Novel Polycyclic Heterocycles. X. Synthesis of 3-Amino Derivatives Derived from 1,2-Dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (1)

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The reactions of the tetracyclic ketone, 1,2-dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**1**) with pyrrolidine, piperazine, *N*-methylpiperazine, and dimethylamine gave the enamines **2**, **13**, **11**, and **4**. These were reduced with sodium borohydride to the corresponding 3-amino derivatives **3**, **14**, **12**, and **5**. The 3-(2-hydroxyethylpiperazino) derivative (**8**) was obtained from the 3-chloro compound (**7**); **7** was prepared from the carbinol (**6**). The 3-NH_2 derivative (**10**) was obtained by reduction of the oxime (**9**). In **3**, **5**, **6**, **7**, **8**, **10**, **12**, and **14**, the -OCH_2 protons were non-equivalent, since in the pmr spectrum of each of these compounds there was seen a symmetrical, perturbed AB quartet, with a common J_{AB} of 12 cps, that must be attributed to geminal interproton coupling. This phenomenon had not previously been observed with **1**, **9**, or the enamines, since in their pmr spectra, the -OCH_2 protons had invariably been seen as singlets.

A number of tetracyclic ketones have been prepared by the cyclization of 5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine-5-propionic acids. Their synthesis, as well as the preparation of their oxime derivatives, have recently been reported (4). One of these ketones, 1,2-dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**1**) and its oxime (**9**) have been utilized to prepare several 3-amino derivatives by the procedures outlined in Chart I.

The formation of enamines from the tetracyclic ketone (**1**) and the relatively non-volatile amines, pyrrolidine, piperazine, and *N*-methylpiperazine, using *p*-toluenesulfonic acid as catalyst, and employing benzene or toluene to remove water azeotropically as it formed, required prolonged heating periods (Method A). With the more volatile dimethylamine, the enamine was prepared by using the titanium tetrachloride complex (5) (Method B). Reduction of these enamines with sodium borohydride-acetic acid (6), gave the respective 3-amino derivatives **3**, **14**, **12**, and **5**. The tetracyclic ketone (**1**) was reduced to the carbinol (**6**) by means of sodium borohydride; **6** with hydrogen chloride-anhydrous calcium chloride (7), gave the 3-chloro derivative **7**. Nucleophiles, like 2-piperazine ethanol, converted **7** to **8** (Method C).

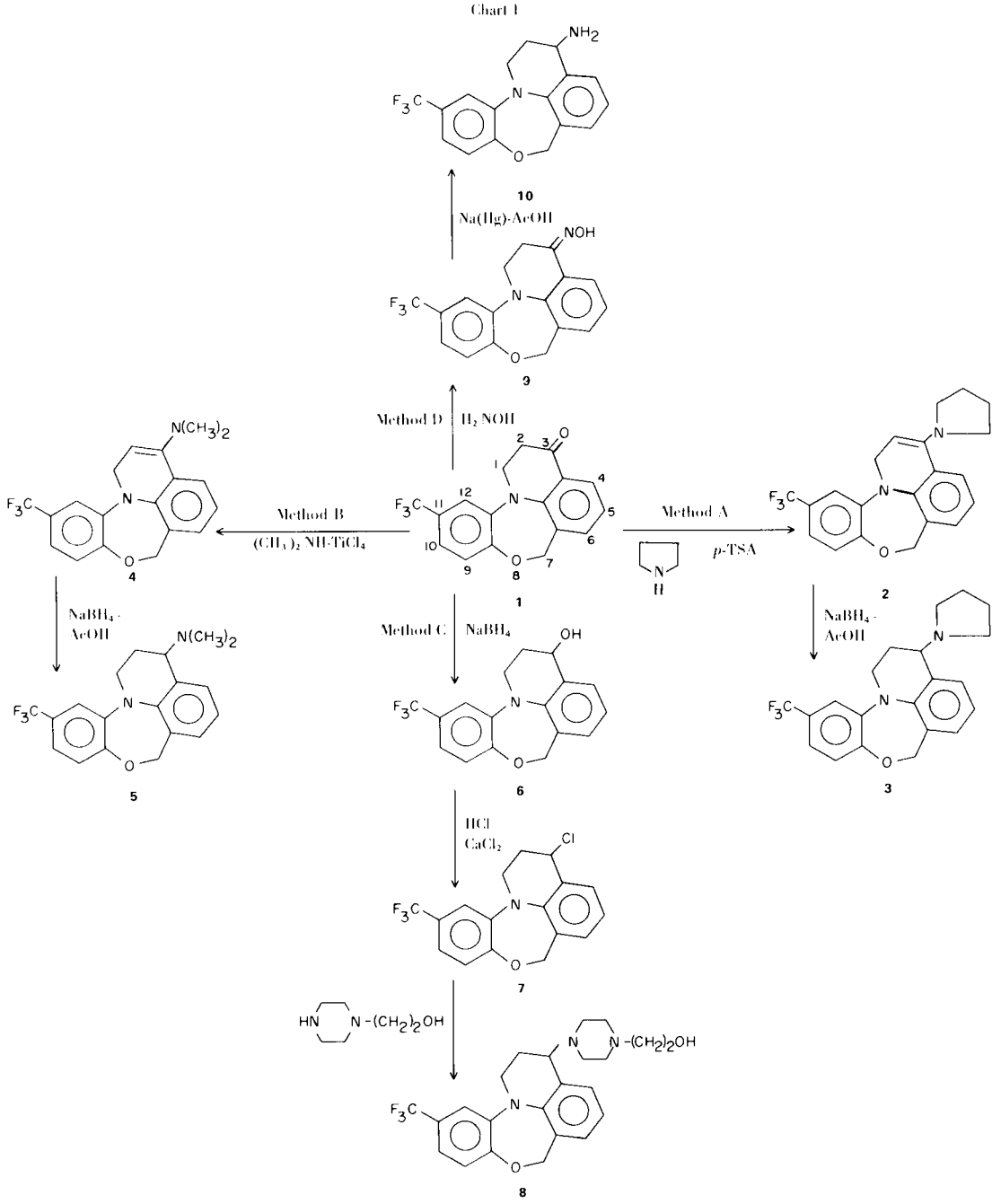
Sodium amalgam was used to convert the oxime (**9**) to the primary amine, (**10**), (Method D). Since some **9** was recovered from this reaction despite the large excess of amalgam used, an alternative route, employing Vitride (8), was investigated, but that reagent was found to be inferior to sodium amalgam in this reduction.

