Rearrangements of 4-(2-Aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester

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The treatment of 4-(2-aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinecarboxylic acid diethyl ester (III) with refluxing toluene or pyridine afforded 1,2,3,6-tetrahydro-2,4-dimethyl-2,6-methano-1,3-benzodiazocine-5,11-dicarboxylic acid diethyl ester (IV) as the major product. In addition, the following minor products were isolated: 2-methyl-3-quinolinecarboxylic acid ethyl ester (V), 3-(2-aminophenyl)-5-methyl-6-azabicyclo[3,3,1]-hept-1-ene-2,4-dicarboxylic acid diethyl ester (VI), and 5,6-dihydro-2,4-dimethyl-5-oxobenzo[*c*][2,7]naphthyridine-1-carboxylic acid ethyl ester (VII). In contrast, acidic conditions caused the conversion of III into V in a 95% yield. The formation of the latter appears to involve IV as an intermediate, since IV degraded rapidly in acid to give V in a quantitative yield.

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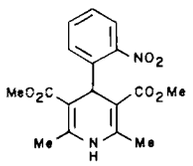
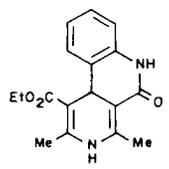
4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid esters have been intensively studied since the discovery of nifedipine (I), an antihypertensive agent which works *via* inhibition of calcium ion reflux at cellular level, in 1971 [1]. Extensive structural modifications of the prototype compound have resulted in numerous clinically effective cardiovascular agents having superior pharmacological properties over the lead compound [2,3]. During the course of our investigation in this area, we discovered the interesting rearrangement reactions of 4-(2-aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester (III) that are the subject of this report.



I

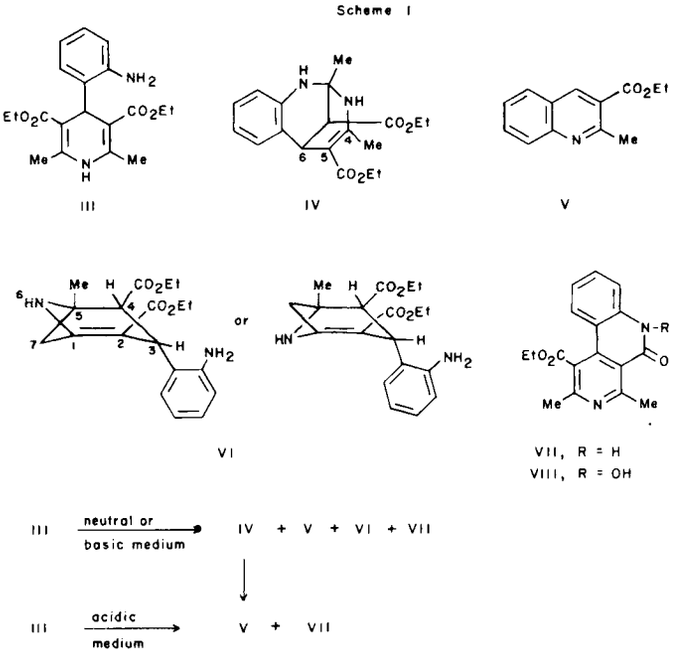


II

4-Aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl esters are shown to have boat-type conformations with varing degrees of puckering [4]. The three dimensional structure and activity relationships derived from X-ray diffraction studies indicated that the Ca^{+2} antagonist activity is indirectly proportional to the degree of the distortion of the dihydropyridine ring [5]. Accordingly, since compounds such as II are expected to assume a rigid planar conformation with respect to the dihydropyridine nucleus, pharmacological evaluation of such compounds as Ca^{+2} antagonists was warranted.

As an initial attempt at the preparation of II, III was heated with toluene under refluxing conditions. The major product obtained from this reaction was not the desired product II, but instead a compound which is isomeric with the starting material. The treatment afforded the following three additional products in minute quantity: 2-methyl-3-quinolinecarboxylic acid ethyl ester (V), 3-(2-aminophenyl)-5-methyl-6-azabicyclo[3,3,1]hept-1-ene-2,4-dicarboxylic acid diethyl ester (VI), and 5,6-dihydro-2,4-dimethyl-5-oxobenzo[*c*][2,7] naphthyridine-1-carboxylic acid ethyl ester (VII) (Scheme I). No desired product was isolated. Careful examination of the spectral data of the major product indicated it to be 1,2,3,6-tetrahydro-2,4-dimethyl-2,6-methano-1,3-benzodiazocine-5,11-dicarboxylic acid diethyl ester (IV) formed by an intramolecular 1,4-addition reaction by the amino group of the C4-phenyl ring. The ^{1}H-nmr spectrum (DMSO-d_6) of the compound displayed two exchangeable amino proton signals at δ 7.34 and 6.48, and proton signals of two methyl groups at 2.08 and 1.68 ppm. The protons at position 6 and 11 showed resonance

