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Studies on Antimetabolites

III. Synthesis of "*Neo*histamine", the β,β-Dimethyl Analogue of Histamine *

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The β,β-dimethyl analogue (II) of histamine, a potential antihistaminic agent, and its N,N-dimethyl derivative (VI), have been prepared. The intermediate ethyl α-4(5)-imidazole*iso*butyrate (IV) was obtained by Bredereck and Theilig's reaction from ethyl γ-bromo-α,α-dimethylacetoacetate. The 4(5)-*tert*butylimidazole and α-4(5)-imidazole*iso*butyronitrile were analogously prepared. Reduction of α-4(5)-imidazole*iso*butyramide with lithium-aluminium hydride afforded "*neo*histamine". Similar treatment of the N,N-dimethylamide gave N,N-dimethyl-"*neo*histamine" (VI). Dimethylaminomethylation of methyl *iso*propyl ketone afforded a high yield of 4-(N,N-dimethylamino)-3,3-dimethylbutanone-2 (VII), which was brominated to (VIII). The attempted ring closure of VIII to VI was not successful.

Among the numerous compounds tested for antihistamine activity those, which are derivatives of histamine or at least contain an imidazole nucleus, deserve special attention, because of their obvious structural relationship to histamine (I) itself. In spite of this fact the number of imidazole derivatives tested is comparably low[1,2,3] and so far no potent histamine antagonist has been detected amongst them. Following up the investigations regarding the possibility of designing antimetabolites by the introduction of a suitably situated *gem*dimethyl group into the molecule of a metabolite, which proved successful in the group of plant growth substances discussed in Part I of this series[4], we have now prepared the α,α-dimethyl analogue (II) of histamine,for convenience called "*neo*histamine", and its N,N-dimethyl derivative. It is the purpose of the present paper to describe the synthetical work, the results of the physiological testing of the compounds will be discussed elsewhere.

The synthesis of 4(5)-alkylimidazoles by conventional methods requires such difficultly available intermediates as α-ketoalcohols, α-ketoaldehydes

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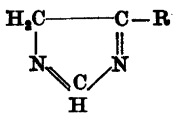


I R = $CH_2CH_2NH_2$

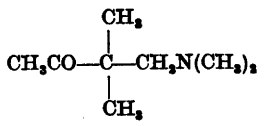
II R = $C(CH_3)_2CH_2NH_2$

III R = $C(CH_3)_3$

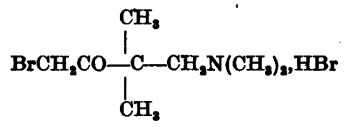
IV R = $C(CH_3)_2COOC_2H_5$

V R = $C(CH_3)_2CN$

VI R = $C(CH_3)_2CH_2N(CH_3)_2$



VII



VIII

or α-aminoketones [5]. Additional difficulties arise from the fact that in the present case the starting material should contain a *gem*dimethyl group adjoining the keto function. Several unsuccessful attempts were made to prepare "*neo*-histamine" along such lines. Recently, however, Bredereck and Theilig demonstrated [6], that α-haloketones are readily converted to imidazole derivatives when heated with formamide. This reaction opened a route to the synthesis of imidazoles carrying a quarternary side chain carbon atom at position 4(5), as it was found that the α-bromoketones required as intermediates could easily be prepared by bromination of the ketones, and directly converted to imidazole derivatives without isolation. In this way pinacolone, ethyl α,α-dimethylacetoacetate, and α,α-dimethylacetoacetonitrile were converted *via* their (not isolated) bromoderivatives into *tert*butylimidazole (III), ethyl α-4(5)-imidazole*iso*butyrate (IV), and α-4(5)-imidazole*iso*butyronitrile (V), respectively, and isolated as their hydrochlorides in 10—35 % yield.

"*Neo*histamine" was obtained from α-4(5)-imidazole*iso*butyric acid *via* the acid chloride and amide by reduction with lithium-aluminium hydride in tetrahydrofuran and isolated as the dihydrochloride. N,N-dimethyl-"*neo*-histamine" (VI) was prepared analogously *via* the N,N-dimethylamide and isolated as the dipicrate. Attempts were made to prepare this compound by ring closure from the hydrobromide of 1-bromo-4-(N,N-dimethylamino)-3,3-dimethylbutanone-2 (VIII), but no crystalline material could be isolated from the reaction mixture, which, however, gave a positive Pauly test suggesting that an imidazole derivative may have been formed. The intermediate bromo-hydrobromide (VIII) was obtained by bromination of the Mannich base (VII), 4-(N,N-dimethylamino)-3,3-dimethylbutanone-2, by the general method of Mannich and Gollasch [7]. The Mannich base (VII) was conveniently prepared by dimethylaminomethylation of methyl *iso*propyl ketone.

All the imidazole derivatives prepared gave a crimson colouration in the Pauly diazo reaction test [8].