The *N*-methylpiperazine enamine **11** was stable on storage and was found to be unaltered, by melting point or spectroscopic comparison, even after six months. In contrast, after several weeks, the gross appearance, melting point, and spectra of the pyrrolidine enamine **2** were significantly altered.

An examination of the pmr spectra obtained from 5,11-dihydrodibenz[*b*,*e*][1,4]oxazepine and its 2-, 3-, 5-, and 7-substituted derivatives has shown that the chemical shift of the -OCH_2 protons in the parent heterocycle was essentially unaffected by substitution and the resonance invariably seen for these protons was a singlet at δ 5.25 ± 0.1 (9). The same characteristic signal was observed also with the tetracyclic ketone (**1**) and its 1,2-dehydro and oxime derivatives (4), and the enamines **2** and **11** derived from **1**. Thus, the -OCH_2 protons in each of these compounds were equivalent and were not coupled mutually or with any other protons.

An examination of the pmr spectra of the carbinol **6**, the 3-chloro **7**, and the 3-amino derivatives **3**, **5**, **8**, **10**, **12**, and **14**, revealed that, in each instance, the -OCH_2 protons were non-equivalent, and the signal for these protons was seen as a symmetrical, perturbed quartet, with a common J_{AB} of 12 cps, and a small calculated ν_{AB}/J_{AB} ratio (10).

Chart I



This phenomenon must be attributed to geminal interproton coupling. The ratio, ν_{AB}/J_{AB}, calculated for these quartets from the spectra obtained in deuteriochloroform varied from 2.96 for **7** to 0.91 for **10**. The data are summarized in Chart II.

As seen from this chart, except for **10**, the value of J_{AB} was independent of solvent, and incidentally, in the amines, independent of *N*-protonation, but the value of ν_{AB} was decreased when the solvent was deuteriodimethylsulfoxide, so that with **10**, and its protonated derivative, the quartets collapsed to singlets.

The symmetry of the quartets excluded from consideration the explanation that the phenomenon was due to interaction with protons outside the AB system, hence, it must be attributed to geminal interproton coupling of the two non-equivalent methylene protons (11). Non-equivalency of methylene protons has been observed as a consequence of the long-range effects of an asymmetric environment produced by the introduction of a chiral center in the molecule, or an unequal conformer popula-

Chart II

Data for Geminal Interproton Coupling for the Non-equivalent Protons in -OC(HA)(HB)

