[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

2,4-Diaminopyrimidines as Antimalarials. III. 5-Aryl Derivatives

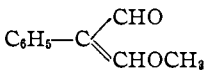
BY PETER B. RUSSELL AND GEORGE H. HITCHINGS

The attempted condensation of guanidine with α-aryl-α-formyl or β-ketoesters to give 2-amino-4-hydroxypyrimidines (derived as intermediates for the corresponding diaminopyrimidines) was found to be limited in its application to the few α-formyl-α-phenyl derivatives, unsubstituted or bearing halogen in the *meta* or *para* position of the benzene ring. A new general synthesis of 4-amino-5-arylpyrimidines has been found in the condensation of amidines or guanidine with β-alkoxy-α-arylacrylonitriles. With guanidine this leads directly to the 2,4-diaminopyrimidines desired for antimalarial testing. In consonance with the findings in previous series, maximal antimalarial activity is found with a 5-phenyl group substituted by an electron-attractive group in the *para* position and an alkyl radical in the pyrimidine-6 position. However, the *p*-chloro- and 3,4-dichlorophenylpyrimidines are significantly more active than the *p*-nitro derivatives, and the optimal 6-alkyl radical appears to be the ethyl. Also in contrast to the phenoxy and benzyl series, the higher homologs in the *p*-chlorophenyl-6-alkyl series have high activities. The general level of activity in this series is much greater than in previous series, reaching values above 1000 times the activity of quinine.

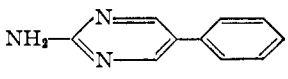
The antimalarial pyrimidines described in the previous papers of this series[1,2] consist of a 2,4-diaminopyrimidine and an aromatic nucleus connected at the 5-position of the pyrimidine by a single (oxygen or carbon) atom. It was of interest to determine the necessity of this atom by eliminating it completely, *i.e.*, by the preparation of 5-arylpyrimidines with and without substituents in the 6-position of the pyrimidine. The systematic synthesis of the 2,4-diamino derivatives *via* the 2-amino-4-hydroxy- and 2-amino-4-chloropyrimidines used for other 5-substituted diaminopyrimidines[1,2] proved to be very unsatisfactory. Although the 5-phenyl and the meta and para chloro and bromophenyl derivatives could be prepared by this route, the yields of the amino-hydroxypyrimidines were exceptionally poor. Moreover, the condensation of ester and guanidine failed entirely with ortho-substituted phenyl derivatives, when the aromatic nucleus was substituted by an electron donor group (*e.g.*, *p*-methoxyl) and with α-phenyl-β-keto esters. The last limitation was considered the most serious in view of the marked enhancement of antimalarial activity which could be obtained in the phenoxy and benzyl series by the introduction of an alkyl (methyl) group into the 6-position of the pyrimidine. The probable importance of the desired derivatives was emphasized when it was found that 2,4-diamino-5-*p*-chlorophenylpyrimidine is, in fact, a very highly active antimalarial (Table II, No. 1).

A number of possible alternative methods of synthesis involving modifications of both the urea derivative and ester were examined. The condensations of substituted ethyl α-formylphenylacetates with thiourea gave no better yields than others had obtained with ethyl pseudothiourea,[3,4] rendering the route *via* the 2,4-dimercaptopyrimidines[5,6] unprofitable. Furthermore the major product appears to be the disulfide[7] of the thiouracil. In analogy with the formation of 4-amino-5-phenylpyrimidine from formamide and phenylacetonitrile[8,9] the reaction of the latter with formylguanidine was investigated, but the required pyrimidine was not obtained. Ethyl α-phenyloxaloacetate and guanidine gave only oxalylguanidine.

The condensation of an acylphenylacetonitrile with guanidine would eliminate several steps in the preparation of 2,4-diaminopyrimidines. The condensation of cyanodesoxybenzoin to give 2,4-diamino-5,6-diphenylpyrimidine had been mentioned by Zerweck.[10] However, neither cyandesoxybenzoin[11] nor any of several other α-acylphenylacetonitriles, under a variety of conditions gave a 2,4-diaminopyrimidine. It seemed probable that the high degree of enolization[12,13,14] and acidity of these β-carbonyl derivatives was fundamentally responsible for their failure to condense. Rupe[15,16] had overcome this difficulty with phenylmalondialdehyde (hydroxymethylenephenacetaldehyde) by condensing guanidine with the enol ether (I) to give 2-amino-5-phenylpyrimidine (II). Likewise Grewe[17] had condensed ethoxymethylenemalononitrile with acetamidine to obtain 4-amino-5-cyano-2-methylpyrimidine.



I



II

ttempts to prepare the desired ethoxymethylenephenylacetonitrile by the condensation of phenylacetonitrile with ethyl orthoformate[17] failed. However, it appeared probable from the work of Arndt[14,18] together with that of Wislicenus[12,13] that the desired enol ethers would be obtainable by treatment of α-acylphenylacetonitriles with diazomethane. Other alkylating agents, on the other hand, would be expected to give primarily alkylation on

(1) E. A. Falco, P. B. Russell and G. H. Hitchings, THIS JOURNAL, **73**, 3753 (1951).

(2) E. A. Falco, S. DuBreuil and G. H. Hitchings, THIS JOURNAL, **73**, 3758 (1951).

(3) H. L. Wheeler and H. S. Bristol, *Am. Chem. J.*, **33**, 448 (1905).

(4) F. H. S. Curd, D. N. Richardson and F. L. Rose, *J. Chem. Soc.*, 378 (1946).

(5) G. B. Elion and G. H. Hitchings, THIS JOURNAL, **69**, 2138 (1947).

(6) P. B. Russell, E. A. Falco, G. B. Elion and G. H. Hitchings, *ibid.*, **71**, 2279 (1949).

(7) W. H. Miller, R. O. Roblin, Jr., and E. B. Astwood, *ibid.*, **67**, 2201 (1945).

(8) W. H. Davies and H. A. Piggott, *J. Chem. Soc.*, 347 (1945).

(9) W. H. Davies, H. A. Piggott and A. W. Johnson, *ibid.*, 352 (1945).

(10) W. Zerweck and K. Keller, U. S. Patent 2,211,710.

(11) 2,4-Diamino-5,6-diphenylpyrimidine, obtained by a modified synthesis, described below, differs in melting point from the product described by Zerweck (*cf.* under Experimental).

(12) W. Wislicenus, G. Butterfass and I. Koken, *Ann.*, **436**, 69 (1924).

(13) W. Wislicenus and H. Reithmuller, *ibid.*, **436**, 82 (1924).

(14) F. Arndt, L. Lowew and R. Ginkok, *Rev. faculte sci. Univ. Istanbul*, Ser. A, II, No. 4, 147 (1946); *Brit. Abstracts*, AII, 508 (1947).

(15) H. Rupe and A. Huber, *Helv. Chim. Acta*, **10**, 846 (1927).

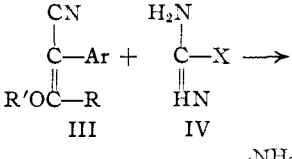
(16) H. Rupe and E. Knup, *ibid.*, **10**, 299 (1927).

(17) R. Grewe, *Z. physiol. Chem.*, **242**, 89 (1936).

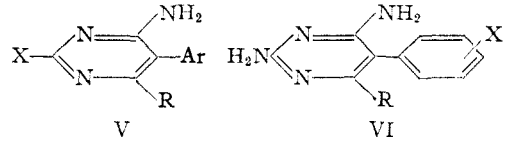
(18) F. Arndt, H. Scholz and E. Frobel, *Ann.*, **521**, 95 (1935).

the α-carbon atom. As shown below the products of the reaction of diazomethane with α-acylphenylacetonitriles do in fact condense with guanidine to give the 5-aryl-2,4-diaminopyrimidines in excellent yields.

