Tetracyclic Benzodiazepines. 3. Synthesis of the 2,3-Dihydro-1*H*-quino[1,8-*ab*][1,5]benzodiazepine Ring System, and Derivatives of Potential Biological Interest

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The synthesis of the 2,3-dihydro-1*H*-quino[1,8-*ab*][1,5]benzodiazepine ring system is described. The key step involves a Bischler-Napieralski type cyclization of the formamide **3**. This was achieved by refluxing in phosphorus oxychloride to effect a cyclodehydration to form the seven-membered central ring. A subgroup of 1*H*-quinobenzodiazepines bearing a pendant *N*-methylpiperazine substituent was synthesized by a similar cyclization of ureas of type **6**. These derivatives **7** are structurally related to the antipsychotic drug clozapine.

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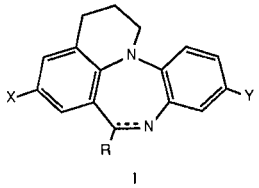
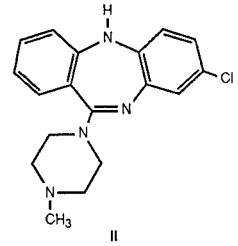
In an earlier paper in this series [1], we reported on the use of the Bischler-Napieralski cyclization reaction [2,3] to design novel heterocyclic ring systems. By synthetic construction of amine bearing side-chains at the central ring nitrogen atom, a series of compounds was obtained which demonstrated significant antidepressant activity [4]. In continuing our work in this field [5], we now wish to report the synthesis of the 1*H*-quinobenzodiazepine ring system of formula I, and several derivatives structurally related to the antipsychotic drug, clozapine II [6].



