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Studies on Local Anesthetics XVIII *

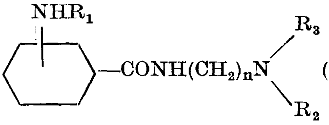
Synthesis of N-(Dialkylaminoalkyl)benzamides

BJÖRN LÜNING

Institute of Organic Chemistry and Biochemistry, University of Stockholm, Stockholm, Sweden

Benzamides of the general structure Ar–CO–NH–R_1–$N(R_2)_2$, in which Ar is a methyl substituted benzene nucleus, have been synthesized. Ar contains 1–3 methyl groups in all possible positions. R_1 represents $-CH_2CH_2-$, $-CH_2CH_2CH_2-$, $-CH(CH_3)CH_2-$, $-CH_2CH(CH_3)-$, $-CH(CH_3)CH(CH_3)-$, or $-CH_2C(CH_3)_2CH_2-$, and R_2 is a methyl or ethyl group. The number of new compounds which have been synthesized is 63. In one case a compound containing two asymmetric carbon atoms was separated into two racemates. The physical constants of 8 unknown benzoyl chlorides are also reported.

A well known local anesthetic is Nupercaine, *i.e.* N-(2-diethylaminoethyl)2-butoxycinchoninamide [1,2]. This compound was the first local anesthetic belonging to the amide type, that was introduced into the market. The discovery of nupercaine led to further research on amides as local anesthetics. Thus Eisleb [3] in a patent describes benzamides of the general structure:



(R_1, R_2, and R_3 = alkyls; $n \geq 2$)

An amide of the anilide type is Xylocaine ®, *i.e.* α-(diethylamino)-2,6-dimethylacetanilide which was introduced clinically in 1948 [4,5a]. Since then an extensive research work on anilides as local anesthetics has been carried out, and in the last few years anesthetics of the benzamide type have been subjected to much interest. Thus Hazard *et al.*[6,7], Hach *et al.*[8], Koelzer and Wehr [9], Moore [10], as well as Löfgren and Stoffel [11] have investigated benzamides in which the aryl group consists of a hydrocarbon residue.

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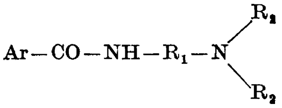
* For paper XVII of this series, see Löfgren and Stoffel [11].

In the present work sixtythree new compounds of the benzamide type have been synthesized, and these will later be investigated for their local anesthetic action; all of these compounds are represented by the formula:



Ar is a methyl substituted benzene nucleus. The number of methyl groups in Ar is one, two, or three — all possible combinations, *viz.* fifteen, being included. R_1 is an alkylene radical presented in Table 1 ; R_2 is methyl or ethyl. Chemical data of the bases synthesized are given in Table 2.

To synthesize N-(dialkylaminoalkyl)benzamides, one mole of acid chloride and 1.6 mole of dialkylaminoalkylamine were mixed in ether, the excess of amine being used as a proton acceptor. If only one mole of amine per mole of acid chloride was used, the yield was considerably lower (*c.f.* p. 1631).

Most of the methyl substituted benzoic acids used in this investigation have recently been described by Smith and Stanfield [12]. The methods of synthesis reported by these investigators were not followed in all cases but the melting points of the acids are in agreement with the reported ones [12].

2,3,5-Trimethylbenzoic acid and 3,4,5-trimethylbenzoic acid were prepared in two different ways. The conventional route, which was first followed, involves the oxidation of *iso*durene with dilute nitric acid [13,14]. However, this process gives a mixture of three monobasic acids, four dibasic acids, nitro

Table 1. Alkylene radicals R_1 (*cf.* above).

Ethylene	$-CH_2-CH_2-$
Trimethylene	$-CH_2-CH_2-CH_2-$
1-Methylethylene	$-\overset{CH_3}{\overset{\vert}{C}}H-CH_2-$
2-Methylethylene	$-CH_2-\overset{CH_3}{\overset{\vert}{C}}H-$
1,2-Dimethylethylene	$-\overset{CH_3}{\overset{\vert}{C}}H-\overset{CH_3}{\overset{\vert}{C}}H-$
2,2-Dimethyl-1,3-propylene	$-CH_2-\underset{CH_3}{\underset{\vert}{\overset{CH_3}{\overset{\vert}{C}}}}-CH_2-$

acids, and an appreciable amount of nonacidic nitro compounds[14]. Only about 10 % of this mixture consists of monobasic acids. 3,4,5-Trimethylbenzoic acid and 2,3,5-trimethylbenzoic acid were isolated from this mixture according to a method described under 3,4,5-trimethylbenzoic acid (*cf.* p.1628). This process differs in several ways from that given by Jannasch and Weiler[14]. Because of the small yield (1 % of each acid) and since the 2,3,5-trimethylbenzoic acid prepared in this way is also very difficult to purify, other routes of synthesis of the two acids were devised. 2,3,5-Trimethylbenzoic acid was prepared by carbonation[15] of the Grignard reagent of 6-bromopseudocumene, which was obtained by a four step procedure from pseudocumene[16]. 3,4,5-Trimethylbenzoic acid was made from 5-bromohemimellitene *via* the Grignard reagent. The bromo compound was prepared by a Sandmeyer reaction[17] from 3,4,5-trimethylaniline, which was obtained by a nuclear methylation of 3,5-dimethylaniline according to a recently published method[18].

