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On the Alkylation at the α-Position of Some N,N-disubstituted Toluene(α)sulphonamides and Diphenylmethane-(α)sulphonamides

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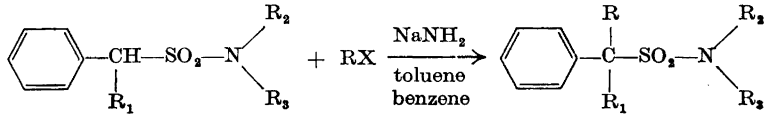
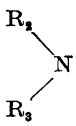
Some N,N-disubstituted toluene(α)sulphonamides and diphenylmethane(α)sulphonamides have been alkylated at the α-position by using sodamide as basic agent and benzene or toluene as solvents. It is shown, that this method is less general and requires more selected reaction conditions than when applied to the corresponding N,N-disubstituted carbonamides. The yields of α-substitution products often are lower. Some of the sulphonamides react very slowly with sodamide. In most of these cases the difficulties can be overcome by using a stronger basic agent, phenylsodium. A survey of the results is given in tabular form.

In a previous paper [1] we have given an account of alkylation at the α-position of N,N-disubstituted arylacetic acid amides. In this context we found it to be of interest to investigate to what extent an exchange of the carbonamide group against a sulphonamide group altered the situation. As expected the activation of the α-hydrogen in many cases proved to be great enough to allow an alkylation by the method applied by us earlier in the carbonamide case, *i.e.* using sodamide as basic agent and benzene or toluene as inert solvent. The reaction can be written



R_1 = H or phenyl,



= dialkylamino, benzyl-*n*-propylamino, dibenzylamino, N-methylanilino, pyrrolidino, piperidino and morpholino groups.

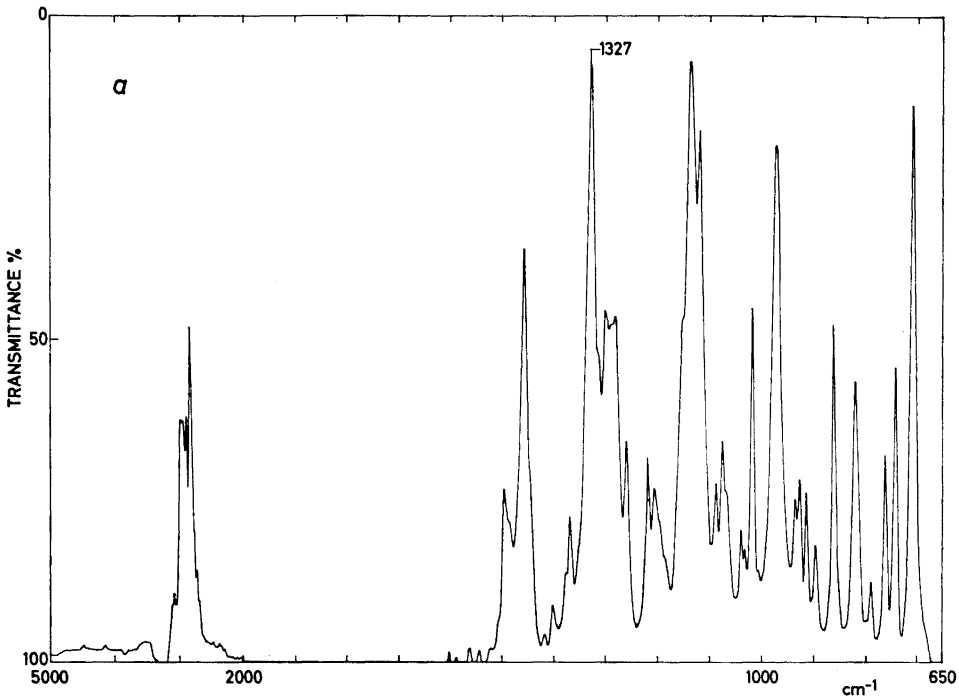
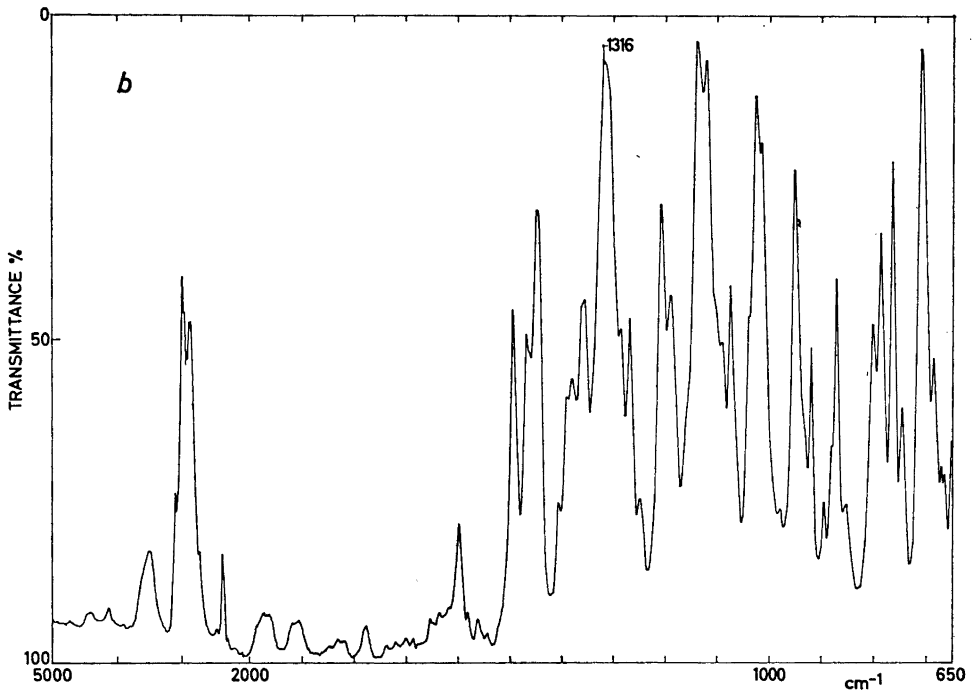


