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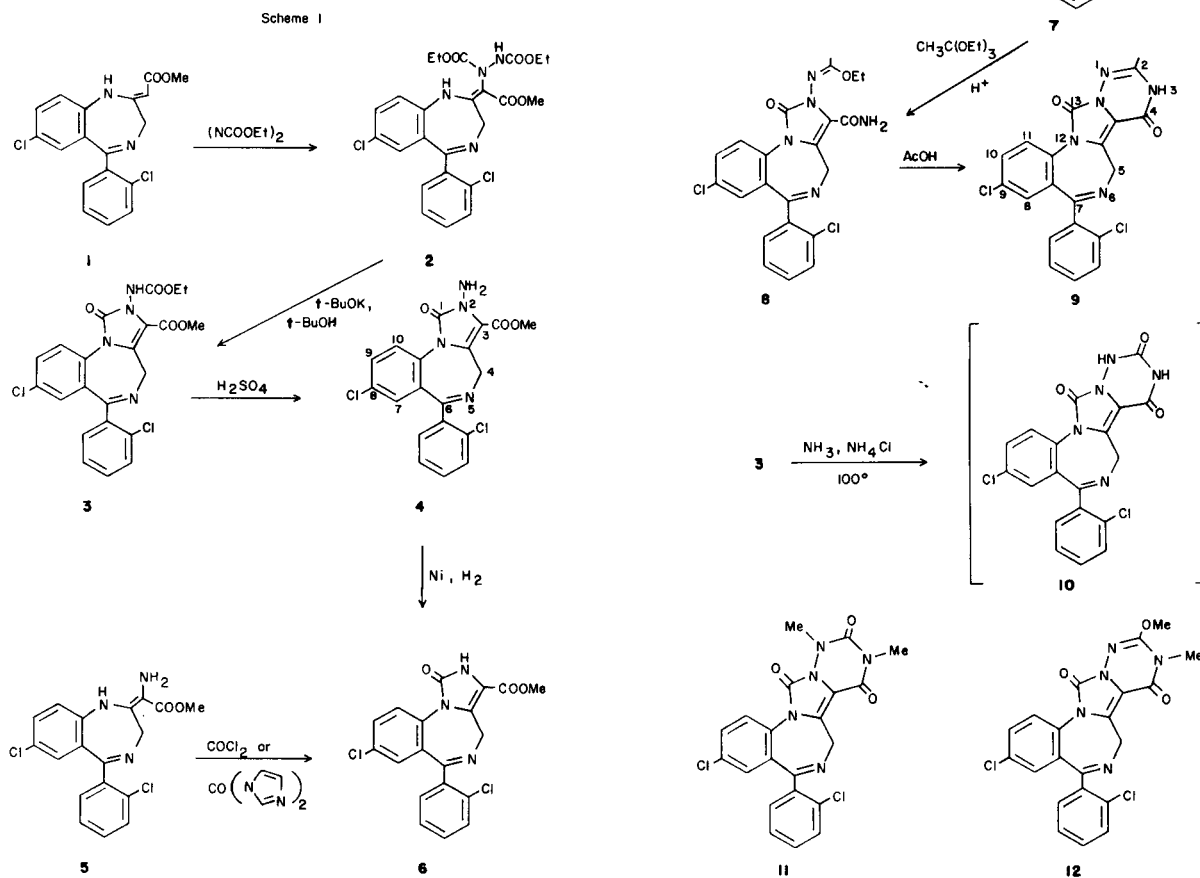
The addition of diethyl azodicarboxylate to an electron rich double bond was employed as the key step for the preparation of the title compounds. Novel tetracyclic [1,2,4]triazino[1',6':3,4]imidazo[1,5-a][1,4]benzodiazepines were accessible from these 2-aminoimidazo[1,5-a][1,4]benzodiazepin-1-ones.

