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α-Diethylamino-4-amino-2,6-dimethylacetanilide and Some Related Compounds

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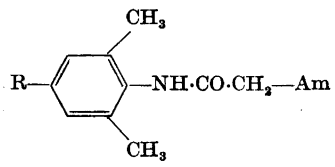
α-Diethylamino-4-amino-2,6-dimethylacetanilide and some alkyl and acyl derivatives have been prepared and tested for local anesthetic activity.

It has been stated by Fosdick and Rapp [1] that the introduction of an amino or a nitro group in the benzene nucleus of α-dialkylaminoacetanilides considerably lowered their anesthetic effect. The same observation was made by Löfgren and Fischer [2] who considered it to be a general rule in the α-dialkylaminoacetanilide series that the anesthetic activity was decreased by substituents with marked inductive or mesomeric effects. Beke, Lempert and and Gyermek [3] found, however, that the introduction of an amino group in the *para* position to the acylamido side chain of an α-diethylamino-2,6-dihalogenoacetanilide enhanced the anesthetic activity. These authors found that in general in this type of compound the introduction of an electron releasing group in the *para* position increased the activity whereas an electron attracting group decreased the activity independently of the mechanism of electron repulsion or attraction (inductive, mesomeric or both). β-Diethylaminobutyranilide and its *p*-amino derivative have been described by Hofstetter and Smith [4] but no definite conclusions can be drawn from their results.

In view of these facts we found it of great interest to study the *p*-amino derivative of α-diethylamino-2,6-dimethylacetanilide (Xylocaine ®). This paper describes the synthesis of this compound (III) and of some of its acyl and alkyl derivatives (IV—VIII). The *p*- amino derivative of α-*n*-propylamino-2,6-dimethylacetanilide (X) was also prepared.

Compound III was synthesised by chloroacetylation of 2,6-dimethyl-4-nitroaniline [5] followed by treatment with diethylamine to give α-diethylamino-4-nitro-2,6-dimethylacetanilide(II) and hydrogenation to the amino compound. This was then acylated with an acyl halide or alkylated by reductive alkylation.

Table 1.



Compound	R	Am	Anesthetic activity [a]	Toxicity [a] LD 50 g/kg
Xylocaine	H	$-N(C_2H_5)_2$	1	0.4
II	NO_2-	»	0.4	1
III	NH_2-	»	0.2	0.24
IV	$CH_3 \cdot CO \cdot NH-$	»	0	0.36
V	$C_2H_5 \cdot CO \cdot NH-$	»	0	0.38
VI	$n\text{-}C_3H_7 \cdot CO \cdot NH-$	»	0.5	0.39
VII	$n\text{-}C_5H_{11} \cdot CO \cdot NH-$	»	3	0.54
VIII	$n\text{-}C_4H_9 \cdot NH-$	»	2.6	0.042
X	NH_2-	$-NH\text{-}n\text{-}C_3H_7$	0	—
XIV	$NH_2 \cdot CO-$	$-N(C_2H_5)_2$	0.4	0.4
XV	$NH_2 \cdot NH \cdot CO-$	»	0	0.6

[a] See text for explanation.

In an attempt to obtain compound III *via* either the Hofmann or the Curtius reaction the 4-carbamoyl, 4-hydrazinocarbonyl, and 4-azidocarbonyl derivatives of Xylocaine were prepared and are described in this paper.

The new compounds were tested for local anesthetic action on rabbit cornea, using Xylocaine as standard. Toxicity tests were made by subcutaneous injection on white mice. The results of the biological tests * are summarised in Table 1.

It is evident from the table that both the electron releasing amino group and the electron attracting carbamoyl, hydrazinocarbonyl, and nitro groups decrease the anesthetic effect. Introduction of an acyl or alkyl residue of suitable size in the amino group restored the activity, but these compounds (VII, VIII) were very irritating and the butylamino compound VIII was extremely toxic.

EXPERIMENTAL

α-Chloro-4-nitro-2,6-dimethylacetanilide (I). Chloroacetyl chloride (6.0 ml, 0.079 mole) was added with vigorous stirring to a solution of 4-nitro-2,6-dimethylaniline [5] (12 g, 0.072 mole) and dry pyridine (5.8 ml, 0.072 mole) in benzene (500 ml). The precipitate formed was collected, washed with water and dried. Recrystallisation from benzene gave light yellow crystals (16.3 g, 93 %), m. p. 229–231°. (Found: 49.3; H 4.64; N 11.5. Calc. for $C_{10}H_{11}ClN_2O_3$: C 49.5; H 4.57; N 11.5.)