Some of the acid chlorides required for the synthesis of the amides have not been hitherto reported in literature; their data are found in Table 3.

Most of the amines used in this investigation have been described by Löfgren and Stoffel[11]. 1-Amino-3-diethylamino-2,2-dimethylpropane was obtained by $LiAlH_4$ reduction[19] of the oxime of diethylaminopivalaldehyde[20].

2-Amino-3-diethylaminobutane contains two asymmetric carbon atoms, and consequently each of the corresponding amides forms two racemates having different chemical properties. In fact, these amides appear as mixtures of crystals and oil. The values given in Table 2 refer to these mixtures. The two racemates were separated completely and collected only in one case, *viz.* the *o*-toluamide. Of the other racemates, only the solid forms were collected. They were obtained as crystalline substances after treating the semisolids on porous plate. The melting points of these substances are given in brackets in Table 2.

Pharmacological data, ultraviolet spectra, and ionization constants will be published elsewhere, together with a discussion of the results.

EXPERIMENTAL *

o-, m-, and p-*Toluic acids* were all available commercially. *2,3-Dimethylbenzoic acid* **, *2,4-dimethylbenzoic acid*, *2,5-dimethylbenzoic acid*, and *3,4-dimethylbenzoic acid* were synthesized from the corresponding amino compounds by diazotization followed by treatment of the diazonium salt with potassium cyanocuprate(I)[21]: The nitriles formed were saponified by treatment with 50 % (vol/vol) sulfuric acid[22].

3,4-Dimethylbenzoic acid was also prepared in the following way: *o*-xylene was brominated[23] to form 3,4-dimethylbromobenzene, which was then converted to the acid by carbonation[15] of the corresponding Grignard reagent.

2,6-Dimethylbenzoic acid. To obtain this acid 2,6-dimethylbromobenzene was prepared by means of a Sandmeyer reaction[17] and then transformed to the acid *via* the Grignard compound[15].

3,5-Dimethylbenzoic acid was made from mesitylene by partial oxidation with dilute nitric acid[24].

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* All melting points are corrected unless otherwise stated.

** The melting points of the acids were all in accordance with those given by Smith and Stanfield[12].

Table 2. Chemical data of N-dialkylaminoalkyl benzamides I—LXIV. Abbreviations for solvents: L.pet.,

