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Studies on Local Anesthetics XIX *

Local Anesthetic Acitivity of N-(Dialkylaminoalkyl)benzamides. Physicochemical Measurements on N-(Dialkylaminoalkyl)benzamides and Benzoic Acids

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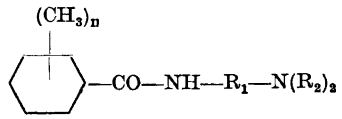
Local anesthetic properties and LD50 values were evaluated for 22 N-(dialkylaminoalkyl)benzamides. Ionization constants were determined for 26 N-(dialkylaminoalkyl)benzamides, for benzoic acid and all mono-, di-, and trimethylbenzoic acids. Ultraviolet spectra were measured on 15 N-(dialkylaminoalkyl)benzamides, 5 dimethyl-, and all trimethylbenzoic acids. The oscillator strength of these compounds for the absorbtion band at 220–240 mμ was determined and a correlation between these values and the ionization constants was found. Infrared spectra were recorded for the two racemates of N-(2-diethylamino-1,2-dimethylethyl)-2-methylbenzamide.

In a previous paper [1] the syntheses of sixty-five N-(dialkylaminoalkyl)-benzamides were reported. Variations were achieved by introducing one, two, or three methyl groups in the benzene nucleus, by using different alkylene chains (R_1) between the nitrogen atoms, and by attaching methyl or ethyl groups to the terminal nitrogen atom, the general structure being defined by the formula:



n=0, 1, 2, or 3.

A representative selection of these benzamides has been subjected to pharmacological tests, *i.e.* toxicity measurements and determinations of their local anesthetic properties. Further, a report is given on the thermodynamic ionization constants of these compounds. Since it is of interest to compare the ionization constants of the amides and the corresponding benzoic acids,

* For paper XVIII of this series see Lüning [1].

the latter compounds were also included in the measurements. Further, an investigation, *i.e.* determination of the oscillator strength, was made on the ultraviolet spectra of the amides and the acids. Infrared spectra of the two racemates of a compound containing two asymmetric carbon atoms are presented. Finally, a comparison is made between the ionization constants and the oscillator strengths.

EVALUATION OF LOCAL ANESTHETIC ACTIVITY AND LD50

The compounds were tested for their local anesthetic action on the rabbit cornea, and compared with Xylocaine ®, the technique of Wiedling [2] being followed (*cf.* also Löfgren and Tegner [3]). Xylocaine and all the other compounds were used as solutions of their hydrochlorides, made isotonic by the aid of sodium chloride. As a measure of the potency, *relative activity* (RA) was used, *i.e.* the quantity which is obtained by dividing the molarity of a standard Xylocaine solution by the molar concentration of the compound in question which gives the same duration of anesthesia as that of the Xylocaine standard. The molarity of the latter was 0.0738 (= 2 % Xylocaine · HCl solution). Before measuring the duration of anesthesia, both the solution of the actual compound and that of Xylocaine, were adjusted to the same pH, *i.e.* 6.5 *. In the toxicity investigations the LD50 values were obtained from subcutaneous injections in white mice and calculated (a) as grams of the base per kilogram of body weight and (b) as moles per kilogram of body weight ("molar" LD50 value). For these determinations, the bases were dissolved in a mixture of 1,2-propylene glycol and water (1:1, vol/vol) and the "pH" adjusted to about 6.5 by the addition of hydrochloric acid.

The ratio of the *molar* LD50 value of Xylocaine to the corresponding value for one of the other compounds is called the *relative toxicity* (RT) of the compound. For the quotient RA/RT the term *anesthetic index* (Q) will be used (*cf.* Löfgren *et al.*[5]). The *relative latency* (RL) is obtained by dividing the latency time for a solution of the compound to be tested by the latency time for a standard Xylocaine solution having the same duration of anesthesia as the test solution. To determine the RA value of a compound, 10—30 animals were used. In general, the maximum error in the RA values is about 20 %. The error in the RT values is less. The results of the pharmacological measurements are collected in Table 1. The numbering of the compounds is the same as that in the previous paper [1] where the chemical properties of the compounds are presented. The following observations can be made on the relationship between the chemical constitution and the pharmacological properties of the material.

A. From Table 1 is found that no systematic correlation can be detected between the local anesthetic activity or the toxicity and the number and positions of methyl groups in the aromatic residue of N-(dialkylaminoalkyl)-benzamides.

* Because of the low buffering effect of the solution of the hydrochloride at the pH used, and the relatively high buffering capacity of the body fluids, the pH value of the solution need not be very accurately measured.

Table 1. Pharmacolocical properties of N-(dialkylaminoalkyl)-benzamides.

Compound		LD50		RT [e]	RA [e]	RL [e]	Q[e]=RA/RT
Number [a]	Name	g/kg	mole/kg 10^{-3}				
I	N-(2-Diethylaminoethyl)-2-methylbenzamide	0.45	1.92	0.76	0 [f]	∞	—
VII	N-(2-Diethylaminoethyl)-3-methylbenzamide	0.46	1.97	0.74	0.4	4.5	0.5
XIII	N-(2-Diethylaminoethyl)-4-methylbenzamide	0.44	1.88	0.77	0 [f]	∞	—
XIX	N-(2-Diethylaminoethyl)-2,3-dimethylbenzamide	0.52	2.10	0.69	0.2	1.3	0.3
XXIII	N-(2-Diethylaminoethyl)-2,4-dimethylbenzamide	0.35	1.41	1.03	0.7	3	0.7
XXVII	N-(2-Diethylaminoethyl)-2,5-dimethylbenzamide	0.40	1.62	0.90	0.4	2.6	0.4
A	N-(2-Diethylaminoethyl)-2,6-dimethylbenzamide [b]	0.57	2.29	0.63	0.5	1.2	0.8
XXXII	N-(2-Diethylaminoethyl)-3,4-dimethylbenzamide	0.36	1.45	1.00	0.3	2.1	0.3
XXXVI	N-(2-Diethylaminoethyl)-3,5-dimethylbenzamide	0.34	1.35	1.07	0.7	2.7	0.7
XLI	N-(2-Diethylaminoethyl)-2,3,4-trimethylbenzamide	0.32	1.22	1.19	0.6	9.0	0.5
XLVI	N-(2-Diethylaminoethyl)-2,3,5-trimethylbenzamide	0.19	0.72	2.0	1.0	3.0	0.5
XLVIII	N-(2-Diethylaminoethyl)-2,3,6-trimethylbenzamide	0.33	1.26	1.15	0.7	3.0	0.6
LIII	N-(2-Diethylaminoethyl)-2,4,5-trimethylbenzamide	0.25	0.95	1.53	0.9	2.3	0.6
LVIII	N-(2-Diethylaminoethyl)-2,4,6-trimethylbenzamide	0.25	0.95	1.53	1.2	3.5	0.8
LXIII	N-(2-Diethylaminoethyl)-3,4,5-trimethylbenzamide	0.29	1.00	1.45	0.5	4.5	0.3
V*a*	N-(2-Diethylamino-1,2-dimethylethyl)-2-methylbenzamide [c]	0.54	2.06	0.70	0.6	1.5	0.9
V*b*	N-(2-Diethylamino-1,2-dimethylethyl)-2-methylbenzamide [c]	0.43	1.64	0.88	0.7	3	0.8
B	N-(3-Diethylaminopropyl)-2,6-dimethylbenzamide [b]	~0.9	~3.4	0.4	0 [f]	∞	—
C	N-(2-Diethylamino-1-methylethyl)-2,6-dimethylbenzamide [b]	0.22	0.84	1.7	2.1	—	1.2
D	N-(2-Diethylamino-2-methylethyl)-2,6-dimethylbenzamide [b]	0.23	0.88	1.6	1.8	—	1.1
E	N-(2-Diethylamino-1,2-dimethylethyl)-2,6-dimethylbenzamide [b,d]	0.075	0.27	5.2	3.4	—	0.7
XXXI	N-(3-Diethylamino-2,2-dimethylpropyl)-2,6-dimethylbenzamide	0.25	0.86	1.7	3.2	3	1.9
F	N-(3-Diethylaminopropyl)-3,5-dimethylbenzamide [b]	0.71	2.71	0.53	0.88	6	1.7
XXXVII	N-(2-Diethylamino-1-methylethyl)-3,5-dimethylbenzamide	0.30	1.15	1.26	0.6	3	0.5
XXXVIII	N-(2-Diethylamino-2-methylethyl)-3,5-dimethylbenzamide	0.22	0.84	1.7	1.0	1	0.6
XXXIX	N-(2-Diethylamino-1,2-dimethylethyl)-3,5-dimethylbenzamide [d]	0.28	1.00	1.45	1.5	2.4	1.0
XL	N-(3-Diethylamino-2,2-dimethylpropyl)-3,5-dimethylbenzamide	0.20	0.70	2.1	1.6	1	0.8
LX	N-(2-Dimethylaminoethyl)-2,4,6-trimethylbenzamide	0.62	2.65	0.55	0 [f]	∞	—
Xylocaine	α-Diethylamino-2,6-dimethylacetanilide [g]	0.34	1.45	1.0	1.0	1.0	1.0

[a] The numbering is chosen in accordance with that given for the same compounds in Lüning [1].
[b] The values given for these compounds are taken from Löfgren *et al.*[4]
[c] These are racemates of the same compound, *cf.* Lüning [1].
[d] Measurements made on mixtures of racemates obtained in the synthesis.
[e] Regarding definitions of these quantities see p. 322.
[f] The compounds, the RA-values of which are denoted as 0, give no measurable anesthesia at a concentration of 0.0738 mole/litre.
[g] See Löfgren [8].

Table 2. Change in relative anesthetic activity (RA), relative toxicity (RT), and anesthetic index for variations in the "intermediate chain" R_1 and positions of methyl groups in Ar (*cf.* formula).

$$Ar-CO-NH-R_1-N(C_2H_5)_2$$

Ar = 2,6-dimethylphenyl or 3,5-dimethylphenyl.

$$R_1{}^a = \begin{cases} -CH_2-CH_2- & (1), \\ -CH_2-CH_2-CH_2- & (2), \\ -CH(CH_3)-CH_2- & (3), \\ -CH_2-CH(CH_3)- & (4), \\ -CH(CH_3)-CH(CH_3)- & (5), \\ \text{or } -CH_2-C(CH_3)_2-CH_2- & (6). \end{cases}$$

Factor f_A, f_T and f_Q indicate the change in RA, RT, and Q respectively.

