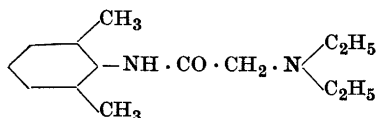


Studies of Local Anaesthetics. VII¹⁻⁶

NILS LÖFGREN and BERTIL TAKMAN

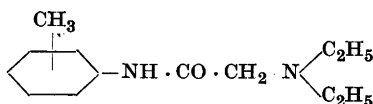
Institute of Organic Chemistry and Biochemistry, University of Stockholm, Stockholm, Sweden

It has already been shown that xylocaine



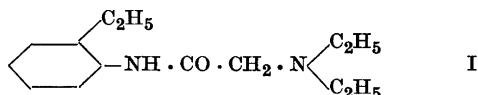
differs markedly from its five nuclear isomers, both in its physico-chemical and its local anaesthetic properties. The *o*-effect in xylocaine has been demonstrated by Löfgren⁵ and by Fischer and Löfgren⁷.

Of the next lower nuclear homologues of xylocaine, *i.e.* the three toluidides,

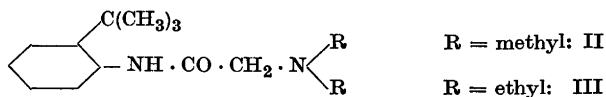


the one with the methyl group in the *o*-position seems to have a somewhat longer duration (tests performed on the tongue, *cf.* also Erdtman and Löfgren⁸), though the effect is not sufficient for the compound to be of use medically (it is also an irritant, *cf.* Löfgren⁵).

In this investigation we have synthesized and studied pharmacologically the *o*-ethyl compound



and two tertiary butyl derivatives



To produce I commercial 2-nitro-ethylbenzene was reduced with iron and acetic acid, essentially by Löfgren's general method^{1, 5}. (The amine has been obtained earlier⁹ by reducing the nitro compound with iron and acetic acid, but with quite a different technique.) From 2-amino-ethylbenzene we prepared ω -chloro-2-ethylacetanilide with the aid of the acetate buffer method¹⁻⁵ and then I in the usual manner.

For the preparation of II and III we started with tert. butylbenzene. This hydrocarbon cannot be nitrated directly to *o*-nitro-tert. butylbenzene, as was found by du Toit Malherbe¹⁰ and by Shoesmith and Mackie¹¹. The latter authors prepared *o*-nitro-tert. butylbenzene by reducing the 4-nitro group in 2,4-dinitro-tert. butylbenzene with H₂S and eliminating the resulting amino group by diazotization in alcoholic solution. We used the same methods of synthesis with slight modifications. 2,4-dinitro-tert. butylbenzene was obtained by Shoesmith and Mackie by nitration of tert. butylbenzene with a nitric-sulphuric acid mixture at 60°, or by nitration of 4-nitro-tert. butylbenzene with nitric acid at 60°. We believe the description of their method must be incomplete, as we could not obtain the desired compound in spite of repeated experiments. After much experimental work we found an acceptable method for preparing 2,4-dinitro-tert. butylbenzene by nitrating 4-nitro-butylbenzene — easily obtained by Shoesmith and Mackie's method — at -10° in a nitric-sulphuric acid mixture, the yield being 86 %. We obtained *o*-amino-tert. butylbenzene from the nitro compound by reducing with iron and acetic acid (a modification of Löfgren's method being applied) and then II and III *via* the chloroacetyl derivative, prepared by the acetate method (*cf.* above); *o*-amino-tert. butylbenzene has been obtained previously¹² by reducing the nitro compound with tin and hydrochloric acid.

All three compounds are active when tested on rabbit cornea. They were compared with xylocaine under the same conditions (pH 6.0). I has about the same duration as xylocaine but a longer latency time. II gives only a very slight anaesthesia, whereas III has twice the duration of xylocaine and a longer latency time. III is weakly irritating to the eye. The toxicities were determined for I and III, the LD₅₀ values as determined from subcutaneous injections in white mice being 0.93 g/kg and 1.52 g/kg respectively. The corresponding value for xylocaine is 0.39 g/kg. Hence, both compounds are less toxic than xylocaine.

