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Further Studies on Amino Esters of Substituted Phenylcarbamic Acids

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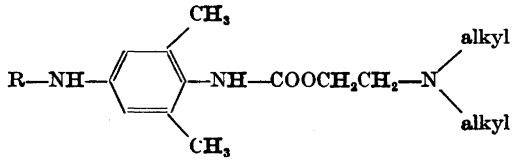
The synthesis of some amino esters of 2,6-dimethylphenylcarbamic acid substituted in the *para* position with an amino group or substituted amino group is described. Two amino esters of 2-chloro-6-methylphenylcarbamic acid were also prepared. The new compounds have been tested for local anesthetic activity.

In a previous paper the synthesis of some esters and amides of 2,6-dimethyl and 2,4,6-trimethylphenylcarbamic acids with basic substituents was described [1]. As an extension of these investigations a number of related compounds of the following type were prepared, R being H, n-C_4H_9 or an acyl group.



The starting material for these syntheses was ethyl 2,6-dimethyl-4-nitrophenylcarbamate (I) which could be prepared from 2,6-dimethyl-4-nitroaniline and ethyl chloroformate. It could also be obtained in good yield by nitration of ethyl 2,6-dimethylphenylcarbamate. The smooth formation of the 4-nitro compound in this case is rather interesting since the nitration of 2,6-dimethylacetanilide and 2,6-dimethylformanilide mainly gives the 3-nitro derivatives [2]. As ethyl 2,6-dimethyl-4-nitrophenylcarbamate is easily hydrolysed to 2,6-dimethyl-4-nitroaniline in almost quantitative yield, this method opens a new satisfactory route to this amine in addition to the method devised by Wepster [2]. The different steps involved in the synthesis of the amino esters (V, VI) and their alkyl and acyl derivatives (VIII-XI) are shown in Fig. 1.

In addition, the β-diethylaminoethyl and β-piperidinoethyl esters of 2-chloro-6-methylphenylcarbamic acid were prepared (XIII, XIV).