Compound			RA	f_A	RT	f_T	$Q\left(=\frac{RA}{RT}\right)$	f_Q
No.	Ar	R_1						
A. Change of R_1 from (1) to (2).								
A[b]	2,6-dimethylphenyl	(1)	0.5	0	0.6	0.7	0.8	0
B[b]	»	(2)	0		0.4		0	
XXXVI	3,5-dimethylphenyl	(1)	0.7	1.3	1.1	0.4	0.7	2.4
F[b]	»	(2)	0.9		0.5		1.7	
B. Change of R_1 from (1) to (3).								
A[b]	2,6-dimethylphenyl	(1)	0.5	4.2	0.6	2.8	0.8	1.5
C[b]	»	(3)	2.1		1.7		1.2	
XXXVI	3,5-dimethylphenyl	(1)	0.7	0.9	1.1	1.2	0.7	0.7
XXXVII	»	(3)	0.6		1.3		0.5	
C. Change of R_1 from (1) to (4).								
A[b]	2,6-dimethylphenyl	(1)	0.5	3.6	0.6	2.7	0.8	1.4
D[b]	»	(4)	1.8		1.6		1.1	
XXXVI	3,5-dimethylphenyl	(1)	0.7	1.4	1.1	1.5	0.7	0.9
XXXVIII	»	(4)	1.0		1.7		0.6	
D. Change of R_1 from (1) to (5).								
A[b]	2,6-dimethylphenyl	(1)	0.5	6.8	0.6	8.7	0.8	0.8
E[b]	»	(5)	3.4		5.2		0.7	
XXXVI	3,5-dimethylphenyl	(1)	0.7	2.1	1.1	1.4	0.7	1.4
XXXIX	»	(5)	1.5		1.5		1.0	
E. Change of R_1 from (1) to (6).								
A[b]	2,6-dimethylphenyl	(1)	0.5	6.4	0.6	2.8	0.8	2.4
XXXI	»	(6)	3.2		1.7		1.9	
XXXVI	3,5-dimethylphenyl	(1)	0.7	2.3	1.1	1.9	0.7	1.1
XL	»	(6)	1.6		2.1		0.8	

[a] The formulas of the radicals R_1 must be read in the same direction as the total formula above.

[b] The values given for these compounds are taken from Löfgren *et al.*[4]

B. The effect of variations in the intermediate chain, R_1, (*cf.* formula above) upon anesthetic activity and toxicity is surveyed in Table 2. If Ar is 2,6-dimethylphenyl, and one methyl group is attached to the intermediate chain (transitions A → C and A → D) the increase in anesthetic activity is three to fourfold. The toxicity increases about three times [4]. The corresponding structural change, when Ar is 3,5-dimethylphenyl (XXXVI → XXXVII and XXXVI → XXXVIII), is accompanied by a smaller increase (f_A* = 1.4) or even a small decrease (f_A = 0.9). The toxicity is increased by about 20—50 %.

When one methyl group is attached to each of the carbon atoms of an ethylene radical constituting the intermediate chain R_1, the anesthetic activity is increased approximately seven times if Ar is 2,6-dimethylphenyl (A → E). The toxicity is increased eight to nine times [4]. On the other hand, if Ar is 3,5-dimethylphenyl, the corresponding change (XXXVI → XXXIX) is accompanied by a doubling of the anesthetic activity. The toxicity increases only about 40 %.

The replacement of ethylene by 2,2-dimethyltrimethylene in the intermediate chain is accompanied by a six to sevenfold increase in anesthetic activity when Ar is 2,6-dimethylphenyl (A → XXXI). The toxicity increases about three times. Ar being 3,5-dimethylphenyl, the corresponding change (XXXVI → XL) is followed approximately by a doubling of the anesthetic activity. The increase in toxicity is about the same.

If R_1 is extended by one carbon atom from ethylene to trimethylene and Ar is 2,6-dimethylphenyl (A → B) [4], the activity is lost, whereas it is increased (f_A = 1.3) when Ar is 3,5-dimethylphenyl (XXXVI → F).

C. If the alkyl group (R_2) at the terminal nitrogen atom is changed from ethyl to methyl the anesthetic activity is lost (LVIII → LX).

D. N-(2-Diethylamino-1,2-dimethylethyl)-2-methylbenzamide appears as two separable racemates V*a* and V*b*. They do not differ significantly regarding toxicity or duration of anesthesia. However, the latency time of V*a* is about half of that of V*b*.

DETERMINATION OF THERMODYNAMIC IONIZATION CONSTANTS

The thermodynamic ionization constants in aqueous solution at 25°C were determined for twenty-six N-(dialkylaminoalkyl)benzamides, benzoic acid and all mono-, di-, and trimethylbenzoic acids. For the benzoic acids the equilibrium

$$BH + H_2O \rightleftharpoons B^- + H_3O^+ \qquad (1)$$

is valid. For the basic amides the corresponding expression is

$$BH^+ + H_2O \rightleftharpoons B + H_3O^+ \qquad (2)$$

From equilibrium (1) the expression

$$pK_a = pH - \log \frac{C_{cat} - C_{an} + C_{H^+} - C_{OH^-}}{C_{tot} - C_{cat} + C_{an} - C_{H^+} + C_{OH^-}} + pf_{B^-} \qquad (3)$$

* The *factor* f_A indicates the change in RA.

Table 3. Ionization constants of benzoic acid and methyl substituted benzoic acids in aqueous solution at 25°C.

Acid	$1/2\Gamma \cdot 10^3$	p/B^-	*	pH	$C_{H^+} \cdot 10^3$ mole/litre	pK_a	pK_a average
Benzoic	4.342	0.029	+0.109	4.297	0.050	4.217	4.21_6
	4.342	0.029	+0.373	4.557	0.028	4.213	
	1.998	0.021	−0.190	4.008	0.098	4.219	
2-Methylbenzoic	3.340	0.026	+0.030	3.933	0.117	3.929	3.93_4
	4.356	0.029	+0.135	4.042	0.091	3.936	
	4.699	0.030	+0.041	3.947	0.113	3.936	
3-Methylbenzoic	3.337	0.026	+0.029	4.299	0.050	4.296	4.28_9
	4.669	0.030	+0.107	4.364	0.043	4.287	
	4.379	0.029	+0.150	4.406	0.039	4.285	
4-Methylbenzoic	4.752	0.030	+0.377	4.770	0.017	4.423	4.41_3
	5.235	0.031	+0.490	4.852	0.014	4.393	
	5.581	0.032	+0.562	4.954	0.011	4.424	
2,3-Dimethylbenzoic	2.051	0.022	+0.050	3.805	0.157	3.777	3.80_0
	3.154	0.026	+0.273	4.049	0.089	3.802	
	3.370	0.026	+0.319	4.116	0.077	3.823	
2,4-Dimethylbenzoic	3.996	0.028	+0.341	4.612	0.024	4.299	4.30_2
	3.590	0.027	+0.497	4.785	0.016	4.315	
	3.696	0.027	+0.507	4.773	0.017	4.293	
2,5-Dimethylbenzoic	2.364	0.022	+0.392	4.419	0.038	4.049	4.04_0
	2.687	0.024	+0.496	4.516	0.031	4.044	
	3.343	0.026	+0.363	4.364	0.043	4.027	
2,6-Dimethylbenzoic	2.514	0.023	+0.477	3.719	0.191	3.265	3.25_5
	3.004	0.025	+0.485	3.718	0.191	3.258	
	1.978	0.021	+0.378	3.600	0.251	3.243	
3,4-Dimethylbenzoic	2.561	0.023	+0.494	4.963	0.011	4.492	4.49_6
	2.504	0.023	+0.469	4.946	0.011	4.500	
3,5-Dimethylbenzoic	2.731	0.023	+0.557	4.906	0.012	4.372	4.39_3
	2.864	0.024	+0.529	4.898	0.013	4.393	
	2.741	0.023	+0.524	4.914	0.012	4.413	
2,3,4-Trimethylbenzoic	1.665	0.019	+0.696	4.752	0.018	4.075	4.06_3
	1.858	0.020	+0.643	4.661	0.022	4.038	
	3.297	0.026	+0.916	4.965	0.011	4.075	
2,3,5-Trimethylbenzoic	1.998	0.021	+0.628	4.634	0.023	4.027	4.00_6
	1.152	0.017	+0.490	4.455	0.035	3.982	
	2.281	0.022	+0.618	4.604	0.025	4.008	
2,3,6-Trimethylbenzoic	2.018	0.022	+0.553	3.877	0.133	3.346	3.33_9
	3.393	0.026	+0.673	3.986	0.103	3.339	
	1.985	0.022	+0.232	3.541	0.288	3.331	
2,4,5-Trimethylbenzoic	3.140	0.025	+0.788	5.138	0.007	4.375	4.37_5
	3.983	0.028	+0.887	5.233	0.006	4.374	
2,4,6-Trimethylbenzoic	2.947	0.025	+0.612	4.138	0.073	3.551	3.54_5
	3.440	0.027	+0.663	4.175	0.067	3.539	
3,4,5-Trimethylbenzoic	1.842	0.020	+1.003[a]	5.519	—	4.536	4.51_9
	1.675	0.019	+1.083[a]	5.569	—	4.505	
	2.328	0.022	+1.149[a]	5.642	—	4.515	

[a] Since the solubility of the trimethylbenzoic acids, is very low (for 3,4,5-trimethylbenzoic acid 10^{-4} mole/litre) in water, the logarithms must be kept at high values.

* $\log \dfrac{C_{Na^+} - C_{Cl^-} + C_{H^+}}{C_{tot} - C_{Na^+} + C_{Cl^-} - C_{H^+}}$

Table 4. Ionization constants of N(2-diethylaminoethyl)benzamides in aqueous solution at 25°C. All compounds were weighed as hydrochlorides for these measurements; thus $C_{Cl} = C_{tot}$ and the expression for pK_a can be simplified accordingly.