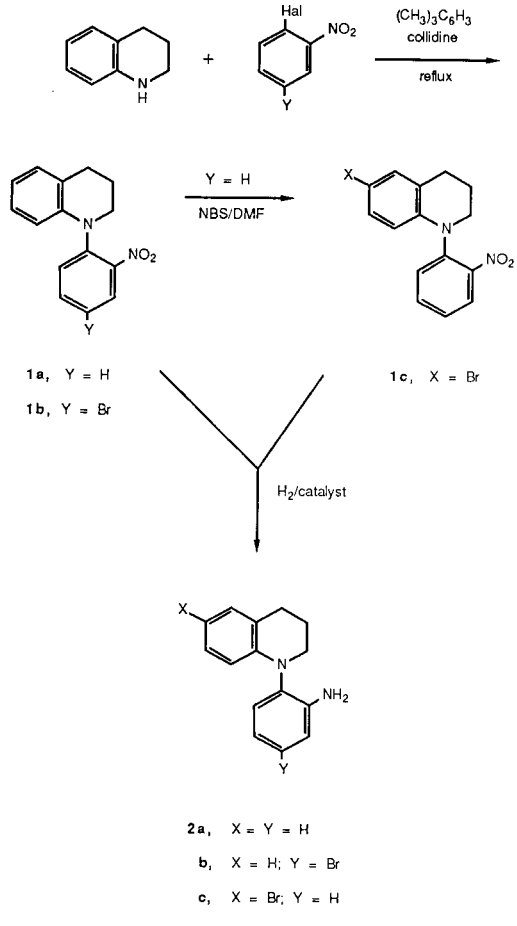
I



II

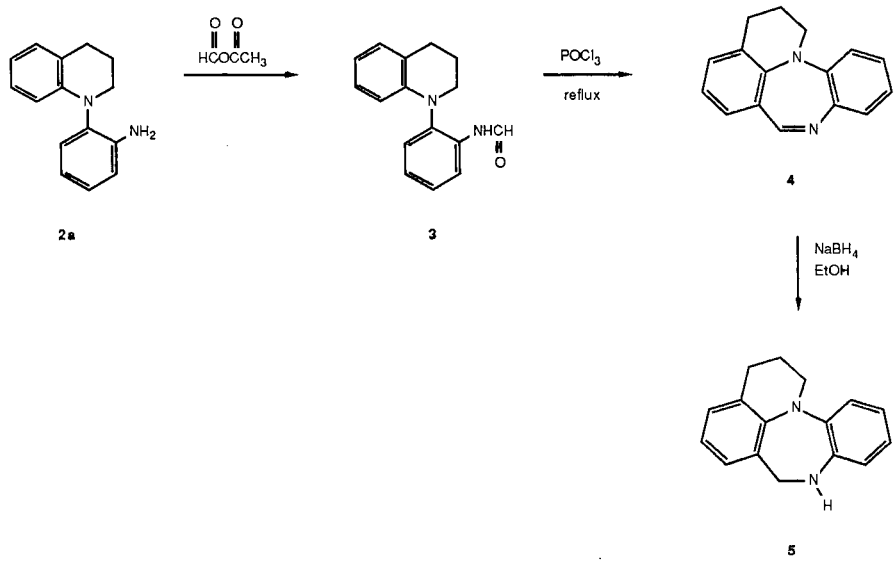
The synthetic pathway to the 1*H*-quinobenzodiazepine ring system is shown in Schemes I and II. In the first step, 1,2,3,4-tetrahydroquinoline was condensed with 1-fluoro-2-nitrobenzene by prolonged heating in an inert high-boiling solvent to afford 1-(2-nitrophenyl)-1,2,3,4-tetrahydroquinoline **1a**. Under these robust conditions, the nitrogen atom of tetrahydroquinoline was sufficiently nucleophilic to displace fluoride from the highly activated nitrobenzene substrate. Collidine was employed as the acceptor base for the hydrogen fluoride generated by the reaction. In order to obtain target quinotetracycles with a halogen substituent, two strategies were employed at this early stage of the synthesis. A 4-bromo substituent could be provided in the pendant phenyl ring by using 2,5-dibromonitrobenzene as substrate in the condensation reaction with 1,2,3,4-tetrahydroquinoline. Alternatively, a bromine substituent could be introduced in the quinoline portion of the molecule by reacting intermediate **1a** with *N*-bromosuccinimide in dimethylformamide as solvent. The pendant phenyl ring of **1a** was sufficiently deactivated towards electrophilic substitution by the *ortho*-NO_2 group that the bromine atom entered quantitatively and regioselectively the 6-position of the quinoline nucleus.

Scheme I



Next, the nitro group of **1a,b,c** was reduced catalytically to the 1-(2-aminophenyl)tetrahydroquinolines **2**. Those substrates bearing aromatic bromine (**1b,c**) were hydrogenated over 1% platinum-on-carbon catalyst in order to

Scheme II

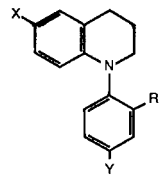


2a 3 4 5

prevent hydrogenolysis of the C-Br bond.

Scheme II illustrates how 1-(2-aminophenyl)-1,2,3,4-tetrahydroquinoline **2a** was used to prepare the parent 1*H*-quinobenzodiazepine ring system. The amino group of **2a** was smoothly formylated with a mixed formic-acetic anhydride to provide the formamide precursor **3** to the Bischler-Napieralski cyclization. When this was refluxed in phosphorus oxychloride, a cyclodehydration took place

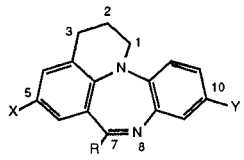
Table I
1-(2-Substituted phenyl)-1,2,3,4-tetrahydroquinolines

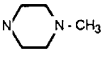
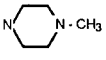
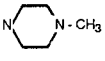