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In an earlier paper (2), we reported the synthesis of imidazo[1,5-a][1,4]benzodiazepines from compound **1** (Scheme I). Nitrosation of the electron rich double bond of **1** was used to introduce the nitrogen functionality required to build the imidazole ring. The reactivity of this enamine towards electrophiles prompted us to explore its interaction with diethyl azodicarboxylate. The reagent added to the enamine **1** in boiling toluene to give **2** in high yield. The nmr spectrum of **2** indicates the presence of two isomers in solution. The assignment of stereochemistry to these isomers was not possible. Treatment of **2** with a catalytic amount of potassium *t*-butoxide in refluxing *t*-butyl alcohol led to the imidazolone **3**. The urethane functionality of **3** was selectively hydrolyzed by heating at

90° in concentrated sulfuric acid. The structure of the resulting amino ester **4** was confirmed both by spectral data and by its conversion to the imidazolone **6** by hydrogenation over Raney nickel. Compound **6** can also be prepared by the reaction of the enediamine **5** with phosgene as previously reported (3), or by treatment with carbonyldiimidazole as described in the experimental.

Scheme 11



The amino ester **4** was converted to the corresponding amide **7** by heating with methanolic ammonia and ammonium chloride in a steel bomb at 100° for 20 hours (Scheme II). Compound **7** reacted with triethyl orthoacetate in the presence of catalytic amounts of *p*-toluene-sulfonic acid to form the imidate **8**. Cyclization of **8** to the desired tetracyclic compound **9** was achieved by boiling in glacial acetic acid.

Reaction of the urethane **3** with ammonia under conditions similar to those used for the conversion of **4** to **7** gave a polar compound which was assigned structure **10**. This product was not characterized but converted to a more tractable material by reaction with diazomethane. The methylation led to a mixture of compounds **11** and **12** which were separated by chromatography. The structures of **11** and the minor product **12** are based on spectral data and therefore the positions of the methyl groups are not firmly established.

EXPERIMENTAL

Melting points were determined in a capillary melting point apparatus or a Reichert hot stage microscope. The uv spectra were measured in 2-propanol on a Cary Model 14 spectrophotometer. Nmr spectra were recorded with a Varian T-60 instrument with TMS as the internal standard. Ir spectra were determined on a Beckman IR-9 spectrometer. Silica gel Merck (70-325 mesh) was used for chromatography and anhydrous sodium sulfate for drying.

1-(1-Methoxycarbonyl-1-[7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-ylidene]methyl)-1,2-hydrazinedicarboxylic Acid Diethyl Ester (**2**).

A solution of 3.61 g. (0.01 mmole) of 7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-2-ylideneacetic acid methyl ester, **1** (**2**), in 50 ml. of toluene was treated with 3 ml. of diethyl azodicarboxylate and then stirred and refluxed for 4 hours. The solution was evaporated and the residue was crystallized from ether to yield 5.1 g. (95%) of product with m.p. 185-192°. Recrystallization from ethyl acetate / hexane gave colorless crystals with m.p. 211-214°; uv: λ infl 215 nm ($\epsilon = 30000$) max 272 (8800) 312 (33500) infl 335 (4000); ir (chloroform): 3400, 3275, 3200 (NH), 1720 (CO), 1675 (CO) 1625; nmr (deuteriochloroform): mixture of two isomers.

Anal. Calcd. for $C_{22}H_{22}Cl_2N_4O_6$: C, 53.84; H, 4.52; N, 10.47. Found: C, 54.15; H, 4.65; N, 10.60.

8-Chloro-6-(2-chlorophenyl)-1,2-dihydro-2-ethoxycarbonylamino-1-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**3**).

A solution of 3.6 g. (6.72 mmoles) of **2** in 75 ml. of *t*-butyl alcohol was treated with 75 mg. (0.67 mmole) of potassium *t*-butoxide and then stirred and refluxed for 20 minutes. Another 75 mg. (0.67 mmole) of potassium *t*-butoxide was added and the refluxing was continued for 30 minutes longer. After acidification with acetic acid the solution was evaporated. The residue was partitioned between methylene chloride, saturated sodium bicarbonate solution and brine. The organic layer was separated, dried and evaporated. The residue was dissolved in 75 ml. of ether, filtered and evaporated. Crystallization from ether yielded 1.92 g. (58.4%) of product with m.p. 207-210°. Recrystallization from analysis from methylene chloride / ether gave colorless crystals with m.p. 208-211°; uv: λ infl 210 nm ($\epsilon = 46200$) max 277 (22850); ir (chloroform): 3410 (NH), 1755 (COOMe) 1735 (COOEt), 1715 (CO) 1630; nmr (deuteriochloroform): δ 1.32 (t, 3, J = 6.5 Hz, CH_2CH_3); 3.88 (s, 3, OCH₃); 4.28 (q, 2, J = 6.5 Hz, OCH₂) 4.13 (d, 1) and 5.85 (d, 1); (AB-

