

Synthesis and Reactions of 2-Aryl-3-(dimethylamino)acroleins

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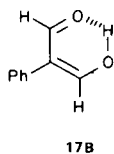
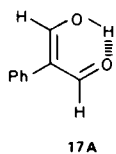
Received August 31, 1973

The preparation of a number of novel 2-aryl-3-(dimethylamino)acroleins and their hydrolyses to 2-arylmaldialdehydes is described. Reactions of the acroleins with amines are discussed as well as the conversion of the 2-arylmaldialdehydes into 3-chloro and 3-alkoxyacroleins.

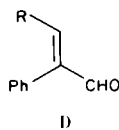
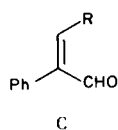
The first preparation of 2-aryl-3-(dimethylamino)acroleins from arylacetic acids was described by Arnold and co-workers (1,2) through the use of the *Vilsmeier-Haack* condensation. We prepared, under slightly modified conditions, a variety of these acroleins in good yields.

Phenylmalondialdehyde (3) was first obtained by Rupe and Knup (4) upon reduction of hydroxymethylenebenzylcyanide followed by mild acidic hydrolysis of the intermediate aldimine. We found that the 2-aryl-3-(dimethylamino)acroleins were readily hydrolyzed under strongly alkaline conditions to produce pure 2-arylmaldialdehydes in high yields.

These compounds are completely enolized and exhibit an interesting nmr spectrum. The aromatic protons appear as a multiplet at their expected position (7.3 δ), but in each instance, the signal for the aldehyde and olefinic protons was seen as a sharp singlet (8.6 δ) with one exchangeable proton downfield (13.0 δ). This would indicate that the enolic proton is not bound to the oxygen but equilibrates rapidly from one oxygen to the

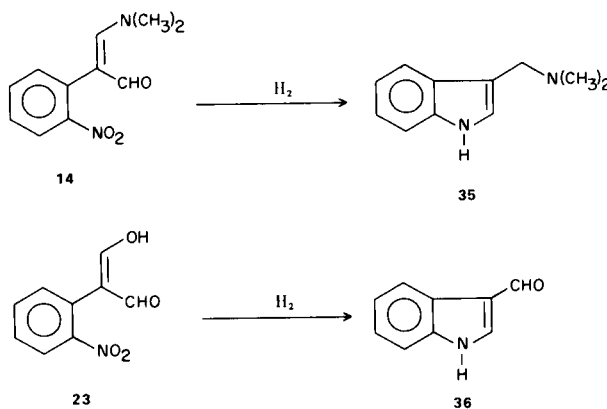


other (17A and 17B). When the equilibrium is blocked by conversion of the dialdehyde to the 3-alkoxyacrolein (25), the aldehyde and olefinic protons appear as two separate singlets (9.4 and 8.6 δ).