Compound	X	Y	R	Mp (°C)	Yield [a] %	Recrystallization Solvent	Molecular Formula	Analyses, % Calcd./Found C	H	N
1a	H	H	NO_2	69-71	22	isopropyl ether	$C_{15}H_{14}N_2O_2$	70.85 70.82	5.55 5.66	11.02 11.00
1b	H	Br	NO_2	163-165 [b]	18		$C_{15}H_{13}BrN_2O_2$	54.07 53.99	3.93 4.02	8.41 8.31
1c	Br	H	NO_2	166-168 [b]	82		$C_{15}H_{13}BrN_2O_2$	54.07 53.73	3.93 4.30	8.41 8.35
2a	H	H	NH_2	119-121	67	ethanol	$C_{15}H_{16}N_2 \cdot C_4H_4O_4$	67.04 67.34	5.92 6.03	8.23 8.53
2b	H	Br	NH_2	88-90	24	ether	$C_{15}H_{15}BrN_2 \cdot C_4H_4O_4$	54.42 54.30	4.57 4.54	6.68 6.59
2c	Br	H	NH_2	113-116	29	ethyl acetate	$C_{15}H_{15}BrN_2 \cdot C_4H_4O_4$	54.42 54.40	4.57 4.60	6.68 6.64
3	H	H	NHCHO	94-96 [c]	50		$C_{16}H_{16}N_2O$	76.16 76.21	6.40 6.61	11.11 11.14
6a	H	H	NHCON(CH2CH2)2N-CH_3	171-173 dec.	44	methanol	$C_{21}H_{26}N_4O \cdot C_4H_4O_4$	64.36 64.29	6.48 6.44	12.01 12.01
6b	H	Br	NHCON(CH2CH2)2N-CH_3	125-128	38	ether	$C_{21}H_{25}BrN_4$	58.74 59.04	5.87 5.86	13.05 12.69
6c	Br	H	NHCON(CH2CH2)2N-CH_3	172-174 dec.	40	methanol	$C_{21}H_{25}BrN_4O \cdot C_4H_4O_4$	55.05 55.15	5.36 5.34	10.27 10.34

[a] These yields represent analytically pure products. No attempt was made to optimize yields.
[b] Kugelrohr oven temperature when distilled at 0.2 mm Hg. [c] Crystalline solid from sublimation at 0.2 mm Hg and a bath temperature of 145-160°.

Table II
7-substituted-2,3-dihydro-1*H*-quino[1,8-*ab*][1,5]benzodiazepines

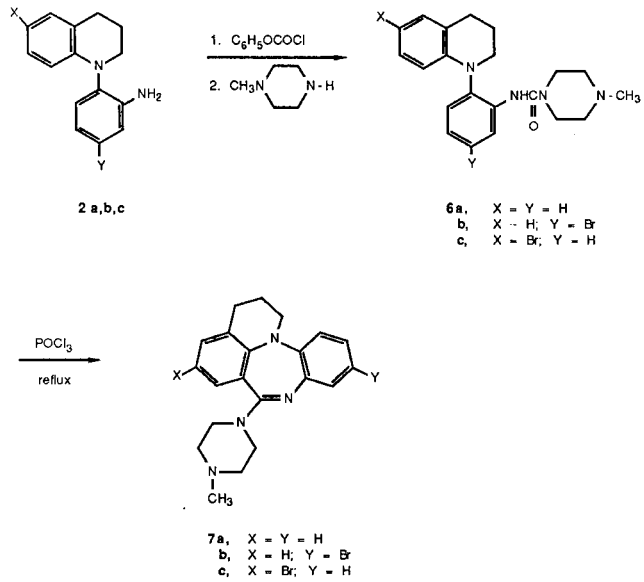


Compound	X	Y	R	Mp (°C)	Yield [a] %	Recrystallization Solvent	Molecular Formula	Analyses, % Calcd./Found C	H	N
4	H	H	H	118-120	38	toluene	$C_{16}H_{14}N_2$	82.02 82.01	6.02 5.91	
7a	H	H		129-132	28	ethanol	$C_{21}H_{24}N_4$	75.87 76.04	7.28 7.44	
7b	H	Br		153-156	18	methanol	$C_{21}H_{23}BrN_4$	61.31 61.13	5.64 5.66	13.62 13.56
7c	Br	H		181-183	63	ethanol	$C_{21}H_{23}BrN_4$	61.31 61.14	5.64 5.75	13.62 13.68