Scheme I

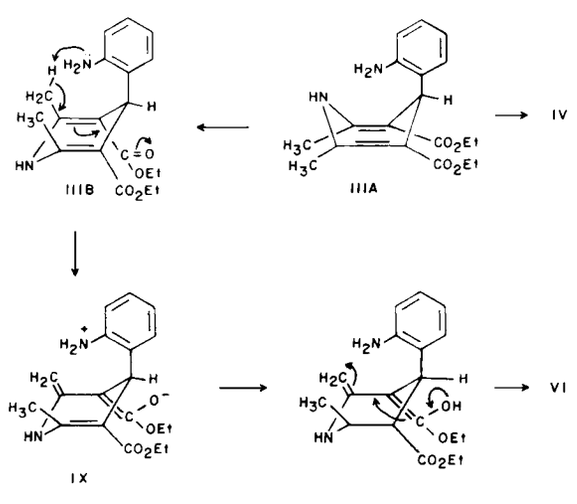


signals at δ 2.66 (J = 6 Hz) and 4.30 ppm (J = 6 Hz), respectively. The use of pyridine as a reaction medium improved the yield of IV to 44%. Compound IV is stable in neutral or basic medium but in acidic conditions, it rapidly disintegrated to form V. In fact, several attempts to form a salt of mineral acid has invariably resulted to give V, even under ice-chilled conditions.

A bicyclic structure VI was assigned for the minor product which melted at 172-174°. The ^{1}H-nmr spectrum of the compound showed the presence of only one methyl group at 1.40 (s), besides two methyl groups of ethyl ester shown at 1.26 (t) and 1.08 ppm (t). There appeared methylene proton signals at δ 2.67 (d) and 2.33 ppm (d) coupled each other with J = 18 Hz. The signals of protons at positions 3 and 4 showed at δ 4.04 (d, J = 5 Hz) and 2.86 ppm (d, J = 5 Hz), respectively. The exchangeable proton signal showed at δ 5.76 (s) was attributed to the amino proton at the 6-position, and the amino protons on the phenyl ring appeared at 7.74 and 6.60 ppm as very broad singlets which may be due to two different conformational states of the molecule. The presence of an aromatic amino group was shown by the two sharp and strong NH stretching bands appearing at 3420 and 3380 cm^{-1} in the infrared spectrum of VI, and a secondary aliphatic amino group at 3317 cm^{-1}. The CH stretching band for the methyl group was shown at 2980 cm^{-1}, and the ester carbonyl absorption band at 1735 cm^{-1}. The result of combustion elemental analysis and mass spectral data (CI m/z 345 (M+H), EI m/z 344, 271, 241, 216) further supported the structure (VI).

The formation of IV and VI may be envisaged by the mechanistic scheme shown below (Scheme II). The X-ray diffraction study on 4-aryl-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid esters showed that the 1,4-dihydropyridine ring assumes a puckered boat-type conformation (IIIA) with the N_1 and C_4 atoms forming apexes,

Scheme II



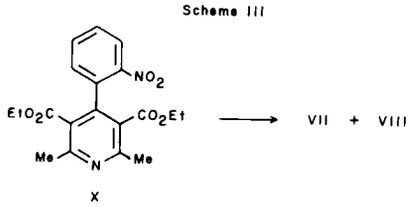
and the phenyl ring bisects the dihydropyridine ring with the *ortho* position residing over the nucleus of the dihydropyridine [5]. In such a conformation the amino group would be positioned in close proximity to the C_2 (or C_6) electrophilic center, causing the addition reaction for the amino group to occur readily to form IV. It is probable that under the reaction conditions the boat conformation of the ground state may transform partly to a chair form, IIIB in which the amino group on the phenyl ring positions itself favorably for the generation of a species such as IX which rearranges to VI, as depicted in Scheme II.

In support for the proposed mechanism, the treatment of 4-(3-aminophenyl)-1,4-dihydro-2,6-dimethyl-3,5-pyridinedicarboxylic acid diethyl ester with refluxing pyridine, under identical conditions, afforded only the unreacted starting material in a quantitive yield.

Compound VII has been erroneously described in the literature, and deserves a comment. In 1946, Petrow [6] claimed to have obtained VII (mp 184-185°) from the reaction of 2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid diethyl ester (X) with stannous chloride in a mixture of acetic and hydrochloric acid. The crude product from the reaction was then treated with alkaline solution to isolate the product. The elemental analytical result, the only supporting data for the structure, as he reported was incompatible with the structure, but agreed with *N*-hydroxy structure VIII. Apparently, the structural assignment was in error. Several years later, Petrow [7] synthesized the *N*-hydroxy compound VIII by the treatment of the same pyridine X with zinc dust and ammonium chloride in aqueous alcohol followed by addition of hydrochloric acid. This product had identical mp with that of his previous compound which he proposed to be VII.

