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Reactions of Aziridines with Acetyl Chloride and Related Compounds

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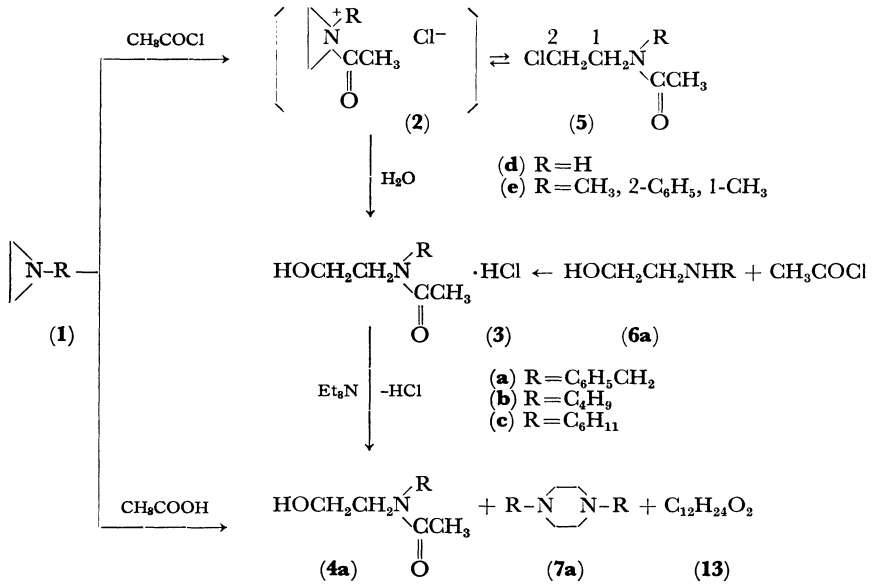
When aziridines (**1**) were treated with acetyl compounds, such as acetyl chloride, acetic acid, acetic anhydride, and thioacetic acid, the corresponding acetamide derivatives were obtained in good yields. In the case of acetyl chloride, some derivatives of *N*-(2-chloroethyl)acetamide (**5**) were found to be unstable in the face of moisture; they were easily hydrolyzed to give *N*-(2-hydroxyethyl)acetamide hydrochlorides (**3**). The NMR spectrum of *N*-(2-mercaptoethyl)-*N*-benzylacetamide (**12**) was discussed.

The reactions of aziridine with acid chlorides to give *N*-(2-chloroethyl)amide derivatives have been described.[1,2] On the other hand, at least two examples of the reactions of *N*-substituted aziridines with acid chlorides have been reported.[3,4] However, no systematic study of this type of reaction has yet been reported. In the present investigation, we studied the reactions of *N*-substituted aziridines with acetyl chloride and other acetyl compounds.

1) H. Bestian, *Ann. Chem.*, **566**, 210 (1950).
2) H. W. Heine, *J. Amer. Chem. Soc.*, **85**, 2743 (1963).
3) L. J. Dolby and H. Biere, *ibid.*, **90**, 2699 (1968).
4) K. Tanaka, *Yakugaku Zasshi*, **70**, 220 (1950).

Results and Discussion

Reaction of Aziridines with Acetyl Chloride. When *N*-benzylaziridine (**1a**) was treated with acetyl chloride in dry benzene under ice cooling, a light yellow sirup was obtained. After being kept for 7 day at room temperature, the sirup crystallized. The crude product was recrystallized from ethanol. *N*-(2-Hydroxyethyl)-*N*-benzylacetamide hydrochloride (**3a**) was thus obtained in a 66% yield. **3a** was characterized by elemental analysis and by means of its IR and NMR spectra. The IR spectrum had absorptions at 2750—2350 cm^{-1} (ν_{NH^+}), 1735 cm^{-1} ($\nu_{C=O}$), and the NMR spectrum



