A New Synthesis of 5-Benzylpyrimidines[1]

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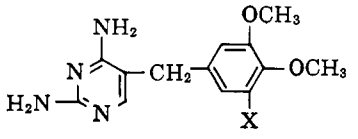
Aromatic aldehydes undergo base-catalyzed condensations with propionitriles having electron-withdrawing substituents in the β-position to give mixtures of isomers resulting from condensation α to the nitrile function. The condensation products react with guanidine to give 2,4-diamino-5-benzylpyrimidines in fair to good yields. It is shown that losses are mainly due to nucleophilic attack of the base on the *para* position of the arylidene propionitrile when that position is substituted by an alkoxy group.

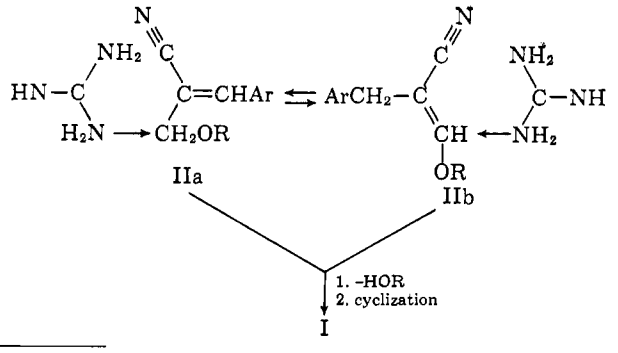
A number of 2,4-diamino-5-benzylpyrimidines, especially Ia and Ib, possess marked antibacterial activity.[2] Utilization of these compounds has been limited by expense, since the previously known synthesis[3] involves seven steps, some of them rather unsatisfactory, with an over-all yield of 20% or less. The synthesis of the closely related 5-arylpyrimidines,[4] on the other hand, is quite efficient. The superiority of the latter synthesis depends on the availability of α-aryl-β-alkoxyacrylonitriles, which are readily prepared by several methods[4] not applicable to the intermediates for benzylpyrimidine synthesis.



Ia, X = H
b, X = OCH_3

If an aldehyde could be condensed with a suitable propionitrile (such as the readily available β-ethoxypropionitrile), the expected product would have the structure IIa which would be in tautomeric equilibrium with IIb. The latter is a homolog of enol ethers used in 5-arylpyrimidine synthesis (IIb, Ar in place of CH_2Ar) and would be expected to cyclize with guanidine along the line of Reaction Scheme A. Alternatively, attack might be initiated on IIa itself which possesses an allylic carbon atom.

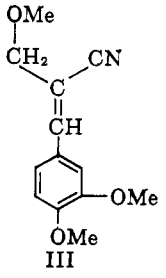
REACTION SCHEME A



In a preliminary experiment veratric aldehyde and β-ethoxypropionitrile were refluxed in a benzene suspension of sodium methoxide and an ethanolic solution of guanidine was added thereto. From the reaction mixture Ia was isolated in about 7% yield. As a result it was decided to investigate the two steps separately and systematically.

The results of condensations of aromatic aldehydes with propionitriles having electron-withdrawing substituents in the β-position are shown in Table I. The reaction appears to be fairly general but no conditions were found that were superior to simple condensations in lower alcohols with alkoxide ion as the base. The products were oils, boiling higher than the parent aldehydes, and appeared to be mixtures of isomers, presumably IIa and IIb, each of which can have two geometrical forms. These crude products are referred to as "benzal nitriles." From three of these "benzal nitriles," namely those derived from veratric aldehyde, piperonaldehyde, and 3,4,5-trimethoxybenzaldehyde, crystalline substances were obtained which are believed to have the structure IIa.

In Fig. 1 is shown the absorption curve 2 for α-veratrylidene-β-methoxypropionitrile (III), which is formed by condensation of veratric aldehyde with β-methoxypropionitrile (or by refluxing the β-ethoxy homolog with catalytic amounts of sodium methylate in methanol). Comparison with the absorption curve 1 of *p*-methoxycinnamonitrile indicated conjugation between the aromatic ring and the nitrile function.[5] While no clear evidence as to the geometry is available, the *trans* position of ring and cyano group seems probable.



III

(1) Presented in part before the Organic Division, 138th National Meeting of the American Chemical Society, New York, N. Y., September, 1960.

(2) For a discussion of these activities, see B. Roth, E. A. Falco, G. H. Hitchings, and S. R. M. Bushby, *J. Med. Pharm. Chem.*, **5**, 1103 (1962).

(3) E. A. Falco, S. DuBreuil, and G. H. Hitchings, *J. Am. Chem. Soc.*, **73**, 3758 (1951).

(4) (a) P. B. Russell and G. H. Hitchings, *ibid.*, **73**, 3763 (1951); (b) P. B. Russell and N. Whittaker, *ibid.*, **74**, 1310 (1952); (c) B. H. Chase, J. P. Thurston, and J. Walker, *J. Chem. Soc.*, 3439 (1951); (d) B. H. Chase and J. Walker, *ibid.*, 3518 (1953); (e) R. Baltzly and P. B. Russell, *J. Org. Chem.*, **21**, 912 (1956).

(5) The additional methoxymethyl substituent would be expected to product a bathochromic shift comparable to that observed (15 mμ) while the lowered absorption coefficient could be caused by steric interference with complete co-planarity.