[a] These yields represent analytically pure products. No attempt was made to optimize yields.

resulting in the formation of a seven-membered central ring. This process furnished the 2,3-dihydro-1*H*-quino-[1,8-*ab*][1,5]benzodiazepine ring system **4**. Reduction of the C_7-N_8 imino linkage with sodium borohydride afforded a 1*H*-quinobenzodiazepine **5** with a fully reduced seven-membered central ring.

Scheme III



2 a,b,c

6 a, X = Y = H
b, X = H; Y = Br
c, X = Br; Y = H

7 a, X = Y = H
b, X = H; Y = Br
c, X = Br; Y = H

Scheme III outlines the synthetic approach to a series of 1*H*-quinobenzodiazepines **7a-c** having a pendant *N*-methylpiperazine substituent. The previously described 1-(2-aminophenyl)-1,2,3,4-tetrahydroquinolines **2a-c** were elaborated into *N*-methylpiperazine ureas *via* a two step procedure. The amino group of **2** was reacted first with phenylchloroformate. The resulting carbamate was not isolated but was reacted further *in situ* with *N*-methylpiperazine. The latter displaced phenoxide ion from the carbamate intermediate to produce the ureas of type **6**. This two step sequence was preferable in yield and purity of product to a direct acylation of the amines with *N*-methylpiperazinecarbonyl chloride.

The ureas **6** were found to undergo a facile Bischler-Napieralski type cyclization in refluxing phosphorus oxychloride to form the clozapine-like analogs **7a-c**. These three compounds were tested in mice for potential antipsychotic activity. They were found to be less active than a related and similarly substituted series of pyrrolobenzodiazepines [7].

EXPERIMENTAL

Melting points were determined in open capillary tubes using a Thomas-Hoover Uni-melt apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 457 grating spectrometer. Nuclear ^1H magnetic resonance spectra were taken on a Varian XL-200 spectrometer. Chemical shift values are reported in δ units (parts per million) relative to tetramethylsilane as an internal standard. Mass spectra were obtained from a Finnigan Model 4000 GC-MS spectrometer equipped with an INCOS data system. Elemental analyses were performed by Micro-Tech Laboratories, Skokie, Illinois. The final yields reported here represent analytically pure products. No effort was made to optimize the yields.

1-(2-Nitrophenyl)-1,2,3,4-tetrahydroquinoline (**1a**).

A stirred mixture, under nitrogen, of 70.6 g (0.50 mole) of 1-fluoro-2-nitrobenzene, 133.2 g (1.00 mole) of 1,2,3,4-tetrahydroquinoline and 121.2 g (1.00 mole) of symmetrical collidine in 500 ml of 1,2,3-trimethylbenzene as solvent was refluxed (bp 178°) for 5 days. The mixture was filtered and then concentrated *in vacuo* to a dark liquid weighing 78.3 g (62%). This material was taken up in 1,000 ml of chloroform and ex-

tracted with 500 ml of 2*N* hydrochloric acid. The aqueous phase was separated and back-extracted with 250 ml of chloroform. The combined organic layers were washed three times with 2*N* hydrochloric acid, then once with 2*N* sodium hydroxide, twice with water and then dried over sodium sulfate. The solvent was removed *in vacuo* leaving 40.7 g (32%) of dark oil. This crude product was dissolved in 300 ml of 1:1 hexane:toluene solution and adsorbed on a tall chromatography column containing 2 kg of silica gel packed in hexane. Elution with 1:1 hexane:toluene eventually brought forth fractions of pure nitro product. These were combined and concentrated to afford 28.2 g (22% overall yield) of tlc pure crystalline product. Recrystallization of 23 g from 80 ml of di-isopropyl ether gave 17.5 g (17% overall yield) of bright orange crystals, mp 69-71°; ir (chloroform): 1595 (aromatic C=C), 1520 and 1350 (Ar-NO_2) cm^{-1}; nmr (deuteriochloroform): δ 2.08 (m, 2H, CH_2), 2.90 (t, 2H, CH_2), 3.60 (t, 2H, CH_2), 6.36-7.92 (m, 8H, Ar-H); ms: m/e (% relative abundance) 254 (M^+, 56), 237 (33), 219 (12), 206 (100), 180 (49), 152 (17), 77 (36), 63 (23), 51 (28).

