SUBSTITUTED 1,2,3,4-TETRAHYDROQUINOLINES

IV. 2-AMINOMETHYL DERIVATIVES*

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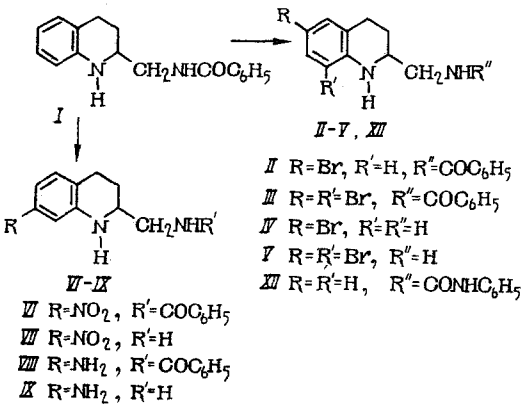
Aminomethyl derivatives of various heterocyclic compounds are widely used in the synthesis of biologically active substances [1-3]. In this series we have synthesized several 2-aminomethyl-1,2,3,4-tetrahydroquinolines containing a substituted benzene ring. The compound 2-benzoylaminomethyltetrahydroquinoline (I), obtained from quinoline through a Reissert compound [4], was subjected to bromination and nitration reactions.

Bromination took place on the carbon atom in position 6, as already reported for tetrahydroquinolines [5, 6], giving 2-benzoylaminomethyl-6-bromotetrahydroquinoline (II). When 2 moles of bromine was used to 1 mole of compound I, 2-benzoylaminomethyl-6,8-dibromotetrahydroquinoline (III) was formed. On hydrolysis of compounds II and III with concentrated or 20% hydrochloric acid, 2-aminomethyl-6-bromotetrahydroquinoline (IV) and 2-aminomethyl-6,8-dibromotetrahydroquinoline (V) were obtained. The site of the second bromine atom in compounds III and V was determined from the PMR spectra. PMR spectrum of V (in carbon tetrachloride) showed, in the aromatic area, a wide proton doublet in position 5 (6.89 ppm) and a proton doublet in position 7 (7.25 ppm, $J_{5,7}$ =2 Hz). The value of the spin-coupling constant, 2 Hz, indicated that the second bromine atom in compound V and, consequently, in compound III also, was in a meta position relative to the first bromine atom located at the carbon atom in position 6. Broadening of the proton signal at the fifth carbon atom was apparently due to spin–spin interaction with a proton in position 4.

The compound 2-benzoylaminomethyl-7-nitrotetrahydroquinoline (VI) was obtained on nitration of I with a mixture of nitric and sulfuric acids. The position of the nitro group in VI was assumed without proof, as it is known that nitration of tetrahydroquinoline with no nitrogen substituent takes place at the seventh carbon atom contrary to other electrophilic substitution reactions [7]. PMR spectrum of 2-aminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline (VII), obtained on hydrolysis of compound VI, conformed with these data. Hydrogenation of VI with hydrogen in the presence of Raney nickel at atmospheric pressure and temperature of about 20°C produced 2-benzoylaminomethyl-7-aminotetrahydroquinoline (VIII), whose hydrolysis yielded 2-aminomethyl-7-aminotetrahydroquinoline (IX).



From 2-aminomethyltetrahydroquinolines and 2-aminomethylquinoline (X), prepared from 2-bromomethylquinoline with N-quinaldylphthalimide (XI), were obtained guanidine, phenylcarbamyl (XII-XIV), and phenylthiocarbamyl (XV) derivatives. Compounds II, III, VI, VIII, IX, and XI-XV, in the hydrochloride form, were studied

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at the Department for Chemotherapy of Infectious Diseases under Prof. G. N. Pershin. Their activity was studied against the $H_{37}R_V$ tuberculosis mycobacterium. Tuberculostatic activity was shown only by hydrochloride of V (in concentration of 2 μg/ml), but its activity sharply decreased in the presence of blood serum. The same compounds, with the exception of XII, were studied for antimicrobial and antifungal activities. None of them showed a high activity in this respect. Synthesis and biological activity of the guanidine derivatives are the subject of the following communication.

EXPERIMENTAL

PMR spectra were recorded on an INM-4H-100 instrument using tetramethylsilane as the internal standard.