TABLE I

"BENZAL NITRILES" FROM ArCHO AND XCH_2CH_2CN

Substitution in Ar	X	Catalyst and reaction conditions[a]	Time, hr.	B.p. of product, °C. (pressure)[b]	Yield, %
3,4-$(MeO)_2$	EtO	1.25 eq. of NaOEt in EtOH[c]	2	155–175 (0.45 mm.)	76[d]
3,4-$(MeO)_2$	EtO	0.75 eq. of $NaNH_2$ in benzene. Reflux	5	150–200 (2 mm.)	27
3,4-$(MeO)_2$	EtO	1 eq. of $NaNH_2$ in liq. NH_3	4	160–180 (0.5 mm.)	29
3,4-$(MeO)_2$	EtO	0.6 eq. of NaOMe in dioxane at 100°	4	172–186 (0.9 mm.)	16
3,4-$(MeO)_2$	EtO	0.5 eq. of NaOMe in MeOH. Reflux	24		38
3,4-$(MeO)_2$	MeO[e]	0.33 eq. of NaOMe + $Mg(OMe)_2$ in MeOH at reflux[f]	7	125–130 (0.1 mm.)	80[d]
3,4-$(MeO)_2$	EtO	0.5 eq. of $NaOC_3H_7$ in n-C_3H_7OH at reflux	24		20
3,4-$(MeO)_2$	EtO	0.5 eq. of $NaOC_4H_9$ in n-C_4H_9OH at reflux	4		20
3,4-$(MeO)_2$	Br	1.5 eq. of NaOEt in EtOH. Reflux[c,g]	3	170–180 (1 mm.)	49
3,4-$(MeO)_2$	Me_2N—	0.5 eq. of NaOEt in EtOH. Reflux[c]	6	150–175	32[h]
3,4-$(MeO)_2$	n-C_3H_7S—	0.67 eq. of NaOEt in EtOH. Reflux[c]	4	(0.7 mm.)	73[i]
None	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3	160–180 (5 mm.)	49
4-Cl	EtO	0.3 eq. of NaOEt in EtOH. Reflux[c]	4		75
4-Me_2N	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3	170–190 (0.5 mm.)	24
3-EtO	EtO	1 eq. of NaOEt in EtOH. Reflux[f,i]	8	140–165 (1 mm.)	50
2-MeO	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	2	148–154 (1.5 mm.)	31
3-MeO-4-C_4H_9O	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3		67
3-MeO-4-C_4H_9O-5-Br	EtO	0.25 eq. of NaOEt in EtOH. Reflux[c]	3		80
3-MeO-4-s-C_4H_9O	EtO	1 eq. of NaOEt in EtOH. Reflux[f,i]	6		80
3-MeO-4-n-$C_8H_{17}O$	EtO	1 eq. of NaOEt in EtOH. Reflux[f,i]	6		70
3,4,5-$(MeO)_3$	EtO	0.5 eq. of NaOEt in EtOH. Reflux[c]	3		87[d]
3,4-OCH_2O—	MeO[e]	0.33 eq. of NaOMe in MeOH + $Mg(OMe)_2$. Reflux[f]	7	135–180 (1 mm.)	75[d]

[a] Except where otherwise stated, the amount of β-substituted propionitrile was equivalent to that of aldehyde. The equivalence of catalyst is reckoned on amount of aldehyde used. [b] Where no boiling point is given, product, in ethereal solution, was washed free of aldehyde, dried, and evaporated *in vacuo* on the steam bath. [c] Azeotropic distillation to remove water. [d] Crystalline isomer obtained. [e] By addition of 2 eq. of acrylonitrile to the methylate solution before addition of aldehyde. [f] Product freed of residual aldehyde by bisulfite treatment. [g] Rapid separation of salt (NaBr) was observed. [h] The product was a mixture of ethoxy and dimethylamino derivatives. [i] Mercaptan odors were noted during the reaction. The product probably was not homogeneous. [j] Azeotropic distillation with added benzene.

The distilled oil from which no more of III could be isolated had the absorption shown by curve 3 in Fig. 1. Assuming that the oil could still contain 25% of III (from comparison of the absorption coefficients at 340 mμ) another curve can be reconstructed for the remaining components of the oil [curve 4, $E_{IV} = {}^4/_3 (E_{III} - {}^1/_4 E_{II})$]. This strongly suggests that the oil contains at least two components of which at least one lacks conjugation between the ring and the CN group. When the oil was refluxed in methanol with a catalytic amount of sodium methylate a further amount of III could be recovered. We take this to indicate that the base-catalyzed tautomeric change between III and its isomers does actually exist. As will be seen later, complete and efficient conversion is probably prevented by other factors.

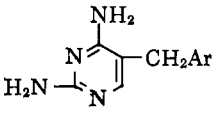
Both the solid III and the unseparated mixture of isomers reacted with guanidine to yield Ia. Yields from III were somewhat the better, reaching a maximum of 40–45% under optimal conditions. The *two* steps together, therefore, afford an over-all yield of about 30%. Cyclization is best accomplished in relatively concentrated solution with methanol as solvent and a considerable excess of guanidine (2–3 equivalents[6]). The best yields were obtained by warming about twenty-four hours at 56° but a shorter reaction period at reflux is not significantly inferior. Use of an inert atmosphere gave no gain in yield. The quantity of ammonia volatilized during such a reaction was found to be somewhat in excess of that produced by heating a methanolic solution of guanidine for the same period, but the quantity was too small to be significant as regards the yield of pyrimidine.

