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Syntheses of N-[(4-Morpholinyl)alkyl]benzamides

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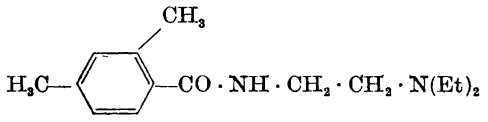
Twelve new N-[(4-morpholinyl)alkyl]benzamides have been synthesized and examined for their sedative and local anesthetic actions. The compounds were prepared from the corresponding 4-(aminoalkyl)-morpholines, three of which have not been described previously. The ionization constant, K_a, of one of the N-[(4-morpholinyl)alkyl]benzamides, *i.e.* N-[2-(4-morpholinyl)ethyl]-2,4-dimethylbenzamide, has been determined.

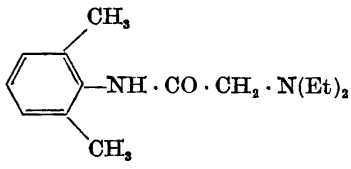
A fairly large number of N-(dialkylaminoalkyl)benzamides have been synthesized by Löfgren and Stoffel [1], and by Lüning [2]. The compounds were studied pharmacologically (toxicity, local anesthetic action) and many of them were also subjected to physico-chemical measurements (ionization constant K_a, absorption in the ultraviolet) [2]. All these benzamides possess local anesthetic action [1,2], and some of them, for instance N-(diethylaminoethyl)-2,4-dimethylbenzamide [2] (A) exhibited — when tested in white mice — a pronounced,



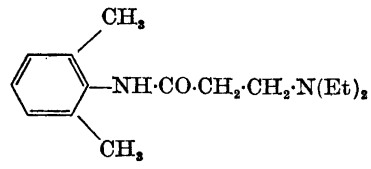
A

though not strong CNS depression (sublethal dose, no convulsions) [3]. Among the local anesthetics of the Xylocaine ® type, Xylocaine itself * and several other members [5] also show a weak though distinct sedative action. If in Xylocaine (B) or in β-diethylaminoethyl-2,6-dimethylpropionanilide (C), the diethylamino group is substituted by the morpholino group, the change in structure is accompanied by a marked increase in the depressive action, and at the same time by a pronounced decrease in local anesthetic potency [6]. With regard to these facts, it seemed of interest to synthesize and investigate pharmacologically N-[(4-morpholinyl)ethyl]-2,4-dimethylbenzamide, *i.e.* a compound that

* See for instance Wiedling [4].



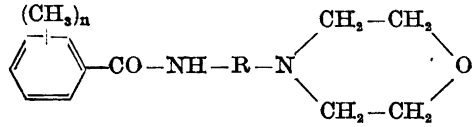
B



C

differs from the CNS-active benzamide A in having a morpholino group instead of a diethylamino group. It was plausible to assume that the new morpholino derivative would possess a stronger CNS-depressive action than the diethylamino derivative. The experiments showed, however, that such a prediction was false (*cf.* below).

In the present work twelve N-[(4-morpholinyl)alkyl]benzamides have been synthesized and studied with regard to their sedative and local anesthetic actions. The compounds are of the general type



where n is 1, 2 or 3, the methyl or methyls belong to the positions 4, 2,4, 2,6, 3,5 or 2,4,6, and R is a lower straight or branched alkylene chain. The combinations of the actual groups are avident from Table 1, where the compounds (I—XII) are listed.

To obtain information of the basic strengths of these morpholino derivatives as compared with the corresponding diethylamino derivatives, one of the

Table 1. Chemical data of bases prepared (I—XII). All the bases are recrystallized from di-*iso*propyl ether.