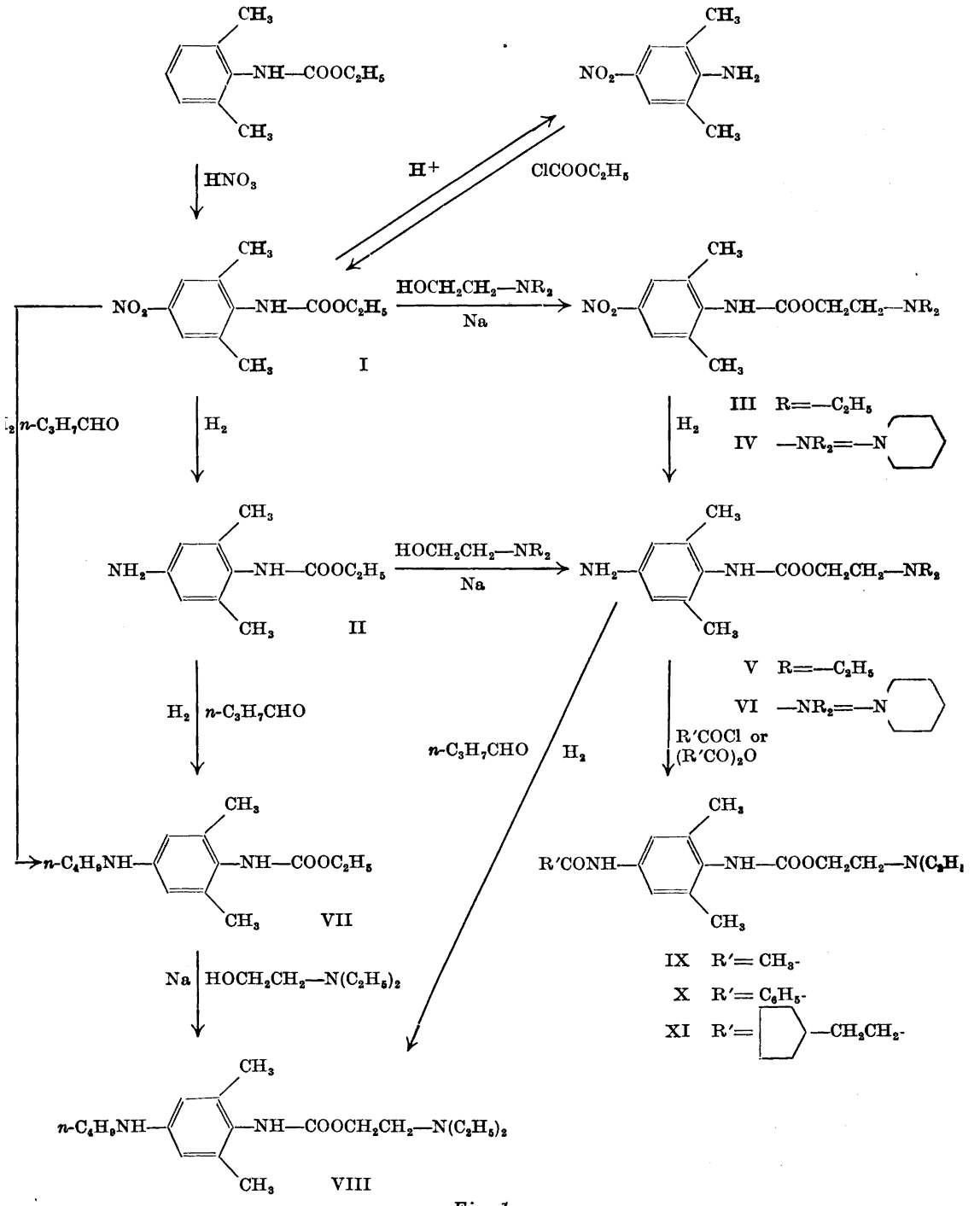

HNO3
H+
ClCOOC2H5
HOCH2CH2—NR2
Na
I
III R=—C2H5
IV —NR2=—N
H2
n-C3H7CHO
II
V R=—C2H5
VI —NR2=—N
R'COCl or
(R'CO)2O
n-C4H9NH—
VII
IX R'=CH3-
X R'=C6H5-
XI R'=
—CH2CH2-
Na
HOCH2CH2—N(C2H5)2
VIII

Fig. 1.

The new compounds were tested for local anesthetic action on the rabbit cornea and compared with Xylocaine *. The *p*-amino derivatives V and VI were devoid of anesthetic activity. The *n*-butylamino derivate VIII had an effect comparable with that of Xylocaine but had a longer latency time, low frequency of anesthesia and more than twice the toxicity. The acyl derivate IX was inactive, and X was only slightly active but XI had a strong anesthetic effect. It was, however, irritating to the rabbit eye and had a long latency time and a low frequency of anesthesia. Strong activity was also displayed by the amino esters of 2-chloro-6-methylphenylcarbamic acid (XIII, XIV), but they were too toxic to be of any clinical value.

EXPERIMENTAL

Ethyl 2,6-dimethyl-4-nitrophenylcarbamate (I). (*a*) 2,6-Dimethyl-4-nitroaniline (8.3 g, 0.05 mole), prepared by hydrolysis of 2,6-dimethyl-4-nitro-1-(*p*-toluenesulfonyl)-aniline according to the method of Wepster [3], and pyridine (5.15 g, 0.065 mole) were dissolved in benzene (600 ml) and ethyl chloroformate (7.0 g, 0.065 mole) was added dropwise with mechanical stirring. The mixture was refluxed for 2.5 h and then filtered hot. The benzene was evaporated and the residue dissolved in ether (800 ml) and extracted with conc. hydrochloric acid (150 + 100 ml) in order to remove unreacted starting material. The ether solution was washed with water, dried over sodium sulphate and the solvent was then evaporated. The crystalline residue (6.9 g, 58 %) melted at 165—168°; recrystallisation from ethanol yielded pale yellow crystals of m.p. 172—173°. (Found: C 55.3; H 5.95; N 11.8. Calc. for $C_{11}H_{14}N_2O_4$: C 55.45; H 5.92; N 11.8).

(*b*) To a solution of nitric acid (76 ml, 2 moles; *d* 1.50) in water (600 ml) were added successively ethyl 2,6-dimethylphenylcarbamate [1] (58 g, 0.3 mole), glacial acetic acid (600 ml) and sodium nitrite (2.1 g, 0.03 mole). The mixture was refluxed for 1.5 h and after cooling to room temperature it was poured into water (1.2 l). The crude nitro compound (56 g, 78 %) of m.p. 169—171° was recrystallised from ethanol giving yellow crystals melting at 172—173°. A mixed m.p. with the product prepared by procedure (*a*) showed no depression.

Hydrolysis of ethyl 2,6-dimethyl-4-nitrophenylcarbamate (I) to 2,6-dimethyl-4-nitroaniline. A mixture of compound I (2.4 g, 0.01 mole) and 85 % sulphuric acid (25 ml) was heated in an oil bath at 140—150°. Evolution of carbon dioxide began at once and had subsided after 45 min. The reaction mixture was then poured into ice water (200 ml) and made alkaline with 5 N sodium hydroxide. The light yellow product (1.55 g, 94 %) melted at 163—164° alone or in admixture with a sample of 2,6-dimethyl-4-nitroaniline prepared according to the method of Wepster [3]. Recrystallisation from aqueous ethanol did not raise the m.p.

