Novel Polycyclic Heterocycles. XIII. Derivatives of the Oxime and Carbinol 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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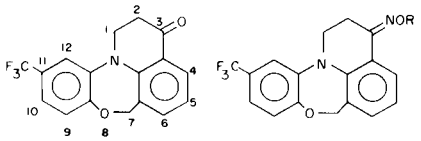
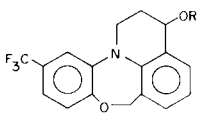
The anions derived from the oxime, **2**, and the carbinol, **3**, generated by reaction with sodium hydride, were reacted with aminoalkyl chlorides and an aroyl chloride to give a number of aminoalkyl ethers and an aroyl ester. In addition, **2** and **3** were reacted with phenylisocyanate to yield *O*-phenylcarbamoyl derivatives. The pmr spectra of several of these compounds are discussed.

Earlier papers have described the synthesis of the tetracyclic ketone, **1**, and the 3-oxime, **2**, and the 3-carbinol, **2**, derived from **1** (4a,b). In the present investigation, **2** and **3** served as substrates for the preparation of a number of aminoalkyl ethers, an ester, and several carbamates.



1

2, R = H
3, R = Na
4, R = $(CH_3)_2N(CH_2)_2$
5, R = $(CH_3)_2NCH(CH_3)CH_2$
6, R = $HO(CH_2)_2$N(piperazine)$(CH_2)_3$
7, R = $Cl(CH_2)_3$
8, R = $CH_3NH(CH_2)_2$
9, R = $CH_3(C_6H_5CH_2)N(CH_2)_2$
10, R = $CH_3(C_2H_5O_2C)N(CH_2)_2$

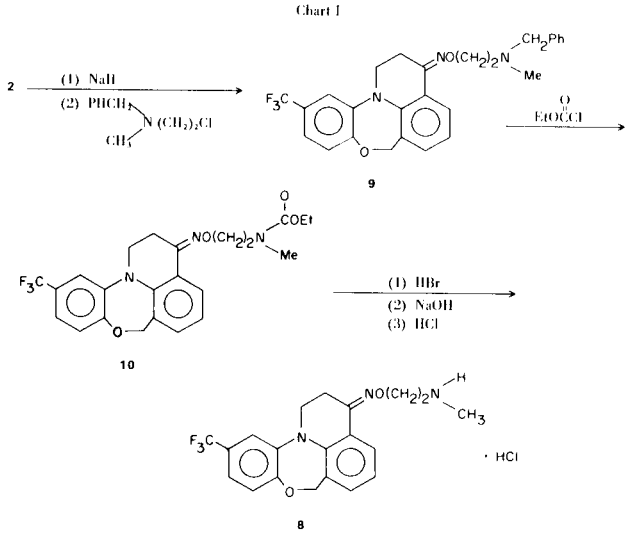


3, R = H
3a, R = Na

In a typical alkylation, the anion, **2a**, formed by reaction of **2** with sodium hydride in toluene, was treated with 2-(dimethylamino)ethyl chloride to give **4**. Since in earlier work, two isomeric *N*-alkylated derivatives were obtained when 2-(dimethylamino)propyl chloride was the alkylating agent (5), it was of interest that in these *O*-alkylations, only one of the two possible isomeric ethers, **5**, was obtained.

An alternative procedure was necessary to prepare the 3-[4-(2-hydroxyethyl)-1-(piperazine)]propyl ether, **6**, since in this instance, the preformed 3-[2-(2-hydroxyethyl)-1-(piperazine)]propyl chloride, while it can be prepared in low yield, is not stable under reaction conditions (6). The method employed involved the reaction of **2a** with 1-bromo-3-chloropropane to give the 3-(chloropropyl)ether, **7**, followed by the displacement of the 3-chloro substituent by nitrogen at position 4 of 2-(1-piperazine)ethanol. An indirect procedure, outlined in Chart I, was also required to

Chart I

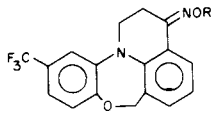
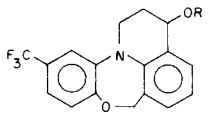


give the 2-(methylamino)ethyl ether, **8**, *via* **9** and **10** (7). These derivatives were characterized as their bases and/or their crystalline hydrochlorides, maleates, or oxalates. Their ir and pmr spectra are given for several typical products in the Experimental, but are discussed in detail with **4** and **5**. In all instances, interpretations of these spectra confirmed the assigned structures.