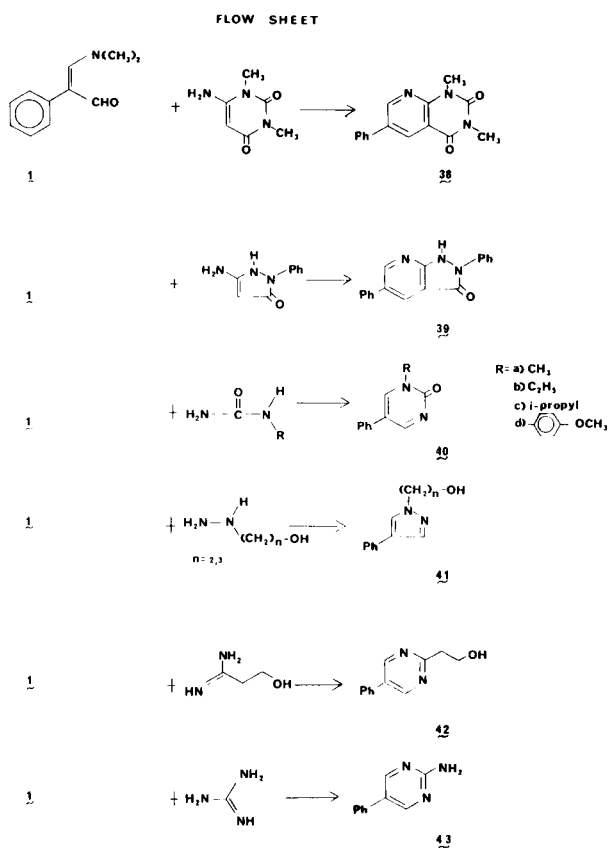
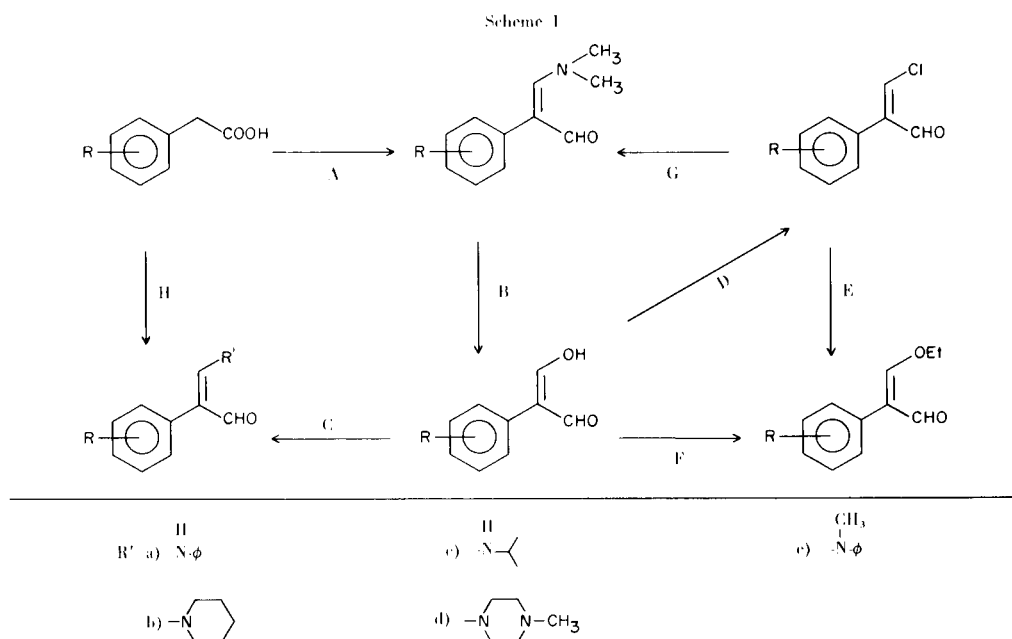


In the derivatives where R is alkoxy, chloro, or substituted amino, no assignment has been made whether the R group is *cis* (C) or *trans* (D) to the formyl group. In this paper, the *cis*-configuration is assumed.

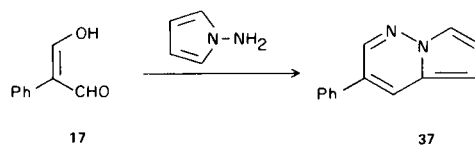
The 2-aryl-3-(dimethylamino)acroleins are known to undergo transformation and condensation reactions with amines (5). We observed that 1 condenses with diamines or β -aminoketones to afford systems of the type described in the Flow Sheet. Not unexpectedly, the catalytic reduction of 2-(2-nitrophenyl)-3-dimethylaminoacrolein (14) over Raney nickel at 3.5 atmospheres produced gramine (35) in moderate yield. Also, reduction of 2-(2-nitrophenyl)malondialdehyde (23) under similar conditions produced indole-3-carboxaldehyde (36). These may be convenient syntheses for a variety of substituted gramines and indoles.



2-Arylmaldialdehydes were found to be versatile intermediates. They behave like vinylogous acids and undergo transformations similar to those acids. When treated with thionyl chloride, they formed vinylogous acid chlorides (Scheme I, reaction D). Reaction of 17 with alkyl halides, in the presence of base, led to the formation of vinylogous esters (Scheme I, reaction F).