	Compound		Yield %	M.p., °C corr.	Equivalen weight [a]	
	Name	Empirical formula			Calc.	Fou
I	N-[2-(4-Morpholinyl)ethyl]-4-methylbenzamide	$C_{14}H_{20}N_2O_2$	78	118—119	248.3	24
II	N-[2-(4-Morpholinyl)ethyl]-2,4-dimethylbenzamide	$C_{15}H_{22}N_2O_2$	64	122—124	262.3	26
III	N-[2-(4-Morpholinyl)ethyl]-3,5-dimethylbenzamide	$C_{15}H_{22}N_2O_2$	93	112—113	262.3	26
IV	N-[2-(4-Morpholinyl)ethyl]-2,6-dimethylbenzamide	$C_{15}H_{22}N_2O_2$	78	110—111	262.3	26
V	N-[2-(4-Morpholinyl)ethyl]-2,4,6-trimethylbenzamide	$C_{16}H_{24}N_2O_2$	78	111—113	276.4	27
VI	N-[3-(4-Morpholinyl)propyl]-4-methylbenzamide	$C_{15}H_{22}N_2O_2$	78	80— 81	262.3	26
VII	N-[3-(4-Morpholinyl)propyl]-2,4-dimethylbenzamide	$C_{16}H_{24}N_2O_2$	73	55— 56	276.4	27
III	N-[3-(4-Morpholinyl)propyl]-2,6-dimethylbenzamide	$C_{16}H_{24}N_2O_2$	82	82— 83	276.4	27
IX	N-[3-(4-Morpholinyl)propyl]-2,4,6-trimethylbenzamide	$C_{17}H_{26}N_2O_2$	91	111—112	290.4	29
X	N-[1-Methyl-2-(4-morpholinyl)ethyl]-2,4-dimethylbenzamide	$C_{16}H_{24}N_2O_2$	93	87— 88	276.4	27
XI[b]	N-[1,2-Dimethyl-3-(4-morpholinyl)propyl]-2,6-dimethylbenzamide	$C_{18}H_{28}N_2O_2$	41	131—132	304.4	30
XII	N-[2,2-Dimethyl-3-(4-morpholinyl)propyl]-2,6-dimethylbenzamide	$C_{18}H_{28}N_2O_2$	83	92— 93	304.4	30

a Concerning the determination of the equivalent weights of the bases, see footnote, p. 1473.

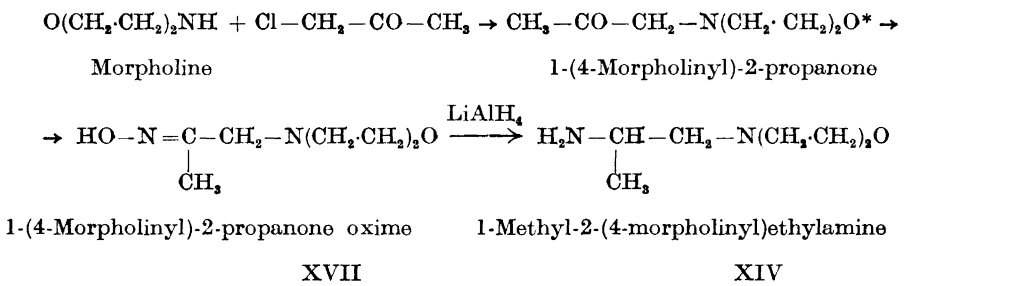
b Data given for compound XI refer to the racemate of lower solubility (in di-*iso*propyl ether; *cf.* above). It w rther purified by recrystallization from di-*n*-butyl ether. (The racemate of higher solubility was not isolated.)

twelve compounds, *i.e.* the above mentioned N-[(4-morpholinyl)ethyl]-2,4-dimethylbenzamide, was subjected to pK_a determination (see p. 1475); the ionization constant of the corresponding diethylamino derivative is known from investigations by Lüning [2] who determined pK_a values of a fairly large number of N-(diethylaminoalkyl)benzamides.

