since it would not be subject to competitive decarboxylation.

Experimental Section

Ethyl 2-Phenylmalonanilate (7).—A catalytic amount of Na metal was added to a suspension of 0.237 g (1.0 mmol) of **4** in 2 ml of absolute EtOH in a dry reaction vessel. The mixture was allowed to stand overnight, giving a yellow-green solution. Evaporation of the solvent and recrystallization of the residue from ethanol–water gave 0.080 g (30%) of the ester **7**, mp 86°; ir (KBr) 3.01 (NH), 5.74 (ester C=O), 6.05 (amide I), and 6.56 μ (amide II); nmr τ 8.76 (t, 3, J = 7.0 Hz), 5.78 (q, 2, J = 7.0 Hz), 5.40 (s, 1), 2.74 (s, 10), and 1.04 (br, 0.96).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94; O, 16.94. Found: C, 71.96; H, 5.91; N, 4.96; O, 17.13.

Reaction of 2-Methyl-4-carbethoxy-3-isoxazolin-5-one (2) with Acetic Acid and Triethylamine.—The nmr spectrum was taken at intervals of a solution of 0.171 g (1.0 mmol) of **2**, 0.14 ml (1.0 mmol) of Et_3N, and 0.05 ml (1.0 mmol) of HOAc in 0.80 ml of $CDCl_3$. After several days, no **2** remained, and the spectrum was that of an enol of **23** (R = Me) isolated below. Evaporation of the solvent and sublimation (0.25 mm at 25°) gave a pure sample of the product, mp 32–33°; ir 3.04, 5.97, and 6.38 μ; nmr τ 8.73 (t, 3, J = 7.0 Hz), 7.70 (s, 3), 7.06 (d, 3, J = 4.5 Hz), 5.93 (q, 2, J = 7.0 Hz), 1.42 (br, 1), −7.96 (s, 1).

Anal. Calcd for $C_8H_{13}NO_4$: C, 51.33; H, 7.00; N, 7.48; O, 34.19. Found: C, 51.25; H, 7.02; N, 7.30; O, 34.06.

Stirring a sample of the product in water with a slight excess of sodium hydroxide resulted in hydrolysis to **1** (identified by nmr comparison with an authentic sample).

Registry No.—**7**, 20628-57-3; **23** (R = Me), 20628-58-4.

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A Novel Benzimidazole Reaction

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Reaction of benzimidazole with ethoxymethylenemalononitrile in ethanol produces **3a** instead of the expected **2** *via* further reaction of **2**. Thermal rearrangement of **4** also produces **3a**. The reaction of benzimidazole with ethoxymethylene compounds was extended to the preparation of **3b** and **3c**, **6a** and **6b**, **7a** and **7b**, and **8a** and **8b**. This reaction illustrates the principle of activation of imidazole rings toward nucleophilic attack by placing sufficiently electron-withdrawing substituents on the ring nitrogen atom.

Reaction of aliphatic and aromatic amines with ethoxymethylenemalononitrile (EMMN) leads to aminomethylenemalononitriles[1] (**1**). In the course of

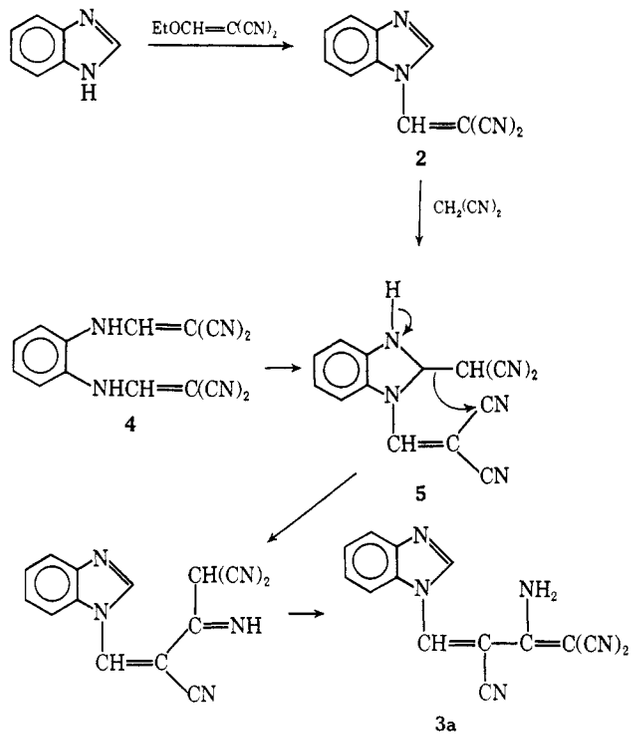
$$RR'NH + EtOCH{=}C(CN)_2 \longrightarrow \underset{\mathbf{1}}{RR'NCH{=}C(CN)_2}$$

