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Esters and Amides of 2,6-Dimethyl- and 2,4,6-Trimethylphenylcarbamic Acid

RICHARD DAHLBOM and LARS-ERIC ÖSTERBERG

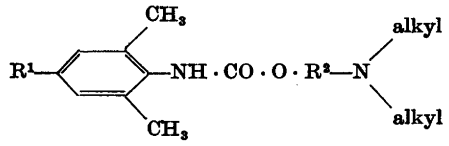
Central Laboratories, AB Astra, Södertälje, Sweden

A number of esters and amides of 2,6-dimethyl- and 2,4,6-trimethylphenylcarbamic acids with basic substituents have been prepared and tested for local anesthetic activity. The esters were active but rather toxic. The amides were devoid of anesthetic properties.

Esters of arylcarbamic acids possessing basic substituents have been reported to be active local anesthetics [1–7]. As it was of interest to study compounds of this class with the same substituents in the aromatic nucleus as Xylocaine, we prepared a series of basically substituted esters of 2,6-dimethyl- and 2,4,6-trimethylphenylcarbamic acids

(I; R^1= H or CH_3; R^2= —$CH_2 \cdot CH_2$— or —$CH(CH_3) \cdot CH_2$—)

and our experiments are reported in this paper. In addition some amides of the carbamic acids with basic substituents were prepared (II; R^1 = H or CH_3; R^2 = —$CH_2 \cdot CH_2$— or —$CH_2 \cdot CH_2 \cdot CH_2$—)



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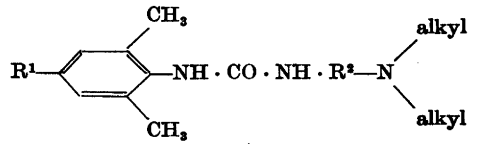

II

The new compounds were easily obtained by the reaction of 2,6-dimethyl- and 2,4,6-trimethylphenyl*iso*cyanate with the appropriate alcohol or amine. The *iso*cyanates used as starting materials were prepared from 2,6-xylidine or mesidine and phosgene. They could also be obtained by distillation of the appropriate ethyl carbamate with phosphorus pentoxide.

The amino esters possessed local anesthetic properties of about the same order of magnitude as Xylocaine when tested on rabbit cornea. However, they all were considerably more toxic.

Some of the least toxic compounds were tested subcutaneously on man and compared with Xylocaine. They were found to have shorter duration.

The amides with basic substituents were devoid of anesthetic properties.

EXPERIMENTAL

2,6-Dimethylphenylisocyanate. (*a*) A mixture of 2,6-xylidine (121.8 g, 1.0 mole) and pyridine (253.1 g, 3.2 moles) was added with ice-cooling to a solution of phosgene (118.7 g, 1.2 moles) in toluene (850 ml). A vigorous reaction commenced. The reaction mixture was kept at 0° for 2 hours and then at 25° for 3 hours. The thick mixture was then treated with 2 N hydrochloric acid (2.4 l). The toluene layer was separated, the aqueous layer extracted with toluene (2 × 200 ml) and the combined toluene solutions were dried over calcium chloride. The solvent was evaporated *in vacuo* and the residue distilled giving a colourless oil (99.4 g, 68 %), b.p. 87–89°/12 mm; n_D^{20} 1.5360. The product was rather irritating to the skin and the eyes. (Found: C 73.7; H 6.29; N. 9.35. C_9H_9NO requires C 73.5; H 6.16; N 9.52).

(*b*) Ethyl 2,6-dimethylphenylcarbamate (5.8 g, 0.03 mole) was thoroughly mixed with phosphorus pentoxide (8.5 g, 0.06 mole) and heated under reflux *in vacuo* (10 mm) at 100° for 10 minutes. The product was then distilled giving a colourless oil (3.7 g, 84 %), b.p. 84–85°/10 mm; n_D^{20} 1.5357.

Ethyl carbamates prepared from the products prepared according to (*a*) and (*b*) had the same m.p. (81–82°) undepressed on admixture.

2,4,6-Trimethylphenylisocyanate. (*a*) This compound was prepared in 52 % yield from mesidine and phosgene according to the procedure described under (*a*) above. The product was distilled *in vacuo* giving an oil of b.p. 100–102°/10 mm, which soon solidified to white crystals of m.p. 44–45°. (Found: C 74.1; H 7.01; N 8.51. $C_{10}H_{11}NO$ requires C 74.5; H 6.88; N 8.69).