α-Diethylamino-4-nitro-2,6-dimethylacetanilide (II). The chloroacetyl derivative I (82 g, 0.34 mole) was refluxed for 10 h with diethylamine (87 ml, 0.85 mole) in dry benzene (400 ml). After cooling the reaction mixture was filtered and then extracted

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

thoroughly with 2 N hydrochloric acid. The extract was made alkaline with 4 N sodium hydroxide, and the precipitated base was collected and recrystallised from ethanol as light yellow crystals (82 g, 86 %), m. p. 98—99°. (Found: C 60.4; H 7.22; N 14.9. Calc. for $C_{14}H_{21}N_3O_3$: C 60.2; H 7.58; N 15.0.)

α-Diethylamino-4-amino-2,6-dimethylacetanilide (III). The nitro compound II (82 g, 0.29 mole), dissolved in ethanol (650 ml), was hydrogenated at 40° and normal pressure over Raney nickel (5 g, moist). The calculated amount of hydrogen was consumed after 2 h. The catalyst was filtered off, and the solvent was evaporated *in vacuo*. The residue was recrystallised from ether, m. p. 98—100° (70 g, 96 %). (Found: C 67.3; H 9.10; N 17.0. Calc. for $C_{14}H_{23}N_3O$: C 67.4; H 9.30; N 16.9.)

α-Diethylamino-4-acetamido-2,6-dimethylacetanilide (IV). A solution of α-diethylamino-4-amino-2,6-dimethylacetanilide (2.5 g, 0.01 mole) in acetone (30 ml), in which potassium carbonate (0.49 g, 0.005 mole) was suspended, was treated with acetyl chloride (0.71 ml, 0.01 mole) added dropwise with stirring. The reaction mixture was refluxed for half an hour and the solvent was then removed under vacuum. The residue was suspended in water and the suspension was made alkaline by the addition of sodium hydroxide. The precipitate was collected and recrystallised from benzene, m. p. 144—145° (2.4 g, 80 %). (Found: C 65.3; H 8.36; N 14.3. Calc. for $C_{16}H_{25}N_3O_2$: C 66.0; H 8.65; N 14.4.)

The following compounds were prepared by essentially the same procedure:

α-Diethylamino-4-propionamido-2,6-dimethylacetanilide (V). M. p. 152—153° (from benzene). Yield 62 %. (Found: C 67.0; H 8.86; N 13.8. Calc. for $C_{17}H_{27}N_3O_2$: C 66.9; H 8.91; N 13.8.)

α-Diethylamino-4-butyramido-2,6-dimethylacetanilide (VI). M. p. 142—143° (from benzene). Yield 62 %. (Found: C 68.0; H 9.09. Calc. for $C_{18}H_{29}N_3O_2$: C 67.7; H 9.15.)

α-Diethylamino-4-hexanoylamino-2,6-dimethylacetanilide (VII). This compound was prepared as described above with the difference that pyridine was used as proton acceptor instead of potassium carbonate. M. p. 118—120° (from benzene-ether). Yield 63 %. (Found: C 69.2; H 9.53; N 12.1. Calc. for $C_{20}H_{33}N_3O_2$: C 69.1; H 9.57; N 12.1.)

*α-Diethylamino-4-*n*-butylamino-2,6-dimethylacetanilide (VIII).* α-Diethylamino-4-amino-2,6-dimethylacetanilide (7.5 g, 0.03 mole) and *n*-butyraldehyde (4.3 g, 0.06 mole) were dissolved in ethanol (75 ml) in which anhydrous sodium acetate (0.3 g) was suspended. The mixture was hydrogenated at normal pressure and room temperature over Raney nickel for 40 min. The reaction mixture was then filtered, concentrated to dryness and the residue was dissolved in N hydrochloric acid. The acid solution was filtered, made alkaline with 4 N sodium hydroxide and the liberated base was extracted with ether. The ethereal solution was dried over sodium sulphate and the reaction product was precipitated as the hydrochloride by the addition of ethereal hydrochloric acid. Repeated recrystallisation from ethanol-benzene (1:1) gave colourless crystals (7.3, 71 %), m. p. 223—225°. The addition of sodium hydroxide to an aqueous solution of the hydrochloride gave the base, m. p. 42—44°. (Found: C 70.7; H 10.0; N 13.7. Calc. for $C_{18}H_{31}N_3O$: C 70.8; H 10.2; N 13.8.)

α-Propylamino-4-nitro-2,6-dimethylacetanilide (IX). The chloroacyl compound I (13 g, 0.054 mole) and *n*-propylamine (16 g, 0.268 mole) were refluxed in benzene solution as described for compound II. The base was crystallised from benzene-petroleum ether (b. p. 40—60°), m. p. 99—100° (11.5 g, 80 %). (Found: C 58.8; H 7.27; N 15.8. Calc. for $C_{13}H_{19}N_3O_3$: C 58.8; H 7.22; N 15.8.)

