Quinazolines and 1,4-Benzodiazepines. LXXXVII (1). Synthesis of 1- and 3-Phenylimidazo[1,5-*a*][1,4]benzodiazepines

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The synthesis of the 1-phenylimidazobenzodiazepine **5** from **1** and the anion of the nitrone **2** is described. The 3-phenyl-derivative **14** was prepared *via* the amino alcohol **11** which was obtained by condensation of the nitrosamine **9** with benzaldehyde followed by catalytic hydrogenolysis of the nitroso group.

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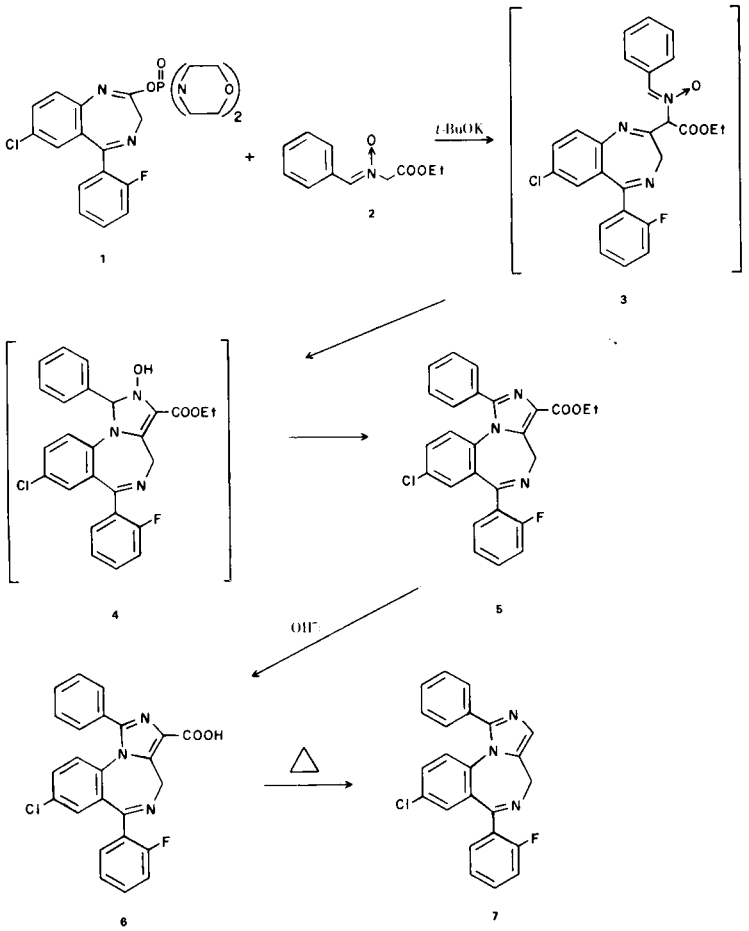
Synthesis of imidazo[1,5-*a*][1,4]benzodiazepines with a variety of substituents in the 1- and 3-positions have been described in previous papers (2,3). We would like to report here, two additional methods which were employed for the preparation of 1- and 3-phenyl substituted compounds. The first method involved condensation of the iminophosphate **1** (4) with the anion of the known nitrone, compound **2** (5), to give the imidazobenzodiazepine **5** in one step (Scheme I).

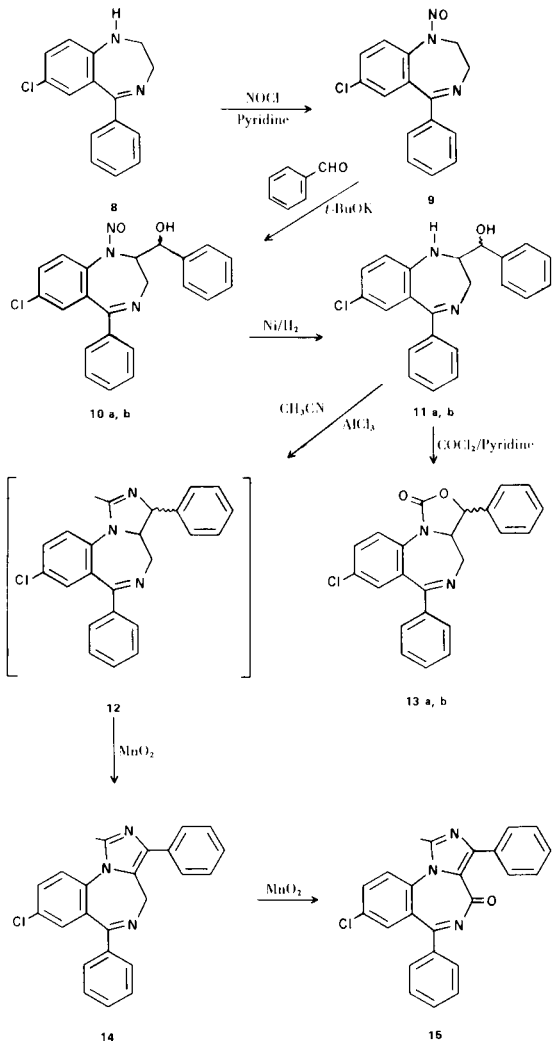
The initial reaction step is believed to be the formation of intermediate **3** which can tautomerize and cyclize to the *N*-hydroxyimidazoline **4**. Spontaneous dehydration of **4** would then give the imidazole **5**. Alkaline hydrolysis of the ester **5** yielded the carboxylic acid **6** which was thermally decarboxylated to give **7**.