Scheme 1

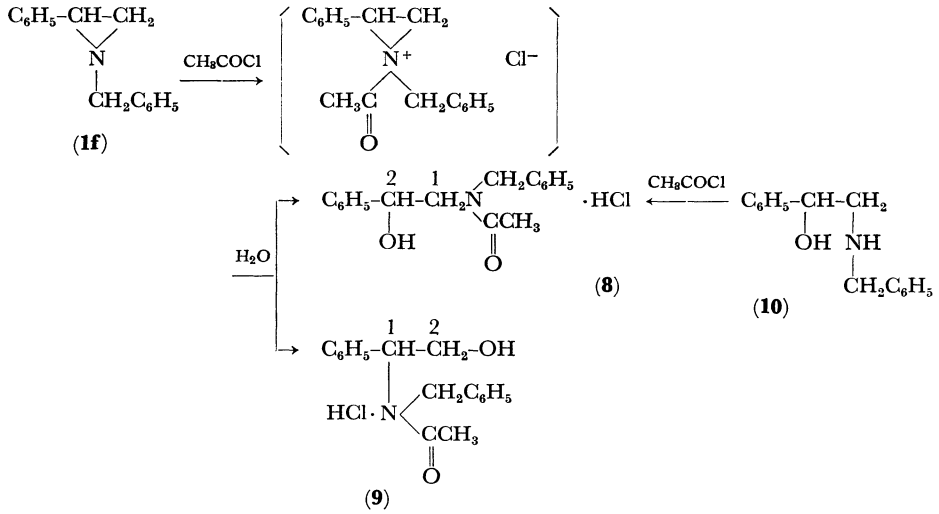
exhibited a broad peak at τ 0.1 (2H) due to –OH and –NH^+–.

Furthermore, the fact that the reaction of **3a** with triethylamine in benzene yielded triethylamine hydrochloride and *N*-(2-hydroxyethyl)-*N*-benzylacetamide (**4a**) supported the idea of the structure of **3a**, while **4a** was also prepared by the reaction of *N*-benzylaziridine (**1a**) with acetic acid. On the other hand, the product prepared from *N*-benzylaminoethanol (**6a**) with acetyl chloride was identical with **3a** in its IR spectrum, and a mixed-melting-point determination showed no depression.

A probable pathway for this reaction involves an initial electrophilic attack of the acetyl group on the basic aziridine nitrogen, followed by the ring opening of the intermediate aziridinium salt (**2a**) to give *N*-(2-chloroethyl)-*N*-benzylacetamide (**5a**). This compound was unstable in the face of moisture and was easily hydrolyzed to **3a**. This fact was explained by the change in the IR bands from 1650 cm^{-1} ($\nu_{>N-C=O}$) to 1735 cm^{-1} ($\nu_{C=O}$).

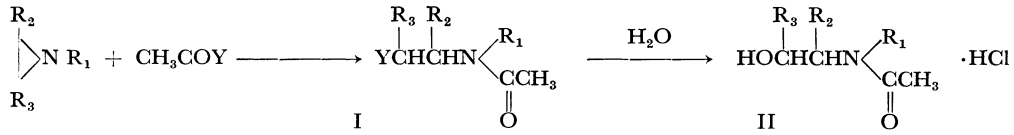
Analogous reactions of *N*-butylaziridine (**1b**) and *N*-cyclohexylaziridine (**1c**) with acetyl chloride resulted in the formation of the corresponding *N*-(2-hydroxyethyl)amide hydrochloride derivatives (**3b, 3c**). These results are summarized in Table 1.

On the contrary, when aziridine (**1d**) or 1,2-dimethyl-3-phenylaziridine (**1e**) was treated with acetyl chloride, a stable *N*-(2-chloroethyl) amide derivative (**5d** or **5e**) was obtained in a 95% or



Scheme 2

Table 1. Reactions of aziridines with acetyl compounds



Compound	R_1	R_2	R_3	Y	Product	Mp°C or Bp°C/mmHg	Yield, %	IR(C=O) cm^{-1}
3a	$C_6H_5CH_2$	H	H	Cl	II	152–153	66	1735
4a				OH	I	174/1.5	58	1620
11				$OCOCH_3$	I	150–151/0.5	72	1650, 1740
12				SH	I	158–160/1.2	73	1640
3b	C_4H_9	H	H	Cl	II	182–183	69	1735
3c	C_6H_{11}	H	H	Cl	II	171–172	95	1745
5d	H	H	H	Cl	I	131/6	95	1655
5e	CH_3	CH_3	C_6H_5	Cl	I	122–124[a]	99	1635
8	$C_6H_5CH_2$	H	C_6H_5	Cl	II	178–181	93	1725

a) Lit, mp 124°C.[4]

