The Synthesis of Halogenated Pyridines Substituted at the Carbon Atom C-3

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Arylation of α-methyleneglutaronitrile (MGN) occurred when arylamines, aminopyridines and 3-aminothiophene were treated with alkylnitrites and copper(I) chloride in dimethyl methylphosphonate (DMMP) solutions. Results from this study exemplified the synthetic advantage of DMMP as a solvent in Meerwein reactions with an olefin of low reactivity, yielding 1-aryl-2 chloro-2,4-dicyanobutanes, and its 3-pyridyl- and thiophen-3-yl analogues. Partial hydrolysis, followed by subsequent ring closure of the substituted 2,4-dicyanobutanes to 2,6-piperidinediones (glutaric acid imides) was effected with a solution of sulfuric acid in acetic acid. The aromatization of the substituted 2,6-piperidinediones with phosphorus oxychloride in the presence of hexamethylphosphoric acid triamide (HMPT) yielded the 2,6-dichloropyridine moiety substituted at the carbon atom C-3.

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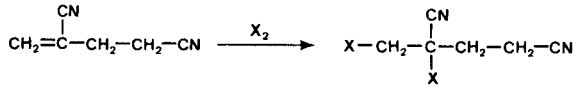
Introduction.

In a previous paper [1] we reported a general and technically feasible synthesis of 2,6-dichloro-3-chloromethylpyridine. The readily available starting material used therein was α-methyleneglutaronitrile (**1**), which is one of the linear dimerization products of acrylonitrile. Many patents attest to the ease of this dimerization, which is generally performed by adding acrylonitrile to a solution of a catalyst comprised of an aliphatic phosphine in an inert solvent such as benzene or toluene, followed by subsequent isolation of **1** by distillation.

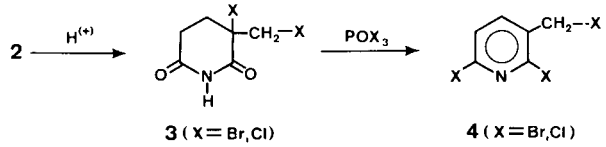
Addition of chlorine or bromine, respectively, to the double bond of **1** produced the dihalogenated dinitriles **2** which in turn were cyclized to the respective 3-chloromethyl- and 3-bromomethylglutarimides **3** using a solution of 80% sulfuric acid in acetic acid [1].



1 **2** (X = Br, Cl)

Formula 1

The following step involved the aromatization of **3** with concomitant halogenation yielding the 2,6-dichloro-3-chloromethylpyridine **4**, (X = Cl) and the brominated analogue **4** (X = Br), respectively. This transformation was achieved by heating the respective glutaric acid imide either with phosphorus oxychloride in an autoclave at temperatures of 160-180°, or alternatively, with phosphorus oxybromide at the considerably lower temperature of 80-100°.



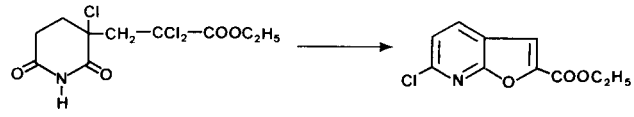
3 (X = Br, Cl) **4** (X = Br, Cl)

Formula 2

These halogenated pyridines gave rise to many additional synthetic transformations involving their reactive substituents [2,3], notably compound **4** (X = Cl) served as starting material in a facile access to 2,6-dihalogenated nicotinic acid and its derivatives by catalytic oxydation of the chloromethyl group at carbon atom C-3 [4,5].

The exchange of the chlorine atoms for iodine with concurrent loss of the carboxyl function has also been reported [6].

A convenient method to achieve the transformation of the glutarimide moiety to a C-3 substituted 2,6-dichloropyridine derivative was advanced in the synthesis of 6-chlorofuro[2,3-*b*]pyridine-2-carboxylic acid (**6**), starting from the piperidine-2,6-dione derivative **5** [7] and using the higher boiling methylphosphonylchloride [8,9,10] (bp 165°) instead of the commonly employed phosphorus oxychloride. This procedure offered the advantage of conducting the reaction without an autoclave, although the yields remained essentially unchanged in the preparation of **4** (X = Cl).



5 **6**

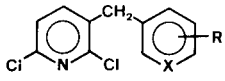
Formula 3

Chloromethylpyridines have been used only in a few instances as alkylating reagents under the conditions of a Friedel-Crafts synthesis. Thus, reactions of chloromethylpyridine hydrochloride with benzene or with chlorobenzene in the presence of aluminum chloride yielded benzylpyridines [11]. Likewise, a number of 2,6-dichloro-3-benzylpyridines were prepared from **4** (X = Cl) and benzene or substituted derivatives thereof in the presence of 1-1.2 equivalents of aluminum chloride [2]. Although, in general, yields were quite comparable with those observed in

the aromatic series, only mixtures of isomers were formed with substituted benzene derivatives.

This made the method of rather a limited value for synthetic purposes.

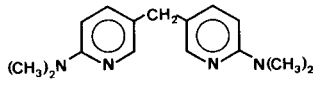
Although the phenyl ring of the 2,6-dichloro-3-benzylpyridines may be subject to a number of selected substitution reactions [2] such as nitration, chlorosulfonation or acylation, yielding well defined products with little or no formation of isomers, there appears to be a lack of a general methodology to prepare 2,6-dichloro-3-benzylpyridines which bear any given substituent attached to the phenyl ring. We endeavoured to develop such a method with a rather general applicability and also to extend the reaction to other aromatic and heterocyclic rings, respectively, linked in the C-3 position by a methylene group, such as shown in Figure 7.



7 (X=CH,N)

Formula 4

There exists, however, among the readily available pyridine derivatives a notable exception in the ability of 2-dimethylamino pyridine to undergo a condensation reaction at the carbon atom C-5. The C-2 and the C-2,6-dimethylamino derivatives of pyridine are known to undergo condensation with formaldehyde to form dimethylamino derivatives of 3-bis(pyridyl)methylene (**8**) [12]. These compounds had once provided the basis for the synthesis of bis- and of tris(pyridyl)methanes, considered to be structural analogues of the triphenylmethane dyestuffs.



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Formula 5

The previously obtained insights into the Meerwein reaction [13a-14], together with the feasibility to construct C-3 substituted pyridines from **1** as starting material have now provided a conceptual frame within which further experiments could be conceived and thus enabled us to construct a pertinent interface with halogenated pyridine derivatives.