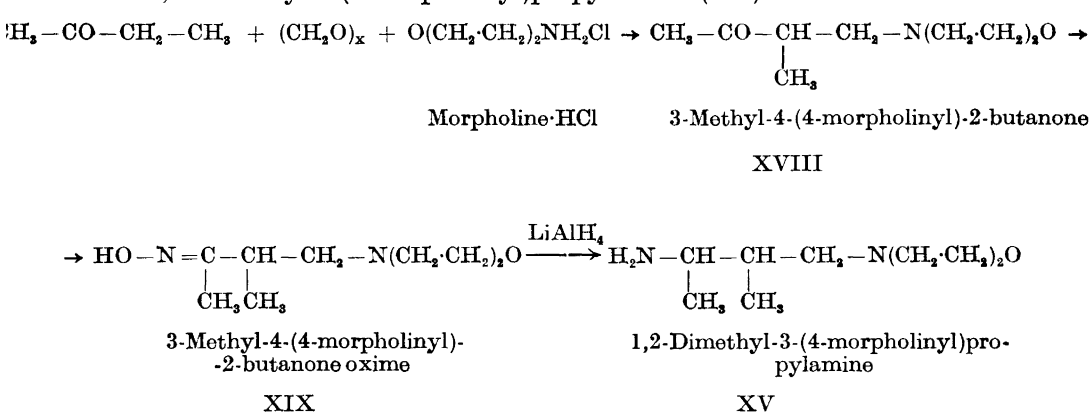
Each of the compounds I—XII was synthesized by condensing a benzoyl chloride with a 4-(aminoalkyl)morpholine in the molar ratio 1:1.6.

4-(2-Aminoethyl)morpholine was prepared according to Hultqvist and Northey [7] by reacting ethylenediamine with bis(β-chloroethyl) ether in the molar ratio 3:1. The same type of synthesis was employed to obtain 4-(3-aminopropyl)morpholine (XIII), ethylenediamine being substituted by trimethylenediamine. XIII has earlier been prepared by Uthermohlen and Hamilton [8] who obtained the compound in a low yield from a Gabriel synthesis. The three other amines, *viz.* 1-methyl-2-(4-morpholinyl)ethylamine (XIV), 1,2-dimethyl-3-(4-morpholinyl)propylamine (XV), and 2,2-dimethyl-3-(4-morpholinyl)propylamine (XVI), were prepared as outlined below under *A*, *B* and *C*.

A. 1-Methyl-2-(4-morpholinyl)ethylamine (XIV):



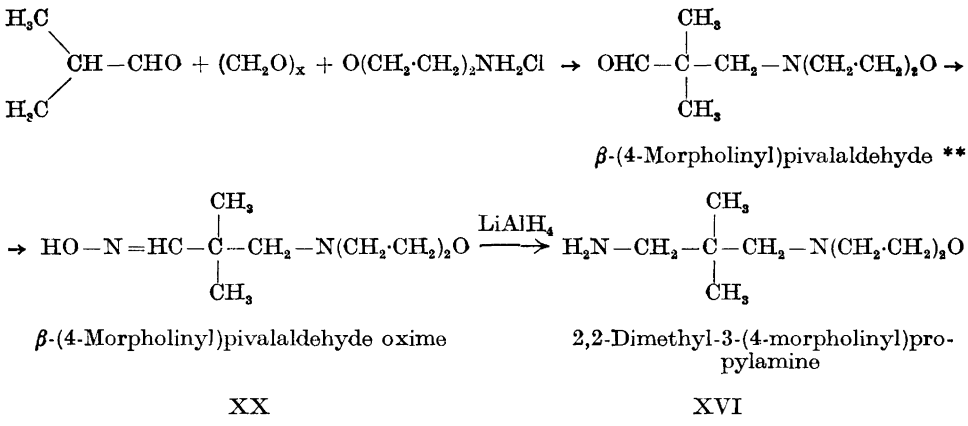
B. 1,2-Dimethyl-3-(4-morpholinyl)propylamine (XV):



* Prepared earlier in this way by Mason and Ross [9].

Compound XVIII was prepared according to the method given by Mannich and Hof [10] for the synthesis of 4-dimethylamino-3-methyl-2-butanone. They obtained the latter compound as a main product in a yield of 80 %. The collected, higher boiling by-product, they supposed to be the linear isomer (satisfactory proof not given). Cardwell [11] has later proved the correctness of the structure of the main product, and found the by-product to be a diamine, *i.e.* either 3,3-bis(dimethylaminoethyl)-2-butanone or 1,5-bis(dimethylamino)-2-methyl-3-pentanone. Recently, Blicke and McCarty [12] were able to show that the last mentioned compound is identical with Mannich and Hof's by-product. In the literature, no evidence can be found that a linear amine is formed from methyl ethyl ketone or methyl propyl ketone in the Mannich reaction *. (*Cf.* for instance the reactions in which (a) methyl ethyl ketone and diethylamine [11,14] (b) methyl ethyl ketone and piperidine [10] or (c) methyl propyl ketone and dimethylamine [10], are involved.