The 4-bromo-2-nitrophenyl compound **1b** of Table I was synthesized in the same way but using 2,5-dibromonitrobenzene as substrate and heating the reaction mixture for 7 days. After chromatography, the pure product was obtained in 18% overall yield. For analysis, a portion was Kugelrohr distilled at an oven temperature of 163-165° (0.2 mm Hg).

6-Bromo-1-(2-nitrophenyl)-1,2,3,4-tetrahydroquinoline (**1c**).

A stirred solution, under nitrogen, of 76.3 g (0.30 mole) of **1a** in 1,000 ml of dimethylformamide was cooled to −10°. Then a solution of 58.7 g (0.33 mole) of *N*-bromosuccinimide in 250 ml of dimethylformamide was added dropwise at such a rate as to keep the reaction temperature below 0° (1.5 hours). Half an hour after the addition was completed, tlc indicated quantitative conversion of starting material to product. The reaction fluid was then poured into 7 liters of 2*N* sodium hydroxide with good stirring. This caused the product to separate as a sticky oil on the walls of the flask. The quench fluids were decanted, and the adhering oil was rinsed several times with water. It was then taken up into 1.5 liters of dichloromethane. The organic solution was washed once with 2*N* sodium hydroxide, thrice with water, then it was dried over sodium sulfate. Concentration afforded 90.0 g (90% yield) of oil that was virtually pure by tlc. This material was dissolved in 250 ml of 1:1 hexane:toluene and the solution was adsorbed on a tall chromatography column containing 2 kg of silica gel packed in 1:1 hexane:toluene. Elution with this solvent mixture brought forth fractions of pure **1c**. These were combined and concentrated *in vacuo* to provide 82.7 g of pure product as an orange-red oil in 82% overall yield. For analysis, a sample was Kugelrohr distilled at an oven temperature of 166-168° (0.2 mm Hg); ir (chloroform): 1610, 1595 (aromatic C=C), 1520 and 1350 (Ar-NO_2) cm^{-1}; nmr (deuteriochloroform): δ 2.08 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.58 (t, 2H, CH_2), 6.18-7.94 (m, 7H, Ar-H); ms: m/e (% relative abundance) 334 (M^++1,25), 333 (M^+,4), 332 (M^+−1,25), 315 (16), 284 (18), 206 (100), 102 (36), 89 (25), 77 (39), 63 (33), 51 (42).

1-(2-Aminophenyl-1,2,3,4-tetrahydroquinoline Maleate (**2a**).

A Parr hydrogenation bottle was charged with 12.7 g (0.050 mole) of **1a**, 1.00 g of 5% palladium-on-carbon catalyst, 100 ml of benzene and 100 ml of ethanol. The mixture was shaken under an initial hydrogen pressure of 55 psi until uptake ceased. The mixture was then filtered to remove the catalyst and the filtrate was concentrated *in vacuo* to 11.2 g (100% yield). This oil was purified as the maleate salt. Accordingly, 8.40 g (0.037 mole) of the crude base was dissolved in 50 ml of ether and then treated with a hot solution of 4.30 g (0.037 mole) of maleic acid in 350 ml of ether. The pure maleate salt **2a** was collected and found to weigh 8.4 g (67% overall yield), mp 119-121°. For analysis, this was recrystallized from ethanol to afford 5.1 g of white crystals, mp unchanged; ir (potassium bromide): 3420 (Ar-NH_3^+), 2600-2525, 1630, 1605, 1500, 1450, 1340, 862 cm^{-1}; nmr (DMSO-d_6): δ 2.04 (broad, 2H, CH_2), 2.82 (t, 2H, CH_2), 3.38 (t, 2H, CH_2), 6.02-7.08 (m, 8H, Ar-H), 6.30 (s, 2H, CH=CH of maleic acid); ms: m/e (% relative abundance) 224 (M^+, 100), 209 (22), 195 (27), 180 (9.3), 167 (6.3), 132 (21), 117 (23), 106 (14), 98 (44), 72 (25), 65 (17), 45 (23).