Compound	$1/2\,\Gamma \cdot 10^3$	pf_{BH+}	*	pH	$C_{OH^-} \cdot 10^3$ mole/litre	pK_a	pK_a average
N-(2-Diethylamino-ethyl)-benzamide	5.775	0.032	−0.071	9.002	0.010	9.041	9.04_9
	6.920	0.035	−0.205	8.881	0.008	9.051	
	5.433	0.032	+0.193	9.279	0.019	9.054	
I	4.123	0.029	−0.314	8.584	—	8.869	8.87_5
	4.540	0.030	+0.148	9.054	0.010	8.876	
	3.279	0.025	−0.079	8.826	0.007	8.880	
VII	2.963	0.025	−0.095	8.980	0.010	9.049	9.04_7
	3.840	0.028	−0.295	8.785	0.006	9.052	
	2.345	0.022	+0.147	9.209	0.016	9.040	
XIII	3.220	0.026	−0.355	8.755	0.006	9.084	9.08_3
	3.464	0.026	+0.309	9.402	0.025	9.081	
	4.258	0.029	−0.041	9.057	0.011	9.083	
XIX	4.685	0.030	+0.388	9.278	0.019	8.860	8.86_2
	4.631	0.030	−0.125	8.767	0.006	8.862	
	7.719	0.037	−0.038	8.863	0.007	8.864	
XXIII	3.557	0.027	+0.114	9.055	0.011	8.914	8.91_7
	3.881	0.028	−0.276	8.665	0.005	8.913	
	5.145	0.031	−0.020	8.934	0.009	8.923	
XXVII	4.494	0.030	−0.374	8.533	—	8.877	8.88_5
	4.371	0.029	+0.130	9.050	0.011	8.891	
	5.740	0.032	−0.013	8.905	0.008	8.886	
A	5.463	0.032	+0.191	8.912	0.008	8.689	8.68_8
	6.553	0.034	−0.359	8.357	—	8.682	
	4.296	0.029	−0.051	8.671	0.005	8.693	
XXXII	4.227	0.029	−0.247	8.847	0.007	9.065	9.07_0
	4.701	0.030	+0.248	9.352	0.023	9.074	
	5.056	0.031	−0.010	9.092	0.012	9.071	
XXXVI	3.614	0.027	−0.238	8.834	0.007	9.045	9.04_6
	3.420	0.026	+0.139	9.210	0.016	9.045	
	4.515	0.030	−0.036	9.041	0.011	9.047	
XLI	5.230	0.032	−0.337	8.592	—	8.897	8.89_3
	5.302	0.032	+0.110	9.040	0.011	8.898	
	5.026	0.031	−0.066	8.850	0.007	8.885	
XLVI	4.243	0.029	−0.352	8.543	—	8.866	8.86_6
	4.197	0.029	+0.175	9.072	0.012	8.868	
	4.564	0.030	−0.001	8.893	0.008	8.864	
XLVIII	3.937	0.028	−0.019	8.710	0.005	8.701	8.69_9
	4.715	0.030	+0.175	8.903	0.008	8.698	
	4.203	0.029	+0.005	8.731	0.005	8.697	
LIII	4.257	0.029	−0.344	8.589	—	8.904	8.91_2
	4.544	0.030	+0.148	9.094	0.012	8.916	
	3.915	0.028	−0.001	8.944	0.009	8.917	
LVIII	3.213	0.026	−0.371	8.352	—	8.697	8.70_5
	3.770	0.027	+0.167	8.902	0.008	8.708	
	3.550	0.027	+0.033	8.771	0.006	8.711	
LXIII	3.745	0.027	−0.364	8.718	0.005	9.055	9.06_7
	4.059	0.028	+0.173	9.280	0.019	9.079	
	5.422	0.032	−0.006	9.092	0.012	9.066	

* $\log \dfrac{C_{Na^+} - C_{OH^-}}{C_{tot} - C_{Na^+} + C_{OH^-}}$

Table 5. Ionization constants of N-(dialkylaminoalkyl)-benzamides of different structures in aqueous solution at 25°C.

Compound	Prepn.	1/2 Γ $\times 10^3$	pf_{BH^+}	*	pH	$C_{OH^-} \times 10^3$	pK_a	pK_a average
V *a*[b]	Base[a]	4.074	0.029	−0.390	9.220	0.017	9.581	9.57_4
		3.826	0.028	+0.124	9.719	0.052	9.567	
		4.906	0.031	−0.035	9.569	0.037	9.573	
V *b*[b]	B HCl	1.945[c]	0.021	−0.272[c]	9.064	0.012	9.315	9.31_2
		1.981[c]	0.021	−0.143[c]	9.182	0.015	9.304	
		1.830[c]	0.020	−0.242[c]	9.094	0.012	9.316	
F	B HCl	4.916	0.031	+0.051	9.917	0.083	9.835	9.83_4
		3.956	0.028	−0.375	9.486	0.031	9.833	
XXXVII	Base[a]	4.466	0.030	−0.435	8.829	0.007	9.234	9.24_1
		4.415	0.029	+0.015	9.285	0.019	9.241	
		5.684	0.032	−0.074	9.205	0.016	9.247	
XXXVIII	B HCl	3.902	0.028	−0.204	9.237	0.017	9.413	9.40_1
		3.894	0.028	+0.407	9.822	0.066	9.387	
		4.096	0.029	−0.020	9.401	0.025	9.403	
XL	Base[a]	3.355	0.027	−0.914[c]	8.358	—	9.245	9.23_4[d]
		4.195	0.029	−1.112[c]	8.167	—	9.250	
		4.915	0.032	−1.108[c]	8.130	—	9.206	
N-(3-Diethylaminopropyl)-2,3,6-trimethylbenzamide	B HCl	3.510	0.027	−0.236	9.461	0.029	9.670	9.67_3
		5.272	0.032	−0.018	9.690	0.049	9.676	
N-(2-Dimethylaminoethyl)-2,3,6-trimethylbenzamide	B HCl	3.442	0.026	−0.348	7.738	—	8.060	8.06_5
		4.538	0.030	+0.017	8.117	—	8.070	
N-(2-Dimethylaminoethyl)-2,4,5-trimethylbenzamide	B HCl	5.560	0.032	−0.369	7.948	—	8.285	8.28_9
		5.204	0.031	+0.163	8.492	—	8.298	
		4.556	0.030	−0.009	8.306	—	8.285	
LX	B HCl	4.424	0.029	−0.366	7.592	—	7.929	7.94_6
		4.891	0.031	+0.176	8.175	—	7.968	
		3.235	0.026	−0.010	7.956	—	7.940	

* $\log \dfrac{C_{tot} - C_{Cl^-} + C_{Na^+} - C_{OH^-}}{C_{Cl^-} - C_{Na^+} + C_{OH^-}}$

[a] The base was dissolved in an excess of HCl, and then neutralized with NaOH.
[b] V *a* and V *b* are racemates of the same compound.
[c] Because of the low solubility of the base in water, it was necessary to make the measurements under conditions where the concentration of base was kept low.
[d] Since in this measurement the ratio between the acid BH^+ and the free base B is great, the accuracy is somewhat lower.

can be derived (*cf.* Lövgren [6]), whereas equilibrium (2) gives

$$pK_a = pH - \log \frac{C_{tot} - C_{an} + C_{cat} - C_{OH^-} + C_{H^+}}{C_{an} - C_{cat} + C_{OH^-} - C_{H^+}} - pf_{BH^+} \qquad (4)$$

In equation (3) C_{tot} is $C_{BH} + C_{B^-}$, whereas in equation (4) this quantity is equal to $C_{BH^+} + C_B$. The quantities C_{cat} and C_{an} represent the concentrations of cations and anions of strong electrolytes. Further,

$$pf_{B^-} = -\log f_{B^-} \; ; \qquad pf_{BH^+} = -\log f_{BH^+} \qquad (5)$$

where f_{B^-} and f_{BH^+} are the activity coefficients of the ions B^- and BH^+ respectively.

The pH values were measured by the aid of a cell of the type:
(—) Glass electrode / H^+(aq) // KCl (satd) / Hg_2Cl_2, Hg (+)

For this cell we have

$$pH = \frac{E - E'}{k} \tag{6}$$

where E is the e.m.f. of the cell and E′ is the standard potential of the cell including the liquid junction potential (assumed to be constant). At 25°C, k is 59.16 mV. Kielland [7] has calculated activity coefficients for a large number of ions at different concentrations in water at 25°C by use of the Debye-Hückel formula

$$-\log f_i = pf_i = \frac{0.358 \cdot z_i^2 \cdot \Gamma^{1/2}}{1 + 10^8 d_i \cdot 0.2325\ \Gamma^{1/2}} \tag{7}$$

where f_i is the activity coefficient of the i-th ion with valence z_i and effective diameter d_i. Γ is the ionic concentration, given by $\Gamma = \Sigma C_i z_i^2$ with C_i in moles per litre.

According to measurements by Löfgren [8], the effective diameter of the BH^+ ions was evaluated to 8×10^{-8} cm. For the B^- ions no determination of the effective diameter was made. A change in d from 5×10^{-8} to 10^{-7} alters pf_i negligibly in comparison with other errors. The values of pf_i for $d = 6 \times 10^{-8}$, $d = 7 \times 10^{-8}$, and $d = 8 \times 10^{-8}$ were plotted against $1/2\ \Gamma$ in a diagram from which pf_{BH^+} and pf_{B^-} were read off directly at any concentration *.

Since it is difficult to obtain a clear survey of the systematic errors, (above all, errors caused by liquid junction potentials) the pK_a values are given to two decimals. For mutual comparison, however, the values can be given with greater accuracy; particularly for the salts of the N-(dialkylaminoalkyl)-benzamides the maximum errors seldom exceed $\pm$ 0.005, whereas for the benzoic acids the errors are somewhat greater.

When calculating pK_a values from (3) or (4), these expressions, for special conditions, can be simplified. Thus, when working at an ionic concentration $> 2 \times 10^{-3}$ mole per litre, C_{H^+} can be neglected at pH > 5, and C_{OH^-} at pH < 9.

Experimental data from the measurements of the thermodynamic ionization constants of benzoic acids in aqueous solution at 25°C are found in Table 3. The ionization constants of the benzoic acids have been measured earlier; good surveys have been presented by Shorter *et al.*[9] and Dippy *et al.*[10,11]. The most accurate determinations given by these authors have, however, been made by conductivity measurements. Since it is essential to obtain a uniformly measured series for mutual comparison, benzoic acid, all mono-, di-, and trimethylbenzoic acids were remeasured. In Table 4 the data from the pK_a determinations of N-(2-diethylaminoethyl)benzamides are given, and in Table

* The three curves did not deviate from each other by more than 0.001 in pf below a value for $\frac{1}{2}\Gamma$ of 8×10^{-3} mole/litre.