synthesis of benzimidazole derivatives for biological studies, we treated benzimidazole with EMMN. This report deals with the unexpected result of this reaction and with the extension of the reaction to a general synthesis of some novel imidazole and benzimidazole derivatives.

Reaction of benzimidazole with 1 equiv of EMMN in hot ethanol produced **3a** (76% yield based on EMMN) instead of the expected (1-benzimidazoyl)methylenemalononitrile (**2**) (see Scheme I). The structure of **3a** was determined by spectral means. The major features of the mass spectrum of **3a** consist of the parent ion at m/e 260, the base ion at m/e 118 (benzimidazole radical cation), and the lower mass region that is remarkably similar to that of benzimidazole itself. The uv spectrum (EtOH) of **3a** reveals the characteristic benzimidazole absorptions at 240 mμ (log ϵ 3.75), 273 (3.89), and 278 (3.50). The uv maxima (EtOH) reported[2] for benzimidazole itself are at 243 mμ (log ϵ 3.68), 272 (3.82), and 279 (3.81). The ir spectrum of **3a** reveals NH_2 and CN absorptions. The nmr spectrum (DMSO) of **3a** reveals the NH_2 signal at τ −1.91 (disappears upon addition of D_2O), the imidazole ring proton as a singlet at 0.42, the benzene ring protons as a multiplet centered at 2.25, and the aliphatic vinyl proton signal at 2.85.

The structure of **3a** was further indicated by an

SCHEME I

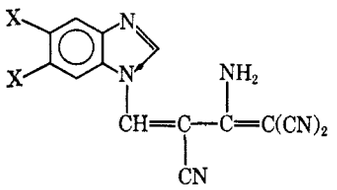


independent synthesis which started with reaction of *o*-phenylenediamine with 2 equiv of EMMN in ethanol at room temperature to give **4**. Thermal cyclization and intramolecular rearrangement of **4** in hot N,N-dimethylacetamide produced **3a** in 69% yield (Scheme I). Reaction of equimolar amounts of benzimidazole, EMMN, and malononitrile in ethanol also produces **3a** (92% yield); this is the preferred method.

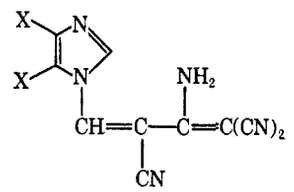
(1) A. A. Santilli, W. F. Bruce, and T. S. Osdene, *J. Med. Chem.*, **7**, 68 (1964).

(2) D. J. Rabiger and M. M. Joullié, *J. Org. Chem.*, **29**, 476 (1964).

