A Versatile New Synthesis of Quinolines and Related Fused Pyridines. Part 11.[1] Conversion of Acylanilides into α-Iminopyridines

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The Vilsmeier formylation of enamidines, readily derived by treatment of acetanilides with PCl_5, allowed the synthesis of 6-chloro-1-aryl-2-iminopyridines. Similarly other acylanilides ($RCH_2CONHAr$) gave 3,5-R_2 disubstituted analogues.

During our examination of the synthesis of 2-chloroquinoline-3-carbaldehydes by Vilsmeier formylation of acetanilides [2] we observed that 2-methoxyacetanilide also gave, as a minor product, a dimer of the anilide. This dimer proved to be the iminopyridine (4) which we conjectured to arise by *N*-acylation of the derived secondary amine (2) by the imidoyl chloride (1) to yield the enamidine (3), which underwent enaminic formylation and subsequent cyclisation (Scheme 1).[3] The amidine (3) was indeed also found as a minor product. We herein report the general synthesis of such iminopyridines by an optimisation of this process.

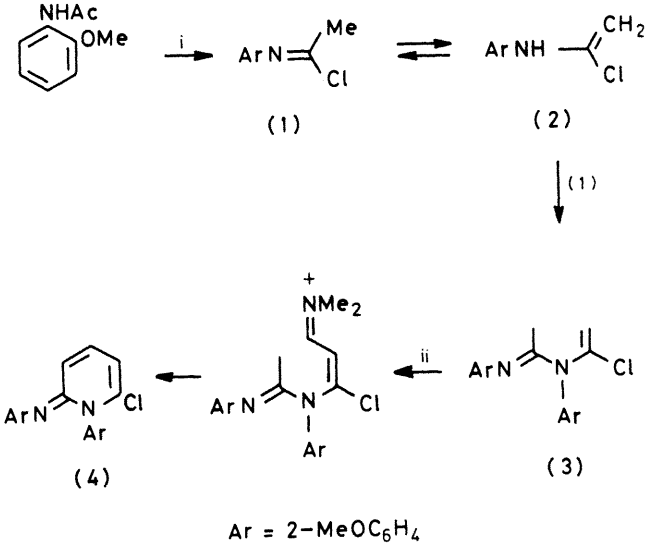
The conversion of acetanilides into enamidines (3) was reported over 50 years ago by von Braun. During his classical work on the synthesis of imidoyl chlorides by the action of phosphorus pentachloride on anilides, he observed that activated anilides gave such enamidines as unwanted products. By using von Braun's original conditions, a variety of such enamidines (3) were readily synthesised in good yield (Table 1) apart from those bearing a deactivating group.

A careful study of the formylactive cyclisation of the enamidine (3) derived from 2-methoxyacetanilide in which the time, temperature, and molar ratios of reactants was varied, was next undertaken. Optimum yields (68%) of the iminopyridine (4) were obtained when the enamidine in a mixture of dimethylformamide (DMF) and phosphoryl chloride (1 : 3 : 7 mol) was stirred for 2 h at ambient temperature followed by 4 h at 75 °C. The product was obtained almost pure merely by filtration and washing. No iminopyridine was formed at room temperature but an intermediate, active towards 2,4-dinitrophenylhydrazine, was observed during a t.l.c. study. We assume that this was the formylated but uncyclised enamidine (Scheme 1). This compound disappeared as the iminopyridine formed. Application of these conditions to the enamidines in Table 1 gave the analogous pyridines recorded in Table 2. Although the reaction may be conducted as a 'one-pot' process (see Experimental section) the yield and purity of the products were considerably reduced (*e.g.* from 2-methoxyacetanilide 31% of the pyridine was isolated as compared with 60% in the two stage process).

When higher acylanilides were used, 3,5-disubstituted 2-iminopyridines were produced. Thus 2-methoxypropionanilide (5a) gave the corresponding enamidine (6a) (73%) and iminopyridine (7a) (51%), while the chloroacetylanilide (5b) gave the enamide (6b) which proved difficult to isolate and was directly cyclised to give, unexpectedly (see later), the pyridone (7b) in 28% yield (Scheme 2).

