Novel Polycyclic Heterocycles. XIV. 1,2-Dihydro-4-(trifluoromethyl)-3*H*-8*H*-quino[1,8-*ab*][4,1]benzoxazepin-3-one and its Derivatives (1)

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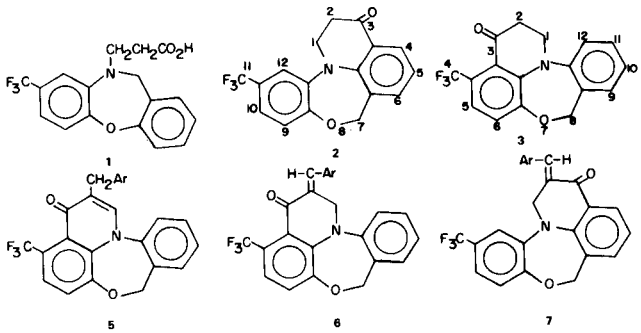
Received December 9, 1974

Procedures for the isolation of 1,2-dihydro-4-(trifluoromethyl)-3*H*,8*H*-quino[1,8-*ab*][4,1]-benzoxazepine, **3**, from reaction mixtures containing **3** as the minor component, and the isomer, 1,2-dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one, **2**, as the major component, are described. The reactivity of **3** toward hydroxylamine and aromatic aldehydes has been investigated and the preparation of derivatives with those reactants is described.

In an earlier paper (4), we reported that the trifluoroacetic anhydride-assisted annulation of **1** gave the single tetracyclic ketone, **2**, in high yield. The homogeneity of **2** was supported by the following observations: (a) uniformity of the product as opaque *rhombic* crystals (5), (b) a single spot in several different solvent systems when **2** was subjected to tlc, and, (c) a single peak when analyzed by glc. These empirical observations were buttressed, in turn, by the presumption that the formation of the isomeric **3** would not be favored, since that mode of cyclization would represent electrophilic substitution *ortho* to a trifluoromethyl group. *A priori*, however, the possible formation of **3** could not be rejected (6), and in subsequent, larger-scale experiments, an investigation was initiated to determine whether **3** was present as one of the reaction products.

In the first of the latter group of experiments, one that gave an 80% yield of homogeneous **2**, partial concentration of the filtrates from the recrystallizations gave a solution that slowly deposited *transparent needles* of **3**, in about 10% yield. In four subsequent experiments, the fortuitous delayed separation of **3** was not observed, and the products from the recrystallizations were mixtures of **2** and **3** which could not be separated by fractional crystallization, by tlc, or by column chromatography. Although separation was easily achieved by glc, the quantities of **3** required as an intermediate for a planned synthetic program made preparative glc an impractical source of that isomer. It should be mentioned at this time that the quantity of **3** present in the mixture was readily estimated from its pmr spectrum, where the integrated area for the signal at δ 8.00 due to the proton at position-4 in **2** was compared with one-half of the area represented by the unresolved singlet at δ 5.20 that was contributed by the methylene protons of the bridging benzyl ether linkage of both **2** and **3**.

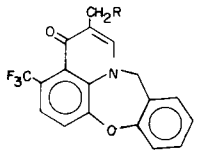
A practical solution of the problem was achieved when advantage was taken of the observation that **3** did not form an oxime under conditions which readily gave the oxime, **4**, of **2**, in 94% yield (4). When the mixture of **2** and **3** was reacted at reflux temperature with hydroxylamine hydrochloride in 70% ethanol and the reaction mixture was subsequently allowed to cool to 20°, essentially pure **3** crystallized while **4** remained in solution. Thus, with an adequate supply of **3** assured by this procedure, its reactions with aromatic aldehydes was investigated. In the base-catalyzed reactions to give *endo*-cyclic α,β-unsaturated ketones like **5**, **3** was essentially as reactive as was **2**; in the acid catalyzed reactions, however, to give the *trans*-exocyclic **6**, the reaction with **3** required 14 days for completion compared with the 14 hours required to prepare the isomeric **7** (7).