The aminoalkyl ethers of the carbinol, **3**, were prepared from the anion, **3a**. These derivatives were, again, characterized as their oxalate or maleate salts. The hydrochlorides of these ethers were unstable and underwent a cleavage of the oxygen-carbon linkage at position 3 during storage.

3,4,5-Trimethoxybenzoyl chloride and **2a** gave the ester, **11**; phenylisocyanate reacted with either **2** or **3**, in pyridine, to give the carbamates, **12** and **13**, respectively.

Derivatives of the Oxime and Carbinol

R	Recrystn. Solvent	Yield, %	M.p., °C.	Molecular Formula	Analyses Calcd. C	H	N	F	Found C	H	N	F
												
$(CH_3)_2N(CH_2)_2$	2-PrOH	66	218-219 (dec.)	$C_{21}H_{22}F_3N_3O_2 \cdot HCl$	57.07	5.25	9.51	12.90	56.79	5.55	9.68	12.67
"	Hexane	76 (a)	98-100	$C_{21}H_{22}F_3N_3O_2$	62.21	5.47	10.37	14.06	62.47	5.46	10.46	13.95
$(CH_3)_2N(CH_2)_3$	2-PrOH	78	203-204 (dec.)	$C_{22}H_{24}F_3N_3O_2 \cdot HCl$	57.95	5.53	9.22	12.50	58.10	5.26	9.11	12.67
"	Hexane	82 (a)	94-96	$C_{22}H_{24}F_3N_3O_2$	63.00	5.77	10.02	13.59	63.20	6.02	9.97	13.97
$(CH_3)_2NCH(CH_3)CH_2$	EtOAc	55	106-108	$C_{22}H_{24}F_3N_3O_2 \cdot (CO_2H)_2$	56.58	5.15	8.25	11.19	56.46	5.30	8.51	10.91
"	--	--	($b_{0.3}$ 190-200°)	$C_{22}H_{24}F_3N_3O_2$	62.99	5.77	10.02	13.59	62.73	5.66	9.78	13.78
$C_6H_5CH_2(CH_3)N(CH_2)_2$	EtOAc	64	184-186 (dec.)	$C_{27}H_{26}F_3N_3O_2 \cdot HCl$	62.50	5.25	8.11	--	62.24	5.33	8.04	--
$C_2H_5O_2C(CH_3)N(CH_2)_2$	Hexane	85	106-108	$C_{23}H_{24}F_3N_3O_4$	59.60	5.22	9.07	12.30	59.49	5.40	8.91	12.10
$CH_3NH(CH_2)_2$	MeCN	42	231-232 (dec.)	$C_{20}H_{20}F_3N_3O_2 \cdot HCl$	56.14	4.95	9.82	13.32	56.12	5.02	9.70	13.44
	2-PrOH	86	213-215 (dec.)	$C_{23}H_{24}F_3N_3O_2 \cdot HCl$	59.03	5.38	8.98	12.18	58.74	5.32	8.71	12.35
"	Hexane	79 (a)	117-119	$C_{23}H_{24}F_3N_3O_2$	64.02	5.61	9.74	13.21	64.27	5.83	9.62	13.07
	2-PrOH	75	208-210 (dec.)	$C_{24}H_{26}F_3O_2 \cdot HCl$	59.80	5.65	8.72	11.83	59.92	5.87	8.42	11.69
"	Hexane	83 (a)	85-87	$C_{24}H_{26}F_3N_3O_2$	64.70	5.59	9.43	12.80	64.86	5.79	9.17	13.04
	2-PrOH	90	198-200 (dec.)	$C_{25}H_{28}F_3N_3O_2 \cdot HCl$	60.53	5.89	8.47	11.50	60.24	5.97	8.38	11.76
	2-PrOH	81	208-210 (dec.)	$C_{23}H_{24}F_3N_3O_3 \cdot HCl$	57.08	5.21	8.68	11.77	56.90	5.16	8.92	11.56
"	Hexane	78 (a)	110-112	$C_{23}H_{24}F_3N_3O_3$	61.73	5.41	9.39	12.74	62.02	5.55	9.39	12.86
	EtOH	70	240-242 (dec.)	$C_{24}H_{27}F_3N_4O_2 \cdot 2HCl \cdot H_2O$	52.27	5.67	10.16	--	52.17	5.68	10.09	--
			238-241 (dec.)	$C_{24}H_{27}F_3N_4O_2 \cdot 2HCl$	54.04	5.48	10.50	--	53.96	5.63	10.36	--
	EtOH	83	235-237 (dec.)	$C_{25}H_{29}F_3N_4O_2 \cdot 2HCl$	54.95	5.72	10.25	10.44	54.71	5.92	10.02	10.37
	MeCN		174-176 (dec.)	$C_{26}H_{31}F_3N_4O_3 \cdot (C_4H_4O_4)_2$	55.43	5.34	7.61	7.74	55.60	5.58	7.58	7.60
$3,4,5\text{-}(CH_3O)_3C_6H_2CO$	C_6H_6	70	218-220	$C_{27}H_{23}F_3N_2O_6$	61.36	4.39	5.31	10.78	61.50	4.66	5.22	10.54
C_6H_5NHCO	C_6H_6	58	216-218 (dec.)	$C_{24}H_{18}F_3N_3O_3$	63.57	4.00	9.27	12.57	63.68	4.23	9.38	12.73
												