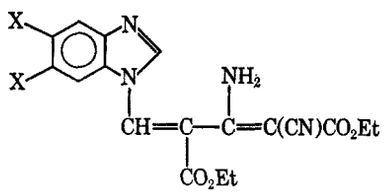
The reaction of benzimidazole with ethoxymethylene compounds and active methylene compounds was extended to the preparations of **3b** and **3c**, **6a** and **6b**, **7a** and **7b**, and **8a** and **8b**. An attempt to extend the reaction to the use of diethyl ethoxymethylenemalonate and diethyl malonate was unsuccessful.[3]



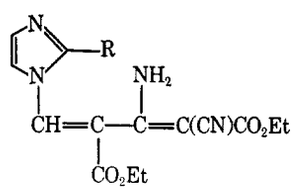
3a, X = H
b, X = CH_3
c, X = Cl



6a, X = H
b, X = C_6H_5



7a, X = H
b, X = CH_3



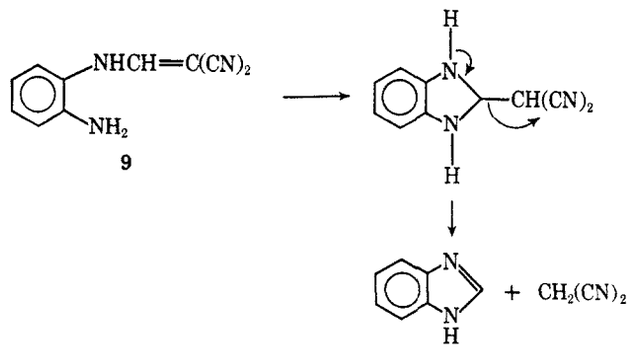
8a, R = H
b, R = CH_3

The most reasonable mechanisms for formation of **3a** from benzimidazole and from **4** are summarized in Scheme I. Evidently, malononitrile and triethyl orthoformate are produced in equilibrium with EMMN in ethanol. Reaction of benzimidazole with EMMN leads initially to **2** which could not be isolated because of its reactivity. The dicyanovinyl group is sufficiently electron withdrawing that the imidazole ring of **2** is strongly activated toward nucleophilic attack by malononitrile anion, which could be generated from malononitrile by proton transfer to unreacted benzimidazole. Intramolecular transfer of the dicyanomethyl group in **5** results in rearomatization and in a ring substituent that is less electron withdrawing. The product, **3a**, is considerably less susceptible to nucleophilic attack; an attempt to add a second molecule of malononitrile to **3a** was unsuccessful.

The first step of the rearrangement of **4** to **3a** *via* **5** parallels the first step of the reported[1] conversion of (2-aminoanilino)methylenemalononitrile (**9**) into benzimidazole (Scheme II). Intramolecular transfer instead of complete expulsion of the dicyanovinyl group in **5** leads to **3a**. An attempt to effect an intermolecular condensation of malononitrile with (3,4-dichloroanilino)-methylenemalononitrile, employing sodium methoxide as a catalyst, was unsuccessful.

(3) The attempt to extend the reaction to diethyl ethoxymethylenemalonate and diethyl malonate was unsuccessful probably because of the relative lack of reactivity of the carbethoxy group to condensation compared with a cyano group.

SCHEME II



9

Acylation of imidazole and benzimidazole under Schotten–Baumann conditions leads to fission of the imidazole ring *via* nucleophilic attack on the acylated imidazole ring.[4] Alkylation of benzimidazole with chlorotrifluoroethylene results in N-(2-chloro-1,1,2-trifluoroethyl)benzimidazole; this derivative is quite susceptible to nucleophilic attack on the imidazole ring with resultant ring opening followed by subsequent reactions dependent upon the nucleophile.[5] The present work provides another example of activation of imidazole rings toward nucleophilic attack by placing sufficiently strong electron-withdrawing groups on the ring nitrogen atom. This principle lends itself to the synthesis of a whole host of novel compounds through judicious selection of the alkylating or acylating agents and of the nucleophiles.

Experimental Section

Melting points were taken in open capillary tubes with a Mel-Temp apparatus and are corrected. Infrared spectra were determined on the compounds in mineral oil mulls with a Beckman IR-5 spectrometer. Nmr spectra were determined on the compounds in DMSO-d_6 solution with internal tetramethylsilane standard with a Varian A-60 spectrometer.

