Novel Polycyclic Heterocycles. XII. Reactions of 1,2-Dihydro-11-(trifluoromethyl)-3*H*-7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-one with Aromatic Aldehydes (1)

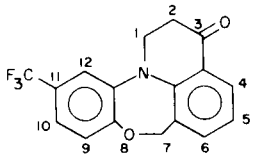
Harry L. Yale (2) and Ramesh B. Petigara (3)

The Squibb Institute for Medical Research, Princeton, N. J. 08540

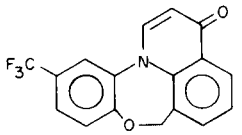
Received March 5, 1974

The Claisen-Schmidt condensation between 1,2-dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino-[8,1-*cd*][1,5]benzoxazepin-3-one, **1**, and aromatic aldehydes has been investigated. The acid catalyzed reactions yielded the *trans*-2-benzylidene derivatives, **4**; the structures and configurations of the group of compounds represented by **4** have been confirmed by pmr in conjunction with the Eu(fod)$_3$ shift reagent. In contrast, catalysis with sodium hydroxide gave the isomeric 2-benzyl-*endo*cyclic α,β-unsaturated ketones, **3**. Finally, the **4** could be isomerized to the corresponding **3** by means of sodium hydroxide. The ir, uv, and pmr spectra of these compounds are discussed.

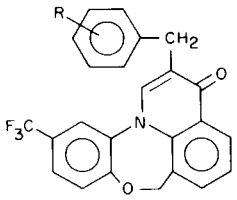
Recently, we described the synthesis of the novel tetracyclic-3-one, **1**, and the preparation, from **1**, of the 3-oxime, the 3-ol, the 3-chloro, and a series of 3-amino derivatives (4a,b). We have continued our program to utilize **1** as a substrate for further chemical alteration, and, in this paper, are reporting the behavior of **1** in base and in acid caralyzed reactions with aromatic aldehydes (5).



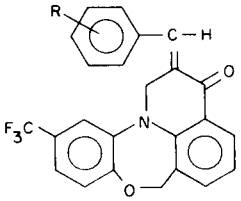
1



2



3



4

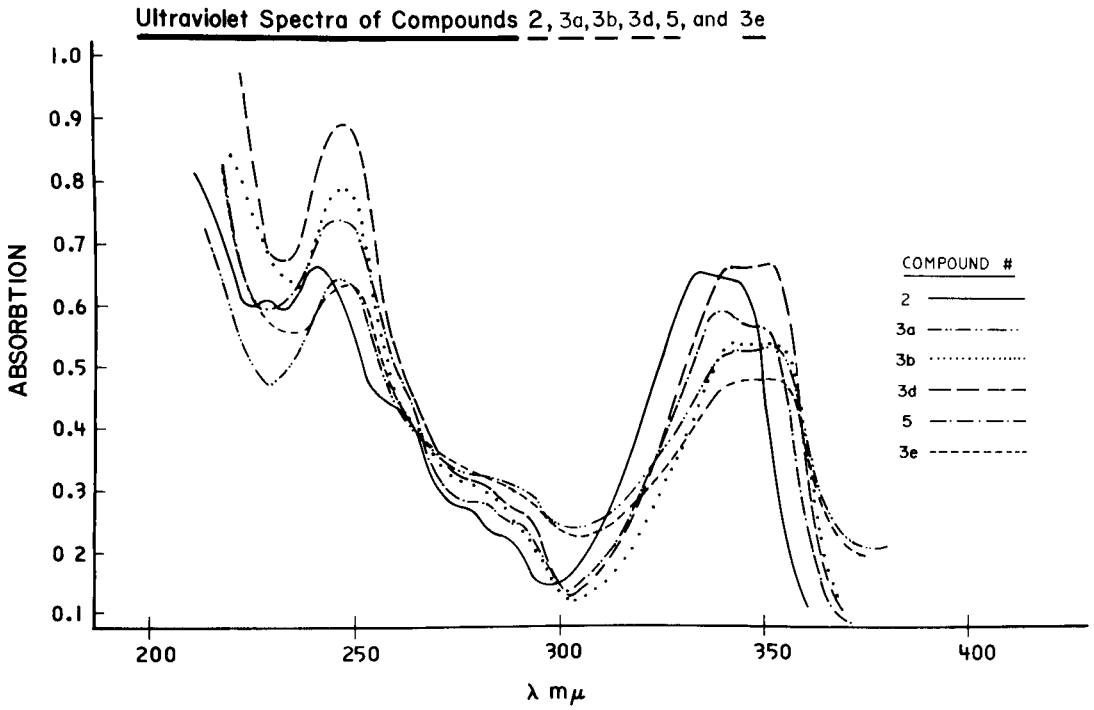
3a, R = H
3b, R = *p*-Cl
3c, R = *p*-Me_2N
3d, R = *p*-$Et_2N(CH_2)_2O$
3e, R = 3,4,5-$(MeO)_3$