Fig. 1. Infrared spectrum of (a) α-(2-morpholinoethyl)-toluene(α)sulphonic acid N,N-dimethylamide and (b) α-(2-morpholinoethyl)-diphenylmethane(α)sulphonic acid N,N-diethylamide. The significant frequency (at 1 327 cm^{-1} and 1 316 cm^{-1}, respectively)

In most cases we have used 2-morpholinoethyl chloride as RX in order to get substitution products which are easily isolated from the reaction mixture, but some further examples are given in Table 1 in which the results have been compiled.

It is true, that most of the parent toluene(α)sulphonamides and at least some of their α-substituted derivatives can be distilled in vacuum at a pressure of some tenths of a mm Hg. However, this procedure provides that the reaction mixture to be worked up is fairly free from by-products which are still more temperature sensitive, hence would disintegrate and make it difficult to keep the pressure low enough. That is not always the case.

In contrast to the N,N-disubstituted arylacetamides, the N,N-disubstituted toluene(α)sulphonamides and diphenylmethane(α)sulphonamides behave very different as to a variation of the substituents of the amide group when treated with sodamide in an inert solvent such as benzene or toluene. Thus, toluene (α)sulphonylmorpholine reacts fairly slowly with sodamide in boiling toluene under salt formation, while the corresponding dimethylamine compound is rapidly destroyed by sodamide in boiling benzene. From the reaction mixture of this last reaction which proceeds under evolution of sulphur dioxide and



has been indicated by its numerical value. — All spectra are drawn with KBr pellet technique on a Unicam SP 100 IR instrument. The experimental error is 2 cm^{-1}.

dimethylamine, stilbene has been isolated. Tentatively, we suggest the reaction can be explained as including a first benzylation step whereafter the benzylated compound disintegrates according to formula (6) given by Hauser and Harris [2]. However, the dimethylamide can be alkylated in fairly good yield with morpholinoethyl chloride at a temperature of about 70° when the chloride is added to the reaction mixture before warming. The difference between the various N,N-disubstituted sulphonamides is sometimes so pronounced that the sodamide procedure seems to be of limited practical importance for the substitution of some of the sulphonamides. In these cases we have tried phenylsodium as basic agent, and generally with success. N,N-Dibenzyl-toluene(α)sulphonamide, for example, reacts very slowly in boiling toluene. After boiling for about 6 h, 60 % of the parent sulphonamide could be recovered, but no substitution product could be isolated from the reaction mixture. When phenylsodium was used, the yield of recrystallized α-(2-morpholinoethyl) compound was about 70 %.

The optimal reaction conditions are not always easy to find. In some cases of slowly reacting sulphonamides an increase in reaction time and/or reaction temperature does not increase the yield appreciably. To what extent

this result depends on a competitive destruction of the parent sulphonamide and/or the final substitution product, is difficult to say.