[*o*-Phenylenebis(iminomethylidyne)]dimalononitrile (4).—A mixture of 100 g (0.926 mol) of *o*-phenylenediamine and 244 g (2.00 mol) of ethoxymethylenemalononitrile in 1500 ml of ethanol was stirred for 2.5 hr at room temperature. The resultant solid, mp 203° dec, was collected and digested with 1.5 l. of hot acetone. The insoluble solid was collected and washed with acetone and ether to give 128 g (53%) of white solid: mp 202–203° dec; nmr τ −0.70 (bs, 2, NH), 1.80 [s, 2, CH=C(CN)$_2$], 2.59 (s, 4, ArH).

Anal. Calcd for $C_{14}H_8N_6$: C, 64.61; H, 3.10; N, 32.29. Found: C, 64.60; H, 3.38; N, 32.02.

2-Amino-4-(1-benzimidazolyl)-1,3-butadiene-1,1,3-tricarbonitrile (3a). Method A.—A solution of 11.8 g (0.10 mol) of benzimidazole, 12.2 g (0.10 mol) of ethoxymethylenemalononitrile, and 6.6 g (0.10 mol) of malononitrile in 200 ml of ethanol was held for 43 hr at reflux and then was allowed to cool. The resultant solid was collected and washed with ethanol to give 24 g (92%) of product: mp 223–224°; ir 3.03, 3.18 (NH), 4.57 (CN), 6.18 (weak), 6.46 μ; uv max (EtOH) 202 mμ (log ϵ 4.5), 240 (3.75), 261 (3.72), 267 (3.84), 273 (3.89), 278 (3.50), 344 (4.51); nmr τ −1.91 (bs, 2, NH_2), 0.42 (s, 1, N=CHN), 2.25 (multiplet, 4, ArH), 2.85 (s, 1, NCH=C).

Anal. Calcd for $C_{14}H_8N_6$: C, 64.61; H, 3.10; N, 32.29; mol wt, 260. Found: C, 64.48, 64.39; H, 3.08, 3.13; N, 32.36, 32.43; mol wt, 259, 262 (osmometry in tetrahydrofuran), 260 (mass spectrometry).

Method B.—A solution of 40 g (0.339 mol) of benzimidazole and 41.5 g (0.340 mol) of ethoxymethylenemalononitrile in 300

(4) K. Hofmann, "Imidazole and Its Derivatives, Part I," Interscience Publishers, Inc., New York, N. Y., 1953, pp 47, 48, 273–276.

(5) W. Reid and H. Lohwasser, *Angew. Chem. Intern. Ed. Engl.*, **5**, 835 (1966).

ml of ethanol was held for 4 days at reflux. The solution was allowed to cool. The resultant solid, 36.1 g, mp 204–215° dec, was crystallized from ethanol to give 33.9 g (76% based on ethoxymethylenemalononitrile) of solid, mp 225–226° dec. The ir spectrum of this material was identical with that of the product obtained by method A.

Method C.—A solution of 60 g (0.231 mol) of [*o*-phenylenebis(iminomethylidyne)]dimalononitrile in 600 ml of N,N-dimethylacetamide was stirred at 100° under nitrogen for 3 hr. The solution was concentrated under vacuum, and the residue was poured into 700 ml of water. The resultant solid, 51.6 g, mp 212–213° dec, was crystallized from 3 l. of hot water (filtration) to give 41.3 g (69%) of product, mp 223–224° dec. The ir spectrum of this material was identical with that of the products obtained by methods A and B.

2-Amino-4-(5,6-dimethyl-1-benzimidazolyl)-1,3-butadiene-1,1,-3-tricarbonitrile (3b).—Reaction of equimolar amounts of 5,6-dimethylbenzimidazole, ethoxymethylenemalononitrile, and malononitrile in ethanol at reflux for 5 days gave white needles, mp 255–256° dec (from ethanol with charcoal treatment), in 75% yield: ir 3.03 sh, 3.20 (NH), 4.58 (CN), 6.20 (weak), 6.46 (C=C) μ; nmr τ −3.95 (s, 2, NH_2), 0.57 (s, 1, N=CHN), 2.42 (s, 2, ArH), 2.93 (s, 1, NCH=C), 7.59 (s, 6, CH_3).