$(CH_3)_2N(CH_2)_2$	MeCOEt	27	140-143 (dec.)	$C_{21}H_{23}F_3N_2O_2 \cdot (CO_2H)_2$	57.25	5.23	5.81	11.81	57.08	5.17	5.99	11.49
$(CH_3)_2N(CH_2)_3$	MeCOEt	67	111-113	$C_{22}H_{25}F_3N_2O_2 \cdot (CO_2H)_2$	58.06	5.49	5.65	11.49	58.14	5.61	5.70	11.72
	EtOH	66	170-172	$C_{25}H_{30}F_3N_3O_2 \cdot (C_4H_4O_4)_2$	57.14	5.52	6.06	8.22	57.00	5.51	6.33	8.37
C_6H_5NHCO	EtOH	56	178-180	$C_{24}H_{19}F_3N_2O_3$	65.46	4.35	6.37	12.95	65.55	4.63	6.25	13.00

(a) The *base* was recovered from the recrystallized *salt* and the yield was based on the quantity of *salt* employed.

Chart II

Analysis of PMR Spectra of **4** and **4a**

Protons	Chemical Shifts in deuteriochloroform, δ	Chemical Shifts in deuteriochloroform, δ
	4	**4a** (HCl salt)
$(CH_3)_2N$	2.13 (s)	2.90 (d, J = 2.5 Hz)
$(CH_3)_2NCH_2$	2.53 (t, J = 6 Hz)	3.27-3.62 (m)
CH_2 at position 2	2.76-3.11 (m)	3.13 (t, J = 6 Hz)
CH_2 at position 1	3.55-3.89 (m)	3.88 (t, J = 6 Hz)
$(CH_3)_2NCH_2CH_2$	4.17 (t, J = 6 Hz)	4.52-4.72 (m)
CH_2 at position 7	5.08 (s)	5.19 (s)
Ar-*H* at positions 5 and 6	6.58-6.89 (m)	6.80-7.00 (m)
Ar-*H* at positions 9, 10 and 12	6.89-7.18 (m)	7.00-7.40 (m)
Ar-*H* at position 4	7.86 (q, J = 2, 8Hz)	7.88 (q, J = 2, 8Hz)

The physical properties, recrystallization solvents, yields, and analytical data for all the compounds are summarized in Table I. Typical alkylation procedures and alternative procedures are described in detail in the Experimental.

Proton Magnetic Resonance Spectra

Chemical shift assignments in the pmr spectra of **4** and **4**·HCl, in deuterochloroform solution, should serve as a typical analysis of the aminoalkyl ethers described in this paper. The data are summarized in Chart II. With but one exception, the protonation of the tertiary amino group in **4a** produced significant downfield shifts for all of the signals seen in the pmr spectrum of **4**; the exception was the signal due to the proton at position 4, already moved far downfield by the deshielding influence of the C:N linkage at position 3.

EXPERIMENTAL

The ir spectra were obtained on mineral oil mulls, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were determined by Dr. M. Puar on deuteriochloroform or DMSO-d_6 solutions employing a Perkin-Elmer R12B spectrophotometer. The microanalyses were performed by Mr. J. F. Alicino and his associates. The melting point determinations were made in capillary tubes, in an electrically heated oil bath, and are not corrected.

