systems, **4** and **6**. In addition, a parent molecular ion peak was observed in the mass spectrum of **9a**, R = H, at *m/e* 220.

In summary, condensation of mercaptoazoles with bromomethyldimethylchlorosilane, followed by cyclodehydrohalogenation, constitutes a simple two-step entry into fused silaazoles. This synthetic pathway should be applicable to other azoles such as mercaptotriazoles and mercaptotetrazoles. Compounds **4**, **6**, **8**, and **9** are currently being screened for pharmacological activity.

Experimental Section

General. Elemental analyses were determined by Hoffmann-La Roche, Nutley, N. J., Pascher Microanalytical Laboratory, Bonn, Germany, and by Heterocyclic Chemical Corp., Harrisonville, Missouri. Infrared spectra were determined using a Perkin-Elmer 457 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian A-60 spectrometer. All mass spectra were obtained from an AEI MS-902 spectrometer.

Bromomethyldimethylchlorosilane and 1,8-bis(dimethylamino)-naphthalene were purchased from Pierce and Aldrich Chemical Co., respectively, and were used as received. The mercaptoazoles were commercially available and were recrystallized from aqueous ethanol and then oven dried, prior to use.

Solvents were purified by standard techniques. All reactions were run under a nitrogen atmosphere. All weighings and reaction work ups were carried out in a glove bag (N_2 atmosphere).

General Procedure for Reactions of Mercaptoazoles (2, 7) with Bromomethyldimethylchlorosilane (3). To a solution of the mercaptoazole in THF (40–70 ml) was added, by syringe techniques, an approximately equimolar amount (7–15 mmol) of bromomethyldimethylchlorosilane. The mixture was stirred at room temperature for 1 day and filtered, and the white solid was washed well with the THF and then dried *in vacuo*. The yields, melting points, and analytical data for **4** and **8** are listed in Table I.

General Procedure for Cyclodehydrohalogenation of 4 and 8. A suspension of **4** or **8** (5–12 mmol) in THF (50–80 ml) containing 1,8-bis(dimethylamino)naphthalene (1.0–1.5:1.0 mol ratio of **5**:**4**,**8**) was stirred for 1 day at room temperature. The solution was filtered to remove protonated **5** and any unreacted **4** or **8**, and the filtrate was evaporated *in vacuo*. The residue obtained was treated with hexane and filtered, and the product (**6**, **9**) was washed well with hexane and dried. The hexane washings contained unreacted **5** (if present). The yields, melting points, and analytical data for **6** and **9** are given in Table I.

Acknowledgment. We are indebted to the National Institutes of Health for support of this research. We thank Mr. R. W. Stout for carrying out some preliminary experiments.

Registry No.—**2a**, 872-35-5; **2b**, 3718-54-5; **3**, 16532-02-8; **4a**, 53178-96-4; **4b**, 53279-97-5; **6a**, 53178-98-6; **6b**, 53178-99-7; **7a**, 583-39-1; **7b**, 6325-91-3; **8a**, 53179-00-3; **8b**, 53179-01-4; **9a**, 53179-02-5; **9b**, 53179-03-6; i, 53179-03-6.

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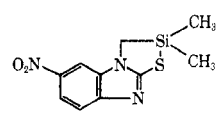

i

Benzimidazole Chemistry. I. Syntheses of the Three *N*-*n*-Propyl Isomers of 4-Amino-2,6-dimethylbenzimidazole

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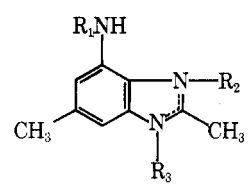
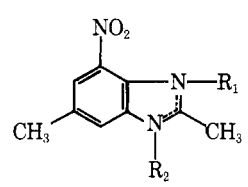
The specific preparations of 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (**1**), 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (**2**), and 4-*n*-propylamino-2,6-dimethylbenzimidazole (**3**) are described. These methods make use of the regiospecific or highly regioselective acylation and alkylation possible in the substrates. A correlation of isomeric structure with nmr spectra is also presented.