C. 2,2-Dimethyl-3-(4-morpholinyl)propylamine (XVI):



All the oximes (XVII, XIX, XX) and diamines (XIV, XV, XVI) are new compounds. The reduction of the oximes with $LiAlH_4$ in ether could not be carried out in the usual way, lumps being formed when the ethereal solution of the oxime was added dropwise to the $LiAlH_4$-suspension. However, the reaction could be performed smoothly by adding the $LiAlH_4$-suspension to the oxime solution. The best yield was obtained when two moles of $LiAlH_4$ per mole of oxime were used. Compound XI contains two asymmetric carbon atoms, and thus appeared as a mixture of two racemates. By recrystallization from di-*iso*propyl ether, the racemate of lower solubility was obtained. It was further purified by another recrystallization from di-*n*-butyl ether. The racemate of higher solubility was difficult to purify, and no definite product was isolated.

Due to the morpholino moiety, compounds I—XII should be rather weak bases. For N-(2-diethylaminoethyl)-2,4-dimethylbenzamide, the pK_a value at 25° is known from measurements by Lüning [2]. In order to compare this pK_a

* Unfortunately, Schröter [13] in a very well-known encyclopedia of synthetic organic chemistry [13] has misinterpreted the work of Cardwell, and reported the above mentioned by-product to be the linear 1-dimethylamino-3-pentanone. This mistake might, in several cases, have given rise to confusion as regards the products in the Mannich reaction with ketones.

** Prepared earlier in this way by Cheney [15].

value with that of N-[2-(4-morpholinyl)ethyl]-2,4-dimethylbenzamide (II), measurements were made on the latter compound, using the same technique as that given by Lüning [2] (*cf.* also Lindström [16], Löfgren [17]).

pH measurements at 25° were made under such conditions that the validity of the equation

$$pK_a = pH - \log \frac{C_B}{C_{BH^+}} - pf_{BH^+} \quad (1)$$

was fulfilled (*cf.* experimental part). pf_{BH^+} was computed from the Debye-Hückel formula:

$$pf_{BH^+} = \frac{0.358 \cdot z^2 \cdot \Gamma^{1/2}}{1 + 10^8 d_{BH^+} \cdot 0.2325\, \Gamma^{1/2}} \quad (2)$$

where $\Gamma = \Sigma C_i z_i^2$ is the ionic concentration, and d_{BH^+} is the effective diameter of the ion BH^+. In the actual case d_{BH^+} is set to 8×10^{-8} cm (*cf.* Löfgren [17], Lindström [16], Lüning [2]).

The apparatus used was a cell of the type:

Glass electrode/H^+(aq.)// KCl (satd.)/Hg_2Cl_2,Hg.

For this cell we have:

$$pH = \frac{E - E_o}{k} \quad (3)$$

(at 25°, $k = 59.16$)

E_o was obtained by making use of the pH values of Hitchcock and Taylor's [18] standard buffers (based on exact thermodynamic pK_a values). Accordingly, E_o may be considered as the sum of two constant quantities:

$$E_1 + E_j = E_o \quad (4)$$

E_1, which is a function of the glass electrode and of the calomel electrode, does not include the junction potential, and E_j should be regarded as the junction potential between satd. KCl and pure water.

Thus, Hitchcock and Taylor [18] standardized their buffers from an E_o value which was obtained from the relation:

$$E' = E - kpK_a + k \log \frac{C_{HA}}{C_A} + kA\sqrt{\mu} = E_o + kB\mu \quad (5)$$

The left member contains known quantities. In plotting E' against μ and drawing the best line to represent the observed points, the intercept E_o at zero ionic strength was obtained. In this way Hitchcock and Taylor derived an E_o value which almost exactly agrees with that of Bates [19] (based on measurements which are different from those of Hitchcock and Taylor).