system, J = 12.5 Hz, C₄-H); 7.08 (d, 1, J = 2 Hz, C₇-H); 7.2-7.8 (m, 5, aromatic H); 8.08 (d, 1, J = 8 Hz, C₁₀-H).

Anal. Calcd. for $C_{22}H_{18}Cl_2N_4O_5$: C, 54.00; H, 3.71; N, 11.45. Found: C, 54.23; H, 4.00; N, 11.53.

2-Amino-8-chloro-6-(2-chlorophenyl)-1,2-dihydro-1-oxo-4H-imidazo[1,5-a]-[1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**4**).

A mixture of 2 g. (4.08 mmoles) of **3** and 15 ml. of concentrated sulfuric acid was heated on the steam bath for 30 minutes. The cooled reaction mixture was poured on ice and the solution was made alkaline with concentrated ammonia. The precipitated product was extracted with methylene chloride. The extracts were dried and evaporated. Crystallization of the residue from 2-propanol / ether gave 1.1 g. of off-white product with m.p. 160-164°. The analytical sample was recrystallized from the same solvents, m.p. 162-165°; nmr (deuteriochloroform): δ 3.94 (s, 3, OCH₃) 4.11 (d, 1) and 5.8 (d, 1) (broad AB-system, J = 12.5 Hz, C₄-H); 4.95 (s, 2, NH₂); 7.08 (d, 1, J = 2 Hz, C₇-H); 7.2-7.7 (m, 5, aromatic H); 8.08 (d, 1, J = 8 Hz, C₁₀-H).

Anal. Calcd. for $C_{19}H_{14}Cl_2N_4O_5$: C, 54.69; H, 3.38; N, 13.43. Found: C, 55.00; H, 3.54; N, 13.40.

8-Chloro-6-(2-chlorophenyl)-1,2-dihydro-1-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxylic Acid Methyl Ester (**6**).

A)

A mixture of 5 g. (11.8 mmoles) of *alpha*-amino-7-chloro-5-(2-chlorophenyl)-1,3-dihydro-2H-1,4-benzodiazepin-1-ylideneacetic acid methyl ester ethanolate (**2**), 2.1 g. (13 mmoles) of carbonyldiimidazole and 75 ml. of pyridine was allowed to sit at room temperature over night. The solvent was removed under reduced pressure and the residue was partitioned between methylene chloride and water. The organic phase was dried and evaporated. Crystallization of the residue from methylene chloride / ethyl acetate gave 3.6 g. (76%) of product with m.p. 278-279°; uv: λ max 223 nm ($\epsilon = 43800$) 276 (21,100) infl 348 (1100); ir (potassium bromide): 3150 (NH), 1720 (COOMe, CO); nmr (deuteriochloroform): δ 3.80 (s, 3, OCH₃) 4.11 (broad d, 1) and 5.58 (broad d, 1) (AB-system, J = 12 Hz, C₄-H); 6.95 (d, 1, J = 2.5 Hz, C₇-H) 7.3-7.8 (m, 5, aromatic H) 7.96 (d, 1, J = 8 Hz, C₁₀-H) 11.19 (broad s, 1, NH).

Anal. Calcd. for $C_{19}H_{13}Cl_2N_3O_3$: C, 56.74; H, 3.26; N, 10.45. Found: C, 56.89; H, 3.43; N, 10.35.