The regiospecificity of acylation and alkylation at multiple sites available in substituted fused imidazoles has received the greatest attention with purine derivatives because of their importance in living systems.[1] These data have received only limited application to the prediction of the reactivity of substitution of benzimidazoles.[2] For this reason the syntheses of 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (**1**), 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (**2**), and 4-*n*-propylamino-2,6-dimethylbenzimidazole (**3**) were attempted in order to obtain authentic examples of the three structures for comparison. Similarly 1-*n*-propyl-2,6-dimethyl-4-nitrobenzimidazole (**4**) was prepared and an unsuccessful attempt was made to synthesize 1-*n*-propyl-2,5-dimethyl-7-nitrobenzimidazole (**5**).



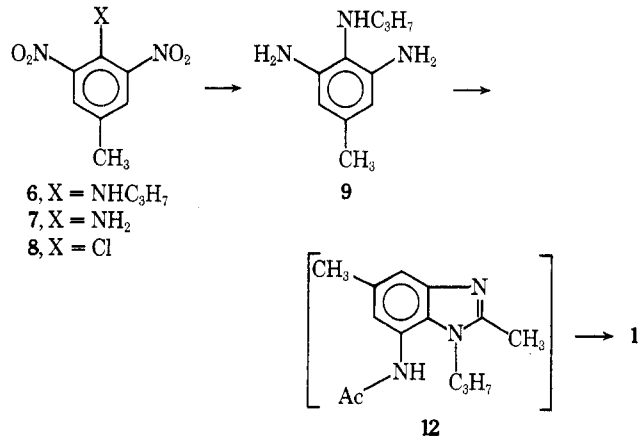
1, R_1 = H; R_2 = *n*-C_3H_7; R_3 =
2, R_1 = H; R_3 = *n*-C_3H_7; R_2 =
3, R_1 = *n*-C_3H_7; R_2 = H; R_3 =



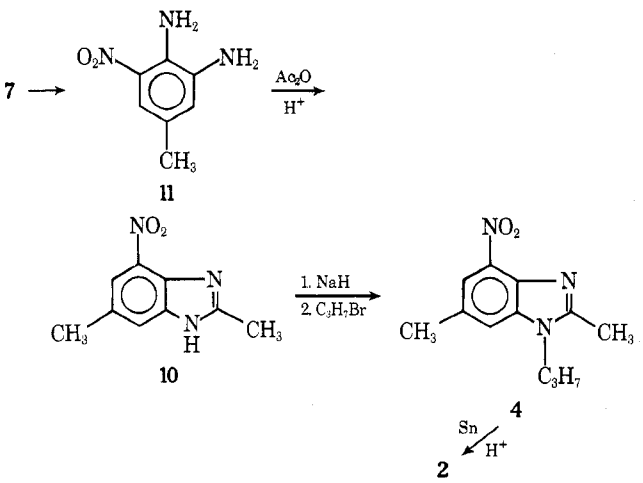
4, R_2 = *n*-C_3H_7; R_1 =
5, R_1 = *n*-C_3H_7; R_2 =

The synthesis of authentic **1** could be accomplished from the symmetrical *N*-*n*-propyl-2,6-dinitro-*p*-toluidine (**6**) obtained from 2,6-dinitro-*p*-toluidine (**7**)[3] by a Sandmeyer

