Synthesis of Imidazo[1,2-*c*]quinazoline and Some of Its Methyl Derivatives.

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The synthesis of imidazo[1,2-*c*]quinazoline was effected by manganese dioxide oxidation of the 5,6-dihydroimidazo[1,2-*c*]quinazoline which was prepared by treatment of 2-(*o*-nitrophenyl)-1-hydroxyimidazole-3-oxide with zinc powder and formic acid. The synthesis of some methyl derivatives of this ring system are also described. Structural assignments for all of the products were made from spectral data.

Imidazo[1,2-*c*]quinazoline (Ia) is a ring system that has been little explored; only a few hydrogenated derivatives are described in the literature (2-7) some of which have interesting pharmacological effects on the central nervous system (6,7). The present paper describes the synthesis of the parent compound Ia and some of its methyl derivatives.

o-Nitrobenzaldehyde was allowed to react with glyoxime in an ethanolic solution of hydrogen chloride (8) to yield 2-(*o*-nitrophenyl)-1-hydroxyimidazole 3-oxide hydrochloride (IIa).

Hydrolysis of IIa with water gave the base IIb (see Chart I). In the preparation of IIb a by-product was obtained which was assigned the structure of 1-hydroxyimidazole-2-aldehyde oxime 3-oxide (IIIa) on the basis of the elemental analysis and proton magnetic resonance spectra of its hydrochloride. The formation of IIIa might be due to condensation of glyoxime with the non-isolable intermediate α-hydroxyiminoacetaldehyde, formed in the reaction medium by the hydrolysis of a hydroxyimino group of the glyoxime.

Treatment of IIb with zinc powder and formic acid at 90-95° produced 6-formyl-5,6-dihydroimidazo[1,2-*c*]-quinazoline (IV) as the main product and 2-(*o*-dimethylaminophenyl)imidazole (V) and 6-methyl-5,6-dihydroimidazo[1,2-*c*]quinazoline (VI) as by-products. Mild alkaline hydrolysis of product IV afforded the corresponding deformylated product VII, which by manganese dioxide oxidation gave the expected imidazo[1,2-*c*]-quinazoline (Ia). In a similar way, from *o*-nitrobenzaldehyde and dimethylglyoxime, the methylated products VIII, previously synthesized by La Parola (8), IX, X, XI, XII and XIII were obtained (see Chart I).

In order to obtain derivatives containing a methyl group at the 5-position, IIb was allowed to react with zinc powder, acetic acid and acetic anhydride (see Chart II). Two products were obtained: 5-methyl-5,6-dihydroimidazo[1,2-*c*]quinazoline (XIV) as the main product and the corresponding 6-acetyl derivative XVa, isolated as its hydrochloride XVb, as a by-product, which by alkaline