The 2-amino-4-bromophenyl analog **2b** of Table I was prepared in exactly the same way except that 1-(4-bromo-2-nitrophenyl)-1,2,3,4-tetrahydroquinoline **1b** was the substrate and 1%-platinum-on-carbon was the catalyst used. Also using 1%-platinum-on-carbon, **1c** was hydrogenated to provide the analogous 6-bromo-2-aminophenyl intermediate **2c** of Table I.

N-[2-(1,2,3,4-Tetrahydro-1-quinolinyl)phenyl]formamide (**3**).

To prepare the mixed anhydride formylating reagent, 153 g (1.50 moles) of acetic anhydride was cooled to −10 to −5° in an ice-methanol bath, and then there was added dropwise, with stirring, 207 g (4.50 moles) of 98% formic acid. The addition was somewhat exothermic, and the reaction temperature was maintained between −10 and −5° by the rate of addition (1 hour). The solution was then stirred at −5° for 3 hours to complete the formation of the mixed formic-acetic anhydride.

The above reagent was then poured in one portion directly into a flask containing 67.3 g (0.30 mole) of 1-(2-aminophenyl)-1,2,3,4-tetrahydroquinoline **2a** (free base). Within a few minutes, with good stirring, a solution resulted accompanied by an exotherm of 23°. After stirring at ambient temperature for 1 hour, the solution was concentrated *in vacuo* to an oil weighing 74.1 g (98%), almost pure by tlc. This material was dissolved in 100 ml of hot methanol to give 52.6 g (74%) of tan crystals. Recrystallization of 20 g from methanol afforded 15.0 g (56% overall yield) of white crystals, pure by tlc. However, this material, as well as samples recrystallized from a wide variety of solvents, incorporated non-integral amounts of solvent in the crystal (by nmr) so that a good elemental analysis and a sharp melting point could not be achieved. Therefore, 10.0 g was sublimed at 0.2 mm Hg with a bath temperature range of 145-160° to provide 8.90 g of pure white crystals, mp 94-96°, free of solvent, in 50% overall yield; ir (potassium bromide): 3240 (NH), 1690 (C=O), 1665, 1600, 1525, 1460, 1305, 760 cm^{-1}; nmr (deuteriochloroform): δ 2.08 (t, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.40 (t, 2H, CH_2), 6.10 (d, 1H, CHO), 6.64-8.72 (m, 9H, Ar-H, NH); ms: m/e (% relative abundance) 252 (M^+, 100), 224 (46), 209 (18), 195 (18), 180 (10), 142 (38), 98 (35), 77 (48), 69 (58), 43 (65).

2,3-Dihydro-1*H*-quino[1,8-*ab*][1,5]benzodiazepine (**4**).