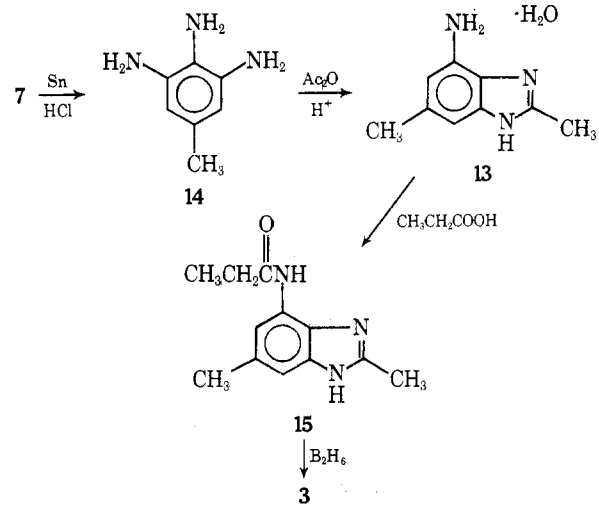
reaction[4] to 4-chloro-3,5-dinitrotoluene (8) followed by nucleophilic displacement of the halogen with *n*-propylamine. The structure of 6 was evident from the method of synthesis and the nmr spectrum which required a symmetrical structure. The reduction of the nitro groups with tin and hydrochloric acid gave the triamine 9, which underwent cyclization with acetic anhydride to the intermediate acylated benzimidazole 12. Hydrolysis of the acetamide gave authentic 1-*n*-propyl-7-amino-2,5-dimethylbenzimidazole (1) in 42% overall yield from 8.



The synthesis of authentic 1-*n*-propyl-4-amino-2,6-dimethylbenzimidazole (2) was based on the selectivity of alkylation of adenine[5] and the anticipated steric interference to alkylation at a nucleophilic position adjacent to the large nitro group. Thus, 4-nitro-2,6-dimethylbenzimidazole (10), prepared from 7 by selective reduction of one nitro group to 3-nitro-5-methyl-*o*-phenylenediamine (11)[6] and ring closure, was converted to the anion with sodium hydride and alkylated with *n*-propyl bromide. The product was reduced with tin and hydrochloric acid to give a compound differing from 1 in melting point and spectral data. The only logical structure for this product is 2 based on the method of formation and spectral data, *vide infra*.



The synthesis of the third isomer, 3, was also based on the selectivity observed on acylation of adenine which was shown to form an unstable diacyl derivative which was rapidly hydrolyzed to the 6-acyladenine.[7] Thus, 4-amino-2,6-dimethylbenzimidazole (13) was prepared by cyclization with acetic anhydride of the triamine 14 formed from the tin and hydrochloric acid reduction of 7. Heating 13 with propionic acid gave a propionamide the infrared spectrum of which showed absorption bands at 1650 and 1538 cm^{-1} indicative of a secondary amide. These data are consistent with the structure 15. Reduction of 15 with diborane[8] gave the desired 4-*n*-propylamino-2,6-dimethylbenzimidazole (3).



The alkylation of the anion of 15 was attempted, for this reaction should give substitution at the amide nitrogen at position 4, or the imidazole nitrogen farthest removed from the amide group, providing an alternate synthesis of 3 or 2, depending on the site of alkylation. The alkylation product was hydrolyzed and the nmr clearly showed that alkylation had occurred on the imidazole ring, for the triplet for the NCH_2 was at about 4 ppm. Further study clearly showed the product to be 4-amino-2,6-dimethyl-1-propylbenzimidazole (2).

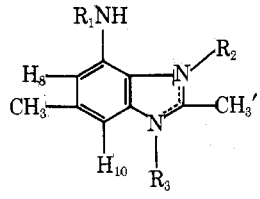
The alkylation of 2,6-dimethyl-4-nitrobenzimidazole (10) provided a synthetic method for 1-*n*-propyl derivative 4 and an alternate route was investigated for the preparation of 2,5-dimethyl-1-*n*-propyl-7-nitrobenzimidazole (5) from the corresponding amino derivative 1. Attempted oxidation of the amino group with peracids[9] or the replacement of the diazonium salt with nitrite ion using a copper catalyst[10] failed to give an isolable product. Apparently extensive decomposition occurred in the former reaction and reduction and phenol formation resulted by the second method. These data suggest that severe steric interaction between a 1-alkyl group and a 7-substituent provides unfavorable interference in the transition state for the formation of 5. No further attempt was made to prepare 5.