5 pK_a values of ten N-(dialkylaminoalkyl)benzamides of different structure have been collected. In a later chapter, a few considerations upon the relationship between chemical structure and the ionization constant will be given.

ULTRAVIOLET AND INFRARED SPECTRA

Ultraviolet spectra have been recorded for methyl substituted benzoic acids and N-(2-diethylaminoethyl)benzamides in the wavelength region 218—310 mμ. In this region two bands are found, one at 220—240 mμ with $\varepsilon_{max} \simeq 10^4$, and one at 260—285 mμ with $\varepsilon_{max} \simeq 300-600$. A band with a higher extinction at about 200—210 mμ is positioned beyond the limits of proper measuring with the solvents used (the benzoic acids in ethanol, and the benzamides in cyclohexane). However, Moser *et al.*[12] have been able to measure the spectrum of benzoic acid and a few methyl substituted benzoic acids between 200 and 220 mμ in other solvents (*e.g.* a mixture of 99.5 % of water 0.5 % of ethanol). According to Hedden *et al.*[13] the band at 260—285 mμ will here be designated as the B-band (B for benzene ring absorption) and that at 220—240 mμ as the C-band (C for conjugation). Particular interest will be focussed on the intensity of the C-band.

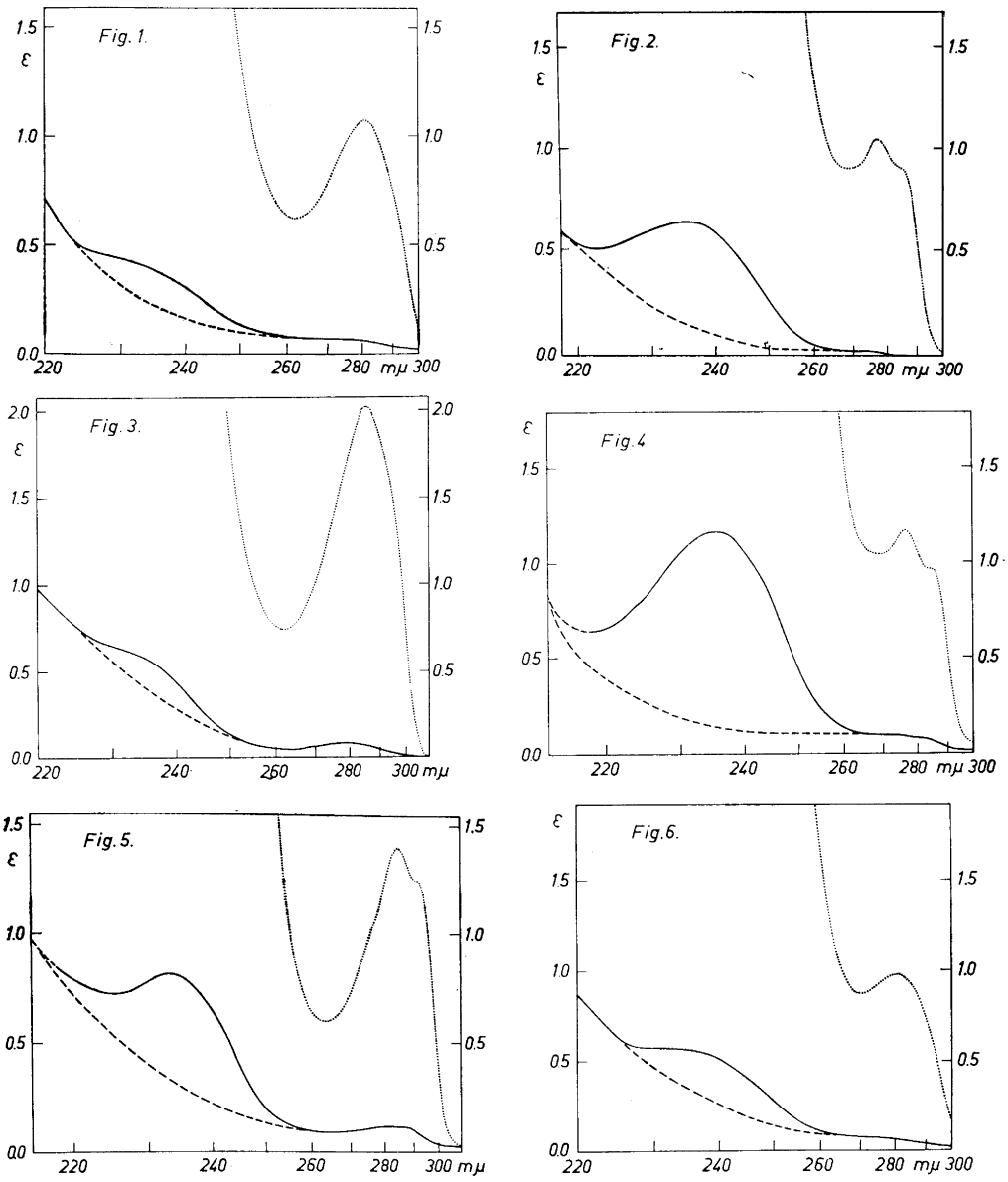
Table 6. Wavelengths, wave numbers (ν), and oscillator strengths of maxima and inflexions of benzoic acids and N-(2-diethylaminoethyl)-benzamides for the ultraviolet absortion band at 220—240 mμ.

Positions and number of methyl groups attached to the aromatic nucleus	Benzoic acids			N-(2-Diethylaminoethyl)-benzamides		
	λ_{max} mμ	ν_{max} $cm^{-1} \times 10^{-4}$	f	λ_{max} mμ	ν_{max} $cm^{-1} \times 10^{-4}$	f
—	228[a]	4.386	0.123_7	222.5	4.494	0.099_8
2-Methyl	228[a]	4.386	0.039_9	—	—	0.000[c]
3-Methyl	232[a]	4.310	0.113_2	226	4.425	0.060_3
4-Methyl	236	4.237	0.207_5	231	4.329	0.192_1
2,3-Dimethyl	235[b]	~4.25	0.021_5	—	—	0.000[c]
2,4-Dimethyl	236	4.237	0.086_6	230[b]	~4.35	0.034_7
2,5-Dimethyl	236[b]	~4.24	0.013_1	—	—	0.000[c]
2,6-Dimethyl	228[a,b]	~4.39	0.014_4	—	—	0.000[c]
3,4-Dimethyl	235.5	4.246	0.191_0	233	4.292	0.115_3
3,5-Dimethyl	233.5	4.283	0.073_0	232	4.310	0.037_1
2,3,4-Trimethyl	237[b]	~4.22	0.036_7	233[b]	~4.29	0.010_8
2,3,5-Trimethyl	239[b]	~4.18	0.008_4	—	—	0.000[c]
2,3,6-Trimethyl	223[b]	~4.48	0.008_3	—	—	0.000[c]
2,4,5-Trimethyl	237	4.219	0.099_1	234[b]	~4.27	0.021_1
2,4,6-Trimethyl	—	—	0.000[c]	—	—	0.000[c]
3,4,5-Trimethyl	238.5	4.193	0.174_9	237	4.219	0.134_2

[a] Values calculated from curves published by Moser *et al.*[12]

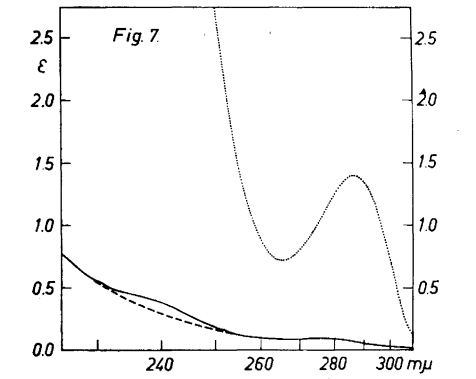
[b] Inflexions; wavelengths and wavenumbers can not be given with any great accuracy.

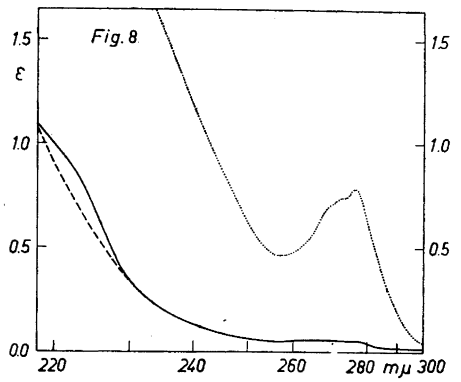
[c] No maximum or inflexion could be observed at the expected wavelength, hence the extinction (and the oscillator strength f) is set equal to zero for the absorbtion band under consideration.

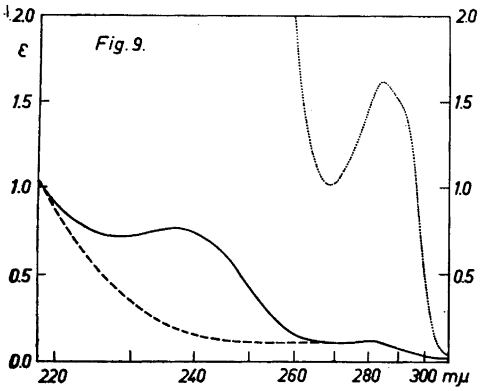


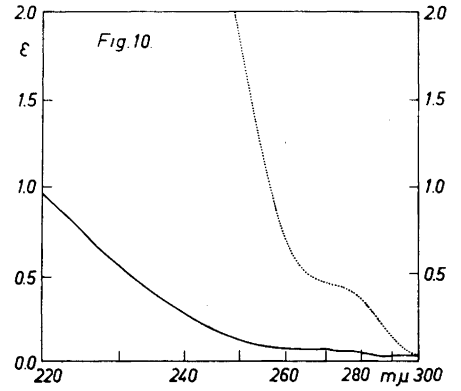
Figs. 1—6. Ultraviolet absorbtion curves of *1:* 2,3-dimethylbenzoic acid; *2:* 2,4-dimethylbenzoic acid; *3:* 2,5-dimethylbenzoic acid; *4:* 3,4-dimethylbenzoic acid; *5:* 3,5-dimethylbenzoic acid; *6:* 2,3,4-trimethylbenzoic acid *.

