The Alkylation of Hantzsch 1,4-Dihydropyridines

John W. Patterson

Syntex Corporation,
Palo Alto, California 94304

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The reaction of carbanions derived from Hantzsch 1,4-dihydropyridines with alkyl halides was studied and methods for mono- and di-alkylation were devised.

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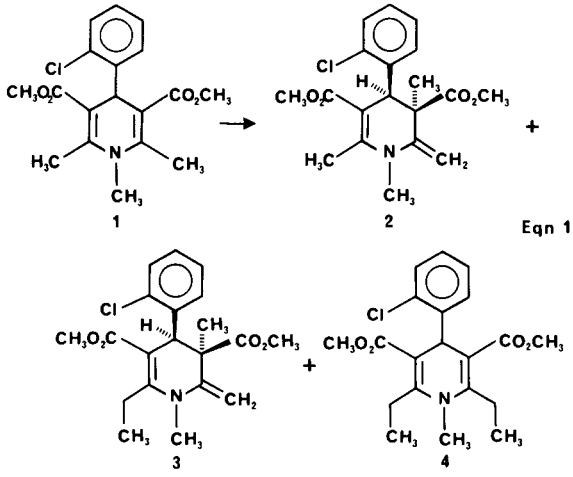
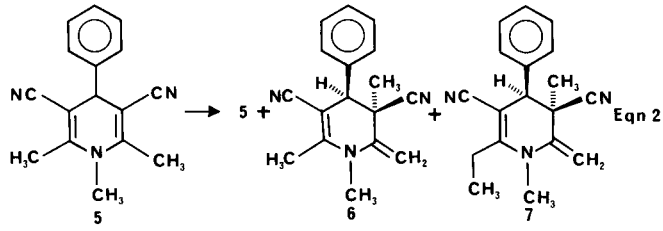
The widespread study of 1,4-dihydropyridines with electron withdrawing groups at the 3- and 5- position as facilators and blockers of the calcium slow channel in cardiac and vascular smooth muscle [2] has stimulated much interest in the synthesis of these compounds in recent years [3]. The chemistry of carbanions derived from 3,5-diester and 3,5-dinitrile derivatives of 1,4-dihydropyridine is the subject of this report.

Initial attempts to generate the lithium enolate of 4-chlorophenyl-3,5-carbomethoxy-1,2,6-trimethyl-1,4-dihydropyridine (**1**) with one equivalent of lithium diisopropylamide followed by quenching this carbanion with methyl iodide led to mixtures of starting material, methylated derivative **2** and two dimethylated products **3** and **4**. This result was in contrast to the generally observed mono-alkylation of simple esters under similar conditions [4]. It was also observed that addition of the enolate to large excess of methyl iodide failed to improve this situation. These results may be rationalized on the basis of a proton transfer between the mono-alkylated product **2** and the enolate derived from **1** which occurs at a rate at least as fast as the alkylation reaction.



Eqn 1

In light of the large amount of synthetic work done with diester dianions in the past several years [5] the formation of di-alkylated products might be explained by the initial generation of a dianion of the dihydropyridine. However, the case of diethyl succinate dianion [5a] is the only example where substantial chemical reactivity data (clean mono-alkylation and sequential di-alkylation with two different halides) and physical data (proton nmr spectrum of the di-enolate) support the existence of the di-enolate ion. The present case of dihydropyridine diesters probably doesn't involve dianions as the less ambiguous example of a 3,5-dicyano-1,4-dihydropyridine illustrates. The dinitrile **5** upon treatment with one equivalent of lithium diisopropylamide and then excess methyl iodide gives a mixture of non-, mono- and di-alkylated products **5**, **6**, and **7** (Eqn 2). This is the direct result of rapid proton exchange between