1,2-Dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-one, [2-(Dimethylamino)ethyl]oxime (4) and its Hydrochloride (**4a**).

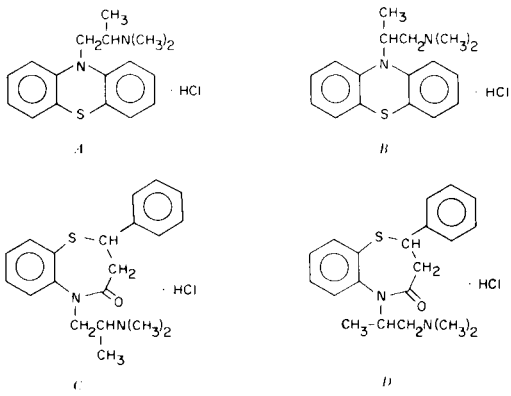
To a suspension of 8.35 g. (0.25 mole) of **2** in 120 ml. of anhydrous toluene was added 1.30 g. (0.026 mole) of sodium hydride (50% mineral oil dispersion), and the mixture stirred and heated for 1 hour under reflux, in a nitrogen atmosphere. The mixture was cooled, 5.40 g. of 2-(dimethylamino)ethyl chloride in 20 ml. of anhydrous toluene was added, and the heating and stirring under reflux was continued for three hours. The usual workup gave 10.6 g. of crude **4**, as a viscous oil. This material, dissolved in 100 ml. of 2-propanol, was treated with 12.0 ml. of 3.24 *N* ethereal hydrogen chloride to give 9.6 g. of crude **4a**, m.p. 212-214° dec. Recrystallization from 300 ml. of 2-propanol gave 7.30 g. of **4a**, m.p. 218-219° dec; ir (mull): ν 2560 (m) 2510 (m), 2460 (s), 2450 (s), 1615 (s), 1600 (w), 1580 (w), 1503 (s), 1470 (m), 1455 (s), 1420 (s), 1415 (m) cm^{-1}; pmr (deuteriochloroform): δ 2.90 [d, 2.5 Hz, 6H, $N(CH_3)_2$], 3.13 [t, (J = 6 Hz), 2H, CH_2 at position 2], 3.27-3.62 [m, 2H, $CH_2N(CH_3)_2$], 3.88 [t, (J = 6 Hz), 2H, CH_2 at position 1], 4.52-4.72 [m, 2H, $(CH_3)_2NCH_2CH_2$], 5.19 (s, 2H, CH_2 at position 7), 6.80-7.00 (m, 2H, 2 Ar-*H* at positions 5 and 6), 7.00-7.40 (m. 3H, 3 Ar-*H* at positions 9, 10, and 12), 7.88 [q (J = 2, 8 Hz), 1H, *H* at position 4].

Recrystallized **4a** (0.50 g.) was added slowly to a stirred mixture of 25 ml. of ether and 0.50 g. of sodium bicarbonate in 10 ml. of water. The ether layer was separated, washed, dried, and concentrated to give a residual solid; this was recrystallized from hexane to give 0.35 g. of **4**, m.p. 98-100°; ir (mull): ν 1615 (m), 1605 (m), 1580 (m), 1510 (m), 1505 (m), 1475 (m), 1445 (s), 1420 (s), 1410 (s), 1370 (m) cm^{-1}; pmr (deuteriochloroform): δ 2.13 [s, 6H, $N(CH_3)_2$], 2.53 [t (J = 6 Hz), 2H $CH_2N(CH_3)_2$], 2.76-3.11 (m, 2H, CH_2 at position 2), 3.55-3.89 (m, 2H, CH_2 at position 1), 4.17 [t (J = 6 Hz), 2H, $(CH_3)_2NCH_2CH_2$], 5.08 (s, 2H, CH_2 at position 7), 6.58-6.89 (m, 2H, 2 Ar-*H* at positions 5 and 6), 6.89-7.18 (m, 3H, 3 Ar-*H* at positions 9, 10, and 12), 7.86 [q (J = 2, 8 Hz), 1H *H* at position 4].

1,2-Dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-one, [2-(Dimethylamino)propyl]oxime (**5**), and its Oxalic Acid Salt (**5a**).