Referring to the proposed Reaction Scheme A, if the bulk of the pyrimidine is formed by attack of guanidine on tautomer IIb present initially as *ca.* 25% of the "benzal nitrile" mixture and replenished by isomeriza-

(6) Higher alcohols are usable but give inferior results both in yield and in rapidity of reaction. One experiment was tried in dimethyl sulfoxide using "guanidine base." Reaction was rapid at room temperature and the only product was the yellow polymer discussed later. "Guanidine base" was the syrup obtained by evaporating a methanolic solution of guanidine *in vacuo*, finally at 0.1-mm. pressure with a Dry Ice trap. The weight of the sirup was consistent not with "guanidine base" but with guanidinium methoxide.

TABLE II

2,4-DIAMINO-5-BENZYLPYRIMIDINES



Ar	M.p., °C.	Yield in cyclization, %	Empirical formula	Anal. % C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
2-$MeOC_6H_4$	154	25	$C_{12}H_{14}N_4O$	62.6	62.9	6.1	6.3	24.4	24.4
3-$EtOC_6H_4$	173.5–174	75	$C_{13}H_{16}N_4O$	63.9	63.7	6.6	6.9	22.9	23.3
3-MeO-4-EtO-C_6H_3	188–190	30	$C_{14}H_{18}N_4O_2$	61.3	61.3	6.6	6.6	20.5	20.6
3,4-(O-CH_2O)C_6H_3	255–256	35	$C_{12}H_{12}N_4O_2$	59.0	58.9	5.0	5.1	22.9	22.6
3-MeO-4-s·C_4H_9O-C_6H_3	181–181.5	20	$C_{16}H_{22}N_4O_2$	63.6	63.2	7.3	7.1	18.5	18.2
3-MeO-4-$C_8H_{17}OC_6H_3$	155.5–156	30	$C_{20}H_{30}N_4O_2$	67.0	67.2	8.4	8.6	15.6	15.7
α-$C_{10}H_7$	240–241	80	$C_{15}H_{14}N_4$	72.0	72.6	5.6	5.7	22.2	22.4
			$C_{15}H_{14}N_4$·HCl	62.8	63.0	5.3	5.5		

tion during the reaction, it is rather surprising that the actual cyclization is so slow in comparison to the 5-arylpyrimidine synthesis (complete in good yield in less than one hour). The unseparated isomer mixture should give a better result than pure IIa. Furthermore, the "benzal nitrile" from *m*-ethoxybenzaldehyde and β-ethoxypropionitrile, whose absorption spectrum suggested presence of a smaller proportion of conjugated isomer, reacted much less rapidly than usual, though eventually giving a good yield. Accordingly we believe that the cyclization is initiated predominantly by attack on IIa.

The other "benzal nitriles" of Table I were cyclized with guanidine to give the corresponding 2,4-diamino-5-benzylpyrimidines. The yields were mainly from 25 to 45%, deviations from which range being critical to the following discussion. Most of the products were known previously. Properties of the new pyrimidines are presented in Table II. Their antibacterial properties have already been reported.[2]

The major loss in these cyclizations is due to development of a yellow gummy material, soluble in hot methanol and in aqueous acid and corresponding roughly to about half the starting nitrile. Attempts to separate it effectively into fractions were unsuccessful. Its intractable nature suggests that it is a polymer. Any further considerable improvement in the synthesis must be dependent on an understanding of the nature of this material and its mode of origin. Its formation evidently is not due to oxidation or to reactions of ammonia present or to a reaction involving the elimination of ammonia.

Further information bearing on the side reaction that produces polymer came from experiments with the "benzal nitriles" derived from α-naphthaldehyde and *m*-ethoxybenzaldehyde. Although crystalline components could be obtained from neither of these condensation products, both gave high yields (80% and 75%) of pyrimidines. In both cases considerable amounts of apparently unchanged "benzal nitrile" could be found when the reactions were stopped while with III not more than traces were present. With neither of these compounds was there any sign of polymer formation. Clearly the formation of polymer is a function of the *p*-alkoxyl group.

Two obvious side reactions that involve a 4-alkoxyl group are possible with such compounds as these "benzal nitriles." These are nucleophilic attacks on the ether alkyl group (1) and on the ring in the *para* position to the conjugated system (2). Both of these points should be made somewhat vulnerable by electron-shift toward the nitrile grouping. It is believed that both these processes do occur, the presumptive nucleophilic reagents being methoxide ion and guanidine base.[7] (See p. 1986, top of col. 1.)