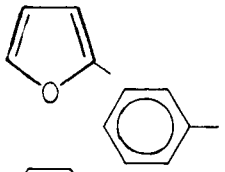
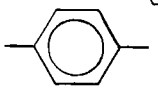
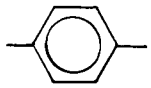
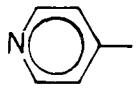


EXPERIMENTAL

Melting points were taken in an electrically heated oil bath in capillary tubes and are uncorrected. The proton nmr spectra were obtained in deuteriochloroform on a Perkin-Elmer R12B spectrometer and chemical shifts are reported in parts per million (δ) downfield from an internal TMS reference. Infrared spectra were

Chart I



R Substitution at position-2	M.p., °C.	Recrystallization Solvent	Yield, %	Molecular Formula	Analyses Calcd. C	H	N	F	Found C	H	N	F
	146-148	Abs. EtOH	34	$C_{22}H_{14}F_3NO_3$	66.55	3.55	3.53	14.36	66.26	3.84	3.51	14.07
	190-192	2-PrOH	74	$C_{24}H_{16}F_3NO_2$	70.82	3.96	3.44	14.00	70.58	3.89	3.34	13.79
Cl 	167-169	Abs. EtOH	60	$C_{24}H_{15}ClF_3NO_2$	65.21	3.42	3.17	8.02 (a)	65.06	3.44	2.99	8.09
$Et_2NCH_2CH_2O$ 	130-132	2-PrOH	35	$C_{30}H_{29}F_3N_2O_3$	68.89	5.59	5.36	10.90	68.97	5.85	5.24	10.68
$3,4,5\text{-}(MeO)_2C_6H_2$	168-170	$(Me_2CH)_2O$	25	$C_{27}H_{22}F_3NO_5$	65.24	4.46	2.82	11.47	65.55	4.67	3.12	11.18
	192-194	2-PrOH	17	$C_{23}H_{15}F_3N_2O_2$	67.70	3.70	6.87	13.97	67.97	3.95	7.14	13.78

(a) Cl

obtained on mineral oil mulls or in solution in deuteriochloroform on a Perkin-Elmer Infracord Model 621 Grating Spectrometer. Ultraviolet spectra were recorded on ethanol solutions on a Cary Model 15 Recording Spectrometer. The authors wish to thank the following members of this Institute: Mr. J. F. Alicino and his associates for performing the microanalyses, Mrs. Barbara Toeplitz for the ir spectra, Dr. M. Puar for the pmr spectra, and Mr. A. Neidermayer for the glc separations.

Separation of **2** from **3**.

(a) By Fractional Crystallization.

Under anhydrous conditions, to a solution of 50.5 g. (0.15 mole) of **1** in 200 ml. of Reagent-grade benzene was added in 17 minutes 22.3 ml. of trifluoroacetic anhydride. Subsequently, the mixture was slowly warmed to reflux during a 50 minute period, the heating under reflux was continued for 10-12 minutes, and the bright red reaction mixture was then stirred into 2 liters of ice-water. An additional 400 ml. of benzene was added, the two phases were allowed to stratify, and then separated. The yellow benzene solution was washed with 2% aqueous sodium carbonate, then with saturated aqueous sodium chloride, dried, and concentrated to dryness *in vacuo*. The yellow colored residual solid, 50.0 g., was recrystallized form 650 ml. of 2-propanol and the filtered solution kept at 20° for 24 hours. The intensely yellow crystalline mass that separated was filtered and dried to give 39.5 g. of **2**, m.p. 134-137°. A second recrystallization from 600 ml. of 2-propanol, with the solution again being kept at 20° for 48 hours, gave 39.1 g. (80% yield) of **2** as opaque *rhombs*, m.p. 141-143° (4).