	Compound Ar—CO—NH—R_1—$N(R_2)_2$		
Number	Name	Ar	R_1
I	N-(2-Diethylaminoethyl)-2-methylbenzamide	2-$CH_3C_6H_4$	CH_2CH_2
II	N-(3-Diethylaminopropyl)-2-methylbenzamide	»	$CH_2CH_2CH_2$
III	N-(2-Diethylamino-1-methylethyl)-2-methylbenzamide	»	$CH(CH_3)CH_2$
IV	N-(2-Diethylamino-2-methylethyl)-2-methylbenzamide	»	$CH_2CH(CH_3)$
Va[e]	N-(2-Diethylamino-1,2-dimethylethyl)-2-methylbenzamide	»	$CH(CH_3)CH(CH_3)$
Vb[e]	N-(2-Diethylamino-1,2-dimethylethyl)-2-methylbenzamide	»	»
VI	N-(3-Diethylamino-2,2-dimethylpropyl)-2-methylbenzamide	»	$CH_2C(CH_3)_2CH_2$
VII	N-(2-Diethylaminoethyl)-3-methylbenzamide	3-$CH_3C_6H_4$	CH_2CH_2
VIII	N-(3-Diethylaminopropyl)-3-methylbenzamide	»	$CH_2CH_2CH_2$
IX	N-(2-Diethylamino-1-methylethyl)-3-methylbenzamide	»	$CH(CH_3)CH_2$
X	N-(2-Diethylamino-2-methylethyl)-3-methylbenzamide	»	$CH_2CH(CH_3)$
XI	N-(2-Diethylamino-1,2-dimethylethyl)-3-methylbenzamide	»	$CH(CH_3)CH(CH_3)$
XII	N-(3-Diethylamino-2,2-dimethylpropyl)-3-methylbenzamide	»	$CH_2C(CH_3)_2CH_2$
XIII	N-(2-Diethylaminoethyl)-4-methylbenzamide	4-$CH_3C_6H_4$	CH_2CH_2
XIV	N-(3-Diethylaminopropyl)-4-methylbenzamide	»	$CH_2CH_2CH_2$
XV	N-(2-Diethylamino-1-methylethyl)-4-methylbenzamide	»	$CH(CH_3)CH_2$
XVI	N-(2-Diethylamino-2-methylethyl)-4-methylbenzamide	»	$CH_2CH(CH_3)$
XVII	N-(2-Diethylamino-1,2-dimethylethyl)-4-methylbenzamide	»	$CH(CH_3)CH(CH_3)$
XVIII	N-(3-Diethylamino-2,2-dimethylpropyl)-4-methylbenzamide	»	$CH_2C(CH_3)_2CH_2$
XIX	N-(2-Diethylaminoethyl)-2,3-dimethylbenzamide	2,3-$(CH_3)_2C_6H_3$	CH_2CH_2
XX	N-(3-Diethylaminopropyl)-2,3-dimethylbenzamide	»	$CH_2CH_2CH_2$
XXI	N-(2-Diethylamino-1-methylethyl)-2,3-dimethylbenzamide	»	$CH(CH_3)CH_2$
XXII	N-(2-Diethylamino-2-methylethyl)-2,3-dimethylbenzamide	»	$CH_2CH(CH_3)$
XXIII	N-(2-Diethylaminoethyl)-2,4-dimethylbenzamide	2,4-$(CH_3)_2C_6H_3$	CH_2CH_2
XXIV	N-(3-Diethylaminopropyl)-2,4-dimethylbenzamide	»	$CH_2CH_2CH_2$
XXV	N-(2-Diethylamino-1-methylethyl)-2,4-dimethylbenzamide	»	$CH(CH_3)CH_2$
XXVI	N-(2-Diethylamino-2-methylethyl)-2,4-dimethylbenzamide	»	$CH_2CH(CH_3)$
XXVII	N-(2-Diethylaminoethyl)-2,5-dimethylbenzamide	2,5-$(CH_3)_2C_6H_3$	CH_2CH_2
XXVIII	N-(3-Diethylaminopropyl)-2,5-dimethylbenzamide	»	$CH_2CH_2CH_2$
XXIX	N-(2-Diethylamino-1-methylethyl)-2,5-dimethylbenzamide	»	$CH(CH_3)CH_2$
XXX	N-(2-Diethylamino-2-methylethyl)-2,5-dimethylbenzamide	»	$CH_2CH(CH_3)$
XXXI	N-(3-Diethylamino-2,2-dimethylpropyl)-2,6-dimethylbenzamide	2,6-$(CH_3)_2C_6H_3$	$CH_2C(CH_3)_2CH_2$
XXXII	N-(2-Diethylaminoethyl)-3,4-dimethylbenzamide	3,4-$(CH_3)_2C_6H_3$	CH_2CH_2
XXXIII	N-(3-Diethylaminopropyl)-3,4-dimethylbenzamide	»	$CH_2CH_2CH_2$
XXXIV	N-(2-Diethylamino-1-methylethyl)-3,4-dimethylbenzamide	»	$CH(CH_3)CH_2$
XXXV	N-(2-Diethylamino-2-methylethyl)-3,4-dimethylbenzamide	»	$CH_2CH(CH_3)$
XXXVI	N-(2-Diethylaminoethyl)-3,5-dimethylbenzamide	3,5-$(CH_3)_2C_6H_3$	CH_2CH_2
XXXVII	N-(2-Diethylamino-1-methylethyl)-3,5-dimethylbenzamide	»	$CH(CH_3)CH_2$
XXXVIII	N-(2-Diethylamino-2-methylethyl)-3,5-dimethylbenzamide	»	$CH_2CH(CH_3)$
XXXIX	N-(2-Diethylamino-1,2-dimethylethyl)-3,5-dimethylbenzamide	»	$CH(CH_3)CH(CH_3)$
XL	N-(3-Diethylamino-2,2-dimethylpropyl)-3,5-dimethylbenzamide	»	$CH_2C(CH_3)_2CH_2$
XLI	N-(2-Diethylaminoethyl)-2,3,4-trimethylbenzamide	2,3,4-$(CH_3)_3C_6H_2$	CH_2CH_2
XLII	N-(3-Diethylaminopropyl)-2,3,4-trimethylbenzamide	»	$CH_2CH_2CH_2$
XLIII	N-(2-Dimethylaminoethyl)-2,3,4-trimethylbenzamide	»	CH_2CH_2
XLIV	N-(2-Diethylamino-1-methylethyl)-2,3,4-trimethylbenzamide	»	$CH(CH_3)CH_2$
XLV	N-(2-Diethylamino-2-methylethyl)-2,3,4-trimethylbenzamide	»	$CH_2CH(CH_3)$
XLVI	N-(2-Diethylaminoethyl)-2,3,5-trimethylbenzamide	2,3,5-$(CH_3)_3C_6H_2$	CH_2CH_2
XLVII	N-(3-Diethylaminopropyl)-2,3,5-trimethylbenzamide	»	$CH_2CH_2CH_2$
XLVIII	N-(2-Diethylaminoethyl)-2,3,6-trimethylbenzamide	2,3,6-$(CH_3)_3C_6H_2$	CH_2CH_2
XLIX	N-(3-Diethylaminopropyl)-2,3,6-trimethylbenzamide	»	$CH_2CH_2CH_2$
L	N-(2-Dimethylaminoethyl)-2,3,6-trimethylbenzamide	»	CH_2CH_2
LI	N-(2-Diethylamino-1-methylethyl)-2,3,6-trimethylbenzamide	»	$CH(CH_3)CH_2$

light petroleum b. p. 40°—60°; Pet., petroleum ether b. p. 60°—85°; *Iso*prop. eth., *iso*propyl ether.