The condensation of β-alkoxy-α-arylacrylonitriles (III) with guanidine (IV, X = NH_2) or amidines (IV, X = hydrogen, aryl or alkyl) is a new general method for the preparation of 4-amino-5-



III IV

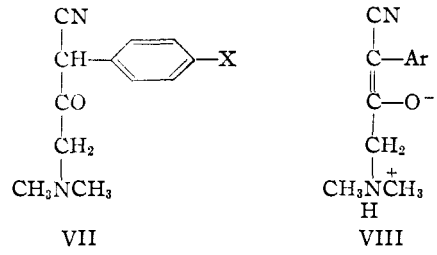


V VI

arylpyrimidines. The condensation of β-methoxy-α-*p*-chlorophenylacrylonitrile (III, R = H, R′ = CH_3, Ar = $C_6H_4Cl(p)$) and the *m*-chloro isomer with guanidine gave diaminopyrimidines, identical with those prepared by the original method, in greatly improved yields (VI, R = H, X = 4-Cl and 3-Cl, respectively). In addition the *ortho* substituted derivatives (VI, R = H, X = 2-Cl, 1,2-CH = CH—CH = CH— etc.) which could not be obtained by the original methods were prepared in excellent yields. Possibly the most important result is that this reaction permits the preparation of 5-arylpyrimidines substituted by a variety of groups in the 6-position (VI, R = alkyl, aryl or heteroaryl).

The reaction proceeds satisfactorily with guanidine, ethylguanidine and a variety of amidines including acetamidine, benzamidine, *p*-toluamidine and formamidine, but ethyl pseudothiourea and thiourea do not condense. With formamidine and β-methoxy-α-phenylacrylonitrile (III, R = H, R′ = CH_3, Ar = $-C_6H_5$), 4-amino-5-phenylpyrimidine (V, X = R = H, Ar = $-C_6H_5$) identical with a sample prepared by the method of Davies and Piggott[8] was obtained. The 2,4-diamino-5-*p*-nitrophenylpyrimidines were prepared by direct nitration and from these the amino and acetamido compounds by reduction and acetylation. The position of the nitro group was determined by cleavage of the resultant pyrimidine with hydrochloric acid and chlorate followed by alkaline permanganate oxidation to give *p*-nitrobenzoic acid.

A wide variety of substituents is possible in the pyrimidine-6 position; however, one limitation has been discovered. Ethyl N,N-dimethylglycinate condensed readily with phenylacetonitrile and *p*-chlorophenylacetonitrile to give crystalline products of the correct analysis for the expected products (VII, X = H, X = *p*-Cl) and ethyl N-phenylglycinate behaved similarly. However, the compounds melted about 100° higher than expected, and they failed to react with diazomethane or to condense with guanidine. The expected ketonitrile and pyrimidine were obtained with ethyl N-methyl-N-phenylglycinate, however. These facts suggest a zwitterionic formulation (VIII) as a possible structure for compounds of this type. Proof of structure VIII and a further study of these compounds will be reported later.



VII VIII

The alkylations of α-formyl- and α-acetylphenylacetonitriles with several alkylating agents were studied by condensation of the products with guanidine. Since in experiments with pure β-alkoxy-α-arylacrylonitriles the yields of pyrimidines vary little from the average of about 70%, the yield of pyrimidine appears to be a valid measure of the extent of O-alkylation.[19] Thus when either of the above acylacetonitriles was treated with diazomethane and condensed with guanidine the yield approximated that expected from the pure enol ether, while alkyl halides and dimethyl sulfate gave only 5 to 15% of the theoretical quantity of pyrimidine.

Attempts to extend this reaction to other β-ketonitriles have been made. Thus α-naphthoylacetonitrile after treatment with diazomethane followed by guanidine gave a 15–20% yield of 2,4-diamino-6-α-naphthylpyrimidine, m.p. 202–204°, although the unmethylated ketonitrile failed to condense. (The identical diaminopyrimidine was obtained in superior yield *via* the usual general synthesis.) Since Arndt, *et al.*,[14] have observed the corresponding benzoylacetonitrile to be only about 12% enolized the low yield probably is to be attributed to a poor conversion of the ketonitrile to its enol ether (however, *cf.* footnote[19]).

The antimalarial activities of some representative 5-aryl-2,4-diaminopyrimidines are shown in Table I.[20] The activities in this series reach very high values; thus 2,4-diamino-5-*p*-chlorophenyl-6-ethylpyrimidine (Table I, No. 3) is about 60 times as active as chlorguanide (N_1-*p*-chlorophenyl-N_5-isopropyl biguanide) when tested against *Plasmodium gallinaceum* in chicks, and about 200 times as active when tested on *P. berghei* in mice[21] (values in the neighborhood of 1,000 times as active as quinine) and also have high activity as suppressants of *P. cynomolgi* in monkeys.[20] In the effects of some structural features on biological activity the phenyl series closely resembles the phenoxy[1] and benzyl[2] series. Thus maximal activity is reached in the phenyl series with an electron-attractive group in the para position and an alkyl group in the pyrimidine-6 position (*e.g.*, Table I, No. 3 *vs.* No. 13, No. 2 and 3 *vs.* No. 1). As in other series the 6-phenyl derivatives are relatively inactive (Table I, No. 14). However, the 4-nitrophenyl derivatives are much less active than the 4-bromo and 4-chloro deriva-

(19) The possibility remains that the proportions of the *cis* and *trans* isomers of the enol ethers may differ with different phenylacetonitriles and various alkylating agents, and the two forms may differ in the ability to condense with guanidine (*cf.* B. Eistert, F. Arndt, L. Lowe and E. Ayça, *Chem. Ber.*, **84**, 156 (1951).

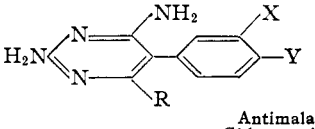
(20) *Cf.* E. A. Falco, L. G. Goodwin, G. H. Hitchings, I. M. Rollo and P. B. Russell, *Brit. J. Pharm.*, **6**, 185 (1951).

(21) L. G. Goodwin, *Nature*, **164**, 1133 (1949).

tives in contrast to the comparative activities of these substituents in the benzyl and phenoxy series (Table I, No. 11 and 12 *vs.* 2, 3, 7 and 8). In this series, also, the 3-chloro derivatives are less active than the 4-chloro even as tested on *P. gallinaceum* (Table I, No. 15 *vs.* No. 3). The 4-fluoro derivatives are about the order of activity of the 4-nitro compounds (Table Nos. 16 and 17). The optimal size and the effects of various alkyl groups also differ in this series from the others. Whereas a sharp peak of activity was obtained with a pyrimidine-6-methyl group in both the phenoxy and benzyl series,[1,2,20] the ethyl derivatives generally are the most active among the substituted phenyl pyrimidines (Table I, No. 3 *vs.* No. 2, No. 8 *vs.* No. 7, No. 10 *vs.* No. 9). Moreover the substances with longer alkyl radicals (in the *p*-chlorophenyl series) retain rather high activity, especially with regard to tests on *P. gallinaceum*. *P. berghei* is more sensitive to the lower members and less sensitive to the higher members of this homologous series than is *P. gallinaceum* (Table I, No. 2, 3, 4, 5, 6). To an indeterminate extent such differences may be attributed to differences in metabolic processes of the mouse and chick hosts rather than to the plasmodia *per se*.