In order to widen the scope of the reaction to unsymmetrically substituted and *N*-alkyliminopyridines (aliphatic amides only yield imidoyl chlorides with PCl_5[5,6]) we next sought alternative approaches. Since N^1,N^2-diarylacetamidines (8) are readily made by the interaction of an aniline, acetanilide, and phosphorus trichloride,[7] and since these compounds proved easy to acetylate giving reasonable precursors (9) to the enamidines, we studied the cyclisation of these potentially diverse intermediates. Attempts to isolate enamidines from the acetylamidines (9) gave only starting material, though a one-pot conversion into the iminopyridine (Scheme 3) was accomplished (Ar = 2-$MeOC_6H_4$) albeit in low yield (12%). Similar treatment of *N*,*N*-diacetylaniline [the oxa analogue of (9)] gave only acetanilide, and hence 2-chloroquinoline-3-carbaldehyde,[2] on work-up.

The iminopyridines proved remarkably stable to hydrolysis,



Scheme 1. *Reagents:* i, $POCl_3$; ii, DMF, $POCl_3$

Table 1. Synthesis of enamidines (3)

Compd.	Ar	Yield (%)	M.p. (°C)	Lit. m.p. (°C)
(3a)	2-$MeOC_6H_4$	88	77.5—78.5	78 [a]
(3b)	3-$MeOC_6H_4$	64	Oil *	
(3c)	4-$MeOC_6H_4$	69	87—88	
(3d)	2-MeC_6H_4	84	49—50	50 [a]
(3e)	3-MeC_6H_4	57	Oil *,†	
(3f)	4-MeC_6H_4	54	Solid *	
(3g)	Ph	72	116—118	119 [b]
(3h)	2,4-$Me_2C_6H_3$	84	Oil †	
(3i)	4-ClC_6H_4	9	Oil †	
(3j)	2-$NO_2C_6H_4$	0		

* Solidified on storage. † Used without purification.
[a] Ref. 4. [b] Ref. 5.

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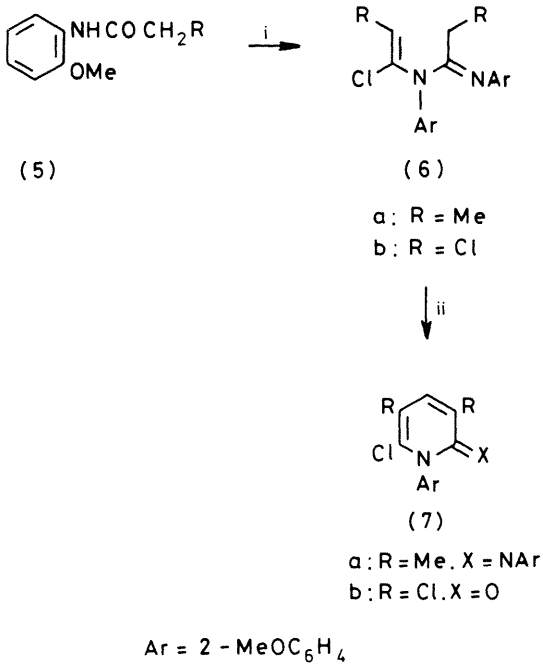
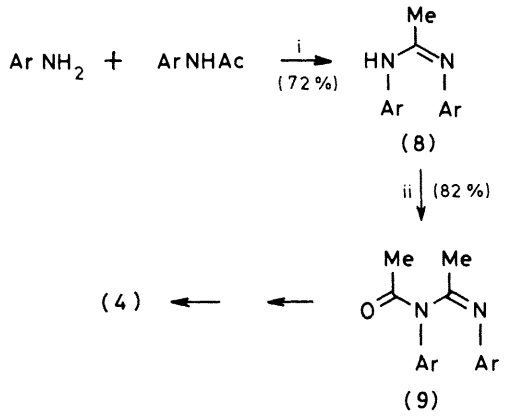
Table 2. Iminopyridines (4) from formylative cyclisation of the enamidines (3)