		Yield %	B. p.		n_D^{25}	M.p., °C	Solvent for recrystallization	Equivalent weight [a]	
$_2$	Empirical formula		°C, uncorr.	Pressure mm Hg		corr.		Calc.	Found
H$_5$	$C_{14}H_{22}N_2O$	63	132—134	0.10	1.5209	—	—	234.3	234
»	$C_{15}H_{24}N_2O$	76	167	0.05	1.5183	—	—	248.4	248
»	$C_{15}H_{24}N_2O$	89	135—137	0.10	1.5125	—	—	248.4	248
»	$C_{15}H_{24}N_2O$	95	146	0.10	1.5168	—	—	248.4	248
»	$C_{16}H_{26}N_2O$	21	123—124	0.20	—	52	L.pet.	262.4	262
»	$C_{16}H_{26}N_2O$	22	—	—	—	111.5—112	L.pet.-*Iso*prop. eth.	262.4	264
»	$C_{17}H_{28}N_2O$	83	152	0.08	1.5132	—	—	276.4	277
»	$C_{14}H_{22}N_2O$	75	163—165	0.10	1.5251	—	—	234.3	235
»	$C_{15}H_{24}N_2O$	90	156—158	0.10	1.5230	—	—	248.4	249
»	$C_{15}H_{24}N_2O$	89	142—143	0.10	—	50—51	—	248.4	248
»	$C_{15}H_{24}N_2O$	90	164	0.15	1.5200	—	—	248.4	249
»	$C_{16}H_{26}N_2O$	85	151—155	0.30	1.5176 [b]	(66—69)	—	262.4	261
»	$C_{17}H_{28}N_2O$	85	155	0.10	1.5177	—	—	276.4	278
»	$C_{14}H_{22}N_2O$	71	140—141	0.15	1.5268	36—37	—	234.3	234
»	$C_{15}H_{24}N_2O$	85	155—157	0.15	1.5253	—	—	248.4	248
»	$C_{15}H_{24}N_2O$	85	—	—	—	75—76	L.pet.-*Iso*prop. eth.	248.4	248
»	$C_{15}H_{24}N_2O$	93	149—150	0.10	—	62—63	—	248.4	248
»	$C_{16}H_{26}N_2O$	87	147—149	0.30	1.5190 [b]	(109—110)	—	262.4	262
»	$C_{17}H_{28}N_2O$	83	156—158	0.10	1.5193 [b]	38—39	—	276.4	277
»	$C_{15}H_{24}N_2O$	74	154	0.15	1.5220	—	—	248.4	249
»	$C_{16}H_{26}N_2O$	84	152—153	0.12	1.5197	—	—	262.4	263
»	$C_{16}H_{26}N_2O$	69	—	—	—	74—75	Pet.-*Iso*prop. eth.	262.4	262
»	$C_{16}H_{26}N_2O$	78	157	0.10	1.5190	—	—	262.4	262
»	$C_{15}H_{24}N_2O$	81	145—147	0.15	1.5202	—	—	248.4	249
»	$C_{16}H_{26}N_2O$	77	164	0.15	1.5184	—	—	262.4	262
»	$C_{16}H_{26}N_2O$	85	149	0.15	1.5127	—	—	262.4	262
»	$C_{16}H_{26}N_2O$	89	151	0.15	1.5172	—	—	262.4	262
»	$C_{15}H_{24}N_2O$	73	163—167	0.05	1.5189 [b]	49.5	—	248.4	250
»	$C_{16}H_{26}N_2O$	78	—	—	—	78—79	Pet.-*Iso*prop. eth.	262.4	265
»	$C_{16}H_{26}N_2O$	85	150	0.15	1.5113	—	—	262.4	262
»	$C_{16}H_{26}N_2O$	91	152	0.15	1.5152	23—24	—	262.4	262
»	$C_{18}H_{30}N_2O$	68	—	—	—	74—74.5	Pet.	290.4	289
»	$C_{15}H_{24}N_2O$	92	160—162	0.15	1.5299 [b]	65	—	248.4	248
»	$C_{16}H_{26}N_2O$	85	171	0.12	1.5280	—	—	262.4	263
»	$C_{16}H_{26}N_2O$	91	162	0.15	1.5241	—	—	262.4	261
»	$C_{16}H_{26}N_2O$	95	161—163	0.14	1.5250	—	—	262.4	261
»	$C_{15}H_{24}N_2O$	90	148—151	0.12	1.5250	—	—	248.4	249
»	$C_{16}H_{26}N_2O$	90	170—173	0.10	1.5182	—	—	262.4	261
»	$C_{16}H_{26}N_2O$	90	177—180	0.10	1.5195	—	—	262.4	262
»	$C_{17}H_{28}N_2O$	84	158—160	0.30	1.5173 [b]	(111—112)	—	276.4	277
»	$C_{18}H_{30}N_2O$	97	158—160	0.10	1.5174	—	—	290.4	292
»	$C_{16}H_{26}N_2O$	93	154	0.10	1.5246	—	—	262.4	259
»	$C_{17}H_{28}N_2O$	95	165—166	0.10	1.5227 [b]	37—38	—	276.4	273
H$_3$	$C_{14}H_{22}N_2O$	85	152—154	0.12	1.5325 [b]	71—72	—	234.3	234
$_2$H$_5$	$C_{17}H_{28}N_2O$	86	159—160	0.10	1.5169 [b]	38—39	—	276.4	273
»	$C_{17}H_{28}N_2O$	69	160	0.10	1.5228 [b]	35	—	276.4	277
»	$C_{16}H_{26}N_2O$	98	—	—	—	51—52	[c] —	262.4	263
»	$C_{17}H_{28}N_2O$	95	—	—	—	64—65	L.pet.-*Iso*prop. eth.	276.4	278
»	$C_{16}H_{26}N_2O$	87	—	—	—	75.5	Pet.-*Iso*prop. eth.	262.4	264
»	$C_{17}H_{28}N_2O$	72	—	—	—	84	» »	276.4	277
H$_3$	$C_{14}H_{22}N_2O$	61	—	—	—	96—97	» »	234.3	236
$_2$H$_5$	$C_{17}H_{28}N_2O$	87	—	—	—	96— 97	» »	276.4	277

Table 2 cont.