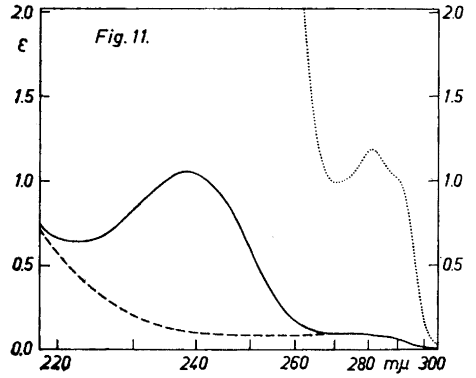
* The extinctions of curves drawn with dotted lines should be multiplied by 10^3, and the extinctions of curves drawn with solid or broken lines should be multiplied by 10^4. Curves drawn with broken lines are estimated, and are used as reference curves for calculation of the integrated extinction $\int \varepsilon_\nu d\nu$.

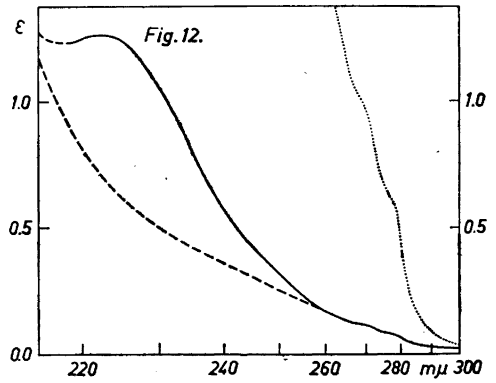






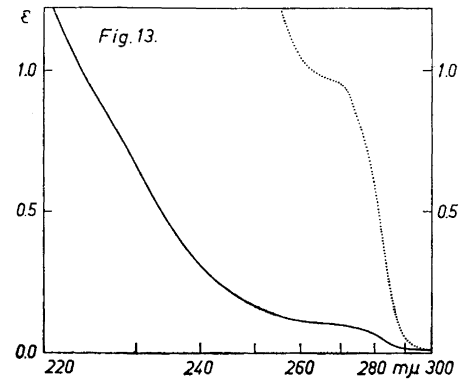


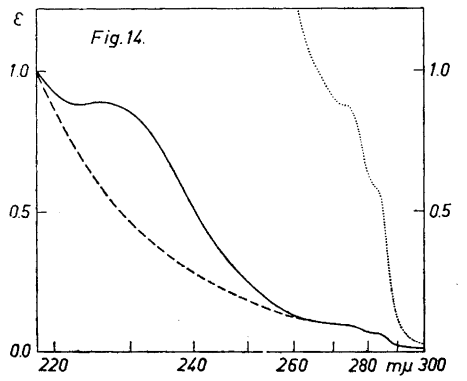


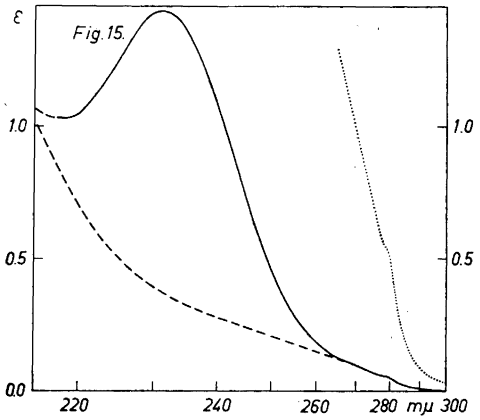


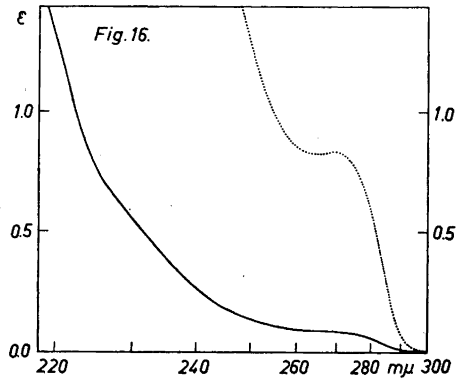
Figs. 7—12. Ultraviolet absorbtion curves of *7:* 2,3,5-trimethylbenzoic acid; *8:* 2,3,6-trimethylbenzoic acid; *9:* 2,4,5-trimethylbenzoic acid; *10:* 2,4,6-trimethylbenzoic acid; *11:* 3,4,5-trimethylbenzoic acid; *12:* N-(2-diethylaminoethyl)-benzamide *.

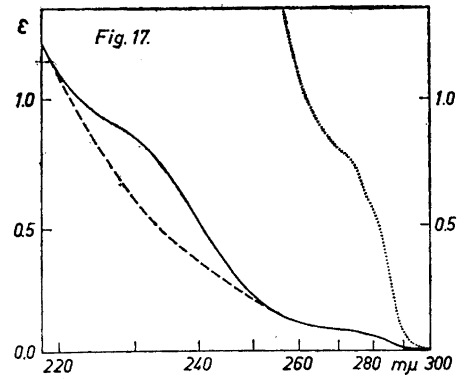
* For designation of the curves see note to Figs. 1—6.











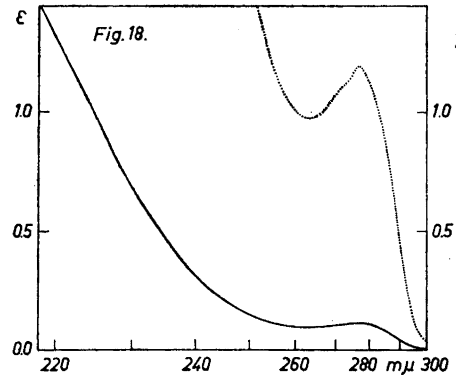
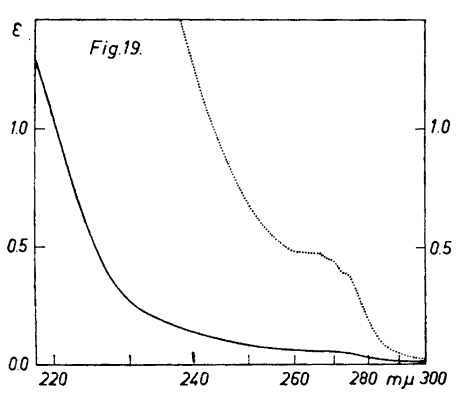
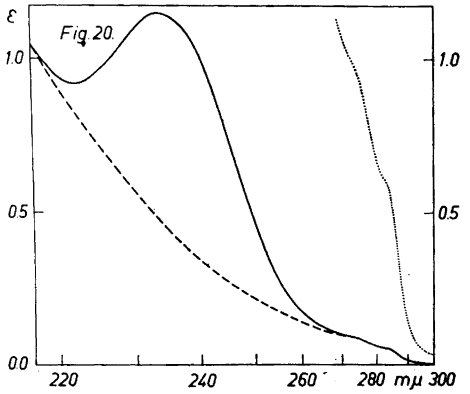
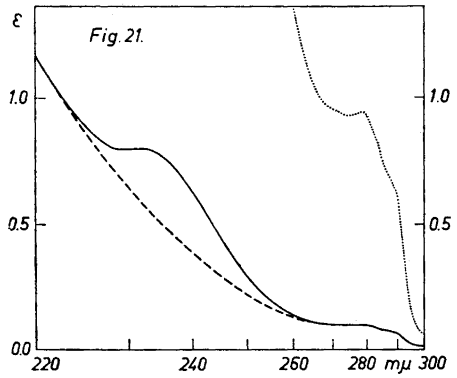


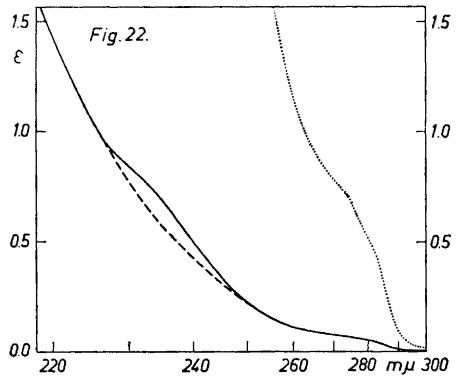
Fig.s 13—18. Ultraviolet absorbtion curves of *13:* I; *14:* VII; *15:* XIII; *16:* XIX; *17:* XXIII; *18:* XXVII *.

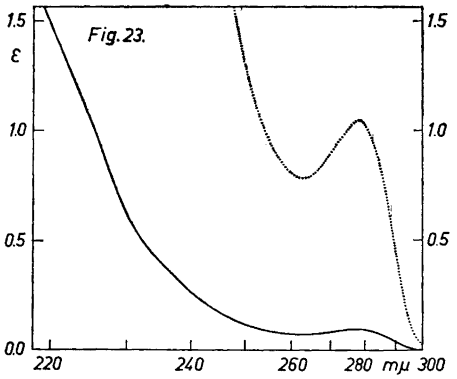
* For designation of the curves see note to Figs. 1—6.