Thus, when measuring pH in an unknown solution of *low ionic strength* (in our case $\mu \sim 5 \times 10^{-3}$, *cf.* Table 2), it may be assumed that the junction potentials included in E and E_0 should, to a high degree, cancel each other. However, it must be emphasized that it is clearly impossible to determine the

pH of a solution that is "unknown" in every sense of the word with an uncertainty less than $\pm$ 0.02 unit (*cf.* Bates [19]).

pK_a of compound II was thus found to be 6.10 (mean value of three different measurements; *cf.* experimental part). Lüning's [2] value for N-(2-diethylaminoethyl)-2,4-dimethylbenzamide is 8.92. Hence, ΔpK_a is 2.82 *. Thus, the morpholino compound is a much weaker base than the diethylamino compound. This is consistent with the theory, since the 3-oxapentamethylene radical, as compared with the two ethyl groups, must have a much smaller electron-repelling effect. — A comparison with the ΔpK_a value for *diethylamine → morpholine* is of interest. The two ΔpK_a values should, of course, not be identical, but should lie close to each other (within a few tenths). For diethylamine, Hall and Sprinkle [20] give a pK_a value (at 25°) equal to 10.98. According to Hall [21], the corresponding morpholine value is 8.36. Hence, ΔpK_a should be equal to 2.62.

The twelve compounds were investigated pharmacologically as to their sedative and local anesthetic actions. Bearing in mind the change in CNS activity that occurs with the "Xylocaines" when the morpholino group is substituted for the diethylamino group (see p. 1467) one could suppose that N-[(4-morpholinyl)ethyl]-2,4-dimethylbenzamide (II) should have a more pronounced hypnotic action than the corresponding diethylamino derivative, *i.e.* N-(diethylaminoethyl)-2,4-dimethylbenzamide (*cf.* p. 1467). However, this was not found to be the case: when tested in white mice (subcutaneous injections), the diethylamino compound gave a distinct though not strong hypnotic effect, whereas the morpholino derivative (II) showed a very weak action, if any**. Nor did the other eleven compounds (I, III—XII) exhibit a distinct positive action.

Table 2. Determination of the ionization constant of N-[2-(4-morpholinyl)ethyl]-2,4-dimethylbenzamide (II). The substance used is the *hydrochloride* (mol. wt. 298.8); NaOH-solution = 0.0333$_0$ M; test solution = 100 ml. The double e.m.f. values arise from the two glass electrodes used.

Salt weighed g	NaOH added ml	$\log \frac{C_B}{C_{BH^+}}$	$1/2\,\Gamma \times 10^3$	pf_{BH^+}	$-E_o$ mV	$+E$ mV	$E-E_o$ mV	pH	pK_a
0.1155	3.98	−0.283	3.865	0.028	157.2 152.7	189.4 193.0	346.6 345.7	5.859	6.11
0.1638	9.80	0.167	5.482	0.032	157.2 152.7	215.2 219.3	372.4 372.0	6.291	6.09
0.1202	5.87	−0.024	4.023	0.028	157.2 152.7	204.2 208.4	361.4 361.1	6.106	6.10
							Mean value =		6.10

* Both pK_a values are subjected to almost the same *systematic* error, caused by the potential at the liquid junction (*cf.* above). In ΔpK_a, however, this type of error is almost eliminated.

** The comparisons made by injections of equimolar doses per kg of body weight.

For three of the compounds, *i.e.* I, II, and X, the LD50 values were determined by subcutaneous injections in white mice. According to these experiments, all three compounds are relatively non-toxic and none of the LD50 values (in grams of the base per kg of body weight) was found to be lower than 0.8 or higher than 1.3.

As regards the local anesthetic action, none of the twelve compounds proved to be active when applied to the human tongue by rubbing *.