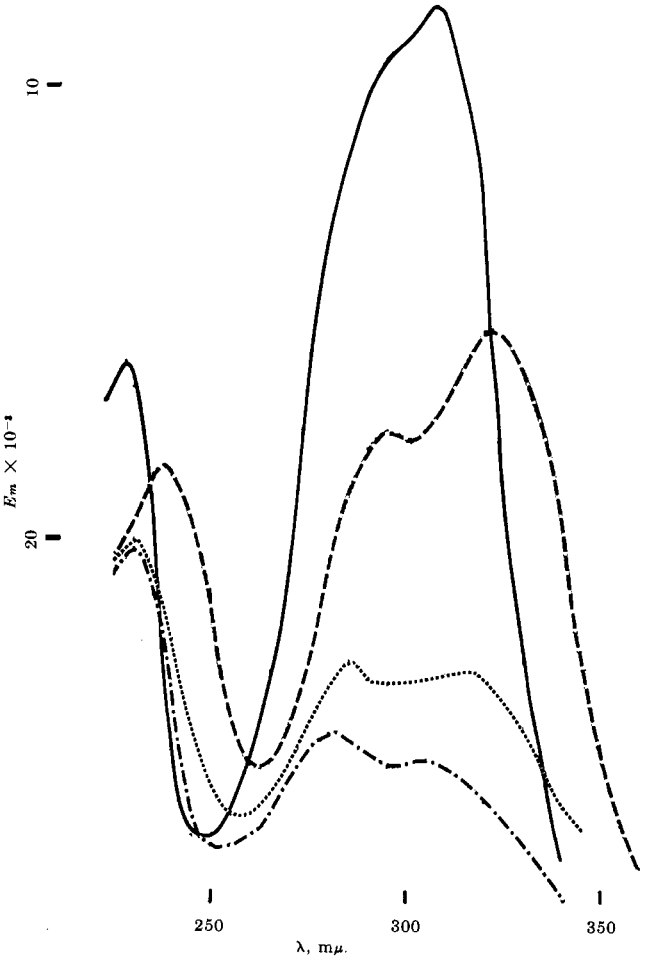
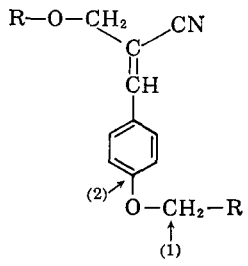


Fig. 1.—Curves 1 ———, *p*-methoxycinnamonitrile; 2, – – – –, compound III; 3, ... , isomer mixture remaining after removal of III; 4, – · – · –, reconstructed curve for other components of isomer mixture.

(7) The relative concentrations of these are uncertain due to lack of precise information as to the acidities of either guanidinium ion or methanol.



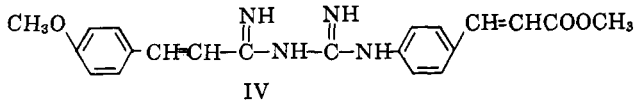
(1) **Attack on the Ether Alkyl Group.**—The products would be phenolic material plus dimethyl ether and methylguanidine. However, it is not apparent why small amounts of phenolic material should lead to formation of polymers under conditions unfavorable to electrophilic substitution.

(2) **Attack on the Ring.**—If methoxide ion engaged in this attack, no alteration would result in III, though compounds with *different* alkoxyl groups would be modified (resulting in diminished yield of the main product). Attack by guanidine base would result in an N-phenyl substituted guanidine. Since that would be a weaker base than guanidine itself, it should be present extensively as base rather than conjugate acid, and should, therefore, enjoy a favored opportunity for further attacks on other molecules of III. Such an operation would thus lead to a polymeric product.

Consideration of such processes involves the effectiveness of guanidine as a nucleophile. On this point exact information is lacking although guanidine is employed extensively in syntheses most readily formulated as involving nucleophilic attack (usually on unsaturated systems and resulting in cyclic products). Experiments involving substitution in 2,4-dichlorobenzyl chloride suggest that, for substitution in aliphatic systems, guanidine is about as active as methoxide ion and much more active than ammonia.

It was possible to demonstrate *both* of these modes of attack through methoxide ion by conducting the cyclization in methanol enriched by $C^{14}H_3OH$. Radioactivity in the isolated pyrimidine Ia corresponded to about 3.5% of exchange, and a radioactive dimethyl ether fraction was obtained corresponding to about two-thirds as much exchange at the methyl group.

Attempts to demonstrate similar substitution on simpler compounds unlikely to cyclize were partially successful. From refluxing solutions of guanidine in methanol, *p*-methoxybenzonitrile and 4-methoxy-α-naphthonitrile were recovered unchanged. However, *p*-methoxycinnamonitrile was largely converted to a yellow polymeric gum similar to that found in the pyrimidine syntheses. Two crystalline substances were isolated in trace amounts during the working up of the reaction product. The first was a hydrochloride with a composition consistent with that of *p*-guanidinocinnamide. The second was obtained as base and as hydrochloride and is formulated as IV.



IV

Both of these structures correspond to probable transformations of primary products from displacement attack of guanidine in the *para* position of *p*-methoxycinnamonitrile.

It, consequently, is believed that diversion of *p*-alkoxy "benzal nitriles" does occur by processes 1 and 2 essentially as outlined earlier. Reactions of this sort have not often been invoked in the past but an analogy can be found in Bunnett's demonstration of attack by methoxide ion on the ester methyl group of methyl benzoate.[8] Such examples will doubtless be multiplied in course of time when suitable techniques are applied to their demonstration.

Experimental

Two main variations were employed in the condensations of aldehydes with β-alkoxy propionitriles. The following illustrate each of these variations. On the subject of the related condensations (in nonalcoholic solvents) it may be said that optimal conditions for reaction have not been determined.

β-Ethoxy-α-veratrylidenepropionitrile.—To a solution of 2.8 g. of sodium methoxide in 140 ml. of absolute ethanol were added 33 g. (0.2 mole) of veratric aldehyde and 20 g. of β-ethoxypropionitrile. The reaction mixture was heated under a fractionating column allowing about 40 ml. to distil each half hour and replacing these quantities with absolute ethanol. After 2 hr., the solution was concentrated *in vacuo* to a thick sirup and partitioned between ether and cold water. Much of the color went into the aqueous layer. The ethereal layer was washed with water until the washings were neutral and then dried over sodium sulfate. The ethereal solution was filtered, the solvent was evaporated, and the residue was distilled at 0.45-mm. pressure, the fraction (37.7 g.) coming over from 155–175° being saved. From a portion of this distillate a solid was obtained. The solid could be recrystallized from ethanol, methanol, or ether–hexane mixture. It melted at 57.5–58° when pure. The absorption spectrum in alcohol showed maxima at 324 mμ (ε 13,600), 295 mμ (ε 10,900), and 238 mμ (ε 10,000). (This curve is virtually identical with curve 2 of Fig. 1.)