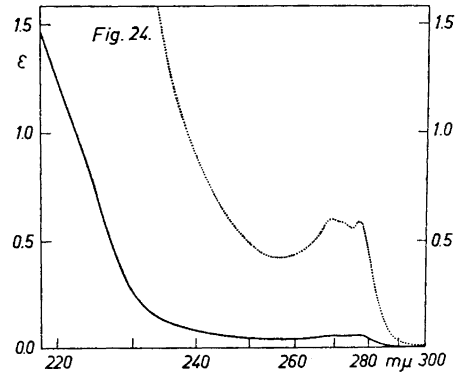






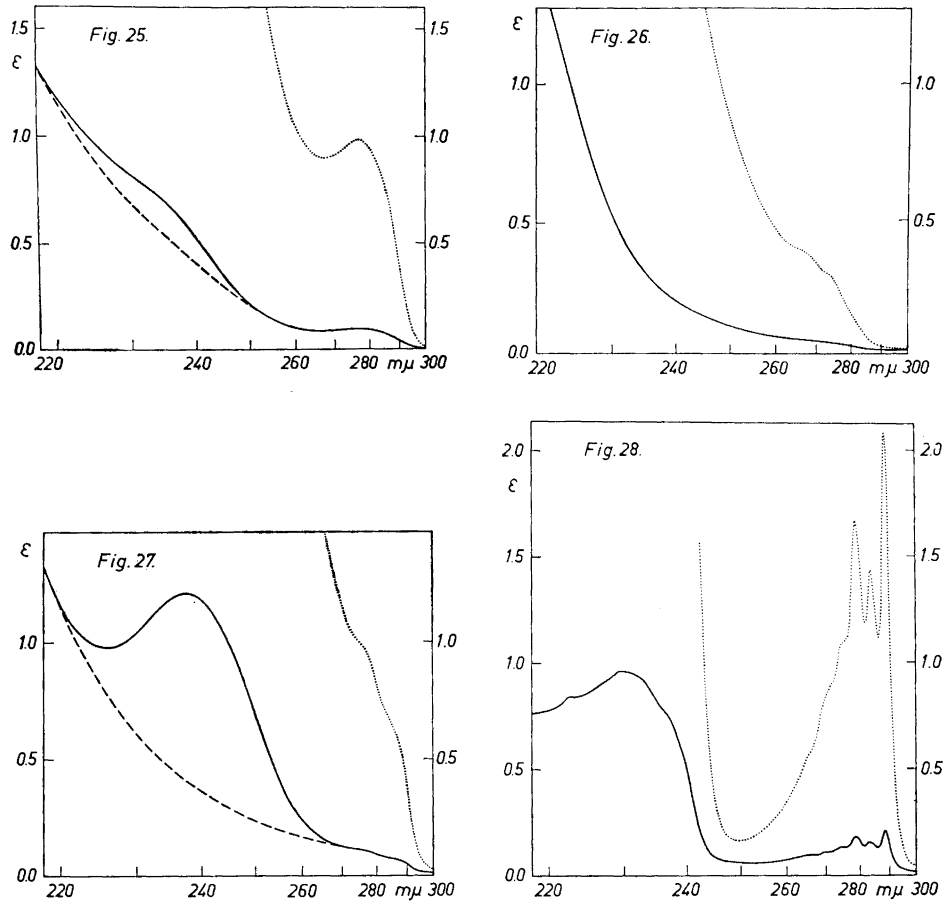






Figs. 19—24. Ultraviolet absorbtion curves of *19:* A; *20:* XXXII; *21:* XXXVI; *22:* XLI; *23:* XLVI; *24:* XLVIII *.

* For designation of the curves see note to Figs. 1—6.



Figs. 25—28. Ultraviolet absorbtion curves of *25:* LIII; *26:* LVIII; *27:* LXIII; *28:* 2,6-dimethylbenzonitrile *.

A quantity which may give some information on the conjugation in a benzoic acid or N-(2-diethylaminoethyl)benzamide is the *oscillator strength f* (of the C-band) which is defined by [14,15]

$$f = \frac{0.1028 \cdot m \cdot c^2}{\pi \cdot e^2 \cdot n} \int_{-\infty}^{+\infty} \varepsilon_\nu d\nu = 4.32 \cdot 10^{-9} \int_{-\infty}^{+\infty} \varepsilon_\nu d\nu \qquad (8)$$

There m and c are the mass of the electron and the velocity of light respectively; and n is the number of molecules in one cm^3, e being the electronic charge,

* For designation of the curves see note to Figs. 1—6.

and $\int_{-\infty}^{+\infty} \varepsilon_\nu d\nu$ the integrated molar extinction over a whole band. Because of overlapping, the band under consideration often occurs as a slight inflexion only. Since intensities in spectra are additive, the integrated molar extinction for a given band can be defined as $\int_{-\infty}^{+\infty} \Delta\varepsilon_\nu d\nu$ in which $\Delta\varepsilon$ is the difference in extinction between the measured curve and a constructed hypothetical curve. The nature of the latter depends on adjacent bands in the spectrum and may be calculated by Fourier analysis, or — as has been done here — be visualized by arbitrary drawing * (see for instance Figs. 1—28).

* The error in the determination of the oscillator strength would of course be smaller by employing Fourier analysis to calculate the integrated extinction. However, this requires that the measurements be extended down to 190 mμ.

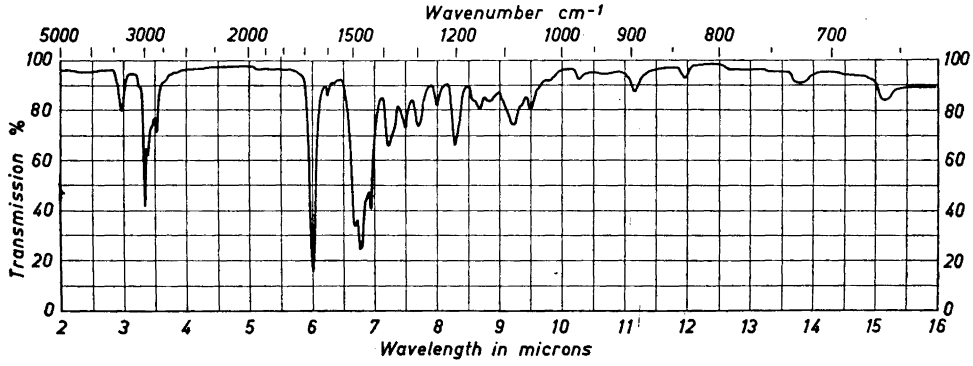


Fig. 29. Infrared spectrogram of V *a*; 4.5 % solution in CCl_4.

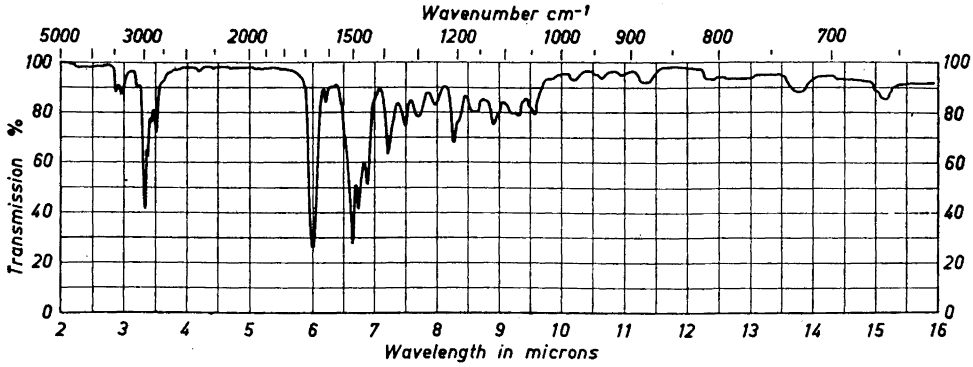


Fig. 30. Infrared spectrogram of V *b*; 4.5 % solution in CCl_4.

The experimental data from the measurements on the ultraviolet absorbtion spectra are found in Table 6 and Figs. 1—28.

Infrared spectra recorded for the two racemates of N-(2-diethylamino-1,2,-dimethylethyl)-2-methylbenzamide in CCl_4 are shown in Figs. 29 and 30. Spectra of the two racemates were also taken up in CS_2 (no diagram shown here). Both racemates showed a relatively strong band at 737 cm^{-1}.

DISCUSSION ON IONIZATION CONSTANTS AND OSCILLATOR STRENGTHS

When attaching a methyl group to the benzene nucleus of a benzoic acid or a N-(2-diethylaminoethyl)benzamide, the pK_a-value is altered in a systematic way. The introduction of a methyl group *para* to the carboxyl group of a benzoic acid is always accompanied by a decrease in acid strength (Table 7). Methyl groups in the positions *ortho* to the carboxyl group cause a marked increase in the acid strength (Table 11). Smaller effects in both directions are brought about by methyl groups in the *meta* positions (Table 9). The influence of methyl groups on the strength of a conjugate acid of the corresponding N-(2-diethylaminoethyl)benzamide is essentially the same as that of the benzoic acid (Tables 8, 10, and 12). — The present results support earlier observations on the strength in aqueous solution of simple alkyl substituted benzoic acids [10,11].

The introduction of a methyl group to the *para* position of acids which do not contain *ortho* methyl groups results in a ΔpK_a equal to $+ 0.18 \pm 0.05$ * (mean of three cases, *cf.* Table 7). This is consistent with the observations by Dippy [10] who compared the ionization constants of benzoic acid and *p*-toluic acid. However, the effect of a *para* methyl group in the presence of one or two *ortho* methyl groups is noticeably increased, *i.e.* ΔpK_a is then equal to $+ 0.31 \pm 0.02$ ** (mean of four cases).

* Maximum error.
** Probable error of the mean.

Table 7. Change in pK_a on the introduction of *p*-methyl groups into benzoic acids.

Structural change Y → Z		ΔpK_a
Y	Z	
Benzoic acid	4-methylbenzoic acid	+ 0.197
2-Methylbenzoic acid	2,4-dimethylbenzoic acid	+ 0.368
3-Methylbenzoic acid	3,4-dimethylbenzoic acid	+ 0.207
2,3-Dimethylbenzoic acid	2,3,4-trimethylbenzoic acid	+ 0.263
2,5-Dimethylbenzoic acid	2,4,5-trimethylbenzoic acid	+ 0.335
2,6-Dimethylbenzoic acid	2,4,6-trimethylbenzoic acid	+ 0.290
3,5-Dimethylbenzoic acid	3,4,5-trimethylbenzoic acid	+ 0.128
		Mean value + 0.26 ± 0.03 [a]

[a] The error given for the mean is the probable error if the number of measurements from which the mean is calculated is four or higher.

Table 8. Change in pK_a on the introduction of *p*-methyl groups into N-(2-diethylamino-ethyl)-benzamides.

Structural change Y → Z		ΔpK_a
Y	Z	
N-(2-Diethylamino-ethyl)-benzamide	XIII	+ 0.034
I	XXIII	+ 0.042
VII	XXXII	+ 0.022
XIX	XLI	+ 0.031
XXVII	LIII	+ 0.027
A	LVIII	+ 0.017
XXXVI	LXIII	+ 0.028
		Mean value + 0.029 ± 0.003[a]

[a] For the error, see note, Table 7.

The values of ΔpK_a for the introduction of *ortho* methyl groups into benzoic acids vary within wide limits (*cf.* Table 11). Exceptionally high numerical values are obtained when introducing methyl groups into the 6-position of 2-methyl substituted benzoic acids. The effect of a methyl group in the *ortho* position of a benzoic acid is also increased by the presence of a neighbouring *meta* methyl group. On the other hand, a *para* methyl group in most cases diminishes the acid strengthening effect of an *ortho* methyl group. This tendency is especially manifest in the difference in ionization constant of *p*-toluic acid and 2,4-dimethylbenzoic acid ($\Delta pK_a = -0.11$) or 3,4-dimethylbenzoic acid and 2,4,5-trimethylbenzoic acid ($\Delta pK_a = -0.12$), where no steric interactions can occur between the *ortho* methyl group and other methyl groups present in the molecule.