TABLE I

ANTIMALARIAL ACTIVITIES OF 5-ARYL-2,4-DIAMINOPYRIMIDINES



Compound	X	Y	R	Antimalarial activity Chlorguanide equivalent *P. gallinaceum*	*P. berghei*
1	H	Cl	H	0.4	30
2	H	Cl	CH_3	15	40
3	H	Cl	C_2H_5	60	200
4	H	Cl	C_3H_7	20	5
5	H	Cl	C_4H_9	7	1
6	H	Cl	C_5H_{11}	40	8
7	H	Br	CH_3	*ca.* 10	*ca.* 15
8	H	Br	C_2H_5	30	80
9	Cl	Cl	CH_3	14	130
10	Cl	Cl	C_2H_5	20	190
11	H	NO_2	CH_3	2	2
12	H	NO_2	C_2H_5	4	>1
13	H	CH_3	CH_3	<1	0
14	H	Cl	C_6H_5	*ca.* 1	<1
15	Cl	H	CH_3	2	2
16	H	F	CH_3	*ca.* 5	3
17	H	F	C_2H_5	5	7

A more complete presentation of the antimalarial activities of the 5-aryldiaminopyrimidines has been published.[20] The biological work was carried out by L. G. Goodwin and I. M. Rollo in the Wellcome Laboratories of Tropical Medicine (London).

The ultraviolet absorption spectra of 2,4-diamino-5-arylpyrimidines (Fig. 1, Curve I) unsubstituted in the 6-position or in the ortho-position of the aryl group exhibit striking differences from those of similar pyrimidines carrying substituents in either or both these positions (Fig. 2, Curves II and III). The latter approximate the spectra of corresponding pyrimidines carrying the aryl group in the 6-position, or to 2,4-diaminopyrimidines carrying no aromatic substituent directly in the ring (Fig. 2, Curve I). The effect of changing the *p*H on the spectrum of a 2,4-diamino-5-arylpyrimidine is also worthy of note; while at *p*H 11 in aqueous solution the spectrum is identical with that in alcohol (Curve I) at *p*H 1 the curve loses all bands in the region investigated (Fig. 1, Curve II). A discussion of these effects will be published later.

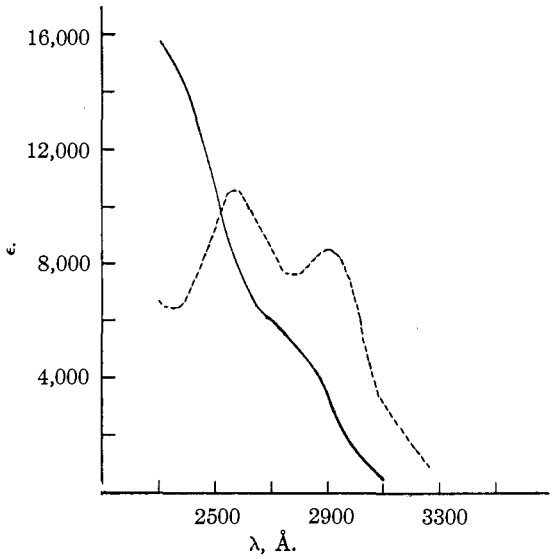


Fig. 1.—Curve I, - - - -, 2,4-diamino-5-phenylpyrimidine in alcohol; Curve II, ———, 2,4-diamino-5-phenylpyrimidine at *p*H 1.

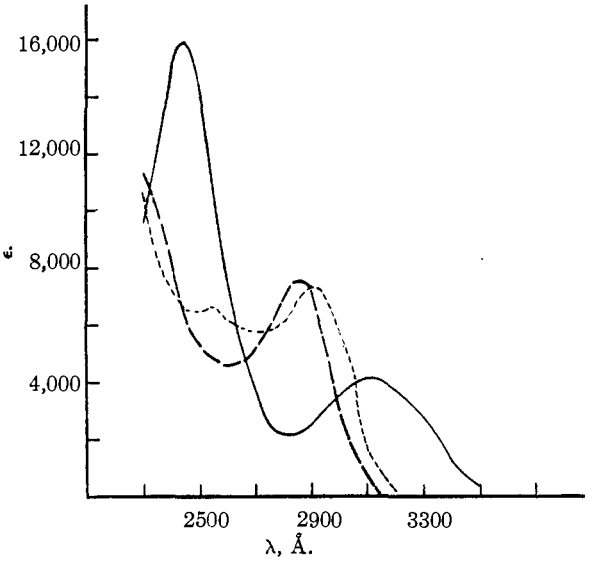


Fig. 2.—Curve I, ———, 2,4-diamino-6-*p*-chlorophenylpyrimidine; Curve II, - - - - -, 2,4-diamino-5-*o*-chloropyrimidine; Curve III, — — —, 2,4-diamino-5-*o*-chlorophenyl-6-methylpyrimidino all in alcohol.

Experimental

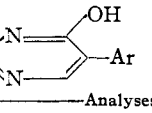
The ultraviolet absorption spectra were determined using the Beckman model *DU* spectrophotometer. All melting points reported are uncorrected.

2-Amino-4-hydroxy-5-arylpyrimidines (Table II).—These compounds were prepared by condensation of the ethyl α-formylarylacetate with guanidine as has been previously described.[1,2] The yields in all cases were poor.

2,4-Diamino-5-arylpyrimidines from the 4-Hydroxy Compounds. Method A.—The hydroxy compounds were

TABLE II

2-AMINO-4-HYDROXY-5-ARYLPYRIMIDINES



Ar	M.p., °C.	Yield, %	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	244–245	20	$C_{10}H_9ON_3$	64.2	4.8		64.7	4.5	
$C_6H_4Cl(4)$	323 dec.	10	$C_{10}H_8ON_3Cl$	54.2	3.6	19.0	54.1	3.5	18.7
$C_6H_4Cl(3)$	255–258	15	$C_{10}H_8ON_3Cl$	54.2	3.6	19.0	53.9	3.6	19.0
$C_6H_3Cl_2(3,4)$	330 dec.	16	$C_{10}H_7ON_3Cl_2$	46.9	2.7		46.5	3.0	
$C_6H_4Br(4)$	313 dec.	23	$C_{10}H_8ON_3Br$	45.2	3.0	15.8	45.4	3.2	15.5

chlorinated with phosphoryl chloride and the chloro compounds aminated with ethanolic ammonia as previously described.[1,2]

Disulfide of 5-(3′,4′-Dichlorophenyl)-4-hydroxy-2-mercaptopyrimidine (5-(3′,4′-Dichlorophenyl)-thiouracil).—A mixture of ethyl formate (20 ml.) and ethyl 3,4-dichlorophenylacetate (54 g.) was added to sodium wire (5.75 g.) under dry ether (200 ml.). After the sodium had all reacted thiourea (19 g.) in ethanol (100 ml.) was added and the mixture refluxed on the steam-bath for six hours. The solution was then poured into water (700 ml.) and filtered with the acid of charcoal. The clear filtrate was acidified with acetic acid and the precipitate filtered off. Some white material dissolved readily in ethanol leaving a deep yellow material. This on recrystallization from ethanol gave deep yellow plates, m.p. 305–309 (dec.) (2.05 g.).

Anal. Calcd. for $C_{20}H_{12}O_2N_4S_2Cl_4$: C, 44.1; H, 1.8; N, 10.3. Found: C, 43.9; H, 2.2; N, 10.2.