Anal. Calcd. for $C_{14}H_{17}N_3O$: C, 68.0; H, 6.9; N, 5.7. Found: C, 68.1; H, 6.9; N, 5.2.

β-Ethoxy-α-(3,4,5-trimethoxybenzylidene)propionitrile.—The condensation was carried out as in the previous preparation. After evaporation of solvent, cold water was added and acetic acid to bring the pH to 6. Ammonia was then added until a pH of 8.5 was reached. The oily product separated and crystallized on further washing with ice–water. After one crystallization from ethanol, the product melted at 74–75°. Further crystallization from methanol raised the melting point to 79–80°.

Anal. Calcd. for $C_{15}H_{19}NO_4$: C, 65.0; H, 6.9. Found: C, 65.3; H, 6.9.

Conversion of β-Ethoxy-α-veratrylidenepropionitrile to β-Methoxy-α-veratrylidenepropionitrile.—The preceding solid isomer (4 g.) melting at 57° was added to 50 ml. of methanol in which 0.1 g. of sodium had been dissolved. The solution was heated on the steam bath for 1 hr. and then cooled. Overnight, a solid separated that melted at 45–48°. The entire material was heated a second hour and a solid again was obtained; melting point was now 61–68.5°. After 2 hr. further heating (at or close to reflux) the solid obtained melted at 69.5–72°. This was identical with the β-methoxy derivative whose preparation is described later.

β-Methoxy-α-veratrylidenepropionitrile.—A solution of magnesium methylate was prepared from 3.5 g. of magnesium and 100 ml. of methanol. To it was added 100 ml. of methanol in which 1.5 g. of sodium had been dissolved. The combined solution was placed in a three-necked flask equipped with a mechanical stirrer and a reflux condenser. To this was added 13 ml. of acrylonitrile rather cautiously. After stirring 15 min., 33.2 g. (0.2 mole) of veratric aldehyde was added and the solution was heated rapidly to reflux. By the time boiling had begun, the solution had become markedly turbid. Methanol was allowed to evaporate until the volume had diminished to about 150 ml., after which the reaction mixture was refluxed 6 hr. and allowed to stand overnight.

Ice was added to the stirred reaction mixture, 150 ml. of 2 *N* hydrochloric acid and about 150 ml. of ether. A considerable

(8) J. F. Bunnett, M. M. Robison, and F. C. Pennington, *J. Am. Chem. Soc.*, **72**, 2378 (1950).

amount of crystalline solid separated. This was filtered off and washed with water and ether, the ethereal layers being combined and separated. The solid was dissolved in 50:50 ether–benzene and was washed successively with water, potassium bisulfite solution, water, dilute sodium hydroxide solution, and again with water. It was then dried over potassium carbonate. The ethereal layers from the original filtration were treated in the same way, bisulfite washing being continued until no more aldehyde was removed. In all, about 3 g. of aldehyde was recovered.

Both solutions, after removal of the desiccant, were put through a short (2 cm.) column of alumina, which removed a small amount of dark impurity, and were evaporated to small volume and diluted with hexane. Several crops of solid were obtained from each, total 26 g.

The mother liquors were combined and distilled at 0.1-mm. pressure (bath temperature, 125–130°). There was obtained 12 g. of a nearly colorless oil. When dissolved in methanol and cooled, this afforded 3 g. more of the solid.

The combined crops of solid were recrystallized from methanol, m.p. 73.5–74°. The absorption spectrum in alcohol is shown in Fig. 1 (curve 2).

Anal. Calcd. for $C_{15}H_{15}NO_5$: C, 66.9; H, 6.5. Found: C, 66.7; H, 6.4.

The oil obtained when the solvent was evaporated from the last mother liquors had the absorption shown in curve 3 of Fig. 1. Two grams of this oil was dissolved in 10 ml. of methanol in which a trace of sodium (*ca.* 0.05 g.) had been dissolved. After refluxing 6 hr. the solution was cooled and seeded. One-half gram more of the 74° melting solid separated.

β-Methoxy-α-(3,4,5-trimethoxybenzylidene)propionitrile.—In 20 ml. of methanol was dissolved 0.1 g. of sodium. To this was added 3.5 g. of the β-ethoxy derivative, m. p. 79–80°, in 50 ml. of methanol. The solution was refluxed 4 hr. and cooled. The solid that separated was recrystallized twice from methanol. It weighed 1.5 g. and melted at 85–85.5°. The mixture melting point with the starting compound showed a large depression.

Anal. Calcd. for $C_{14}H_{17}NO_4$: C, 63.9; H, 6.5. Found: C, 64.1; H, 6.5.

The absorption spectrum of this compound was simpler than those of the 3,4-disubstituted derivatives, showing λ_{max} at 232 mμ (ε 15,140) and 308 mμ (ε 15,060) and λ_{min} at 260 mμ (ε 2760).