LII	N-(2-Diethylamino-2-methylethyl)-2,3,6-trimethylbenzamide	$2,3,6\text{-}(CH_3)_3C_6H_2$	$CH_2CH(CH_3)$
LIII	N-(2-Diethylaminoethyl)-2,4,5-trimethylbenzamide	$2,4,5\text{-}(CH_3)_3C_6H_2$	CH_2CH_2
LIV	N-(3-Diethylaminopropyl)-2,4,5-trimethylbenzamide	»	$CH_2CH_2CH_2$
LV	N-(2-Dimethylaminoethyl)-2,4,5-trimethylbenzamide	»	CH_2CH_2
LVI	N-(2-Diethylamino-1-methylethyl)-2,4,5-trimethylbenzamide	»	$CH(CH_3)CH_2$
LVII	N-(2-Diethylamino-2-methylethyl)-2,4,5-trimethylbenzamide	»	$CH_2CH(CH_3)$
LVIII	N-(2-Diethylaminoethyl)-2,4,6-trimethylbenzamide [d]	$2,4,6\text{-}(CH_3)_3C_6H_2$	CH_2CH_2
LIX	N-(3-Diethylaminopropyl)-2,4,6-trimethylbenzamide	»	$CH_2CH_2CH_2$
LX	N-(2-Dimethylaminoethyl)-2,4,6-trimethylbenzamide	»	CH_2CH_2
LXI	N-(2-Diethylamino-1-methylethyl)-2,4,6-trimethylbenzamide	»	$CH(CH_3)CH_2$
LXII	N-(2-Diethylamino-2-methylethyl)-2,4,6-trimethylbenzamide	»	$CH_2CH(CH_3)$
LXIII	N-(2-Diethylaminoethyl)-3,4,5-trimethylbenzamide	$3,4,5\text{-}(CH_3)_3C_6H_2$	CH_2CH_2
LXIV	N-(3-Diethylaminopropyl)-3,4,5-trimethylbenzamide	»	$CH_2CH_2CH_2$

[a] Titration of the base in 30 % ethanol with 0.1 N HCl; mixed indicator methylene blue — methyl red.

[b] Supercooled.

[c] Purified *via* the hydrochloride, see Table 3.

2,3,4-Trimethylbenzoic acid was synthesized from 2,6-dimethylaniline, which was first converted to 2,6-dimethyliodobenzene by means of a Sandmeyer reaction [25]. 2,6-Dimethyliodobenzene was converted to hemimellitene by treatment of the corresponding Grignard reagent with dimethyl sulfate according to a general method [26]. The hemimellitene was brominated to form 4-bromohemimellitene [27] from which the acid was obtained by carbonation [15] of the Grignard reagent.

2,3,5-Trimethylbenzoic acid was synthesized by oxidation of *iso*durene as is described under *3,4,5-trimethylbenzoic acid (cf.* below). The 2,3,5-trimethylbenzoic acid was also made by nitration of pseudocumene, and the 5-nitropseudocumene thus formed was then reduced with iron and acetic acid [5b] to pseudocumidine. This was brominated in concentrated hydrochloric acid [16,27] giving 2-bromo-3,4,6-trimethylanilinium chloride, which was then de-aminated by treatment with ethyl nitrite and concentrated sulfuric acid in ethanol solution [29]. The acid was obtained from the bromo compound by carbonation [15] of the corresponding Grignard reagent; yield 33 %; m. p. 126°—127°. (Jannasch and Weiler [14] state m. p. 127° for this acid.)

2,3,6-Trimethylbenzoic acid was made in a good yield from pseudocumene according to Smith and Stanfield [12].

2,4,5-Trimethylbenzoic acid was obtained by partial oxidation of durene with dilute nitric acid [30].

2,4,6-Trimethylbenzoic acid was prepared from mesitylene by bromination [23] and subsequent carbonation [15] of the corresponding Grignard reagent.

*3,4,5-Trimethylbenzoic acid. Iso*durene, 50 g (0.37 mole), was added to 225 ml of water and 75 ml of nitric acid (d = 1.40; 1.15 mole) and the mixture was refluxed for 6 h. After cooling, the reaction products were taken up in ether, which was then extracted with potassium carbonate solution. The oily residue remaining after evaporation of the ether was subjected to another oxidation with nitric acid. The potassium carbonate solutions obtained from the two runs were combined and acidified. After cooling to 0°, the aqueous layer was decanted off and rejected. The residue was dissolved in 100 ml of glacial acetic acid, 5 g of zinc powder were added, and the mixture boiled for 30 min. Water, 700 ml, was added and the aqueous solution containing acetic acid was decanted off from the sticky yellow residue, which was dissolved in 375 ml of ethanol. To this solution, dry hydrogen chloride was introduced at a "fairly rapid rate" [31] for 30 min. A large excess of water was added and the esters formed were taken up in ether, which was then washed three times with dilute sodium carbonate solution. The ether was evaporated, and the residual esters were saponified on the steam bath with 5 % potassium hydroxide in

Table 2 cont.