Cpd. No.	ν_{AB}, cps (a)	ν_{AB}, cps (b)	J_{AB}, cps (a,b)	ν_{AB}/J_{AB} (a)	ν_{AB}/J_{AB} (b)	δA (a)	δB (a)	δA (b)	δB (b)
						ppm			
7	35.5	---	12	2.96	---	5.58	4.98	---	---
6	25.5	12.0	12	2.12	1.00	5.42	4.98	5.40	5.20
3	16.0	13.7	12	1.33	1.14	5.33	5.08	5.27	4.96
3·$C_4H_4O_4$	---	10.0	12	---	0.83	---	---	5.27	5.08
5	22.0	---	12	1.83	---	5.38	5.04	---	---
5·$C_4H_4O_4$	---	18.0	12	---	1.50	---	---	5.36	5.08
5·HCl	---	18.0	12	---	1.50	---	---	5.33	5.12
8	19.0	---	12	1.58	---	5.40	5.05	---	---
8·$2C_4H_4O_4$	---	18.0	12	1.50	---	---	---	5.42	5.10
10	11.0	---	12	0.91	---	5.26	5.07	---	---
Singlet **10**	---	0	0	0	---	---	---	(5.26)	
Singlet **10**·HCl	---	0	0	0	---	---	---	(5.25)	

(a) In deuteriochloroform. (b) In DMSO-d_6.

tion (12). Either or both of these factors can be operating with the compounds described in this paper. It is evident, also, from Chart II, that the relative magnitudes of the non-equivalencies are affected by the presence of oxygen in the 3-carbinol and by chlorine in the 3-chloro derivative (13).

Another interesting observation with **10** was that in its pmr spectrum the two NH_2 protons appeared as a singlet at δ 1.60. On protonation with hydrochloric acid, a striking change in the spectrum was observed, since the NH_3^+ signal was now seen as a three-proton, broad singlet at δ 8.70.

EXPERIMENTAL

Melting points were determined in capillary tubes in a heated oil bath and are uncorrected. The pmr spectra were obtained by Dr. A. Cohen and Dr. M. Puar on a Varian A-60, in deuteriochloroform as solvent, unless otherwise specified. The chemical shifts are reported in ppm (δ) downfield from an internal TMS reference and the abbreviations employed are conventional, s(singlets), d(doublet), t(triplet), q(quartet), and m(multiplet). The ir spectra were obtained by Mrs. B. Toeplitz on a Perkin-Elmer Infracord, Model 621, on mineral oil mulls, unless specified otherwise. The ultraviolet spectra were obtained by Dr. J. Dunham on methanol solutions in a Cary Model 15. The microanalyses were carried out by Mr. J. F. Alicino and his associates.

3-(1-Pyrrolidinyl)-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepine (**2**) (Method A).

A solution of 8.6 g. (0.027 mole) of **1**, 3.8 g. (0.054 mole) of pyrrolidine, and 0.2 g. of *p*-toluenesulfonic acid, in 65 ml. of anhydrous benzene, was heated under reflux using a Dean-Stark water separator. After 4 hours, an additional 3.8 g. of pyrrolidine was added and the heating under reflux continued for an additional 15 hours. A total of 0.7 ml. of water collected during the entire heating period. The benzene solution was concentrated *in vacuo* to give 9.5 g. of crude **2**. This, 3.0 g., and 150 ml. of hexane were heated under reflux, filtered, the filtrate cooled, and the crystalline material filtered to give 0.7 g. of unreacted **1**. The filtrate was concentrated to about 50 ml. and cooled to give 1.0 g. (32% yield) of **2**, m.p. 138-141°; ir ν max no C=O absorption, 1615, 1550, 1335, 1130 cm^{-1}; pmr δ 6.69-7.62 (m, 6H, 6-aromatic *H*), 5.35 (s, 2H, OCH_2), 5.23 (t, J = 4.5 cps, 1H, olefinic *H* at position-2) (14), 4.27 (d, J = 4.5 cps, 2H, NCH_2), 2.90-3.18 (m, 4H, two α-CH_2 of pyrrolidine), 1.75-2.06 (m, 4H, two β-CH_2 of pyrrolidine).

Anal. Calcd. for $C_{21}H_{19}F_3N_2O$: C, 67.73; H, 5.14; N, 7.52; F, 15.30. Found: C, 67.49; H, 5.05; N, 7.34; F, 15.09.

2,3-Dihydro-3-(1-pyrrolidinyl)-11-(trifluoromethyl)-1*H*,7*H*-quino-[8,1-*cd*][1,5]benzoxazepine (**3**) Maleate Salt (1:1).