The use of α-methyleneglutaronitrile as an olefinic component in Meerwein reactions as means to construct a carbon-carbon bond between an olefin and an aromatic counterpart - in partucular the anthraquinone moiety - has been amply demonstrated [14]. A study of a variety of reaction conditions, as they are generally used, revealed that **1** reacts, however, only sluggishly and yields remained low. On the other hand, the selection of dimethyl methylphosphonate as solvent greatly improved the rate of reaction, enhanced the yields considerably and thus became the controlling factor of the reaction. This proved especially important in the synthesis of anthradipyrans [14], where an intramolecular Meerwein reaction of anthraquinone and of α-methyleneglutaronitrile led in a one step synthesis to a derivative of this class of compounds.

In contrast hereto, some Meerwein reactions which involve the C-1 substituted anthraquinone moiety are conducted in methanol as solvent, furnishing excellent yields of C-1 substituted anthraquinones, whereby the reaction products which are formed *via* the Sandmeyer process contributed only to a minor extent to the overall reaction [15].

In those reactions, however, anthraquinone diazoniumhydrogensulfate must be used, as the corresponding anthraquinone hydrogenhalide furnished only halogenated anthraquinones [15].

The introduction of dimethyl methylphosphonate as the solvent in Meerwein reactions found its technical application in a one-pot synthesis of 2-methoxybenzanthrone in which the crucial step of the carbon-carbon bond formation involved a Meerwein reaction of the anthraquinone diazoniumhydrogensulfate with methacrylonitrile [16].

Yields of arylation products depend considerably on the structure of the olefinic compound and the diazonium salt, as well as on the reaction variables including the *p*H-range and most notably the solvent [13a,b]. In the procedure normally employed for the Meerwein reaction, the diazonium halide is prepared separately in an aqueous solution of hydrochloric acid and then the olefin is added in a solvent such as acetone or acetonitrile.

While acrylonitrile reacted with various substituted aryldiazonium salts in aqueous acetone at room temperature and furnished β-chlorohydrocinnamonitriles [17], the Meerwein reaction of the higher structural analogue α-methyleneglutaronitrile yielded the corresponding products only in very modest yields. The recently reported successful application of alkylnitrites as nitrosating reagent [18] together with the exceptional solvating properties of dimethyl methylphosphonate as solvent, not only to promote Meerwein reactions which failed to proceed in the more commonly employed solvents for these reactions [14], but to greatly enhance the yield of products, have led us to apply a combination of these two methods to Meerwein reactions with **1** as the olefinic component.

Results.

Addition of isoamyl nitrite (1 mole) to a dimethyl methylphosphonate solution containing the aromatic amine (1 mole), aqueous hydrogen chloride (1.5 moles), α-methyleneglutaronitrile (1.5 moles) and copper(I) chloride, resulted in the evolution of nitrogen and in the formation of the arylation products from the addition of the aryl group and a chlorine atom to the carbon-carbon double bond. The

temperature varied somewhat with the amine, but the reaction was usually conducted in the range of 55-70°. In most cases, the nitrogen evolution commenced at 50-55°, and the addition of the isoamyl nitrite was done as rapidly as possible allowing for the nitrogen evolution. The reaction did not proceed at all in the temperature range of 0-15°.

There appeared to be, however, at the outset of experiments, some principal disadvantage in this method. Dimethyl methylphosphonate is a solvent which is not only miscible with many organic solvents, but also with water. Its rather high boiling point of 182° also renders it cumbersome to remove from reaction mixtures by distillation. However, it was found that on diluting the reaction mixtures with water, followed subsequently by extraction with ether, only less than 1% of dimethyl methylphosphonate was taken up by the ether layer. The excess of **1** was removed by distillation of the ether extract under reduced pressure (110°/3 mm) because **1** is only slightly soluble in water and thus remained largely in the ether phase.

A detailed study of the arylation of **1** using different reagents for the diazotization step, and also applying various solvents revealed that, in spite of the above mentioned experimental disadvantages in using high boiling solvents such as dimethyl methylphosphonate, the yield of product thus realized, justified its use for large scale runs. Table I shows representative examples of experimental details for the arylation of **1** using different solvents and methods for the diazotization of aniline. A comparison of the results with respect to yields show the prominence of dimethyl methylphosphonate as the most advantageous solvent, but it seems noteworthy that also dimethylformamide and sulfolane, respectively, gave yields as high as 73%.

Table 1

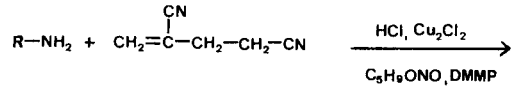
Yields of 1-Phenyl-2-chloro-2,4-dicyanobutane from Reactions of Aniline with α-Methyleneglutaronitrile in Different Solvents

No.	Nitrosating Reagent [a,b]	Solvent	Yield %
1	Sodium nitrite	Acetone	5 [c]
2	Sodium nitrite	Acetone/Dimethyl methylphosphonate (4:1)	17 [c]
3	Methyl nitrite	Dimethyl methylphosphonate	63
4	Isoamyl nitrite	Dimethyl methylphosphonate	86 [d]
5	Isoamyl nitrite	Acetone	67
6	Isoamyl nitrite	Methanol	47
7	Isoamyl nitrite	1,2-Dimethoxyethane	73
8	Isoamyl nitrite	Dimethylformamide	73
9	Isoamyl nitrite	Sulfolane	74

[a] Catalyst: copper(I) chloride. [b] Reaction temperature: 50-55°, except in experiment No. 1 with a temperature of 0-5°. [c] After distillation. [d] After recrystallization was the yield 74%.

We have used copper(I) chloride as catalyst throughout this work, largely as a matter of convenience but also because earlier results obtained [14] with different catalysts in dimethyl methylphosphonate indicated no improvement in product yields.

A series of aromatic and heterocyclic amines, listed in Table 2, were reacted with **1** resulting in the formation of 1-aryl-2-chloro-2,4-dicyanobutanes **9-28** (Table 2) as well as heterocyclic derivatives.



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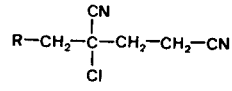


9 – 28

Formula 6

The structures of compounds **9-28** were confirmed by their analytical and by their spectral data. The infrared absorption spectra showed a characteristic band for the nitrile absorption at 2245 cm^{-1}.