β-Methoxy-α-piperonylidenepropionitrile.—The preparation followed the procedure described for the veratrylidene analog. Since the product did not crystallize during the early working up, it was distilled after washing and drying. About half of the distillate was obtained as a solid, m.p. 50–51°, after crystallization from methanol.

Anal. Calcd. for $C_{12}H_{11}NO_3$: C, 66.3; H, 5.1. Found: C, 66.6; H, 4.9.

The absorption curve of this compound was virtually identical with that of its veratrylidene analog (curve 2, Fig. 1), λ_{max} 237 mμ (ε 11,200), 291 mμ (ε 9500), 327 mμ (ε 13,500); and λ_{min} 265 mμ (ε 3700), 301 mμ (ε 8100).

Preparation of 2,4-Diamino-5-(3′,4′-dimethoxybenzyl)pyrimidine from β-Methoxy-α-veratrylidenepropionitrile.—One-tenth g.-atom (2.3 g.) of sodium was dissolved in 40 ml. of methanol. Ten grams (0.102 mole) of guanidine hydrochloride was dissolved in 25 ml. of warm methanol. The solution was allowed to cool and added to the sodium methylate solution. The sodium chloride was filtered off and the filtrate was made up to 100 ml. A 5-ml. portion was diluted with water and titrated electrometrically against standard hydrochloric acid. From the curve it was deduced that the guanidine solution was 0.83 *M* in guanidine and 0.05 *M* in ammonia.

Forty milliliters of the preceding guanidine solution and 4.7 g. (0.02 mole) of β-methoxy-α-veratrylidenepropionitrile were placed in a flask heated by boiling acetone.[9] A slow stream of nitrogen was passed through the reaction mixture and thereafter through a gas-wash bottle containing water acidified by 1 ml. of 1.75 *N* perchloric acid and containing methyl red indicator. As the reaction solution became concentrated by evaporation of methanol it was replenished by adding more of the standard guanidine solution. In all, 25 ml. of this solution was added. Heating was continued through 26 hr. During this time the evolution of ammonia was followed, a total of 5.8 mmoles being collected. Since the guanidine solution originally contained 3.3 mmoles of ammonia 2.5 mmoles in excess had developed. (Similar aeration of 30 ml. of the guanidine solution for 21 hr. resulted in collection of 1.7 mmoles of excess ammonia.)

The reaction mixture was initially colorless but was markedly yellow within 2 hr. and solid had begun to precipitate. After 26 hr., the contents of the flask were filtered hot and the precipitate was washed with hot methanol. It weighed 2.3 g. (calcd. 5.4 g.) and, though still yellow, was almost pure Ia.

A duplicate experiment employing 30 ml. of a guanidine solution initially 2.03 *M* in guanidine and 0.05 *M* in ammonia resulted in collection of 6 mmoles of ammonia. The yield of product was 2.4 g. (44% yield). Comparable runs with 1 and 2 equiv. of guanidine to 1 of nitrile gave 25% and 40% yields of Ia, respectively.

No difficulties have been observed in preparation on a much larger scale.

Preparation of Ia Using $C^{14}H_3OH$.—The same apparatus was employed as in the experiment described before. No gas was passed through the reaction chamber but the outlet was connected to a Dry Ice trap.

One-tenth g.-atom (2.3 g.) of sodium was dissolved in 40 ml. of methanol and added to a solution of 10 g. guanidine hydrochloride in 25 ml. of methanol. After filtration, the solution was taken down *in vacuo* to about 15 ml. and filtered into a 25-ml. volumetric flask. After making up to volume, 1 ml. was removed and titrated against standard acid. The solution was 3.8 molar. Fourteen milliliters of this solution was placed in the reaction chamber together with 4 g. (0.017 mole) of β-methoxy-α-veratrylidenepropionitrile. To this was added in 5 ml. of ordinary methanol 8 mg. (0.5 mc.) of $C^{14}H_3OH$. The acetone in the outer chamber of the apparatus was brought to reflux and heating was continued for 23 hr. After cooling for an hour, a boiling chip and 5 ml. of ethyl ether were introduced into the reaction chamber and heating was resumed for 1 hr. The Dry Ice trap was then opened, attached to a vessel containing ordinary dimethyl ether, and 4 g. of that was distilled into the trap. This was closed and left in the Dry Ice bath overnight.

The contents of the reaction vessel was filtered and washed with hot methanol, the filtrate and washings being saved for recovery.

The precipitate (Ia) was dissolved in 10% acetic acid, treated with charcoal, and re-precipitated by ammonia. The solid was filtered off, washed with water, and recrystallized from 80% ethanol. It was subjected to counting at this stage and recrystallized twice more with re-counting at each stage. The average of the counting values corresponded to $1.3 \pm 0.3 \times 10^{-5}$ μc./mg. or to 3.5 ± 1% exchange of the *p*-methoxyl group.

The trap containing the dimethyl ether was removed from the Dry Ice dewar and connected to a vial immersed in Dry Ice. A portion (0.88 g.) of the liquid was distilled by placing the original trap in cold water. The vial was sealed and dispatched for counting.[10] The value obtained was 0.21 μc. for the 0.88 g. = 2.3×10^{-4} mc./g. corresponding to 2.3% exchange at the methyl group of the 4-methoxyl moiety (in relation to the total amount of nitrile used).