2-Benzoylaminomethyl-6,8-dibromo-1,2,3,4-tetrahydroquinoline (III). To a solution of I (3 g, 0.011 moles) in acetic acid (60 ml), a solution of bromine (3.6 g, 0.022 moles) in acetic acid (20 ml) was added dropwise with stirring and cooling. The color disappeared rapidly and a yellow precipitate was formed at the end of the addition. The reaction mixture was then poured into water (250 ml), the precipitate filtered, washed with water, and dried. A technical grade III was obtained, 4.3 g, 90%, mp 161.5-163°C (from absolute ethanol). Calculated for $C_{17}H_{16}Br_2N_2O$: C 48.14; H 3.80; Br 37.68%. Found: C 48.24; H 3.74; Br 37.44%.

2-Aminomethyl-6-bromo-1,2,3,4-tetrahydroquinoline (IV). To a solution of I (7.7 g, 0.029 moles) in chloroform (50 ml) was gradually added a solution of bromine (4.65 g, 0.029 moles) in chloroform (25 ml) at about 20°C. Stirring was continued for an additional 1.5 h and the mixture was concentrated to dryness under reduced pressure.* Hydrochloric acid (20%, 120 ml) was added to the residue and the mixture was heated at 140°C with stirring for 12 h. Benzoic acid was filtered and the mother liquor cooled to give IV, technical grade, 6.4 g, 79.5%, mp 257-258°C (with decomposition, from alcohol). Calculated for $C_{10}H_{13}BrN_2 \cdot HCl$: C 43.27; H 5.09; Cl^- 12.77%. Found: C 43.04; H 4.95; Cl^- 12.71%.

2-Aminomethyl-6,8-dibromo-1,2,3,4-tetrahydroquinoline (V). Compound III (3.4 g) in concentrated hydrochloric acid (50 ml) was heated at 100-120°C with stirring for 14 h. After cooling, benzoic acid was collected, the filtrate concentrated, and the residue recrystallized from water to give the hydrochloride of V, 2.1 g, 73%, mp 259.5-261°C (with decomposition, from water). Calculated for $C_{10}H_{12}Br_2N_2 \cdot HCl$: C 33.69; H 3.68; N 7.85%. Found: C 33.80; H 3.90; N 7.76%.

The action of aqueous sodium hydroxide on the analytically pure hydrochloride yielded the base V. This was extracted with benzene, the extract dried over potassium carbonate, and the benzene removed under reduced pressure to give a self-crystallizing oil. PMR spectra (in carbon tetrachloride): multiplet with centers at 1.60 and 2.70 ppm (2-H, 2-CH_2, 3-H_2, 4-H_2), singlet at 0.98 ppm (NH_2), broad singlet at 5.14 ppm (NH), broad doublet at 6.89 ppm (5H), and doublet at 7.25 ppm, $J_{5,7} = 2$ Hz (7-H).

2-Benzoylaminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline (VI). To a solution of I (5 g, 0.019 moles) in concentrated sulfuric acid (25 ml) was gradually added a mixture of concentrated nitric acid (d = 1.55, 0.8 ml) and concentrated sulfuric acid (8 ml) keeping the temperature of the reaction mixture at 0°C. Stirring was continued at 0°C for 2 h, the mass was poured into water (500 ml), and neutralized with a sodium hydroxide solution. The precipitate was collected, washed with water and dried to give VI, technical grade, 5.7 g, 97.4%, mp 168.5-170°C (from methanol). Calculated for $C_{17}H_{17}N_3O_3$: C 65.58; H 5.50; N 13.50%. Found: C 65.38; H 5.64; N 13.63%.

2-Aminomethyl-7-nitro-1,2,3,4-tetrahydroquinoline (VII). Compound VI (4 g) in concentrated hydrochloric acid (40 ml) was heated at 130°C for 20 h. After cooling, the precipitate was collected and dried with ether to remove benzoic acid. Dihydrochloride VII, 3.4 g, 95%, mp 207-209.5°C (with decomposition, from dilute hydrochloric acid 1:1). Calculated for $C_{10}H_{13}N_3O_2 \cdot 2HCl$: C 42.87; H 5.40; Cl^- 25.31%. Found: C 42.98; H 5.40; Cl^- 25.30%.

The dihydrochloride of VII (1.75 g, 0.0063 moles) was dissolved in water, made alkaline with a dilute sodium hydroxide solution, and the precipitate was collected and washed with water to give base VII, 1.29 g, 100%, mp 113-115°C (from absolute alcohol). Calculated for $C_{10}H_{13}N_3O_2$: C 57.95; H 6.32; N 20.28%. Found: C 57.70; H 6.37; N 20.44%. PMR spectra (a mixture of acetone-d_6 and CCl_4): 1.52-3.17 (2-H, 2-CH, 3-H_2, 4-H_2), 6.26 (broad singlet, NH), 6.98 (doublet, $J_{5,6} = 7.5$ Hz, 5-H), 7.17 (quartet, $J_{6,5} = 7.5$ Hz, $J_{6,8} = 2$ Hz, 6-H), and 7.32 (doublet, $J_{8,6} = 2$ Hz, 8-H) ppm.