4a, R = H
4b, R = *m*-O_2N
4c, R = *p*-$Et_2N(CH_2)_2O$
4d, R = 3,4,5-$(MeO)_3$

Thus, while an organic base, like piperidine, in absolute ethanol, even after prolonged heating under reflux, did not induce reaction between **1** and several aromatic aldehydes (6), the reaction was very rapid in ethanolic sodium hydroxide and gave a series of products which have been assigned structure **3**. Piperidine benzoate, hydrochloric acid, or *p*-toluenesulfonic acid gave a series of isomeric products, and these have been assigned structure **4** (7). Finally, ethanolic sodium hydroxide catalyzed the rearrangement of several of the **4** to the corresponding **3**, but piperidine benzoate did not effect a rearrangement, in one typical example of **3**, to the correspondingly substituted **4** (7).

Derivatives of structure **3** were obtained as very pale yellow to colorless crystalline solids. The structure assignment could have been made, arbitrarily, on the basis of color alone, since all of the structurally related α,β-unsaturated *endo*cyclic ketones described in the literature are pale yellow in color, wheras the *exo*cyclic α,β-unsaturated ketones invariably range in color from orange to red (7). That the assignment was indeed correct could be shown more convincingly, however, by an interpretation of the ir, uv, and pmr spectra of this class of compounds.

In the ir, the saturated ketone, **1**, showed carbonyl absorption of 1686 cm^{-1}; the corresponding absorption for **2** was seen at 1631 cm^{-1} (4a). All of the derivatives obtained by the ethanolic sodium hydroxide procedure gave products whose ir spectra showed carbonyl absorption at *ca.* 1630 cm^{-1}. In contrast, the ir spectra of the *exo*cyclic α,β-unsaturated derivatives, **4**, showed carbonyl absorption at *ca.* 1660 cm^{-1}, a shift of *ca.* 30 cm^{-1} away from that observed with the **3**, and in the region of the



carbonyl absorption observed with **1**. Juxtaposed, these observations suggest that the structure assignments are correct.

In the uv spectrum of **1**, the two longer wave length absorptions at 299 and 381 mμ have extinction coefficients of 7200 and 3300, respectively: the corresponding values for **2** at 286, 343; and 355 mμ are 4800, 18200, and 18000 (4a). All of the derivatives prepared by the ethanolic sodium hydroxide procedure have extinction coefficients, at the longer wave lengths, that fall in the ranges shown by **2** and not those shown by **1** (7). A composite of five of these uv spectra, along with **2**, are shown in Fig. 1; it is readily seen that all of the spectra reveal striking similarities both in pattern and intensity of absorption.

In their pmr spectra in deuteriochloroform solution, each of the derivatives of structure **3**, prepared by the ethanolic sodium hydroxide procedure, showed two, two-proton singlets. The chemical shifts of these signals were somewhat dependent on the nature of the substituent R, but in any event, the shifts varied only be *ca.* 0.1 ppm. The downfield signals at *ca.* δ 5.3-5.4 were assigned to the two methylene protons at position-7, while the upfield signals at *ca.* δ 3.8-3.9 were attributed to the methylene protons in the benzylic substituents at position-2. With each of these derivatives of structure **3**, the vinylic proton at position-1 was not discernible, but was, instead, a component of the aromatic proton envelope in the *ca.* δ 6.6-7.9 region. In the *exo*benzylidene derivatives, **4**, again in deuteriochloroform, two, two-proton singlets were seen, and again, the chemical shifts were dependent on the substituent R, and now varied by 0.1-0.2 ppm. Thus, the two signals were seen at *ca.* δ 4.9-5.1 and *ca.* δ 5.4-5.5, and were assigned, respectively to the methylene groups at position-1 and -7, while the vinylic protons, in the *trans*-configuration, deshielded by the carbonyl oxygen atom, were shifted downfield and were now clearly demarcated in the region of *ca.* δ 7.95-8.05.