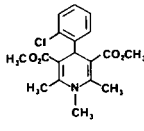
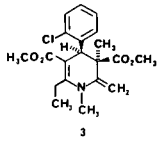
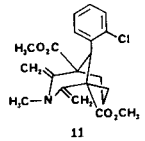
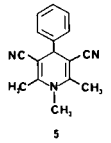
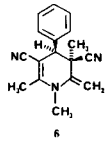
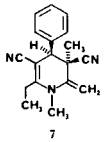
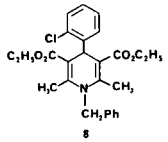
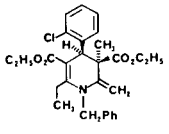
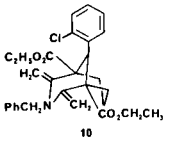
Eqn 2

the starting enolate and the mono-alkylated product **6** which is mediated by diisopropyl amine because irreversible deprotonation of **5** with *n*-butyllithium [6] in the absence of amine followed by quenching with methyl iodide gives only the mono-alkylated product **6**. Furthermore in the case of dinitrile **5** reaction with two equivalents of *n*-butylithium and excess methyl iodide gave only low yields of the dimethylated product **7** arguing against the intermediacy of a dianion. Finally, the reaction of **5** with two equivalents of lithium diisopropylamide and excess methyl iodide gave the dimethylated product **7** in good yield with virtually none of the mono-alkylated product **6** being formed. This latter experiment indicates that the deprotonation of **6** by lithium diisopropylamide is more rapid than even the quenching of the second equivalent of lithium diisopropylamide by methyl iodide.

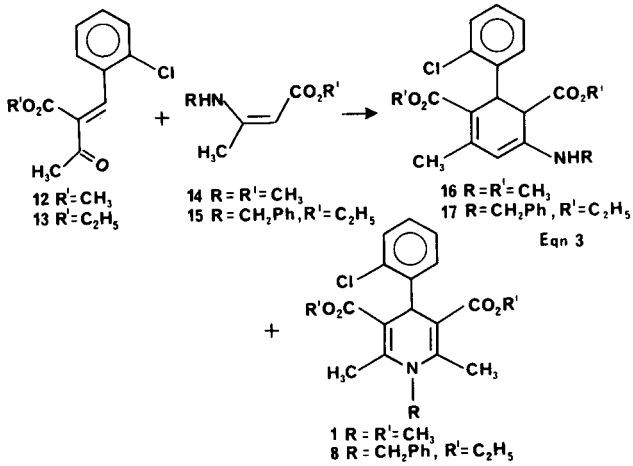
This rapid proton exchange between lithium diisopropylamide and product was exploited by using two equivalents of lithium diisopropylamide to prepare di-alkylation products in good yields as shown in Table I. The structures of these products were readily apparent by proton

nmr spectroscopy. In particular, the mono-alkylated compounds possess a methylene group and the di-alkylated products display both a methylene and an isolated ethyl group. An NOE difference proton nmr spectrum of compound **3** confirmed that steric effects result in introduction of the C-3 methyl group *trans* to the aryl group. Di-alkylations could also be accomplished with 1,3-dibromopropane resulting in the formation of the bicyclic structures **10** and **11**. In this case the formation of a six-membered ring by intramolecular alkylation overrides the steric propensity of the second alkylation to occur on the carbon γ to the carbonyl. These results are compatible with the formation of a simple enolate which undergoes alkylation and subsequent deprotonation by the second equivalent of lithium diisopropylamide or enolate ion and then second alkylation.

Table I. Alkylation of 1,4-Dihydropyridines.

Starting Material	Halide	Base (Equivalents)	Product	Yield
 1	CH_3I	LDA (2)	 3	55%
1	$Br(CH_2)_3Br$	LDA (2)	 11	48%
 5	CH_3I	n-BuLi (1)	 6	75%
5	CH_3I	LDA (2)	 7	42%
 8	CH_3I	LDA (2)	 9	65%
8	$Br(CH_2)_3Br$	LDA (2)	 10	94%

The 1-alkyl dihydropyridines starting materials used in this study were prepared by one of two conventional methods: the condensation of *N*-alkyl β-aminocrotonates with benzylidine acetoacetic esters [7] or the *N*-alkylation of the amide ion derived from the 1-H dihydropyridine [8]. The condensation of *N*-alkyl-β-aminocrotonates (either isolated from a separate reaction or prepared *in situ* from ethyl acetoacetate and a primary amine) with benzylidine acetoacetates has occassionally been reported to produce 1,4-dihydropyridines. In the present case attempts to prepare the 1-methyl and 1-benzyl dihydropyridines **1** and **8** conducting this condensation under the usual Hantzsch conditions (refluxing ethanol) the yields of dihydropyridines were about 5 percent and the major product were the cyclohexyldienamines **16** and **17** (Eqn 3). Fortunately,