CHART I

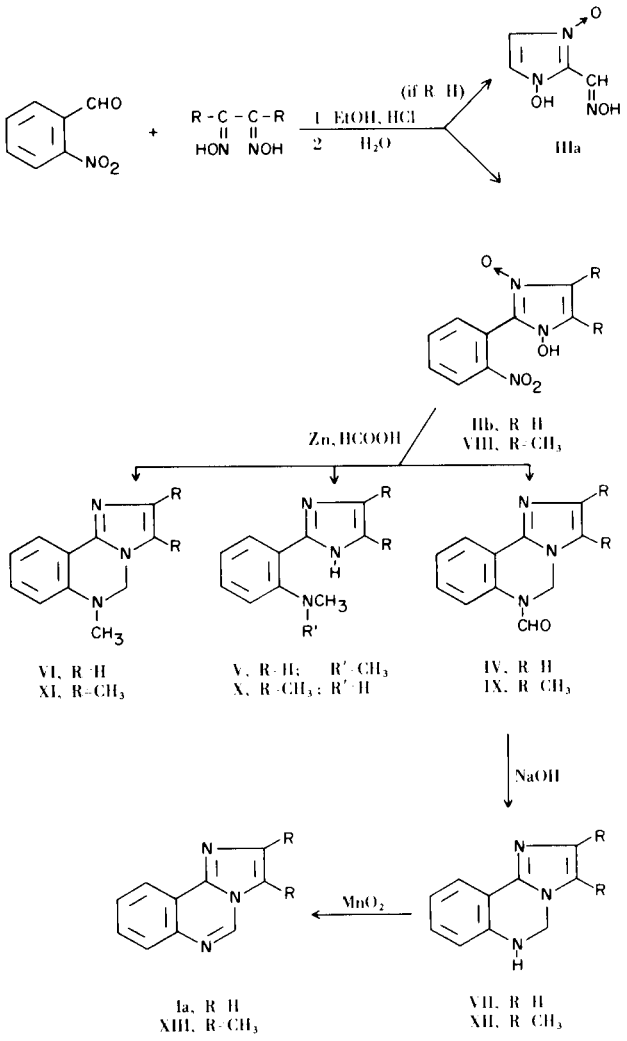
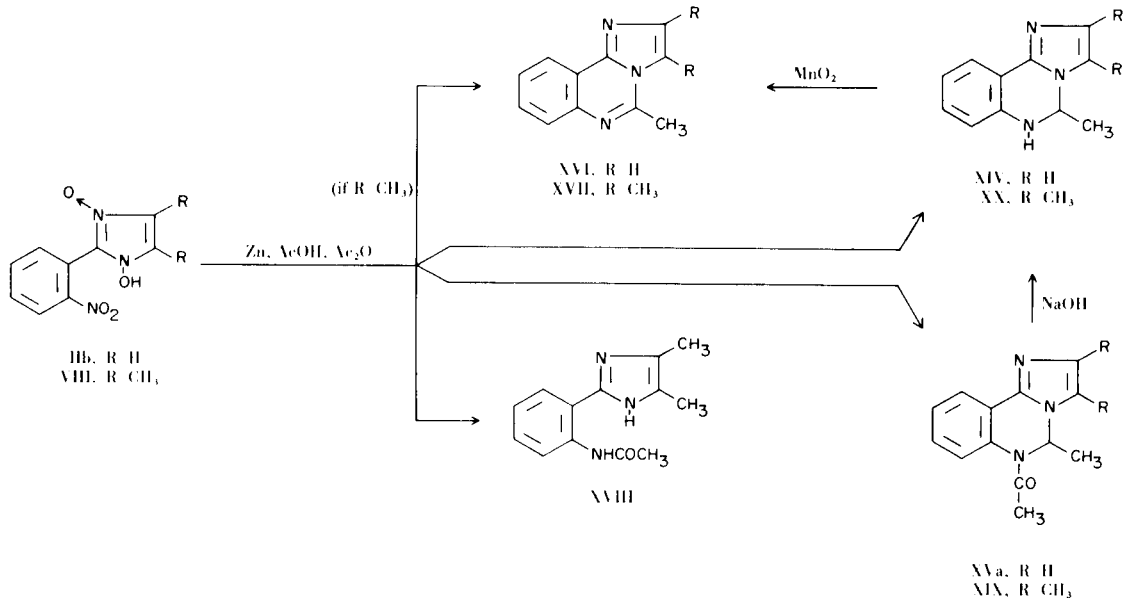


CHART II



hydrolysis gave a further amount of XIV. Manganese dioxide oxidation of XIV gave the fully aromatic product XVI.

A similar reaction of acetylation in reductive medium on VIII gave a complex mixture of products from which was isolated 2,3,5-trimethylimidazo[1,2-*c*]quinazoline (XVII), 2-(*o*-acetylaminophenyl)-4,5-dimethylimidazole (XVIII), 2,3,5-trimethyl-6-acetyl-5,6-dihydroimidazo-[1,2-*c*]quinazoline (XIX) and the corresponding deacetylated product XX. Mild alkaline hydrolysis of XIX afforded a further amount of XX which in turn could be transformed into XVII by manganese dioxide oxidation.

The structures proposed for the synthesized products were confirmed by the elemental analyses and the ultraviolet, infrared and proton magnetic resonance spectra described in the experimental section.

