloride was prepared by adding ethanolic HCl to a solution of the base III in acetone. Upon recrystallizing from 2-propanol–acetone, small white needles, m.p. 192–197°, were obtained. A mixture melting point with the N-oxide hydrochloride (II·HCl) showed a marked depression.

Anal. Calcd. for $C_{14}H_{13}ClN_2O$: N, 10.75. Found: N, 10.53.

N,N-Diphenylacetamide.—A mixture of 7.4 g. (0.03 mole) of 2-chloro-N,N-diphenylacetamide,[16] 2 g. of 10% palladium on charcoal, and 140 ml. of absolute ethanol was shaken on a Parr hydrogenator until the theoretical amount of hydrogen was absorbed (5–6 hr.).[17] After removing the catalyst and solvent, the residue was crystallized from a small volume of 2-propanol to give 5.0 g. (79%) of white solid, m.p. 96–101°. Identity with authentic diphenylacetamide was proven by mixture melting point and infrared comparison.

2-Methylbenzimidazole Hydrochloride.—Hydrogenation of 5 g. (0.03 mole) of 2-(chloromethyl)benzimidazole with 200 mg. of platinum oxide in 95 ml. of absolute ethanol was complete in 2.25 hr. The product was crystallized from ethanol–ether to give 2 g. (40%) of tan solid, m.p. 293–298° dec. Comparison with authentic material by mixture melting point and infrared spectra proved the structure.

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(7) This compound has previously been prepared from 2'-anilinoacetanilide by treatment with acid,[8-10] from N-phenyl-*o*-phenylenediamine, acetic anhydride, and aqueous hydrochloric acid,[9] and from compound V and aqueous acid.[1]

(8) L. Wolff, *Ann.*, **394**, 59 (1912).

(9) M. A. Phillips, *J. Chem. Soc.*, 2820 (1929).

(10) F. Hunziker, F. Künzle, O. Schindler, and J. Schmutz, *Helv. Chim. Acta*, **47**, 1163 (1964).

(11) The uncatalyzed cyclization does not take place readily. Refluxing for 2 hr. in xylene gave a mixture which still contained starting material while heating V without solvent at 150–155° for 4 hr. gave back over 50% of unreacted amide. On the other hand, a sample of V which had been kept in the dark at room temperature for 5.5 years had completely cyclized to VI.

(12) The isomeric amide, 2'-anilinoacetanilide,[8,9] gave chiefly recovered starting material under these conditions.

(13) We were unable to induce the hydrochloride of V to crystallize. It is possible that the reported hydrochloride of V, m.p. 210–211°, is actually that of the benzimidazole VI; no analytical values were given.[9]

(14) 2'-Anilinoacetanilide[8,9] gave the hydrochloride of VI in comparable yield under these conditions.

(15) N_{AP} refers to determination of basic nitrogen by titration with perchloric acid in acetic acid.

(16) H. Frerichs, *Arch. Pharm.*, **241**, 220 (1903).

(17) When platinum was used, results were erratic. When the reaction was stopped after 1 mole of hydrogen had been taken up, over 60% of recovered starting material was obtained. Presumably, reduction of the aromatic rings occurred.