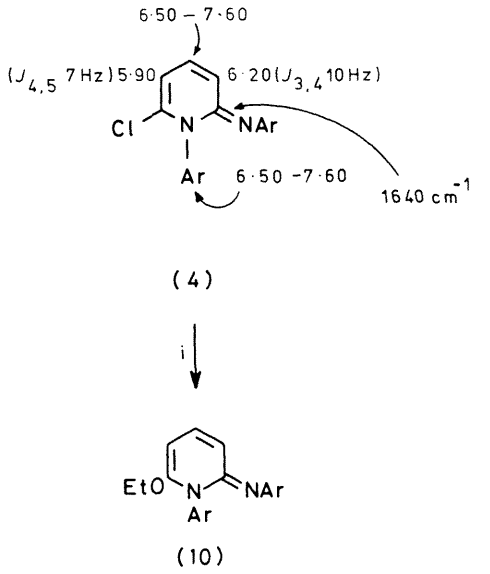
Compound	Ar	Yield (%)	M.p. (°C)
(4a)	2-$MeOC_6H_4$	68	176.5—178
(4b)	3-$MeOC_6H_4$	29	135.5—137
(4c)	4-$MeOC_6H_4$	75	134—136
(4d)	2-MeC_6H_4	31	165—166
(4e)	3-MeC_6H_4	47	153—154.5
(4f)	4-MeC_6H_4	42	190—191.5
(4g)	Ph	49	183—185
(4h)	2,4-$Me_2C_6H_3$	31	162—163



Scheme 2. *Reagents:* i, PCl_5; ii, DMF, $POCl_3$



Scheme 3. *Reagents:* i, PCl_3; ii, AcCl, NEt_3



Scheme 4. *Reagents:* i, 10% KOH in EtOH, heat, 2 h

even after being heated at 180 °C with concentrated hydrochloric acid for 4 h. This stability is reminiscent of a similar situation which is known to apply to trisubstituted amidines.[5,8] With ethanolic potassium hydroxide, although the amino group was not cleaved, a rapid transformation into the 6-ethoxy-2-iminopyridine imine (10) was observed. However, potassium hydroxide in t-butyl alcohol was totally without effect.

Typical ^1H n.m.r. and infrared characteristics are shown in Scheme 4. The iminopyridines also gave correct mass spectral molecular ions with losses of H, Me, and Cl from this ion.

Experimental

The general conditions are given in ref. 1. The anilides were bought (Aldrich) or prepared by standard literature methods, from anilines distilled from zinc dust. Ether refers to diethyl ether.

Synthesis of the Enamidines (3) *and* (6). *General Method.*[4]—The anilide (1 mol) and phosphorus pentachloride (1.2 mol) were shaken together; an exothermic reaction ensued eliminating hydrochloric acid and resulting in a yellow liquid. This was heated for 1 h at 75 °C, cooled, and washed with ether several times. The residual resinous mass was dissolved in aqueous hydrochloric acid (2M), charcoaled, and then basified with ammonium hydroxide (*d*, 0.880) and extracted with chloroform. The extract was dried ($MgSO_4$) and evaporated to give the enamidines (3), recorded in Table 1. The solids were recrystallised from light petroleum to give white crystals but the oils were utilised directly. The spectral properties of (3) are recorded in Table 3.

N^1-(1-*Chloroprop*-1-*enyl*)-N^1,N^2-*bis*(2-*methoxyphenyl*)-*propanamidine* (6a). Isolated as a viscous yellow oil. $\nu_{max.}$ (liquid film) 1 655, 1 635, 1 590, and 745 cm^{-1}. δ($CDCl_3$) 0.90t (Me), 1.75d (Me), 2.22m (CH_2), 3.73s (OMe), 3.82s (OMe), 5.85q (CH), 6.68—7.50m (aromatic H's).

N^1-(1,2-*Dichloroethenyl*)-N^1,N^2-*bis*(2-*methoxyphenyl*)-*chloroacetamidine* (6b). Isolated as a fawn-coloured solid, m.p. 186.5—188 °C, and used directly without further purification. $\nu_{max.}$ (Nujol) 1 645, 1 625, 1 600, and 790 cm^{-1}. δ($CDCl_3$) 3.97s (Me), 4.08s (Me), 5.02s (CH_2), and 6.36—7.48m (CH and aromatic H's).