The limitation of the alkylation methods applied here are presumably the same as those of the carbonamide case. Some of the sulphonamides are also definitely less soluble in toluene and benzene than the corresponding carbonamides and therefore require more solvent. It should also be pointed out that several of the parent sulphonamides are not easily prepared by conventional methods. Thus, according to our experience to-date, the diphenylmethane(α) sulphonamides can be prepared only *via* diphenyldiazomethane (see also under Experimental). Some of the toluene(α)sulphonamides which otherwise are easily synthetized from toluene(α)sulphonyl chloride and the appropriate secondary amine, may be difficult to prepare or cannot be obtained by this route. Thus, toluene(α)sulphonyl chloride in benzene reacts with di-*iso*propylamine under formation of considerable amounts of a compound with high melting point (240—241.5°C after recrystallization from chloroform), almost insoluble in benzene and most other conventional solvents, including water. Judging from the composition and the fact that not the entire expected amount of amine is consumed during the reaction, we presume this compound to be α-[(toluene(α')sulphonyl)]-toluene(α)sulphonyldi*iso*propylamine, $C_6H_5CH(SO_2CH_2C_6H_5)SO_2N(C_3H_7)_2$.

The results are collected in Table 1. From the above it follows that the alkylations have been carried out by applying three procedures. The first one (1:b) includes more or less incomplete salt formation by boiling the parent sulphonamide with sodamide in toluene for some hours, followed by adding the alkyl halide and further refluxing. It is this procedure which was applied by us as standard method for alkylation of N,N-disubstituted arylacetic acid amides. When it has failed or has not given satisfactory results for the sulphonamides, we have tried a procedure (I:a) which is a slightly modified version of the preceding one. All the reaction components have been mixed together in toluene, and the mixture gently heated until a distinct evolution of ammonia begins and is kept at this temperature until the ammonia evolution has definitely decreased. The third procedure (II) includes the use of phenylsodium as basic agent and has been applied in some cases where the sodamide procedures have not given the desired results. For practical examples of the three procedures see under Experimental.

In order to show that the substituted compounds actually contain the sulphonamide group after alkylation, we have checked the infrared spectra of four of the compounds with reference to the SO_2 frequencies of the sulphonamide group. In Fig. 1 the most significant frequency of the sulphonamide group in the 1 320 cm^{-1} range has been indicated on the curves for two of the compounds investigated.

Some tentative efforts have also been made to condense esters with N,N-disubstituted sulphonamides in the presence of sodium methoxide as condensing agent and with xylene as medium, but these trials have not been encouraging. From a mixture of dimethyl oxalate and N,N-dimethyltoluene(α)sulphonamide only approximately half the theoretical amount of methanol could be distilled off when the temperature was raised to 90°C, and 75 % of the parent sulphonamide could be isolated from the reaction mixture. In order to try

whether a condensation including ring closure would be more easy to carry out or not, we applied the same method to methyl N-(*p*-chlorotoluene(*a*) sulphonyl)-N-*iso*propyl-2- aminopropionate. In this case not less than 87.5 % of N-*iso*propyl-p-chlorotoluene(*a*)sulphonamide (m.p. 137—139°C) could be isolated from the acrylate smelling reaction mixture, indicating that a fission of the amide bond had taken place.

EXPERIMENTAL

As mentioned above the N,N-disubstituted toluene(*a*)sulphonamides have been prepared from toluene(*a*)sulphonyl chloride and the appropriate secondary amines according to known methods and generally with benzene as solvent. Rather few compounds of this type have been reported previously [3,4]. Of course the sulphonamides have considerably higher melting point and boiling point than the corresponding carbonamides and are less soluble than these. That is also the case with the *a*-substitution products. As to the N,N-disubstituted diphenylmethane(*a*)sulphonamides, only the piperidide seems to have been reported earlier [5]. With some minor modifications, which to some extent have been inspired by a recent short communication by Miller [6], we have used the method given by these authors. We have therefore merely collected the melting and/or boiling points of the N,N-disubstituted sulphonamides mentioned in this paper or otherwise known.