EXPERIMENTAL *

α,α-Dimethylacetoacetonitrile. This compound has been described [9–11], but no details appear to be available for its preparation. — α-Methylacetoacetonitrile [11] (97 g) was added to a stirred solution of sodium (23 g) in anhydrous ethanol (300 ml), followed by methyl iodide (142 g). After standing overnight at room temperature the mixture was refluxed for 4 hours on the water bath. A solution of sodium (4.6 g) in anhydrous ethanol (75 ml) was added followed by methyl iodide (30 g). After refluxing for 6 hours most of the solvent was removed by distillation using a short column, the residual semi-solid mass pored into water, the oil taken up in ether, dried (Na_2SO_4) and fractionated. The yield of almost colourless oil, b. p. 162—165°, was 72 g (65 %). Lit. b. p. 163—164° [10,11]; 162°/748 mm [12].

Imidazole derivatives from α-bromoketones. General procedure. The keto compound (1.2 moles) was dissolved in carbon tetrachloride (200 ml) and brominated with stirring by slow addition of a solution of bromine (1.0 mole) in carbon tetrachloride (100 ml), the temperature being kept below 10° by external cooling. As soon as the bromine colour had disappeared the solvent and dissolved hydrogen bromide was carefully removed by distillation *in vacuo* on a water bath at maximum 30°. Formamide (400 ml) free from ammonia was added, and the mixture stirred at 160—180° for 4 hours. Excess formamide was distilled off *in vacuo* (maximum 190° in the bath), the semi-solid mass dissolved in a little water, made alkaline with solid potassium carbonate and continuously extracted with ether for 15 hours. The extract was distilled *in vacuo*, yielding faintly yellow oils, which only partly crystallised. They were dissolved in a little anhydrous ethanol, and their solutions saturated with dry hydrogen chloride. The hydrochlorides were obtained in crystalline state by careful addition of dry ether until a permanent cloudiness resulted.

4(5)-Tertbutylimidazole (III) (from pinacolone) was collected at 140—145°/7 mm. The *hydrochloride* formed colourless prisms from diethyl malonate, m. p. 168—169°. Yield 35 %. (Found: Cl 21.8; N 17.2, 17.3. $C_7H_{13}ClN_2$ requires: Cl 22.1; N 17.4.)

α-4(5)-Imidazoleisobutyronitrile (V) (from α,α-dimethylacetoacetonitrile) was collected at 140—200°/7 mm. The *hydrochloride* crystallised from ethanol-ether in prisms, m. p. 153—155°. Yield 10 %. (Found: Cl 20.4; N 24.3. $C_7H_{10}ClN_3$ requires: Cl 20.6; N 24.5.)

Ethyl α-4(5)-imidazoleisobutyrate (IV) (from ethyl α,α-dimethylacetoacetate [13]) was collected at 140—200°/7 mm. The *hydrochloride* formed prisms from ethanol-ether, m. p. 125—126°. Yield 25 %. (Found: Cl 15.8; N 12.6, 12.7; C_2H_5O 20.7. $C_9H_{15}ClN_2O_2$ requires: Cl 16.2; N 12.8; C_2H_5O 20.6.)

α-4(5)-Imidazoleisobutyric acid hydrochloride was obtained by refluxing the ethyl ester with excess 20 % hydrochloric acid and evaporation of the solvent *in vacuo* on the water bath. The residual syrup crystallised on standing for some hours. For analysis it was recrystallised from anhydrous ethanol-ether. Prisms, m. p. 183—184°. (Found: Cl 18.3; N 14.5, 14.6. $C_7H_{11}ClN_2O_2$ requires: Cl 18.6; N 14.7.) — An identical compound (mixed m. p.) was obtained by refluxing α-4(5)-imidazole*iso*butyronitrile (1.0 g) with 20 % hydrochloric acid (25 ml) for 4 hours, evaporation to dryness, dissolving the solid in anhydrous ethanol (25 ml) filtering from undissolved material, evaporation to dryness and crystallisation of the residual solid from ethanol-ether.

"Neohistamine", β,β-dimethylhistamine (II). Crude α-4(5)-imidazole*iso*butyric acid hydrochloride (from 29 g of the ethyl ester) was heated under reflux for 1/2 hour with thionylchloride (75 ml). Excess thionylchloride was evaporated, the last traces being removed *in vacuo*, and the residual oil was cautiously treated with concentrated aqueous ammonia (50 ml) with cooling in an ice bath. When the oil had dissolved, excess ammonia and water was completely removed by evaporation *in vacuo* on the water bath. The semi-solid residue was dried overnight under reduced pressure at 60° over phosphorus pentoxide. To the dry salt mixture there was added anhydrous tetrahydrofuran (300 ml) and, with stirring, powdered lithium-aluminium hydride (15 g) in small portions. After the addition the mixture was refluxed overnight on the water bath, and worked up by the general procedure of Amundsen and Nelson [14]. Water (16 ml) was carefully added with vigorous stirring, followed by 20 % aqueous sodium hydroxide (12 ml) and again water (55 ml). The organic layer was separated from the precipitated salts by filtration with

* All boiling and melting points uncorrected.