β-Methoxy-α-(naphthylmethylene)propionitrile.—The procedure was the same as that described for the veratrylidene analog. When the product could not be induced to crystallize, purification was attempted by chromatography on alumina. This removed much of the color but none of the fractions could be induced to crystallize. The collected material was then distilled at 1-μ pressure. Most of the material came over at 90–100° (bath temperature). Thirty-four grams of distillate was collected (from a 0.2-mole run: a quantity of α-naphthoic acid equivalent to 7% of the starting aldehyde was recovered—it was presumably contained in the aldehyde).

The absorption spectrum of this material in ethanol showed a medium peak at 280 mμ (ε 6360 calcd. for mol. wt., 223) and a strong peak (ε 36,700) at 226 mμ. There is a possible shoulder at about 290 mμ.

2,4-Diamino-5-(α-menaphthyl)pyrimidine.—Twelve grams of this nitrile was added to 100 ml. of methanol containing guanidine base from 15 g. of guanidine hydrochloride. The solution was heated with stirring and methanol allowed to evaporate until the volume had been diminished to about 75 ml. Refluxing was continued for 22 hr. Solid began to separate after about 3 hr. refluxing, but no increase in depth of color was noted at any

(9) The apparatus consists of a 1-l. round-bottom flask having a 24:40 joint available for a condenser. Sealed into it with only the outlet protruding is a 50-ml. spherical flask whose outlet is a female 14:35 joint.

(10) Counting was done by the New England Nuclear Assay Corp.

time. The reaction mixture was filtered hot and the precipitate was washed with water, methanol, and finally with ether; weight, 9.8 g. From the mother liquors 0.4 g. more was obtained. Recrystallization from a rather large volume of 80% ethanol gave material melting at 240–241°. On titration in 50% methanol, the pK_a appears to be about 7 (the situation was complicated by the sparing solubility of both the base and its hydrochloride). The neutral equivalent was 250. The hydrochloride is moderately soluble in alcohol and very sparingly soluble in water.

Condensation of *m*-Ethoxybenzaldehyde with β-Ethoxypropionitrile.—Twenty milliliters of β-ethoxypropionitrile and 22.5 g. (0.15 mole) of *m*-ethoxybenzaldehyde were added to 160 ml. of absolute ethanol in which 2.5 g. of sodium had been dissolved. Forty milliliters of benzene was added and the solution was boiled under a fractionating column for 6 hr., about half of the solvent being allowed to distil during that time. The solution was allowed to stand overnight, concentrated rapidly, and the residue was partitioned between ether and water. The ethereal layer was washed with water, bisulfite solution, and again with water. It was dried briefly over a little calcium chloride, passed through a short alumina column (which removed most of the color), concentrated, and distilled at 1-mm. pressure. A 17.5-g. sample was obtained over the range 140–165°. This oil showed λ_{max} 224 mμ (ε 11,300), 275 mμ (ε 3050); and λ_{min} 259 mμ (ε 2000), from which it is concluded that much of the material was not conjugated completely.

2,4-Diamino-5-(*m*-ethoxybenzyl)pyrimidine.—A guanidine solution was prepared from 30 g. of guanidine hydrochloride and sodium methylate (from 7.2 g. of sodium). After filtration of salt, the solution was concentrated *in vacuo* to 150 ml. To it was added 12.8 g. (0.055 mole) of the described nitrile; the solution was stirred and refluxed for 20 hr. Stirring was continued while the solution (still nearly colorless) was allowed to cool and 100 ml. of water was added. A solid separated that was filtered off, washed with ether, and dried. It melted at 164–166° and weighed 3.5 g. Further evaporation of the mother liquors gave 1 g. more of this solid but there was also obtained 8 g. of an ether-soluble neutral oil, spectrometrically identical with the starting nitrile.

This recovered nitrile together with a further portion to make a total of 11 g. (0.048 mole) was recyclized with a guanidine solution as before, except that the refluxing period was 48 hr. and the solution was allowed to stand overnight. The product, washed with methanol, water, acetone, and ether, weighed 8.3 g. and melted at 166–167.5°. The mother liquors afforded 0.7 g. more of this solid, m.p. 164–166°, and also about 3 g. of neutral, ether-soluble oil.

For analysis, the main crop was recrystallized from 150 ml. of methanol, 6.8 g. being obtained and with melting point unchanged.

4-*n*-Octyloxy-3-methoxybenzaldehyde.—This was prepared from vanillin with octyl iodide and alkali in alcoholic solution. It boils at 165–167° at 1 mm. and melts at 40–42° after crystallization from pentane.

Anal. Calcd. for $C_{16}H_{24}O_3$: C, 72.7; H, 9.2. Found: C, 72.8; H, 9.4.

Reactions of 2,4-Dichlorobenzyl Chloride with Guanidine and Other Nucleophiles. (a) Guanidine at Room Temperature.—A solution of 0.2 mole of guanidine and 0.3 mole of 2,4-dichlorobenzyl chloride in 140 ml. of methanol was allowed to stand 8 days at room temperature. There were obtained 2.5 g. of a base hydrochloride soluble in cold water and 1.5 g. of an insoluble one. The former proved to be 2,4-dichlorobenzylguanidine hydrochloride, m.p. 146–147°.

Anal. Calcd. for $C_8H_9Cl_2N_3 \cdot HCl$: C, 37.7; H, 4.0; N, 16.5. Found: C, 37.6; H, 4.1; N, 16.3 (Kjeldahl).

The sulfate crystallized from water, m.p. 219°.