from a synthetic point of view, the ratio of products could be reversed to favor the dihydropyridines by changing the reaction solvent from ethanol to benzene or toluene. In this way aminocrotonate **15** in toluene gave 20 percent of **17** and 28 percent of dihydropyridine **8**. This effect was even more pronounced with the *N*-methyl crotonate **14** in benzene which gave 5 percent of **16** and 36 percent of the dihydropyridine **1**. The 1-methyl-3,5-dicyanodihydropyridine **5** was prepared from 3,5-dicyano-2,6-dimethyl-4-phenyl-1,4-dihydropyridine [9] by methylation of the corresponding potassium salt.

In summary this work describes methods for both mono- and di-alkylating Hantzsch-type 1,4-dihydropyridines, including the use of dihalides to prepare bicyclic compounds. Some evidence supports the mechanism of the di-alkylation reactions as proceeding through mono-enolates which undergo facile proton exchanges. Those alkylation products were subjected to a variety of *in vitro* biological studies but were found to be virtually devoid of calcium modulatory activity.

Table II

Spectral Data

Compound Number	IR (cm^{-1})	^1H-NMR (δ ppm)
1	2950, 1690, 1640, 1570, 1440, 1190, 1160	7.3-7.0 (m, 4H), 5.50 (s, 1H), 3.67 (s, 6H), 3.25 (s, 3H), 2.45 (s, 6H)
3	2950, 1743, 1690, 1585, 1225, 1150, 1080	
4	2960, 1695, 1670, 1620, 1560, 1200, 1140	7.26 (d, 1H), 7.12-7.02 (m, 3H), 5.45 (s, 1H), 3.67 (s, 6H), 3.28 (s, 3H), 3.02 (h, 2H, J = 8 Hz), 2.85 (h, 2H, J = 8 Hz), 1.16 (t, 6H, J = 8 Hz)
5	2200, 1650, 1590, 1390, 1310, 1000, 700	7.4-7.1 (m, 5H), 4.25 (s, 1H), 3.17 (s, 3H), 2.2 (s, 6H)
6	2200, 1610, 1400, 1370 1020	7.4-7.1 (m, 5H), 4.8 (d, 1H, J = 3 Hz), 4.6 (d, 1H, J = 3 Hz), 3.5 (s, 1H), 3.28 (s, 3H), 2.38 (s, 3H), 1.63 (s, 3H)
7	2990, 2180, 1620, 1600, 1390, 1199, 750	7.4-7.0 (m, 5H), 4.8 (d, 1H, J = 3 Hz), 4.6 (d, 1H, J = 3 Hz), 3.47 (s, 2H), 3.26 (s, 3H), 2.75 (q, 2H, J = 8 Hz), 1.65 (s, 3H), 1.3 (t, 3H, J = 8 Hz)
8	2980, 1700, 1670, 1570, 1200, 1160	7.4-7.0 (m, 4H), 5.5 (s, 1H), 4.9 (s, 2H), 4.1 (q, 4H, J = 8 Hz), 2.3 (s, 6H), 1.2 (t, 3H, J = 8 Hz)
9	2980, 1720, 1680, 1570, 1210, 1135, 940	7.45-7.0 (m, 4H), 5.5 (d, 1H, J = 18 Hz), 4.88 (d, 1H, J = 18 Hz), 4.63 (s, 1H), 4.42 (d, 1H, J = 4 Hz), 4.17 (d, 1H, J = 4 Hz), 4.03-3.90 (m, 4H), 3.2 (h, 1H, J = 7 Hz), 2.93 (h, 1H, J = 7 Hz), 1.57 (s, 3H), 1.25 (t, 3H, J = 7 Hz), 1.1 (t, 3H, J = 8 Hz), 0.95 (t, 3H, J = 8 Hz)
10	2960, 1740, 1720, 1610 1220, 1150	7.5-7.1 (m, 4H), 5.1 (s, 2H), 4.2 (d, 2H, J = 3 Hz), 4.15 (s, 1H), 4.0 (d, 1H, J = 3 Hz), 3.8 (q, 4H, J = 8 Hz), 2.6-1.9 (m, 6H), 0.85 (t, 6H, J = 8 Hz)
11	2950, 1730, 1590, 1430 1340, 1150	7.3-7.0 (m, 4H), 4.25 (d, 1H, J = 3 Hz), 4.10 (s, 1H), 4.05 (d, 2H, J = 3 Hz), 3.3 (s, 6H), 3.15 (s, 3H), 2.6-1.7 (m, 6H)
16	3300, 2950, 1735, 1670 1640, 1590, 1440	8.9 (bs, 1H), 7.4-7.0 (m, 4H), 6.25 (s, 1H), 5.0 (s, 1H), 3.7 (s, 3H), 3.5 (s, 3H), 3.0 (d, 3H, J = 4 Hz), 1.9 (s, 3H)
17	3380, 2990, 1740, 1660 1570, 1470, 1280	9.35 (t, 1H, J = 6 Hz), 7.4-7.0 (m, 4H), 6.2 (s, 1H), 5.07 (s, 1H), 4.56 (d, 2H, J = 6 Hz), 3.73 (s, 3H), 3.53 (s, 3H), 3.17 (s, 1H), 1.77 (s, 3H)