When treated with amines, 2-aryl-3-(*N*-substituted)acroleins were obtained (Table 1, procedure C). The condensation of **17** with 1-aminopyrrole produced 3-phenylpyrrolo-[1,2-*b*]pyridazine (**37**) in 60% yield. Although in many reactions **1** and **17** can be used interchangeably, in some



reactions it was found that using the malondialdehyde instead of the 2-aryl-3-(dimethylamino)acrolein as the substrate greatly improved the yield of the reaction. For example, when **1** was treated with *N*-methylurea, **40a** was isolated in 30% yield but when **1** was replaced with the dialdehyde (**17**), **40a** was produced in 84% yield. Scheme 1 shows versatility and interconvertibility of the various intermediates obtained from the hydrolyses of 2-aryl-3-(dimethylamino)acroleins.

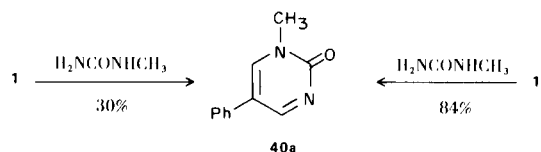
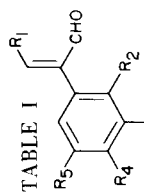


TABLE I






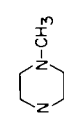
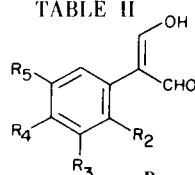
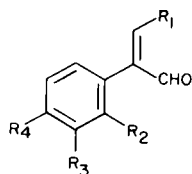
Compound Number	R ₁	R ₂	R ₃	R ₄	R ₅	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis		
									Calcd.	Found	Cl
									H	N	
1	N(CH ₃) ₂	H	H	H	H	Oil	A, 52 G, 92	C ₁₁ H ₁₃ NO	5.8	6.7	16.9
2	N(CH ₃) ₂	H	H	Cl	H	118-122	A, 65	C ₁₁ H ₁₂ NOCl	5.8	6.5	17.1
3	N(CH ₃) ₂	H	Cl	Cl	H	111-114	A, 91	C ₁₁ H ₁₁ NOCl ₂	4.6	5.7	29.0
4	N(CH ₃) ₂	H	H	OCH ₃	H	90-91	A, 37	C ₁₂ H ₁₅ NO ₂	7.4	6.8	28.8
5	N(CH ₃) ₂	H	OCH ₃	OCH ₃	H	126-129	A, 53	C ₁₃ H ₁₇ NO ₃	7.3	6.0	
6	N(Et) ₂	H	OCH ₃	OCH ₃	H	66-68	C, 50	C ₁₅ H ₂₁ NO ₃	8.0	5.3	
7	NH- 	H	OCH ₃	OCH ₃	H	96-98	C, 35	C ₁₄ H ₁₉ NO ₃	7.7	5.6	
8	NH- 	H	OCH ₃	OCH ₃	H	204-207	C, 43	C ₁₇ H ₁₇ NO ₃	6.1	4.9	
9		H	OCH ₃	OCH ₃	H	120-122	C, 10	C ₁₈ H ₁₉ NO ₃	6.5	4.7	
10		H	OCH ₃	OCH ₃	H	106-109	C, 34 H, 11	C ₁₆ H ₂₁ NO ₃	7.7	5.1	
11		H	OCH ₃	OCH ₃	H	105-107	C, 43	C ₁₆ H ₂₂ N ₂ O ₃	7.6	9.7	
12	N(CH ₃) ₂	H	-O-CH ₂ -O-		H	99-101	A, 40	C ₁₂ H ₁₃ NO ₃	6.0	6.4	
13	N(CH ₃) ₂	H	OCH ₃	OCH ₃	OCH ₃	100-103	A, 75	C ₁₄ H ₁₉ NO ₄	7.2	5.3	
14	N(CH ₃) ₂	NO ₂	H	H	H	116-119	A, 58	C ₁₁ H ₁₂ N ₂ O ₃	5.5	12.7	
15	N(CH ₃) ₂	H	CH ₃	H	H	69-73	A, 68	C ₁₂ H ₁₅ NO	8.0	7.4	
16	N(CH ₃) ₂	H	H	CH ₃	H	127-130	A, 80	C ₁₂ H ₁₅ NO	8.0	7.4	