Table 2. Elemental analysis

Compound	Formula	Calcd, %				Found, %			
		C	H	N	Cl(S)	C	H	N	Cl(S)
3a	$C_{11}H_{16}NO_2Cl$	57.50	6.70	6.10	15.44	57.68	6.84	6.18	15.51
4a	$C_{11}H_{15}NO_2$	68.37	7.82	7.25		68.36	7.99	7.24	
11	$C_{13}H_{17}NO_3$	66.36	7.28	5.95		65.79[a]	7.22	6.28	
12	$C_{11}H_{15}NOS$	63.14	7.23	6.69	15.29	64.18[a]	7.14	6.96	14.83
3b	$C_8H_{18}NO_2Cl$	49.10	9.21	7.16		49.17	9.04	7.38	
3c	$C_{10}H_{20}NO_2Cl$	54.20	9.04	6.32	16.05	54.46	8.92	6.56	16.52
5d	C_4H_8NOCl	39.51	6.58	11.52		39.65	6.82	11.67	
5e	$C_{12}H_{16}NOCl$	63.83	7.15	6.21	15.75	63.99	6.89	6.08	15.71
8	$C_{17}H_{20}NO_2Cl$	66.78	6.55	4.58	11.62	66.57	6.43	4.42	11.73

a) The elemental analysis did not give a good agreement with the calculated values because of a very viscous oil.

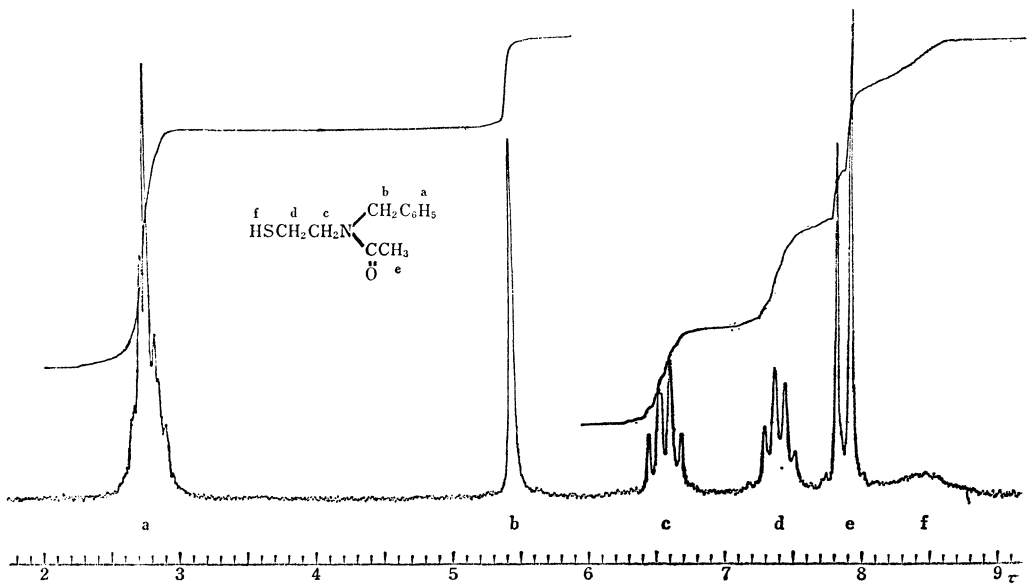


Fig. 1. NMR spectrum of *N*-(2-mercaptoethyl)-*N*-benzylacetamide (**12**) at 100 Mc in $CDCl_3$ using TMS as standard (23°C).