In deuteriochloroform solution, in the 60 MHz spectrum of **1**, the proton at position-4, due to *o*- and *m*-coupling, was seen as a well-defined quartet, but, again, shifted downfield; under the same conditions, in the spectrum of **2**, that proton was observed as a downfield *multiplet*. These spectal characteristics implied that long-range coupling was significantly greater with the *endo*cyclic α,β-unsaturated ketone (4a). In their 60 MHz spectra, again in deuteriochloroform solution, in derivatives of structure **4**, the proton at position-4 appeared as a one-proton multiplet upon which was superimposed the somewhat further upfield vinylic proton signal. In derivatives of structure **3**, the proton at position-4 appeared to form a broadly segmented "triplet". For example, in *3a*, the "triplet" was seen centered at δ 8.55 (J = 6 Hz). In the 100 MHz spectrum of **5**, in deuteriochloroform solution, the same proton appeared again to resonate as a "triplet"; in perdeuteriobenzene solution, however, the signal was seen as a "quartet". Thus, in this instance, the contrasting behavior in deuteriochloroform and perdeuteriobenzene appeared to represent an observation that fitted ideally into the concept of "inert" and "active" solvents (8). Closer examination of these signals, and, subsequently, expansion of the

signals, revealed, however, that in all instances, the "triplet" and the "quartet" were, in reality, multiplets, and that in derivatives of structure **3**, the proton at position-4 is being subjected to long-range coupling, in part from the methylene protons at position-7, and, from other, as yet unidentified protons (10).

While it is recognized that pmr spectroscopy can give definitive assignments of stereochemistry to *cis*- and *trans*-isomers only when both isomers are available, in this particular area of the Claisen-Schmidt reaction, the benzylidene derivatives obtained *via* the piperidine, piperidine benzoate, hydrochloric acid, or *p*-toluenesulfonic acid catalysis of the reaction between a fused, polycyclic ketone and an aromatic aldehyde have been shown, invariably, to possess the *trans*-configuration (7). Furthermore, in a number of instances, the *trans*-stereoisomer has been isomerized to the *cis*-derivative. There is, therefore, ample evidence in the literature (7), that the vinylic proton *cis*- to the carbonyl oxygen (*trans*-configuration) will resonate at *ca.* δ 8.0-8.1, downfield by about 1 ppm from the corresponding *trans*-proton (*cis*-configuration), which generates a signal at *ca.* δ 6.7-7.0.

Several attempts to convert compounds of structure **4** to an isomeric *exo*cyclic benzylidene derivative were unsuccessful, due presumably to steric factors. Consequently, use was made of the observation mentioned above concerning the signal of the vinylic *cis*-proton in the pmr spectrum. Thus, for example, with **4a-d**, the vinylic protons were found to resonate at δ 8.00-8.05, 7.98, and 8.10, respectively, and these data served to assign, tentatively, the *trans*-configuration to the class of compounds represented as **4**.