The procedure employed to prepare **4** was followed. From 5.35 g. (0.016 mole) of **2**, 100 ml. of anhydrous toluene, 1.10 g. (0.023 mole) of sodium hydride (50%), and 9.80 g. (0.80 mole) of 2-(dimethylamino)propyl chloride in 30 ml. of anhydrous toluene, was obtained 7.80 g. of crude **5**, as a viscous yellow oil. To the crude **5**, 7.30 g., in 200 ml. of anhydrous ether was added 2.0 g. (0.022 mole) of oxalic acid in 5.0 ml. of 2-propanol; a solid separated immediately. The solid was filtered and dried to give 8.20 g. of crude **5a**, m.p. 80-90°. One recrystallization from 300 ml. of ethyl acetate gave 6.0 g. of material, m.p. 105-106° dec., a second recrystallization from 100 ml. of ethyl acetate gave 4.5 g. of **5a**. m.p. 106-108° dec.; ir (mull): 1770-1700 (s, broad), 1695 (s), 1610 (s), 1580 (s), 1505 (s), 1445 (s), 1420 (s), 1370 (s) cm^{-1}; pmr (DMSO-d_6): δ 1.33 [d, (J = 7 Hz), 3H, $(CH_3)_2NCH(CH_3)CH_2$], 2.75 [s, 6H, $(CH_3)_2N$], 2.90-3.50 [m, 3H, CH_2 at position 2 plus $(CH_3)_2NCH(CH_3)$], 3.50-4.10 (m, 2H, CH_2 at position 1), 4.30-4.50 [m, 2H, $(CH_3)_2NCH(CH_3)CH_2$], 5.26 (s, 2H, CH_2 at position 7), 6.92-7.52 (m, 5H, 5 Ar-*H* at positions 5, 6, 9, 10, and 12), 7.76-8.05 (m, 1H, *H* at position 4).

The structure assignment for **5a** was based on a comparison of its pmr spectrum with that of phenergan, *A*, isophenergan, *B* (δ), *C* and *D* (9). In the pmr spectra of *A* and *C*, two compounds that possessed the $(CH_3)_2NCH(CH_3)CH_2$ side chain, the protons of the



methyl group at position 2 were seen as a *3-proton doublet* at δ 1.40 (J = 6 Hz) whereas in *B* and *D*, the *3-proton multiplet* was seen at δ 1.60-1.90. In **5a**, the *3-proton doublet* resonated at δ 1.33 (J = 7 Hz), thus suggesting that the structure assigned to **5a** was correct (10).

The ethyl acetate filtrates from the two recrystallizations that gave **5a** were concentrated to dryness, *in vacuo*. The residual solid, 1.2 g., yielded 0.7 g. of an oily base, and, the latter, again converted to its oxalate salt, and recrystallized from acetone-ether, gave 0.3 g. of solid, m.p. 93-97°. Although the melting point was lower than that given above for **5a**, this material gave good elemental analyses.

Anal. Calcd. for $C_{24}H_{26}F_3N_3O_6$: C, 56.58; H, 5.15; N, 8.25. Found: C, 56.34; H, 5.40; N, 7.97.

However, the pmr spectrum of this material in DMSO-d_6 was identical with that of **5a**, above, and, significantly, showed the doublet at δ 1.33. This signal integrated for 3 protons using the singlet of the CH_2 group at position 7 as the reference integration. Thus, the two products, m.p. 106-108° and 93-97° must be considered different crystalline forms of **5a**.

When twice recrystallized **5a**, m.p. 106-108°, 0.50 g., was treated with ether and aqueous sodium bicarbonate and the reaction mixture was worked up as described for **4**, the product was isolated as an oil. Distillation gave 0.30 g. of **5**, b.p. 190-200° (0.3 mm.); pmr (deuteriochloroform): δ 1.12, 1.24 [two overlapping identical doublets (J = 7 Hz), 3H $(CH_3)_2NCH(CH_3)CH_2$], 2.32 [d, (J = 3 Hz), 6H, $(CH_3)_2N$], 2.44-2.72 [m, 1H, $(CH_3)_2NCH(CH_3)$], 2.72-3.26 (m, 2H, CH_2 at position 2), 3.63-4.00 (m, 2H, CH_2 at position 1), 4.09-4.37 [m, 2H, $(CH_3)_2NCH(CH_3)CH_2$)], 5.19 (s, 2H, CH_2 at position 7), 6.75-7.03 (m, 2H, 2 Ar-*H* at positions 5 and 6), 7.03-7.36 (m, 3H, 3 Ar-*H* at positions 9, 10, and 12), 7.89-8.11 (m, 1H, Ar-*H* at position 4).