I_5	$C_{17}H_{28}N_2O$	88	160–162	0.12	1.5163 [b]	39– 40	—	276.4	276
	$C_{16}H_{26}N_2O$	71	—	—	—	62	Pet.-*Iso*prop. eth.	262.4	263
	$C_{17}H_{28}N_2O$	81	—	—	—	73– 74	» »	276.4	278
I_3	$C_{14}H_{22}N_2O$	68	—	—	—	80– 81	» »	234.3	236
I_5	$C_{17}H_{28}N_2O$	93	155–157	0.12	—	69	—	276.4	274
	$C_{17}H_{28}N_2O$	96	168–171	0.10	1.5205 [b]	44– 45	—	276.4	276
	$C_{16}H_{26}N_2O$	70	150–151	0.10	—	71– 72	Pet.-*Iso*prop. eth.	262.4	263
	$C_{17}H_{28}N_2O$	76	—	—	—	67– 68	» »	276.4	277
$_3$	$C_{14}H_{22}N_2O$	61	—	—	—	86– 87	» »	234.3	236
I_5	$C_{17}H_{28}N_2O$	85	164	0.10	1.5063 [b]	52– 53	—	276.4	275
	$C_{17}H_{28}N_2O$	84	165–167	0.10	—	46– 48	—	276.4	277
	$C_{16}H_{26}N_2O$	95	—	—	—	74– 75	[c] —	262.4	262
	$C_{17}H_{28}N_2O$	97	—	—	—	53– 54	[c] —	276.4	276

[d] During the course of this work compound LVIII was synthesized by Hach *et al.*[8] and studied pharmacologically by Koelzer and Wehr [9]. Hach *et al.*[8] describe the compound as melting at 64°. Moreover, they did not succeed in preparing the hydrochloride of LVIII. (*cf.* Table 3.)

[e] *cf.* p. 1632.

ethanol. After precipitation of the "*iso*durylic" acids with dilute hydrochloric acid, they were dissolved in thionyl chloride. The solution was refluxed for 5 h, and after removing excess thionyl chloride the residue was distilled at 10 mm Hg. A fraction boiling at 120°–135° was collected and hydrolyzed at room temperature with 30 % sodium hydroxide. The mixture of acids was precipitated and dissolved in an equivalent amount of 10 % sodium hydroxide. The solution was washed with ether, and an excess of saturated barium chloride solution added. A voluminous precipitate separated from the solution, and was collected. The acid, liberated from this slightly soluble barium salt, is 3,4,5-trimethylbenzoic acid; m. p. 215°; yield (based on 450 g, *i. e.* 3.36 mole of *iso*durene): 7.3 g (0.044 mole, 1.3 %); recorded m. p. [13,14] 215°. The filtrate which was separated from the barium salt precipitate (*cf.* above) gave another acid, which after several recrystallizations from different solvents (*e. g.* ethanol, light petroleum) melted at 108°. This must be impure 2,3,5-trimethylbenzoic acid since dry distillation with soda lime gave an oil, which after sulfonation yielded a sulfonamide of m. p. 172°–174°. Very probably this compound was identical with pseudocumenesulfonamide with a recorded m. p. at 174° [13,32] *.

The yield of acid was 4.8 g (0.030 mole, 0.9 %). (Melting point of pure 2,3,5-trimethylbenzoic acid, *cf.* above.) (Found: equiv. wt.** 161. Calc. for $C_{10}H_{12}O_2$: 164.)

3,4,5-Trimethylbenzoic acid was also obtained by carbonation of the Grignard reagent of 5-bromohemimellitene, this compound being prepared from 3,4,5-trimethylaniline.

3,4,5-Trimethylaniline ***. 3,5-Dimethylaniline, 47 g (0.39 mole), was dissolved in 30 ml of 37 % HCl (0.36 mole) and 200 ml of water. After cooling to 0°, 75 ml of 37 % (1.0 mole) formaldehyde solution was added under stirring. The temperature was kept at 0° for 60 min and was then allowed to reach 20°. After adding a large excess of sodium carbonate solution, the orange coloured sludge was filtered and the collected solid was dried at 80°. The resulting yellow powder, after mixing with 60 g (0.81 mole) of calcium hydroxide, was dry distilled in a wide necked distillation apparatus, heated by means of a metal bath which was kept at 500°. A semi-solid distillate formed which was taken up in a mixture of ether and 20 % hydrochloric acid. Following removal of the ether phase,

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* No mixed melting point could be determined because of lack of substance.

** Titration of the acid with NaOH, using phenolphtalein as an indicator.

*** This compound has been obtained previously but in a very low yield [33,34]. The method applied here is a modification of one described by Barclay *et al.* [18], and has given a relatively good yield.

Table 3. Data of acid chlorides synthesized in this investigation.

Acyl radical	B. p.		M. p.	n_{D}^{25}	Yield	Cl	
	°C, uncorr.	Pressure mm Hg	°C, corr.		%	Calc.	Found
2,3-Dimethylbenzoyl	122—123	15	+2	1.5530	63	21.0	20.9
2,5-Dimethylbenzoyl	112—114	13	—	1.5490	81	21.0	21.0
3,4-Dimethylbenzoyl	122	10	−3— −1	1.5563	78	21.0	21.0
2,3,4-Trimethylbenzoyl	138—140	14	—	1.5614	84	19.5	19.3
2,3,5-Trimethylbenzoyl	126—127	10	35—37	1.5515[a]	65	19.5	19.3
2,3,6-Trimethylbenzoyl	116—117	10	—	1.5295	85	19.5	19.1
2,4,5-Trimethylbenzoyl	142—145	15	20—21	1.5595	85	19.5	19.5
3,4,5-Trimethylbenzoyl	137—139	10	44—46	—	86	19.5	19.6

[a] Measurement made on supercooled compound.

the base was liberated from the aqueous acid solution and distilled. Yield of 3,4,5-trimethylaniline boiling at 238°—248° was 11.3 g (0.084 mole, 22 %); m. p. 68°—72°. Acetyl derivative recrystallized from methanol; m. p. 163°—164°. (Recorded melting point [33,34] of base is 76°, and of acetyl derivative 164°.)