Insofar as we are aware, no one has studied the deshielding effects of a shift reagent on the normal pmr spectrum of an *exo*cyclic unsaturated Claisen-Schmidt reaction product. In the present study, use was made of the shift reagent, Eu(fod)$_3$ (9a) which, since it coordinated preferentially with carbonyl oxygen (9b), should induce almost equivalent downfield shifts of the resonances for the *cis*-vinylic proton and the proton at position-4, a lesser downfield shift for the two protons at position-1, and relatively insignificant shifts in the resonances of the remaining protons. The compound studied was **10**, and the experimental observations confirmed those predictions: the vinylic proton signal was shifted from δ 8.00 to δ 14.82, the proton at position-4 resonated at δ 14.96, rather than at the normal δ 8.07, and the two protons at position-1 gave a signal at δ 7.38, rather than at the original δ 4.94; in contrast, the methylene protons at position-7 were but slightly affected and now resonated at δ 5.36, instead of the normal, at δ 5.31. Thus, use of Eu(fod)$_3$ confirmed the assignment of a *trans*-configuration to the series of compounds described above as **4** which possess the *exo*-cyclic arylidene substituent at position-2 (10).

EXPERIMENTAL

The ir spectra were obtained on mineral oil mulls or on deuteriochloroform solutions, employing a Perkin-Elmer 621 spectrophotometer. The pmr spectra were obtained on a Perkin-Elmer R12B or on a Varian XL-100-15 spectrophotometer. The authors are indebted to Dr. M. Puar for these spectra and to him and Dr. A. Cohen for helpful discussions concerning them. The uv spectra were determined on a Cary 15 recording spectrophotometer. The microanalyses were performed by Mr. J. F. Alicino and his associates. The authors acknowledge, in addition, the assistance of Dr. J. A. Bristol in one aspect of the laboratory work and for helpful discussions.

The melting points were determined in capillary tubes, in an electrically heated oil bath, and are not corrected.

2-Benzyl-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**3a**).

A mixture of 3.20 g. (0.010 mole) of **1**, 1.16 g. (0.011 mole) of benzaldehyde, 0.05 g. of powdered sodium hydroxide, and 80 ml. of aboslute ethanol was stirred and heated to reflux. The color changed from yellow to orange and within 3 minutes, under reflux, a clear orange solution had formed; within 2 additional minutes, under reflux, the solution became cloudy, and almost immediately a dense yellow solid seapratęd. The heat was removed but an exothermic reaction continued for an additional 3-4 minutes. The mixture was allowed to cool spontaneously to room temperature, and the solid filtered; its air-dried weight was 3.45 g. m.p. 200-202°. The filtrate was cooled at 0° to give an additional 0.10 g., m.p. 201-203°. The combined solids were recrystallized from 220 ml. of absolute ethanol to give 2.13 g. (47% yield) of **3a**, as pale yellow plates, m.p. 201-203°; ir deuteriochloroform: ν 1626 (s), 1587 (s), 1570 (m), 1512 (w), 1477 (m), 1437 (m) cm^{-1}; uv λ max (methanol): 248, 278 (sh), 290 (sh), 343 (sh), 351 mμ (ε 24,650, 7190, 5820, 18,150, 18,400); pmr (deuteriochloroform): (60 MHz), δ 4.05 (s, 2H, C*H*$_2$Ph), 5.41 (s, OC*H*$_2$), 7.20-7.60 (m, 11H, 10 Ar-*H* plus *H* at position-1), δ 8.25-8.75 (m, 1H, Ar-*H* at position-4). (deuteriochloroform) (100 MHz) δ 4.01, 5.34, 7.22-7.64, 8.51; (perdeuteriobenzene); (100 MHz) δ 3.80, 4.62, 6.48-7.35, 8.80.

Anal. Calcd. for $C_{24}H_{16}F_3NO_2$: C, 70.82; H, 3.96; N, 3.44; F, 14.00. Found: C, 70.59; H, 3.90; N, 3.14; F, 13.81.

2-(*p*-Chlorobenzyl)-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]-benzoxazepin-3-one (**3b**).

The procedure described for **3a** was employed with 3.2 g. (0.010 mole) of **1**, 1.41 g. (0.010 mole) of *p*-chlorobenzaldehyde, 0.50 of sodium hydroxide, and 100 ml. of absolute ethanol and gave 2.90 g. (66% yield) of the pale yellow crystalline **3b**, m.p. 228-230° (absolute ethanol), ir (mull): ν 1630 (s), 1610 (s), 1590 (s), 1580 (s), 1570 (s), 1515 (m), 1485 (s), 1470 (s), 1450 (s) cm^{-1}; uv λ max (methanol): 248, 277 (sh), 289 (sh), 342, 350 mμ (ε 25,200, 7810, 6130, 18,200, 18,500); pmr (deuteriochloroform): δ 3.97 (s, 2H, C*H*$_2$C$_6$H$_4$Cl-*p*), 5.39 (s, 2H, OC*H*$_2$), 7.30-7.60 (m, 10H, 9 Ar-*H* plus *H* at position-1), 8.30-8.75 (m, 1H, Ar-*H* at position-4).