To a solution of 6.5 g. (0.017 mole) of crude **2** in 150 ml. of anhydrous tetrahydrofuran, under nitrogen and with stirring, was added in one portion, 5.0 g. (0.13 mole) of sodium borohydride, followed by the dropwise addition of 30 ml. of glacial acetic acid. After stirring at 40° for 2 hours, the mixture was cooled to 0°, 150 ml. of water added, the mixture was made alkaline with 20% aqueous sodium hydroxide, and extracted with two-150 ml. portions of ether. The combined ether extracts were washed, dried, treated with Darco, and filtered. To the filtrate was added a solution of 2.3 g. (0.02 mole) of maleic acid in 15 ml. of absolute ethanol. The solid that separated was filtered and air-dried to give 6.1 g. of solid, m.p. 183-185° dec. This was recrystallized from 2-propanol to give 5.5 g. (64% yield) of the maleate salt of **3**, m.p. 183-185° dec.; ir ν max 1690, 1590, 1580, 1340, 1120 cm^{-1};

pmr (DMSO-d_6) δ 6.86-7.59 (m, 6H, 6-aromatic *H*), 6.05 (s, 2H, two olefinic *H* of maleic acid), δ_A 5.27, δ_B 5.08 (q, J_{AB} = 12 cps, 2H, OCH_2).

Anal. Calcd. for $C_{21}H_{21}F_3N_2O \cdot C_4H_4O_4$: C, 61.22; H, 5.14; N, 5.72; F, 11.62. Found: C, 61.42; H, 5.14; N, 5.70; F, 11.70.

The above salt of **3**, 0.4 g. was suspended in 30 ml. of water, the solution cooled in ice water and made alkaline with 50% aqueous sodium hydroxide. The oil that separated was extracted into 2-60 ml. portions of ether, the ether extracts were washed, dried, and concentrated to give a viscous oil. This was distilled to give 0.24 g. of **3** as a yellow oil, b.p. 178-183° (0.3 mm.); ir ν max (deuteriochloroform) 2800, 1610, 1590, 1580, 1510, 1450, 1330, 1120 cm^{-1}; pmr δ 6.79-7.26 (m, 6H, 6-aromatic *H*) δ_A 5.33, δ_B 5.08 (q, J_{AB} = 12 cps, 2H, OCH_2), 3.40-4.27 (m, 3H, NCH_2 and the tertiary *H* at position-3), 2.04-2.83 (m, 6H, NCH_2CH_2 and two α-CH_2 of pyrrolidine), 1.63-2.01 (m, 4H, two β-CH_2 of pyrrolidine), (DMSO-d_6), δ_A 5.27, δ_B 4.96 (q, J_{AB} = 12 cps, 2H, OCH_2).

Anal. Calcd. for $C_{21}H_{21}F_3N_2O$: C, 67.37; H, 5.65; N, 7.48; F, 15.22; N.E. ($HClO_4$) 374. Found: C, 67.20; H, 5.73; N, 7.42; F, 15.13; N.E. 373.

3-(4-Methyl-1-piperazinyl)-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepine (**11**) (Method A).

A solution of 14.4 g. (0.045 mole) of **1**, 10.0 g. (0.1 mole) of *N*-methylpiperazine, 0.5 g. of *p*-toluenesulfonic acid and 100 ml. of anhydrous toluene was heated under a Dean-Stark trap for 5 days, an additional 10.0 g. of *N*-methylpiperazine was added and the heating continued for an additional 6 days. Workup gave 14.0 g. of crude **11**; of this, 4.0 g. was recrystallized from 170 ml. of hexane to give 2.5 g. (48% yield) of the enamine **11**, m.p. 179-181°; ir ν max no C=O absorption, 1619, 1560, 1502, 1335, 1135 cm^{-1}; uv λ max (methanol) 225, 285 mμ (ε, 39,200, 7,900); after 0.5 hour, λ max 225, 285 (ε, 35,700, 7,800); pmr δ 6.72-7.55 (m, 6*H*, 6-aromatic *H*), 5.34 (s, 2H, OCH_2), 5.37 (t, J = 4.5 cps, 1H, olefinic *H* at position-2), 4.25 (d, J = 5 cps, 2H, NCH_2), 2.50-3.08 (m, 8H, $4CH_2$ of piperazine ring), 2.40 (s, 3H, N-CH_3).

Anal. Calcd. for $C_{22}H_{22}F_3N_3O$: C, 65.82; H, 5.53; N, 10.47; F, 14.20. Found: C, 65.73; H, 5.78; N, 10.27; F, 14.03.

2,3-Dihydro-3-(4-methyl-1-piperazinyl)-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepine (**12**) Maleate Salt (1:1).