To a stirred solution, under nitrogen, of 32.8 g (0.13 mole) of *N*-[2-(1,2,3,4-tetrahydro-1-quinolinyl)phenyl]formamide **3** in 500 ml of azeotropically dried toluene was added 99.6 g (0.65 mole) of phosphorus oxychloride. The initial solution was heated for 5 hours at 75°, and then stirred at room temperature overnight. The solvent and excess phosphorus oxychloride was then removed at aspirator pressure with mild heating. The resulting dark residue was washed twice with ether and twice with hexane to remove traces of phosphorus oxychloride. The residue was then triturated and heated with 25 ml of absolute ethanol. The ethanol was removed on the rotovac and the resulting crude product was treated with 1 liter of ethyl acetate and 500 ml of dilute sodium hydroxide solution. The two phases were stirred vigorously until the residue dissolved, except for some interfacial material. The dark aqueous layer was separated and back-extracted with 250 ml of ethyl acetate. The organic layers were combined and filtered free of the interfacial material. This solution was then washed 4 times with water, dried over anhydrous sodium sulfate and concentrated *in vacuo* to leave 25.2 g (83%). Part of this (20 g) was purified further by chromatography using 500 g of silica gel packed in dichloromethane and using the latter as eluant. The appropriate fractions were combined and concentrated to afford 9.1 g of tlc pure crystalline product in 38% overall yield. For analysis, this material was recrystallized from a small volume of toluene which provided 4.90 g (21% overall) of **4** with mp 118-120°; ir (chloroform): 1640, 1585 (C=N, aromatic C=C), 1455, 1250 cm^{-1}; nmr (deuteriochloroform): δ 2.02 (m, 2H, CH_2), 2.80 (t, 2H, CH_2), 3.64 (broad, 2H, CH_2), 6.84-7.24 (m, 7H, Ar-H), 8.35 (s, 1H, CH=N); ms: m/e (% relative abundance) 234 (M^+, 100), 219 (15), 206 (21), 117 (6.8), 103 (12), 89 (6.5), 77 (7.3), 63 (5.3), 51 (6.4).

2,3,7,8-Tetrahydro-1*H*-quino[1,8-*ab*][1,5]benzodiazepine (**5**).

To a stirred solution, under nitrogen, of 4.92 g (0.021 mole) of 2,3-di-

hydro-1*H*-quino[1,8-*ab*][1,5]benzodiazepine **4** in 60 ml of absolute ethanol was added 3.0 g (0.084 mole) of sodium borohydride in small portions over a 30 minute period. After stirring at room temperature for 4 hours, the mixture was treated dropwise with 150 ml of water, very slowly and cautiously at first, then faster towards the end. This caused a fine yellow solid to separate which was filtered off, washed several times with water, and dried over phosphorus pentoxide to afford 3.98 g (81%), mp 130-135°. This crude product was dissolved in 30 ml of dichloromethane and the solution was adsorbed on a chromatography column containing 120 g of silica gel packed in dichloromethane. Elution with the latter solvent brought forth fractions of pure product. These were combined and concentrated *in vacuo* to 3.2 g (64% overall yield) of tlc pure crystals, mp 136-140°. Recrystallization from a small volume of toluene provided 2.50 g of almost white crystals in 51% overall yield, mp 137-140°; ir (chloroform): 1595 (aromatic C=C), 1500, 1460, 1315 cm^{-1}; nmr (deuteriochloroform): δ 2.10 (m, 2H, CH_2), 2.88 (t, 2H, CH_2), 3.64 (t, 2H, CH_2), 3.82 (broad s, 1H, NH, exchangeable with deuterium oxide), 4.44 (s, 2H, CH_2), 6.50-7.04 (m, 7H, Ar-H); ms: m/e (% relative abundance) 236 (M^+, 100), 220 (46), 207 (27), 192 (8.2), 180 (5.1), 110 (5.6), 104 (10), 77 (12), 63 (5.1), 51 (6.7).

Anal. Calcd. for $C_{16}H_{16}N_2$: C, 81.32%; H, 6.83%; N, 11.85%. Found: C, 81.27%; H, 6.86%; N, 11.87% (by difference).

4-Methyl-*N*-[2-(1,2,3,4-tetrahydro-1-quinolinyl)phenyl]piperazinecarboxamide Maleate (**6a**).