Anal. Calcd. for $C_{24}H_{15}ClF_3NO_2$: C, 65.24; H, 3.42; N, 3.17; F, 12.91. Found: C, 65.26; H, 3.70; N, 3.05; F. 12.85.

2-[*p*-(Dimethylamino)benzyl]-11-(trifluoromethyl)-3*H*,7*H*-quino-[8,1-*cd*][1,5]benzoxazepin-e-one (**3c**).

The procedure described for **3a**, in an 0.01 molar experiment, gave pale yellow, crystalline **3c** in 57% yield, m.p. 198-200° (absolute ethanol); ir (mull): ν 1625 (s), 1605 (s), 1590 (s), 1580 (s), 1560 (s), 1510 (s), 1475 (s), 1450 (s); uv λ max (methanol): 252, 290 (sh), 343, 350 mμ (ϵ 32,100, 8825, 17,550, 17,500); pmr (deuteriochloroform): δ 2.91 [s, 6H, N(CH_3)$_2$], 3.88 [s, 2*H*, $CH_2C_6H_4N(CH_3)_2$], 5.34 (s, 2H, OCH_2), 6.65-7.65 (m, 10H, 9-Ar-*H* plus *H* at position-1), 8.40-8.80 (m, 1H, Ar-*H* at position-4).

Anal. Calcd. for $C_{26}H_{21}F_3N_2O_2$: C, 69.32; H, 4.70; N, 6.22; F, 12.66. Found: C, 69.46; H, 4.90; N, 6.00; F, 12.91.

2-[*p*-[2-(Diethylamino)ethoxy]benzyl]-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**3d**).

A mixture of 4.80 g. (0.105 mole) of **1**, 3.40 g. (0.015 mole) of *p*-[2-(diethylamino)ethoxy]benzaldehyde, 1.2 g. powdered sodium hydroxide, and 75 ml. of absolute ethanol was heated for 1 hour at 55° and 1 hour at 75°. No solid separated on cooling; the volatiles were removed *in vacuo* and the residue partitioned between 400 ml. of ether and 300 ml. of water. The ether layer was separated, cooled, and extracted with 2-100 ml. portions of *N* aqueous hydrochloric acid. The acid extracts were combined, cooled, and treated with an excess of 50% aqueous sodium hydorxide. The oil that separated was isolated *via* extraction with chloroform. The chloroform extracts were concentrated to give 6.60 g. of viscous residue. Trituration with 20 ml. of petroleum ether gave 5.6 g. of solid, m.p. 130-150°. Recrystallization from 100 ml. of 2-propanol gave 2.70 g. (34% yield) of off-white, crystalline **3d**, m.p. 157-159°; ir (mull): ν 1630 (s), 1610 (s), 1590 (s), 1570 (m), 1505 (s), 1480 (m), 1460 (m) cm^{-1}; uv λ max (methanol): 247, 277 (sh), 343, 353 mμ (ϵ 26,700, 9100, 17,700, 17,600); pmr (deuteriochloroform): δ 1.08 [t, J = 6 Hz), 6H, $N(CH_2CH_3)_2$], 2.48-3.08 [m, 6H, $CH_2N(CH_2CH_3)_2$], 3.93 [s, 2H, $CH_2C_6H_4O(CH_2)_2NEt_2$], 4.03 [t, (J = 5Hz), 2H, -$C_6H_4OCH_2$], 5.36 (s, 2H, CH_2 at position-7, 6.80-7.85 (m, 10H, 9-Ar-*H* plus *H* at position-1), 8.05-8.40 (m, 1H, Ar-*H* at position-4).