I and III were tested for their efficiency on man; xylocaine was compared with I in block anaesthesia (finger anaesthesia), and with III in intercutaneous wheal. Both compounds showed a much shorter duration than xylocaine and, contrary to it, they were strong irritants. Further I, II,

and III were tested for their spasmolytic and histaminolytic power. No appreciable effects were found.

EXPERIMENTAL *

2-Amino-ethylbenzene, $C_8H_{11}N$ (121.2). A solution of 0.16 mole (24 g) of 2-nitro-tert. butylbenzene in 40 ml of ethanol was placed in a beaker fitted with a Hershberg stirrer. 1.33 moles (80 g) of glacial acetic acid were divided into three equal portions, one of which was mixed with the alcoholic solution. Under vigorous stirring 40 ml of water was added and then 0.54 g atom (30 g) of iron powder. The temperature began to rise immediately and was kept below 70° by adding crushed ice directly to the reaction mixture. The remaining two portions of the acetic acid were introduced after 15 and 30 minutes, respectively. When the temperature had dropped to 45° the mixture was heated to 85° for 35 minutes, vigorous stirring being maintained. Then 100 ml of water was added, and the oxide sludge centrifuged off and washed well with 80 ml of 1 *N* acetic acid (the centrifugated solutions protected against atmospheric oxygen by CO_2 -current). The combined aqueous solutions were mixed with 60 g of Rochelle salt dissolved in 60 ml of water, and an excess of concd. ammonia. The liberated base was taken up in ether. After drying (K_2CO_3), the ether was evaporated and the residue distilled under reduced pressure; b.p. $97-100^\circ/16$ mm; (the recorded⁹ b.p. is $210-211^\circ$ at ordinary pressure); yield 0.12 mole (14.5 g; 75 %).

ω -Chloro-2-ethylacetanilide, $C_{10}H_{12}ClNO$ (197.7). 0.120 mole (14.5 g) of 2-aminoethylbenzene was dissolved in 94 ml of glacial acetic acid. After cooling to 10° , 0.132 mole (14.9 g) of chloroacetyl chloride was added rapidly. A solution of 40 g of $AcONa \cdot 3 H_2O$ in 170 ml of water was added quickly under vigorous shaking. After 35 minutes, shaking was discontinued. The precipitate was filtered off, well washed with water and dried in air. The yield was 0.101 mole (20.0 g; 84 %) of colourless crystals. The m.p. of this non-recrystallized product was $91-92^\circ$. Without further purification and elementary analysis, the product was used as the starting material for ω -diethylamino-2-ethylacetanilide.

ω -Diethylamino-2-ethylacetanilide, $C_{14}H_{22}N_2O$ (234.3). In a flask fitted with a reflux condenser protected with a soda-lime tube, a mixture of 0.097 mole (19 g) of ω -chloro-2-ethylacetanilide, 135 ml of dry benzene, and 0.26 mole (19 g) of diethylamine was boiled for six hours. The precipitated diethylammonium chloride was filtered off and washed with dry ether; yield 0.094 mole (10 g; 97 %). The combined benzene and ether solutions were extracted sufficiently with 3 *N* HCl. The aqueous solution was made alkaline with ammonia and the liberated base taken up in ether. The ethereal solution was dried over K_2CO_3 , the solvent evaporated and the residue distilled under reduced pressure. A colourless oil boiling at $131-132^\circ/0.25$ mm was obtained; $n_D^{20} = 1.5269$.

Calcd. C	71.8	H	9.46	Equiv.-weight:	Calcd.	234
Found »	71.7	»	9.41	»	Found **	234

Picrate, $C_{20}H_{25}N_5O_8$ (463.4). Small, yellow laths from methanol-ethanol; m.p. $178-182^\circ$.

* All our melting points are uncorrected.

** Titration of the base in 30 % ethanol with 0.1 *N* HCl, mixed indicator methylene blue - methyl red.

The hydrochloride, the sulphate, and the nitrate are very hygroscopic.

2,4-Dinitro-tert.butylbenzene, $C_{10}H_{12}N_2O_4$ (224.2). 8.8 moles of nitric acid of sp. gr. 1.52 (556 g) and 5.6 moles of concd. sulphuric acid (556 g) were placed in a beaker provided with a mechanical stirrer and surrounded by a freezing mixture. 0.932 mole (167 g) of 4-nitro-*tert.*butylbenzene (prepared by Shoemith and Mackie's method¹¹) was added during two hours, so that the temperature of the reaction mixture was kept at -10° . Stirring was continued for another hour at the same temperature. The reaction mixture was poured on ice. The solid was filtered off, washed with 2 *N* NaOH solution and then with water. After drying, the product was recrystallized from petroleum ether. The compound appeared as small colourless crystals of m.p. $61-63^\circ$. (The recorded¹¹ m.p. is $61-62^\circ$.) The yield was 0.803 mole (180 g; 86 %).