EXPERIMENTAL

All reactions were run under a dry nitrogen atmosphere with magnetic stirring. THF was purified by distillation from sodium/benzophenone immediately prior to use. Infrared spectra were recorded on a Pye Unicam 3-200 spectrometer as neat films or potassium bromide pellets. The ^1H nmr spectra were recorded in deuteriochloroform with tetramethylsilane as an internal standard on a Varian EM 390 spectrometer (90 MHz) or a Bruker WM 300 spectrometer (300 MHz). Melting points are uncorrected and were recorded on a Hoover-Thomas apparatus.

3,5-Dicarbomethoxy-4-(2-chlorophenyl)-1,2,6-trimethyl-1,4-dihydropyridine (**1**).

A mixture of 23.8 g (0.1 mole) of the benzylidene acetoacetate **12** [10], 12.9 g (0.1 mole) of methyl 3-methylaminocrotonate (**14**) [11] and 200 ml of benzene was refluxed using a Dean-Stark trap for 2 hours. The reaction mixture was cooled to room temperature and the benzene evaporated *in vacuo*. The resulting residue was diluted with 20 ml of hexane: acetone: ether (10:1:1). Crystallization began immediately and after standing 1 hour at 0° filtration gave 10.6 g of **1**, mp 147-148°.

Anal. Calcd. for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; N, 4.00. Found: C, 61.83; H, 5.78; N, 3.96.

The filtrate was chromatographed on silica gel and elution with ether/hexane mixtures gave 1.825 g (5.2%) of the dienamine by-product **16**, mp 177-178° after crystallization from acetone/hexane.

Anal. Calcd. for $C_{18}H_{20}ClNO_4$: C, 61.80; H, 5.76; N, 4.00. Found: C, 61.86; H, 5.80; N, 3.97.

Further elution with ether/hexane gave another 1.951 g of dihydropyridine **1** (total yield 36%).

1-Benzyl-4-[2-chlorophenyl]-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (**8**).

A solution of 2.52 g (10 mmoles) of benzylidene acetoacetate **13** [10], and 2.25 g of ethyl 3-benzylaminocrotonate (**15**) [12] in 20 ml of toluene was refluxed with a Dean Stark trap for 3.5 hours. The solvent was then evaporated and the residue chromatographed on silica gel eluting with ether-hexane mixtures to give after crystallization from ethyl acetate-hexane 0.932 g (20%) of the cyclohexadienamine **17**, mp 100-103°.

Anal. Calcd. for $C_{26}H_{28}ClNO_4$: C, 68.78; H, 6.22; N, 3.09. Found: C, 68.84; H, 6.27; N, 3.08.

Further elution with ether-hexane gave 1.287 g (28%) of the dihydropyridine **8**, mp 151-153° after crystallization from ethanol.

Anal. Calcd. for $C_{26}H_{28}ClNO_4$: C, 68.78; H, 6.22; N, 3.09. Found: C, 68.76; H, 6.26; N, 3.09.