Anal. Calcd. for $C_{30}H_{29}F_3N_2O_3$: C, 68.95; H, 5.60; N, 5.37; F, 10.91. Found: C, 69.02; H, 5.76; N, 5.62; F, 10.69.

2-(4-Pyridylmethyl)-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*]-[1,5]benzoxazepin-3-one (**5**).

In a 0.010 molar run, the reaction between **1**, 4-pyridinecarboxaldehyde, and sodium hydroxide, following the procedure employed to prepare **3a**, gave a 51% yield of colorless, crystalline **5**, m.p. 216-218° (2-propanol), ir (mull): ν 1630 (s), 1610 (s), 1580 (s), 1570 (s), 1555 (m), 1510 (m), 1475 (m) cm^{-1}; uv λ max (methanol): 245, 249, 280 (sh), 290 (sh), 340, 349 mμ (ϵ 22,800, 22,600, 7150, 5960, 17,850, 16,900); pmr (deuteriochloroform): δ 3.96 (s, 2H, CH_2Py), 5.37 (s, 2H, OCH_2), 7.20-7.70 (m, 8H, 5-Ar-*H*, plus 2 Py-*H* at positions-3′ and 5′, plus 1*H* at position-1), 8.35-8.75 (m, 3H, 2 Py-*H* at positions-2′ and 6′ plus Ar-*H* at position-4).

Anal. Calcd. for $C_{23}H_{15}F_3N_2O_2$: C, 67.63; H, 3.71; N, 6.86; F, 13.96. Found: C, 67.82; H, 3.99; N, 7.06; F, 14.10.

1,2-Dihydro-2-*trans*-benzylidene-11-(trifluoromethyl)-3*H*,7*H*-quino-[8,1-*cd*][1,5]benzoxazepin-3-one (**4a**).

(a) To a solution of 3.20 g. (0.010 mole) of **1** in 35 ml. of glacial acetic acid was added 1.10 g. (0.010 mole) of benzaldehyde, and 1.2 ml. of concentrated sulfuric acid. The mixture was stirred at room temperature for 30 hours and concentrated to dryness *in vacuo*. The residual solid was washed and air-dried to give 3.1 g. of solid, m.p. 95-140°. The solid was dissolved in 75 ml. of boiling glacial acetic acid, decolorized, filtered, the filtrate concentrated to about 15 ml. and cooled. The orange crystals that separated were filtered and dried *in vacuo* to give 0.43 g. (11% yield) of **4a**, m.p. 188-190°, ir (mull): ν 1665 (s), 1610 (s), 1600 (s), 1565 (m), 1505 (m), 1485 (s), 1445 (s) cm^{-1}; uv λ max (methanol): 223, 252, 298, 408 mμ (ϵ 29,400, 14,600, 20,400, 14,900): pmr (deuteriochloroform): δ 4.96 (s, 2H, N-CH_2), 5.34 (s, 2H, OCH_2), 6.50-8.00 (m, 10H, 10 Ar-*H*), 8.00 (s, 1H, *exo*-vinylic-*H*), 7.98-8.30 (m, 1H, Ar-*H* at position-4) [TLC (silica gel), R_f (chloroform), 0.73; benzene, 0.52; 2-propanol, 0.68; cyclohexane, 0.0].

Anal. Calcd. for $C_{24}H_{16}F_3NO_2$: C 70.74; H, 3.96; N, 3.44; F, 14.21. Found: C, 70.95; H, 4.17; N, 3.59; F, 14.26.

The workup of the acetic acid filtrate from **4a** gave no identifiable product.

(b) A mixture of 3.20 g. (0.010 mole) of **1**, 1.30 g. (0.012 mole) of benzaldehyde, 60 ml. of 10% aqueous hydrochloric acid, and 100 ml. of 2-propanol was heated under reflux for 48 hours; only after this heating period was there no discernible carbonyl absorption at 1686 cm^{-1}. The orange solid that crystallized from the cooled reaction mixture was filtered and recrystallized from 600 ml. of 1:1 2-propanol-absolute ethanol to give 2.20 g. (55% yield) of **4a** m.p. and mixture m.p. with the product from (a), 188-190°; the ir and pmr spectra of the two products were identical.

