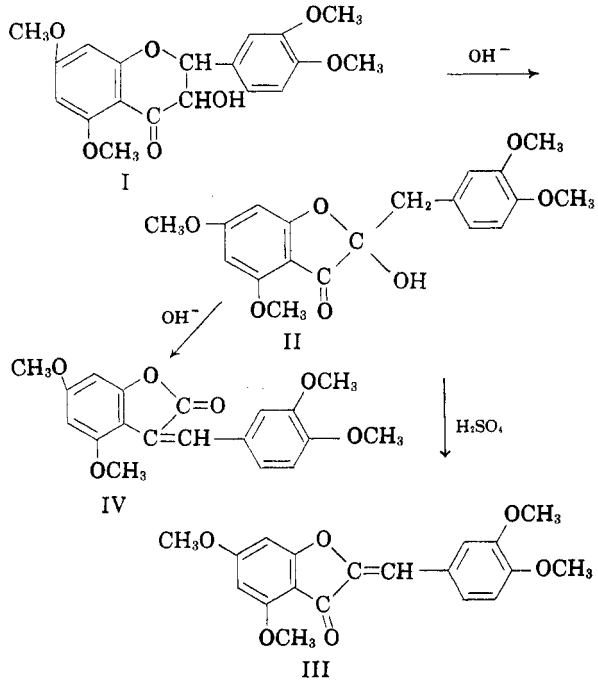
II with alkali also gives III is contrary to expectations. One would expect that such a treatment should, through a benzilic acid rearrangement, finally lead to 3-(3,4-dimethoxybenzylidene)-4,6-dimethoxycoumaran-2-one (IV), isomeric with III.[3,4,5]



As a matter of fact we synthesized the compound IV, making thereby the remark, that it should be formed from taxifolintetramethylether upon treatment with alkali.[5]

That it is indeed IV that is formed when II, and hence also I, is boiled with alkali has now been confirmed by a direct comparison of the product with synthetic IV, thereby establishing their identity. II was prepared by the method of Kimura[6] and gave, in agreement with Hergert, Coad and Logan,[1] upon treatment with concentrated sulfuric acid, III, identified by comparison with an authentic sample prepared according to Geissman and Fukushima.[7]

The isomeric compounds III and IV have nearly the same melting points, 171.5–172° and 173.5–174°, respectively, but they give a definite depression of melting point in a mixture test. They further differ in their color reactions with concentrated sulfuric acid. III gives a stable crimson-magenta color,[7] whereas IV in sufficient dilution gives a green color, which upon standing turns brown.

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(5) Gripenberg and Juselius, *Acta Chem. Scand.*, **8**, 734 (1954).
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EXPERIMENTAL

2-(3,4-Dimethoxybenzyl)-2-hydroxy-4,6-dimethoxycoumaran-3-one (II). 2'-Hydroxy-3,4,4',6',α-pentamethoxychalcone[6] (1 g.) was dissolved in ethanol (100 ml.). To this was added 2*N* sulfuric acid (20 ml.) and the solution was refluxed for 24 hours. After removing the ethanol the product was taken up in ether. The ether solution was extracted with 1*N* sodium hydroxide. Acidification gave a precipitate, which was taken up in chloroform. Removal of the chloroform and recrystallization once from light petroleum-chloroform and once from methanol gave 0.6 g. white crystals, m.p. 176.5°. (Reported, 176°.[1,6])

3-(3,4-Dimethoxybenzylidene)-4,6-dimethoxycoumaran-2-one (IV). 2-(3,4-Dimethoxybenzyl)-2-hydroxy-4,6-dimethoxycoumaran-2-one (II) (0.5 g.) was dissolved in 48% ethanol (14 ml.) containing potassium hydroxide (0.5 g.). The solution was refluxed for one hour, acidified, and extracted with ether. The ether was removed and the residue recrystallized from ethanol giving 0.07 g. of yellow crystals, m.p. 173.5–174°, undepressed when mixed with an authentic sample.[5] It dissolved in concentrated sulfuric acid with a green color, slowly turning brown.