Anal. Calcd for $C_{16}H_{12}N_6$: C, 66.66; N, 4.20. Found: C, 66.50; H, 4.20.

2-Amino-4-(5,6-dichloro-1-benzimidazolyl)-1,3-butadiene-1,1,-3-tricarbonitrile (3c).—*Caution: skin irritant.* By a procedure similar to that employed for **3b** (reaction time, 1 day), the product, mp 268° dec (placed in melting point apparatus at 261°; melting point dependent on rate of heating), was obtained in 71% yield: ir 3.20 (NH), 4.56 (CN), 6.20 (weak), 6.50 μ.

Anal. Calcd for $C_{14}H_6Cl_2N_6$: C, 51.09; H, 1.84; N, 25.53. Found: C, 51.01; H, 1.75; N, 25.57.

2-Amino-4-(1-imidazolyl)-1,3-butadiene-1,1,3-tricarbonitrile (6a).—From equimolar amounts of imidazole, ethoxymethylenemalononitrile, and malononitrile in ethanol solution was obtained, after 18 hr at 23°, a solid product, mp 163–165°, in 46% yield: ir 3.1, 3.2 (NH), 4.58 (CN), 6.35, 6.48 μ; nmr τ −3.75 (bs, 2, NH_2), 0.70 (t, 1, J = 1 Hz, N=CHN), 2.07 (d, 2, J = 1 Hz, HC=CH), 2.82 (s, 1, NCH=C).

Anal. Calcd for $C_{10}H_6N_6$: C, 57.14; H, 2.87; N, 39.98. Found: C, 56.88; H, 2.94; N, 39.79.

2-Amino-4-(4,5-diphenyl-1-imidazolyl)-1,3-butadiene-1,1,3-tricarbonitrile (6b).—A solution of 11.0 g (0.050 mol) of 4,5-diphenylimidazole and 12.2 g (0.10 mol) of ethoxymethylenemalononitrile in 150 ml of ethanol was held for 4 days at reflux. The solvent was removed under vacuum, and the residual solid was crystallized from aqueous ethanol (charcoal) to give 4.3 g (24%) of product: mp 204–205° dec; ir 3.20 (NH), 4.57 (CN), 6.50 μ.

Anal. Calcd for $C_{22}H_{14}N_6$: C, 72.92; H, 3.89. Found: C, 72.82; H, 3.93.

Diethyl 3-Amino-4-(1-benzimidazolylmethylene)-2-cyanoglutaconate (7a).—A solution 11.8 g (0.10 mol) of benzimidazole, 16.9 g (0.10 mol) of ethyl 2-cyano-3-ethoxyacrylate, and 11.3 g (0.10 mol) of ethyl cyanoacetate in 100 ml of ethanol was held for 4 days at reflux and then was allowed to cool. The resultant solid, 28.0 g (79%), mp 193–195°, was collected: ir 3.2 (NH), 4.56 (CN), 5.90, 6.12, 6.20, 6.50 μ; nmr τ −3.19 (bs, 2, NH_2), 0.43 (s, 1, N=CHN), 1.93 (s, 1, NCH=C), 2.25 (multiplet, 4, ArH), 5.90 (q, 4, OCH_2CH_3), 8.80 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{18}H_{18}N_4O_4$: C, 61.01; H, 5.11; N, 15.81. Found: C, 60.77; H, 5.20; N, 15.64.