*α-*n*-Propylamino-4-amino-2,6-dimethylacetanilide (X).* The nitro compound IX (9 g, 0.034 mole) was hydrogenated over Raney nickel as described for compound III. The base was crystallised from benzene-petroleum ether (40—60°), m. p. 111—112° (5.5 g, 69 %). (Found: C 66.5; H 9.06; N 17.6. Calc. for $C_{13}H_{21}N_3O$: C 66.3; H 9.00; N 17.9.)

3,5-Dimethyl-4-nitrobenzamide (XI). An ice-cooled solution of 3,5-dimethyl-4-nitrobenzoyl chloride [6] (12 g, 0.056 mole) in benzene (150 ml) was treated with ammonia gas for 30 min. The temperature of the solution slowly rose to 30°. The solvent was evaporated and the residue was washed with water to remove ammonium chloride formed during the reaction. Recrystallisation from benzene gave colourless crystals, m. p. 169—171° (10.2 g, 93 %). (Found: C 55.4; H 5.36; N 14.3. Calc. for $C_9H_{10}N_2O_3$: C 55.7; H 5.19; N 14.5.)

4-Carbamoyl-2,6-dimethylaniline (XII). The nitro derivative XI (9.7 g, 0.05 mole) was dissolved in ethanol (200 ml) and hydrogenated over Raney nickel at room temperature and a pressure of 90 kg/cm². After 45 min the catalyst was filtered off and the solu-

tion was evaporated to dryness under reduced pressure. The residue was recrystallised from petroleum ether (40—60°)-ethanol, m. p. 181—182° (5.9 g, 72 %). (Found: C 65.9; H 7.43; N 17.0. Calc. for $C_9H_{12}N_2O$: C 65.8; H 7.37; N 17.1.)

α-Chloro-4-carbamoyl-2,6-dimethylacetanilide (XIII). 4-Carbamoyl-2,6-dimethylaniline was chloroacetylated in the same manner as described for compound I. The chloroacetyl derivative was obtained as colourless needles from ethanol, m. p. 241—243°. Yield 84 %. (Found: C 54.9; H 5.54; N 11.7. Calc. for $C_{11}H_{13}ClN_2O_2$: C 54.9; H 5.44; N 11.6.)

α-Diethylamino-4-carbamoyl-2,6-dimethylacetanilide (XIV). The chloroacetyl compound XIII (2.7 g, 0.011 mole) was refluxed with diethylamine (2.2 g, 0.03 mole) in benzene (50 ml) for 8 h at 70°. The base was isolated as described for compound II giving slightly yellow crystals, m. p. 175—177° (2.3 g, 74 %). On recrystallisation (charcoal) from ethanol-benzene (1:1) it gave colourless crystals, m. p. 176—178°. (Found: C 64.9; H 8.51; N 15.1. Calc. for $C_{15}H_{23}N_3O_2$: C 64.9; H 8.36; N 15.2.)

α-Diethylamino-4-hydrazinocarbonyl-2,6-dimethylacetanilide (XV). α-Diethylamino-4-methoxycarbonyl-2,6-dimethylacetanilide [6] (5.0 g, 0.017 mole) was refluxed with hydrazine hydrate (2.1 g, 0.043 mole) in propanol (5 ml) for 8 h and the reaction mixture was allowed to stand at room temperature over night. The hydrazide that separated was then recrystallised from ethanol, m. p. 185—186° (4.7 g, 94 %). (Found: C 61.4; H 8.35; N 19.0. Calc. for $C_{15}H_{24}N_4O_2$: C 61.6; H 8.27; N 19.2.)

α-Diethylamino-4-azidocarbonyl-2,6-dimethylacetanilide (XVI). The hydrazide XV (8.8 g, 0.03 mole) suspended in ice water (40 ml) containing hydrochloric acid (12.5 ml 5 N) was treated with a solution of sodium nitrite (2.2 g, 0.032 mole) in water (5 ml), added dropwise with stirring. The temperature of the reaction mixture was not allowed to rise above 10°. When all the nitrite had been added, the reaction mixture was neutralised by the addition of cold dilute ammonia and was then extracted thoroughly with ether. The extract was washed with water and dried over sodium sulphate. The solvent was removed and the residue was recrystallised from ether, m. p. 89—90° (7.2 g, 76 %). (Found: C 59.4; H 7.18; N 22.8. Calc. for $C_{15}H_{21}N_5O_2$: C 59.4; H 6.98; N 23.1.)

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