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Some 4(or 5)-(2'-Aminopropyl)imidazoles

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The substitution of a 2-aminopropyl group in place of the 2-aminoethyl side chain of phenethylamines was found by Alles[3] to produce but little change in the intensity of their peripheral sympathomimetic activities though the duration of such actions is much prolonged. The effects of corresponding substitution of the 2-aminoethyl side chain of histamine and of its 5(or 4)-methyl derivative that has similar physiological activities was of interest.

It was found that a synthesis of histamine itself could be accomplished from 1,4-diaminobutanone-2, and this synthesis has been recently reported by Fraser and Raphael.[4] The success of this method suggested the possibility of using it for preparing the corresponding 2-aminopropyl imidazole from 1,4-diaminopentanone-2. The preparation of this intermediate from 2-phthalimidobutyryl chloride has been improved over that described by Erne, Ramirez, and Burger.[5] Condensation of the so derived 1,4-diaminopentanone-2 with potassium thiocyanate gave 4(or 5)-(2'-aminopropyl)-2-thiolimid-

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(3) G. A. Alles, *J. Pharmacol.*, **47**, 337 (1933).
(4) M. M. Fraser and R. A. Raphael, *J. Chem. Soc.*, 226 (1952).
(5) M. Erne, F. Ramirez, and A. Burger, *Helv. Chim. Acta*, **34**, 143 (1951).

azole and this on oxidation gave the desired 4(or 5)-(2′-aminopropyl)imidazole. Its picrate and some other salts and derivatives are described.

The plan of synthesis of 5(or 4)-methyl-4(or 5)-(2′-aminopropyl)imidazole reported by Sarasin[6] was followed. The steps involving preparation of isonitroso-allylacetone and of amino-allylacetone had to be modified in our hands to obtain a sufficient amount of the resultant imidazole for pharmacological studies.

Studies of the depressor activities[7] of the 2-aminopropyl-imidazoles here described showed that each was only about one-hundredth as active as the corresponding 2-aminoethyl-imidazole. The 2-aminopropyl-imidazoles were found active in stimulating gastric secretion[8] and were included in some studies on cutaneous anesthesia and pain.[9]

EXPERIMENTAL

1-Chloro-4-phthalimidopentanone-2 (I). 2-Phthalimidobutyric acid was prepared following the procedure of Erne, Ramirez, and Burger,[5] and on drying at 80° under 15 mm. pressure melted at 121.5–122.5°. Its conversion to the acid chloride gave a product which crystallized from benzene, m.p. 85–86°. This was converted into (I) in almost 100% yield as follows: A solution of 2-phthalimidobutyryl chloride (31 g., 0.125 mole) in a liter of dry ether was added dropwise to an ice cold solution of diazomethane (15.5 g., 0.37 mole) in 500 ml. dry ether. After keeping overnight at −5° C. dry hydrogen chloride was passed in for 2 hr. at that temperature. After 12 hr. keeping at −5° removal of ether gave 32.3 g. of (I), m.p. 104°, after recrystallization from acetone, m.p. 105–106°.

1,4-Diphthalimidopentanone-2 (II). Potassium phthalimide (40.4 g., 0.22 mole) and 56.0 g. (0.205 mole) of (I) in 300 ml. dimethyl formamide were heated at 90° with stirring for 90 min. then cooled to 200° and any solid filtered off. To the filtrate 1000 ml. chloroform and 1200 ml. water were added and the heavy layer separated, then washed with 550 ml. of 0.3*N* sodium hydroxide solution and with 200 ml. water. After drying the chloroform extract with anhydrous sodium sulfate the chloroform was distilled at 15 mm. and the residue washed with ether, then recrystallized from benzene to give (II), 50 g. (64%).

Anal. Calcd. for $C_{21}H_{16}N_2O_5$: N, 7.4. Found: N, 7.3.