Toluene(*a*)sulphonic acid: dimethylamide m. p. 100—101°; diethylamide m. p. ca 30°, b.p. 135—140°/0.3 mm; di-*n*-butylamide b.p. 136—138°/0.1 mm; N-methylanilide m. p. 102—104°; N-ethylanilide m. p. 118—119°; *n*-propyl-benzylamide b.p. 183—188°/0.3 mm; pyrrolidide m. p. 93—94°; piperidide m. p. 136—138°; morpholide m. p. 174—176°.

p-Chlorotoluene(*a*)sulphonic acid: piperidide m. p. 160—162°C; *iso*propyl(*β*-carbomethoxyethyl)-amide m. p. 64.5—66°.

Diphenylmethane(*a*)sulphonic acid: diethylamide m. p. 135—136°; pyrrolidide 175—177°; piperidide m. p. 167—168°.

N,N-Dimethyl-a-(2-morpholinoethyl)-toluene(a)sulphonamide (Method I:a). In a 250 ml flask, equipped with a reflux condenser, stirrer and thermometer, 19.9 g (0.1 mole) of N,N-dimethyltoluene(*a*)sulphonamide, 150 ml of dry toluene, 15.5 g (14.9 g = 0.1 mole) of 2-morpholinoethyl chloride and 4.2 g of commercial, ground sodamide are mixed together. The mixture is warmed gently while stirring. At a temperature of 60—65° a strong evolution of ammonia begins. The reaction mixture is now kept at a temperature of ca 70° for 6 h (a reaction time which perhaps may be shortened). The contents of the flask are cooled to room temperature, water is added and the toluene layer washed with water. The toluene layer is extracted with dilute hydrochloric acid. The united acid solutions are washed with ether, and the base is liberated by adding 5 N sodium hydroxide. When the stirred mixture is inoculated, the oil crystallizes fairly rapidly. The precipitate is filtered off and washed with water and petroleum ether. Yield 22.0 g (70.5 %) m. p. 75.5—77°. After two recrystallizations, the last one including treatment with active carbon, the yield is 17.1 g (55 %) m. p. 76—77°. For analytical data see Table 1.

The hydrochloride can be precipitated in excellent yield from an ether solution of the base by means of alcoholic hydrochloric acid. After recrystallization from methanol and ether the melting point is 203—205°. Yield 83 % (from 5.0 g of the base).

a-(2-Morpholinoethyl)-diphenylmethane(a)sulphonylpyrrolidine (Method I:b). A mixture of 15.1 g (0.05 mole) of diphenylmethane(*a*)sulphonylpyrrolidine, 2.1 g of commercial, ground sodamide and 100 ml of dry toluene is refluxed while stirring for one hour. During this time ammonia is evolved and some precipitate is formed in the flask. The mixture is cooled to about 60° and 8.5 g (theoret. 7.5 g) of 2-morpholinoethyl chloride is added. The mixture is heated again and refluxed for 5 h. After cooling to room temperature, water is added and the mixture washed with water. When excess of 2 N hydrochloric acid is added to the toluene layer under continuous stirring a viscous oil separates, form-

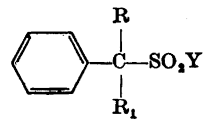
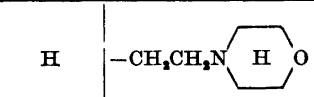
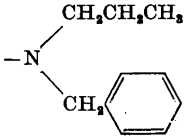
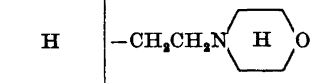
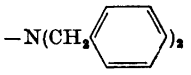
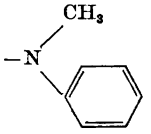
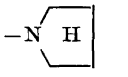


Table 1. Compounds prepared by alkylation at the α-position of some N,N-

R	R_1	Y	Method	React. time, h. Temp.°C	Yield %
H		$-N(CH_3)_2$	I:a	8; 70	70 55 83
H	»	$-N(C_2H_5)_2$	I:a	1; 80	32 23
	»	»	II I:a	1; 110 3; 100	35 10
H	»	$-N(n-C_4H_9)_2$	II I:a	1; 105 8; 110	26 0
H	$-CH_2CH_2N(C_2H_5)_2$		I:b	1; 110	70 38
H			II I:a	1; 110 6; 110	69 63 0
H	»		II I:a	0.5; 105 5; 110	32 0
H	»		I:a	6; 90	68
	»	»	II I:b	2; 110 5; 110	47 28 53 31

disubstituted toluene(α)-sulphonamides and diphenylmethane(α)sulphonamides.