TABLE II



Compound Number	R ₂	R ₃	R ₄	R ₅	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis			
								C	H	N	Cl
17	H	H	H	H	92-95	B, 75	C ₉ H ₈ O ₂	73.0 (72.9)	5.4 (5.8)		
18	H	Cl	Cl	H	169-171	B, 62	C ₉ H ₆ O ₂ Cl ₂	49.8 (49.7)	2.8 (2.9)		32.7 (33.0)
19	H	H	OCH ₃	H	146-148	B, 71	C ₁₀ H ₁₀ O ₃	67.4 (67.4)	5.7 (5.8)		
20	H	OCH ₃	OCH ₃	H	132-135	B, 89	C ₁₁ H ₁₂ O ₄	63.4 (63.1)	5.8 (5.8)		
21	H	-O-CH ₂ -O-		H	137-140	B, 80	C ₁₀ H ₈ O ₄	62.5 (62.4)	4.2 (4.3)		
22	H	OCH ₃	OCH ₃	OCH ₃	177-180	B, 87	C ₁₂ H ₁₄ O ₅	60.5 (60.8)	5.9 (6.3)		
23	NO ₂	H	H	H	121-123	B, 72	C ₉ H ₇ NO ₄	56.0 (55.7)	3.7 (3.8)	7.3 (7.3)	
24	H	H	CH ₃	H	129-132	B, 85	C ₁₀ H ₁₀ O ₂	74.1 (74.4)	6.2 (6.5)		

TABLE III



Compound Number	R ₁	R ₂	R ₃	R ₄	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis			
								C	H	Cl	
25	OEt	H	H	H	Oil	F, 60	C ₁₁ H ₁₂ O ₂	75.0 (74.5)	6.9 (6.9)		(a)
26	OEt	H	OCH ₃	OCH ₃	Oil	F, 74	C ₁₃ H ₁₆ O ₄	66.1 (65.8)	6.8 (6.8)		
27	Cl	H	H	H	Oil	D, 74	C ₉ H ₇ OCl	64.9 (64.1)	4.2 (3.9)	21.3 (21.8)	(a)
28	Cl	H	OCH ₃	OCH ₃	93-95	D, 80	C ₁₁ H ₁₁ O ₃ Cl	58.3 (58.4)	4.9 (5.0)	15.6 (15.9)	
29	Cl	NO ₂	H	H	Oil	D, 77	C ₉ H ₆ NO ₃ Cl	No Analysis			

(a) Reanalysis of the sample did not improve the values.

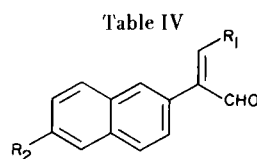
EXPERIMENTAL (6)

Melting points were determined on a Thomas-Hoover unimelt apparatus and are uncorrected. The infrared spectra were recorded on a Perkin-Elmer model 257 and 457 spectrophotometers. All pure materials were run as Nujol or halocarbon mulls. Nuclear magnetic resonance spectra were determined on Varian

A-60 and T-60 spectrophotometers using tetramethylsilane as an internal reference. All elemental analyses were performed by Mr. William Bonkoski and associates, at Sandoz-Wander, Inc.

Interpretation of nmr data: δ chemical shift ppm (multiplicity, number of protons). S = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet.

2-Aryl-3-(dimethylamino)acroleins (7) (Table I).



Compound Number	R ₁	R ₂	M.p., °C	Procedure Yield, %	Molecular Formula	Analysis		
						Calcd. (Found)	C	H
30	N(CH ₃) ₂	H	131-135	A, 51	C ₁₅ H ₁₅ NO	79.2 (79.2)	6.7 6.9	6.6 6.3
31	N(CH ₃) ₂	OCH ₃	145-147	A, 81	C ₁₆ H ₁₇ NO ₂	75.3 (75.1)	6.7 6.9	5.5 5.8
32	OH	OCH ₃	174-176	B, 91	C ₁₄ H ₁₂ O ₃	73.7 (73.2)	5.3 5.2	
33	OEt	OCH ₃	83-85	32	C ₁₆ H ₁₆ O ₃	75.0 (75.3)	6.3 6.6	
34	Cl	OCH ₃	94-97	51	C ₁₄ H ₁₁ O ₂ Cl	No Analysis		

(a) Reanalysis of the sample did not improve the values.