Ethyl *p*-chlorophenylacetate treated in the same manner gave yellow plates of the disulfide of 5-*p*-chlorophenylthiouracil, m.p. 335–337° (dec.).

Anal. Calcd. for $C_{20}H_{12}O_2N_4S_2Cl_2$: C, 50.5; H, 2.5; N, 11.8. Found: C, 50.6; H, 2.7; N, 11.6.

5-(3′,4′-Dichlorophenyl)-2-thiouracil.—The above disulfide (0.54 g., 0.001 mole) was dissolved in a slight excess of 0.5 *N* sodium hydroxide and sodium hydrosulfite (0.3 g., 0.0015 mole) added. Some colorless material soon separated and the yellow solution slowly lost its color. When colorless the solution was acidified with 0.5 *N* sulfuric acid and the precipitate filtered off. It was redissolved in 0.5 *N* sodium hydroxide, charcoaled and precipitated with 0.5 *N* sulfuric acid once again. The almost colorless solid was recrystallized from aqueous ethanol forming pale yellow needles, m.p. 308–311° (dec.) depressed to 295–299° (dec.) on admixture with the deep yellow starting material.

Anal. Calcd. for $C_{10}H_6ON_2SCl_2$: C, 44.0; H, 2.2. N, 10.3. Found: C, 44.1; H, 2.3; N, 10.2.

5-(3′,4′-Dichlorophenyl)-uracil.—The corresponding disulfide (2.0 g.) was mixed with chloroacetic acid (2.0 g.), water (10 ml.) and concentrated hydrochloric acid (1 ml.). The solution was refluxed for eight hours, cooled and filtered. The solid was dissolved in 2 *N* sodium hydroxide treated with charcoal and filtered. The uracil was precipitated with hot acetic acid. When dry it melted at 358° after darkening from 290°.

Anal. Calcd. for $C_{10}H_6O_2N_2Cl_2$: C, 46.7; H, 2.3; N, 10.9. Found: C, 46.8; H, 2.3; N, 11.2.

Condensation of Formylguanidine and Phenylacetonitrile.—Formylguanidine[22] (9.1 g., 0.1 mole) and phenylacetonitrile (11.7 g., 0.1 mole) were heated in a bomb with ethanol (25 ml.) at 150°. On cooling the ethanol was evaporated, the solution diluted with water and made strongly alkaline with ammonium hydroxide. The solid was collected, dissolved in dilute acetic acid and precipitated with sodium hydroxide. After recrystallization from aqueous ethanol it melted unsharply at about 140°. After recrystallization from benzene it formed colorless needles, m.p. 139°.

Anal. Calcd. for $C_7H_6N_2$: C, 63.7; H, 4.5; N, 31.9. Found: C, 63.7; H, 4.5; N, 31.9.

Arylacetonitriles.—These compounds were, for the most part, prepared by the action of potasslum cyanide on the benzyl halides, which when not commercially available were prepared by the excellent method of Kharasch and Brown.[23]

(22) W. Traube, *Ber.*, **43**, 3589 (1910).

(23) M. S. Kharasch and H. C. Brown, THIS JOURNAL, **61**, 2142 (1939).

The known nitriles prepared by this method were: *p*-chlorophenylacetonitrile,[24] *m*-chlorophenylacetonitrile,[25] *o*-chlorophenylacetonitrile,[26] *o*-bromophenylacetonitrile,[27] *m*-bromophenylacetonitrile,[27] *p*-bromophenylacetonitrile,[28] *p*-fluorophenylacetonitrile,[29] *p*-tolylacetonitrile,[30] α-naphthylacetonitrile[31] and *p*-phenylphenylacetonitrile.[32] *p*-Methoxy- and 3,4-dimethoxyacetonitrile were prepared by dehydration and decarboxylation of the oximes obtained from the thiopyruvic acids.[33] The new compounds are listed in Table III.

TABLE III

PHENYLACETONITRILES

Acetonitriles	M.p. or b.p., (mm.), °C.	Formula	Nitrogen, % Calcd.	Found
2,4-Dichlorophenyl	57–59	$C_8H_5NCl_2$	7.5	7.1
3,4-Dichlorophenyl	41–42[a]	$C_8H_5NCl_2$	7.5	7.3
3,4-Dibromophenyl	68–69	$C_8H_5NBr_2$	5.1	4.7
2,5-Dibromophenyl	112–113	$C_8H_5NBr_2$	5.1	4.9
3-Fluorophenyl	B. 124–126 (10)	C_8H_6NF	10.4	10.0
2-Fluorophenyl	B. 122–126 (10)	C_8H_6NF	10.4	10.2

[a] B.p. 160–170° (10 mm.).

α-Acylarylacetonitriles.—These compounds were all prepared by the condensation of the appropriate ethyl esters and nitriles in the presence of sodium ethoxide. The following α-acylarylacetonitriles have been described previously: α-formylphenylacetonitrile,[34] α-acetylphenylacetonitrile,[35] α-formyl 1-naphthylacetonitrile,[12] α-acetyl-*p*-bromophenylacetonitrile,[36] *p*-chloro-α-cyandesoxybenzoin[23] and cyandesoxybenzoin.[37] An example of the preparative method is given below. The compounds are shown in Table IV.

α-Acetyl-*p*-chlorophenylacetonitrile.—Sodium (11.5 g.) was dissolved in ethanol (250 ml.) and to this solution was added a mixture of *p*-chlorophenylacetonitrile (76 g.) and ethyl acetate (44 g.). The solution was refluxed on the steam-bath for five hours. After cooling it was poured into water (2.5 liters). The insoluble oil was extracted with ether. The aqueous solution was acidified with *N* sulfuric acid and the separated oil extracted with ether. The ether solution after washing with sodium bicarbonate solution and again with water was dried over sodium sulfate. On removal of ether the residue crystallized (56 g.). A sample recrystallized from ether petroleum–ether melted at 124°.

Treatment of α-Acylarylacetonitriles with Diazomethane.—In general the α-acylarylacetonitriles were treated with diazomethane in ether and the crude product condensed with guanidine to give the pyrimidine. However, in several cases the α-aryl-β-methoxyacrylonitriles were isolated and characterized.