A different approach was employed for the synthesis of the 1-methyl-3-phenyl derivative **14** (Scheme II). The 1-nitrosobenzodiazepine **9**, which was readily obtained by reaction of compound **8** (6) with nitrosyl chloride in pyridine, was condensed with benzaldehyde in the presence of potassium *t*-butoxide to give the diastereomeric alcohols **10a** and **10b**. This constitutes another example of the reaction of nitrosamine carbanions with electrophiles (7). An intramolecular version of this condensation in particular has been reported earlier (8). The diasteromers **10a** and **10b** were separated by chromatography and re-

Scheme I



Scheme II



duced catalytically over Raney nickel to yield the corresponding amino alcohols **11a** and **11b**.

Although the stereochemistry of these compounds was of no consequence for the synthesis of the imidazole **14**, we tried to assign the oenfiguration of these isomers on the basis of their nmr spectra. Since neither the pair of nitroso compounds **10** nor the amino alcohols **11** allowed such an assignment, the latter were converted to the oxazolines **13** by treatment with phosgene in pyridine.

The stereochemistry of the protons on adjacent carbons in cyclopentanes can be determined on the basis of different coupling constants and we expected that a similar correlation would be possible for the oxazolines **13a** and **13b**. Unfortunately, the coupling constants were found to be similar for both isomers, 9 Hz for **13a** and 7.5 Hz for **13b**, and therefore useless for the determination of the stereochemistry. An assignment on the basis of chemical shift differences seems more appropriate in this case. The proton at position **3a** in compound **13b** is deshielded by 0.32 ppm relative to the same proton in **13a**. Assuming that this deshielding is due to the coplanarity of the proton with the adjacent phenyl ring, **13b** should have the *trans* configuration.

Condensation of the amino alcohol **11a** with acetonitrile and aluminum chloride gave the imidazoline **12** which was not characterized but directly oxidized with activated manganese dioxide to yield the imidazole **14**. Compound **15** was obtained as a minor by-product of this oxidation and was isolated by chromatography. The structure of **15** was assigned on the basis of analytical and spectral data. It was further formed by oxidation of compound **14**. A similar oxidation had been observed during the study of the reaction of benzodiazepines with ruthenium tetroxide (9).

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 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.

8 -Chloro-6-(2-fluorophenyl)-1-phenyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine-3-carboxylic Acid Ethyl Ester (**5**).

A solution of 4.15 g. (20.1 mmoles) of ethyl 2-[(phenylmethylene)amino]acetate *N*-oxide (**2**) (5) in 200 ml. of tetrahydrofuran was cooled to -73° and 13.2 ml. (21.2 mmoles) of *n*-butyl lithium in hexane (MCB) was added slowly dropwise to give a light orange solution. After 15 minutes, a solution of 10.15 g. (20 mmoles) of 7-chloro-5-(2-fluorophenyl-2-[bis(morpholino)phosphinyloxy]-3*H*-1,4-benzodiazepine (**1**) (4) in 225 ml. of tetrahydrofuran was added slowly dropwise and the resulting dark brown suspension was allowed to warm to room temperature and stirred overnight. The mixture was quenched with 3 ml. of water and the solvent was removed *in vacuo*. The residue was diluted with 300 ml. of water and extracted repeatedly with ether; the combined organic layers were washed twice with water, once with brine, dried with anhydrous magnesium sulfate and concentrated *in vacuo* to give the crude product as a light yellow solid, 8.7 g. (95%). Recrystallization from aqueous acetone gave the product as a white crystalline solid, 5.9 g. (65%). Concentration of the mother liquor gave a further 2.1 g. for a total of 8.0 g. (87%), m.p. 228-230°; uv: λ max 222 nm (ε 49,700), sh 245 (33,000), sh 265 (22,500); ir (potassium bromide): 1715 cm^{-1} (COOEt); nmr (deuteriochloroform): δ 1.40 (t, 3, J = 8 Hz, CH_3), 4.40 (q, 2, J = 8 Hz, OCH_2), 4.06 (d, 1) and 6.13 (d, 1) (AB-system, J = 12,5 Hz, C_4-H) 6.8-8.0 (m, 12, aromatic H).