(*b*) The same product was prepared in 64 % yield by distillation of ethyl 2,4,6-trimethylphenylcarbamate with phosphorus pentoxide as described under (*b*) above.

2,4,6-Trimethylphenyl*iso*cyanate has been prepared by Eisenberg [8] according to procedure (*b*). Eisenberg gives b.p. 218–220° at normal pressure.

Ethyl 2,6-dimethylphenylcarbamate. (*a*) Ethyl chloroformate (32.6 g, 0.3 mole) was added dropwise to a solution of 2,6-xylidine (94.5 g, 0.78 mole) in benzene (150 ml). After the vigorous reaction had subsided the mixture was kept at room temperature for 30 minutes and was then heated to the boiling point. After cooling the precipitated xylidine hydrochloride was removed by filtration and the benzene solution was extracted with N hydrochloric acid and dried over sodium sulphate. The solvent was evaporated and the white crystalline residue (54.5 g, 94 %) of m.p. 76–78° was crystallised from light petroleum giving a product of m.p. 82–83°. (Found: C 67.8; H 7.97; N 7.34. $C_{11}H_{15}NO_2$ requires C 68.4; H 7.82; N 7.25).

(*b*) 2,6-Dimethylphenyl*iso*cyanate (0.44 g) was refluxed in ethanol (5 ml) for 15 minutes. Evaporation of the solvent afforded white crystals (0.52 g, 90 %), which were recrystallised from light petroleum, m.p. 81–82°, undepressed on admixture with the compound prepared by method (*a*).

Ethyl 2,4,6-trimethylphenylcarbamate. (*a*) This compound was obtained in 81 % yield from mesidine and ethyl chloroformate as described above. The product was crystallised from light petroleum, m.p. 89–90°. (Found: C 69.8; H 8.34; N 6.69. $C_{12}H_{17}NO_2$ requires C 69.5; H 8.27; N 6.76).

(*b*) Reaction of 2,4,6-trimethylphenyl*iso*cyanate with ethanol afforded the same compound in 93 % yield, m.p. 89–90°, alone or in admixture with the product from (*a*). The synthesis of this compound has also been described by Eisenberg [8]. However, the m.p. recorded by Eisenberg is 61–62°.

β-Chloroethyl 2,6-dimethylphenylcarbamate. A solution of 2,6-dimethylphenyl*iso*cyanate (18.5 g) and ethylene chlorohydrin (15.0 g) in toluene (50 ml) was refluxed for 2 hours. On cooling white crystals (12.5 g) of m.p. 79–81° separated. Concentration of the mother liquor yielded further crystals (4.6 g) of the same m.p. The combined products (17.1 g, 60 %) were recrystallised from toluene, m.p. 80–81°. (Found: C 58.3; H 6.39; Cl 15.7. $C_{11}H_{14}ClNO_2$ requires C 58.0; H 6.20; Cl 15.6).

β-Chloroethyl 2,4,6-trimethylphenylcarbamate. Prepared similarly in 71 % yield. M.p. 89—90° (from toluene). (Found: C 59.9; H 6.64; Cl 15.0. $C_{12}H_{16}ClNO_2$ requires C 59.6; H 6.67; Cl 14.7).

N-(2,6-Dimethylphenyl)-urea. 2,6-Dimethylphenyl*iso*cyanate (3.7 g) was dissolved in toluene (15 ml) and a slow stream of gaseous ammonia was passed through the mixture with ice-cooling. White crystals began to separate almost instantaneously. After 2 hours the precipitate was collected (3.6 g, 88 %) and recrystallised from methanol, m.p. above 300°. (Found: C 66.1; H 7.23; N 17.2. $C_9H_{12}N_2O$ requires C 65.8; H 7.37; N 17.1).

N-Diethyl-N¹-(2,6-dimethylphenyl)-urea. A solution of 2,6-dimethylphenyl*iso*cyanate (3.7 g, 0.25 mole) and diethylamine (3.7 g, 0.05 mole) in toluene (10 ml) was refluxed for 2 hours. The precipitate (5.2 g, 95 %) melted at 178—179.5°. Recrystallisation from light petroleum-ethanol (5 : 1) did not raise the melting point. (Found: C 71.7; H 8.65; N 12.6. $C_{13}H_{20}N_2O$ requires C 70.9; H 9.15; N 12.7).