Table 9. Change in pK_a on the introduction of *m*-methyl groups into benzoic acids.

Structural change Y → Z		ΔpK_a
Y	Z	
Benzoic acid	3-methylbenzoic acid	+ 0.073
2-Methylbenzoic acid	2,3-dimethylbenzoic acid	− 0.134
2-Methylbenzoic acid	2,5-dimethylbenzoic acid	+ 0.106
3-Methylbenzoic acid	3,5-dimethylbenzoic acid	+ 0.104
4-Methylbenzoic acid	3,4-dimethylbenzoic acid	+ 0.083
2,3-Dimethylbenzoic acid	2,3,5-trimethylbenzoic acid	+ 0.206
2,4-Dimethylbenzoic acid	2,3,4-trimethylbenzoic acid	− 0.239
2,4-Dimethylbenzoic acid	2,4,5-trimethylbenzoic acid	+ 0.073
2,5-Dimethylbenzoic acid	2,3,5-trimethylbenzoic acid	− 0.034
2,6-Dimethylbenzoic acid	2,3,6-trimethylbenzoic acid	+ 0.084
3,4-Dimethylbenzoic acid	3,4,5-trimethylbenzoic acid	+ 0.025
		Mean value + 0.03 ± 0.04[a]

[a] For the error, see note, Table 7.

Table 10. Change in pK_a on the introduction of *m*-methyl groups into N-(2-diethylaminoethyl)-benzamides.

Structural change Y → Z		ΔpK_a
Y	Z	
N-(2-Diethylaminoethyl)-benzamide	VII	− 0.002
I	XIX	− 0.013
I	XXVII	+ 0.010
VII	XXXVI	− 0.001
XIII	XXXII	− 0.014
XIX	XLVI	+ 0.004
XXIII	XLI	− 0.024
XXIII	LIII	− 0.005
XXVII	XLVI	− 0.019
A	XLVIII	+ 0.011
XXXII	LXIII	+ 0.005
		Mean value − 0.004±0.004[a]

[a] For the error, see note, Table 7.

Table 11. Change in pK_a on the introduction of *o*-methyl groups into benzoic acids.

Structural change Y → X		ΔpK_a
First *o*-methyl group:		
Y	Z	
Benzoic acid	2-methylbenzoic acid	− 0.282
3-Methylbenzoic acid	2,3-dimethylbenzoic acid	− 0.489
3-Methylbenzoic acid	2,5-dimethylbenzoic acid	− 0.249
4-Methylbenzoic acid	2,4-dimethylbenzoic acid	− 0.111
3,4-Dimethylbenzoic acid	2,3,4-trimethylbenzoic acid	− 0.433
3,4-Dimethylbenzoic acid	2,4,5-trimethylbenzoic acid	− 0.121
3,5-Dimethylbenzoic acid	2,3,5-trimethylbenzoic acid	− 0.387
		Mean value − 0.30 ± 0.05[a]
Second *o*-methyl group:		
Y	Z	
2-Methylbenzoic acid	2,6-dimethylbenzoic acid	− 0.679
2,3-Dimethylbenzoic acid	2,3,6-trimethylbenzoic acid	− 0.461
2,4-Dimethylbenzoic acid	2,4,6-trimethylbenzoic acid	− 0.757
2,5-Dimethylbenzoic acid	2,3,6-trimethylbenzoic acid	− 0.701
		Mean value − 0.65 ± 0.07[a]

[a] For the error, see note, Table 7.

Table 12. Change in pK_a on the introduction of *o*-methyl groups into N-(2-diethylaminoethyl)-benzamides.

Structural change Y → Z		ΔpK_a
First *o*-methyl group:		
Y	Z	
N-(2-Diethylaminoethyl)-benzamide	I	− 0.174
VII	XIX	− 0.185
VII	XXVII	− 0.162
XIII	XXIII	− 0.166
XXXII	XLI	− 0.176
XXXII	LIII	− 0.157
XXXVI	XLVI	− 0.180
		Mean value − 0.171 ± 0.004 [a]
Second *o*-methyl group:		
Y	Z	
I	A	− 0.187
XIX	XLVIII	− 0.163
XXIII	LVIII	− 0.212
XXVII	XLVIII	− 0.186
		Mean value − 0.187 ± 0.010 [a]

[a] For the error, see note, Table 7.

A methyl group introduced in the *meta* position of a benzoic acid will cause a small decrease in acid strength ($\Delta pK_a = + 0.09 \pm 0.02$ *; mean of seven cases), provided that no methyl group is located in the *ortho* position between the entering methyl group and the carboxyl. A *meta* methyl group adjacent to an *ortho* methyl is often acid strengthening (*cf.* Table 9).

The effect of *meta* and *para* methyl groups in the N-(2-diethylaminoethyl)-benzamides is about 10 % of that in the corresponding benzoic acids, whereas the effect of *ortho* methyl groups in the basic amides is about 40 % of that in the benzoic acids. The variation in ΔpK_a when introducing methyl groups into the *ortho* positions of benzoic acids (*cf.* above) has not been observed in the benzamide series.

An extensive critical survey of current ideas dealing with the influence of substitution in the benzene nucleus on the ionization constant of benzoic acids has been given by Brown *et al.*[16] The acid strength of benzoic acid is governed by two factors acting in opposite directions. The inductive effect

* Probable error of the mean.

of the benzene nucleus (being electron-attracting) is acid-strengthening, and the resonance between the carboxyl group and the benzene nucleus is acid-weakening. *Para* and *meta* alkyl groups are acid-weakening by means of an electron-repelling * effect [16]. The actual observations in many cases support these theories. Deviations will be discussed below. Brown *et al.*[16] consider the effect of alkyl substituents in the *ortho* positions to be *mainly* of a steric nature. This is ascribed to a twisting of the carboxyl group out of the plane of the ring. An *ortho* methyl should be acid weakening by means of its electron-repelling effect. This is, however, outweighed by the strong effect of resonance inhibition. The more bulky the *ortho* alkyl groups, the more pronounced is the steric inhibition of resonance. Thus, *o-tert*-butylbenzoic acid is three times stronger than *o*-toluic acid, despite the electron-repelling effect of *tert*-butyl being greater than that of methyl [10,11,16].

This theory may explain the abnormal acid-strengthening effect of a *meta* methyl group adjacent to an *ortho* methyl group. The crowding of bulky substituents may enhance the twisting of the carboxyl group out of the plane of the ring. The resulting increase in acid strength is apparently large enough to compensate for the acid weakening effect of the *meta* methyl group. A similar explanation of this *ortho-meta*-effect is given by Dippy *et al.*[11]

The surprisingly large effect of *ortho* methyl groups on the pK_a of the benzamides may be due to steric interference between the bulky dialkylamino-alkyl group and the *ortho* methyl groups. The concept of steric hindrance would also explain the observation (*cf.* above) that a *para* methyl group diminishes the acid strengthening effect of an *ortho* methyl group. The effect may also be expressed as an increase in the acid weakening property of the *para* methyl group in presence of *ortho* methyl groups. Considering the influence of the *para* methyl group on the effect of the *ortho* methyl group, it seems reasonable to assume that the *para* methyl, by virtue of its electron repelling effect, counteracts the twisting of the carboxyl group out of the plane of the ring (*cf.* Dippy [11]).

As a general rule, the introduction of a *para* methyl group is accompanied by an increase in oscillator strength (f) of the ultraviolet absorption band at 220—240 mμ. Hedden *et al.*[13] give a value of + 0.04 for the change in f when a methyl group is introduced in the *para* position of acetophenones. The corresponding value in the present determinations is + 0.06 for the benzoic acids, and + 0.05 for N-(2-diethylaminoethyl)benzamides (*cf.* Tables 13 and 14). The surprisingly low f value for 2,4,6-trimethylbenzoic acid as compared with that of 2,6-dimethylbenzoic acid is consistent with the values for the corresponding acetophenones as reported by Braude [18], but not with those given by Schwartzman *et al.* [25]

When introducing a methyl group into a *meta* position of a benzoic acid or N-(2-diethylaminoethyl)benzamide, f is in most cases slightly decreased. The average change in f is −0.02 for the acids and −0.03 for the basic amides (Tables 15 and 16).

* Throughout this paper no differentiation has been made between the inductive effect of alkyl groups and the so called hyperconjugation which has recently been brought into question (*cf.* for instance Ref.[17]). Thus, when discussing the electron-repelling effect of an alkyl group, the true inductive effect and a possible "hyperconjugation" effect are included.

Table 13. Change in f on the introduction of p-methyl groups into benzoic acids.

Structural change Y → Z		Δf
Y	Z	
Benzoic acid	4-methylbenzoic acid	+ 0.0838
2-Methylbenzoic acid	2,4-dimethylbenzoic acid	+ 0.0467
3-Methylbenzoic acid	3,4-dimethylbenzoic acid	+ 0.0778
2,3-Dimethylbenzoic acid	2,3,4-trimethylbenzoic acid	+ 0.0152
2,5-Dimethylbenzoic acid	2,4,5-trimethylbenzoic acid	+ 0.0860
2,6-Dimethylbenzoic acid	2,4,6-trimethylbenzoic acid	− 0.0144 [b]
3,5-Dimethylbenzoic acid	3,4,5-trimethylbenzoic acid	+ 0.1019
		Mean value + 0.057±0.016[a]

[a] For the error, see note, Table 7.
[b] Regarding this value see text p. 341.

Table 14. Change in f on the introduction of p-methyl groups into N-(2-diethylaminoethyl)-benzamides.

Structural change Y → Z		Δf
Y	Z	
N-(2-Diethylaminoethyl)-benzamide	XIII	+ 0.0923
I	XXIII	+ 0.0347
VII	XXXII	+ 0.0550
XIX	XLI	+ 0.0108
XXVII	LIII	+ 0.0211
XXXVI	LXIII	+ 0.0971
		Mean value + 0.052±0.015[a]

[a] For the error, see note, Table 7.

The introduction of a methyl group in an *ortho* position is accompanied by a strong decrease in oscillator strength (Tables 17 and 18). The change in f — associated with the introduction of the first methyl group in the benzoic acids — had a value of −0.10. The corresponding value in the benzamide series was found to be −0.09. In the acetophenones the change of f is −0.07 when methyl groups are introduced in the *ortho* positions [13]. On introducing a methyl group in the 6-position of a 2-methyl substituted benzoic acid or N-(2-diethylaminoethyl)benzamide, the change is smaller, being −0.03. From Table 6 is seen that for most amides, *one ortho* methyl group is sufficient to diminish the oscillator strength almost to zero. For the benzoic acids, even *two ortho* methyl groups do not give such a strong effect.