Anal. Calcd. for $C_{26}H_{19}ClFN_3O_2$: C, 67.90; H, 4.16; N, 9.14. Found: C, 67.88; H, 4.08; N, 9.16.

8-Chloro-6-(2-fluorophenyl)-1-phenyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine-3-carboxylic Acid (**6**).

To a solution of 2.66 g. (5.77 mmoles) of **5** in 50 ml. of refluxing methanol was added a solution of 755 mg. (11.5 mmoles) of potassium hydroxide in 10 ml. of water and the resulting mixture was heated for 2.5 hours. The solvent was removed *in vacuo*, the residue was dissolved in 50 ml. of hot acetic acid and the solution was then poured into 100 ml. of cold water. The product

was collected, washed with water and air dried to give 2.5 g. (100%) of the title compound as an off-white solid. An analytical sample was recrystallized form benzene, m.p. 267-269°.

Anal. Calcd. for $C_{24}H_{15}ClFN_3O_2$: C, 66.75; H, 3.50; N, 9.73. Found: C, 66.66; H, 3.51; N, 9.61.

8-Chloro-6-(2-fluorophenyl)-1-phenyl-4*H*-imidazo[1,5-*a*][1,4]-benzodiazepine (**7**).

A suspension of 1.5 g. (3.48 mmoles) of **6** in 20 ml. of mineral oil was stirred vigorously at 190° for 0.5 hours. The dark suspension was then slurried with hexanes and extracted twice with 1*N* hydrochloric acid. The acidic aqueous layer was then washed once with hexanes and neutralized with 5% aqueous sodium carbonate. The precipitated product was collected and air dried to yield 800 mg. (59%); concentration of the filtrate gave an additional 220 mg., for a total of 1.02 g. (75%) of the title compound as an off-white solid. An analytical sample was obtained by column chromatography on silica gel eluting with ethyl acetate, m.p. 241-243°; uv: λ infl 217 nm (ε 39,000), infl 250 (17,800), sh 275 (12,400); nmr (deuteriochloroform): δ 4.05 (d, 1) and 5.10 (d, 1) (AB-system, J = 12 Hz, C_4-H), 6.7-8.0 (m, 13, aromatic H and C_3-H).

Anal. Calcd. for $C_{23}H_{15}ClFN_3$: C, 71.23; H, 3.90; N, 10.83. Found: C, 71.15; H, 3.84; N, 10.63.

7-Chloro-2,3-dihydro-1-nitroso-5-phenyl-1*H*-1,4-benzodiazepine (**9**).

Nitrosyl chloride was introduced into a solution of 20 g. (0.078 mole) of 7-chloro-2,3-dihydro-5-phenyl-1*H*-1,4-benzodiazepine (**8**) (6) in 200 ml. of methylene chloride and 20 ml. of pyridine with cooling in ice-water. When the color of the reaction mixture changed from orange to almost colorless, the addition of nitrosyl chloride was stopped and the mixture was partitioned between methylene chloride and ice cold, 10% aqueous sodium carbonate solution. The organic layer was dried and evaporated and the residue was crystallized from 2-propanol to yield 21 g. (94%) of product. The analytical sample was recrystallized from methanol to give a slightly yellow prisms with m.p. 119-121°.

Anal. Calcd. for $C_{15}H_{12}ClN_3O$: C, 63.05; H, 4.23; N, 14.71. Found: C, 63.17; H, 3.98; N, 14.45.

7-Chloro-2,3-dihydro-2-(*alpha*-hydroxybenzyl)-1-nitroso-5-phenyl-1*H*-1,4-benzodiazepines (**10a** and **10b**).