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Table IV

Preparation of α-Acylarylacetonitriles Ar—CH(R—CO)—CN

Ar	Ethyl ester	R	M.p., °C.	Formula	Nitrogen, % Calcd.	Found
$C_6H_4Cl(4)$	Formate	H	164–165	C_9H_6ONCl	7.8	8.2
$C_6H_4Cl(4)$	Acetate	CH_3	124–125	$C_{10}H_8ONCl$	7.2	7.3
$C_6H_4Cl(4)$	Propionate	CH_2CH_3	50–52	$C_{11}H_{10}ONCl$	6.7	6.5
$C_6H_4Cl(4)$	Butyrate	$(CH_2)_2CH_3$	86–87	$C_{12}H_{12}ONCl$	6.3	6.1
$C_6H_4Cl(4)$	Valerate	$(CH_2)_3CH_3$	69–70	$C_{13}H_{14}ONCl$	5.9	5.7
$C_6H_4Cl(4)$	*n*-Caproate	$(CH_2)_4CH_3$	65–67	$C_{14}H_{16}ONCl$	5.6	5.2
$C_6H_4Cl(4)$	*n*-Heptylate	$(CH_2)_5CH_3$	48–50	$C_{15}H_{18}ONCl$	5.3	5.1
$C_6H_4Cl(4)$	*n*-Caprylate	$(CH_2)_6CH_3$	[a]			
$C_6H_4Cl(4)$	Laurate	$(CH_2)_{10}CH_3$	60–61	$C_{20}H_{28}ONCl$	4.2	4.5
$C_6H_4Cl(4)$	Isovalerate	$CH_2CH_2(CH_3)_2$	84–85	$C_{13}H_{14}ONCl$	5.9	5.9
$C_6H_4Cl(4)$	Methoxyacetate	CH_2OCH_3	107	$C_{11}H_{10}O_2NCl$	6.3	6.3
$C_6H_4Cl(3)$	Formate	H	176–177	C_9H_6ONCl	7.8	8.0
$C_6H_4Cl(3)$	Acetate	CH_3	84–86	$C_{10}H_8ONCl$	7.2	7.4
$C_6H_4Cl(2)$	Formate	H	118–120	C_9H_6ONCl	7.8	7.7
$C_6H_4Cl(2)$	Acetate	CH_3	[a]			
$C_6H_4Br(4)$	Propionate	CH_2CH_3	60–63	$C_{11}H_{10}ONBr$	5.6	5.1
$C_6H_4Br(3)$	Acetate	CH_3	95	$C_{10}H_8ONBr$	6.1	5.9
$C_6H_4Br(2)$	Formate	H	120–121	C_9H_6ONBr	6.3	6.2
$C_6H_4F(4)$	Formate	H	146–148	C_9H_6ONF	8.6	8.5
$C_6H_4F(4)$	Acetate	CH_3	89–90	$C_{10}H_8ONF$	7.9	7.6
$C_6H_4F(4)$	Propionate	CH_2CH_3	[a]			
$C_6H_4F(3)$	Acetate	CH_3	117–118	$C_{10}H_8ONF$	7.9	7.7
$C_6H_4F(2)$	Formate	H	125	C_9H_6ONF	8.6	8.7
$C_6H_3Cl_2(2,4)$	Formate	H	158–160	$C_9H_5ONCl_2$	6.5	6.3
$C_6H_3Cl_2(3,4)$	Acetate	CH_3	161–163	$C_{10}H_7ONCl_2$	6.1	5.9
$C_6H_3Cl_2(3,4)$	Propionate	CH_2CH_3	105–106	$C_{11}H_9ONCl_2$	5.8	5.5
$C_6H_3Cl_2(3,4)$	Butyrate	$(CH_2)_2CH_3$	101	$C_{12}H_{11}ONCl_2$	5.5	5.2
$C_6H_3Cl_2(3,4)$	Valerate	$(CH_2)_3CH_3$	[a]			
$C_6H_3Br_2(3,4)$	Propionate	CH_2CH_3	108	$C_{11}H_9ONBr_2$	4.2	3.9
$C_6H_4OCH_3(4)$	Formate	H	100–102	$C_{10}H_9NO_2$	8.0	7.7
$C_6H_4CH_3(4)$	Formate	H	152–153	$C_{10}H_9ON$	8.8	8.6
C_6H_4–$C_6H_5(4)$	Formate	H	210–210	$C_{15}H_{11}ON$	6.3	6.4
$C_6H_3(OCH_3)_2(3,4)$	Acetate	CH_3	98	$C_{12}H_{13}O_3N$	6.4	6.5
$C_{10}H_7(\alpha)$	Acetate	CH_3	[a]			

[a] Obtained only as an uncrystalline oil.

α-2,4-Dichlorophenyl-β-methoxyacrylonitrile.—α-Formyl-2,4-dichlorophenylacetonitrile (8.0 g.) was treated with excess diazomethane (from nitrosomethylurea (10 g.)) in ether (200 ml.). The evolution of nitrogen was violent on mixing but subsided in a matter of seconds. The solution was allowed to stand overnight. The ether and excess diazomethane were evaporated on a steam-bath. The residue on crystallization from ethanol gave a yellow solid (5.0 g.) which on recrystallization from ethanol melted at 105–107°.

Anal. Calcd. for $C_{10}H_7ONCl_2$: C, 52.6; H, 3.1; N, 6.1. Found: C, 53.0; H, 3.0; N, 6.4.

α-*p*-Fluorophenyl-β-methoxyacrylonitrile.—α-Formyl-*p*-fluorophenylacetonitrile (8 g.) was treated with diazomethane (from nitrosomethylurea (10 g.)) in ether (150 ml.). The methoxy compound separated at once. Recrystallized from ethanol it formed colorless silky needles, m.p. 197–198°.

Anal. Calcd. for $C_{10}H_8ONF$: N, 7.9. Found: N, 8.2.

α-*o*-Fluorophenyl-β-methoxyacrylonitrile.—α-Formyl-*o*-fluorophenylacetonitrile (8.0 g.) was treated with diazomethane (from nitrosomethylurea (10 g.)) in ether (150 ml.). The separated material was filtered off and after recrystallization from methanol it melted at 156–157°.

Anal. Calcd. for $C_{10}H_8ONF$: C, 67.8; H, 4.5; N, 7.9. Found: C, 67.8; H, 4.5; N, 8.3.

α-3,4-Dichlorophenyl-β-methoxy-β-methylacrylonitrile.—α-Acetyl-3,4-dichlorophenylacetonitrile (11.4 g.) was treated with diazomethane (from nitrosomethylurea (10 g.)). The reaction subsided in a few seconds. After standing for five hours the ether was evaporated. The residue recrystallized from ethanol as plates melting at 71–73°.

Anal. Calcd. for $C_{11}H_9ONCl_2$: N, 5.8. Found: N, 6.0.

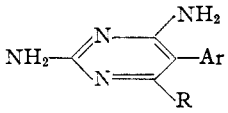
Methylation and Condensation of α-Acylarylacetonitriles with Guanidine to Give 2,4-Diamino-5-arylpyrimidines.—The 2,4-diaminopyrimidines prepared by this method are listed in Table V. Several examples of the general procedure will be given.

2,4-Diamino-5-phenylpyrimidine.—α-Formylphenylacetonitrile (7.25 g.) was dissolved in ether (100 ml.) and diazomethane (from nitrosomethylurea (10 g.) in ether (100 ml.)) was added. Nitrogen was evolved at once. After standing overnight the ether and excess diazomethane were evaporated. The residue was dissolved in ethanol (25 ml.) and a solution of guanidine (from the hydrochloride (4.75 g.) in ethanol (50 ml.)) was added. The solution was heated on a steam-bath for three hours. The ethanol was then removed and concentrated sodium hydroxide solution was added to the residue. The insoluble material was filtered off. This was dissolved in glacial acetic acid (10 ml.) and diluted with water (30 ml.). After treating with charcoal and filtering, the colorless solution was made alkaline with 2 *N* sodium hydroxide. The white precipitate was filtered off and washed with water. After recrystallization from water it formed colorless plates melting at 162–164°, the melting point being undepressed on admixture with an authentic sample of 2,4-diamino-5-phenylpyrimidine which was prepared by method A above.