EXPERIMENTAL

A. Syntheses **

4-(3-Aminopropyl)morpholine (XIII). This compound was made by following the directions of Hultqvist and Northey [7], who prepared 4-(2-aminoethyl)morpholine. Instead of 57.5 % ethylenediamine, 81.5 % trimethylenediamine was used. 4-(3-Aminopropyl)morpholine distilled as a colourless oil, b.p. 139—140°/43—45 mm, n_D^{20} 1.4768. (These values agree with those given by Uthermohlen and Hamilton [8], who prepared the amine by a Gabriel synthesis). Yield 41 %.

1-(4-Morpholinyl)-2-propanone oxime (XVII). Saturated water solutions of hydroxylamine·HCl, 113 g (1.63 moles), and of $NaOAc \cdot 3H_2O$, 440 g (3.23 moles), were prepared. To 230 g (1.61 moles) of 1-(4-morpholinyl)-2-propanone [9], the hydroxylamine and the acetate solutions were consecutively added. The oxime immediately precipitated as a white crystalline mass. After cooling, the crystals were sucked off an extracted with the minimum quantity of boiling benzene. The hot combined extracts were dried with anhydrous sodium sulphate. This was removed by filtration, and on cooling colourless crystals of m.p. 103—104° (corr.) were obtained; yield 162 g (1.02 moles, 63 %). (Found: Equiv. wt. 158. Calc. for $C_7H_{14}N_2O_2$: 158.2.)

1-Methyl-2-(4-morpholinyl)ethylamine (XIV). In a three-necked 2 l flask equipped with a reflux condenser, a sealed Hershberg stirrer and a dropping funnel, 80 g (0.51 mole) of 1-(4-morpholinyl)-2-propanone oxime (XVII) were dissolved in 750 ml of absolute ether. To this solution a suspension (*cf.* p. 1470) of 40 g (1.1 moles) of $LiAlH_4$ in 500 ml of dry ether was added under rapid stirring during 3 h. The complex formed, as well as the excess of $LiAlH_4$, were decomposed as described by Amundsen and Nelson [22]. The inorganic salts were filtered off and washed with ether. After removing the solvent, the amine was distilled as a colourless oil, b.p. 96—98°/20 mm, n_D^{25} 1.4620, yield 20.5 g (0.142 mole, 28 %). (Found: Equiv. wt. 72.0. Calc. for $C_7H_{16}N_2O$ (144.2): 72.1.)

3-Methyl-4-(4-morpholinyl)-2-butanone (XVIII). According to Mannich and Hof's [10] preparation of 4-dimethylamino-3-methyl-2-butanone, a mixture of 144 g (2.00 moles) methyl ethyl ketone, 123.5 g (1.00 mole) of morpholine·HCl, 40 g of paraformaldehyde (1.3 moles of formaldehyde) and 50 ml of *iso*propyl acolhol was refluxed on the steam bath for 6 h. After cooling, the volatile products were driven off under reduced pressure. 200 g of a 50 % sodium hydroxide solution were added, and the mixture was extracted three times with 200 ml of ether. The combined extracts were dried over Na_2SO_4 and after filtering and removing the ether, the residue was purified by distillation. The main fraction (70 g) distilled at 100—115°/12 mm. After redistillation through a 30 cm asbestos-wrapped Vigreux column, 52 g of a colourless oil of b.p. 136—139°/31—32 mm were collected; n_D^{25} 1.4657. (Found: Equiv. wt. 173. Calc. for $C_9H_{17}NO_2$: 171.2.)

Hydrochloride. Colourless crystals from acetone-methyl ethyl ketone of m.p. 146—147° (corr.). (Found: Cl*** 17.1. Calc. for $C_9H_{18}ClNO_2$ (207.7): Cl 17.1.)

3-Methyl-4-(4-morpholinyl)-2-butanone oxime (XIX). This oxime was obtained from 3-methyl-4-(4-morpholinyl)-2-butanone (XVIII), hydroxylamine hydrochloride, and

* The *bases* as well as the *hydrochlorides* were tested.

** The determination of equivalent weights of the synthesized bases was made by titrating them in glacial acetic acid with 0.1 N perchloric acid; BZL-Blue (CIBA) was used as an indicator.