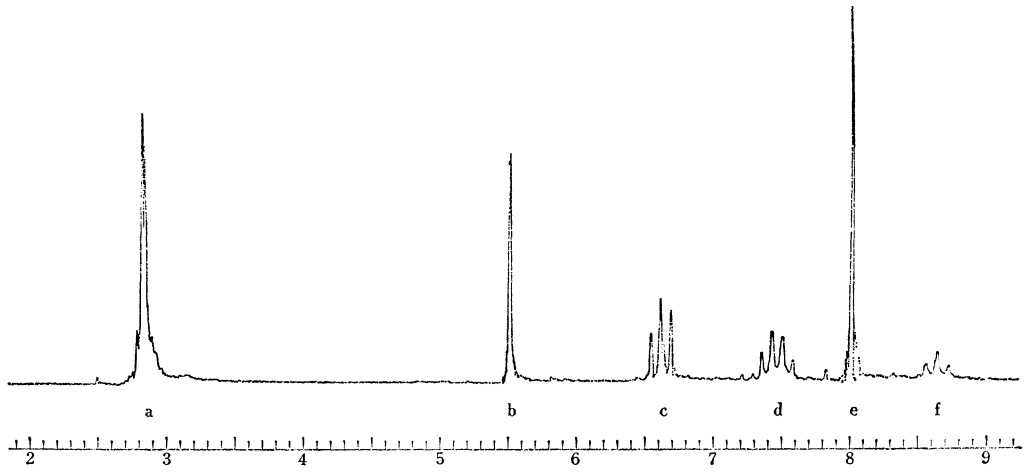


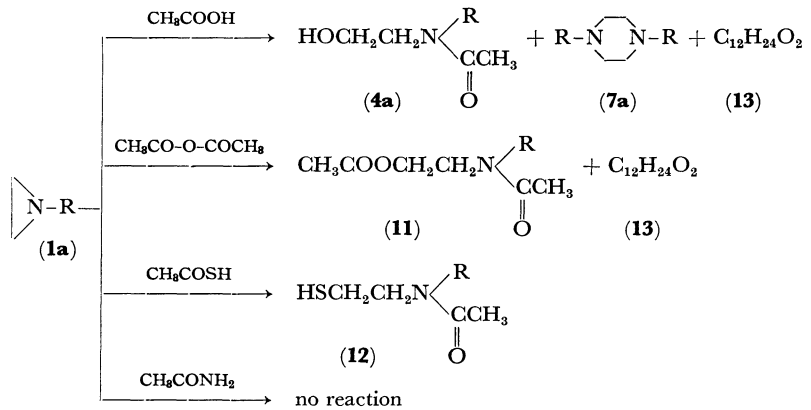
Fig. 2. NMR spectrum of **12** (100°C).

99% yield (Scheme 1).[5]

Two isomers (**8**,**9**) are possible through the ring opening of the aziridine moiety in the reaction of 1-benzyl-2-phenylaziridine (**1f**) with acetyl chloride. The product was found to be *N*-(2-phenyl-2-hydroxyethyl)-*N*-benzylacetamide hydrochloride (**8**). **8** was identified by a comparison of its IR spectrum with that of a sample prepared from 1-phenyl-2-benzylaminoethanol (**10**) with acetyl chloride; a mixed-melting-point determination supported this structure (Scheme 2).

Reaction of Aziridines with Other Acetyl Compounds. When 1-benzylaziridine (**1a**) was treated with other acetyl compounds, such as acetic acid,[6] acetic anhydride[7] or thioacetic acid,[6] the corresponding acetamide derivatives (**4a**, **11**, **12**) were obtained in good yields. When a reagent with a lower electrophilicity, such as acetamide, was used as an acetyl compound, the starting materials were recovered even after refluxing for 7 hr.

In the NMR spectra of these compounds (**4a**, **11**, **12**), acetyl protons exhibited a doublet at 23°C, and the doublet became a singlet at 100°C. This fact establishes that acetyl protons are nonequivalent due to the partial doublebond character of the >N–C-bond. As an example, the NMR spectrum of **12** is shown in Fig. 1 and Fig. 2.



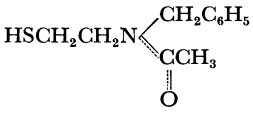
R = $CH_2C_6H_5$

Scheme 3

5) *N*-(2-Chloroethyl)-*N*-methylacetamide was already prepared, bp 100—101°C/5 mmHg. A. F. Nikolaev, M. E. Rosenberg, N V. Daniel and G. P. Tereschenko, *Zh. Obshch. Khim.*, **33**, 391 (1963); *Chem. Abstr.*, **59**, 424d (1963).

6) P. E. Fanta, "Heterocyclic Compounds with Three- and Four-Membered Rings," Part I, ed. by A. Weissberger, Interscience Publishers, Inc., New York. N.Y. (1964), pp. 553—554.

7) P. Loewrigkeit, G. J. Del Franco and N. Georgalas, *J. Org. Chem.*, **33**, 3344 (1968); M. G. Voronkov and L. A. Fedotova, *Khim. Geterotsikl. Soedin*, 302 (1967); *Chem. Abstr.*, **67**, 116687 s (1967); Badische Anilin- & Soda-Fabrik Akt.-Ges., Brit. 784058 (1957): *Chem. Abstr.*, **52**, 5034 h (1958).