Discussion of Nmr Spectra

The chemical shifts relative to TMS for the protons of the three isomers are listed in Table I. In comparing compounds 1 and 2, it is worthwhile to compare the aromatic protons (H_8 and H_{10}) and the *N*-methylene group of each. When the propyl group is in the 3 position (R_2) both aromatic protons are relatively unaffected; thus, H_{10} appears at 7.01 ppm and H_8 at 6.37 ppm. When the propyl group is in the 1 position (R_3) in compound 2, H_{10} should be shielded and, therefore, be shifted. H_8 has the exact same chemical shift in 1 and 2. The chemical shift of the NCH_2 group has also changed. This is due presumably to the fact that this group in the 3 position (R_2) is deshielded by the 4-amino function. Thus, there is an upfield shift of 0.16 ppm for the NCH_2 in going from compound 1 to 2.

As one might expect, there is a large difference in the chemical shifts of 3 relative to those of 1 and 2. The electron-poor imidazole ring as well as the aromatic ring current deshield the methylene protons of the NCH_2 leading to an 0.8–1.0 ppm downfield shift in 1 and 2 as compared with 3. The aromatic protons are shifted upfield due to the inductive effect of the propyl group.

Table I[11]
Nmr Spectra of *N*-*n*-Propylbenzimidazole



Compd	R_1	R_2	R_3	H_{10} (s)	H_8 (s)	CH_3' (s)	CH_3 (s)	n-C_3H_7 NCH_2 (t)	n-C_3H_7 CH_2 (h)	n-C_3H_7 CH_3 (t)
1	H	n-C_3H_7		7.01	6.37	2.52	2.36	4.12	1.84	0.96
2	H		n-C_3H_7	6.52	6.37	2.55	2.39	3.96	1.81	0.95
3	n-C_3H_7	(H)	(H)	6.41	6.12	2.41	2.34	3.12	1.58	0.91

It is evident from these data that within a series of substituted benzimidazoles the location of a substituent can be determined by nmr spectroscopy.

The position of alkylation and acylation of 4-amino-2,6-dimethylbenzimidazole can be compared with the corresponding reactions in purines. The primary amino group on the benzo ring is acylated more readily than the imidazole nitrogens and gives a more stable acyl derivative. Alkylation of the benzimidazole anion occurs at the less hindered nitrogen of the imidazole ring.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus and were not corrected Elemental analyses were determined using an F&M Model 185, C, H, and N analyzer. Infrared spectra were determined using a Perkin-Elmer Model 337 spectrometer with samples prepared as KBr pellets. The nuclear magnetic resonance spectra were determined using a JEOL Model MH-100 spectrometer.

4-Chloro-3,5-dinitrotoluene (8). A solution of 5.6 g (0.081 mol) of sodium nitrite in 120 ml of concentrated sulfuric acid was cooled to 20° and a slurry of 14.7 g (0.075 mol) of 4-amino-3,5-dinitrotoluene (7) in 150 ml of warm glacial acetic acid was added at such a rate to keep the temperature below 40°. After stirring for 0.5 hr at 40°, the solution was added in portions to 15.8 g (0.16 mol) of cuprous chloride in 150 ml of concentrated hydrochloric acid. After the addition was finished, the reaction mixture was heated at 80° for 0.5 hr. The yellow solid which had separated was removed by filtration. The solid was boiled in 500 ml of benzene and the solution was decanted from the inorganic solids. Evaporation of the benzene gave 12.4 g (76.5%) of 4-chloro-2,5-dinitrotoluene (8) as a yellow solid: mp 112–114° (lit.[12] mp 113–114°).