A stirred solution, under nitrogen, of 4.50 (0.02 mole) of 1-(2-aminophenyl)-1,2,3,4-tetrahydroquinoline **2a** free base and 3.04 g (0.030 mole) of triethylamine in 50 ml of dichloromethane was cooled to 0°. Then there was added dropwise 4.70 g (0.030 mole) of phenylchloroformate at such a rate as to keep the reaction temperature below 5°. This addition took 10 minutes. The mixture was then stirred for 1 hour at ice-bath temperature, followed by 1 hour at room temperature to complete formation of the phenylcarbamate intermediate. Then there was added dropwise 8.02 g (0.080 mole) of *N*-methylpiperazine over a 5 minute period causing a 7° rise in reaction temperature. The solution was stirred for 2 hours when an additional charge of 4.01 g of *N*-methylpiperazine was made before stirring overnight. The next day, 100 ml of water was added with vigorous stirring. The layers were separated and the organic phase was washed twice with water before drying over anhydrous sodium sulfate. Concentration of the solvent *in vacuo* left 6.0 g (86%) of crude urea as an oil. This was dissolved in 100 ml of ethanol and treated with a warm solution of 2.60 g (0.022 mole) of maleic acid in 15 ml of ethanol. After several hours, the maleate salt was collected and found to weigh 6.10 g (65% overall yield) with mp 168-170° dec. and virtually pure by tlc. Recrystallization from methanol afforded 4.10 g (44% overall yield) of pure white crystals, mp 171-173° dec; ir (potassium bromide): 1710 (NCON), 1645, 1585 cm^{-1}; nmr (DMSO-d_6): δ 2.02-3.50 (4m, 14H, CH_2; 2.52 s, 3H, CH_3), 6.04 (s, 2H, CH=CH), 6.58-7.92 (m, 8H, Ar-H); ms: m/e (% relative abundance) 350 (M^+, 34), 250 (100), 223 (28), 221 (22), 180 (10), 127 (6), 70 (4).

Similarly prepared was the 6-bromo urea **6c** of Table I using **2c** as substrate. The 5-bromophenyl urea **6b** was synthesized in the same manner using **2b** as starting material, but required a chromatography for purification. Elution from silica gel first with toluene, followed by increasing percentages of dichloromethane in toluene (25% per step), and finally with 2% methanol in dichloromethane brought forth the pure urea which was then recrystallized from ether (*cf.* Table I).

7-(4-Methyl-1-piperazinyl)-2,3-dihydro-1*H*-quino[1,8-*ab*][1,5]benzodiazepine (**7a**).

A stirred mixture of 15.9 g (0.045 mole) of urea **6a** (as the free base) in 300 ml of phosphorus oxychloride was heated under nitrogen at reflux for 6 hours. The excess phosphorus oxychloride was then removed on the rotovac with mild heating. The residue was chilled in an ice-bath (with exclusion of moisture), and then treated first with 500 ml of ice-cold 2*N* sodium hydroxide solution to destroy residual acid, then with 500 ml of dichloromethane. The mixture was stirred and triturated until all the residue dissolved. The organic phase was separated, washed again with 2*N* sodium hydroxide, then twice with water, dried over anhydrous sodium sulfate, and concentrated *in vacuo* to 13.7 g (92%) of a yellow film. This was recrystallized (charcoal) twice from ethanol to afford 4.1 g of bright yellow crystals in 28% overall yield, mp 129-132°; ir (potassium bromide): 1620, 1580 (C=N and aromatic C=C), 1450 cm^{-1}; nmr (deuteriochloroform): δ 1.84-4.00 (4m, 12H, CH_2; 2.34, s, 3H, CH_3; 2.84, t, 2H, CH_2), 6.84-7.10 (m, 7H, Ar-H); ms: m/e (% relative abundance) 332 (M^+, 29), 262 (82), 249 (100), 233 (40), 205 (46), 70 (9).

The procedure described above was used to prepare the analogous 10-bromo tetracycle **7b** of Table II from urea **6b**, and the 5-bromo tetracycle **7c** from urea **6c**.

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