EXPERIMENTAL

The melting points were determined in capillary tubes on a Buchi apparatus and are uncorrected. The infrared spectra were recorded with an UNICAM SP-200 spectrometer in Nujol; the ultraviolet spectra were taken in ethanol with an UNICAM SP-800 spectrometer. The proton magnetic resonance spectra were measured on a JEOL JNH-MH-60 spectrometer. Unless otherwise stated, tetramethylsilane (TMS) was used as internal standard. In reporting NMR data the following abbreviations are used: s = singlet, d = doublet, q = quartet and m = multiplet. R_f values were measured on "Kieselgel GF_{254} nach Stahl" with ethyl acetate.

2-(*o*-Nitrophenyl)-1-hydroxyimidazole 3-Oxide Hydrochloride (IIa) and Base (IIb).

To a solution of 5.14 g. (0.034 mole) of *o*-nitrobenzaldehyde in 60 ml. of ethanol was added 3 g. (0.034 mole) of glyoxime. Anhydrous hydrogen chloride was bubbled through the suspension for 1 hour. After standing overnight at room temperature the solution was evaporated and the crude oil obtained was solidified by the addition of ethyl acetate. The solid was collected and washed with ethyl acetate; the product IIa was recrystallized three times from acetone-methanol, yield 3 g. (34.2%), m.p. 169-170° dec.

Anal. Calcd. for $C_9H_7N_3O_4$·HCl: C, 41.96; H, 3.13; N, 16.31. Found: C, 41.34; H, 3.28; N, 16.52.

The base IIb was obtained by dissolving the hydrochloride IIa in water; a yellow solid precipitated which was collected, washed with water and recrystallized from water, m.p. 230-231° dec.; ir cm^{-1}, 1540 (NO_2), 3120 (OH).

Anal. Calcd. for $C_9H_7N_3O_4$: C, 48.87; H, 3.19; N, 19.00. Found: C, 49.13; H, 3.36; N, 18.90.

1-Hydroxyimidazole-2-aldehyde Oxime 3-Oxide (IIIa) and the Hydrochloride (IIIb).

The aqueous filtrate from the yellow solid obtained by dissolving crude IIa in water was made basic with a dilute sodium carbonate solution and then acidified to *p*H 4-5 with dilute acetic acid; after some time a white precipitate formed, which was collected and recrystallized twice from water, m.p. 180-181° dec.; ir cm^{-1}, 3220, 3110 (OH).

Anal. Calcd. for $C_4H_5N_3O_3$: C, 33.57; H, 3.52; N, 29.37. Found: C, 33.32; H, 3.73; N, 29.60.

This product, upon heating with 38% hydrochloric acid, gave a solution which, after removal of the solvent, afforded the hydrochloride IIIb, which was crystallized from anhydrous ethanol, m.p. 171-173° dec.; nmr (DMSO-d_6, TMSP) δ 8.05 (2H, s, H-4,5), 8.40 (1H, s, CH=N), 10.85 (3H, broad s, OH).

Anal. Calcd. for $C_4H_5N_3O_3$·HCl: C, 26.75; H, 3.36; N, 23.40. Found: C, 26.88; H, 3.52; N, 23.51.

6-Formyl-5,6-dihydroimidazo[1,2-*c*]quinazoline (IV), 2-(*o*-Dimethylaminophenyl)imidazole (V) and 6-Methyl-5,6-dihydroimidazo-[1,2-*c*]quinazoline (VI).

To a stirred solution of 6 g. (0.027 mole) of IIb in 100 ml. of anhydrous formic acid heated to 90-95° was slowly added 20 g. of zinc powder. The reaction mixture was stirred at the same temperature for 3 hours; the solid which formed was collected and washed twice with 50 ml. of ethanol. After evaporation of the filtrate an oil was obtained which was dissolved in water; the water solution was made basic with a dilute sodium carbonate solution and extracted with ethyl acetate. Evaporation of the organic extract gave a semisolid residue which solidified upon addition of ethyl acetate. The solid was collected and crystallized from ethyl acetate to yield 1.2 g. of IV (22.2%), m.p. 217-219°; uv λ max (log ε) 244 (4.28), 288 (4.16), 301 mμ (sh) (4.02); ir cm^{-1}, 1670 (C=O); nmr (DMSO-d_6, TMSP) δ 5.82, 5.86 (2H, two s in the 1:5 ratio, H-5), 7.05, 7.44 (2H, two d, J = 0.2 Hz, H-2,3), 7.25-8.17 (4H, m, H-7,8,9.10), 8.50, 8.70 (1H, two s in the 1:5 ratio, CHO); the hindered internal rotation about the bond N–CHO is evident in the nmr spectrum of this amide which shows a doubling of signals due to methylene and formyl protons (9,10).