N-Diethyl-N¹-(2,4,6-trimethylphenyl)-urea. This compound was prepared similarly in 71 % yield, m.p. 122—123° (from 30 % methanol). (Found: C 71.7; H 9.40; N 11.7. $C_{14}H_{22}N_2O$ requires C 71.75; H 9.46; N 12.0).

N-Ethyl-N¹-(2,6-dimethylphenyl)-urea. A solution of 2,6-dimethylphenyl*iso*cyanate (3.7 g) and ethylamine (5 ml) in toluene (20 ml) was kept at room temperature in a sealed bottle overnight. The precipitate (3.3 g, 69 %) was recrystallised from light petroleum-ethanol (2 : 1), m.p. 226—228° (decomp). (Found: C 68.8; H 8.55; N 14.4. $C_{11}H_{16}N_2O$ requires C 68.7; H 8.39; N 14.6).

N,N¹-Bis(2,6-dimethylphenyl)-urea. A solution of 2,6-dimethylphenyl*iso*cyanate (5.7 g) and 2,6-xylidine (4.7 g) in toluene (15 ml) was refluxed for 2 hours. The crystalline product (10.0 g, 97 %) was recrystallised from glacial acetic acid. It sublimated at 330°. (Found: C 75.5; H 7.46; N 10.5. $C_{17}H_{20}N_2O$ requires C 76.1; H 7.51; N 10.4).

N,N¹-Bis(2,6-dimethylphenylcarbamyl)-ethylenediamine. This compound was prepared similarly from 2,6-diphenyl*iso*cyanate (4.4 g) and ethylenediamine hydrate (1.2 g) in toluene (15 ml). The reaction product (5.1 g, 97 %) was purified by extraction with hot ethanol. It sublimated at about 310°. (Found: C 67.8; H 7.45; N 15.8. $C_{20}H_{26}N_4O_2$ requires C 67.8; H 7.39; N 15.8).

Basically substituted esters of 2,6-dimethyl- and 2,4,6-trimethylphenylcarbamic acids*

These compounds were all prepared in the same way. The appropriate *iso*cyanate (0.04 mole) was refluxed with a basic alcohol (0.06 mole) in thoroughly dried toluene (15 ml) for 2 hours. (Small amounts of moisture caused the formation of small quantities of high melting products, which could be identified as N,N¹-bis(2,6-dimethylphenyl)- and N,N¹-bis(2,4,6-trimethylphenyl)-urea respectively). The toluene solution was washed with water and then extracted with 2 N hydrochloric acid. The extract was made alkaline with sodium carbonate solution and the precipitated base, which usually soon solidified, was collected and recrystallised. When it was impossible to obtain the base in crystalline form it was converted to the hydrochloride or the oxalate by the addition of an ethereal solution of hydrogen chloride or oxalic acid to an ethereal solution of the base.

β-Diethylaminoethyl 2,6-dimethylphenylcarbamate oxalate. M.p. 112—114° (decomp.), from acetone : light petroleum; yield 66 %. (Found: C 57.7; H 7.41; N 7.76. $C_{17}H_{26}N_2O_6$ requires C 57.6; H 7.40; N 7.91).

β-Diethylaminoethyl 2,4,6-trimethylphenylcarbamate. M.p. 44—45° (from light petroleum); yield 81 %. (Found: C 69.1; H 9.39; N 10.3. $C_{16}H_{26}N_2O_2$ requires C 69.0; H 9.41; N 10.1).

β-Dimethylaminoisopropyl 2,6-dimethylphenylcarbamate oxalate. M.p. 156—157° (decomp., from acetone); yield 85 %. (Found: C 56.5; H 7.18; N 8.35. $C_{16}H_{24}N_2O_6$ requires C 56.5; H 7.11; N 8.23).

* After the present work had been completed, the preparation of some of these esters was reported in a series of Swedish patent applications from AB Bofors. However, no melting points or other characteristic data were given.