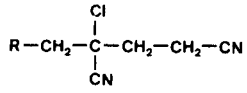
This method shortcuts the intermediates preparation of the respective arenediazonium chloride and produces the Meerwein products generally in good yields.

Optimum conditions were not worked out in detail for all of the amines employed in this study, but the general procedure for the arylation reactions allowed some conclusions to be drawn about competitive processes. Polymerization of **1** which would effectively lower the yields of α-chloro-β-aryl-2,4-butanedinitriles, was not observed in these reactions which correlates well with the earlier observations in reactions of **1** with anthraquinones [14]. The most surprising features were displayed in the neat formation of Meerwein adducts from **1** with diazotized 3-aminopyridine **24**, with some chlorinated 3-aminopyridines **25**,-**26**,**27**, and also with a derivative of 3-aminothiophene **28**. No other products were found in these reactions with arylamines which indicated that neither the Sandmeyer process nor potentially competitive processes involving the arylation intermediate adversely effected the formation of Meerwein products.

Although heterocyclic primary amines comprise rather a large class of compounds, reports about successful Meerwein reactions with these amines are noteworthy for their paucity [13a,b, 19]. While the diazotization and the subsequent Meerwein reaction of the above mentioned heterocyclic amines proceeded normally, the diazotization of

Table 2

1-Chloro- 2- Aryl-2,4-dicyanobutanes

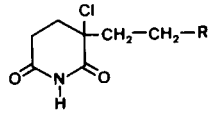


Compound No.	R	Mp °C (Solvent)	Yield %	Formula	Analysis % Calcd./Found C	H	Cl	F	N	S
9	C_6H_5	70-71 (Methanol)	85	$C_{12}H_{11}ClN_2$	65.91 66.09	5.07 5.11	16.21 16.03		12.81 12.91	
10	4-CH_3-C_6H_4	68-69 (Methanol)	86	$C_{13}H_{13}ClN_2$	67.10 66.90	5.63 5.70	15.24 15.31		12.04 12.01	
11	4-CH_3O-C_6H_4	55-55.5 (Methanol)	82	$C_{13}H_{13}ClN_2O$	62.78 62.82	5.27 5.52	14.25 14.21		11.26 11.22	
12	4-Cl-C_6H_4	68-70 (Methanol)	51 [a]	$C_{12}H_{10}Cl_2N_2$	56.94 57.12	3.98 4.11	28.01 28.00		11.07 11.21	
13	4-F-C_6H_4	oil (b)	58	$C_{12}H_{10}ClFN_2$	60.90 61.21	4.26 4.48	14.98 14.52	8.03 7.72	11.84 12.11	
14	3-CF_3-C_6H_4	50.5-51 (Methanol)	80	$C_{13}H_{10}ClF_3N_2$	54.47 54.51	3.52 3.62	12.37 12.41	19.88 19.81	9.77 9.82	
15	4-CN-C_6H_4	143-144 (Acetonitrile)	82	$C_{13}H_{10}ClN_3$	64.07 64.11	4.14 3.92	14.55 14.41		17.25 17.40	
16	4-NO_2-C_6H_4	99-100 (Methanol)	84	$C_{12}H_{10}ClN_3O_2$	54.66 54.71	3.82 4.01	13.45 13.31		15.94 15.86	
17	2-CH_3OOC-C_6H_4	oil (B.p. 170 2×10^{-2}Torr)	60	$C_{14}H_{13}ClN_2O_2$	60.77 60.71	4.74 4.62	12.81 12.52		10.12 10.21	
18	4-CH_3OOC-C_6H_4	72-73 (Methanol)	76	$C_{14}H_{13}ClN_2O_2$	60.77 60.41	4.74 4.81	12.81 12.70		10.12 10.11	
19	2,5-Cl_2-C_6H_3	68-69 (Methanol)	65	$C_{12}H_9Cl_3N_2$	50.12 50.15	3.15 3.21	36.98 37.00		9.74 9.81	
20	3,4-Cl_2-C_6H_3	105.5-106.5 (Methanol)	73	$C_{12}H_9Cl_3N_2$	50.12 50.17	3.15 3.22	36.98 37.00		9.74 9.82	
21	2-CH_3,4-NO_2-C_6H_3	84-85 (Methanol)	64 [a]	$C_{13}H_{12}ClN_3O_2$	56.23 56.21	4.36 4.31	12.77 12.90		15.13 15.30	
22	2-CF_3,5-NO_2-C_6H_3	oil (b)	38	$C_{13}H_9ClF_3N_3O_2$	47.08 47.28	2.74 2.91	10.69 10.41	17.18 16.92	12.67 12.48	
23	3-NO_2,4-Cl-C_6H_3	99-100 (Methanol)	62	$C_{12}H_9Cl_2N_3O_2$	48.35 48.21	3.04 3.01	23.78 23.80		14.10 14.10	
24	3-Pyridyl	89-91 (Methanol)	43	$C_{11}H_{10}ClN_3$	60.14 60.01	4.59 4.61	16.14 16.21		19.13 19.29	
25	2-Cl,3-pyridyl	109-110 (Methanol)	68	$C_{11}H_9Cl_2N_3$	51.99 52.01	3.57 3.69	27.90 27.90		16.54 16.61	
26	2,6-Cl_2,3-pyridyl	77-78 (Methanol)	66	$C_{11}H_8Cl_3N_3$	45.78 45.81	2.79 2.82	36.86 37.04		14.56 14.61	
27	2,5,6-Cl_3,3-pyridyl	112-113 (Methanol)	35	$C_{11}H_7Cl_4N_3$	40.90 40.62	2.19 2.21	43.90 43.71		13.01 13.28	
28	2-CH_3OOC-thiophen-3-yl	53.5-55 (Methanol)	60	$C_{12}H_{11}ClN_2O_2S$	50.98 50.81	3.92 4.00	12.54 12.51		9.91 10.11	11.34 11.21

[a] After recrystallization. [b] Purified by chromatography.