The absorption band studied is considered to be associated with the conjugation between the aromatic nucleus and the carbonyl group [13,18]. The oscillator

Table 15. Change in f on the introduction of *m*-methyl groups into benzoic acids.

Structural change Y → Z		Δf
Y	Z	
Benzoic acid	3-methylbenzoic acid	− 0.0105
2-Methylbenzoic acid	2,3-dimethylbenzoic acid	− 0.0184
2-Methylbenzoic acid	2,5-dimethylbenzoic acid	− 0.0268
3-Methylbenzoic acid	3,5-dimethylbenzoic acid	− 0.0402
4-Methylbenzoic acid	3,4-dimethylbenzoic acid	− 0.0165
2,3-Dimethylbenzoic acid	2,3,5-trimethylbenzoic acid	− 0.0131
2,4-Dimethylbenzoic acid	2,4,5-trimethylbenzoic acid	+ 0.0125
2,4-Dimethylbenzoic acid	2,3,4-trimethylbenzoic acid	− 0.0499
2,5-Dimethylbenzoic acid	2,3,5-trimethylbenzoic acid	− 0.0047
2,6-Dimethylbenzoic acid	2,3,6-trimethylbenzoic acid	− 0.0061
3,4-Dimethylbenzoic acid	3,4,5-trimethylbenzoic acid	− 0.0161
		Mean value − 0.017±0.005[a]

[a] For the error, see note, Table 7.

Table 16. Change in f on the introduction of *m*-methyl groups into N-(2-diethylaminoethyl)-benzamides.

Structural change Y → Z		Δf
Y	Z	
N-(2-Diethylaminoethyl)-benzamide	VII	− 0.0395
VII	XXXVI	− 0.0232
XIII	XXXII	− 0.0768
XXIII	LIII	− 0.0136
XXIII	XLI	− 0.0239
XXXII	LXIII	+ 0.0189
		Mean value − 0.026±0.013[a]

[a] For the error, see note, Table 7.

strength gives a measure of the probability for a given transition, and hence also of the degree of conjuagtion. The low value of f when *ortho* methyl groups are present is probably due to the out-of-plane twisting of the carbonyl group (*cf.* above and Refs.[13,18,26,27]). This theory is supported by UV spectra of the benzonitriles, which do *not* show any *ortho* effect. Thus, benzonitrile [19], *o*-tolunitrile [19], and 2,6-dimethylbenzonitrile (see Fig. 28) for the actual band have about the same ε_{max} value, *i.e.* $\sim 9.5 \times 10^3$.

The effect of *meta* and *para* methyl groups upon the intesities of spectra is not yet fully understood.

Since the degree of conjugation between the carbonyl group and the benzene nucleus influences both the ionization constant and the oscillator strength,

Table 17. Change in f on the introduction of *o*-methyl groups into benzoic acids.

Structural change Y → Z		Δf
First *o*-methyl group:		
Y	Z	
Benzoic acid	2-methylbenzoic acid	− 0.0838
3-Methylbenzoic acid	2,3-dimethylbenzoic acid	− 0.0917
3-Methylbenzoic acid	2,5-dimethylbenzoic acid	− 0.1001
4-Methylbenzoic acid	2,4-dimethylbenzoic acid	− 0.1209
3,4-Dimethylbenzoic acid	2,3,4-trimethylbenzoic acid	− 0.1543
3,4-Dimethylbenzoic acid	2,4,5-trimethylbenzoic acid	− 0.0919
3,5-Dimethylbenzoic acid	2,3,5-trimethylbenzoic acid	− 0.0646
		Mean value − 0.101±0.011[a]
Second *o*-methyl group:		
Y	Z	
2-Methylbenzoic acid	2,6-Dimethylbenzoic acid	− 0.0255
2,3-Dimethylbenzoic acid	2,3,6-trimethylbenzoic acid	− 0.0132
2,5-Dimethylbenzoic acid	2,3,6-trimethylbenzoic acid	− 0.0048
2,4-Dimethylbenzoic acid	2,4,6-trimethylbenzoic acid	− 0.0866
		Mean value − 0.033±0.019[a]

[a] For the error, see note, Table 7.

a certain parallellism might occur between ΔpK_a and Δf. Hence, in Table 19 ΔpK_a and Δf for the various structural changes studied, have been listed side by side.

EXPERIMENTAL

The *N-(dialkylaminoalkyl)benzamides* and their *hydrochlorides* were analytical samples of high purity. Regarding the preparation and purification of these, see Lüning [1].

N-(2-Diethylaminoethyl)benzamide was obtained from benzoyl chloride and 1-amino-2-diethylaminoethane by the general method described by Lüning [1]. The hydrochloride was prepared and recrystallized several times from a mixture of *iso*propyl ether and methyl ethyl ketone m. p. 88°−89°. (Found: Cl 13.8. Calc. for $C_{13}H_{21}ClN_2O$: Cl 13.8.) The melting point of the hydrochloride does not agree with that given for the same compound by Hazard *et al.*[20] who give neither an acceptable method of synthesis nor any proof of the composition. The base was liberated from the hydrochloride and taken up in ether, which was evaporated, leaving the base as an oil; $n_D^{25} = 1.5281$. (Found: Equiv. wt. 223. Calc. for $C_{13}H_{20}N_2O$: Equiv. wt. 220.3.)

Concerning the preparation of *benzoic acids* see Lüning [1]. Each benzoic acid was recrystallized several times from ethanol; all the melting points agreed with those given by Smith and Stanfield [21]. The melting points of 2,3,5-trimethylbenzoic acid and 3,4,5-trimethylbenzoic acid, which were not reported by these authors, were in accordance with those given by Jannasch and Weiler [22].

Table 18. Change in f on the introduction of *o*-methyl groups into N-(2-diethylaminoethyl)-benzamides.

Structural change Y → Z		Δf
First *o*-methyl group:		
Y	Z	
N-(2-Diethylaminoethyl)-benzamide	I	− 0.0988
VII	XIX	− 0.0603
XIII	XXIII	− 0.1574
VII	XXVII	− 0.0603
XXXII	XLI	− 0.1045
XXXII	LIII	− 0.0942
XXXVI	XLVI	− 0.0371
		Mean value − 0.088±0.015[a]
Second *o*-methyl group:		
Y	Z	
XXIII	LVIII	− 0.034 $_7$

[a] For the error, see note, Table 7.

Table 19. Comparison between ΔpK_a and Δf for substitution of methyl groups into different positions in the benzene nucleus of benzoic acids and N-(2-diethylaminoethyl)-benzamides. The number of calculations underlying each mean is given in parenthesis.

Position of methyl group introduced	Benzoic acids		N-(2-Diethylaminoethyl)-benzamides	
	Δf	ΔpK_a	Δf	ΔpK_a
First *ortho* [a]	−0.101 ± 0.011 [b] (7)	−0.30±0.05[b] (7)	−0.088 ± 0.015 [b] (7)	−0.171 ± 0.004 [b] (7)
Second *ortho* [a]	−0.033 ± 0.019 [b] (4)	−0.65±0.07[b] (4)	−0.035 (1)	−0.187 ± 0.010 [b] (4)
Meta	−0.017 ± 0.005 [b] (11)	+0.03±0.04[b] (11)	−0.026 ± 0.013 [b] (6)	−0.004 ± 0.004 [b] (11)
Para	+0.057 ± 0.016 [b] (7)	+0.26±0.03[b] (7)	+0.052 ± 0.015 [b] (6)	+0.029 ± 0.003 [b] (7)

[a] The first and the second *ortho* methyl group often give rise to different variations of f and pK_a values, see also text p. 338.
[b] For the error, see note, Table 7.

2,6-Dimethylbenzonitrile was prepared from 2,6-dimethylaniline by a Sandmeyer reaction, and purified by means of sublimation.

The duration and latency time of anesthesia were measured on rabbit cornea according to the method given by Wiedling [2] *. The LD50 values were calculated by the method of Kärber [23]. For each toxicity determination, at least 60 male white mice were used. The compound, in the form of a 3 "per cent" solution (weight/volume), was injected under the dorsal skin. The base was dissolved in 1,2-propylene glycol, the equivalent amount of hydrochloric acid was added, followed by water to give the proportion propylene glycol: water equal to 1:1 (v/v). The "pH value" was adjusted to 6.5 before injection.

The solutions for pK_a determinations were prepared in four different ways: (1) Benzoic acids were dissolved in water by gentle heating for a short period, and the solutions neutralized to about 50 % with NaOH. (2) Benzoic acids were dissolved in a slight excess of carbonate-free NaOH which was then titrated back to about 50 % with HCl. (3) Hydrochlorides of bases were dissolved in water and neutralized to 30—60 % with NaOH. (4) Bases were dissolved in a slight excess of HCl which was then titrated back to about 50 % with NaOH. The pH values given in Tables 3—5 are the means of two measurements, obtained by the aid of different glass electrodes. For details in the measurements, and a diagram of the cell used, see Löfgren [8] and Lindström [24].

The ultraviolet absorbtion spectra were measured with the aid of a Beckman DK2 recording quartz spectrophotometer, using a hydrogen lamp as a light source. The wavelength scale is logarithmic. The values of $\int_{-\infty}^{+\infty} \Delta\varepsilon_\nu d\nu$ were obtained by calculation of $\sum_{-\infty}^{+\infty} \Delta\varepsilon\Delta\nu$ of the area between the recorded curve and an arbitrary reference curve, as is demonstrated in Figs. 1—28. $\Delta\varepsilon$ is the difference in molar extinction between the measured curve and the reference curve. The reference curves are included in the figures as dashed lines.

The infrared spectra were measured with the aid of a Beckman IR 5 double beam Infrared Recording Spectrophotometer, using a sodium chloride cell (0.1 mm).

The toxicity determinations were made at the *Battelle Institute*, Frankfurt, Germany, with the aid of a grant from *Aktiebolaget Astra*, Södertälje, Sweden. The measurements of the local anesthetic activity were performed in the research laboratories of *Aktiebolaget Astra*.

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* *Cf.* also Löfgren and Tegner [3].

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