The reduction procedure used for **2** was also employed with 10.0 g. (0.025 mole) of crude **11**, 8.0 g. (0.21 mole) of sodium borohydride, 500 ml. of anhydrous tetrahydrofuran, and 50 ml. of glacial acetic acid to give 6.2 g. (40% yield) of the maleate salt, of **12**, m.p. 160-162° dec., after recrystallization from absolute ethanol; ir ν max 1695, 1620, 1550, 1338, 1130 cm^{-1}; pmr (DMSO-d_6), δ 6.81-7.65 (m, 6H, 6-aromatic *H*), 6.17 (s, 4H, olefinic *H* of maleic acid), δ_A 5.37, δ_B 5.07 (q, J_{AB} = 12 cps, 2H, OCH_2), 3.56-4.16 (m, 3H, NCH_2 and the tertiary *H* at position-3), 2.78 (s, 3H, NCH_3).

Anal. Calcd. for $C_{22}H_{24}F_3N_3O \cdot 2C_4H_4O_4$: C, 56.69; H, 5.08; N, 6.61; F, 8.98; N.E. (NaOH), 159; N.E. ($HClO_4$), 318. Found: C, 56.43; H, 5.30; N, 6.58; F, 8.74; N.E. (NaOH) 159; N.E. ($HClO_4$), 314.

2,3-Dihydro-3-(1-piperazinyl)-11-(trifluoromethyl)-1*H*,7*H*-quino-[8,1-*cd*][1,5]benzoxazepine (**14**) Maleate Salt (1:2) (Method A).

The procedure employed for **2** was used with 6.4 g. (0.02 mole) of **1**, 6.9 g. (0.08 mole) of anhydrous piperazine, 0.3 g. of *p*-toluenesulfonic acid, and 120 ml. of anhydrous toluene. The residue remaining from the concentration was heated at 70°/0.4 mm. to remove excess piperazine and gave 6.0 g., of crude enamine **13**. This was reduced by employing the procedure used for the reduction of **2** to give 3.0 g. of **14**, as a viscous oil. To this, in 15 ml. of 2-propanol, was added 2.0 g. (0.017 mole) of maleic acid in 10 ml. of 2-propanol, and the solution diluted with anhydrous ether until slightly turbid. On keeping in the cold, a solid separated. This was filtered to give 2.2 g. of colorless solid, m.p. 143-146° dec. Recrystallization from acetonitrile gave 1.1 g. (9% yield) of the maleate salt of **14**, m.p. 148-150° dec.; ir ν max 1699, 1620, 1580, 1340, 1120 cm^{-1}; pmr (DMSO-d_6) δ 6.78-7.14 (m, 6H, 6-aromatic *H*), 6.13 (s, 4H, olefinic *H* of maleic acid), δ_A 5.37, δ_B 5.04 (q, J_{AB} = 12 cps, 2H, OCH_2), 3.51-4.17 (m, 3H, NCH_2 and the tertiary *H* at position-3).

Anal. Calcd. for $C_{21}H_{22}F_3N_3O \cdot 2C_4H_4O_4$: C, 56.04; H, 4.86; N, 6.77; N.E. (NaOH), 156. Found: C, 55.92; H, 4.98; N, 6.81; N.E., 166.

3-(Dimethylamino)-2,3-dihydro-11-(trifluoromethyl)-1*H*,7*H*-quino-[8,1-*cd*][1,5]benzoxazepine (**5**) Maleate Salt (1:1) (Method B).

To 8.0 g. (0.025 mole) of **1** in 400 ml. of anhydrous ether was added 7.7 g. (0.17 mole) of dimethylamine in 50 ml. of anhydrous ether. The solution was cooled to -5°, and to it was added, dropwise, 3.2 g. (0.17 mole) of titanium tetrachloride in 30 ml. of anhydrous benzene. The mixture was kept for 3 days at room temperature, filtered, and the filtrate concentrated to dryness *in vacuo* to give 8.4 g. of crude enamine, **4**. The **4**, 300 ml. of tetrahydrofuran, 5.0 g. (0.13 mole) of sodium borohydride and 35 ml. of glacial acetic acid were reacted as described above for **2** to give 8.1 g. of crude **5**, as a viscous oil. This was dissolved in 100 ml. of boiling acetonitrile and to this solution was added a boiling solution of 3.0 g. (0.025 mole) of maleic acid in 50 ml. of acetonitrile. The crystalline product that separated on cooling was filtered to give 3.2 g. of solid, m.p. 190-192° dec. Concentration of the filtrate gave 2.9 g. of solid, m.p. 184-187° dec. The combined solids were recrystallized from a mixture of 2-propanol-absolute ethanol (2:1) to give 4.3 g. (37% yield) of the maleate salt of **5**, m.p. 190-192° dec.; ir ν max 1685, 1615, 1560, 1410, 1335, 1100 cm^{-1}; pmr (DMSO-d_6) δ 6.87-7.68 (m, 6H, 6-aromatic *H*), 6.08 (s, 2H, olefinic *H* of maleic acid), δ_A 5.36, δ_B 5.08 (q, J_{AB} = 12 cps, 2H, OCH_2), 4.58-4.90 (m, 1H, tertiary *H* at position-3), 2.68 [s, 6H, $N(CH_3)_2$].