The two 2-propanol filtrates from the recrystallizations were combined, concentrated to a volume of 300 ml. and kept at 20° for 48 hours. The crystalline product that separated slowly was filtered to give 6.2 g. of transparent needles, m.p. 146-152°. Recrystallization from 150 ml. of methanol followed by keeping for 48 hours at 20° gave 5.1 g. (10% yield) of **3**, m.p. 152-154°; uv λ max (ethanol): 246, 285, 392 mμ (ε, 16,000, 8,000, 7,000); ir (mull): ν 1695(s), 1605(m), 1595(m), 1585(m), 1575(m), 1500(s), 1485(s), 1460(s), 1410(s) cm^{-1}; pmr (deuteriochloroform): δ 3.02 [t (J = 7 Hz), 2H, C*H*$_2$ at position-2], 4.12 [t (J = 7 Hz), 2H, C*H*$_2$ at position-1], 5.22 (s, 2H, C*H*$_2$O), 6.75-7.65 (m, 7 Ar-*H*). The absence of any resonance in the δ 8.0 region established the structure of this tetracyclic ketone as **3** (4).

Anal. Calcd. for $C_{17}H_{12}F_3NO_2$: C, 63,94; H, 3.79; N, 4.39. Found: C, 63.69; H, 4.00; N, 4.24.

(b) By Fractional Crystallization of **3** from **4**.

In a reaction carried out as in (a) but employing 101.0 g. of **1**, 400 ml. of Reagent-grade benzene, and 44.6 ml. of trifluoroacetic anhydride, the crude product was recrystallized twice from 2-propanol to give 54.6 g. (57% yield) of **2**, m.p. 141-143°. The 2-propanol filtrates were combined, concentrated to one-quarter volume, and kept at 20°. The crystalline solid that separated was filtered and air-dired to give 17.7 g. of material, m.p. 117-125°. Trial recrystallizations of this material failed to give pure **3**. Manual separation of the transparent needles from the opaque rhombs in the mixture furnished **3**, m.p. 151-153°, but the procedure was not practical. From the pmr spectrum of the mixture, it was possible to estimate the approximate composition. For this purpose, one-half of the integrated area of the methylene proton signal of the -CH_2O- group at δ 5.20 represented the reference one-proton, H_R value contributed by both **2** and **3**. The integrated area for the resonance at δ 8.00 would represent the H_2 value for the diagnostic proton at position-4 contributed only by **2**. Thus, the fraction of **2** in the mixture was shown by the expression, H_2/H_R. By this technique, it was estimated that the 17.7 g. of solid, m.p. 117-125°, contained *ca.* 5.4 g. of **2** and *ca.* 12.3 g. of **3**. A solution of 17.0 g. (0.17 mole of **2** and 0.039 mole of **3**) of the mixture, 0.95 g. (0.014 mole) of hydroxylamine hydrochloride, **7**, and 400 ml. of 70% aqueous ethanol was heated under reflux for 4.5 hours. At this point, tlc (Brinkman precoated analytical silica gel plates developed in either methylene chloride or diethyl ether) showed the presence of **3**, **4**, and a small amount of **2**. An additional 0.45 g. of **7** was added, and the heating under reflux continued for an additional 2 hours. The hot solution was allowed to cool spontaneously to 20°, kept at that temperature for 2 hours, and the precipitated solid filtered and air-dried to give 8.5 g. of material shown by tlc (*vide supra*) to be **3** containing a small amount of **4**. Recrystallization from 145 ml. of 2-propanol gave 7.1 g. (58% recovery) of **3**, m.p. 152-154°, whose pmr and ir spectra were identical in all respects with the corresponding spectra of the product obtained in (a).

Anal. Found: C, 63,76; H, 3.74; N, 4.20; F, 18.15.

(c) By GLC.

The mixture of **2** and **3** employed in the separation in (b) was dissolved in Reagent-grade tetrahydrofuran and injected into a glc system with the following characteristics: glass column, 6 feet 6 inches x 1/8 inch, filled with 80-100 mesh Chromosorb HG coated with 1% methyl phenyl silicone (OV-17); vaporizer temperature, 270°; column temperature, 265°; detector, 300°; and, helium, as carrier gas, at 20 psig. Under these conditions, a clean separation occurred with **2** having a residence time of 6.75 minutes and **3**, a residence time of 10.0 minutes (8).