B)

A mixture of 50 mg. of **4**, 10 ml. of methanol and 0.5 g. of Raney nickel was hydrogenated at atmospheric pressure for 4 hours. The catalyst was filtered off and the filtrate was evaporated. Crystallization of the residue from ethanol gave 35 mg. (72%) of colorless crystals with m.p. and mixture m.p. 273-275°.

2-Amino-8-chloro-6-(2-chlorophenyl)-1,2-dihydro-1-oxo-4H-imidazo[1,5-a]-[1,4]benzodiazepine-3-carboxamide (**7**).

A mixture of 3 g. (7.2 mmoles) of **4**, 2 g. of ammonium chloride and 30 ml. of methanol containing 20% (v/v) of ammonia was heated in an autoclave on the steam bath for 20 hours. The reaction mixture was partially evaporated and diluted with water. The solids were collected by filtration, washed with water and methanol and recrystallized from methylene chloride / ethanol / methanol to give 2.7 g. (96%) of product with m.p. 188-192°. The analytical sample was recrystallized from tetrahydrofuran / ethanol, m.p. unchanged; nmr (DMSO): δ 4.05 (broad d, 1) and 6.01 (broad d, 1) (AB-system, J = 12 Hz, C₄-H) 5.8 (s, 2, NH₂) 6.98 (d, 1, J = 2 Hz, C₇-H) 7.3-7.9 (m, 6, aromatic H, NH) 7.95 (d, 1, J = 8 Hz, C₁₀-H) 8.8 (broad s, 1, NH).

Anal. Calcd. for $C_{18}H_{13}Cl_2N_3O_2$: C, 53.75; H, 3.26; N, 17.41. Found: C, 53.48; H, 3.30; N, 17.14.

8-Chloro-6-(2-chlorophenyl)-2-[(1-ethoxyethylidene)amino]-1,2-dihydro-1-oxo-4H-imidazo[1,5-a][1,4]benzodiazepine-3-carboxamide (**8**).

A mixture of 0.3 g. (0.75 mmole) of 7, 5 ml. of triethyl orthoacetate and a few crystals of *p*-toluenesulfonic acid was heated to reflux for 45 minutes. The reagent was evaporated and the residue was chromatographed over 5 g. of silica gel using ethyl acetate / methylene chloride 1:1 (v/v). The combined clean fractions were evaporated and the residue was recrystallized from ethyl acetate to yield 0.21 g. (60%) of colorless crystals with m.p. 255-257°; nmr (deuteriochloroform): δ 1.44 (t, 3, J = 6.5 Hz, CH₂CH₃) 2.08 (s, 3, CH₃) 4.06 (d, 1) and 6.23 (d, 1) (AB-system, J = 12 Hz, C₄-H) 4.36 (q, 2, J = 6.5 Hz, OCH₂) 6.86 (broad s, 2, NH₂) 7.05 (d, 1, J = 2 Hz, C₇-H) 7.2-7.7 (m, 5, aromatic H) 8.0 (d, 1, J = 8 Hz, C₁₀-H).

Anal. Calcd. for C₂₂H₁₉Cl₂N₅O₃: C, 55.94; H, 4.05; N, 14.82. Found: C, 56.15; H, 3.82; N, 15.01.

9-Chloro-7-(2-chlorophenyl)-2-methyl-3*H*-[1,2,4]triazino[1',6':3,4]imidazo[1,5-*a*][1,4]benzodiazepine-4,13-[5*H*]dione (9).

A mixture of 1.2 g. (2.5 mmoles) of 8 and 20 ml. of glacial acetic acid was heated to reflux for 1 hour. The precipitated crystals were collected and washed with ethanol to give 0.65 g. of pure product. The filtrate was evaporated and the residue was crystallized from methylene chloride / ethanol to yield an additional 0.25 g. of crystals for a total of 0.9 g. (83%). The analytical sample was recrystallized from methylene chloride / ethyl acetate, m.p. > 300°; uv λ max 218 nm (ϵ 39100), 244 (33500) sh 250 (33000) sh 303 (4900) 239 (6200); ir (potassium bromide): 3220, 3160 (NH) 1705, 1668 (CO), 1627 (C=N); nmr (DMSO): δ 2.12 (s, 3, CH₃), 4.24 (broad d, 1) and 5.57 (broad d, 1) (AB-system, J = 12 Hz, C₅-H), 6.99 (d, 1, J = 2.5 Hz, C₆-H) 7.3-7.8 (m, 5, aromatic H); 8.04 (d, 1, J = 8 Hz, C₁₁-H).