suction, and the filter cake was thoroughly washed with several portions of hot tetrahydrofuran. The combined filtrate and washings were concentrated to an oil, which was dissolved in anhydrous ethanol (50 ml) and saturated with dry hydrogen chloride. "*Neo*-histamine" dihydrochloride at once started to separate. After storing for some hours in the refrigerator, the crystals were collected and washed with ethanol. Yield 12.1 g. An additional amount was obtained by concentration of the mother liquor to a small volume. Total yield 12.9 g (46 %). The product was crystallised from methanol-ether. Prisms, m. p. 240–245° (decomp.). The compound was very soluble in water and soluble in methanol but almost insoluble in hot or cold ethanol. (Found: C 39.5; H 6.96; Cl 33.1; N 19.7. $C_7H_{15}Cl_2N_3$ requires: C 39.6; H 7.13; Cl 33.4; N 19.8.) The *dipicrate* formed long yellow needles from water, m. p. 209–211°. (Found: C 38.2; H 3.36; N 20.9. $C_{19}H_{19}N_9O_{14}$ requires: C 38.2; H 3.21; N 21.1.)

N,N-Dimethyl-"neohistamine", β,β,N,N-tetramethylhistamine (VI) was analogously prepared from ethyl α-4(5)-imidazole*iso*butyrate hydrochloride (11 g) *via* the N,N-dimethylamide (from 25 % aqueous dimethylamine). The dihydrochloride was obtained as a glass, which could not be induced to crystallise. It was dissolved in water (100 ml) and poured into a hot solution of picric acid (15 g) in water (700 ml). On cooling the *dipicrate* separated as long yellow needles. Yield 7.0 g. For analyses it was repeatedly recrystallised from water. M. p. 200–201°. (Found: C 40.2; H 3.76; N 20.0. $C_{21}H_{23}N_9O_{14}$ requires: C 40.3; H 3.71; N 20.2.) – The *dihydrochloride* was obtained by treatment of the picrate with concentrated hydrochloric acid, extraction of the picric acid with hot benzene, treatment with decolourising carbon and evaporation to dryness. A glass was obtained which slowly crystallised. Prisms from ethanol-ether. M. p. 207–210° (decomp.). (Found: C 45.0; H 7.99; Cl 29.6; N 17.4. $C_9H_{19}Cl_2N_3$ requires: C 45.0; H 7.97; Cl 29.5; N 17.5.)

4-(N,N-Dimethylamino)-3,3-dimethylbutanone-2 (VIII) Methyl *iso*propyl ketone (725 g), dimethylamine hydrochloride (240 g), 40 % aqueous formaldehyde (260 ml) and ethanol (500 ml) were mixed and heated at reflux on the water bath overnight. The mixture, which initially formed two layers, slowly became homogenous. Volatile products were distilled off on the water bath under reduced pressure, the re idual syrupy mass or crystalline cake was dissolved in water, made strongly alkaline with 6 *N* sodium hydroxide, ice being added to prevent an excessive raise in temperature, and the free base extracted with ether. The combined extracts were washed and dried (K_2CO_3). The ether was removed and the residual oil fractionated *in vacuo* using an efficient column. The Mannich base formed a colourless liquid, b. p. 54–56°/10 mm. (Found: N 9.56; neutr. equiv. 143. $C_8H_{17}NO$ requires: N 9.78; neutr. equiv. 143.2.) The amine gave a positive iodoform test. – *Hydrochloride*, colourless needles from acetone, m. p. 146–146.5°. (Found: Cl 19.9; N 7.7. $C_8H_{18}ClNO$ requires: Cl 19.7; N 8.0). *Semicarbazone* of the free amine, needles from water, m.p. 132–133°. (Found: C 54.1; H 9.87; N 27.6. $C_9H_{20}N_4O$ requires: C 54.0; H 10.0; N 28.0.) *Methiodide*, from the free amine and excess methyl iodide in ethanol, crystal powder which decomposed at about 182° without melting. (Found: I 44.5; N 5.0. $C_9H_{20}INO$ requires: I 44.4; N 4.9.)

Hydrobromide of 1-bromo-4-(N,N-dimethylamino)-3,3-dimethylbutanone-2. (VIII). The aminoketone (VII) (143 g) was dissolved in glacial acetic acid (200 ml), 66 % aqueous hydrobromic acid (100 ml) added with cooling followed by a solution of bromine (160 g) in glacial acetic acid (100 ml). The mixture was heated on a water bath until the bromine colour had disappeared. The solvent was removed *in vacuo* on the water bath, and the syrupy residue at once dissolved in acetone (400 ml). (It is important to avoid heating this mixture for an unnecessarily long time, as this causes decomposition of the bromoketone.) On cooling a crystalline product was obtained, which was isolated and thoroughly washed with acetone. Crystallisation from ethanol-ether yielded glistening prisms (192 g, 65 %) m. p. 130–132°. (Found: Br 52.2; N 4.65. $C_8H_{17}Br_2NO$ requires: Br 52.8; N 4.62.)

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