Table 3

C-3 Substituted 2,6-Piperidinediones



Compound No.	R	Mp °C (Solvent)	Yield %	Formula	Analysis, % Calcd./Found C	H	Cl	F	N	S
29	C_6H_5	157-158 (Acetonitrile)	91	$C_{12}H_{12}ClNO_2$	60.64 60.51	5.09 5.10	14.92 14.91		5.89 6.01	
30	4-CH_3-C_6H_4	197-198 (Acetonitrile)	95	$C_{13}H_{14}ClNO_2$	62.03 61.82	5.61 5.60	14.09 14.11		5.57 5.62	
31	4-CH_3O-C_6H_4	140.5-141 (Acetonitrile)	90	$C_{13}H_{14}ClNO_3$	61.76 61.50	4.84 5.11	12.15 12.40		4.80 5.10	
32	4-Cl-C_6H_4	161-162 (Acetonitrile)	96	$C_{12}H_{11}Cl_2NO_2$	52.97 52.81	4.08 4.21	26.06 25.88		5.15 5.10	
33	4-F-C_6H_4	171-173 (Acetonitrile)	96	$C_{12}H_{11}ClFNO_2$	56.37 56.50	4.34 4.31	13.86 13.61	7.43 7.51	5.48 5.59	
34	3-CF_3-C_6H_4	127.5-129 (Acetonitrile)	22	$C_{13}H_{11}ClF_3NO_2$	51.08 51.10	3.63 3.51	11.60 11.42	18.64 18.32	4.58 4.80	
35	4-NO_2-C_6H_4	191-192 (Acetonitrile)	96	$C_{12}H_{11}ClN_2O_4$	50.99 51.11	3.92 4.09	12.54 12.50		9.91 10.00	
36	2-CH_3OOC-C_6H_4	113-114 (Methanol)	51	$C_{14}H_{14}ClNO_4$	56.86 56.98	4.77 4.91	11.99 11.75		4.74 4.70	
37	4-CH_3OOC-C_6H_4	172-174 (Methanol)	95	$C_{14}H_{14}ClNO_4$	56.86 56.71	4.77 4.91	11.99 11.91		4.74 4.71	
38	2,5-Cl_2-C_6H_3	199-200.5 (Acetonitrile)	96	$C_{12}H_{10}Cl_3NO_2$	47.01 47.00	3.29 3.58	34.69 34.81		4.57 4.61	
39	3,4-Cl_2-C_6H_3	151-152 (Acetonitrile)	99	$C_{12}H_{10}Cl_3NO_2$	47.01 46.92	3.29 3.40	34.69 34.60		4.57 4.71	
40	2-CH_3,4-NO_2-C_6H_3	228-229 (Ethyl cellosolve)	97	$C_{13}H_{13}ClN_2O_4$	52.63 52.92	4.42 4.59	11.95 11.90		9.44 9.51	
41	2-CF_3,5-NO_2-C_6H_3	185-186 (Acetonitrile)	91	$C_{13}H_{10}ClF_3N_2O_4$	44.53 44.52	2.87 2.91	10.11 10.12	16.25 16.03	7.99 8.11	
42	3-NO_2,4-Cl-C_6H_3	173-173.5 (Acetonitrile)	99	$C_{12}H_{10}Cl_2N_2O_4$	45.45 45.61	3.18 3.32	22.36 22.30		8.84 8.98	
43	3-Pyridyl	147-148 (Acetonitrile)	50	$C_{11}H_{11}ClN_2O_2$	55.36 55.21	4.65 4.71	14.85 14.61		11.74 11.70	
44	2-Cl,3-pyridyl	147-148 (Acetonitrile)	75	$C_{11}H_{10}Cl_2N_2O_2$	48.38 48.21	3.69 3.70	25.96 25.92		10.26 10.92	
45	2,6-Cl_2,3-pyridyl	189-190 (Acetonitrile)	79	$C_{11}H_9Cl_3N_2O_2$	42.96 42.91	2.95 2.99	34.58 34.31		9.11 9.21	
46	2-CH_3OOC-thiophen-3-yl	146-148 (Acetonitrile)	90	$C_{12}H_{12}ClNO_4S$	47.77 48.00	4.01 4.07	11.75 11.55		4.64 4.71	10.63 10.82

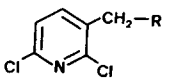
2-aminopyridine and its chlorinated derivatives took essentially the same course as it did in hydrochloric acid or in hydrobromic acid, yielding halogenated pyridines and pyridones [20,21,22].

C-3 Substituted 2,6-Piperidinediones (Glutaric Acid Imides).

The cyclization of the substituted 1,3-dinitriles to 2,6-piperidinediones (glutaric acid imides) disubstituted at carbon atom C-3 was performed following an earlier reported procedure [1]. A selected number of dinitriles **9-28** were heated in a mixture of acetic acid and 78% sulfuric acid yielding the C-3 disubstituted 2,6-piperidinediones **29-46** listed in Table 3. With a few exceptions such as **34**, **36** and **43** the product yields proved to be well above 90%.