Potassium *t*-butoxide, 15 g. (0.133 mole), was added to a solution of 17.2 g. (0.06 mole) of **9** and 9 g. (0.085 mole) of benzaldehyde in 200 ml. of tetrahydrofuran cooled to 0°. After stirring for 30 minutes at 0° to 5° the reaction mixture was acidified by addition of 12 ml. of acetic acid and partitioned between toluene and saturated sodium bicarbonate solution. The organic layer was dried and evaporated and the residue was chromatographed over 500 g. of silica gel using 15% (v/v) of ethyl acetate in methylene chloride. The clean fractions containing the main product **10a** were combined and evaporated. The residue was crystallized from ether to yield 7.4 g. (30.5%) of product. The analytical sample was recrystallized from methylene chloride/ether/hexane to give colorless crystals with m.p. 170-172° dec.; uv: λ infl 225 nm (ε 27,200), max 251 (15,300); ir (potassium bromide): 3500 cm^{-1} (OH); nmr (deuteriochloroform): δ 2.96 (d, 1, J = 5 Hz, OH), 3.32 (t, 1, J_{AB} = 12 Hz, J_{AX} = 12 Hz, C_3-H), 4.1 (q, 1, J_{AB} = 12 Hz, J_{AX} = 4 Hz, C_3-H), 4.75 (t, 1, $J_{C_2\text{-}H}$ = 6.5 Hz, J_{OH} = 5 Hz, *alpha* proton), 6.55 (double q, J_{AX} = 12 Hz, J_{BX} = 4 Hz, $J_{\alpha\text{-}H}$ = 6.5 Hz, C_2-H), 7.0-7.8 (m, 13, aromatic H).

Anal. Calcd. for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72. Found: C, 67.47; H, 4.53; N, 10.69.

Partial crystallization of the less polar fractions from ethyl/acetate/hexane yielded 0.6 g. of the stereoisomer **10b** with m.p. 180-183° dec.; uv: λ max 218 nm (ε 37,200), 252 (16,800); nmr (deuteriochloroform): δ 2.82 (d, 1, J = 4 Hz, OH), 3.5-4 (m, 2, AB-part of ABX-system, J_{AB} = 12 Hz, J_{AX} = 12 Hz, J_{BX} = 5 Hz, C_3-H), 5.13 (dd, 1, J_{OH} = 4 Hz, $J_{C_2\text{-}H}$ = 2 Hz, *alpha*-H), 5.36 (double q, J_{AX} = 12 Hz, J_{BX} = 5 Hz, $J_{\alpha\text{-}H}$ = 2 Hz, C_2-H), 7.1-7.7 (m, 13, aromatic H).

Anal. Calcd. for $C_{22}H_{18}ClN_3O_2$: C, 67.43; H, 4.63; N, 10.72. Found: C, 67.27; H, 4.83; N, 10.47.

7-Chloro-2,3-dihydro-2-(*alpha*-hydroxybenzyl)-5-phenyl-1*H*-1,4-benzodiazepine (**11a**).

A mixture of 5 g. (0.0127 mole) of **10a**, 100 ml. of ethanol and 1 teaspoonful of Raney nickel was hydrogenated for 2 hours at room temperature and atmospheric pressure. The catalyst was separated by filtration and the filtrate was evaporated. Crystallization of the residue from ethanol/ether yielded 3.8 g. of colorless crystals. A second crop of 0.5 g. was obtained from the mother liquor for a total yield of 92.8%.

The analytical sample was recrystallized from ethyl acetate/hexane, m.p. 196-197°; nmr (DMSO-d_6): δ 3.0-4.1 (m, 3, C_2- and C_3-H), 4.5 (q, 1, $J_{C_2\text{-}H}$ = 7 Hz, J_{OH} = 4 Hz, benzylic proton), 5.75 (d, 1, J = 4 Hz, OH), 5.91 (broad s, 1, NH), 6.77 (d, 1, J = 2 Hz, C_6-H), 7.0 (d, 1, J = 9 Hz, C_9-H), 7.1-7.6 (m, 11, aromatic H).

Anal. Calcd. for $C_{22}H_{19}ClN_2O$: C, 72.82; H, 5.28; N, 7.72. Found: C, 72.97; H, 5.34; N, 7.61.

8-Chloro-3,3a-dihydro-3,6-diphenyl(1*H*,4*H*)oxazolo[3,4-*a*][1,4]-benzodiazepin-1-one (**13a**).

A solution of phosgene in benzene (1 ml., 12%) was added to a solution of 0.1 g. of **11a** in 10 ml. of pyridine. The mixture was warmed on the steam bath for 5 minutes and was evaporated under reduced pressure. The residue was partitioned between methylene chloride/toluene and saturated sodium bicarbonate solution. The organic phase was dried and evaporated and the residue was chromatographed over 4 g. of silica gel using methylene chloride. Crystallization of the clean fractions from ether/hexane gave 20 mg. of product with m.p. 143-146°; nmr (deuteriochloroform): δ 3.48 (dd, 1, J_{AB} = 13 Hz, J_{AX} = 5 Hz, C_4-H), 4.15 (d, 1, J_{AB} = 13 Hz, C_4-H), 4.48 (dd, 1, $J_{C_2\text{-}H}$ = 5 Hz, $J_{C_3\text{-}H}$ = 9 Hz, C_{3a}-H), 5.67 (d, 1, $J_{C_{3a}\text{-}H}$ = 9 Hz, C_3-H), 7.1-7.8 (m, 13, aromatic H).