Formation of the Iminopyridines (4) *and* (7). *General Method.*—To a constant temperature flask (equipped with an outer

Table 3. Spectral properties of the enamidines (3)

Compound	I.r. $\nu_{max.}$ (cm^{-1}) [a]	^1H N.m.r. $\delta(CDCl_3)$
(3a)	1 650, 1 630, 1 590, 760	1.72s (Me), 3.73s (Me), 3.82s (Me), 5.30d (CH_2), 6.30—7.50m (ArH)
(3b)	1 660, 1 630, 1 590, 780, 690	1.93s (Me), 3.75s (2 Me), 5.40d (CH_2), 6.30—7.35m (ArH)
(3c) [b]	1 640, 1 625, 1 610, 835	1.87s (Me), 3.77s (Me), 3.80s (Me), 5.35d (CH_2), 6.57—7.37m (ArH)
(3d)	1 655, 1 630, 1 600, 760	1.72s (Me), 2.13s (Me), 2.18s (Me), 5.19d (CH_2), 6.53—7.35m (ArH)
(3e)	1 650, 1 630, 1 600, 790, 700	1.87s (Me), 2.27s (Me), 2.31s (Me), 5.30d (CH_2), 6.45—7.30m (ArH)
(3f)	1 645, 1 625, 1 605, 820	1.90s (Me), 2.30s (Me), 2.35s (Me), 5.35d (CH_2), 6.60—7.30m (ArH)
(3g)	1 640, 1 625, 1 590, 725, 695	1, 87s (Me), 5.30d (CH_2), 6.60—7.40m (ArH)
(3h)	1 650, 1 630, 1 610, 865, 820	1.75s (Me), 2.10s (Me), 2.25s (Me), 2.30s (Me), 2.35s (Me), 5.25d (CH_2), 6.50—7.30 (ArH)
(3i)	1 650, 1 630, 1 590, 930	1.95 (Me) 5.40d (CH_2), 6.50—7.40m (ArH)

[a] Spectra taken for mulls in Nujol or for liquid films. [b] Found: C, 65.5; H, 5.7; N, 8.5. $C_{18}H_{19}ClN_2O_2$ requires C, 65.35; H, 5.8; N, 8.5%. *m/z* 332, 330.

Table 4. Properties of the iminopyridines (4)

	Analysis (%)								
	Found				Required			I.r. $\nu_{max.}$ (Nujol) (cm^{-1})	^1H N.m.r. $\delta(CDCl_3)$
Compd.	C	H	N	Formula	C	H	N		
(4a)	66.9	5.0	8.4	$C_{19}H_{17}ClN_2O_2$	67.0	5.0	8.2	1 640, 1 580, 1 520, 1 500, 1 485, 1 240, 1 170, 775, 760, 740	3.70s (Me), 3.89s (Me), 5.93d (5-H, $J_{4,5}$ 7 Hz), 6.13d (3-H, $J_{3,4}$ 10 Hz), 6.59—7.60m (4-H and ArH)
(4b)	66.9	5.1	8.3	$C_{19}H_{17}ClN_2O_2$	67.0	5.0	8.2	1 645, 1 600, 1 555, 1 520, 770	3.71s (Me), 3.79s (Me), 5.88d (5-H, $J_{4,5}$ 6 Hz), 6.20—7.40m (3-, 4-H and ArH)
(4c)	67.4	5.1	8.4	$C_{19}H_{17}ClN_2O_2$	67.0	5.0	8.2	1 640, 1 575, 1 520, 840, 780	3.70s (Me), 3.77s (Me), 5.87d (5-H, $J_{4,5}$ 7 Hz), 6.28d (3-H, $J_{3,4}$ 10 Hz), 6.45—7.30m (4-H and ArH)
(4d)	73.85	5.5	8.85	$C_{19}H_{17}ClN_2$	73.9	5.55	9.1	1 640, 1 570, 1 520, 780, 720	2.04s (Me), 2.34s (Me), 5.98d (5-H, $J_{4,5}$ 7 Hz), 6.17d (3-H, $J_{3,4}$ 10 Hz), 6.65—7.45m (4-H and ArH)
(4e)	74.1	5.5	9.0	$C_{19}H_{17}ClN_2$	73.9	5.55	9.1	1 640, 1 575, 1 520, 770, 710, 695	2.29s (Me), 2.41s (Me), 5.90d (5-H, $J_{4,5}$ 8 Hz), 6.33d (3-H, $J_{3,4}$ 10 Hz), 6.60—7.40m (4-H and ArH)
(4f)	74.0	5.6	9.0	$C_{19}H_{17}ClN_2$	73.9	5.55	9.1	1 640, 1 515, 1 575, 1 520, 840, 820, 770, 720	2.20s (Me), 2.35s (Me), 5.90d (5-H, $J_{4,5}$ 7 Hz), 6.32d (3-H, $J_{3,4}$ 9 Hz), 6.50—7.40m (4-H and ArH)
(4g)	72.5	4.7	10.0	$C_{17}H_{13}ClN_2$	72.7	4.7	10.0	1 640, 1 590, 1 565, 1 520, 775, 765, 695	5.90d (5-H, $J_{4,5}$ 7 Hz), 6.30d (3-H, $J_{3,4}$ 9 Hz), 6.55—7.60m (4-H and ArH)
(4h)	74.7	6.3	8.4	$C_{21}H_{21}ClN_2$	74.9	6.3	8.3	1 640, 1 580, 1 520, 825, 780, 720	1.99s (Me), 2.27s (2 Me), 2.38s (Me), 5.92d (5-H, $J_{4,5}$ 7 Hz), 6.13d (3-H, $J_{3,4}$ 9 Hz), 6.60—7.25m (4-H and ArH)