*** Potentiometr. titration.

sodium acetate in the same manner as described in the preparation of XVII. The oxime appeared as an oily layer, which was taken up in ether. The ethereal solution was dried over Na_2SO_4, the ether removed, and the residue distilled. The oxime was collected as a colourless viscous oil, b.p. 172—174°/24—25 mm, n_D^{25} 1.4896, yield 73 %. (Found: Equiv. wt. 186. Calc. for $C_9H_{18}N_2O_2$: 186.3.)

1,2-Dimethyl-3-(4-morpholinyl)propylamine (XV). 60 g (0.32 mole) of 3-methyl-4-(4-morpholinyl)-2-butanone oxime (XIX) in 300 ml of absolute ether was reduced with 25 g (0.66 mole) of $LiAlH_4$ in 400 ml of absolute ether as described under compound XIV. By distillation the amine was obtained as a colourless oil, b.p. 124—125°/17—18 mm, n_D^{25} 1.4672, yield 18.5 g (0.107 mole, 33 %). (Found: Equiv. wt. 86.0. Calc. for $C_9H_{20}N_2O$ (172.3): Equiv. wt. 86.1.)

β-(4-Morpholinyl)pivalaldehyde oxime (XX). This oxime was made from β-(4-morpholinyl)pivalaldehyde, hydroxylamine·HCl, and sodium acetate in the same manner as described in the preparation of XVII. The oxime separated as an oily layer, and was taken up in ether. The ethereal solution was dried over Na_2SO_4, the ether removed, and the residue distilled under reduced pressure. The main fraction which was obtained in a yield of 86 % was a colourless oil of distinct b.p., but titration of the base gave an equivalent weight (191) that differed a few per cent from the calculated one (186). Another distillation did not result in an acceptable value. Therefore, the base was dissolved in a mixture of dry acetone-dry ether and the *hydrochloride* was precipitated by adding somewhat more than the calculated amount of dry ether·HCl. The crystals were washed with a mixture of dry acetone-dry ether and then recrystallized from absolute ethanol. The salt was obtained in the form of colourless needles. On chlorine analysis the salt gave the theoretical value (*cf.* below). From this hydrochloride, the base was regenerated and isolated by distillation. Viscous colourless oil, b.p. 166—167°/24—25 mm, n_D^{25} 1.4846. The over-all yield from β-(4-morpholinyl)pivalaldehyde was 46 %. (Found: Equiv. wt. 187. Calc. for $C_9H_{18}N_2O_2$: 186.3.)

Hydrochloride. Colourless needles from absolute ethanol (*cf.* above); m.p. 186—187° (decomp., corr.). (Found *: Cl 15.9. Calc. for $C_9H_{19}ClN_2O_2$ (227.7): Cl 15.9.) **

2,2-Dimethyl-3-(4-morpholinyl)propylamine (XVI). 100 g (0.54 mole) of β-(4-morpholinyl)pivalaldehyde oxime in 500 ml of absolute ether was reduced with 42 g (1.1 moles) of $LiAlH_4$ in 500 ml of absolute ether in the same way as described under compound XIV. The amine distilled as a colourless oil, b.p. 118—120°/22—23 mm, n_D^{25} 1.4661, yield 32 g (0.19 mole, 35 %). (Found: Equiv. wt. 86.0. Calc. for $C_9H_{20}N_2O$ (172.3): Equiv. wt. 86.1.)

N-[(4-Morpholinyl)alkyl]benzamides (I—XII, *cf.* Table 1). All twelve compounds were synthesized according to the same method by reacting a benzoyl chloride with an 4-(aminoalkyl)morpholine; the composition of the reactants is evident from Table 1. (The syntheses of the 4-(aminoalkyl)morpholines are described in text above.) The following method was used: A solution of 0.059 mole of the methyl substituted benzoyl chloride in 50 ml of absolute ether is placed in a three-necked flask equipped with a reflux condenser, a dropping funnel and a teflon sealed stirrer. Under vigorous stirring, a solution of 0.094 mole of the 4-(aminoalkyl)morpholine in 50 ml of dry ether is introduced during a period of 30 min. The apparatus is then arranged for downward distillation *in vacuo*. To the turbid mixture, 50 ml of 2 M sodium hydroxide (0.10 mole) are added. Under reduced pressure and vigorous stirring, the ether is then driven off at a bath temperature of 30 °. The precipitate is sucked off, washed two times with small quantities of ice-cold 6 M ammonia and dried in a desiccator. From di-*iso*propyl ether the product is obtained as colourless crystals. The crude product of compound XI consisted of two racemates. On recrystallization from di-*iso*propyl ether, the racemate of lower solubility was easily collected and further purified by another recrystallization from di-*n*-butyl ether. The racemate of higher solubility was not isolated. Yields, melting points and analytical data of the twelve bases are shown in Table 1.