M.p., °C B = base S = hydrochloride	Formula	Analyses							
		Calc.				Found			
		C	H	N	S	C	H	N	S
B 75.5–77 76–77 [a] S 203–205 [g]	$C_{15}H_{24}N_2O_3S$	57.66	7.74	8.97		58.19	7.84	9.11	
B 50– 54 56.5–58 [a]	$C_{17}H_{28}N_2O_3S$	59.97	8.29	8.23		60.07	8.36	8.27	
B 98–99 [a]	$C_{23}H_{32}N_2O_3S$	66.31	7.74	6.73		66.69	7.74	6.81	
B 97– 99 [a]									
B 59.5–61 [b]	$C_{21}H_{36}N_2O_3S$	63.60	9.15	7.07	8.08	63.80	9.27	7.18	8.06
B oil S 128–132 [c]	$C_{23}H_{35}ClN_2O_2S$	62.91	8.04	6.38		62.88	8.14	6.47	
S 168–170 [c] B 121–122 [a]	$C_{27}H_{32}N_2O_3S$	69.80	6.94	6.03	6.90	70.23	7.19	6.10	6.61
S 173–180 183–185 [d]	$C_{20}H_{27}ClN_2O_3S$	58.45	6.62		7.80	57.86	6.60		7.51
B 85.5–87 [a] S 203–206 [ce]	$C_{17}H_{26}N_2O_3S$	60.32	7.74	8.28		60.66	7.87	8.25	
S dec. 165 [c] B 110–112 [a] S dec. 165 [c] B 110–112 [a]	$C_{23}H_{31}ClN_2O_3S$	61.25	6.93	6.21	7.11	60.80	7.01	6.23	7.21

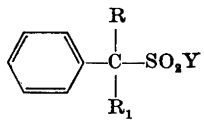
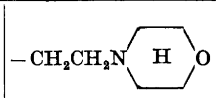
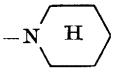
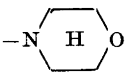
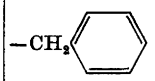
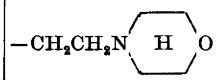
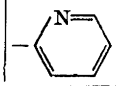


Table 1. Continued.

R	R_1	Y	Method	React. time, h. Temp.°C	Yield %
			I:a	5; 105	75 61
H[h]	$-CH_2CH_2CH_2N(C_2H_5)_2$	»	I:b	1; 110	63 45
H	$-CH_2CH_2C(CH_3)_3$		I:a	13; 110	65 30
H		»	I:b	3; 110	60 15
H	$-CH_2CH_2N(C_2H_5)_2$	»	I:b	4; 110	33 24
H		»	I:a II	10; 100 1.5; 110	50 48
H		»	I:b	6; 110	12

Notes: It should be observed that one of the parent sulphonamides, *p*-chlorotoluene(*a*)sulphonylpiperidine (and the corresponding substitution product) has a chlorine atom in *para* position (see note h) which is not indicated in the general formula in the heading. — With the exception of 2-bromopyridine, chlorides have been used as alkylating agents. — For methods I:a, I:b and II see the introductory text and under Experimental. — When the substitution products are tertiary amines, B indicates base and S hydrochloride. — The yields are the total ones and refer to the parent sulphonamide. When more than one yield figure is given under a certain method, the compound prepared according to this method has been further purified by recrystall-

ing a third phase. It crystallizes on scratching. The precipitate is filtered off, washed with water and ether. The yield of this almost pure hydrochloride of the substitution compound is 12.0 g (53.5 %) m. p. 163.5—165°. For analytical data see Table 1.

The base can be precipitated from a dilute aqueous solution of the hydrochloride by dilute sodium hydroxide. After recrystallization from *cyclo*hexane the m. p. is 110—112°.

M. p., °C B = base S = hydro-chloride	Formula	Analyses							
		Calc.				Found			
		C	H	N	S	C	H	N	S
B 70–72.5 72–73.5[a]	$C_{18}H_{28}N_2O_3S$	61.33	8.01	7.95		61.45	8.05	8.04	
B oil S 169–172.5[c]	$C_{19}H_{32}Cl_2N_2O_3S$	53.89	7.62		7.57	53.97	7.62		7.44
B 123 –129 128.5–131[a]	$C_{17}H_{27}NO_3S$	62.74	8.36	4.30		62.37	8.34	4.46	
B 134 –141 155.5–157[e]	$C_{18}H_{21}NO_3S$	65.23	6.39	4.23		65.16	6.43	4.20	
B 48–53 54 – 56[b]	$C_{17}H_{23}N_2O_3S$	59.97	8.29	8.23	9.42	60.25	8.39	8.26	9.31
B 84.5–86 B 83–84.5[a]	$C_{17}H_{26}N_2O_4S$	57.60	7.39	7.90		57.74	7.47	7.95	
B 154–156[f]	$C_{16}H_{18}N_2O_3S$	60.35	5.70	8.80	10.07	60.55	5.72	8.96	9.89