removable jacket containing ethyl acetate, capable of being heated under reflux) was added phosphoryl chloride (21.75 g, 0.14 mol) and to this ice-cold, stirred material was added dropwise, DMF (4.40 g, 0.06 mol) followed by the enamidine (3) or (6) (0.02 mol). After being stirred for 2 h at ambient temperature the flask was maintained at 75 °C for a further 4 h. The dark red-brown solution was poured into ice–water (300 ml) and gave on standing a precipitate or separation of an oil. This product was filtered [and washed with a little light petroleum–ethyl acetate mixture (1 : 1)] or extracted with chloroform and eluted through alumina using chloroform–light petroleum as eluant. The products listed in Table 2 were all recrystallised from light petroleum–ethyl acetate as bright yellow crystals and showed the properties listed in Tables 2 and 4.

6-*Chloro*-1-(2-*methoxyphenyl*)-2-(2-*methoxyphenylimino*)-3,5-*dimethyl*-1,2-*dihydropyridine* (7a). Obtained as yellow *crystals* (51%) from light petroleum–ethyl acetate, m.p. 138—139 °C (Found: C, 68.2; H, 5.8; N, 7.6. $C_{21}H_{21}ClN_2O_2$ requires C, 68.4; H, 5.7; N, 7.6%). $\nu_{max.}$ (Nujol) 1 650, 1 610, 1 545, and 745 cm^{-1}. $\delta(CDCl_3)$ 1.90s (Me), 2.00s (Me), 3.60s (Me), 3.70s (Me), 6.40—7.30m (4-H and aromatic H's).

3,5,6-*Trichloro*-1-(2-*methoxyphenyl*)*pyridin*-2(1H)-*one* (7b). Obtained as pale yellow *crystals* (28%), m.p. 198—199.5 °C (Found: C, 47.1; H, 2.5; N, 4.4. $C_{12}H_8Cl_3NO_2$ requires C, 47.3; H, 2.65; N, 4.6%). $\nu_{max.}$ (Nujol) 1 675, 1 585, 1 495, 1 300, 1 280, 1 260, and 760 cm^{-1}. $\delta(CDCl_3)$ 3.89s (Me), 6.95—7.56m (aromatic H's), and 7.65s (4-H).

One-pot Method for Formation of Iminopyridines.—2-Methoxyacetanilide (3.30 g, 0.02 mol) and phosphorus pentachloride (4.16 g, 0.02 mol) were shaken together and the resulting melt heated at 75 °C for 75 min. To the cooled mixture at 0 °C was added with stirring phosphoryl chloride (10.75 g, 0.07 mol) followed, dropwise, by DMF (2.20 g, 0.03 mol). The mixture was then treated as before, yielding

6-chloro-1-(2-methoxyphenyl)-2-(2-methoxyphenylimino)-1,2-dihydropyridine (4a) (31%). In a similar way, from 2-methoxypropionanilide was obtained the 6-chloro-bis(2-methoxyphenyl)-3,5-dimethylpyridine (7a) (27%).