3,5-Dicyano-1,2,6-trimethyl-4-phenyl-1,4-dihydropyridine (**5**).

A mixture of 2.55 g (20 mmoles) of potassium *t*-butoxide in 40 ml of tetrahydrofuran was cooled to 0°. A solution of 4.75 g (20 mmoles) of 3,5-dicyano-2,6-dimethyl-4-phenyl-1,4-dihydropyridine in 30 ml of tetrahydrofuran was added over a period of 2 minutes. After 1 minute, 5 ml (80 mmoles) of methyl iodide was added. The reaction mixture was stirred for an additional 1 hour at 0° and then poured into ice water. Extraction with ethyl acetate, washing of the organic layer with brine, drying over magnesium sulfate and evaporation gave a solid product which was recrystallized from ethanol to yield 3.38 g (67%) of **5**, mp 190-192°.

Anal. Calcd. for $C_{16}H_{15}N_3$: C, 77.08; H, 6.06; N, 16.85. Found: C, 76.98; H, 6.16; N, 16.95.

3β,5-Dicarbomethoxy-4β-(2-chlorophenyl)-6-ethyl-1,3α-dimethyl-2-methylene-1,2,3,4-tetrahydropyridine (**3**) and 3,5-Dicarbomethoxy-4-(2-chlorophenyl)-2,6-diethyl-1-methyl-1,4-dihydropyridine (**4**).

A solution of 1.12 ml (8 mmoles) of diisopropylamine in 16 ml of tetrahydrofuran was cooled to −20° and treated with 5.5 ml of 1.5 *N* *n*-butyllithium (8.25 mmoles). The reaction mixture was cooled to −75° and a solution of 1.40 g (4 mmoles) of 3,5-dicarbomethoxy-4-(2-chlorophenyl)-1,2,6-trimethyl-1,4-dihydropyridine (**1**) in 16 ml of tetrahydrofuran was added. Stirring of the reaction mixture was continued for 30 minutes at −70° at which time the mixture was added *via* cannula to a solution of 6 ml of methyl iodide in 14 ml of tetrahydrofuran also at −70°. After an additional 30 minutes at −70° the reaction mixture was poured into water and extracted with ethyl acetate. The extracts were washed with brine, dried over magnesium sulfate and concentrated *in vacuo*. The resulting oil was chromatographed on silica gel (200 g). Eluting with ethyl acetate/hexane gave 990 mg (65%) of **3** as a viscous oil. An analytical sample of **3** was obtained by evaporation distillation at 130°/0.02 mm.

Anal. Calcd. for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.63; H, 6.43; N, 3.71.

Further elution with ethylacetate/hexane gave 102 mg (7%) of **4**. Recrystallization from *t*-butylmethyl ether gave material of mp 110-111°.

Anal. Calcd. for $C_{20}H_{24}ClNO_4$: C, 63.57; H, 6.40; N, 3.71. Found: C, 63.39; H, 6.40; N, 3.69.

3β,5-Dicyano-1,2,3α-trimethyl-2-methylene-4β-phenyl-1,2,3,4-tetrahydropyridine (**6**).

A solution of 250 mg of 3,5-dicyano-1,2,6-trimethyl-4-phenyl-1,4-dihydropyridine (**5**) (1 mmole) in 6 ml of tetrahydrofuran was cooled to −60° and treated with 0.62 ml of 1.6 *N n*-butyllithium in hexane (1 mmole) over 15 minutes. The reaction mixture was stirred at −70° for 20 minutes and then treated with 0.3 ml (4.8 mmoles) of methyl iodide in 0.7 ml of tetrahydrofuran. After stirring 20 minutes at −70° the reaction mixture was allowed to warm to −20° and then poured into 100 ml of water. Extraction with ethyl acetate, washing with brine, drying over magnesium sulfate and evaporation of the solvents gave a tan oil which was crystallized from ethyl acetate/hexane to give 197 mg (75%) of **6**, mp 118-121°.

Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.53; H, 6.51; N, 15.96. Found: C, 77.29; H, 6.61; N, 15.85.

3β,5-Dicyano-6-ethyl-1,3α-dimethyl-2-methylene-4β-phenyl-1,2,3,4-tetrahydropyridine (**7**).