Anal. Calcd. for $C_{19}H_{19}F_3N_2O \cdot C_4H_4O_4$: C, 59.47; H, 5.00; N, 6.03; F, 12.27; N.E. (NaOH), 232; N.E. ($HClO_4$), 465. Found: C, 59.65; H, 5.05; N, 5.88; F, 12.02; N.E. (NaOH), 232; N.E. ($HClO_4$), 467.

The maleate salt of **5**, 0.3 g., was suspended in 30 ml. of water, the solution was made alkaline with 50% aqueous sodium hydroxide and the base was extracted into two-60 ml. portions of ether. The extracts were washed, dried, and concentrated. The residual solid was recrystallized from hexane to give 0.2 g. of **5**, m.p. 125-127°; ir ν max 1610, 1590, 1580, 1505, 1455, 1325 cm^{-1}; pmr δ 6.77-7.36 (m, 6H, 6-aromatic *H*), δ_A 5.38, δ_B 5.04 (q, J_{AB} = 12 cps, 2H, OCH_2), 3.51-4.00 (m, 3H, NCH_2 and the tertiary *H* at position-3), 1.97-2.51 (m, 2H, NCH_2CH_2), 2.3 [s, 6H, $N(CH_3)_2$].

Anal. Calcd. for $C_{19}H_{19}F_3N_2O$: C, 65.50; H, 5.50; N, 8.04; F, 16.36; N.E. ($HClO_4$), 348. Found: C, 65.72; H, 5.50; N, 8.33; F, 16.36; N.E., 346.

The base, 0.06 g., was dissolved in 15 ml. of anhydrous ether and the solution was treated with 1.0 ml. of 3.24 *N* ethereal-hydrogen chloride to give 0.05 g. of the hydrochloride of **5**, m.p. 206-209° dec.; pmr (DMSO-d_6), δ 6.90-8.28 (m, 6H, 6-aromatic *H*), δ_A 5.33, δ_B 5.12 (q, J_{AB} = 12 cps, 2H, OCH_2), 4.75-5.10 (m, 1H, tertiary H at position-3), 3.6-4.4 (m, 2H, NCH_2), 3.39

[s, 6H, $N(CH_3)_2$], 2.73-3.10 (m, 2H, NCH_2CH_2).

Anal. Calcd. for $C_{19}H_{19}F_3N_2O \cdot HCl$: N.E. ($HClO_4$), 385. Found: N.E., 376.

2,3-Dihydro-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-ol (**6**).

To 9.6 g. (0.03 mole) of **1** in 200 ml. of dioxane at 10° was added, in 3 minutes, a cooled solution of 1.2 g. (0.031 mole) of sodium borohydride in a mixture of 45 ml. of water and 15 ml. of dioxane. The mixture was stirred for 1 hour at room temperature, heated to 60-65° for several minutes, cooled to 10°, and diluted with 1 l. of 2% aqueous hydrochloric acid. The solid that separated was filtered and dried to give 9.3 g. of crude **6**; recrystallization from benzene-cyclohexane (1:3) gave 8.6 g. (89% yield) of **6**, m.p. 127-129°; ir ν max 3340-3250 (OH), 1602, 1540, 1500, 1450, 1330, 1100 cm^{-1}; pmr δ 6.8-7.5 (m, 6H, 6-aromatic *H*) no quartet at δ 8.00 as is characteristically observed with **1** (4), 3.65-3.90 (m, 2H, $-NCH_2$), 2.01-2.35 (m, 2H, $-NCH_2CH_2$), 4.81 [t, J = 3.5 cps, 1H, CH(OH)] (15), δ_A 5.42, δ_B 4.98 (q, J_{AB} = 12 cps, 2H, OCH_2), 1.85 [s, 1H, CH(O*H*), equilibrates in deuterium oxide]; pmr (DMSO-d_6) 6.85-7.65 (m, 6H, 6-aromatic H), 3.55-3.90 (m, 2H, $-NCH_2$), 1.90-2.30 (m, 2H, NCH_2CH_2), 4.82 [t, J = 3.5 cps, 1H, CH(OH)], δ_A 5.4, δ_B 5.2 (q, J_{AB} = 12 cps, 2H, OCH_2), 5.41 [s, 1H, CH(O*H*), equilibrates in deuterium oxide].