2,4-Diamino-5-phenyl-6-methylpyrimidine.—α-Acetylphenylacetonitrile (8.0 g.) was treated with diazomethane (from nitrosomethylurea (10 g.)) as in the previous experi-

TABLE V

5-ARYL-2,4-DIAMINOPYRIMIDINES (METHOD B)



Ar	R	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
C_6H_5	H[a,b]	162–164	$C_{10}H_{10}N_4$	64.5	5.4	30.1	64.9	5.4	..
C_6H_5	CH_3[c]	249–250	$C_{11}H_{12}N_4$	66.0	6.0	28.0	65.9	6.0	28.2
C_6H_5	CH_2CH_3	237–240	$C_{12}H_{14}N_4$	67.3	6.5	26.2	67.2	6.4	26.1
C_6H_5	C_6H_5	241–242[d]	$C_{16}H_{14}N_4$	73.3	5.3	21.4	73.2	5.3	21.0
$C_6H_4Cl(4)$	H[a]	194–195	$C_{10}H_9N_4Cl$	54.4	4.1	25.4	54.6	3.7	25.0
$C_6H_4Cl(4)$	CH_3	264–265	$C_{11}H_{11}N_4Cl$	56.3	4.7	23.9	56.2	4.6	23.8
$C_6H_4Cl(4)$	CH_2CH_3	233–234	$C_{12}H_{13}N_4Cl$	57.9	5.2	22.5	58.0	5.1	22.1
$C_6H_4Cl(4)$	$(CH_2)_2CH_3$[e]	171–174	$C_{13}H_{15}N_4Cl$	59.4	5.7	21.3	59.8	6.1	20.9
$C_6H_4Cl(4)$	$(CH_2)_3CH_3$	208–210	$C_{14}H_{17}N_4Cl$	60.8	6.1	20.2	61.0	6.0	20.4
$C_6H_4Cl(4)$	$CH_2CH(CH_3)_2$[f]	147–149	$C_{14}H_{17}N_4Cl$	60.8	6.1	20.3	60.9	6.0	20.0
$C_6H_4Cl(4)$	$(CH_2)_4CH_3$	188–190	$C_{15}H_{19}N_4Cl$	62.0	6.5	19.3	62.2	6.4	..
$C_6H_4Cl(4)$	$(CH_2)_5CH_3$	172–173	$C_{16}H_{21}N_4Cl$	63.1	6.9	18.4	62.8	6.5	18.7
$C_6H_4Cl(4)$	$(CH_2)_6CH_3$	156	$C_{17}H_{23}N_4Cl$	64.1	7.2	17.6	64.2	7.3	17.4
$C_6H_4Cl(4)$	$(CH_2)_{10}CH_3$[c]	139–140	$C_{21}H_{31}N_4Cl$	67.3	8.3	15.0	67.4	8.2	14.7
$C_6H_4Cl(4)$	CH_2OCH_3	218–219	$C_{12}H_{13}ON_4Cl$	54.4	4.9	21.2	54.8	4.6	21.2
$C_6H_4Cl(4)$	C_6H_5[f]	268–270	$C_{16}H_{13}N_4Cl$	64.8	4.4	18.9	64.7	4.4	18.7
$C_6H_4Cl(3)$	H[a]	204–206	$C_{10}H_9N_4Cl$	54.4	4.1	25.4	54.2	4.3	25.2
$C_6H_4Cl(3)$	CH_3	219–220	$C_{11}H_{11}N_4Cl$	56.3	4.7	23.9	56.1	4.5	23.9
$C_6H_4Cl(2)$	H[f]	125–128	$C_{10}H_9N_4Cl$	54.4	4.1	25.4	54.4	4.2	25.1
$C_6H_4Cl(2)$	CH_3[f]	225	$C_{11}H_{11}N_4Cl$	56.3	4.7	23.9	56.2	4.5	23.9
$C_6H_4Br(4)$	H[g]	205–207	$C_{10}H_9N_4Br$	45.3	3.4	21.1	45.2	3.5	21.2
$C_6H_4Br(4)$	CH_3	263–265	$C_{11}H_{11}N_4Br$	47.3	3.9	20.1	47.6	4.1	20.4
$C_6H_4Br(4)$	CH_2CH_3	213–216	$C_{12}H_{13}N_4Br$	49.2	4.4	19.1	49.5	4.4	18.7
$C_6H_4Br(3)$	CH_3	236	$C_{11}H_{11}N_4Br$	47.3	3.9	20.1	47.6	3.9	20.0
$C_6H_4Br(2)$	H[f]	140–141	$C_{10}H_9N_4Br$	45.3	3.4	21.1	45.2	3.5	21.3
$C_6H_4F(4)$	H	207	$C_{10}H_9N_4F$	58.8	4.4	27.5	59.1	4.1	27.7
$C_6H_4F(4)$	CH_3	295	$C_{11}H_{11}N_4F$	60.6	5.0	25.7	60.3	4.9	..
$C_6H_4F(4)$	CH_2CH_3	269	$C_{12}H_{13}N_4F$	62.1	5.6	24.1	62.2	5.4	23.7
$C_6H_4F(3)$	CH_3	237	$C_{11}H_{11}N_4F$	60.6	5.0	25.7	61.1	5.1	..
$C_6H_3Cl_2(2,4)$	H	178	$C_{10}H_8N_4Cl_2$	47.1	3.1	22.0	46.8	3.0	22.2
$C_6N_3Cl_2(3,4)$	H[f]	208–210	$C_{10}H_8N_4Cl_2$	47.1	3.1	22.0	46.8	3.0	22.3
$C_6H_3Cl_2(3,4)$	CH_3	275–276	$C_{11}H_{10}N_4Cl_2$	49.1	3.7	20.8	49.0	3.5	21.2
$C_6H_3Cl_2(3,4)$	CH_2CH_3	230	$C_{12}H_{12}N_4Cl_2$	50.9	4.2	19.8	51.0	4.2	19.5
$C_6H_3Cl_2(3,4)$	$(CH_2)_2CH_3$	174-176	$C_{13}H_{14}N_4Cl_2$	52.5	4.7	18.9	52.8	4.8	18.4
$C_6H_3Cl_2(3,4)$	$(CH_2)_3CH_3$	192	$C_{14}H_{16}N_4Cl_2$	54.0	5.1	18.0	53.8	5.0	17.7
$C_6H_3Br_2(2,5)$	H[f]	220	$C_{10}H_8N_4Br_2$	35.0	2.3	16.3	35.2	2.5	16.5
$C_6H_3Br_2(3,4)$	CH_2CH_3	225	$C_{12}H_{12}N_4Br_2$	38.7	3.2	15.1	39.1	3.2	14.8
$C_6H_4OCH_3(4)$	H	202–203	$C_{11}H_{12}ON_4$	61.1	5.6	25.4	61.4	5.3	26.1
$C_6H_4CH_3(4)$	H	200	$C_{11}H_{12}N_4$	66.0	6.0	28.0	66.3	5.9	28.4
$C_6H_4CH_3(4)$	CH_3	241	$C_{12}H_{14}N_4$	67.3	6.5	26.2	67.2	6.4	26.5
C_6H_4–$C_6H_5(4)$	H	204–205	$C_{16}H_{14}N_4$	73.3	5.3	21.4	72.9	5.2	21.0
$C_6H_3(OCH_3)_2(3,4)$	CH_3	*ca.* 300	$C_{13}H_{16}O_2N_4$	60.0	6.2	21.5	59.8	6.6	21.3
$C_{10}H_7(\alpha)$	H	179–180	$C_{14}H_{12}N_4$	71.2	5.1	23.7	70.9	5.3	23.2
$C_{10}H_7(\alpha)$	CH_3[f]	160	$C_{15}H_{14}N_4$	72.0	5.6	22.4	72.3	5.8	22.3

[a] Also prepared by Method A (Table II). [b] Recrystallized from water. [c] Recrystallized from alcohol, the solvent used in every case except where noted. [d] Zerweck and Keller, reference 10, give m.p. 221°. [e] Recrystallized from methanol–benzene. [f] Recrystallized from benzene or benzene–petroleum ether. [g] Prepared by Method A only.

ment. The product, after removal of the ether and excess diazomethane, was treated with guanidine (from the hydrochloride (4.5 g.) and sodium (1.3 g.) in ethanol (150 ml.)), and heated on a steam-bath for two to three hours. The product, which was isolated as in the previous example, crystallized from methanol as colorless plates melting at 249–250°.