Anal. Calcd. for $C_{11}H_9N_3O$: C, 66.32; H, 4.55; N, 21.10. Found: C, 66.32; H, 4.37; N, 20.90.

Evaporation of the filtrate above gave an oil which was chromatographed on a silica gel column eluting with ethyl acetate. Removal of the solvent from the portion of the eluate containing a product with R_f = 0.68, gave a solid (V) which was crystallized from ethyl acetate-*n*-hexane, yield 0.4 g. (5.0%), m.p. 118-119°; uv λ max (log ε) 246 (4.07), 277 mμ (4.00); nmr (deuteriochloroform) δ 2.82 (6H, s, CH_3–N–CH_3), 7.80-7.41 (5H, m, three aromatic and imidazole ring protons), 8.66-8.40 (1H, m, an *ortho* aromatic proton), 11.57 (1H, s, NH).

Anal. Calcd. for $C_{11}H_{13}N_3$: C, 70.56; H, 7.00; N, 22.44. Found: C, 70.52; H, 6.88; N, 22.48.

Evaporation of the fraction of eluate containing a product with R_f 0.54 gave the base VI as a slightly impure oil which was then converted to its hydrochloride with dry hydrogen chloride in acetone. The solid was collected and recrystallized from anhydrous ethanol, yield 0.55 g. (10.9%), m.p. 249-251°.

Anal. Calcd. for $C_{11}H_{11}N_3$·HCl: C, 59.59; H, 5.45; N, 18.95. Found: C, 59.31; H, 5.75; N, 19.00.

The hydrochloride was converted to the free base by treatment with dilute sodium carbonate solution followed by extraction twice with ethyl acetate. The ethyl acetate extract was washed with water, dried over sodium sulfate and evaporated to an oil, n_D^{25} 1.637; uv λ max (log ε) 228 (4.17), 245 (4.27), 277 (3.86), 286 (3.86), 330 mμ (3.67); nmr (deuteriochloroform) δ 2.84 (3H, s, CH_3), 5.00 (2H, s, CH_2), 6.90, 7.25 (2H, two d, J = 0.5 Hz, H-2,3), 7.48-6.70 (3H, m, H-7,8,9), 8.10 (1H, d of d, J = 1, 5 Hz, H-10).

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.51; H, 6.18; N, 22.83.

5,6-Dihydroimidazo[1,2-c]quinazoline (VII).

A solution of 0.5 g. of IV in 15 ml. of ethanol and 10 ml. of 8% sodium hydroxide was refluxed for two hours, concentrated under vacuum and extracted with ethyl acetate. Evaporation of the organic extract gave an oil which was chromatographed on a silica gel column eluting with ethyl acetate; after removal of a by-product, evaporation of the eluate afforded a product (VII) which was crystallized from ethyl acetate-*n*-hexane, yield 0.2 g. (46.6%), m.p. 110-112°; uv λ max (log ε) 228 (sh) (4.14), 243 (4.22), 274 (3.82), 283 (3.83), 330 mμ (3.72); ir cm^{-1}, 3130 (NH); nmr (deuteriochloroform) δ 5.24 (3H, s, CH_2 and NH), 6.90, 7.25 (2H, two d, J = 0.5 Hz, H-2,3), 7.44-6.74 (3H, m, H-7,8,9), 8.05 (1H, d of d, J = 1, 5 Hz, H-10).

Anal. Calcd. for $C_{10}H_9N_3$: C, 70.15; H, 5.30; N, 24.55. Found: C, 70.32; H, 5.45; N, 24.40.

Imidazo[1,2-c]quinazoline Base (Ia) and the Hydrochloride (Ib).