Anal. Calcd. for $C_{17}H_{14}F_3NO_2$: C, 63.54; H, 4.40; N, 4.36; F, 17.74. Found: C, 63.37; H, 4.62; N, 4.22; F, 17.41.

3-Chloro-2,3-dihydro-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*]-[1,5]benzoxazepine (**7**).

Into a stirred suspension of 6.0 g. (0.19 mole) of crude **6**, 100 ml. of anhydrous benzene, and 4.0 g. (0.036 mole) of anhydrous powdered calcium chloride, was passed a slow stream of hydrogen chloride for 1.5 hours, and the mixture then kept 18 hours at room temperature. The insoluble material was removed by filtration and the filtrate was concentrated to dryness *in vacuo* to give 5.9 g. of solid, m.p. 115-118°. Recrystallization from petroleum ether-absolute ethanol (20:1) gave 4.6 g. (73% yield) of **7**, m.p. 122-124° dec.; ir ν max 1613, 1595, 1580, 1330, 1110 cm^{-1}; pmr δ 6.84-7.54 (m, 6H, 6-aromatic *H*), 3.85-4.15 (m, 2H, NCH_2), 2.35-2.65 (m, 2H, NCH_2CH_2), 5.36 [t, J = 3.5 cps, 1H, CHCl], δ_A 5.58, δ_B 4.98 (J_{AB} = 12 cps, 2H, OCH_2).

Anal. Calcd. for $C_{17}H_{13}ClF_3NO$: C, 60.09; H, 3.86; N, 4.12; Cl, 10.44; F, 16.78. Found: C, 60.06; H, 4.08; N, 4.00; Cl, 10.24; F, 16.87.

2,3-Dihydro-3-[4-(2-hydroxyethyl)-1-piperazinyl]-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepine (**8**) Maleate Salt (1:2) (Method C).

To a solution of 4.1 g. (0.012 mole) of crude **7** in 30 ml. of chloroform was added a solution of 3.3 g. (0.025 mole) of 1-(2-hydroxyethyl)piperazine in 30 ml. of chloroform and the mixture heated under reflux for 7 hours. The mixture was concentrated to dryness *in vacuo* and the residue distributed between 200 ml. of water and 100 ml. of benzene. The benzene layer was separated, the water layer was reextracted with two-50 ml. portions of benzene and the combined benzene solutions were extracted with two-100 ml. portions of 5% aqueous hydrochloric acid. The acid extracts were cooled, treated with an excess of 20% aqueous sodium hydroxide, and the base extracted with two-50 ml. portions of benzene. The combined benzene extracts were washed, dried, filtered, and concentrated *in vacuo* to give 2.5 g. of a low-melting solid. This, in 15 ml. of boiling absolute ethanol, and 1.8 g. (0.015 mole) of maleic acid in 10 ml. of boiling absolute ethanol, were mixed rapidly and then allowed to cool to give 3.4 g. of solid, m.p. 147-154° dec. Recrystallization from acetonitrile gave 2.5 g. (31% yield) of the maleate salt of **8**, m.p. 161-163° dec.; ir ν max 3490, 1690, 1620, 1452, 1340, 1100 cm^{-1}; pmr (DMSO-d_6) δ 6.84-7.71 (m, 6H, 6-aromatic *H*), 6.16 (s, 4H, olefinic *H* of maleic acid), δ_A 5.42, δ_B 5.10 (q, J_{AB} = 12 cps, 2H, OCH_2).

Anal. Calcd. for $C_{23}H_{26}F_3N_3O_2 \cdot 2C_4H_4O_4$: C, 55.93; H, 5.15; N, 6.32; F, 8.56; N.E. (NaOH), 166; N.E. ($HClO_4$), 332. Found: C, 55.56; H, 5.09; N, 6.17; F, 8.37; N.E., 169; N.E., 323.

From the preceding maleate salt, 0.2 g., there was obtained 0.08 g. of crystalline **8**, m.p. 53-56°, after recrystallization from hexane; ir (potassium bromide) ν max 3410, 1610, 1590, 1508, 1505, 1320, 1110 cm^{-1}; pmr δ 6.81-7.75 (m, 6H, 6-aromatic *H*), δ_A 5.40, δ_B 5.05 (q, J_{AB} = 12 cps, 2H, OCH_2), 4.14 (s, 1H, O*H*, equilibrates in deuterium oxide), 3.22-4.41 (m, 7H), 2.01-2.80 (m, 8H), 0.82-1.60 (m, 2H).