N^1-*Acetyl*-N^1,N^2-*diarylacetamidines* (9).—To a stirred solution of *N*^{1},*N*^{2}-diphenylacetamidine [7] (1.75 g, 0.0083 mol) in dry pyridine (10 ml) at 0 °C was added dropwise acetyl chloride (0.31 g, 0.0167 mol). After being stirred for a further 1 h at 0 °C the mixture was poured into water and extracted with ether. The extract was washed with citric acid solution and then water, dried ($MgSO_4$), and evaporated to give *N*^{1}-acetyl-*N*^{1},*N*^{2}-diphenylacetamidine (1.92 g, 92%) as a colourless oil. $\nu_{max.}$ (liquid film) 1 685, 1 655, 1 595, 11 490, 1 365, 1 205, 1 020, 800, 755, and 695 cm^{-1}. δ($CDCl_3$) 1.95s (Me), 2.07s (Me), 6.55d (2 aromatic H), 6.97—7.35m (aromatic H's).

In a similar manner from *N*^{1},*N*^{2}-bis(2-methoxyphenyl)-acetamidine [9] was obtained *N*^{1}-acetyl-*N*^{1},*N*^{2}-bis(2-methoxyphenyl)acetamidine as a pale yellow oil (82%). $\nu_{max.}$ (liquid film) 1 685, 1 660, 1 600, 1 495, 1 280, 1 245, 1 020, and 750 cm^{-1}. δ($CDCl_3$) 2.00s (Me), 2.26s (Me), 3.72s (Me), 3.84s (Me), and 6.55—7.40m (aromatic H's).

Attempted Conversion of Acetyldiarylacetamidines into Iminopyridines.—The amidines (8) were treated as indicated above with DMF and phosphoryl chloride. Only starting material was isolated on work-up. On use of the ' one-pot ' conditions *N*^{1}-acetyl-*N*^{1},*N*^{2}-bis(2-methoxyphenyl)acetamidine gave the 6-chloro-bis(2-methoxyphenyl)pyridine (4a) (12%).

Hydrolysis of 6-*Chloro*-2-*iminopyridines* (4).—(*a*) *Under alkaline conditions*. The 6-chloro-bis(2-methoxyphenyl)-pyridine (4a) (3.40 g, 0.01 mol) and ethanolic potassium hydroxide (200 ml, 10% w/v) were heated under reflux for 2 h. The resulting brown solution was evaporated to dryness and treated with water (250 ml) from which precipitated a fawn coloured solid. This was filtered, washed, dried and recrystallised to give 6-*ethoxy*-1-(2-*methoxyphenyl*)-2-(2-*methoxyphenylimino*)-1,2-*dihydropyridine* (10) (74%) as pale yellow needles from ethyl acetate, m.p. 131—132 °C (Found: C, 71.9; H, 6.4; N, 8.0. $C_{21}H_{22}N_2O_3$ requires C, 72.0; H, 6.3; N, 8.0%). $\nu_{max.}$ (Nujol) 1 655, 1 585, 1 540, 1 240, 1 180, 760, and 745 cm^{-1}. δ($CDCl_3$) 1.15t (Me), 3.70s (Me), 3.90s (Me), 3.97q (CH_2), 5.18d (5-H, $J_{4,5}$ 7 Hz), 5.85d (3-H, $J_{3,4}$ 10 Hz), 6.70—7.45m (4-H and aromatic H's). *m*/*z* 350 (*M*$^+$, 44%), 319 (*M* − OMe, 100), 291 (*M* − C_3H_7, 56), and 290 (*M* − C_3H_8O, 38%).

(*b*) *Under acidic conditions*. After the same iminopyridine (1.00 g) in aqueous hydrochloric acid (50 ml, 20% w/v) had been heated at 180 °C for 4 h in an autoclave, work-up gave solely the unchanged material.

The iminopyridine (1.0 g) was unchanged after being heated for 2 h at 100 °C with sodium hydroxide (2 g) in dimethyl sulphoxide (200 ml) or with potassium hydroxide (5 g) in water (5 ml) and dioxane (40 ml). Use of phase-transfer conditions [dichloromethane (50 ml), aqueous potassium hydroxide (50 ml; 10% w/v), tetra-n-butylammonium hydroxide (1.0 ml; 40% aqueous solution) 4 days stirring] was also ineffective. Also after 12 h refluxing in t-butyl alcohol (100 ml) containing potassium hydroxide (10 g) no reaction occurred.

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