The catalytic hydrogenation of X in the presence of Palladium-charcoal followed by the treatment of the crude product with boiling pyridine afforded a mixture of products, VII and VIII in the ratio of approximately 1:1 (Scheme III). The major product from this reaction exhibited spectral data consonant with structure VIII, and had the same mp as that of Petrow's VIII. The spectral

Scheme III

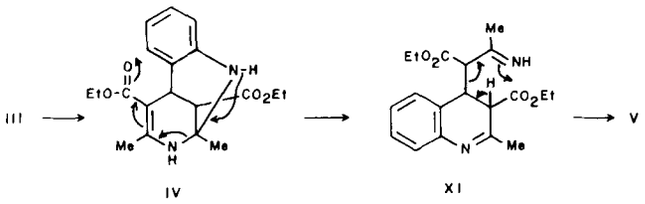


and combustion analytical data of the minor product (mp 243-244°) indicated it to be VII [8].

As an alternative approach for the preparation of II, III was treated with ethanol pretreated with hydrogen chloride gas. To our surprise, the compound that was ob-

tained in a 95% yield was proven to be V. Considering the earlier observation of the facile formation of V from IV under acidic conditions, the conversion of III into V most likely proceeds through IV as an intermediate. A plausible reaction mechanism for the conversion may thus involve the acidic cleavage of the N-C-N bond of IV to give XI which produces the final product V with the loss of ethyl 3-aminocrotonate, as shown in Scheme IV.

Scheme IV



EXPERIMENTAL

Melting points were taken in capillary tubes using a Thomas-Hoover melting point apparatus and are uncorrected. The ir spectra were obtained in potassium bromide pellets on a Perkin-Elmer 21 spectrophotometer. The nmr spectra were determined with a Varian XL-300 or Varian FI-80A spectrometer using tetramethylsilane as the internal reference. Combustion elemental analyses were performed by the Analytical Section of these Laboratories.

Rearrangement Reaction of 1,2-Dihydro-4-(2-aminophenyl)-2,6-dimethyl-3,5-pyridinedicarboxylic Acid Diethyl Ester (III) [9].

A mixture of III (2.5 g, 7.3 mmole) and pyridine (70 ml) was heated under reflux for 4 hours, then evaporated on a rotary evaporator to give a thick dark green oil. The following three products were isolated from the crude product by a preparative hplc:

2-Methyl-3-quinolinecarboxylic acid ethyl ester (V) that was eluted first was recrystallized from ethyl acetate, yield 0.33 g (21%), mp 70-72°, lit mp [9] 71-72°; ^{1}H-nmr (DMSO-d_6): δ 2.40 (t, 3H, CH_3), 2.88 (s, 3H, CH_3), 4.42 (q, 2H, CH_2), 7.60-8.09 (m, 4H, aromatic H's), and 8.86 (s, 1H, H-4); ms: m/z 215 (M^+), 170 and 142.

Second fraction from the preparative hplc was proven to be a binary mixture which was separated by further preparative hplc purification. 3-(2-Aminophenyl)-5-methyl-6-azabicyclo[3,3,1]hept-1-ene-2,4-dicarboxylic acid diethyl ester (VI) was eluted first, giving 0.1 g (4%) as white crystals. The analytical sample that was recrystallized from ether melted at 172-174°. Mixture mp with IV was depressed. Spectral data are reported in the text.

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; H, 8.14. Found: C, 66.23; H, 7.03; N, 8.03.

5,6-Dihydro-2,4-dimethyl-5-oxobenzo[*c*][2,7]naphthyridine-1-carboxylic acid ethyl ester (VII) was obtained from later eluents and recrystallized from ethyl acetate, giving 0.1 g (5%), mp 243-244°; ir: 2980 (CH_3), 1720 (ester CO) and 1670 cm^{-1} (amide CO); ^{1}H-nmr (DMSO-d_6): δ 1.30 (t, 3H, CH_3), 2.54 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 4.48 (q, 2H, CH_2), 7.20-7.82 (m, 4H, aromatic H's), and 11.82 (s, 1H, NH); ms: m/z 296 (M^+), 267 and 251.

Anal. Calcd. for $C_{17}H_{16}N_2O_3$: C, 68.90; H, 5.44; N, 9.46. Found: C, 68.71; H, 5.47; N, 9.34.