5-Bromohemimellitene. 3,4,5-Trimethylaniline was converted to 5-bromohemimellitene by a Sandmeyer reaction [17]. This compound appeared as an orange coloured oil; b. p. 109°—114°/12 mm Hg; n_{D}^{25} 1.5560; yield 34 % (*cf.* Ref.[35]). The low yield is probably due to instability, even at 0°, of the diazonium salt. 3,4,5-Trimethylbenzoic acid was obtained from the bromo compound by carbonation [15] of the corresponding Grignard reagent; yield 64 %; m. p. 214° (*cf.* above).

Acid chlorides. The acids were converted to the corresponding acid chlorides by treatment with thionyl chloride and subsequent distillation [36]. In Table 3 the physical constants, yields, and analyses are given for those acid chlorides which have not been described previously.

1-Amino-2-dimethylaminoethane was prepared by a Mannich reaction between dimethylammonium chloride, paraformaldehyde, and cyanide ion [37] and subsequent reduction of the condensation product according to a general method with $LiAlH_4$ [19]: b. p. 103°—108°; yield 36 % (*cf.* Ref.[37]).

1-Amino-2-diethylaminoethane was available commercially.

1-Amino-3-diethylaminopropane has been obtained by cyanoethylation of diethylamine [38], and subsequent reduction of the cyano group with $LiAlH_4$ [19] (*cf.* Refs.[11,38]).

2-Amino-1-diethylaminopropane. From diethylaminoacetone the oxime was prepared, the general method given by Vogel [39] being followed; yield 80 %; b. p. 98°—100°/10 mm Hg; m. p. 40°. (Found: equiv. wt.* 143. Calc. for $C_7H_{16}N_2O$: 144.2.) The desired amine was obtained from the oxime in accordance with a method given for the reduction of nitriles with $LiAlH_4$ [19]; yield 53 % (*cf.* Ref.[11]).

1-Amino-2-diethylaminopropane was prepared *via* the nitrile [40] (Mannich reaction), reduction being carried out with $LiAlH_4$ [19] (*cf.* Ref.[11]).

2-Amino-3-diethylaminobutane was made [11] by bromination of ethyl methyl ketone, and subsequent separation of the isomeric bromo ketones [41]. The resulting 3-bromo-2-butanone was treated with diethylamine to form 3-diethylamino-2-butanone; this was converted to the corresponding oxime which was then reduced with $LiAlH_4$ [19]; yield 58 % (*cf.* Ref.[11]).

*1-Amino-3-diethylamino-2,2-dimethylpropane. Iso*butyraldehyde, paraformaldehyde, and diethylammonium chloride were condensed by a Mannich reaction to diethylamino-

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* Titration with 0.1 N HCl in 30 % ethanol; mixed indicator methylene blue — methyl red.

Table 4. Chemical data of hydrochlorides prepared. Abbreviations for solvents: *iso*Prop. eth., di-*iso*propyl ether; *iso*Prop.-ol, *iso*propanol; Me.am.ket., methyl amyl ketone; Me.et.ket., methyl ethyl ketone.

Compound *B* · *HCl*		M.p., °C	Solvent for recrystallization	Analyses Cl	
B	Empirical formula	corr.		Calc.	Found
I	$C_{14}H_{23}ClN_2O$	105	*iso*Prop.eth.-*iso*Prop.-ol	13.1	12.9
V*b*	$C_{16}H_{27}ClN_2O$	165–166	» »	11.9	11.8
VII	$C_{14}H_{23}ClN_2O$	106	» »	13.1	13.0
XIII	$C_{14}H_{23}ClN_2O$	99—100	» »	13.1	13.1
XIX	$C_{15}H_{25}ClN_2O$	121—122	» »	12.4	12.3
XXIII	$C_{15}H_{25}ClN_2O$	122—123	» »	12.4	12.3
XXVII	$C_{15}H_{25}ClN_2O$	106—107	» »	12.4	12.3
N-(2-Diethylaminoethyl)-2,6-dimethylbenzamide [a]	$C_{15}H_{25}ClN_2O$	139—140	» »	12.4	12.4
XXXII	$C_{15}H_{25}ClN_2O$	150—151	» »	12.4	12.4
XXXVI	$C_{15}H_{25}ClN_2O$	117—118	» »	12.4	12.4
N-(3-Diethylaminopropyl)-3,5-dimethylbenzamide [a]	$C_{16}H_{27}ClN_2O$	117—118	» »	11.9	11.9
XXXVIII	$C_{16}H_{27}ClN_2O$	139—140	» »	11.9	11.8
XLI	$C_{16}H_{27}ClN_2O$	154—155	» »	11.9	11.9
XLVI	$C_{16}H_{27}ClN_2O$	139—140	» »	11.9	11.8
XLVIII	$C_{16}H_{27}ClN_2O$	138—139	» »	11.9	11.9
XLIX	$C_{17}H_{29}ClN_2O$	142—143	» »	11.3	11.2
L	$C_{14}H_{23}ClN_2O$	163—164	» »	13.1	13.1
LIII	$C_{16}H_{27}ClN_2O$	132—133	» »	11.9	11.8
LV	$C_{14}H_{23}ClN_2O$	171	» »	13.1	12.9
LVIII	$C_{16}H_{27}ClN_2O$	114—115	Me.am.ket.-*iso*Prop.-ol	11.9	11.8
LX	$C_{14}H_{23}ClN_2O$	152—154	*iso*Prop. eth.-*iso*Prop.-ol	13.1	13.1
LXIII	$C_{16}H_{27}ClN_2O$	207	Me.et.ket.-*iso*Prop.-ol	11.9	11.9
LXIV	$C_{17}H_{29}ClN_2O$	175	» »	11.3	11.5