Procedure A.

With vigorous stirring, 81 g. (1.1 moles) of dimethylformamide was added dropwise to 138 g. (0.9 mole) of phosphorus oxychloride. During the addition the temperature was maintained at 30° by intermittent cooling. After the addition was complete, the mixture was stirred for 5 minutes, then a solution of 0.3 mole of the appropriate arylacetic acid in 150 ml. of dimethylformamide was added over a period of five minutes. The resulting solution was stirred at 70° for 18 hours and then was poured on 1.25 kg. of ice and was neutralized by the addition of anhydrous potassium carbonate. The resulting solution was made strongly alkaline by the addition of 300-400 ml. of 50% aqueous sodium hydroxide (during addition the temperature was maintained at 50°). After the evolution of dimethylamine ceased, the mixture was cooled and the resulting precipitate was filtered, washed well with water, and recrystallized from ether.

Procedure C (Table I).

A mixture of 0.025 mole of the appropriate malondialdehyde, 0.027 mole of the amine and 0.1 g. of *p*-toluenesulfonic acid in 75 ml. of benzene was refluxed for 18 hours in an apparatus fitted with a Dean-Stark water separator. The resulting solution was washed twice with dilute sodium bicarbonate and water. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure. The resulting residue was usually crystallized from methylene chloride/ether.

2-Arylmalondialdehydes (8) (Table II).

Procedure B.

To a stirred solution of 0.1 mole of the appropriate 2-aryl-3-(dimethylamino)acrolein in 150 ml. of ethanol was added 200 ml. of 25% aqueous sodium hydroxide. The resulting two phase mixture was refluxed for 3 hours after which the ethanol was distilled from the reaction. The reaction mixture was then cooled and the sodium salt of the product was filtered and washed with methylene chloride. It was then dissolved in water and acidified with 6*N* hydrochloric acid. The resulting crystalline precipitate was filtered, washed with water, and recrystallized from ether.

2-(3,4-Dimethoxyphenyl)-3-ethoxyacrolein (**26**).

Procedure F.

To a stirred solution of 2.0 g. of **20** in 25 ml. of *N,N*-dimethylacetamide was added 400 mg. of 57% sodium hydride (pentane washed) in portions. After the evolution of hydrogen ceased, the solution was stirred at 25° for 30 minutes. Ethyl iodide (1.5 g.) was then added and the solution was stirred at 25° for 24 hours. The solvent was removed *in vacuo* and water was added to the residue. The resulting oil was extracted into ethyl acetate, washed with water and saturated aqueous sodium chloride solution. The organic phase was dried over sodium sulfate and the solvent was removed under reduced pressure to give an oil which, upon distillation, yielded 1.7 g. (74%) of **26**, b.p. 0.1 mm = 195-200°, *ir* (chloroform): 2950, 2830, 2720, 1660, 1620, 1300, 1240, 1020 cm⁻¹; *nmr* (deuteriochloroform): δ 9.3 (s, 1), 7.0 (m, 4), 4.2 (q, 2), 3.8 (s, 6), 1.4 (t, 3) ppm.

Anal. Calcd. for C₁₃H₁₆O₄: C, 66.1; H, 6.8. Found: C, 65.8; H, 6.8.

Note: Compound **26** can also be obtained by the reaction of **28** with ethanol (Procedure E) but the yields are substantially less.

3-Chloro-2-(3,4-dimethoxyphenyl)acrolein (**28**).

Procedure D.