1,4-Diaminopentanone-2 dihydrochloride (III). Recrystallized II (14 g., 0.037 mole) was refluxed 12 hr. with 500 ml. of 20% hydrochloric acid and, after the addition of 350 ml. more acid, was refluxed 12 hr. more. The cooled solution was filtered and the filtrate evaporated, then cooled and again filtered. After filtering off the phthalic acid, the filtrate was evaporated to dryness and the residue recrystallized several times from ethanol with ether. The white crystalline product melted at 192–193° with effervescence, after browning at 190°. It gave a chlorplatinate crystallizing in orange needles from ethanol which blackened at 180–200° without melting.

Anal. Calcd. for $C_5H_{12}N_2O \cdot H_2PtCl_6$: Pt, 37.1. Found: Pt, 37.6.

The dipicrate in yellow prisms for water darkened at 200–210° without melting. The dibenzoyl derivative after recrystallization from ethanol melted at 184–185°.

4(or 5)-(2′-Aminopropyl)-2-thiolimidazole hydrochloride (IV). Total crude material from a preparation of (III) as above was dissolved in 20 ml. water and filtered, then heated with 3.27 g. potassium thiocyanate (0.024 mole) and after evaporating to a syrup was heated on the steam bath 1 hr. The syrup was then evaporated *in vacuo* and the residue taken up with boiling methanol. Evaporation gave (IV) 4.2 g. (59%).

Anal. Calcd. for $C_6H_{11}N_3S$: C, 37.2; H, 6.2; Cl, 18.3. Found: C, 37.1; H, 6.1; Cl, 18.1.

4(or 5)-(2′-Aminopropyl)imidazole dipicrate (V). A solution of 8.4 g. of (IV) in 150 ml. water with 58.5 g. ferric chloride hexahydrate in 350 ml. water were heated on a steam bath for 1 hr. Then 110 ml. of 20% sodium carbonate solution were added and to the boiling solution 16.5 g. picric acid in 450 ml. water were further added. The crude picrate (18.8 g., 81%) that separated was recrystallized from hot water with charcoal to give bright yellow prisms, m.p. 202–204° (11.2 g., 48%).

Anal. Calcd. for $C_{18}H_{17}N_6O_{14} \cdot H_2O$: C, 35.9; H, 3.2; H_2O loss in weight, 3.1%. Found: C, 36.1; H, 3.3; H_2O, 2.9%.

The dihydrochloride was prepared from the dipicrate but could not be obtained as a crystalline solid. The platinichloride was prepared from a solution of the dihydrochloride as fine orange needles from ethanol and it backened at 250–260° without melting.

Anal. Calcd. for $C_6H_{11}N_3 \cdot H_2PtCl_6$: Pt, 36.5. Found: Pt, 36.3.

A hygroscopic dihydrobromide was obtained after crystallization from alcohol with addition of acetone, m.p. 172–273°. It is rapidly deliquescent in air and must be stored in a desiccator.

Anal. Calcd. for $C_6H_{11}N_3 \cdot HBr$: C, 25.1; H, 4.6; Br, 55.7. Found: C, 25.3; H, 4.6; Br, 56.3.

The oxalate was prepared by making a solution of the dihydrochloride basic with sodium carbonate, evaporating to dryness, and taking the base into ethanol, then adding oxalic acid. Acetone was further added and the product crystallized in colorless needles, m.p. 120–122°.

Anal. Calcd. for $C_6H_{11}N \cdot H_2C_2O_4 \cdot H_2O$: $H_2C_2O_4$, 27.9; N, 13.0. Found: $H_2C_2O_4$, 28.1; N, 13.0.

4(or 5)-(2′-Aminopropyl)imidazole (VI). Twenty-one and two-tenths grams of (V) were treated with 175 ml. 5*N* hydrochloric acid and 800 ml. benzene and the layers separated. Residual picric acid was removed from the aqueous layer with benzene and final treatment with charcoal. Evaporation at 15 ml. to about 10 ml. gave a solution which on addition of sodium hydroxide to *p*H 8 gave a base that was extracted with chloroform or methylene chloride. Drying of the extract with anhydrous sodium sulfate and then distillation gave the base (VI), 2.0 g. (44%) that distilled at 132°/0.01 mm., 158°/0.2 mm., and 182°/4 mm.