[a] For the preparation of these bases see Löfgren and Stoffel [11].

pivalaldehyde [20]. From this aldehyde the oxime was prepared [39]; yield 89 %; b. p. 132°—133°/22 mm Hg; n_{D}^{20} 1.4649. Without further characterization this compound was reduced according to general methods by (a) sodium in ethanol [42] (b) $LiAlH_4$ [19]. The desired amine was obtained in a yield of 42 % and 45 %, respectively; b. p. 105°/52 mm Hg; n_{D}^{20} 1.4442. (Found: equiv. wt.* 78.8. Calc. for $C_9H_{22}N_2$: 79.1.)

Preparation of dialkylaminoalkylamides of methyl substituted benzoic acids. The appropriate dialkylaminoalkylamine (0.040 mole) was dissolved in 50 ml of highly purified ether in a 300 ml three necked round bottomed flask, equipped with a sealed Hershberg stirrer, funnel, and a condenser ($CaCl_2$). The desired acid chloride (0.025 mole) was dissolved in 50 ml of ether. Stirring was started, and the acid chloride solution was added to the amine solution during a period of 30 min, agitation being maintained for another 2 h. Then 100 ml of 2 N NaOH were added. The ethereal layer was separated off and washed twice with water. After drying (Na_2SO_4), the ether was driven off and the base was recrystallized or distilled. Characterization of the compounds is found in Table 2.

In order to study the same reaction but with the reactants in another proportion an experiment was carried out using 3,5-dimethylbenzoyl chloride and 1-amino-2-diethyl-

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* Titration with $HClO_4$ in glacial acetic acid; indicator BZL-BLUE (Ciba) [43].

aminoethane in the ratio 1:1.1; the yield of N-(2-diethylaminoethyl)3,5-dimethylbenzoyl chloride was 53 %. When using the molar proportion 1:1.6 as is described in the general method above the yield of the same product was 90 %.

Hydrochlorides were prepared from the bases by dissolving them in dry ether and adding an appropriate amount of dry hydrogen chloride in dry ether. The colourless microcrystalline precipitates were recrystallized from suitable solvents. Melting points, solvents for recrystallization, and analytical data are found in Table 4.

Separation of the racemates of N-(2-diethylamino-1,2-dimethylethyl)2-methylbenzamide (V). From the oily crude base which remained after evaporation of the ether, crystals slowly deposited, at room temperature resulting in a semi-solid mass. The two phases were separated from each other according to the excellent method described by Morton [44] and Hicks [45]. The solid component was recrystallized twice from *iso*propyl ether containing light petroleum. The separated oil was then distilled. The oil is called V*a* and the solid V*b*. For further characterization *the picrate of V*a was made, and after two recrystallizations from *iso*propanol and one from dioxane, yellow rhombic plates of m. p. 146° were obtained. (Found: C 54.0; H 6.22; N 14.24; O 26.06. Calc. for $C_{22}H_{29}N_5O_8$: C 53.8; H 5.95; N 14.25; O 26.04.) The salt (2 g) was dispersed in 50 ml of ethanol and 175 ml of water. To the suspension thus formed, 150 ml * of moist Amberlite IRA 400 anion exchanger (chloride form) was added, the mixture being stirred for 6 h. From the colourless solution the base was liberated and taken up in ether. The solvent was evaporated leaving V*a* as a crystalline solid which was recrystallized once from light petroleum. Characterizations of the bases are found in Table 2.

*Di-picrate of V*b; needles from *iso*propanol of m. p. 126°. (Found: C 47.0; H 4.47; N 15.75; O 32.60. Calc. for $C_{28}H_{32}N_8O_{15}$: C 46.7; H 4.48; N 15.55; O 33.30.)

N-(2-Diethylamino-1,2-dimethylethyl)3-methylbenzamide (XI), N-(2-diethylamino-1,3-dimethylethyl)4-methylbenzamide (XVII), and N-(2-diethylamino-1,2-dimethylethyl)-3,5-dimethylbenzamide (XXXIX). After distillation of these bases, all of them appeared as semi-solid mixtures of crystals and oil. The refractive indices of these bases, given in Table 2, refer to the super-cooled mixtures. A small portion of each of the three bases was left on porous plate for three days. The crystals were scraped off and the melting points determined. These melting points are given in brackets in Table 2 (concerning theory see Morton [44]).

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* A moist ion exchanger is most accurately measured by volume.

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