*Crystallization of the dry residue from methanol yielded compound II, mp 169-170°C. Calculated for $C_{17}H_{17}BrN_2O$: C 59.14; H 4.96%. Found: C 59.00; H 5.00%.

2-Benzoylaminomethyl-7-amino-1,2,3,4-tetrahydroquinoline (VIII). Compound VI (2 g, 0.0064 moles) was dissolved in absolute alcohol (200 ml) and hydrogenated in the presence of Raney nickel catalyst at atmospheric pressure and at a temperature of around 20°C until hydrogen ceased to be absorbed. The catalyst was filtered, and the mother liquor was partially concentrated under reduced pressure and cooled to yield VIII, 1.5 g, 83%, mp 161-162°C (from absolute alcohol). Calculated for $C_{17}H_{19}N_3O$: C 72.57; H 6.81; N 14.93%. Found: C 72.59; H 6.82; N 15.20%.

2-Aminomethyl-7-amino-1,2,3,4-tetrahydroquinoline (IX). Compound VIII (1.19 g, 0.0042 moles) in concentrated hydrochloric acid (10 ml) was heated at 120°C with stirring for 12 h. Benzoic acid was extracted with chloroform, the acidic solution concentrated to dryness, and the residue crystallized from a mixture of concentrated hydrochloric acid and absolute alcohol (1:1) to give the hydrochloride of IX, 0.75g, 62%, mp 225°C (with decomposition). Calculated for $C_{10}H_{15}N_3 \cdot 3HCl$: C 41.90; H 6.33; Cl 37.11%. Found: C 41.44; H 6.20; Cl 36.98%.

2-Aminomethylquinoline (X). Potassium phthalimide (14 g, 0.076 moles) was dissolved in dimethylformamide (400 ml) with boiling, and 2-bromomethylquinoline [10] (15.5 g, 0.07 moles) in dimethylformamide (50 ml) was added. The reaction mixture was refluxed for 1 h, cooled and poured into water (350 ml). An oil separated, which was extracted with chloroform. The extract was washed with a 1% solution of sodium hydroxide, followed with water and drying over magnesium sulfate. The solution was then reduced to a small volume under reduced pressure and cooled to give XI, 12.6 g, 63%, mp 174.5-177°C (from absolute alcohol). Calculated for $C_{18}H_{12}N_2O_2$: C 74.98; H 4.19; N 9.72%. Found: C 75.00; H 4.43; N 9.53%.

To XI (22 g, 0.076 moles) in ethanol (200 ml) was added hydrazine hydrate (3.8 g, 0.076 moles) and the mixture was heated for 1 h on an oil bath. A gradual dissolution was following by reprecipitation. The reduction mixture was cooled, diluted with water (100 ml), and the alcohol removed under reduced pressure. Concentrated hydrochloric acid (100 ml) was added to the residue, the mixture heated for 1 h, and cooled. Crystalline phthalyl hydrazide was filtered and the filtrate made alkaline with a 20% solution of sodium hydroxide. Compound X separated as an oil and was extracted with benzene. The extract was dried over potassium carbonate, concentrated under reduced pressure, and the residue distilled in a stream of nitrogen to give X (8.3 g, 68.5%) as a rapidly crystallizing oil, bp 124-129°C (0.8 mm). The picrate of X melted at 182°C with decomposition (from alcohol). Calculated for $C_{10}H_{10}N_2 \cdot C_6H_3N_3O_7$: C 49.63; H 3.39; N 18.6%. Found: C 49.71; H 3.39; N 17.98%. It was obtained by adding an alcoholic solution of picric acid to X in alcohol. Ref. [11]: bp 152°C (7 mm).

2-(N-phenylcarbamylaminomethyl)-1,2,3,4-tetrahydroquinoline (XII). To a solution of 2-aminomethyl-1,2,3,4,-tetrahydroquinoline [9] (0.6 g, 0.0038 moles) in ethyl acetate (5 ml) was added phenyl isocyanate (0.45 g, 0.0038 moles) and the mixture was heated on a water bath for 30 min. On cooling, compound XII was obtained, 0.92 g, 87.3%, mp 164-165°C (from absolute alcohol). Calculated for $C_{17}H_{19}N_3O$: C 72.57; H 6.81; N 14.93%. Found: C 72.78; H 6.76; N 14.96%.