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* Potentiometr. titration.

** The *hydrochloride* has been prepared previously by Cheney [15] who gave the m.p. 175.5° (decomp.). (The *base* has not been described previously.)

Table 3. Melting points and analytical data of the *hydrochlorides* of compounds I—XII.

Hydrochloride of	Empirical formula	M.p., °C corr.	Analysis, % Calc. Cl	Analysis, % Found Cl [a]
I	$C_{14}H_{21}ClN_2O_2$	196—197	12.5	12.6
II	$C_{15}H_{23}ClN_2O_2$	171—172	11.9	11.8
III	$C_{15}H_{23}ClN_2O_2$	193—195	11.9	11.9
IV	$C_{15}H_{23}ClN_2O_2$	157—158	11.9	11.8
V	$C_{16}H_{25}ClN_2O_2$	187—188	11.3	11.4
VI	$C_{15}H_{23}ClN_2O_2$	167—168	11.9	11.9
VII	$C_{16}H_{25}ClN_2O_2$	142—143	11.3	11.2
VIII	$C_{16}H_{25}ClN_2O_2$	190—191	11.3	11.3
IX	$C_{17}H_{27}ClN_2O_2$	211—213	10.9	10.9
X	$C_{16}H_{25}ClN_2O_2$	141—142	11.3	11.3
XI[b]	$C_{18}H_{29}ClN_2O_2$	232—234	10.4	10.5
XII	$C_{18}H_{29}ClN_2O_2$	228—230	10.4	10.5

[a] The hydrochlorides were titrated potentiometrically with 0.1 M $AgNO_3$.
[b] The hydrochloride of the racemate that has the *lower* solubility (*cf.* p. 1474).

Hydrochlorides of compounds I—XII. In 20 ml of dry acetone 0.0040 mole of the base was dissolved. To this solution 0.0060 mole of dry hydrogen chloride in dry ether was added, and the precipitation completed by the addition of absolute ether. The precipitate was filtered off and recrystallized from a solvent mixture di-*iso*propyl ether-*iso*propanol. Melting points and analytical data of the hydrochlorides are found in Table 3.

B. Determination of the ionization constant K_a for N-[2-(4-morpholinyl)ethyl]-2,4-dimethylbenzamide (II) at 25°.

As pointed out above (*cf.* p. 1471) the determination of the ionization constant, $pK_a^{25°}$, of compound II was carried out by using a cell of the type:

Glass electrode/H^+(aq.)//KCl (satg.)/Hg_2Cl_2, Hg *

To standardize the electrodes, Hitchcock and Taylor's [18] 0.1 M acetate and 0.025 M phosphate buffers were used. Calibration of the cell was made immediately before measuring the solution of unknown pH. The E_0 values (*cf.* Table 2) for the cell, obtained from the two buffer solutions, were never found to deviate more than 0.1 mV from each other. The *hydrochloride* of *N*-[2-(4-morpholinyl)ethyl]-2,4-dimethylbenzamide (II) was weighed, and dissolved in water having a specific conductivity of about 5×10^{-6} $ohm^{-1}cm^{-1}$. A suitable amount of sodium hydroxide was added, and after diluting to definite volume (ionic strength $\sim 5 \times 10^{-3}$) the solution was subjected to pH measurement. The primary data and the results are given in Table 2.

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* As to the technical details of the set, see Löfgren [17], Lindström [16] or Lüning [3].

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