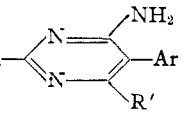
Nitration of 2,4-Diamino-5-phenylpyrimidine.—The pyrimidine (3 g.) was dissolved in concentrated sulfuric acid (25 ml.) and the solution cooled to between −5 and −10° and stirred. Potassium nitrate (1.62 g. powdered) was added over one hour. After the addition the stirring was continued for one hour. The acid was then poured onto crushed ice (200 g.). An almost colorless precipitate was obtained which turned yellow on washing with water. The precipitate was suspended in water which was then made alkaline with sodium hydroxide solution. The yellow product was recrystallized from boiling ethanol. It formed yellow prisms melting at 315–317°.

Anal. Calcd. for $C_{10}H_9O_2N_5$: C, 51.9; H, 3.9; N, 30.3. Found: C, 52.3; H, 3.7; N, 31.0.

Nitration of 2,4-Diamino-5-phenyl-6-methyl and 6-Ethylpyrimidines.—The 6-substituted derivatives were nitrated as in the previous preparation. Both compounds were purified by solution in hot aqueous alcoholic hydrochloric acid from which they separated as microcrystalline powders on basification and cooling. Both melted above 350° with decomposition.

Table VI

4-Amino-5-arylpyrimidines



R	R′	Ar	M.p., °C.	Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
H	H	C_6H_5	152–153[a]							
CH_3	H	$C_6H_4Cl(4)$	178	$C_{11}H_{10}N_3Cl$	60.1	4.6	19.1	59.8	4.8	18.9
CH_3	CH_3	$C_6H_4Cl(4)$	201–202	$C_{12}H_{12}N_3Cl$	61.7	5.1	18.0	52.0	5.4	17.6
$C_6H_4CH_3(4)$	H	$C_6H_4Cl(4)$	186	$C_{17}H_{14}N_3Cl$	69.0	4.7	14.2	68.8	4.6	14.4
CH_3	C_6H_5	$C_6H_4Cl(4)$	201–202	$C_{17}H_{14}N_3Cl$	69.0	4.7	14.2	69.2	4.9	14.5
$C_6H_4CH_3(4)$	H	$C_6H_4Cl(2)$	180	$C_{17}H_{14}N_3Cl$	69.0	4.7	14.2	69.1	4.7	14.0
C_6H_5	C_6H_5	C_6H_5	161	$C_{22}H_{17}N_3$	81.7	5.3	13.0	82.0	5.5	12.7
C_6H_5	CH_3	$C_6H_4Cl(4)$	154–155	$C_{17}H_{14}N_3Cl$	69.0	4.7	14.2	68.8	4.6	13.8
CH_3	H	$C_6H_3Cl_2(2,4)$	230	$C_{11}H_9N_3Cl_2$	52.0	3.5	16.5	52.5	3.5	16.9

[a] Identical with a sample prepared by method of Davies and Piggott, reference 8.

Anal. Calcd. for $C_{11}H_{11}O_2N_5$: C, 53.9; H, 4.5; N, 28.6. Found: C, 53.8; H, 4.2; H, 27.9.

Calcd. for $C_{12}H_{13}O_2N_5$: C, 55.6; H, 5.0; N, 27.0. Found: C, 55.1; H, 4.7; N, 26.6.

Oxidation of 2,4-Diamino-5-*p*-nitrophenyl-6-ethylpyrimidine.—The degradation of this pyrimidine (0.2 g.) to *p*-nitrobenzoic acid was carried out as for the benzyl compound.[2] The crystals (0.07 g.) after recrystallization from aqueous methanol melted at 237–239° undepressed on admixture with an authentic sample of *p*-nitrobenzoic acid. 2,4-Diamino-5-*p*-nitrophenyl-6-methylpyrimidine and 2,4-diamino-5-*p*-nitrophenylpyrimidine were both oxidized to *p*-nitrobenzoic acid in a similar manner. Alkaline permanganate alone failed to cleave the pyrimidines, the substances being recovered unchanged after attempted oxidation by this means.

2,4-Diamino-5-*p*-aminophenylpyrimidine.—The nitro compound (1.25 g.) was dissolved in 50% aqueous ethanol containing 3 equivalents of 2 *N* hydrochloric acid (in all 150 ml.) and the solution shaken in an atmosphere of hydrogen in the presence of Adams catalyst. When the calculated amount of hydrogen had been absorbed the catalyst was removed and the alcohol evaporated. The solution was basified with 2 *N* sodium hydroxide and the amino compound separated as colorless plates melting at 233°.

Anal. Calcd. for $C_{10}H_{11}N_5$: C, 59.7; H, 5.5; N, 34.8. Found: C, 59.6; H, 5.5; N, 35.1.

Acetylation of 2,4-Diamino-5-*p*-aminophenylpyrimidine.—The above pyrimidine (75 g.) was refluxed with acetic anhydride (6 ml.) and anhydrous sodium acetate (0.5 g.) for one-half hour. The mixture was poured into ice-cold dilute ammonia solution (50 ml.). On standing colorless needles separated which melted at 241–242°. The analysis indicated that the starting material had now one acetyl group and one molecule of acetic acid.

Anal. Calcd. for $C_{14}H_{17}N_5O_3$: N, 23.1. Found: N, 23.0, 22.8.

The compound (0.3 g.) and 2.25 *N* sodium hydroxide (0.5 ml.) were mixed. The material went into solution at once with the formation of a yellow color. Water (10 ml.) was added and the solution warmed on a steam-bath for three hours. On cooling yellowish needles separated which melted at 237°.

Analysis of this product indicated that it is a monoacetyl derivative. Since it fails to give the color test for aromatic amino groups (diazotization and coupling with β-naphthol) the compound is identified as 5-*p*-acetamidophenyl-2,4-diaminopyrimidine.

Anal. Calcd. for $C_{12}H_{13}N_5O$: C, 59.3; H, 5.3; N, 28.8. Found: C, 59.7, H, 5.2; N, 28.8.

Condensation of Ethylguanidine with α-*p*-Chlorophenyl-β-methoxyacrylonitrile.—The crude nitrile (prepared from α-formyl-*p*-chlorophenylacetonitrile (17.9 g.) and diazomethane) was treated with ethyl guanidine (from the hydrobromide (16.9 g.) and sodium (2.3 g.) in alcohol (100 ml.)). The solution was heated for 8 hours and worked up in the usual manner. The solid (12 g.) was recrystallized from benzene–petroleum ether; several recrystallizations failed to reveal the presence of more than one substance which formed plates m.p. 200–202°.

Anal. Calcd. for $C_{12}H_{13}N_4Cl$: C, 57.7; H, 5.2; N, 22.5. Found: C, 58.0; H, 6.9; N, 22.8.

No information is available to determine the position of the ethyl group. The compound was inactive as an antimalarial.

Condensation of Methylated α-Acylarylacetonitriles with Amidines.—This condensation was carried out exactly as with guanidine. Two examples are given below. The compounds prepared are listed in Table VI.