A mixture of 4.0 g. of **20** and 35 ml. of thionyl chloride was heated at 50° for five hours, after which the thionyl chloride was removed under reduced pressure. Fifty ml. of benzene was added to the residue and was removed under reduced pressure (this procedure was repeated twice). The resulting oil was distilled at 0.5 mm yielding 3.6 g. (82%) of **28**, b.p. = 141-142°. Upon standing, the oil crystallized and an analytical sample was crystallized from ether, m.p. = 93-95°; *ir* (chloroform): 2840, 2730, 1695, 1595, 1510, 1260, 1035, 855 cm⁻¹; *nmr* (deuteriochloroform): δ 9.7 (s, 1), 7.3 (s, 1), 6.9 (m, 3), 3.9 (s, 6) ppm.

3-Chloro-2-(6-methoxy-2-naphthyl)acrolein (**34**).

A solution of 1.0 g. of **32** and 0.7 g. of thionyl chloride in 15 ml. of benzene was stirred at 25° for three days. After standard work up, the oily residue was crystallized from ether/pentane to yield 550 mg. (51%) of **34**, m.p. = 94-97°; *ir* (chloroform): 2830, 2720, 1690, 1630, 1480, 1390, 1260, 1030, 850 cm⁻¹; *nmr* (deuteriochloroform): δ 9.7 (s, 1), 7.7 (m, 3), 7.3 (s, 1), 7.2 (m, 3), 3.9 (s, 3) ppm.

Gramine (**35**).

A solution of 1.9 g. of **14** in 50 ml. of ethanol was hydrogenated in the presence of Raney nickel at 3.5 atmospheres for five hours. The catalyst was filtered and the solvent was removed under reduced pressure. The resulting oily solid was dissolved in methylene chloride, extracted into 0.5*N* hydrochloric acid and was washed twice with methylene chloride. The aqueous phase was made basic with 2*N* sodium hydroxide and the resulting precipitate was filtered, washed twice with water and dried to yield 200 mg. (25%) of **35**.

Indole-3-carboxaldehyde (**36**).

A solution of 1.0 g. of **23** in 50 ml. of ethyl acetate was hydrogenated in the presence of Raney nickel at 3.5 atmospheres for 17 hours. After standard work up, the resulting oily solid was triturated with ether to yield 100 mg. (15%) of **36**.

3-Phenylpyrrolo[1,2-*b*]pyridazine (**37**).

A solution of 1.8 g. of **17** and 1.0 g. of 1-aminopyrrole (9) in 25 ml. of glacial acetic acid was refluxed for one hour. The reaction mixture was poured on ice and the precipitate was extracted into methylene chloride. The organic phase was washed with water and dried over sodium sulfate. The solvent was removed under reduced pressure and the resulting oil was chromatographed on a column of silica gel using methylene chloride to elute the product. The resulting oil was crystallized from methanol to yield 1.4 g. (60%) of **37**, m.p. = 66-69°; ir (chloroform): 1620, 1600, 1490, 1330, 1285, 1260, 1065, 895 cm⁻¹; nmr (deuteriochloroform): δ 8.3 (d, 1), 7.8 (m, 2), 7.4 (m, 5), 6.85 (m, 1), 6.5 (m, 1) ppm.

Anal. Calcd. for C₁₃H₁₀N₂: C, 80.4; H, 5.2. Found: C, 80.3; H, 5.4.

1,3-Dimethyl-6-phenylpyrido[2,3-*d*]pyrimidine-2,4-(1*H*,3*H*)dione (**38**).

A suspension of 16.0 g. of **1** and 8.5 g. of 6-amino-1,3-dimethyluracil in 300 ml. of 50% aqueous acetic acid was refluxed for 15 minutes. The resulting solution was cooled to 40° and the precipitate that formed was filtered and washed with methanol. The resulting solid was recrystallized from methanol to yield 4.5 g. (31%) of **38**, m.p. = 157-159°; ir (chloroform): 1710, 1660, 1610, 1480, 1350, 1295 cm⁻¹; nmr (deuteriochloroform): δ 8.9 (d, 1), 8.6 (d, 1), 7.6 (m, 5), 3.7 (s, 3), 3.5 (s, 3) ppm.

Anal. Calcd. for C₁₅H₁₃N₃O₂: C, 67.4; H, 4.9; N, 15.7. Found: C, 67.6; H, 5.9; N, 15.3.