(12)

In the cases of acetic acid or acetic anhydride, an unknown substance with the composition of $C_{12}H_{24}O_2$ (**13**) was obtained as a by-product; this substance's structure is now under investigation (Scheme 3).

Experimental

Benzene was dried over sodium. All the concentrations and evaporations were carried out under reduced pressure. All the melting points and boiling points are uncorrected.

Aziridines (**1**). These compounds were prepared by the methods in the literature. *N*-Benzyl-(**1a**), bp 77.5°C/7 mmHg;[8] *N*-butyl-(**1b**), bp 102—105°C;[9] *N*-cyclohexyl-(**1c**), bp 64.5—65.5°C/25 mmHg;[8] 1,2-dimethyl-3-phenyl-(**1e**), bp 82°C/14 mmHg;[10] 1-benzyl-2-phenylaziridine (**1f**), bp 138—139°C/1 mmHg[10] and aziridine (**1d**) 56—57°C, a commercial product.

Reaction of *N*-Benzylaziridine (1a) with Acetyl Chloride. A solution of acetyl chloride (2.36 g, 0.03 mol) in benzene (10 m*l*) was stirred, drop by drop, into a solution of **1a** (3.99 g, 0.03 mol) in benzene (30 m*l*) under ice cooling. The mixture was stirred at room temperature for 1 hr, and then refluxed for 3 hr. The mixture was concentrated to give a light yellow sirup, which was identified as *N*-(2-chloroethyl)-*N*-benzylacetamide (**5a**) by means of its IR spectrum. After standing for 7 day at room temperature, the sirup crystallized to give *N*-(2-hydroxyethyl)-*N*-benzylacetamide hydrochloride (**3a**). The crude product was collected by filtration, washed with benzene, and dried (4.55 g, 66% yield). Recrystallization from ethanol gave colorless needles; mp 152—153°C. IR (KBr): 2920, 2770, 2550, 2350, 1735, 1430, 1240, 1065, 980, 745 and 700 cm^{-1}; NMR (CD_3SOCD_3): τ 7.95 (3H, singlet) due to CH_3CO, τ 6.85 (2H, triplet) due to $>NCH_2-$, τ 5.83 (2H, singlet) due to $C_6H_5-CH_2-$, τ 5.65 (2H, triplet) due to $HOCH_2-$, τ 2.25—2.7 (5H, multiplet) due to aromatic protons, and τ 0.1 (2H, broad) due to –OH and $-NH^+$.

An attempt to obtain *N*-(2-chloroethyl)-*N*-benzylacetamide hydrochloride by the treatment of the sirup with hydrogen chloride failed, while **3a** was obtained through hydrolysis.

In a similar procedure, other aziridines (**1b**, **1c**, **1e**) were treated with acetyl chloride; the results are summarized in Table 1.

Reaction of 2-Benzylaminoethanol (6a) with Acetyl Chloride. A solution of acetyl chloride (7.85 g, 0.1 mol) in benzene (20 m*l*) was stirred, drop by drop, into a solution of **6a** (15.10 g, 0.1 mol) in benzene (100 m*l*) under cooling. The mixture was stirred for 5 hr at room temperature, and then refluxed for 1 hr. After cooling, the precipitated **3a** (16.70 g, 73%) was collected by filtration. Recrystallization from ethanol afforded colorless plates, mp 151—153°C; this was shown to be the same product as that prepared by the reaction of **1a** with acetyl chloride by a mixed-melting-point determination and by a study of its IR spectrum.

Reaction of Aziridine (1d) with Acetyl Chloride. A solution of acetyl chloride (7.85 g, 0.1 mol) in chloroform (10 m*l*) was stirred, drop by drop, into a solution of **1d** (4.31 g, 0.1 mol) in chloroform (50 m*l*) under ice cooling. The mixture was stirred at room temperature for 1 hr and then concentrated to give a light yellow oil; this oil was distilled to give *N*-(2-chloroethyl)-acetamide (**5d**) (7.30 g, 60%); bp 131°C/16 mmHg.