Anal. Calcd. for C₂₀H₁₅Cl₂N₅O₂: C, 56.35; H, 3.07; N, 16.43. Found: C, 56.23; H, 3.14; N, 16.39.

9-Chloro-7-(2-chlorophenyl)-1,3-dimethyl-5*H*-[1,2,4]-triazino[1',6':3,4]-imidazo[1,5-*a*][1,4]benzodiazepine-2,4,13-(1*H*,3*H*,13*H*) trione (11) and 9-chloro-7-(2-chlorophenyl)-3,5-dihydro-2-methoxy-3-methyl[1,2,4]triazino[1',6':3,4]imidazo[1,5-*a*][1,4]benzodiazepine-4,13-(4*H*,13*H*)dione (12).

A mixture of 5 g. (10.2 mmoles) of 3, 5 g. of ammonium chloride and 100 ml. of 20% ammonia in methanol solution was heated in an autoclave for 18 hours. The reaction mixture was then evaporated. The residue was slurried with 50% acetic acid, filtered and washed with water. Recrystallization from methylene chloride / methanol yielded 2.9 g. (66%) of 10 which was suspended in a mixture of 20 ml. of methanol and 200 ml. of methylene chloride and then treated with excess

diazomethane in ether. The excess diazomethane was destroyed with acetic acid and the solution was evaporated. The residue was chromatographed over 70 g. of silica gel using 50% ethyl acetate in toluene. The fractions containing the less polar, major product were combined and evaporated. Crystallization from ethyl acetate / ether yielded 0.9 g. (29%) of crystals with m.p. 223-225°. Recrystallization for analysis from ethyl acetate / ether gave yellow crystals with m.p. 223-225°; uv: λ max 215 nm (ϵ = 50800), sh 238 (26600), sh 255 (16000), 312 (10100); ir (chloroform): 1730, 1708 (CO) 1674 (NCON); ms: m/e 455 (M⁺); nmr (deuteriochloroform): δ 3.33 (s, 3, NCH₃), 3.93 (s, 3, NCH₃), 4.16 (broad d) and 5.98 (broad d) (AB-system, J = 12.5 Hz, CH₂), 7.13 (d, 1, J = 2 Hz, C₆-H) 7.2-7.8 (m, 5, aromatic H), 8.05 (d, 1, J = 8 Hz, C₁₁-H).

Anal. Calcd. for C₂₁H₁₅Cl₂N₅O₃: C, 55.28; H, 3.31; N, 15.35. Found: C, 55.54; H, 3.51; N, 15.27.

Fractions containing the more polar by-product were also combined and evaporated. Crystallization of the residue from ethyl acetate / ether gave 0.25 g. (8%) of yellow crystals with m.p. 251-254°. Recrystallization for analysis from the same solvents did not raise the m.p.; uv: λ sh 215; nm (ϵ = 40500), max 239 (32500), sh 306 (5700) 329 (6830); ir (chloroform): 1722, 1700, 1672 (CO) 1625 (CN); ms: m/e 455 (M⁺); nmr (deuteriochloroform): δ 3.33 (s, 3, NCH₃), 4.1 (s, 3, OCH₃), 4.22 (broad d, 1) and 5.92 and (broad d, 1) (AB-system, J = 12.5 Hz, CH₂) 7.1 (d, 1, J = 2 Hz, C₆-H), 7.2-7.8 (m, 5, aromatic H), 8.15 (d, 1, J = 8 Hz, C₁₁-H).

Anal. Calcd. for C₂₁H₁₅Cl₂N₅O₃: C, 55.28; H, 3.31; N, 15.35. Found: C, 55.24; H, 3.48; N, 14.93.

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