4-*N*-Propylamino-3,5-dinitrotoluene (6). A solution of 5.0 g (0.023 mol) of 8 in 40 ml of benzene and 5 ml of triethylamine was placed in a 250-ml round-bottomed flask and 7.4 g (0.125 mol) of *n*-propylamine was added. The mixture was heated under reflux for 2 hr and the solvent was evaporated to give a mixture of solid and oil. This mixture was triturated with 70 ml of hot pentane and the insoluble material removed by filtration. The filtrate was evaporated in a hood, leaving behind 4-*N*-propylamino-3,5-dinitrotoluene (6) as orange solid. Recrystallization from hexane afforded 5.5 g (100%) of 6: mp 65–66° (lit.[13] 55°).

Anal. Calcd for $C_{10}H_{13}N_3O_4$: C, 50.21; H, 5.48; N, 17.57. Found: C, 49.90; H, 5.54; N, 17.33.

4-Amino-2,6-dimethyl-3-propylbenzimidazole (1). A three-necked 500-ml round-bottomed flask, fitted with a condenser and overhead stirrer, was charged with 120 ml of concentrated hydrochloric acid. Mossy tin (18.0 g) was carefully added, followed by 7.2 g (0.030 mol) of 6 and the mixture was heated for 1 hr. After cooling to 5° with an ice bath, 75 ml of $CHCl_3$ was added. The mixture was made basic with 140 g of 50% NaOH, then filtered to remove the insoluble inorganics. The $CHCl_3$ layer was separated from the filtrate and the aqueous layer was extracted four more times with 25-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were washed with 50 ml of H_2O, dried over Na_2SO_4, filtered, and evaporated to give 4.0 g (74.1%) of 9 as a light red oil: nmr ($CDCl_3$, in ppm) 6.03 (s, 2 H), 3.44 (br, 5 H), 2.84 (t, 2 H), 2.14 (s, 3 H), 1.58 (h, 2 H), 0.96 (t, 3 H).

This oil was immediately treated with 20 ml of acetic anhydride in a 250-ml round-bottomed flask and heated on a steam bath for 15 min. After cooling, the mixture was treated with 60 ml of 3 *N* hydrochloric acid, and then heated under reflux for 2.5 hr. The mixture was cooled, made basic with concentrated NH_4OH, and extracted four times with 25-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were evaporated, and the residue was added to 40 ml of 6 *N* HCl and heated under reflux for 2.5 hr. The mixture was made basic with concentrated NH_4OH and extracted three times with 30-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried over Na_2SO_4, filtered, and evaporated leaving behind a crude solid. Recrystallization of the solid from 25% aqueous ethanol afforded 2.3 g (51.5%) of 1 as light brown needles, mp 185–186°.

Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.87; H, 8.54; N, 20.73.

3,4-Diamino-5-nitrotoluene (11). A solution of 11.82 g (0.0600 mol) of 7 in 150 ml of dimethoxyethane and 15 ml of chloroform was hydrogenated over 600 mg of 10% Pd/C at ambient temperature and a pressure of 3 atm. The mixture was allowed to absorb the amount of hydrogen required to reduce one nitro group during 1.5 hr. The catalyst was removed by filtration through a Celite pad, and the filtrate was concentrated by evaporation in a hood to give a dark solid residue. Recrystallization of the solid from 40% aqueous ethanol gave 8.1 g (81%) of 11 as a dark red crystalline solid: mp 152–154° (lit.[14] 152–154°).

2,6-Dimethyl-4-nitrobenzimidazole (10). A solution of 7.5 g (0.045 mol) of 11 and 25 ml of acetic anhydride was heated in a 500-ml round-bottomed flask on a steam bath for 0.5 hr. The flask was fitted with a condenser, and 80 ml of 3 *N* hydrochloric acid was added to the cooled reaction mixture. The mixture was heated under reflux 1 hr and diluted with 100 ml of H_2O. The solution was boiled with Norit briefly and then filtered through a Celite pad. The cooled filtrate was made basic by addition of concentrated NH_4OH. The precipitate which formed was removed by filtration and dried. Recrystallization of the solid from 35% aqueous EtOH gave 4.8 g (56%) of 10 as a tan solid, mp 238–240° (lit.[14] 238–240°).