Reaction of 1-Phenyl-2-benzylaminoethanol (10)[10] with Acetyl Chloride. A solution of acetyl chloride (4.71 g, 0.06 mol) in benzene (15 m*l*) was stirred, drop by drop, into a solution of **10** (4.54 g, 0.02 mol) in benzene (100 m*l*) under ice cooling. The mixture was refluxed for 3 hr and then concentrated to give a light yellow oil. Ethanol containing hydrochloric acid (10 m*l*) was added to the oil, after which the mixture was concentrated to give *N*-(2-phenyl-2-hydroxyethyl)-*N*-benzylacetamide hydrochloride (**8**) (6.10 g, 99%); mp 178—181°C.

Found: C, 66.67; H, 6.42; N, 4.68%. Calcd for $C_{17}H_{20}NO_2Cl$: C, 66.78; H, 6.55; N, 4.58%.

Reaction of 1-Benzylaziridine (1a) with Acetic Acid. A solution of acetic acid (2.40 g, 0.04 mol) in benzene (12 m*l*) was added, drop by drop, to a solution of **1a** (5.30 g, 0.04 mol) in benzene (40 m*l*). The mixture was refluxed for 3 hr and then concentrated to give a light yellow oil; this oil was subsequently distilled at 53—65°C/2 mmHg (redistilled, 89°C/18 mmHg) to give **13** (1.00 g). IR (NaCl): 3300, 2900, 1705, 1460, 1375 and 1035 cm^{-1}. NMR ($CDCl_3$): τ 9.1, τ 8.7, τ 8.0, τ 7.15, τ 6.5 and τ 6.05.

Found: C, 71.39; H, 13.00%, MW 190—200 (VPM). After the mixture had stood for a day, the precipitated 1,4-dibenzylpiperazine (**7a**)[11] (0.53 g, 10%) was filtered off. The filtrate was redistilled to give *N*-(2-hydroxyethyl)-*N*-benzylacetamide (**4a**) (4.47 g, 58%); bp 174°C/1.5 mmHg.

Reaction of 1-Benzylaziridine (1a) with Acetic Anhydride. A solution of acetic anhydride (3.06 g, 0.03 mol) in benzene (9 m*l*) was added, drop by drop, to a solution of **1a** (3.99 g, 0.03 mol) in benzene (30 m*l*). The mixture was refluxed for 3 hr and then concentrated to give a light yellow oil; this oil was distilled at 50—54°C/4 mmHg to give **13** (0.90 g). This product was identified as **13** by a comparison of its IR spectrum with that of the product from the reaction of **1a** with acetic acid. Distillation at 155—159°C/1 mmHg gave *N*-(2-acetoxyethyl)-*N*-benzylacetamide (**11**) (5.40 g, 72%). An analytical pure sample was obtained by redistillation; bp 150—151°C/0.5 mmHg.

Reaction of 1-Benzylaziridine (1a) with Thioacetic Acid. A solution of thioacetic acid (1.52 g, 0.02 mol) in methanol (10 m*l*) was stirred, drop by drop, into a solution of **1a** (2.66 g, 0.02 mol) in methanol (10 m*l*) under ice cooling. The mixture was refluxed for 3 hr and then concentrated to give a red viscous

8) A. T. Bottini and J. D. Poberts, *J. Amer. Chem. Soc.*, **80**, 5203 (1958).

9) R. C. Elderfield and H. A. Hageman, *J. Org. Chem.*, **14**, 605 (1949).

10) I. Okada, K. Ichimura and R. Sudo, This Bulletin, **43**, 1185 (1970).

11) I. Okada, N. Itoh and R. Sudo, *ibid.*, **42**, 547 (1969).

oil; this oil was distilled at 159—163°C/1.5 mmHg to give *N*-(2-mercaptoethyl)-*N*-benzylacetamide (**12**) (3.05, 73%). An analytical pure sample was obtained by redistillation; bp 158—160°C/1.2 mmHg.

Treatment of *N*-(Hydroxyethyl)-*N*-benzylacetamide Hydrochloride (3a) with Triethylamine. **3a** (4.60 g, 0.02 mol) and triethylamine (3.03 g, 0.03 mol) were dissolved in benzene (50 m*l*), after which the mixture was stirred. The triethylamine hydrochloride thus precipitated was filtered off. The filtrate was concentrated to give an oil which was subsequently distilled at 174—175°C/1 mmHg. Its IR spectrum was superimposed on that of **4a**.

Found: C, 67.91; H, 7.30; N, 7.12%. Calcd for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25%.