Bis-N-2,4-dinitrophenyl derivative (VII). Heating (VI) and chloro-2,4-dinitrobenzene in ethanol at 80° for 15 min. followed by the evaporation of the solvent under 15 mm. gave a red glass, which recrystallized from ethanol with acetone gave orange plates, m.p. 159.5–161°.

Anal. Calcd. for $C_{18}H_{15}N_7O_8$: C, 47.3; H, 3.3. Found: C, 47.0; H, 3.3.

As a comparison compound, imidazole was reacted with chloro-2,4-dinitrobenzene in ethanol, then the solution concentrated and crystallized. After recrystallization, light brown rhombic crystals, m.p. 145.5–146.5°, were obtained.

Anal. Calcd. for $C_9H_6O_4N_4$: C, 46.2; H, 2.6; N, 23.9. Found: C, 45.7; H, 2.9; N, 24.6.

5(or 4)-Methyl-4(or 5)-(2′-aminopropyl)imidazole dihydrochloride. Following Sarasin[6] isonitroso-allylacetone was prepared and reduced to amino-allylacetone which was converted into 5(or 4)-methyl-4(or 5)-allyl imidazole. Hydrobromic acid was added and the 2-bromopropyl compound reacted with ammonia. The desired product was obtained as the hydrochloride in colorless needles, m.p. 215–217°.

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Anal. Calcd. for $C_7H_{13}N_3 \cdot 2HCl$: C, 39.6; H, 7.12; Cl, 33.4. Found: C, 40.0; H, 7.5; Cl, 33.4.

The first two steps of this synthesis required modification: *Isonitroso-allylacetone.* Hydrolysis of 50 g. of ethyl allylacetoacetate was carried out by dissolving it in a cold solution of 36 g. potassium hydroxide in 650 ml. of water and allowing to stand 24 hr. Twenty grams of sodium nitrite in concentrated solution were added, the mixture was cooled to 0°, and 88 g. sodium dihydrogen phosphate monohydrate in a little water were added. A cold solution of 52 g. sulfuric acid (96%) in 250 ml. water was slowly added, with the temperature kept below 0°, and the mixture stirred for 15 min. Three extractions with ether and then shaking the ether extracts with 100 ml. 4 *N* sodium hydroxide solution gave an aqueous layer that was acidified with 100 ml. 4*N* sulfuric acid. The separated oil was taken up with ether, dried over potassium carbonate and on evaporating the ether 28.4 g., m.p. 76° (degrees) were obtained.

Amino-allylacetone hydrochloride. Isonitroso-allylacetone (18.5 g.) in small portions was added to a solution of stannous chloride dihydrate in 100 ml. 12*N* hydrochloric acid. The temperature was kept at 20–30° and 34.7 g. mossy tin were added, then the mixture kept at 50° for 15 min. After separating unreacted tin the filtrate was made up to 1400 ml. with water and saturated with hydrogen sulfide. After filtering, the solution was evaporated under reduced pressure. The residue crystallized from ethanol with addition of acetone to give 11.1 g. (51%) of m.p. 153–154°.

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Steroidal Sapogenins. XXXVIII.[1] 5-Pregnene-3β,17α-diol-12,20-dione 3-Acetate

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In a previous publication[2] we described the preparation and properties of a new 12-keto sapogenin, gentrogenin. In continuation of previously described researches on 12-keto compounds of the C_{21} series[2] we have used gentrogenin as a source of C_{21} compounds containing both the 12-keto group and the 5,6-olefinic bond. It will be recalled that the sapogenin degradation product 5,16-pregnadien-3β-ol-12,20-dione acetate prepared by Marker[3] was reported to melt from 226 to 228°, while our product, I, from gentrogenin melted from 173 to 175°.[2]