Anal. Calcd. for $C_8H_9Cl_2N_3 \cdot 0.5H_2SO_4$: C, 36.0; H, 3.7. Found: C, 35.9; H, 3.8.

The less soluble hydrochloride appeared to be a mixture of more highly alkylated bases. About 100 mg. of one component, probably N,N'-bis(2,4-dichlorobenzyl)guanidine hydrochloride, m.p. 180–181°, was isolated by repeated crystallization from hot water.

Anal. Calcd. for $C_{15}H_{13}Cl_4N_3 \cdot HCl$: C, 43.6; H, 3.4; N, 10.2. Found: C, 43.3; H, 3.7; N, 10.0 (Kjeldahl).

The total amount of the bases corresponded to 7% of the original guanidine.

(b) **Ammonia at Room Temperature.**—A solution of 0.2 mole of 2,4-dichlorobenzyl chloride and 1.5 moles of ammonia in 200 ml. of methanol was allowed to stand 21 days at room temperature. The bases formed were separated as a water-insoluble hydrochloride (5.2 g.) and a water-soluble hydrochloride. The latter (6.5 g.) was identified as the hydrochloride of 2,4-dichlorobenzylamine by melting point and conversion to the guanidine described above. The water-insoluble hydrochloride melted at 212–215° and is the salt of bis(2,4-dichlorobenzyl)amine.

Anal. Calcd. for $C_{14}H_{11}Cl_4N \cdot HCl$: C, 45.3; H, 3.3; N, 3.8. Found: C, 44.7; H, 3.0; N, 3.9 (Kjeldahl).

(c) **Guanidine in Methanol at Reflux.**—One-half mole of "guanidine" and 50 g. (0.255 mole) of 2,4-dichlorobenzyl chloride were refluxed 16 hr. in methanol (total volume 300 ml.). The reaction mixture, after partial evaporation of solvent, was partitioned between water and hexane. Analysis of the aqueous layer showed the presence of chloride equivalent to 0.233 mole (90% of the original dichlorobenzyl chloride). The hexane layers were evaporated and 2,4-dichlorobenzylguanidine equivalent to 0.04 mole isolated by conversion to the hydrochloride and sulfate described before. It is evident that about one-sixth of the dichlorobenzyl chloride had reacted with guanidine and most of the rest with methoxide ion. As mentioned previously, the concentrations of these nucleophiles cannot be calculated. On the assumption that pK_a values for guanidinium ion and methanol are the same, the concentration of methoxide would have been much larger.

(d) **Guanidine in Dimethyl Sulfoxide.**—"Guanidine base" (0.5 mole obtained by evaporation of a methanolic solution *in vacuo*) was dissolved in 130 ml. of dimethyl sulfoxide (it is substantially insoluble in ether, benzene, and dioxane). On addition of 0.25 mole of 2,4-dichlorobenzyl chloride, an exothermic reaction ensued and the temperature was around 50° despite cooling under the tap. The reaction product was a mixture of bases whose hydrochlorides were largely insoluble in water. The only substance that could be isolated in pure form (by crystallization from dimethyl sulfoxide) melted at 279–280° dec. and had the composition of tris(2,4-dichlorobenzyl)guanidine hydrochloride.

Anal. Calcd. for $C_{22}H_{17}Cl_6N_3 \cdot HCl$: C, 45.1; H, 3.2; N, 7.3. Found: C, 45.2; H, 3.5; N, 7.4 (Dumas). About 12 g. of this compound was isolated.

Reaction of Guanidine with *p*-Methoxycinnamonitrile.—To a solution of guanidine (0.15 mole) in methanol was added 8 g. (0.05 mole) of *p*-methoxycinnamonitrile (wt. of solution, 55 g.). The solution was refluxed for 30 hr.; it was then a deep yellow. Most of the methanol was boiled off and water and ether were added to the residue from which a yellow gum precipitated. The gum was collected, redissolved in methanol, and reprecipitated by dilution with water. The ethereal washes were evaporated; the residue weighed less than 0.5 g.

The yellow gum was largely soluble in acetone. After filtering off a small amount of undissolved material, dilute hydrochloric acid was added to bring the pH to about 4, water was added, and the solution was allowed to stand. By gradual evaporation small amounts of two crystalline compounds were obtained (A and B) but the bulk of the material remained gummy and reminiscent of the polymeric by-product of the benzylpyrimidine syntheses.

Compound A was a yellow solid melting at 284–288° and at 286–288° after recrystallization from methanol.

Anal. Calcd. for $C_{10}H_{12}N_4O \cdot HCl$: C, 50.1; H, 5.5; N, 23.3. Found: C, 50.4; H, 5.9; N, 23.0 (Dumas).

Compound B forms a hydrochloride crystallizing in yellow needles from methanol. The color deepens to an orange-red in concentrated hydrochloric acid. When made basic the color disappeared and a colorless base crystallizing from methanol in needles was isolated. It had no useful melting point.

Anal. (of base). Calcd. for $C_{21}H_{22}N_4O_3$: C, 66.7; H, 5.8; N, 14.8. Found: C, 67.2; H, 5.7; N, 14.8 (Dumas).

Anal. (of hydrochloride). Calcd. for $C_{21}H_{22}N_4O_3 \cdot HCl \cdot CH_4O$: C, 59.1; H, 6.1; N, 12.5; CH_4O, 7.2. Found: C, 58.5; H, 5.9; N, 12.5; loss in weight at 90° and 1-μ pressure, 7.1%.

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