β-Dimethylaminoisopropyl 2,4,6-trimethylphenylcarbamate hydrochloride. M.p. 211—212° (decomp., from ethanol); yield 63 %. (Found: C 59.5; H 8.52; Cl 11.5. $C_{15}H_{25}ClN_2O_2$ requires C 59.9; H 8.38; Cl 11.8).

β-Morpholinoethyl 2,6-dimethylphenylcarbamate hydrochloride. M.p. 185—187° (decomp., from ethanol); yield 71 %. (Found: C 57.1; H 7.23; Cl 11.4. $C_{15}H_{23}ClN_2O_3$ requires C 57.2; H 7.36; Cl 11.3).

β-Piperidinoethyl 2,6-dimethylphenylcarbamate. M.p. 85—86° (from light petroleum); yield 71 %. (Found: C 69.7; H 8.66; N 10.3. $C_{16}H_{24}N_2O_2$ requires C 69.5; H 8.75; N 10.1).

β-Piperidinoethyl 2,4,6-trimethylphenylcarbamate. The base was isolated as its *oxalate*, m.p. 153—154° (decomp., from acetone); yield 74 %. (Found: C 59.7; H 7.22; N 7.58. $C_{19}H_{28}N_2O_6$ requires C 60.0; H 7.42; N 7.37). From the pure oxalate the *base* was obtained in crystalline form, m.p. 87—88° (from light petroleum). (Found: C 70.6; H 8.67; N 9.45. $C_{17}H_{26}N_2O_2$ requires C 70.3; H 9.03; N 9.65).

Basically substituted amides of 2,6-dimethyl- and 2,4,6-trimethylphenylcarbamic acids

The appropriate *iso*cyanate (0.025 mole) was refluxed with a dialkylaminoalkylamine (0.038 mole) in dry toluene (10 ml) for 2 hours. On cooling the base usually separated in crystalline form. Two compounds were isolated by precipitation of the toluene solution with ethereal oxalic acid.

γ-Diethylaminopropylamine and γ-piperidinopropylamine used as starting materials were prepared in *ca.* 90% yield by the reduction of β-diethylaminopropionitrile [9] and β-piperidinopropionitrile [9] with lithium aluminium hydride according to the general procedure described by Amundsen and Nelson [10].

N-(β-Diethylaminoethyl)-N¹-(2,6-dimethylphenyl)-urea. M.p. 105—106° (from methanol); yield 87 %. (Found: C 68.6; H 9.38; N 15.8. $C_{15}H_{25}N_3O$ requires C 68.4; H 9.57; N 15.95).

N-(β-Diethylaminoethyl)-N¹-(2,4,6-trimethylphenyl)-urea. M.p. 129—130° (from 70 % methanol); yield 80 %. (Found: C 69.4; H 9.48, N 15.2. $C_{16}H_{27}N_3O$ requires C 69.3; H 9.81; N 15.15).

N-(γ-Diethylaminopropyl)-N¹-(2,6-dimethylphenyl)-urea. The compound was isolated as the oxalate from which the crystalline base was obtained, m.p. 105—106° (from light petroleum); yield 65 %. (Found: C 68.9; H 9.63; N 15.1. $C_{16}H_{27}N_3O$ requires C 69.3; H 9.81; N 15.15).

N-(γ-Diethylaminopropyl)-N¹-(2,4,6-trimethylphenyl)-urea. The compound was isolated by means of oxalic acid. The base melted at 121—122° (from light petroleum); yield 65 %. (Found: C 69.5; H 9.85; N 14.6. $C_{17}H_{29}N_3O$ requires C 70.1; H 10.0; N 14.4).

N-(γ-Piperidinopropyl)-N¹-(2,6-dimethylphenyl)-urea. M.p. 127—128° (from light petroleum-ethanol 2 : 1); yield 71 %. (Found: C 70.3; H 9.20; N 14.8. $C_{17}H_{27}N_3O$ requires C 70.55; H 9.41; N 14.5).

N-(γ-Piperidinopropyl)-N¹-(2,4,6-trimethylphenyl)-urea. M.p. 168—170° (from ethanol-light petroleum 2 : 1); yield 97 %. (Found: C 70.9; H 9.31; N 13.9. $C_{18}H_{29}N_3O$ requires C 71.25; H 9.63; N 13.85).

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