Table 4

C-3 Substituted 2,6-Dichloropyridines

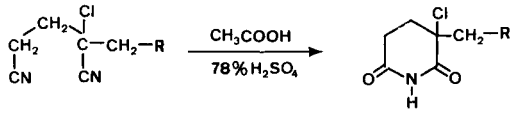


Formula 11

Compound No.	R	Reaction Temperature °C	Reaction Time Hours	Mp °C (Solvent) Bp °C (Torr)	Yield %	Formula	Analysis, % Calcd./Found					
							C	H	Cl	F	N	S
47	C_6H_5	170	2.5	118-120 (2×10^{-2})	50	$C_{12}H_9Cl_2N$	60.53 60.80	3.81 4.08	29.78 29.50		5.88 6.08	
48	4-CH_3-C_6H_4	165	3	oil [b]	73	$C_{13}H_{11}Cl_2N$	61.93 61.91	4.40 4.59	28.12 27.88		5.56 5.69	
49	4-CH_3O-C_6H_4 (a)	175	3	134-136 (2×10^{-2})	49	$C_{13}H_{11}Cl_2NO$	58.23 58.22	4.14 4.19	26.45 26.18		5.23 5.21	
50	4-Cl-C_6H_4 (a)	170	3	82-84 (Methanol)	76	$C_{12}H_8Cl_3N$	52.88 52.91	2.96 3.01	39.02 38.81		5.14 5.08	
51	4-F-C_6H_4 (a)	170	3	73-74 (Methanol)	55	$C_{12}H_8Cl_2FN$	56.28 56.31	3.15 3.21	27.69 27.45	7.42 7.40	5.47 5.60	
52	3-CF_3-C_6H_4	165	3	oil [b]	72	$C_{13}H_8Cl_2F_3N$	51.01 51.28	2.64 2.61	23.16 22.95	18.62 18.42	4.58 4.78	
53	4-NO_2-C_6H_4 (a)	150	3	131-132 (Ethanol)	91	$C_{12}H_8Cl_2N_2O_2$	50.91 50.73	2.85 2.91	25.05 25.28		9.90 9.72	
54	2-CH_3OOC-C_6H_4	165	2	69-70 (Methanol)	56	$C_{14}H_{11}Cl_2NO_2$	56.78 57.01	3.74 3.80	23.94 23.78		4.73 5.02	
55	2,5-Cl_2-C_6H_3	165	3	57-58 (Acetonitrile)	72	$C_{12}H_7Cl_4N$	46.95 47.11	2.30 2.45	46.19 45.88		4.56 4.81	
56	3,4-Cl_2-C_6H_3 (a)	170	3	94.5-96 (Acetonitrile)	93	$C_{12}H_7Cl_4N$	46.95 47.09	2.30 2.48	46.19 45.91		4.56 4.82	
57	2-CH_3,4-NO_2-C_6H_3	165	3	118-119 (Ethanol)	67	$C_{13}H_{10}Cl_2N_2O_2$	52.55 52.61	3.39 3.40	23.86 23.71		9.43 9.41	
58	2-CF_3,5-NO_2-C_6H_3	170	2.5	79-79.5 (Methanol)	46	$C_{13}H_7Cl_2F_3N_2O_2$	44.47 44.51	2.01 2.00	20.20 19.98	16.23 16.31	7.98 7.91	
59	3-NO_2,4-Cl-C_6H_3	170	3	91-92 (Methanol)	88	$C_{12}H_7Cl_3N_2O_2$	45.39 45.49	2.22 2.31	33.49 33.21		8.82 8.81	
60	3-Pyridyl	165	3	55-56 (Diisopropyl ether)	52	$C_{11}H_8Cl_2N_2$	55.26 55.02	3.37 3.40	29.66 29.60		11.72 11.74	
61	2-Cl,3-pyridyl	165	3.5	108-109 (Acetonitrile)	83	$C_{11}H_7Cl_3N_2$	48.30 48.32	2.58 2.61	38.88 38.82		10.24 10.30	
62	2,6-Cl_2,3-pyridyl	160	4	142-143 (Acetonitrile)	82	$C_{11}H_6Cl_4N_2$	42.90 43.09	1.96 2.09	46.04 45.82		9.10 9.31	
63	2-CH_3OOC-3-thiophen-3-yl	165	3.5	103-104 (Methanol)	23	$C_{12}H_9Cl_2NO_2S$	47.70 47.81	3.00 3.25	23.47 23.19		4.64 4.51	10.61 10.80

[a] Reactions were performed without HMPT. [b] Purified by chromatography.

The infrared absorption spectra for compounds **29-46** exhibited characteristic frequencies for the cyclic imide structure at 1690-1695, 1720-1735, 3030-3050 and 3120-3150 cm^{-1}.

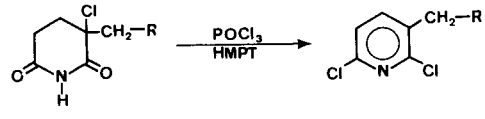


9–28 29–46

Formula 8

C-3 Substituted 2,6-Dichloropyridines.

The aromatization of a few members of the 3,3-disubstituted piperidinedione series (Table 4) could be performed using the same method which has been applied earlier [1]. Heating the piperidinediones with phosphorus oxychloride to 160-180° furnished various 2,6-dichloropyridines **47-63** substituted at carbon atom C-3 (Table 4).



29–46 47–63

Formula 10

This method has been well established and its synthetic usefulness has been proven earlier particularly in the synthesis of 2,6-dichloro-3-chloromethylpyridine, and it has now been applied accordingly to prepare compounds **49**, **50**, **51**, **53** and **56**. But among the series of the newly synthesized 2,6-piperidinediones were several ones, notably **43-45** which could not be induced to aromatize, even at extended reaction times, but they rather indicated their tendency to undergo uncontrolled thermal destruction above 200°.

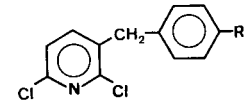
Further experimental variations of the aromatization reaction were largely designed to conduct it at lower temperatures and they centered mainly around the addition of feasible catalysts. Addition of hexamethyl phosphoric acid triamide (HMPT) in about 10% to phosphorus oxychloride effected clean formation of the pyridine moiety resulting in yields which compared favorably with those obtained in the synthesis of **4a**. This method became especially advantageous in the course of attempts to succeed with the synthesis of compounds involving two chlorinated pyridine rings linked by a methylene group. In particular, compounds **60-62** were prepared using this technique. Only the aromatization of the imide moiety linked to the thiophene ring **63** proceeded in rather a low yield.

These compounds were mostly obtained as colorless crystals, only some of them remained in the liquid state and could not be induced to crystallize. The infrared spectra of compounds **47-63** exhibited characteristic frequencies at ν = 1575 and 1550 cm^{-1}, respectively, which are assigned to the 2,6-dichloro-3-pyridyl moiety [1].

None of these compounds indicated any of the strongly skin or mucous irritating properties as they are known from the 3-chloromethylpyridine analogues.

Several of these compounds have been reported earlier [2], however, only a few ones were isolated in pure state **47**, **48**, **53**, **59**, but generally they were obtained as mixtures of isomers. The have been synthesized by aluminum chloride catalyzed Friedel-Crafts reactions of 2,6-dichloro-3-chloromethylpyridine **4** (X = Cl) with benzene or an appropriately substituted derivative thereof. Some substitutions of the phenyl ring of **4** such as nitration or chlorosulfonation were achieved by direct substitution of 2,6-dichloro-3-benzylpyridine. The present method supplements now a different and rather a general approach to the synthesis of this type of C-3 substituted pyridines.

The *N,N*-dimethylamino substituted derivative **65** could not be prepared using this technique, because 1-*N,N*-dimethylamino-4-aminobenzene yielded the Meerwein product with **1** in only about 5% yield and ranks as an exception in the list of those otherwise successful reactions. Therefore, **65** was prepared stepwise, first by reduction of the nitro compound **53**, followed by methylation of the amine **64** thus obtained, using the well established technique or methylating an amino group with dimethyl methylphosphonate [23,24] to yield finally the compound **65**.