In this present note we wish to describe the conversion of our 5,16-pregnadien-3β-ol-12,20-dione acetate, I, of melting point 173–175° to the 16α,17α-epoxide, II, and subsequently to the derived bromohydrin, III, and 17α-hydroxy desbromo compounds, IV. This route for introduction of the 17α-hydroxyl group was first used by Julian, *et al.*[4] Parallels to the present reactions have been described in the hecogenin series[5] and diosgenin series[4]; however, in the present case the analogy could not be followed to the point of introduction of the 21-acetoxy group. We were not able to prepare 3β,21-diacetoxy-5-pregnen-17α-ol-12,20-dione from IV by treatment in sequence with bromine, potassium iodide, and sodium acetate.[6]

EXPERIMENTAL

16α,17α-Epoxy-5-pregnen-3β-ol-12,20-dione Acetate, II. 5,16-Pregnadien-3β-ol-12,20-dione acetate, 0.63 g., was dissolved in 80 ml. of methanol. To the solution cooled in an ice bath was added 5 ml. of 30% hydrogen peroxide followed by 2.3 ml. of 4*N* sodium hydroxide. After storing overnight at 10°, 80 ml. of water and 2.3 ml. of 4*N* hydrochloric acid were added. On concentration of the solution *in vacuo* to 40 ml., a crop of crystalline plates separated and was collected by filtration. A small additional amount of product was isolated by extracting the filtrate with methylene chloride. Acetylation of the product with 60 ml. of 1:1 acetic anhydride-pyridine overnight at room temperature, dilution with water, extraction with ether, washing the organic layer with dilute hydrochloric acid and dilute sodium bicarbonate, drying with sodium sulfate, and concentration to 50 ml. gave a crystalline precipitate of 512 mg. of hexagonal, broad blades, m.p. 235.8–236.3°. Concentration to 7 ml. gave an additional crop of 88 mg., total yield 89%. The analytical sample, recrystallized from ether, showed transition to long spicules, m.p. 238.0–238.2°, $[\alpha]_D^{25}$ +29.4° ($CHCl_3$).

Anal. Calcd. for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.44; H, 7.99.

16β-Bromo-5-pregnene-3β,17α-diol-12,20-dione 3-Acetate, III. A solution of 500 mg. of epoxide in 15 ml. of glacial acetic acid was cooled to 15° and treated with 5 ml. of a solution of 2 ml. of 48% hydrobromic acid dissolved in 12 ml. of acetic acid. After standing 16 hr. at room temperature, the solvents were evaporated at 35° under water-aspiration. The slushy residue was diluted with ether, and the organic layer was washed with water, 2% sodium bicarbonate, and saturated brine, and after drying with sodium sulfate, was concentrated to 30 ml. on the steam bath and allowed to evaporate slowly, depositing 510 mg. of large hexagonal prisms, m.p. 214–217°, yield 86%. Recrystallization was effected by dissolution in a minimal volume of methylene chloride, dilution with ether, and boiling to remove the methylene chloride azeotropically. Repeated crystallization by this procedure gave dense polyhedra undergoing transition over 190° on the Kofler block to hexagonal plates with characteristic degenerate trapezoidal forms having a double melting point within the narrow range 219.2 to 220.5°, $[\alpha]_D^{25}$ −35°. The infrared carbonyl spectrum strongly resembled that of the hecogenin analogue shown in figure 1-A in reference 5 with strong bands at 1734, 1720, and 1695 $cm.^{-1}$.

Anal. Calcd. for $C_{23}H_{31}BrO_5$: C, 59.10; H, 6.69; Br, 17.10. Found: C, 59.28; H, 6.92; Br, 17.57.

5-Pregnene-3β,17α-diol-12,20-dione 3-Acetate, IV. The epoxide, 4.8 g. in 144 ml. of glacial acetic acid, and 48 ml. of hydrobromic acid in 200 ml. of acetic acid were mixed and reacted as described above. The solvents were evaporated under reduced pressure (water aspirator). The semi-solid residue in acetone acidified with 3 ml. of acetic acid

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