2,6-Dimethyl-4-nitro-1-propylbenzimidazole (4). A mixture of 4.78 g (25.0 mmol) of 10, 1.06 g (25.0 mmol) of a 57% NaH–paraffin oil dispersion, and 100 ml of dry tetrahydrofuran was heated under reflux for 3 hr. To the cooled solution was added 12.3 g (0.100 mol) of *n*-propyl bromide, and the mixture was heated at reflux for 36 hr. The mixture was cooled and 200 ml of H_2O was added. The aqueous solution was extracted four times with 30-ml portions of $CHCl_3$, and the combined $CHCl_3$ layers were dried (K_2CO_3), filtered, and evaporated, leaving 3.8 g (66%) of a brown solid, the nmr of which showed the presence of only 4. Recrystallization from 40% aqueous EtOH afforded 4 as gold needles, mp 135.5–136°.

Anal. Calcd for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48; N, 18.01. Found: C, 61.53; H, 6.48; N, 17.63.

4-Amino-2,6-dimethyl-1-propylbenzimidazole (2). A mixture of 1.00 g (4.30 mmol) of 4, 3.0 g of mossy tin, and 20 ml of concentrated hydrochloric acid was placed in a 100-ml round-bottomed flask and heated on a steam bath for 1.5 hr. The cooled mixture was made basic with 30 g of 50% NaOH, and then extracted four times with 25-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried over Na_2SO_4, filtered, and evaporated leaving an oil, which solidified when triturated with pentane. Recrystallization of the solid from hexane afforded 0.66 g (75.9%) of 2 as white needles, mp 94–95°.

Anal. Calcd for $C_{12}H_{17}N_3$: C, 70.90; H, 8.43; N, 20.67. Found: C, 70.79; H, 8.58; N, 20.52.

3,4,5-Triaminotoluene (14). A mixture of 3.9 g (0.020 mol) of **7**, 9.0 g of mossy tin, and 60 ml of concentrated hydrochloric acid was placed in a three-necked 500-ml round-bottomed flask, fitted with a condenser and overhead stirrer, and heated on a steam bath for 1 hr. The cooled mixture was made basic with 80 g of 50% NaOH, then extracted four times with 50-ml portions of $CHCl_3$. The combined $CHCl_3$ layers were dried over Na_2SO_4, filtered, and evaporated leaving behind a white solid. Recrystallization of the solid from benzene afforded 1.7 g (63%) of **14** as white needles, mp 100–102.5° (lit.[15] 105°).

4-Amino-2,6-dimethylbenzimidazole Monohydrate (13). A mixture of 3.7 g (0.027 mol) of **14** and 25 ml of acetic anhydride was heated in a 250-ml round-bottomed flask on a steam bath for 15 min. After cooling the mixture, 50 ml of 3 *N* hydrochloric acid was added, and the reaction was heated under reflux for 2 hr. The mixture was cooled, made basic with concentrated NH_4OH, and extracted four times with 40-ml portions of $CHCl_3$. Evaporation of the combined $CHCl_3$ layers yielded an oily residue, which was treated with 60 ml of 6 *N* hydrochloric acid and heated under reflux for 3 hr. The cooled mixture was made basic with concentrated NH_4OH, and allowed to sit in the refrigerator for 3 hr, resulting in the formation of 3.0 g (62.5%) of **13** as long light gold needles, mp 97–98.5° (lit.[16] 100°). This was used without further purification.

4-Propionamide-2,6-dimethylbenzimidazole (15). A mixture of 3.0 g (0.017 mol) of **13** and 50 ml of propionic acid was heated under reflux for 6 hr. The mixture was poured into 100 ml of ice water, and made basic with concentrated NH_4OH. The resulting precipitate was removed by filtration and washed liberally with water. After drying the solid it was recrystallized from tetrahydrofuran to yield 2.7 g (75.7%) of **15** as a white crystalline solid, mp 139° dec.