1,2-Dihydro-2,5-diphenyl-3*H*-pyrazolo[3,4-*b*]pyridin-3-one (**39**).

A suspension of 20.0 g. of **1** and 17.5 g. of 3-amino-1-phenyl-2-pyrazolin-5-one was reacted and worked up as in the above procedure. The precipitate was recrystallized from *N,N*-dimethylacetamide to yield 15.5 g. (55%) of **39**, m.p. = 289-293°. The material was found pure enough for further use; nmr (deuterio-trifluoroacetic acid): δ 9.3 (d, 1), 8.9 (d, 1), 7.7 (m, 11) ppm.

1-Methyl-5-phenyl-2-(1*H*)pyrimidone (**40a**) (10).

A mixture of 35 g. of **17**, 33 g. of *N*-methylurea, and 3.5 g. of *p*-toluenesulfonic acid in 200 ml. of toluene was refluxed for 30 minutes in an apparatus fitted with a Dean-Stark water separator. The reaction mixture was cooled and the resulting precipitate was filtered and then dissolved in methylene chloride. The organic phase was washed with water, dried over sodium sulfate, and concentrated to yield 37 g. (84%) of **40a**, m.p. = 186-189° (lit. m.p. = 170°) (4).

4-Phenylpyrazole-1-ethanol (**41**, *n* = 2) (11).

A solution of 20.0 g. of **1** and 10.0 g. of 2-hydroxyethyl-

hydrazine in 150 ml. of benzene was refluxed for 2.5 hours. The solvent was removed under reduced pressure and the residue was crystallized from ether to yield 20 g. (95%) of **41**, m.p. = 94-98°; ir (chloroform): 3610, 3400, 2960, 2870, 1610, 1565, 1440, 1370, 1065, 990, 955, 870, 855 cm⁻¹; nmr (deuteriochloroform): δ 7.7 (d, 2), 7.3 (m, 5), 4.1 (m, 5).

Anal. Calcd. for C₁₁H₁₂N₂O: C, 70.2; H, 6.4; N, 14.9. Found: C, 70.1; H, 6.3; N, 14.8.

5-Phenyl-2-pyrimidineethanol (**42**).

To a solution of 2.5 g. of sodium in 300 ml. of ethanol was added 13.7 g. of 3-hydroxypropionamide hydrochloride (12). After five minutes, the precipitated sodium chloride was filtered. Compound **1** (20.7 g.) was added to the filtrate and the resulting solution was refluxed for six hours. The solvent was removed under reduced pressure and the residue was dissolved in chloroform. The organic phase was washed with sodium sulfite solution followed by water. After drying over sodium sulfate, the solvent was removed under reduced pressure. The resulting solid was crystallized from ethyl acetate/pentane to yield 12.4 g. (52%) of **42**, m.p. = 92-97°; ir (chloroform): 3440, 1590, 1545, 1450, 1060, 1045 cm⁻¹; nmr (deuteriochloroform): δ 8.8 (s, 2), 7.5 (s, 5), 4.1 (m, 3), 3.25 (t, 2).

Anal. Calcd. for C₁₂H₁₂N₂O: C, 72.0; H, 6.0; N, 14.0. Found: C, 72.2; H, 6.1; N, 13.8.

2-Amino-5-phenylpyrimidine (**43**).

A suspension of 10.0 g. of **1** and 7.5 g. of guanidine nitrate in 100 ml. of pyridine was refluxed for 17 hours. The solvent was removed *in vacuo* and the resulting residue was dissolved in chloroform and was washed with 2*N* sodium hydroxide followed by water. Upon evaporation of the solvent under reduced pressure, the resulting solid was chromatographed on a column of silica gel using 10% methanol/chloroform to elute the product. Recrystallization from methylene chloride/pentane yielded 2.6 g. (27%) of **43**, m.p. = 152-156° (lit. m.p. = 161-163°).

Acknowledgement.

The authors wish to thank Dr. Sandor Barcza and his associates for running all ir and nmr spectra and Mr. William Bonkoski and associates for performing the microanalyses.

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