ization. — Melting points and boiling points are uncorrected. The former have been read from short normal thermometers covering intervals of 50°. — The alkylations have been carried out with 0.1–0.05 mole of parent sulphonamide.

a–g): Recrystallization from a) *cyclo*hexane; b) petroleum ether; c) acetone; d) ethylene chloride; e) methanol; ce) a mixture of acetone and methanol; f) benzene; g) a mixture of methanol and ether;

h): The parent amide is *p*-chlorotoluene(*α*)sulphonylpiperidine.

N,N-Dibenzyl-α-(2-morpholinoethyl)-toluene(α)sulphonamide (Method II). 50 ml of sodium dispersion (prepared from 12.5 g of sodium, 250 ml of dry toluene and 0.3 ml of oleic acid under nitrogen, by means of an "Ultra-Turrax" dispergator and cooled to room temperature) is pipetted into a 0.5 l flask equipped with reflux condensor, thermometer, stirrer and a dropping funnel. A slow flux of nitrogen is allowed to pass through this

equipment About 10 ml of a solution of 5.7 g (about 0.05 mole) of chlorobenzene in 25 ml of dry toluene is added to the dispersion *via* the dropping funnel in order to start the formation of phenylsodium. When the reaction has started, the remaining chlorobenzene solution is added to the sodium dispersion, while stirring, at such a rate that under intermittent cooling with a dry ice-alcohol bath the reaction temperature is kept at about 25°. When all the chlorobenzene solution has been added, the cooling bath is removed and the black reaction mixture is allowed to stand while stirring for about 15 min. If the temperature increases again during this period, the mixture should be cooled again. A solution of 17.5 g (0.05 mole) of N,N-dibenzyl-toluene (*a*)sulphonamide in about 120 ml of warm, dry toluene (this sulphonamide like some others, *e. g.* the morpholino compound, is only slightly soluble in cold toluene) is added *via* the funnel while stirring, and the flask is warmed to 55° for about 10 min. During this procedure the black colour of phenylsodium disappears and the contents of the flask become grayish. The flask contents are cooled to about 40° and a solution of 8.0 g (7.5 g = 0.05 mole) of 2-morpholinoethyl chloride in 25 ml of dry toluene is added while stirring *via* the funnel. The reaction mixture is now heated. At about 90° the grayish precipitate disappears and the reaction mixture becomes almost clear. The temperature is kept at about 110° for one hour. The flask contents are now cooled to room temperature and water is added carefully. The toluene layer is washed with water. When 2 N hydrochloric acid is added to the toluene phase the hydrochloride of the morpholinoethyl derivative precipitates as a third oily phase, which crystallizes on scratching. The precipitate is filtered off and washed with water and ether. Yield 18.3 g (78.5 %) m. p. about 140°. Recrystallization from a mixture of toluene and acetone gives 14.2 g with m. p. 168—170°. From the mother liquor another 1.5 g can be obtained with the same m. p. Total yield 69 %.

The base was liberated from 5.0 g of the hydrochloride and taken up in ether. When the ether is evaporated, 4.6 g of the base is obtained. After recrystallization from 50 ml of *cyclo*hexane, the yield is 4.3 g (91 %). For analytical data see Table 1.

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REFERENCES

1. Mårtensson, O. and Nilsson, E. *Acta Chem. Scand.* **14** (1960) 1129.
2. Hauser, C. R. and Harris, Th. M. *J. Am. Chem. Soc.* **81** (1959) 1157.
3. Marvel, C. S. and Gillespie, H. B. *J. Am. Chem. Soc.* **48** (1926) 2943.
4. Ingold, C. K. and Wilson, J. S. *J. Chem. Soc.* **1927** 813.
5. Kloosterziel, H., Deinema, M. H. and Backer, H. J. *Rec. trav. chim.* **71** (1952) 1228.
6. Miller, J. B. *J. Org. Chem.* **24** (1959) 560.

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