A mixture of 2 g. (0.023 mole) of manganese dioxide and 0.6 g. (0.0035 mole) of VII in 30 ml. of methylene chloride was stirred at room temperature for 3 hours and filtered. The filtrate was evaporated and the solid (Ia) was crystallized from ethyl acetate-*n*-hexane, yield 0.3 g. (50.6%), m.p. 127-129°; uv λ max (log ε) 245 (4.64), 257 (sh) (4.21), 268 (3.92), 279 (3.90), 290 mμ (3.72); nmr (deuteriochloroform) δ 7.90-7.30 (5H, m, H-2,3, 7,8,9), 8.95-8.70 (1H, m, H-10), 9.20 (1H, s, H-5).

Anal. Calcd. for $C_{10}H_7N_3$: C, 70.99; H, 4.17; N, 24.84. Found: C, 70.78; H, 3.89; N, 24.75.

The hydrochloride of Ia (Ib) was prepared by dissolving the base in acetone and adding gaseous hydrogen chloride. The solid which formed was collected and recrystallized from anhydrous ethanol, m.p. 231-233°.

Anal. Calcd. for $C_{10}H_7N_3$·HCl: C, 58.40; H, 3.92; N, 20.43. Found: C, 58.20; H, 3.89; N, 20.58.

2,3-Dimethyl-6-formyl-5,6-dihydroimidazo[1,2-c]quinazoline (IX), 2-(*o*-Methylaminophenyl)-4,5-dimethylimidazole (X) and 2,3,6-Trimethyl-5,6-dihydroimidazo[1,2-c]quinazoline (XI).

Compound VIII (8) (6 g., 0.024 mole) was reacted with zinc powder and formic acid in a similar manner as for IIb giving a solid residue (IX) which was crystallized from a small amount of ethyl acetate, yield 1.1 g. (20.1%), m.p. 154-156°; uv λ max (log ε) 249 (4.23), 311 mμ (4.27); ir cm^{-1}, 1675 (C=O).

Anal. Calcd. for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.80; H, 6.05; N, 18.23.

The crystallization solvent above was evaporated and the residue was chromatographed on a silica gel column eluting with ethyl acetate. Evaporation of the first eluate (R_f = 0.93) gave a residue (X) which was crystallized from ethyl acetate-*n*-hexane, yield 0.2 g. (4.8%), m.p. 215-217°; uv λ max (log ε) 229 (4.09), 249 (4.27), 273 (4.00), 288 (sh) (3.92), 340 mμ (3.97); ir cm^{-1}, 3340, 3130 (NH); nmr (DMSO-d_6, TMSP) δ 2.02, 2.15 (6H, two s, CH_3-4,5), 2.81 (3H, d, J = 4 Hz, CH_3–N), 7.77-6.35 (4H, m, aromatic), 8.90-8.57 (1H, m, aromatic NH), 11.93 (1H, s, imidazole NH).

Anal. Calcd. for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.63; H, 7.28; N, 21.13.

Further elution of the silica gel column with ethyl acetate gave an eluate containing a product with R_f = 0.53; removal of the solvent gave a residue (XI) which was crystallized from ethyl acetate-*n*-hexane, yield 0.4 g. (7.84%), m.p. 133-135°; uv λ max (log ε) 225 (4.12), 252 (4.17), 284 (sh) (3.82), 295 (3.86), 336 mμ (3.86); nmr (deuteriochloroform) δ 2.25, 2.35 (6H, two s, CH_3-2,3), 3.02 (3H, s, CH_3–N), 5.06 (2H, s, CH_2), 7.76-6.92 (3H, m, H-7,8,9), 8.31 (1H, d of d, J = 1, 5 Hz, H-10).

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.05; H, 6.85; N, 19.83.

2,3-Dimethyl-5,6-dihydroimidazo[1,2-c]quinazoline (XII).

The product IX was hydrolyzed in a similar way as for IV; cooling of the alkaline solution gave a solid (XII) which was collected, washed with water and recrystallized from ethanol-water, yield 55.3%, m.p. 202-204°; uv λ max (log ε) 225 (4.20), 250 (4.23), 283 (sh) (3.90), 294 (3.95), 336 mμ (3.93); ir cm^{-1}, 3120 (NH); nmr (deuteriochloroform) δ 2.25, 2.45 (6H, two s, CH_3-2,3), 4.50 (1H, s, NH), 5.18 (2H, s, CH_2), 7.50-6.70 (3H, m, H-7,8,9), 8.05 (1H, d of d, J = 1, 5 Hz, H-10).