53 R = NO_2
64 R = NH_2
65 R = $N(CH_3)_2$

Formula 12

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. The ^1H nmr spectra were recorded on a Bruker HX-360 nmr spectrometer in the fourier transform mode.

Samples of the infrared spectra were prepared in potassium bromide pellets. Pure dimethyl methylphosphonate (DMMP) was employed (>98%) and distilled before use. Hexamethylphosphoric acid triamide (HMPT) was of commercial quality.

Gas chromatography was performed on 2000 mm columns with an inner diameter of 2 mm, Dexsil 3% on Chromosorb G, temperature range 110-280°C/10°/min, Injector block temperature: 280°.

General Procedure.

In the procedure employed for the reactions reported in Tables I and II, the respective aminophenyl derivative, dimethyl methylphosphonate, α-methyleneglutaronitrile, copper(I) chloride and concentrated hydrochloric acid were added to a three necked flask which was equipped with a stirrer, reflux condensor, addition funnel and a thermometer. The resulting, stirred mixture was warmed to 55-65° and then the source of ex-

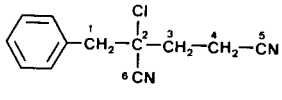
ternal heating was removed. Isoamylnitrite was added at such a rapid rate as the nitrogen evolution proved practicable to be controlled and to maintain the temperature without further heating. After the gas evolution had ceased, the reaction temperature was allowed to reach room temperature, and the solution was then poured into water. Crystalline products were filtered and washed with water. Oily products were extracted with ether which was washed with water and dried over anhydrous sodium sulfate. The ether was removed under reduced pressure and the crude oily products distilled under vacuum, or in a few instances they could be recrystallized from methanol at low temperatures. With some compounds, small samples had to be chromatographed so as to obtain crystalline specimen which were used to induce crystallization of bulk solutions in methanol.

Product analysis were performed by gas chromatography of the crude products isolated. The yields given in Tables I and II, respectively, refer to the percent of product present in the reaction mixture.

1-Phenyl-2-chloro-2,4-dicyanobutane (**9**).

Method A. Reaction in Dimethyl Methylphosphonate.

To 500 ml of dimethyl methylphosphonate were added successively 93 g (1 mole) of aniline, 152 g (1.5 moles) of concentrated hydrochloric acid, 159 g (1.5 moles) of α-methyleneglutaronitrile and 0.75 g of copper(I) chloride. The solution was stirred and heated to 55-60°. The external source of heating was removed and 123.2 g (1 mole, 95%) of isoamyl nitrite was added dropwise over a period of 1.5 hours. The rate of addition was largely determined by the rate of nitrogen evolution and the exothermic course of the reaction. After the addition had been completed stirring was continued for an additional 1.5 hours without further heating. Then the solution was added to 2 l of water. The oily suspension solidified within 1.5 hours to a granular product which was filtered and washed on the filter with 500 ml of water. It was suspended again and stirred in 500 ml of water to obtain finely divided crystals. Filtration and repeated washings with water furnished 183 g (84%) of crystals. They were heated in 200 ml of methanol, the solution cooled to 0°, crystals filtered and washed with 70 ml of methanol of −60°, yielding 163 g; ir: cm^{-1}, 2261, 1496, 1450, 1045, 819, 776, 705; ^{13}C-nmr (deuteriochloroform): δ 131.94-128.68 (aromatic), 117.41 C-5, 116.93, C-6, 59.55 C-2, 481.8 C-1, 36.85 C-3, 13.82 C-4.



Formula 13

The following experiment is representative for the runs listed in Table I.

Method B. Reaction in Sulfolane.

To 50 ml of sulfolane were added 9.3 g (0.1 mole) of aniline, 15.2 g (0.15 mole) of concentrated hydrochloric acid, 15.9 g (0.15 mole) of α-methyleneglutaronitrile and 0.1 g of copper(I) chloride. The solution was heated to 55-60° and 12.3 g (0.1 mole) of 95% isoamyl nitrite was added dropwise over a 30 minute period to the rapidly stirred mixture. Stirring was continued for an additional 40 minutes and the solution added to 100 ml of water. The aqueous suspension was extracted with ether (four times 100 ml each), the combined ethereal solutions washed with water (2 × 200 ml) and dried over sodium sulfate. Evaporation of the solvent yielded an oily sample which was analyzed by gas chromatography. The bulk was dissolved in 27 ml of methanol, cooled to −20°, and crystals filtered from the solution yielding 12.3 g of **9**.

1-Tolyl-2-chloro-2,4-dicyanobutane (**10**).

Isopentyl nitrite (12.3 g, 95%, 0.1 mole) was added dropwise at 55-60° over a 20 minute period to a stirred mixture of 10.7 g (0.1 mole) of *p*-toluidine, 50 ml of dimethyl methylphosphonate, 15.2 g (0.15 mole) of concentrated hydrochloric acid, 15.3 g (0.15 mole) of **1** and 0.1 g of copper(I) chloride. The source of heating was removed during the addition of the isopenyl nitrite, since the temperature of the reaction mixture was easily maintained by the rate of addition. Stirring was continued for an additional 30 minutes, then the solution was poured into 150 ml of water, and extracted three times with 100 ml portions of ether. The combined ether solutions were washed two times with 50 ml portions of water and dried over sodium sulfate. The ether solution was concentrated under reduced pressure to yield 26.1 g of an oil. It was recrystallized from 37 ml of methanol and crystals deposited filtered from the solution at −15°, washed on the filter with 10 ml of methanol (−20°) yielding 15.6 g of pure **10**.

1-(*p*-Methoxyphenyl)-2-chloro-2,4-dicyanobutane (**11**).

The reaction with 0.1 mole of *p*-methoxyaniline and the work-up procedure were performed according to the preparation of **10** yielding 25.9 g of crude product. Recrystallization of 22.5 g from 25 ml of methanol at 20° yielded 13.2 g of **11**.

1-(*p*-Fluorophenyl)-2-chloro-2,4-dicyanobutane (**13**).

The compound was prepared from *p*-fluoroaniline according to the procedure above, yielding 16.0 g of oil which was distilled at 185°/10^{-2} mm. An analytical sample was obtained by chromatography on silica (Merck 7734) with toluene/acetone (8:2) as eluent.