1,2-Dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one, [2-(Methylamino)ethyl]oxime, Hydrochloride (8).

a. 1,2-Dihydro-11-(trifluoromethyl-3*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-one, [2-(*N*-Benzyl-*N*-methylamino)ethyl]oxime, Hydrochloride (**9**).

The procedure described for **4** was followed, using 8.02 g. (0.024 mole) of **2**, 1.65 g. (0.033 mole) of sodium hydride (50%) and 48.0 ml. (0.048 mole) of a 1.0 *M* solution of *N*-(2-chloroethyl)-*N*-methylbenzylamine in toluene. The yield of **9**, m.p. 184-186°, was 8.0 g.; ir (mull): 2620-2440 (m, broad), 1660 (m), 1605 (s), 1585 (s), 1510 (s), 1465 (s), 1450 (s) cm^{-1}; pmr (deuteriochloroform): δ 2.90 [d (J = 2.5 Hz), 3H, NCH_3] 2.97 3.79 (m, 4H, $NOCH_2CH_2$), 3.97 [t (J = 6 Hz), 2H, CH_2 at position 2], 4.43 [d (J = 5 Hz), 2H, $PhCH_2$), 4.85 [t (J = 6 Hz), 2H, CH_2 at position 1), 5.30 (s, 2H, CH_2 at position 7), 6.67-7.99 (m, 11H, 11 Ar-*H*).

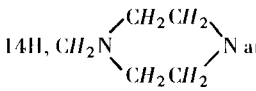
b. 1,2-Dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-one, [2-(*N*-Carbethoxy-*N*-methylamino)ethyl]-oxime (**10**).

A mixture of 5.30 g. (0.011 mole) of the *base* derived from **5**, 2.72 g. (0.025 mole) of ethyl chloroformate, and 50 ml. of anhydrous benzene was heated under reflux for 20 hours, the solution was cooled, washed, dried, and concentrated to give 6.2 g. of a solid residue. This was recrystallized from hexane to give 4.40 g. of **10**, m.p. 106-108°; ir (mull): ν 1680 (s), 1620 (w), 1610 (2), 1585 (w), 1515 (m), 1510 (m), 1490 (m), 1470 (m), 1450 (s), 1420 (m) cm^{-1}; pmr (deuteriochloroform): δ 1.23 [t, (J = 7 Hz), 3H, $CH_3CH_2O_2C$], 3.00-3.23 (s superimposed on q, 5H, $CH_3N(CO_2CH_2CH_3)CH_2$], 3.40-4.63 [m, 8H, $CH_3CH_2O_2CNCH_2CH_2$ plus two CH_2 at positions 2 and 1], 5.26 [s, 2H, CH_2 at position 7), 6.90-7.10 (m, 2H, 2 Ar-*H* at positions 5 and 6), 7.10-7.40 (m, 3H, 3 Ar-*H* at positions 9, 10, and 12), 7.90-8.15 (m, 1H, Ar-*H* at position 4).

c. To a cooled solution of 2.60 g. (0.0055 mole) of *b* in 7 ml. of glacial acetic acid was added 8 ml. of 30% hydrogen bromide in glacial acetic acid, and the mixture was stirred at room temperature for 60 hours. To this was added 200 ml. of anhydrous ether; the solid that separated was filtered, washed with 200 ml. of ether, and then dissolved in 100 ml. of water. The solution was cooled, made alkaline, and the product isolated *via* ether extraction. The residual oil recovered from the ether was dissolved in 10 ml. of 2-propanol and the solution was treated with 2.0 ml. of 4.8 *N* 2-propanolic hydrogen chloride. The hydrochloride that separated, 1.10 g., was recrystallized from acetonitrile to give 0.80 g. of **8**, m.p. 231-232° dec.; ir (mull): ν 2990-2840 (s, broad), 2510 (m), 2470 (m), 2430 (m), 1640 (m), 1595 (m), 1580 (s), 1510 (s) cm^{-1}; pmr (DMSO-d_6): δ 2.53 (s, 3H, NCH_3), 2.70-3.35 (m, 4H, $=NOCH_2CH_2$), 3.85 [t (J = 7), 2H, 2*H* at position 2], 4.32 [t (J = 6), 2H, 2*H* at position 1], 5.25 (s, 2H, 2*H* at position 7), 6.90-7.50 (m, 1H, 5 Ar-*H*), 7.90 (q, 1H, *H* at position 4), 9.00 (broad s, 2H, N^+H_2).