Anal. Calcd. for $C_{12}H_{13}N_3$: C, 72.33; H, 6.57; N, 21.09. Found: C, 72.29; H, 6.74; N, 20.96.

2,3-Dimethylimidazo[1,2-*c*]quinazoline (XIII).

This product was prepared as Ia by manganese dioxide oxidation of XII. Removal of the methylene chloride gave a residue (XIII) which was crystallized from ethyl acetate, m.p. 173-175°; uv λ max (log ε) 256 (4.62), 264 (sh) (4.22), 290 (3.86), 303 mμ (3.90); nmr (deuteriochloroform) δ 2.43, 2.48 (6H, two overlapping s, CH_3-2,3), 8.35-7.70 (3H, m, H-7,8,9), 8.93-8.64 (2H, m, H-5,10).

Anal. Calcd. for $C_{12}H_{11}N_3$: C, 73.07; H, 5.62; N, 21.31. Found: C, 72.18; H, 5.47; N, 21.05.

5-Methyl-5,6-dihydroimidazo[1,2-*c*]quinazoline (XIV) and 5-Methyl-6-acetyl-5,6-dihydroimidazo[1,2-*c*]quinazoline Hydrochloride (XVb).

To a stirred solution of 6 g. (0.027 mole) of IIb in 150 ml. of glacial acetic acid heated to 90-95° was slowly added 20 g. of zinc powder followed by 20 ml. of acetic anhydride. The reaction mixture was stirred to the same temperature for 3 hours. Cooling gave a solid removed by filtration and washed twice with 50 ml. of ethanol. Evaporation of the filtrate gave a liquid which was dissolved in water; the water solution was made basic with dilute sodium carbonate solution and extracted with ethyl acetate. Evaporation of the organic extract gave a semisolid residue which solidified upon addition of a small amount of ethyl acetate. The solid (XIV) was collected and crystallized from ethanol, yield 1.2 g. (23.9%), m.p. 182-184°; uv λ max (log ε) 229 (sh) (4.25), 242 (4.33), 274 (3.86), 284 (3.86), 332 mμ (3.78); ir cm^{-1}, 3130 (NH); nmr (deuteriochloroform) δ 1.64 (3H, d, J = 6 Hz, CH_3-5), 4.56 (1H, s, NH), 5.46 (1H, q, J = 6 Hz, H-5), 6.83, 7.12 (2H, two d, J = 0.5 Hz, H-2,3), 7.30-6.58 (3H, m, H-7,8,9), 7.89 (1H, d of d, J = 1, 5 Hz, H-10).

Anal. Calcd. for $C_{11}H_{11}N_3$: C, 71.33; H, 5.99; N, 22.69. Found: C, 71.52; H, 5.88; N, 22.90.

Removal of the solvent used for solidifying XIV gave a residue which was chromatographed on a silica gel column eluting with ethyl acetate. The first fraction of eluate gave 0.2 g. of XIV; the remaining eluate contained the product XVa mixed with a small amount of XIV. Evaporation of the latter fraction gave an oily residue which was converted into the hydrochloride of the base XVa by dissolving the oil in acetone and adding dry hydrogen chloride. The solid hydrochloride (XVb) was collected and recrystallized from anhydrous ethanol-ether, yield 0.4 g. (5.6%), m.p. 242-244°; ir cm^{-1}, 1665 (C=O).

Anal. Calcd. for $C_{13}H_{13}N_3O$·HCl: C, 59.20; H, 5.35; N, 15.92. Found: C, 59.04; H, 5.08; N, 16.14.

The hydrochloride XVb was hydrolyzed in similar manner as for IV; cooling of the alkaline solution gave the base XIV as a solid which was collected and crystallized from ethanol.

5-Methylimidazo[1,2-*c*]quinazoline (XVI).