Anal. Calcd. for $C_{23}H_{26}F_3N_3O_2$: C, 63.72; H, 6.05; N, 9.70. Found: C, 63.44; H, 5.78; N, 9.47.

3-Amino-2,3-dihydro-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*]-[1,5]benzoxazepine (**10**) Hydrochloride Salt (1:1) (Method D).

To a suspension of 4.0 g. (0.012 mole) of the oxime of **1**, **9** (4), in 280 ml. of warm absolute ethanol, with stirring, was added four separate portions of 15.5 g. of 5% sodium amalgam. During this period, a total of 3.8 g. of glacial acetic acid was added dropwise. The mixture was subsequently stirred for 1 hour at room temperature and then diluted with 200 ml. of water. The aqueous ethanolic phase was separated from the mercury and extracted with two-250 ml. portions of ether. The ether extracts were combined, washed, dried, filtered, and the filtrate concentrated to dryness *in vacuo*. The residue, 3.8 g., was dissolved in 30 ml. of benzene, then diluted with hexane to turbidity, and cooled to give 1.5 g. of unreacted **9**. The filtrate was again concentrated to dryness *in vacuo* and the residue recrystallized from hexane to give 1.4 g. (36% yield) of **10**, m.p. 73-75°; ir ν max 3380 (w) (NH_2), 1602, 1550, 1455, 1325, 1120, 1105 cm^{-1}; pmr δ 6.91-7.51 (m, 6H, aromatic *H*), δ_A 5.26, δ_B 5.07 (q, J_{AB} = 12 cps, 2H, OCH_2), 4.10 [t, J = 12 cps, $CH(NH_2)$] (16), 3.78 (t, J = 11 cps, 2H, $N\text{-}CH_2$), 1.94-2.38 (m, 2H, NCH_2CH_2) 1.60 (s, 2H, $CH(NH_2)$); pmr δ (DMSO-d_6) 6.81-7.70 (m, 6H, aromatic *H*), 5.26 (s, 2H, OCH_2), 3.94 (unresolved t, 1H, $CH(NH_2)$), 3.73 (t, J = 11 cps, 2H, $N\text{-}CH_2$), 2.70-3.40 [broad s, 2H, $CH(NH_2)$], 1.7-2.35 (m, 2H, NCH_2CH_2).

Anal. Calcd. for $C_{17}H_{15}F_3N_2O$: C, 63.73; H, 4.73; N, 8.75; F, 17.80. Found: C, 63.51; H, 4.85; N, 8.60; F, 18.05.

To **10**, 1.3 g., in 75 ml. of anhydrous ether was added 15 ml. of 3.24 *N* ethereal hydrogen chloride. The solid that separated, when filtered and dried, melted at 225-231° dec. Recrystallization from 2-propanol gave 1.3 g. (90% yield) of the hydrochloride of **10**, m.p. 229-231° dec.; ir ν max 3560, 3380, (w), 1605, 1585, 1505, 1458, 1415, 1340, 1090 cm^{-1}; pmr (DMSO-d_6) δ 6.88-7.85 (m, 6H, 6-aromatic *H*), 5.25 (s, 2H, OCH_2), 4.40-4.75 [m, 1H, $CH(NH_3)^+$], 3.73-3.98 (m, 2H, NCH_2), 1.95-2.41 (m, 2H, NCH_2CH_2), δ 8.7 (broad s, 3H, NH_3).

Anal. Calcd. for $C_{17}H_{15}F_3N_2O \cdot HCl$: C, 57.22; H, 4.52; N, 7.88; Cl, 9.94; F, 15.98; N.E. (NaOH), 357. Found: C, 57.06; H, 4.45; N, 7.59; Cl, 9.83; F, 16.29; N.E., 357.

When the reduction of **9** was carried out with Vitride, the yield of **10** was 17%.

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(10) The notation employed here is that of L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press, Elmsford, N. Y., 2nd Ed. 1969, pp. 129-130, for a two-spin system. The difference between the chemical shifts in cps (ν_{AB}) for the non-equivalent $-OC-\overset{HA}{\underset{HB}{<}}$ protons was derived from the equation $\nu_{AB} = \sqrt{(1\text{-}4)(2\text{-}3)}$, and the actual values of ν_A and ν_B could then be obtained by adding or subtracting, respectively, $\nu_{AB}/2$ from the center of the AB quartet. The ν_A and ν_B were then converted to ppm and these values listed as δ_A and δ_B for the compounds in Chart II and in the Experimental.

(11) See Reference (10), pp. 129-130.

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