4-Amino-5-phenylpyrimidine.—α-Formylphenylacetonitrile (3.6 g.) was dissolved in dry ether and methylated with diazomethane (from nitrosomethylurea (5 g.)). After standing overnight the ether was removed and the residue dissolved in ethanol (10 ml.). This solution was added to a solution of formamidine (prepared from the hydrochloride (2 g.)) in ethanol (30 ml.). The mixture was heated on a steam-bath for three hours, the alcohol was evaporated and the product made alkaline with strong sodium hydroxide solution. The insoluble material was filtered off and recrystallized from benzene when it formed plates melting at 152–154° undepressed on admixture with authentic 4-amino-5-phenylpyrimidine prepared by the method of Davies and Piggott.[8]

4-Amino-2-*p*-tolyl-5-*p*-chlorophenylpyrimidine.—α-Formyl-*p*-chlorophenylacetonitrile (8.5 g.) was methylated with diazomethane in the usual manner. The product was treated with *p*-toluamidine (from the hydrochloride (9.0 g.)) as before. The product, recrystallized from ethanol, formed pale yellow prisms melting at 186°.

Anal. Calcd. for $C_{17}H_{14}N_3Cl$: C, 69.0; H, 4.7; N, 14.2. Found: C, 68.8; H, 4.6; N, 14.4.

Alkylation of an α-Acylarylacetonitrile with an Alkyl Halide and Alkali Followed by Condensation with Guanidine.—The general method is given below. The α-acylarylacetonitrile (0.1 mole) was dissolved in 2 *N* sodium hydroxide (50 ml.) and methanol (75–100 ml.). To this solution was added the alkylating agent (0.12 mole) and the whole was heated on the steam-bath for four hours. The methanol was then evaporated, the oil extracted with ether and the ether washed with water. After drying and removal of the ether, the residue was dissolved in ethanol (100 ml.) and guanidine (from the hydrochloride (0.1 mole)) was added. The mixture was heated for three hours and then worked up as previously described. The yields range from about 5% with dimethyl sulfate to 15% with ethyl bromide.

α-(N-Methyl-N-phenylaminoacetyl)-phenylacetonitrile.—Ethyl N-phenyl-N-methylaminoacetate[38] (38.6 g.) and phenylacetonitrile (23.4 g.) were added to a solution of sodium ethoxide prepared from sodium (4.6 g.) and ethanol (200 ml.). The mixture was refluxed for 24 hours. After cooling it was poured into water (1 liter). After removal of the insoluble material with ether the solution was neutralized with 2 *N* sulfuric acid. The product separated as colorless needles, which after recrystallization from ethanol melted at 111°.

(38) J. F. Thorpe and A. S. Wood, *J. Chem. Soc.*, **103**, 1607 (1913).

Anal. Calcd. for $C_{17}H_{16}ON_2$: C, 77.3; H, 6.1; N, 10.6. Found: C, 77.4; H, 5.7; N, 10.7.

2,4-Diamino-5-phenyl-6-(N-methyl-N-phenylaminomethyl)-pyrimidine.—The above nitrile (6.6 g.) in a mixture of ethanol and ether (200 ml., 1:1) was treated with diazomethane (from nitrosomethylurea (5 g.)). After standing overnight the diazomethane and solvent were evaporated. The residue was dissolved in ethanol (50 ml.) and treated with an alcoholic solution of guanidine (from the hydrochloride (2.2 g.) and sodium (0.6 g.) in ethanol (100 ml.). After heating for four hours the alcohol was evaporated and the solution made alkaline with strong sodium hydroxide solution. The residue was dissolved in ether, the ether solution washed with water and dried with sodium sulfate. After removal of the ether the residue was recrystallized from benzene–petroleum ether giving yellow prisms melting at 150–151°.

Anal. Calcd. for $C_{18}H_{19}N_5$: C, 70.8; H, 6.2; N, 23.0. Found: C, 71.2; H, 5.9; N, 22.6.

Condensation of Ethyl N,N-Dimethylaminoacetate with *p*-Chlorophenylacetonitrile.—The ester[39] (26 g.) and *p*-chlorophenylacetonitrile (30 g.) were mixed and added to a solution of sodium ethoxide in ethanol (from sodium (4.6 g.) in ethanol (150 ml.)). The solution was heated for five hours on the steam-bath. After cooling it was poured into water, the insoluble material removed with ether and the aqueous solution was carefully neutralized with 1 *N* sulfuric acid. The separated crystals were washed with water and recrystallized from ethanol. The compound melted with effervescence at 225–231° and melted again sharply with decomposition at 240°.

Anal. Calcd. for $C_{12}H_{13}N_2OCl$: C, 60.9; H, 5.5; N, 11.8. Found: C, 60.7; H, 5.4; N, 12.2.

With phenylacetonitrile in an exactly similar manner a compound was obtained which formed colorless plates melting at 239°.

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.3; H, 6.9; N, 13.9. Found: C, 71.6; H, 7.0; N, 14.2.

Neither of these compounds reacted with diazomethane.

Condensation of Ethyl N-Phenylaminoacetate and *p*-Chlorophenylacetonitrile.—The ester (17.9 g.) and the nitrile (15.1 g.) were added to a solution of sodium ethoxide (from sodium (2.3 g.) in ethanol (100 ml.)). The reaction and isolation of the product were carried out exactly as before. The crystalline product after recrystallization from ethanol melted at 225° (dec.).

Anal. Calcd. for $C_{16}H_{12}ON_2Cl$: C, 67.7; H, 4.2; N, 9.9. Found: C, 68.0; H, 4.5; N, 10.3.

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The Determination of Sedimentation Constants from Fresnel Diffraction Patterns[1]

BY GERSON KEGELES AND FREDERICK J. GUTTER

A precision method is described for the experimental determination of sedimentation constants, which makes use of micro-comparator measurement of Fresnel diffraction fringes to locate the center of the sedimenting boundary. These fringes, which are symmetrical in pairs about the center of the boundary, originate with the introduction of a bar as diagonal diaphragm into the cylinder lens refractive index gradient recording optical systems. With the aid of this method, which is found to reproduce protein sedimentation constants to considerably better than 1% at concentrations above 0.5%, a study has been made of the concentration dependence of the sedimentation constants of several proteins. Comparison of this observed concentration dependence with available hydrodynamic theories indicates the approximate validity of the theory of Burgers for unhydrated spheres. However, it is believed that residual discrepancies between experiment and theory would justify the extension of the Burgers theory to the actual case of hydrated, elongated, interacting particles.

Introduction

The original application by Svedberg and coworkers of the ultracentrifuge[2] to the study of protein molecules has provided impetus to a continuous development of optical methods for investigating boundary layers in electrophoresis, diffusion and ultracentrifuge studies. These methods have the aim, when applied to sedimentation rate determinations, of determining that level in the boundary where the concentration of sedimenting solute is half that in the constant composition portion of the column below the boundary. For a sedimenting substance showing ideal behavior, it is to a very close approximation the movement of this median concentration level which determines the sedimentation constant. At this level, also, the refractive index gradient passes through a maximum for ideal sedimentation. The refractometric cylinder lens schlieren optical arrangements of Philpot,[3] Svensson,[4] and Andersson[5] possess the marked labor saving advantage over the Lamm refractometric scale method[6] of automatically depicting the refractive index gradient *versus* radius relationship. However, the automatic recording systems do not, within the limit of our experience, provide ultracentrifuge results of satisfactory reproducibility or accuracy, when evaluated by the customary procedure of measurement on enlarged tracings. A very decided improvement has been made by measuring these refractive index gradient diagrams directly on the photographic records with a microcomparator.[7] It is the purpose of this paper to present a method which further facilitates the attainment of high accuracy in the evaluation of sedimentation constants with automatic recording optical systems.

When the diagonal diaphragm or slit of the customary cylinder lens schlieren optical arrangements

(1) Presented at the 117th Meeting of the American Chemical Society in Philadelphia, Pa., April 12, 1950.

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