Anal. Calcd for $C_{12}H_{15}N_3O$: C, 66.34; H, 6.96; N, 19.34. Found: C, 65.98; H, 6.98; N, 19.27.

2,6-Dimethyl-4-*N*-propylaminobenzimidazole (3). A three-necked 250-ml round-bottomed flask, fitted with a condenser, addition funnel, and septum, was charged with 20.5 ml (20.5 mmol) of a 1 *M* borane–THF solution. A solution of 1.77 g (8.20 mmol) of **15** in 80 ml of hot dry THF was added to the mixture over a 10-min period and the reaction was heated under reflux for 3.5 hr. To the cooled mixture 60 ml of 6 *N* hydrochloric acid was added slowly. The THF was removed by distillation at atmospheric pressure. Sodium hydroxide pellets were added to saturate the aqueous phase and the latter was extracted three times with a total of 60 ml of ether. The ether was evaporated leaving behind an oil which was treated with 60 ml of 6 *N* hydrochloric acid and heated at reflux for 2 hr. After cooling sodium hydroxide pellets were added until the mixture was basic and the latter was extracted a total of three times with 60 ml of ether. After drying with Na_2SO_4, the ether was evaporated leaving behind a solid. Recrystallization from 40% EtOH–H_2O afforded 1.0 g (60.2%) of **3** as a white amorphous solid, mp 87–88°.

Anal. Calcd for $C_{12}H_{17}N_3 \cdot 0.5H_2O$: C, 67.89; H, 8.55; N, 19.79. Found: C, 68.19; H, 8.86; N, 19.94.

Acknowledgment. The authors wish to express appreciation to Ciba-Geigy, Greensboro, N.C., for their encouragement and assistance during this investigation.

Registry No.—**1,** 53369-82-7; **2,** 53369-83-8; **3,** 53369-84-9; **4,** 53369-85-0; **6,** 2078-03-7; **7,** 6393-42-6; **8,** 5264-65-3; **9,** 53369-86-1; **10,** 53369-87-2; **11,** 53369-89-4; **13,** 19364-67-1; **14,** 27530-48-9; **15,** 53369-88-3; *n*-propylamine, 107-10-8; *n*-propyl bromide, 106-94-5; propionic acid, 79-09-4.

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Aril Azines. III.[1] Reaction of Benzil Benzal Monoazine with Sodium Methoxide

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Reaction of benzil benzal monoazine (**5**) with sodium methoxide in ether gives as the major product benzil diazine (**9**). Several other products are formed, which include benzonitrile, benzamide, benzoic acid, 5-methoxy-1,2,5-triphenyl-3,4-diaza-2,4-pentadien-1-one (**2**), 3,4,5-triphenylpyrazole (**6**), *N*-benzylbenzamide (**7**), and a dihydro derivative of benzil diazine (**10**). It is suggested that the products are formed *via* two primary reaction pathways: (i) nucleophilic attack by methoxide ion on the benzal carbon atom of **5**, and (ii) abstraction of a proton from this carbon atom by methoxide ion.

The reaction of benzil monoazine (**1**) with sodium methoxide in ether has been shown to give the products depicted in Scheme I.[2] A possible pathway for the formation of the dihydro product **3** has been proposed to be that shown in Scheme II.[2] This postulate has led us to attempt to generate the anionic species **4** in an alternative fashion.

To this end the reaction of benzil benzal monoazine (**5**) with sodium methoxide was investigated in the hope that reaction might proceed, at least in part, by removal of the azomethine proton followed by fragmentation to benzonitrile and the anion **4**. In the event, treatment of **5** with sodium methoxide in boiling ether led to the rapid development of a blue coloration that later became dark red-brown; after 5 days aqueous work-up gave a plethora of products, which did not include **3**. These are shown in Scheme III; only **9** was isolated in major amount (35%).

Compounds **2** and **6** were identified by direct comparison with samples of those compounds that had been obtained previously in our work with benzil monoazine.[2] *N*-Benzylbenzamide (**7**) was identified by comparison with an au-