Diethyl 3-Amino-2-cyano-4-[(5,6-dimethyl-1-benzimidazolyl)-methylene]glutaconate (7b).—Prepared by the procedure for **7a** with a reaction time of 19 hr, the product, mp 203–204°, was obtained in 65% yield: nmr τ −3.51 (bs, 2, NH_2), 0.57 (s, 1, N=CHN), 1.94 (s, 1, NCH=C), 2.37 (s, 2, ArH), 5.92 (q, 4, OCH_2CH_3), 7.59 (s, 6, CH_3), 8.82 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{20}H_{22}N_4O_4$: C, 62.82; H, 5.80; N, 14.65. Found: C, 62.55; H, 5.84; N, 15.00.

Diethyl 3-Amino-2-cyano-4-[(1-imidazolyl)methylene]glutaconate (8a).—Prepared by the procedure for **7a**, the product obtained after removal of the solvent was crystallized from water to give a yellow solid, mp 152–154°, in 59% yield: nmr τ −3.62 (bs, 2, NH_2), 0.91 (t, 1, J = 1 Hz, N=CHN), 1.91 (s, 1, NCH=C), 2.31 (d, 2, J = 1 Hz, HC=CH), 5.91 (q, 4, OCH_2CH_3), 8.82 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.14; H, 5.38; N, 18.20.

Diethyl 3-Amino-2-cyano-4-[(2-methyl-1-imidazolyl)methylene]glutaconate (8b).—Prepared by the procedure for **7a**, the product, mp 183–185°, was obtained in 91% yield: nmr τ −2.11 (b, 2, NH_2), 1.91 (s, 1, NCH=C), 2.43 (s, 2, HC=CH), 5.90 (q, 4, OCH_2CH_3), 7.41 (s, 3, CH_3), 8.82 (t, 6, OCH_2CH_3).

Anal. Calcd for $C_{15}H_{18}N_4O_4$: C, 56.60; H, 5.70; N, 17.60. Found: C, 56.62; H, 5.82; N, 17.40.

Registry No.—**3a**, 20406-91-1; **3b**, 20406-92-2; **3c**, 20546-01-4; **4**, 20406-93-3; **6a**, 20406-98-8; **6b**, 20406-94-4; **7a**, 20406-99-9; **7b**, 20406-95-5; **8a**, 20406-96-6; **8b**, 20406-97-7.

The Synthesis of Substituted 2,1-Benzisothiazoles

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Received March 7, 1969

2,1-Benzisothiazole (**3**) and nine substituted 2,1-benzisothiazoles have been synthesized by the reaction of thionyl chloride with an appropriately substituted 2-aminotoluene (*o*-toluidine) in xylene at reflux temperature. Yields as high as 80% may be obtained. Liquid benzisothiazoles are conveniently isolated as picrate salts. The mechanism of formation of **3** is discussed and an intermediate benzylidenesulfinyl compound (**8**) is postulated. Nmr and uv data are presented.

2,1-Benzisothiazole (**3**) and its derivatives have received little attention from chemists in the 70 years since the parent compound was prepared by Gabriel and Stelzner.[1] The original method, reduction by stannous chloride and hydrochloric acid of 2-nitrotoluene-α-thiol, was recently supplemented by a procedure involving the iodine oxidation of an alkaline solution of 2-aminotoluene-α-thiol.[2]

Both of these methods suffer from the disadvantage of requiring relatively inaccessible, air-sensitive thiols, and, although in principle such methods could be extended to the synthesis of many substituted 2,1-benzisothiazoles, in practice such an approach is tedious. In exploratory work, we prepared 5-bromo-2,1-benzisothiazole by the oxidative cyclization of the corresponding aminothiol, but the yield was low. The only substituted 2,1-benzisothiazoles so far reported are those with 3-amino substituents, prepared by peroxide oxidation of 2-aminophenylthioamides.[3,4] By contrast,

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(2) J. Goerdeler and J. Kandler, *ibid.*, **92**, 1679 (1959).
(3) Parke, Davis & Co., Netherlands Patent Application 6408290 (1965); *Chem. Abstr.*, **63**, 1768b (1965).
(4) R. F. Meyer, B. L. Cummings, P. Bass, and H. O. J. Collier, *J. Med. Chem.*, **8**, 515 (1965).