1,2-Dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-one, [3-[4-(2-Hydroxyethyl)-1-piperazinyl]propyl]-oxime, Maleate Salt (**6**).

A suspension of 6.74 g. (0.02 mole) of **2** and 1.40 g. (0.028 mole) of sodium hydride (50%) in 160 ml. of anhydrous toluene was heated under reflux and in a nitrogen atmosphere for 0.75 hour and then cooled to 10°. To the mixture was added 10.0 g. (0.062 mole) of 1-bromo-3-chloropropane, the mixture was heated under reflux for 5 hours, cooled, an additional 10.0 g. (0.125 mole) of 1-bromo-3-chloropropane was added, and the reflux was continued for 14 hours. The reaction mixture was cooled, washed, dried, and concentrated *in vacuo* to give 8.70 g. of **7** as a viscous oil. The **7** was dissolved in 130 ml. of 2-propanol and to the solution was added 3.00 g. (0.02 mole) of sodium iodide and 5.20 g. (0.04 mole) of 2-(1-piperazine)ethanol and the mixture heated under reflux for 30 hours. Subsequently, the reaction mixture was cooled, filtered, and the filtrate concentrated *in vacuo* to give 8.90 g. of a viscous residue. This was dissolved in 300 ml. of ether, the ether solution was washed, and then extracted with two 40 ml. portions of 5% aqueous hydrochloric acid. The combined acid solutions were cooled and treated with an excess of sodium hydroxide; the *base*, isolated *via* ether extraction, weighed 0.75 g. and was obtained as a viscous oil. The oil was dissolved in 10 ml. of acetonitrile and the solution treated with 0.45 g. of maleic acid. The solid that separated was filtered and recrystallized from acetonitrile to give 0.27 g. of **6**, m.p. 174-176° dec.; ir (mull): 3330 (m, broad), 2500-2200 (m, broad), 1690 (m), 1620 (s), 1575 (s), 1510-1420 (s, broad), 1375 (s), 1355 (s), cm^{-1}; pmr (DMSO-d_6): δ 2.68-3.20 [m,


14H, CH_2N (CH_2CH_2)$_2$N and $OCH_2CH_2CH_2N$] 3.20-4.36 (m, 8H, $OCH_2CH_2CH_2N$, two CH_2 at positions 1 and 2, $HOCH_2CH_2$), 5.30 (s, 2H, CH_2 at position 7), 6.18 [s, 4H, (HO_2CCH:$CHCO_2H$], 6.90-7.90 (m, 8H, 7 Ar-*H*, O*H*).

N-[2,3-Dihydro-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-ylidene]-*O*-(3,4,5-trimethoxybenzoyl)hydroxylamine (**11**).

To **2a**, prepared from 8.35 g. (0.025 mole) of **2**, 1.30 g. (0.026 mole) of sodium hydride (50%) in 120 ml. of anhydrous toluene, was added at 20°, a solution of 8.1 g. (0.035 mole) of 3,4,5-trimethoxybenzoyl chloride in 50 ml. of anhydrous toluene. The mixture was heated under reflux for 5 hours and cooled. The solid that separated was filtered, washed, dried, and recrystallized from benzene to give 9.90 g. of **11**, m.p. 218-220°; ir (mull): 1750 (s), 1615 (m), 1590 (s), 1575 (s), 1515 (s), 1500 (s), 1450 (s), 1420 (s), 1410 (s) cm^{-1}; pmr (deuteriochloroform): δ 3.32 [t (J = 6 Hz), 2H, CH_2 at position 2], 3.67-4.17 [m, 11H, (CH_3O)$_3$ plus CH_2 at position 1], 5.23 (s, 2H, CH_2 at position 7), 6.83-7.42 (m, 7 Ar-*H*), 8.24 [q, (J = 2 Hz), 1H, Ar-*H* at position 4).

N-[2,3-Dihydro-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-ylidene]-*O*-(phenylcarbamoyl)hydroxylamine (**12**).