1,2,3,6-Tetrahydro-2,4-dimethyl-2,6-methano-1,3-benzodiazocine-5,11-dicarboxylic acid diethyl ester (IV) was obtained (0.3 g) from the third fraction. This product was also obtained during the preparation of the hplc sample by dissolution of the crude product in ethyl acetate as an insoluble residue. The combined material was recrystallized from ethanol to give 0.7 g (28%), mp 174-177°. An analytical sample that was recrystallized from ethanol melted at 175-177°; ir: 3380 (NH), 3300 (NH), and 1710 cm^{-1} (CO); ms: m/z 344 (M^+), 270, 241, and 215.

Anal. Calcd. for $C_{19}H_{24}N_2O_4$: C, 66.26; H, 7.02; N, 8.14. Found: C, 66.04; H, 6.95; N, 8.05.

1,2,3,6-Tetrahydro-2,4-dimethyl-2,6-methano-1,3-benzodiazocine-5,11-dicarboxylic Acid Diethyl Ester (IV).

A mixture of III (20.64 g, 0.06 mole) and pyridine (450 ml) was heated under reflux for 5 hours, then evaporated on a rotary evapotor to give a thick oily residue. The residue was dissolved in a small amount of hot ethyl acetate with warming on a steam bath. When the solution was allowed to sit at room temperature overnight, there was separated a precipitate which was collected on a filter and washed with ethyl acetate to give 9.05 g (44%) of product which is identical with IV obtained by a preparative hplc purification, mp 173-176°.

Conversion of IV into V.

Two grams of IV were dissolved in about 60 ml of hot ethanol, and the solution was chilled in ice. To the chilled ethanol solution was added ethanolic hydrogen chloride solution until the *p*H of the solution reached 1.0 by a *p*H paper. The resulting solution was diluted with anhydrous ether to the total volume of 200 ml, and chilled in ice. A precipitate was collected on a filter, and washed with ether to give V as hydrochloric acid salt (1.25 g), mp 190-191°. An additional crop was obtained when the filtrate was diluted with 200 ml of hexane to give the total yield of 1.48 g (100%); ir: 1702 cm^{-1} (CO); ms (CI): m/z 216 (M + H).

Anal. Calcd. for $C_{13}H_{13}NO_2 \cdot HCl$: C, 62.03; H, 5.61; N, 5.56; Cl^- 14.09. Found: C, 62.10; H, 5.81; N, 5.41; Cl^-, 14.07.

Conversion of III into V.

A mixture of III (2.5 g, 7.3 mmoles), ethanolic hydrogen chloride solution (20 ml), and ethanol (50 ml) was heated under reflux for 1 hour, then concentrated on a rotary evaporator to approximately 30 ml, diluted with ether (100 ml), and chilled in ice. The precipitate that was collected on a filter and washed with ether was amounted to 2.05 g (95%), mp 192-195°. This material is identical with the product from IV described above.

Catalytic Reduction of 2,6-Dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic Acid Diethyl Ester [10] to give 5,6-Dihydro-6-hydroxy-2,4-dimethyl-5-oxobenzo[*c*][2,7]naphthyridine-1-carboxylic Acid Ethyl Ester (VIII) and 5,6-Dihydro-2,4-dimethyl-5-oxobenzo[*c*][2,7]naphthyridine-1-carboxylic Acid Ethyl Ester (VII).

Twelve and one half g of 2,6-dimethyl-4-(2-nitrophenyl)-3,5-pyridinedicarboxylic acid diethyl ester (12.5 g) were dissolved in ethanol (160 ml), and hydrogenated in the presence of 10% Palladium on charcoal catalyst using a Parr hydrogenator until the consumption of hydrogen was ceased. Since a precipitate separated, the mixture was heated on a steam bath with an additional amount of ethanol, and filtered using a bed of Celite. Chilling of the combined filtrate and washings in ice caused separation of a precipitate which was collected on a filter to give 10.1 g of material (mp 168-172°) which was shown to be a mixture of two products. The mixture was triturated with 0.1*N* sodium hydroxide solution. The alkaline insoluble material was collected on a filter, and washed with 0.1*N* sodium hydroxide solution, then with water. The filter residue (1.0 g (9%), mp 240-242°) was identical with VII that was obtained from III (ir and mixture mp). The combined filtrate and washings from the alkaline trituration was acidified with dilute hydrochloric acid to cause separation of a precipitate which was collected on a filter and washed with water to give 9.0 g (79%) of VIII, mp 183.5-185°, lit mp [7] 183.5-184.5°; ir: 3180 (OH) and 1720 cm^{-1} (CO); ^{1}H-nmr (DMSO-d_6): δ 1.34 (t, 3H, CH_3), 2.60 (s, 3H, CH_3), 3.08 (s, 3H, CH_3), 4.46 (q, 2H, CH_2), 7.38-7.90 (m, 4H, aromatic H's), and 11.50 (s, 1H, OH); ms: (CI) m/z 313 (M + H) and 297.

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.37; H, 5.16; N, 8.97. Found: C, 65.02; H, 5.19; N, 8.95.

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