Ethyl 4-amino-2,6-dimethylphenylcarbamate (II). Ethyl 2,6-dimethyl-4-nitrophenylcarbamate (14.3 g), dissolved in ethanol (125 ml), was hydrogenated at about 50° and normal pressure with Raney nickel as catalyst. The calculated amount of hydrogen was consumed after 4 h. The solution was filtered and the solvent evaporated. The crystalline residue (12.5 g, 100 %) was recrystallised from benzene giving a product (10.0 g) of m.p. 107—108°. (Found: C 63.9; H 8.01; N 13.1. Calc. for $C_{11}H_{16}N_2O_2$: C 63.4; H 7.74; N 13.4).

β-Diethylaminoethyl 2,6-dimethyl-4-nitrophenylcarbamate (III). A mixture of ethyl 2,6-dimethyl-4-nitrophenylcarbamate (71.4 g, 0.3 mole) and β-diethylaminoethanol (195 g, 1.65 mole) in which a piece of sodium (1.5 g) had been dissolved was heated at 75—80° for 3 h at a pressure of 80—100 mm/Hg. The excess of the amino alcohol was evaporated off and the residue washed with water and extracted with 2 N hydrochloric acid. The acid solution was extracted with ether and made alkaline with dilute sodium hydroxide. The precipitated, semisolid base was extracted with ether. Evaporation of the ether yielded a crystalline residue (75.0 g, 81 %) of m.p. 46—48°. Since further purification of the base proved to be difficult, it was converted to the *hydrochloride* which was recrystallised

* Acknowledgement is made to Dr. S. Wiedling for performing these tests.

from ethanol-ether; m.p. 164—165°. (Found: C 51.9; H 6.94; Cl 10.4. Calc. for $C_{15}H_{21}ClN_2O_4$: C 52.1; H 6.99; Cl 10.25).

β-Piperidinoethyl 2,6-dimethyl-4-nitrophenylcarbamate (IV). This compound was prepared in 90 % yield from ethyl 2,6-dimethyl-4-nitrophenylcarbamate and β-piperidinoethanol by the same method as that described for III. The amino ester base was recrystallised from methanol-water; m.p. 139—140°. (Found: C 60.0; H 7.52; N 12.7. Calc. for $C_{16}H_{23}N_3O_4$: C 59.8; H 7.21; N 13.1).

β-Diethylaminoethyl 4-amino-2,6-dimethylphenylcarbamate (V). (*a*) The nitro compound III (4.2 g) was dissolved in ethanol (50 ml) and hydrogenated at about 50° and normal pressure with Raney nickel as catalyst. The calculated amount of hydrogen was consumed in 2 h. The catalyst was removed by filtration and the solvent evaporated. The colourless oily residue (3.6 g, 95 %) was converted to the *dihydrochloride;* m.p. 299—301° after recrystallisation from ethanol-ether. (Found: C 51.3; H 7.85; Cl 20.4. Calc. for $C_{15}H_{27}Cl_2N_3O_2$: C 51.1; H 7.72; Cl 20.1).

(*b*) Transesterification of ethyl 4-amino-2,6-dimethylphenylcarbamate with diethylaminoethanol as described for III yielded the *dihydrochloride* of V in 50 % yield. M.p. after recrystallisation from ethanol-ether 300—302°.

β-Piperidinoethyl 4-amino-2,6-dimethylphenylcarbamate (VI). The nitro compound IV was hydrogenated as described above for V (*a*) and the piperidino ester was isolated as the *dihydrochloride* in 80 % yield. M.p. 291—293° (decomp.) after recrystallisation from ethanol-ether. (Found: C 52.55; H 7.54; N 11.3. Calc. for $C_{16}H_{27}Cl_2N_3O_2$: C 52.7; H 7.47; N 11.5).

Ethyl 4-n-butylamino-2,6,dimethylphenylcarbamate (VII). (*a*) A solution of ethyl 4-amino-2,6-dimethylphenylcarbamate (4.15 g, 0.02 mole), *n*-butyraldehyde (0.04 mole) and fused sodium acetate (1 g) in ethanol (50 ml) was hydrogenated with Raney nickel as catalyst at normal pressure and room temperature for one hour. The catalyst was removed by filtration and the solvent evaporated. The residue was dissolved in 2 N hydrochloric acid, the acid solution was extracted with ether and then made alkaline with dil. sodium hydroxide. The precipitate was extracted with ether and the solvent was evaporated yielding a crystalline residue (4.7 g, 90 %) of m.p. 73—74°. Recrystallisation from aqueous methanol raised the m.p. to 76—77°. (Found: C 68.15; H 9.01; N 10.5. Calc. for $C_{15}H_{24}N_2O_2$: C 68.15; H 9.15; N 10.6).