A solution of lithium diisopropylamide prepared from 0.56 ml (4 mmoles) of diisopropylamine in 12 ml of tetrahydrofuran and 2.6 ml of 1.6 *N* (4 mmoles) of *n*-butyllithium was cooled to −75° and treated with 0.50 g (2 mmoles) of dihydropyridine **5** in 8 ml of tetrahydrofuran over 5 minutes. After stirring 30 minutes at −75° 0.8 ml (12 mmoles) of methyl iodide in 1 ml of tetrahydrofuran was added in one portion. The reaction mixture was stirred for 30 minutes at −75° and then poured into ice water. The product was isolated by ethyl acetate extraction and chromatography on silica gel eluting with ethyl acetate/hexane mixtures to give 0.26 g of **7**, mp 149-151°, after recrystallization from ethyl acetate/hexane.

Anal. Calcd. for $C_{16}H_{19}N_3$: C, 77.94; H, 6.90; N, 15.14. Found: C, 77.85; H, 6.95; N, 15.13.

1-Benzyl-3β,5-dicarbethoxy-4β-(2-chlorophenyl)-6-ethyl-3α-methyl-2-methylene-1,2,3,4-tetrahydropyridine (**9**).

Lithium diisopropylamide was prepared by addition of 1.8 ml (2.7 mmoles) of 1.5 *N n*-butyllithium in hexane to 0.28 ml (2.0 mmoles) of diisopropylamine in 4 ml of tetrahydrofuran at −10°. The reaction mixture was cooled to −70° and a solution of 430 mg (0.95 mmole) of 1-benzyl-4-(2-chlorophenyl)-3,5-dicarbethoxy-2,6-dimethyl-1,4-dihydropyridine (**8**) in 4 ml of tetrahydrofuran was added. After stirring at −70° for 1 hour the reaction mixture was transferred *via* cannula to a solution of 1.8 ml (2.9 mmoles) of methyl iodide in 8 ml of tetrahydrofuran at −70°. The reaction mixture was stirred at −70° for 10 minutes and poured into 100 ml of water. The product was extracted with ethyl acetate, washed with brine and dried over magnesium sulfate. Evaporation and recrystallization from methylene chloride-hexane gave 296 mg (65%) of **9**, mp 109-111°.

Anal. Calcd. for $C_{28}H_{32}ClNO_4$: C, 69.77; H, 6.69; N, 2.91. Found: C, 69.85; H, 6.71; N, 2.79.

3-Aza-3-benzyl-1,5-dicarbethoxy-9-(2-chlorophenyl)-2,4-dimethylene bicyclo[3.3.1]nonane (**10**).

A solution of lithium diisopropylamide prepared from 0.56 ml (4 mmoles) of diisopropylamine and 3.0 ml (4.5 mmoles) of 1.5 *N n*-butyllithium was cooled to −70° and treated with 0.86 g (1.9 mmoles) of dihydropyridine **8** in 8 ml of tetrahydrofuran. The reaction mixture was stirred 80 minutes at −70° and treated with 0.4 ml (2 mmoles) of 1,3-dibromopropane in 1 ml of tetrahydrofuran. The cooling bath was removed and the reaction temperature rose to +10° over 15 minutes. The reaction mixture was then poured into water and the product extracted with ether. After drying over potassium carbonate evaporation of the solvent gave a residue which was recrystallized from ether-hexane to give 0.887 g (94%) of bicyclononane **10**, mp 126-128°.

Anal. Calcd. for $C_{29}H_{32}ClNO_4$: C, 70.50; H, 6.53; N, 2.84. Found: C, 70.57; H, 6.57; N, 2.83.

3-Aza-1,5-dicarbomethoxy-9-(2-chlorophenyl)-3-methyl-2,4-dimethylene-bicyclo[3.3.1]nonane (**11**).

In a reaction similar to that immediately above 3,5-dicarbomethoxy-4-(2-chlorophenyl)-1,2,6-trimethyl-1,4-dihydropyridine (**1**) was transformed into bicyclononane **11**, mp 120-121°, in 48% yield.

Anal. Calcd. for $C_{21}H_{24}ClNO_4$: C, 64.69; H, 6.20; N, 3.59. Found: C, 65.03; H, 6.29; N, 3.53.

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