This product was prepared as Ia, by manganese dioxide oxidation of XIV in benzene-dioxane; in this case it was necessary to extend the reaction time for 24 hours. After removal of the solvent, a residue was obtained which was crystallized from *n*-hexane, m.p. 124-126°; uv λ max (log ε) 247 (4.59), 256 (sh) (4.23), 268 (3.94), 278 (3.92), 285 mμ (sh) (3.72); nmr (deuteriochloroform) δ 2.85 (3H, s, CH_3-5), 8.15-7.62 (5H, m, H-2,3,7,8,9), 8.86-8.60 (1H, m, H-10).

Anal. Calcd. for $C_{11}H_9N_3$: C, 72.11; H, 4.95; N, 22.94. Found: C, 72.31; H, 5.22; N, 23.07.

2,3,5-Trimethylimidazo[1,2-*c*]quinazoline (XVII), 2-(*o*-Acetylaminophenyl)-4,5-dimethylimidazole (XVIII), 2,3,5-Trimethyl-6-acetyl-5,6-dihydroimidazo[1,2-*c*]quinazoline (XIX) and 2,3,5-Trimethyl-5,6-dihydroimidazo[1,2-*c*]quinazoline (XX).

Six g. of VIII (0.024 mole) was reacted with zinc powder, glacial acetic acid and acetic anhydride as was IIb. Removal of the solvent gave a semisolid residue which solidified upon addition of a small amount of ethyl acetate. The solid (XVII) was collected and crystallized from ethyl acetate, yield 0.4 g. (7.8%), m.p. 214-216°; uv λ max (log ε) 248 (sh) (4.53), 256 (4.57), 265 (sh) (4.14), 292 (3.85), 305 mμ (3.88); nmr (deuteriochloroform) δ 2.32, 2.51, 2.88 (9H, three s, CH_3-2,3,5), 7.97-7.50 (3H, m, H-7,8,9), 8.65-8.40 (1H, m, H-10).

Anal. Calcd. for $C_{13}H_{13}N_3$: C, 73.90; H, 6.20; N, 19.89. Found: C, 73.68; H, 6.26; N, 19.88.

Evaporation of the filtrate from XVII gave a residue which was chromatographed on a silica gel column eluting with ethyl acetate. The eluate containing a product with R_f = 0.94 was evaporated to give a solid (XVIII) which was crystallized from ethyl acetate, yield 0.15 g. (2.7%), m.p. 234-236°; uv λ max (log ε) 251 (4.36), 259 (4.36), 305 (4.30), 320 mμ (sh) (4.14); ir cm^{-1}, 3140 (NH), 1665 (C=O).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.38; H, 6.74; N, 18.27.

Evaporation of the eluate containing a mixture of XIX (R_f = 0.51) and XX (R_f = 0.45) gave a semisolid residue which was extracted three times with 20 ml. of hot *n*-hexane; the more soluble product (XIX) dissolved and evaporation of the solvent gave a residue which was recrystallized from ethyl acetate-*n*-hexane, yield 0.2 g. (3.4%), m.p. 137-138°; uv λ max (log ε) 249 (4.20), 309 mμ (4.20); ir cm^{-1}, (C=O).

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.32; H, 6.42; N, 18.40.

The residue (XX) remaining after extraction of XIX, was solidified with ethyl acetate and recrystallized from this solvent, yield 0.6 g. (11.7%), m.p. 164-166°; uv λ max (log ε) 225 (4.20), 249 (4.22), 281 (sh) (3.87), 292.5 (3.94), 336 mμ (3.94); ir cm^{-1}, 3130 (NH); nmr (deuteriochloroform) δ 1.37 (3H, d, J = 6 Hz, CH_3-5), 2.07, 2.20 (6H, two s, CH_3-2,3), 6.09-5.35 (2H, m, H-5,6), 7.40-6.51 (3H, m, H-7,8,9), 7.90 (1H, d of d, J = 1, 5 Hz, H-10)

Anal. Calcd. for $C_{13}H_{15}N_3$: C, 73.21; H, 7.09; N, 19.70. Found: C, 73.35; H, 6.98; N, 19.83.

This product was also obtained by hydrolysis of XIX with 8% sodium hydroxide.

Manganese dioxide oxidation of XX in similar manner as VII, gave a residue containing several products, among them XVII, which was separated on a silica gel column eluting with ethyl acetate. Evaporation of the first eluate afforded a solid which was crystallized from ethyl acetate.

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