(*b*) This compound could also be prepared in 82 % yield by using ethyl 2,6-dimethyl-4-nitrophenylcarbamate (I) as starting material in the reductive alkylation described above (*a*). The reaction was, however, rather sluggish; the calculated amount of hydrogen was consumed after 6 h.

β-Diethylaminoethyl 4-n-butylamino-2,6-dimethylphenylcarbamate (VIII). (*a*) A solution of β-diethylaminoethyl 4-amino-2,6-dimethylphenylcarbamate (3.9 g, 0.014 mole), *n*-butyraldehyde (1.3 g, 0.018 mole) and sodium acetate (1.0 g) in ethanol (50 ml) was hydrogenated at normal pressure and room temperature over Raney nickel for one hour. The reaction mixture was worked up as described above for compound VII (*a*). The product was isolated as the *dihydrochloride* (3.6 g, 62 %); m.p. 236—237° (decomp.) after recrystallisation from ethanol-ether. (Found: C 55.6; H 8.72; N 9.93. Calc. for $C_{19}H_{35}Cl_2N_3O_2$: C 55.9; H 8.64; N 10.3).

(*b*) This compound was also obtained by transesterification of ethyl 4-*n*-butylamino-2,6-dimethylphenylcarbamate with β-diethylaminoethanol according to the procedure described for compound III. The yield of the *dihydrochloride* was 63 %.

β-Diethylaminoethyl 4-acetamido-2,6-dimethylphenylcarbamate (IX). A suspension of compound V (2.8 g free base, 0.01 mole) in acetic anhydride (10 ml) was heated to 60° for 30 min and was then poured into water (100 ml). The mixture was made alkaline and extracted with ether. The ether solution was filtered through a short column of aluminium oxide and evaporated. The solid residue (1.7 g, 53 %) was recrystallised from benzene; m.p. 122—123°. (Found: C 63.0; H 8.45; N 13.1. Calc. for $C_{17}H_{27}N_3O_3$: C 63.5; H 8.47; N 13.1).

β-Diethylaminoethyl 4-benzamido-2,6-dimethylphenylcarbamate (X). Compound V was treated with benzoyl chloride in pyridine-benzene. A heavy precipitate consisting of the hydrochloride of X was formed. The salt was suspended in water, the suspension made alkaline and the base extracted with ether. Evaporation of the ether yielded a crystalline residue which was recrystallised from benzene; m.p. 144—145°. (Found: 69.4; H 7.65; N 10.8. Calc. for $C_{22}H_{29}N_3O_3$: C 68.9; H 7.62; N 11.0).

β-Diethylaminoethyl 4-(β-cyclopentylpropionamido)-2,6-dimethylphenylcarbamate (XI) was prepared similarly in 71 % yield from V and *β-cyclo*pentylpropionyl chloride; m.p. 115—116° after recrystallisation from benzene-light petroleum. (Found: C 68.4; H 9.19; N 10.45. Calc. for $C_{23}H_{37}N_3O_3$: C 68.45; H 9.24; N 10.4).

Ethyl 2-chloro-6-methylphenylcarbamate (XII). To a stirred solution of 2-chloro-6-methylaniline (28.3 g, 0.2 mole) and pyridine (20 g, 0.25 mole) in benzene (200 ml), ethyl chloroformate (27.1 g, 0.25 mole) was added dropwise over a period of one hour. The temperature gradually rose to 45°. The stirring was then continued for one hour and the pyridine hydrochloride formed was removed by filtration. The benzene solution was washed successively with water, 2 N hydrochloric acid and water and was then evaporated to dryness. The residue (38.5 g, 90 %) melted at 75—77° and was recrystallised from aqueous methanol; m.p. 76—77°. (Found: C 56.3; H 5.69; N 6.62. Calc. for $C_{10}H_{12}ClNO_2$: C 56.2; H 5.66; N 6.56).

β-Diethylaminoethyl 2-chloro-6-methylphenylcarbamate (XIII). This compound was prepared by transesterification of the ethyl ester XII with β-diethylaminoethanol by the method described for compound III. The oily base was converted to the *oxalate*. Yield 51 %; m.p. 127—128° after recrystallisation from 80 % ethanol. (Found: C 51.7; H 6.51; N 7.35. Calc. for $C_{16}H_{23}ClN_2O_2$: C 51.3; H 6.18; N 7.48).

β-Piperidinoethyl 2-chloro-6-methylphenylcarbamate (XIV) was prepared similarly from β-piperidinoethanol and XII. The oily base was isolated as the *hydrochloride*. Yield 87 %; m.p. 172—173° after recrystallisation from ethanol-ether. (Found: C 54.1; H 6.47; N 8.39: Calc. for $C_{15}H_{22}Cl_2N_2O_2$: C 54.05; H 6.66; N 8.41).

REFERENCES

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