Anal. Calcd. for $C_{23}H_{17}ClN_2O_2$: C, 71.04; H, 4.41; N, 7.20. Found: C, 71.07; H, 4.22; N, 7.06.

8-Chloro-3,3a-dihydro-3,6-diphenyl(1*H*,4*H*)oxazolo[3,4-*a*][1,4]-benzodiazepin-1-one (**13b**).

A solution of 0.5 g. of the nitroso compound **10b** in 20 ml. of ethanol was hydrogenated over Raney nickel at atmospheric pressure for 1 hour. The catalyst was separated by filtration over Celite and the filtrate was evaporated, at the end azeotropically with toluene. The crude amino alcohol **11b** obtained was dissolved in 25 ml. of pyridine and treated with 5 ml. of a 12% solution of phosgene in benzene as described above. The same work up followed by chromatography over 5 g. of silica gel using methylene chloride and crystallization from ether/hexane gave 90 mg. of colorless crystals with m.p. 187-189° uv: λ sh 212 nm (ε 54,600), sh 260 (9,200); ir (chloroform): 1755 cm^{-1} (CO); nmr (deuteriochloroform): δ 3.23 (dd, 1, J_{AB} = 12 Hz, J_{AX} = 5 Hz, C_4-H), 3.56 (dd, 1, J_{AB} = 12 Hz, J_{BX} = 1.5 Hz, C_4-H), 4.80 (ddd, 1, J_{AX} = 5 Hz, J_{BX} = 1.5 Hz, $J_{C_3\text{-}H}$ = 7.5 Hz, C_{3a}-H), 5.73 (d, 1, J = 7.5 Hz, C_3-H), 7.1-7.8 (m, 13, aromatic H).

Anal. Calcd. for $C_{23}H_{17}ClN_2O_2$: C, 71.04; H, 4.41; N, 7.20. Found: C, 71.13; H, 4.47; N, 6.88.

8-Chloro-1-methyl-3,6-diphenyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine (**14**) and 8-chloro-1-methyl-3,6-diphenyl-4*H*-imidazo-[1,5-*a*][1,4]benzodiazepin-4-one (**15**).

A mixture of 3 g. (8.26 mmoles) of **11a**, 10 ml. of acetonitrile and 6 g. of aluminum chloride was heated up to 160° with stirring. The reddish paste was cooled and partitioned between methylene chloride and 1 *N* sodium hydroxide solution. The organic phase was dried and evaporated at the end azeotropically with toluene. The residue was dissolved in 200 ml. of toluene and the solution was heated to reflux for 15 minutes after addition of 15 g. of activated manganese dioxide. The inorganic material was separated by filtration over Celite and the filtrate was evaporated. The residue was crystallized from ether to yield 1.7 g. (53%) of crude product. It was purified by chromatography over 70 g. of silica gel using 5% (v/v) of ethyl acetate in methylene chloride.

The fractions containing the less polar impurity **15** were evaporated and crystallized from ethyl acetate/hexane to yield 75 mg. (2.28%) of yellow crystals with m.p. 262-264°; uv: λ max 233 nm (ε 34,800), 277 (18,200), 352 (5,200); ir (chloroform): 1680 cm^{-1} (CO), 1620 (-C=N-); nmr (deuteriochloroform): δ 2.62 (s, 3, CH_3), 7.1-8.2 ppm (m, 13, aromatic H).

Anal. Calcd. for $C_{24}H_{16}ClN_3O$: C, 72.45; H, 4.05; N, 10.56. Found: C, 72.38; H, 4.15; N, 10.45.

The fractions containing the more polar main product were combined and evaporated. Crystallization from ether/hexane yielded 1.3 g. of colorless crystals with m.p. 180-182°; uv: λ infl 215 nm (ε 45,300), max 247 (30,800), sh 270 (22,600), infl 340 (4,800); nmr (deuteriochloroform): δ 2.6 (s, 3, CH_3), 4.07 (d, 1) and 5.45 (d, 1) (AB-system, J = 13 Hz, C_4-H), 7.2-7.9 ppm (m, 13, aromatic H).

Anal. Calcd. for $C_{24}H_{18}ClN_3$: C, 75.09; H, 4.72; N, 10.95. Found: C, 75.31; H, 4.68; N, 11.00.

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