1-(3-Trifluoromethylphenyl)-2-chloro-2,4-dicyanobutane (**14**).

The compound was prepared from 3-trifluoromethylaniline in a manner identical with that above yielding 30.1 g of a yellow oil (76% of **14** by gas chromatography). A crystalline sample was obtained after chromatography on silica (toluene/acetone, 8:2 as eluent). The bulk of crude oil was dissolved in 30 ml of methanol, and the crystals obtained previously were added at −40°, whereupon the entire product crystallized. Filtration at −20° yielded 6.6 g of **14**.

1-(*p*-Nitrophenyl)-2-chloro-2,4-dicyanobutane (**16**).

Isopentylnitrite (18.47 g, 0.15 mole, 95%) was added dropwise at 55-60° over a 90 minute period to a stirred mixture of 20.7 g (0.15 mole) of 4-nitroaniline, 75 ml of dimethyl methylphosphonate, 22.8 g (0.225 mole) of concentrated hydrochloric acid, 23.85 g (0.15 mole) of **1** and 0.15 g of copper(I) chloride. The source of external heating was removed and the temperature controlled by the rate of addition of the isopentyl nitrite. Stirring was continued for an additional one hour. The solution was poured into 350 ml of water and stirred. The aqueous phase was decanted from the crystals, which were washed again with 250 ml of water, filtered and dried, yielding 33.0 g of **16**.

1-(3-Pyridyl)-2-chloro-2,4-dicyanobutane (**24**).

Isopentylnitrite (61.6 g, 0.5 mole, 95%) was added dropwise at 55-65° over a one hour period to a stirred mixture of 47 g (0.5 mole) of 3-aminopyridine, 250 ml of DMMP, 55 ml (0.5 mole) of concentrated hydrochloric acid, 79.5 g (0.75 mole) of **1** and 0.4 g of copper(I) chloride. The source of external heating was removed at the commencement of addition and the temperature controlled by the rate of addition. Stirring was continued for an additional one half hour during which time the vigorous gas evolution had subsided. The solution was added to a mixture of 1 l of water and 300 ml of concentrated sodium hydrogencarbonate solution. The suspension was then extracted four times with 250 ml portions of chloroform. The combined chloroform extractions were washed with saturated sodium chloride solution and dried over sodium sulfate. Rotary evaporation of the solvent yielded 58.8 g of an oil. This was dissolved in 60 ml of hot methanol, filtered and cooled to −40°. After stirring for four hours at this temperature, crystals were filtered and washed with 10 ml of methanol at −50°, yielding 31 g of **24**.

1-(2,6-Dichloro-3-pyridyl)-2-chloro-2,4-dicyanobutane (**26**).

The compound was prepared from 3-amino-2,6-dichloropyridine (0.5 mole) in a manner identical with that reported for **24**, yielding 47.8 g of crude oil which contained 60.2% of **26** by gas chromatography. The oil was dissolved in 75 ml of boiling methanol, cooled to −20°, crystals filtered from the solution, and washed with 20 ml of methanol (−20°) yield-

ing 20.7 g of **26**.

1-(2-Carboxymethylthiophen-3-yl)-2-chloro-2,4-dicyanobutane (**28**).

The compound was prepared from 3-amino-2-carboxymethylthiophene (0.1 mole) in a manner identical with that reported for **24**, yielding 30.8 g of an oil which consisted of 56% of **28** according to gas chromatography. A sample of 4 g was fractionated in a high vacuum by short path distillation yielding 1.4 g of product which was recrystallized from 3 ml of methanol yielding 0.72 g of crystalline **28**, from which the spectral and the analytical data were obtained; ir: cm^{-1} 2250 (CN), 1710 ($COOCH_3$), 1544 (thiophene ring). The bulk of crude **28** was cyclized to the glutaric acid imide derivative **46**.

3-Chloro-3-aryl-2,6-piperidinediones (Glutaric Acid Imides). General Procedure.

The dinitriles were heated in a mixture of acetic acid and 78% sulfuric acid for 2-6 hours. The piperidinediones having pyridyl substituents **43-45** required 15-17 hours for completion of the reaction.

3-Chloro-3-(benzyl)-2,6-piperidinedione (**29**).

A stirred suspension of 6.55 g (0.03 mole) of 1-phenyl-2-chloro-2,4-dicyanobutane (**9**) in a mixture of 16.5 ml of acetic acid and 3.7 g of 78% sulfuric acid was heated to reflux for two hours. The crystalline suspension was poured into 100 ml of water and stirred for two hours. Filtration and washing with 100 ml of water furnished 6.25 g of crystals. An analytical sample was prepared by crystallization of 1 g from 6 ml of acetonitrile yielding 0.26 g of **29**; ir: cm^{-1} 3145, 3040, 1730, 1690.

3-Chloro-3-(3'-trifluoromethylbenzyl)-2,6-piperidinedione (**34**).

A solution of **14** in 42 ml of acetic acid and 8 g of 78% sulfuric acid was heated to reflux for a period of 6 hours. The solution was added to 300 ml of water and stirred. The aqueous phase was decanted from the oil and replaced by 200 ml of water. The oil was separated and allowed to stand for 48 hours in order to crystallize. Crystals were filtered (15.5 g) and crystallized from 20 ml of acetonitrile to furnish 3.4 g of **34**; ir: cm^{-1} 1695 (imide), 1135 (CF_3).

3-Chloro-3-(3'α-methylpyridyl)-2,6-piperidinedione (**43**).

A suspension of 10.98 g (0.05 mole) of **24** in a mixture of 55 ml of acetic acid and 12.5 g of sulfuric acid (78%) was heated to reflux for 15 hours. The solution was added to 250 g of ice and 130 g of a 30% aqueous solution of sodium hydroxyde. The resinous precipitate was stirred for 5 minutes and the aqueous phase decanted. The crystalline residue (5.9 g) was dispersed in water, again filtered off and recrystallized from 13 ml of acetonitrile, yielding 4.7 g of **43**; ir: cm^{-1} 1730, 1695 (imide), 1570 (pyridine).

3-Chloro-3-(3'α-methyl-2',6'-dichloropyridyl)-2,6-piperidinedione (**45**).