4-Amino-2-nitro-tert.butylbenzene, $C_{10}H_{14}O_2N_2$ (194.2). A mixture of 0.714 mole (160 g) of 2,4-dinitro-*tert.*butylbenzene, 80 ml of ammonia ($d = 0.88$), and 610 ml of ethanol was placed in a beaker provided with a coil tube for cooling water. Under shaking, a rather slow gas-stream of H_2S was bubbled into the reaction mixture. By regulating the water flow of the cooling system the temperature was not allowed to exceed 25° . H_2S was let in until a sample of the mixture did not give an oily residue when boiled for some minutes with about four times its volume of 3 *N* HCl. The reaction mixture, diluted with water, was put into a refrigerator overnight. The solid was filtered off and repeatedly washed with ice-water. The slightly red filtrate was rejected. The solid was then heated under reflux with an excess of 3*N* HCl for five minutes and filtered hot from sulphur. When the hydrochloride commenced to crystallize, an excess of ammonia ($d = 0.88$) was immediately added. A solidifying oil separated from the now red liquid. After one hour in a refrigerator the nitroamine was sucked off, washed with diluted ammonia and dried on porous plates. After recrystallization from alcohol the yield was 0.554 mole (108 g; 78 %) of yellow plates; m.p. $45-50^\circ$. (The recorded¹¹ m.p. is 55° .)

2-Amino-tert.butylbenzene, $C_{10}H_{15}N$ (149.2). The starting material, 2-nitro-*tert.*butylbenzene, was prepared from 4-amino-2-nitro-*tert.*butylbenzene by Shoemith and Mackie's method¹¹ without any modifications.

The amine was prepared by reducing 0.243 mole (43.5 g) of the nitro compound with 0.790 g atom (44.1 g) of iron and 1.88 moles (114 g) of glacial acetic acid in the same way as described for the preparation of 2-amino-ethylbenzene (*cf.* above). However, the amine base was so weak that it could not be extracted sufficiently from the iron oxide sludge in the usual manner with acetic acid, evidently because of its strong *o*-effect. The sludge was therefore dissolved in the minimum quantity of 4 *N* HCl, and, after filtering, the solution was mixed with 90 g of Rochelle salt dissolved in 90 ml of water and with an excess of concd. ammonia. The liberated base was extracted from the dark-coloured solution with ether. After drying (K_2CO_3), the solvent was evaporated and the residue distilled under reduced pressure; yield 0.171 mole (25.5 g; 70 %); b.p. $111-112^\circ/18-19$ mm. (The recorded¹² b.p. is $233-235^\circ$ at ordinary pressure.) The acetyl derivative, synthesized in the usual manner with glacial acetic acid and acetic anhydride, was obtained as colourless needles with m.p. 162° . (The recorded¹¹ m.p. is 161° .)

ω -Chloro-2-tert.butylacetanilide, $C_{12}H_{16}ClNO$ (225.7). This compound was prepared in the same manner as described for ω -chloro-2-ethylacetanilide (*cf.* above). The yield of non-recrystallized product was 82 %. Recrystallized from *n*-butyl ether and from methanol-water the m.p. of the compound was $96-97^\circ$.