2=C(N-phenylcarbamylaminomethyl)-6-bromo-1,2,3,4-tetrahydroquinoline (XIII). This was obtained by heating base IV with an equimolar amount of phenylisocyanate in ethyl acetate, mp 178-181°C (from isopropyl alcohol). Calculated from $C_{17}H_{18}BrN_3O$: C 56.67; H 5.03%. Found: C 56.70; H 5.15%.

2-(N-phenylcarbamylaminomethyl) Quinoline (XIV). To a solution of X (0.86 g, 0.0054 moles) in ethyl acetate (10 ml) was added phenylisocyanate (0.65 g, 0.0054 moles) and the reaction mixture was kept at about 20°C for 30 min. The precipitate was filtered and recrystallized from 96% ethanol to give XIII, 1.32 g, 82.5%, mp 183-183.5°C. Calculated from $C_{17}H_{15}N_3O \cdot H_2O$: C 69.13; H 5.80; N 14.22%. Found: C 69.17; H 5.49; N 14.30%.

2-(N-phenylthiocarbamylaminomethyl) Quinoline (XV). To a solution of X (0.7 g, 0.004 moles) in absolute ethanol (10 ml) was added phenylisothiocyanate (0.6 g, 0.004 moles) and the mixture was heated on a water bath for 15 min. On cooling, XIV was obtained, 1.01 g, 79%, mp 160-161°C (from absolute alcohol). Calculated for $C_{17}H_{15}N_3S$: C 69.59; H 5.16; S 10.93%. Found C 69.31; H 5.29; S 10.79%.

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SYNTHESIS AND NEUROPHARMACOLOGICAL ACTIVITY OF SATURATED 1,3-DIOXOLANES AND 1,3-DIOXANES

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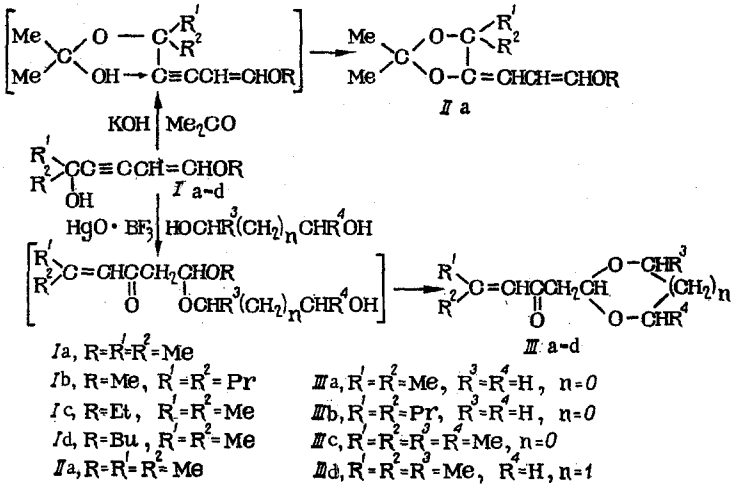
Some compounds in the 1,3-dioxolane and 1,3-dioxane series show physiological activity. Thus, iodomethylates of N-substituted 1,3-dioxolanes show muscarine-like activity [1] and cause a significant lowering of the arterial pressure in dogs when administered at 0.1 μg/kg dose (2 μg/kg dose is usually lethal). The compound 2-trichloromethyl-4-oxymethyl-1,3-dioxolane (cis- and trans- isomers) produces a temporary anesthesia in mice [2]. Alkyl(phenyl)substituted 1,3-dioxolanes and 1,3-dioxanes with nitrogenous substituents are characterized by spasmolytic [3, 4] and antihistaminic [4] activities, while 2,5-dialkyl-5α-alkoxymethyl-1,3-dioxanes show antibacterial, fungicidal, and fungistatic activities [5, 6]. Some 1,3-dioxolanes and 1,3-dioxanes were found to act as insecticides [7] or synergists and plant growth stimulators [8-10]. We have synthesized, on the basis of 1-alkoxyene-1-in-3-carbinols (Ia-d), the unsaturated 1,3-dioxolanes (IIa, IIIa-c) and 1,3-dioxanes (IIId) and have studied their neuropharmacological activity.



Tertiary alkoxyenein alcohol Ia, on reacting with acetone [11] in the presence of potassium hydroxide at 90-100°C for 15-20 h, produced substituted 1,3-dioxolane IIa containing a diene group in its side branch (in a 55% yield). The structure of IIa was determined on the basis of the elemental analysis data and the IR spectrum which showed absorptions due to a COC group (1090-1180 cm^{-1}) and to a diene fragment (1577, 1625, 1670, and 3060-3080 cm^{-1}).

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