A suspension of 10.1 g (0.035 mole) of **26** in a mixture of 38.5 ml of acetic acid and 8.8 g of 78% sulfuric acid was heated to reflux for 17 hours. The suspension was added to 150 g of ice followed by a concentrated solution of sodium hydroxyde until a *p*H of 9 was indicated. Crystals were filtered and washed with 50 ml of water yielding 8.05 g of **45**; ir: cm^{-1} 3030, 1722, 1695, 1575, 1550.

3-Chloro-(3'α-methyl-2-carboxymethyl)thiophen-3-yl-2,6-piperidinedione (**46**).

The compound was prepared using the unpurified material obtained in the preparation of **28** in a manner identical with that reported for **30**, yielding a resinous precipitate which crystallized on standing for 24 hours. It was filtered (16 g) and recrystallized from 60 ml of acetonitrile yielding 7.8 g of **46**; ir: cm^{-1} 1715, 1695, 1533.

3-(2,6-Dichloropyridyl)phenylmethane (**47**).

A suspension of 4.75 g (0.02 mole) of **29** in 7.6 ml of phosphorus oxychloride and 1.0 g of HMPT was heated under reflux for 7 hours. The cold solution was added to 35 ml of water, and stirred for 20 minutes. The aqueous suspension was extracted three times 30 ml each with ether. The combined ether extracts were washed neutral with water and dried over sodium sulfate. Evaporation of the solvent yielded 3.1 g of an oil which crystallized after distillation at 118-120°/0.02 mm (2.4 g); ir: cm^{-1} 1575, 1550. A comparison of the infrared spectra with the spectrum of a known sample [1] proved them to be identical.

3-(2,6-Dichloropyridyl)-*p*-chlorophenylmethane (**50**).

A suspension of 4.08 g (0.015 mole) of **32** in 22 ml of phosphorus oxychloride was heated in an autoclave to 170° (bath temperature) for 3 hours. The solution was added slowly to 120 ml of water and stirred for 20 minutes. Excess of water was decanted and the residue dissolved in 250 ml of ether. The ether phase was washed twice each with 80 ml of water and dried over sodium sulfate. Evaporation of the solvent gave 3.1 g of crystalline **50**; ir: cm^{-1} 1570, 1550.

3-(2,6-Dichloropyridyl)-3'-trifluoromethylphenylmethane (**52**).

A suspension of 3.06 g (0.01 mole) of **34** in 15 ml of phosphorus oxychloride and 1 ml of HMPT was placed in a sealed tube and heated to 165° for 3 hours. The work-up procedure was analogous to the one reported for **50**, yielding 2.2 g of a semisolid residue which was purified by column chromatography (220 g of silica 60, Merck 7734, toluene/acetone 8:2 as eluent) yielding 1.66 g of **52** as an oil; ir: cm^{-1} 1575, 1550, 1130 (CF_3).

3-(2,6-Dichloropyridyl)-*p*-nitrophenylmethane (**53**).

A suspension of 56.5 g (0.2 mole) of **35** in 300 ml of phosphorus oxychloride and 20.5 ml of HMPT was placed in an autoclave and heated to 150-160° for 3 hours. The solution was slowly added to 2400 ml of water and stirred for one hour. Filtration and subsequent washing with 1 l of water yielded 51.7 g of crude crystalline **53**. It was transferred into a soxhleth and extracted with ether, leaving 42.8 g of **53** after evaporation of the ether.

3-(2,6-Dichloropyridyl)-3'-pyridylmethane (**60**).

A suspension of 2.39 g (0.01 mole) of **43** in 15 ml of phosphorus oxychloride and 1 ml of HMPT was heated to 160° for 3 hours. The solution was then slowly added to 120 ml of water and the *p*H adjusted to 8.5 by addition of 75 ml of a concentrated aqueous solution of sodium hydroxyde. The precipitate was extracted three times with 40 ml each of ether. The ether solution was washed with 30 ml of saturated sodium chloride solution and dried over sodium sulfate. Evaporation of the solvent yielded an oil which was purified by column chromatography in a manner analogous to the one described above, yielding 0.94 g of **60** which crystallized on standing; ir: cm^{-1} 1575, 1550.

Bis[3-(2,6-Dichloropyridyl)]methane (**62**).

A suspension of 9.23 g (0.03 mole) of **45** in a mixture of 45 ml of phosphorus oxychloride and 3 ml of HMPT was heated to 160° in an autoclave for 4 hours. The suspension formed was slowly added to 350 ml of water and stirred for 30 minutes. Crystals were filtered from the aqueous suspension and washed with 300 ml of water yielding 7.6 g of **62**; ir: cm^{-1} 1570, 1545.

3-(2,6-Dichloropyridyl)-*p*-aminophenylmethane (**64**).

A solution of 14.15 g (0.05 mole) of **53** in 250 ml of dioxane was hydrogenated in the presence of 2.5 g of Raney nickel until the hydrogen uptake had ceased. The catalyst was filtered from the solution and the solvent evaporated yielding 11.9 g (94%) of a yellow viscous oil. A sample was purified by chromatography (silica 60, Merck 7734, toluene-acetone 7:3 as eluent); ir: cm^{-1} 3420, 3300, 1625, 1575, 1550.

Anal. Calcd. for $C_{12}H_{10}Cl_2N_2$: C, 56.94; H, 3.98; Cl, 28.01; N, 11.07. Found: C, 57.24; H, 4.15; Cl, 28.12; N, 10.98.

3-(2,6-Dichloropyridyl)-*p*-dimethylaminophenylmethane (**65**).

A suspension of 12.14 g (0.048 mole) of **64** and 6.62 g (0.048 mole) of potassium carbonate in 60 ml of dimethyl methylphosphonate was heated under reflux for 2.5 hours. The solution was poured into 300 ml of water and stirred for 30 minutes. The oil was extracted three times with 100 ml

each of ether, and the ether phase washed with water and dried over sodium sulfate. Evaporation of the solvent gave 8.55 g (70%) of an oil which was recrystallized from 40 ml of methanol yielding 7.15 g of white crystals of **65**, mp 46-47°; ir: cm^{-1} 1610, 1645, 1615.

Anal. Calcd. for $C_{14}H_{14}Cl_2N_2$: C, 59.80; H, 5.02; Cl, 25.22; N, 9.96. Found: C, 59.69; H, 5.03; Cl, 25.30; N, 10.04.

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