Calcd. C	63.6	H	7.15
Found »	63.6	»	7.25

ω-Dimethylamino-2-*tert*-butylacetanilide, $C_{14}H_{22}N_2O$ (234.3). In an iron autoclave a mixture of 0.044 mole (10 g) of *ω*-chloro-2-*tert*-butylacetanilide and a solution of 0.13 mole (6 g) of dimethylamine in 60 ml of dry benzene was heated at 100° for 6 ½ hours. After cooling, the solid was filtered off and washed with dry benzene. From the combined benzene solutions the solvent was evaporated and the residue extracted with hot 3 *N* HCl. After filtering, the solution was purified by shaking out with some ether and then mixed with 10 g of Rochelle salt dissolved in 15 ml of water. An excess of concd. ammonia was added and the liberated base taken up in ether. After drying with K_2CO_3 , the solvent was evaporated and the residue distilled under reduced pressure. A faintly violet oil boiling at 141–142°/0.6 mm was obtained. In spite of repeated distillations the colour remained. The oil was therefore dissolved in dry ether and a dry ethereal solution of HCl added in some excess. The precipitated hydrochloride was filtered off, washed with dry ether and recrystallized from isobutyl alcohol – ethanol. From this salt, the free base was regenerated and again distilled; b.p. 136°/0.3 mm.; yield 0.037 mole (8.7 g; 84 %); $n_D^{20} = 1.5291$.

Calcd. C	71.8	H	9.46	Equiv.-weight:	Calcd.	234
Found »	71.5	»	9.35	»	»	Found 234

Hydrochloride, $C_{14}H_{23}ClN_2O$ (270.8). Colourless leaflets from *n*-propanol-ethanol, easily soluble in water; m.p. 264–265° (decomp.).

Calcd. Cl	13.09
Found »	13.05 (Mohr)

ω-Diethylamino-2-*tert*-butylacetanilide, $C_{16}H_{26}N_2O$ (262.4). In a flask fitted with a reflux condenser protected with a soda-lime tube, a mixture of 0.044 mole (10 g) of *ω*-chloro-2-*tert*-butylacetanilide, 0.115 mole (8.4 g) of diethylamine, and about 50 ml of dry benzene was boiled for ten hours. The precipitated diethylammonium chloride (0.037 mole, 4.1 g, 84 %) was filtered off and washed with dry benzene. The combined benzene solutions were extracted sufficiently with 2 *N* hydrochloric acid. The aqueous solution was purified by extracting once with ether and then made alkaline with ammonia. The liberated base was isolated in the usual manner (*cf.* the preparation of *ω*-diethylamino-2-ethylacetanilide). A colourless oil boiling at 157°/0.7 mm. was obtained; $n_D^{20} = 1.5271$; yield 0.033 mole (8.6 g; 75 %).

Calcd. C	73.2	H	9.99	Equiv.-weight:	262
Found »	72.8	»	10.0	»	» 261

Hydrochloride, $C_{16}H_{27}ClN_2O$ (298.8). Long, thin rods from isobutyl alcohol – butyl ether, easily soluble in water, ethanol, and propanol; m.p. 202–205°.

Calcd. Cl	11.86
Found »	11.88 (Mohr)

SUMMARY

ω-Diethylamino-2-ethylacetanilide, *ω*-dimethylamino-2-*tert*-butylacetanilide, and *ω*-diethylamino-2-*tert*-butylacetanilide have been tested for their local anaesthetic, spasmolytic, and histaminolytic power.

Acknowledgements are made to Dr. S. Wiedling of the Biological Department of A.B. Astra, Södertälje, for performing the pharmacological tests and to Dr. T. Gordh of the Caroline Hospital, Stockholm, who carried out the intercutaneous tests on man.

LITERATURE

1. Löfgren, N. *Arkiv Kemi, Mineral. Geol.* **A 22** (1946) no. 1.
2. Löfgren, N., and Lundquist, B. *Svensk Kem. Tid.* **58** (1946) 206.
3. Löfgren, N., and Fischer, I. *Svensk Kem. Tid.* **58** (1946) 219.
4. Löfgren, N., and Widmark, G. *Svensk Kem. Tid.* **58** (1946) 323.
5. Löfgren, N. *Studies on Local Anaesthetics. Xylocaine, a new Synthetic Drug.* (1948).
Dissertation, Stockholm.
6. Löfgren, N., and Takman, B. *Acta Chem. Scand.* **6** (1952).
7. Fischer, I., and Löfgren, N. *Acta Chem. Scand.* **4** (1950) 1408.
8. Erdtman, H., and Löfgren, N. *Svensk Kem. Tid.* **49** (1937) 163.
9. Panksch, H. *Ber.* **17** (1884) 767.
10. du Toit Malherbe, D. *Ber.* **52** (1919) 319.
11. Shoesmith, J. B., and Mackie, A. *J. Chem. Soc.* **1928**, 2334.
12. Seńkowski, M. *Ber.* **23** (1890) 2412.

Received July 25, 1951.