A solution of 5.00 g. (0.014 mole) of **2**, 1.80 g. (0.014 mole) of phenyl isocyanate and 1.20 g. (0.014 mole) of pyridine, in 25 ml. of benzene was heated under reflux for 1 hour, then cooled, and filtered to give 7.0 g. of a solid. This was recrystallized from benzene to give 3.70 g. of **12**, m.p. 216-218° dec.; ir (mull): 3370 (s), 1750 (s), 1600 (s), 1590 (s), 1580 (m), 1525 (s, broad), 1505 (s), 1445 (s), cm^{-1}; pmr (deuteriochloroform): δ 3.33 [t (J = 7 Hz), 2H, 2*H* at position 2], 3.95 [t (J = 7 Hz), 2 *H* at position 1], 5.25 (s, 2H, 2*H* at position 7), 6.38-8.34 (m, 12H, 11, Ar-*H* plus N*H*).

2,3-Dihydro-3-[3-(4-methyl-1-piperazine)propoxy]-11-(trifluoromethyl)-1*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin (**13**), and its Maleate Salt (**13a**).

To a solution of 5.80 g. (0.018 mole) of **3**, in 100 ml. of anhydrous toluene was added 1.00 g. (0.02 mole) of sodium hydride (50%), the mixture was heated at 100° for 0.75 hour, then cooled, and to it was added a solution of 3.90 g. (0.022 mole) of 2-(3-chloropropyl)-4-methylpiperazine in 20 ml. of anhydrous toluene. The mixture was heated under reflux for 5 hours, and filtered hot. The filtrate was concentrated *in vacuo* to give 9.0 g. of an oily residue. This was dissolved in 200 ml. of absolute ethanol and the solution was treated with a solution of 4.60 g. of maleic acid in 15 ml. of absolute ethanol. The solid that separated was filtered to give 12.1 g. of material, m.p. 165-170°. Two recrystallizations from absolute ethanol gave 8.30 g. of **13a**, m.p. 170-172°; ir (mull): ν 2500-2000 (m, broad), 1685 (m), 1615 (s), 1570 (s), 1480-1430 (s, broad) 1420 (s), 1370 (s), 1350 (s) cm^{-1}. The pmr spectrum of **13a** was very complex. Consequently, the base, **13**, was isolated in the usual manner, but short path distillation resulted in some decomposition. The oil obtained, b.p. 180° (0.4 mm.) in deuteriochloroform gave a simpler spectrum that was analyzed as follows: δ 1.50-2.26 (m, 15H, 4-piperazine-CH_2 groups, CH_3 at position 4 and CH_2 at position 1 of piperazine, CH_2 at position 2), 3.10-3.79 [m, 6H, (OCH_2CH_2) plus CH_2 at position 1, 4.12-4.33 (m, 1H, *H* at position 3), 5.53, 5.90 [AB q (ν_{AB} = 21 Hz, J_{AB} = 12 Hz), 2H, CH_2 at position 7], 6.50-7.25 (m, 6H, 6 Ar-*H* at positions 4, 5, 6, 9, 10, and 12).

REFERENCES

(1) For Paper XII, see *J. Heterocyclic Chem.*, 11, 497 (1974).

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(4a) R. B. Petigara and H. L. Yale, *J. Heterocyclic Chem.*, **8**, 455 (1971); (b) *Idem, ibid.*, **9**, 1275 (1972).

(5) H. L. Yale, F. Sowinski, and J. Bernstein, *J. Am. Chem. Soc.*, **79**, 4375 (1957); H. L. Yale and F. Sowinski, *ibid.*, **80**, 1651 (1958).

(6) H. L. Yale, B. Beer, Jelka Pluscec, and E. R. Spitzmiller, *J. Med. Chem.*, **13**, 713 (1970).

(7) H. L. Yale and F. Sowinski, *Arzneim.-Forsch.* **16**, 550 (1966).

(8) Samples of authentic phenergan and isophenergan were obtained through the courtesy of Dr. W. Comer of Wyeth Laboratories, Division of American Home Products Corp., P. O. Box 8299, Philadelphia, Pa.

(9) J. Krapcho and C. F. Turk, *J. Med. Chem.*, **9**, 191 (1966).

(10) See, also, A. F. Casy, "PMR Spectroscopy in Medicinal and Biological Chemistry," Academic Press, London, 1971, pp. 20-22.

(11) As reported in Reference 4b, the introduction of a chiral center at position 3 of the tetracycle resulted in a non-equivalency of the methylene protons at that position; the consequence of the non-equivalency was geminal interproton coupling and the appearance in the pmr spectrum of an AB quartet.