Preparation of the Oxime of **3**, **8**.

(a) No reaction occurred when 1.92 g. (0.006 mole) of **3**, 0.90 g. (0.012 mole) of **7**, and 200 ml. of 70% aqueous ethanol were heated under reflux for 19 hours. When **2** and **7**, in the same solvent system, were heated under reflux for 4 hours, the oxime of **2** was obtained in 94% yield (4).

(b) A solution of 1.92 g. of **3**, 2.0 g. (0.026 mole) of **7**, 4.0 ml. of pyridine, and 75 ml. of 95% ethanol was heated under reflux for 6 hours and then cooled. The solid that crystallized was filtered to give 1.80 g. of material that softened at 145° and then melted, with decomposition, at 198-200°. This was recrystallized from 50 ml. of benzene to give 1.0 g. (50% yield) of **8**, m.p. 220-222° dec.; ir (mull): ν 3280(s), 3250(s), 1600(m), 1580(s), 1495(s), 1485(s), 1460(s), 1415(s) cm^{-1}; pmr (deuteriochloroform): δ 3.39 [t (J = 7 Hz), 2H, C*H*$_2$ at position-2], 3.83 [t (J = 7 Hz), 2H, C*H*$_2$ at position-1], 5.19 (s, 2H, C*H*$_2$O), 5.86-6.36 (m, 1H, O*H*), 6.79-7.76 (m, 7H, 7 Ar-*H*).

Anal. Calcd. for $C_{17}H_{13}F_3N_2O_2$: C, 61.07; H, 3.92; N, 8.38; F, 17.05. Found: C, 61.25; H, 3.99; N, 8.64; F, 16.95.

(c) A solution of 1.50 g. (0.0047 mole) of **3**, 0.97 g. (0.014 mole) of **7**, 0.28 g. (0.007 mole) of sodium hydroxide, 10 ml. of water, and 35 ml. of 95% ethanol was heated under reflux for 8 days. Even at the end of that time, tlc showed the presence of unreacted **3**. When the mixture was cooled, a solid separated. This was filtered and air-dried to give 1.47 g. of crude **8**. Repeated crystallization from 90% aqueous ethanol gave 0.50 g. (30% yield) of **8**, m.p. 220-222°, whose ir and pmr spectra were identical with those obtained with the product from (b).

2-[4-(Dimethylamino)benzyl]-4-(trifluoromethyl)-3*H*,8*H*-quino-[1,8-*ab*][4,1]-benzoxazepin-3-one, **9**.

A solution of 2.50 g. (0.008 mole) of **3**, 1.20 g. (0.008 mole)

of *p*-dimethylaminobenzaldehyde, 0.5 g. of sodium hydroxide, and 65 ml. of absolute ethanol was heated under reflux for 2.25 hours and then cooled to 0°. The product that crystallized was filtered and recrystallized from absolute ethanol to give 3.25 g. (93% yield) of **9**, m.p. 198-200°, ir (mull) ν 1640(s), 1620(s), 1590(s), 1580(s), 1570(s), 1525(m), 1500(m), 1485(m), 1465(m), 1455(m), 1440(m), 1410(w) cm^{-1}; pmr (deuteriochloroform): δ 2.85 [s, 6H, $N(CH_3)_2$], 3.85 (s, 2H, CH_2Ar), 5.22 (s, 2H, CH_2O), 6.55-7.80 (m, 11H, 10 Ar-*H* plus *H* at position -1.

Anal. Calcd. for $C_{26}H_{21}F_3N_2O_2$: C, 69.39; H, 4.70; N, 6.23; F, 12.67. Found: C, 69.21; H, 4.87; N, 6.50; F, 12.41.

A number of structurally similar derivatives were prepared by the same procedure and Chart I summarizes the relevent data for those compounds.

trans-2-[4-(Dimethylamino)benzylidene]-1,2-dihydro-4-(trifluoromethyl)-3*H*,8*H*-quino[1,8-*ab*][4,1]benzoxazepin-3-one, **10**.

A solution of 2.50 g. (0.008 mole) of **3**, 1.20 g. (0.008 mole) of *p*-dimethylaminobenzaldehyde, 0.20 g. of *p*-toluenesulfonic acid, 1.0 ml. of piperidine, and 65 ml. of absolute ethanol was heated under reflux for 14 days. Only at the completion of that time was it possible to demonstrate, by tlc, the absence of unreacted **3**. The mixture was concentrated to dryness *in vacuo* and the residue recrystallized once from 50 ml. of benzene-cyclohexane (1:1) to give 1.60 g. of solid, m.p. 169-172°; that solid was recrystallized from 260 ml. of benzene-diisopropyl ether (1:2) to give 0.63 g. (18% yield) of **10**, m.p. 178-185°; ir (mull): ν 1660(s), 1600(s), 1570(s), 1520(s), 1490(w), 1480(w), 1460(w), 1405(s) cm^{-1}; pmr (deuteriochloroform): δ 3.01 [s, 6H, $N(CH_3)_2$], 4.97 (broad s, 2H, CH_2 at position-1), 5.29 (s, 2H, CH_2O), 6.50-7.60 (m, 10H, 10 Ar-*H*), 7.78 (broad s, 1H, vinylic *H*).

Anal. Calcd. for $C_{26}H_{21}F_3N_2O_2$: C, 69.39; H, 4.70; N, 6.23; F, 12.67. Found: C, 69.64; H, 4.84; N, 5.94; F, 12.39.

In similar fashion was prepared the related 2-(4-chlorophenyl) derivative, m.p. 165-178° (the broad m.p. is not readily explained), after recrystallization from absolute ethanol. The yield was 55%.

Anal. Calcd. for $C_{24}H_{15}ClF_3NO_2$: C, 65.21; H, 3.43; N, 3.17; Cl, 8.02. Found: C, 65.15; H, 3.58; N, 3.13; Cl, 8.20.

REFERENCES

(1) Paper XIII, H. L. Yale and R. B. Petigara, *J. Heterocyclic Chem.*, **11**, 791 (1974).

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(3) Present addresses: (a) Schering Corporation, Bloomfield, N. J.; (b) Rohm and Haas, Spring House, Pa.

(4) R. B. Petigara and H. L. Yale, *J. Heterocyclic Chem.*, **8**, 455 (1971).

(5) In the earlier paper, (4), the isomeric 4-chloro-1,2-dihydro-3*H*,8*H*-quino[1,8-*cd*][1,5]benzoxazepin-3-one and 11-chloro-1,2-dihydro-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one could not be separated by fractional crystallization or by chromatographic procedures, and were, as a last resort, separated manually, since the crystalline forms of the isomers are so strikingly different.

(6) For example, in the literature, there are but two references to the electrophilic substitution pattern for α,α,α-trifluorotoluene at temperatures > 80°. Thus, S. Robota and E. A. Bellmore U. S. Patent 2,234,292 [*Chem. Abstr.*, **64**, 11125e (1966)] report that the chlorination of α,α,α-trifluorotoluene at 65° gave 54% *m*-, 4.7% *p*-, and 2.9% *o-chloro derivatives.* Again, although the nitration of α,α,α-trifluorotoluene was reported by H. S. Booth, H. M. Elsey, and P. E. Burchfiled [*J. Am. Chem. Soc.*, **57**, 2064 (1935)] to give only the *m*-isomer, the interested chemical manufacturers and suppliers have known for the past fifteen years that the nitration product contains about 5% of the *o*-isomer. This was first called to the attention of one of the authors (HLY) by a representative of the Nease Chemical Co., State University, Pa. As a consequence, commercial α,α,α-trifluoro-*m*-toluidine, prepared by reduction of that mixture of nitro derivatives contained about 5% of α,α,α-trifluoro-*o*-toluidine. Selective oxidation has been employed by Nease and others to remove the impurity.

(7) H. L. Yale and R. B. Petigara, *J. Heterocyclic Chem.*, **11**, 497 (1974), have described the preparation of the Claisen-Schmidt reaction products of **2**.