Anal. Found: C, 70.85; H, 3.96; N, 3.37; F, 14.21.

1,2-Dihydro-2-*trans*-(*m*-nitrobenzylidene)-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**4b**).

A mixture of 2.30 g. (0.007 mole) of **1**, 1.10 g. (0.007 mole) of *m*-nitrobenzaldehyde, 0.10 g. of *p*-toluenesulfonic acid, and 60 ml. of anhydrous benzene was heated under reflux for 5 hours, employing a Dean-Stark water separator. The orange-red reaction mixture was concentrated *in vacuo* and the residue triturated with 100 ml. of petroleum ether to give a deep orange solid. This was recrystallized from 300 ml. of 2-propanol to give 2.10 g. (66% yield) of orange colored **4b**, m.p. 183-186°, ir (mull): ν 1670 (s), 1615 (s), 1595 (m), 1580 (m), 1525 (s), 1505 (m), 1470 (s), 1460 (s), 1450 (s) cm^{-1}; uv λ max (methanol): 223, 265 (sh), 280 mμ (ϵ 41,500, 21,800, 28,500); pmr (deuteriochloroform): δ 4.92 (s, 2H, NCH_2), 5.33 (s, 2H, OCH_2), 6.40-7.90 (m, 7H, 7 Ar-*H*), 8.05 (s, 1H, vinylic-*H*), 8.14-8.55 (m, 3H, 2 Ar-*H ortho* to O_2N group plus Ar-*H* at position-4).

Anal. Calcd. for $C_{24}H_{15}F_3N_2O_4$: C, 63.71; H, 3.34; N, 6.19; F, 12.60. Found: C, 63.69; H, 3.34; N, 6.15; F, 12.55.

2-*trans*-[*p*-[2-(Diethylamino)ethoxy]benzylidene]1,2-dihydro-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**4c**).

A solution of 3.20 g. (0.010 mole) of **1**, 2.20 g. (0.010 mole) of *p*-(2-diethylaminoethoxy)benzaldehyde, 0.5 ml. of piperidine, and 110 ml. of absolute ethanol was heated under reflux for 5 hours. A probe of the reaction mixture revealed that no reaction had occurred. To the mixture was added 0.010 g. of benxoic acid and the heating under reflux continued for 14 hours. The solution was concentrated to dryness *in vacuo*. The viscous residue solidified when triturated with 20 ml. of petroleum ether. The solid was filtered and recrystallized from 200 ml. of hexane to give 2.80 g. (54% yield) of the orange-colored, crystalline **4c**, m.p. 110-112°, ir (mull): ν 1665 (s), 1610 (s), 1600 (s), 1510 (s), 1470 (s), 1450 (s), 1420 (s) cm^{-1}; uv λ max (methanol): 227, 249, 305, 240

mμ (ε 39,800, 23,000, 14,900, 20,600); pmr (deuteriochloroform): δ 1.10 [t (J = 11Hz), 6H, $N(CH_2CH_3)_2$], 2.74 [q (J = 6, 12 Hz), 4H, $N(CH_2CH_3)_2$], 2.97 [t (J = 10 Hz), 2H, $CH_2N(CH_2CH_3)_2$], 4.18 [t, (J = 11Hz), 2H, OCH_2CH_2], 5.0 (s, 2H, CH_2 at position-1), 5.37 (s, 2H, CH_2 at position-7), 6.73-7.70 (m, 9H, 9 Ar-*H*), 8.10 (s, 1H, vinylic-*H*), 8.10-8.40 (m, 1H, Ar-*H* at position-4).

Anal. Calcd. for $C_{30}H_{29}F_3N_2O_3$: C, 68.95; H, 5.60; N, 5.37; F, 10.91. Found: C, 68.97; H, 5.61; N, 5.22; F, 10.78.

1,2-Dihydro-11-(trifluoromethyl)-2-*trans*-(3,4,5-trimethoxybenzylidene)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**4d**).

A solution of 2.40 g. (0.0075 mole) of **1**, 1.50 g. (0.0075 mole) of 3,4,5-trimethoxybenzaldehyde, 50 ml. of anhydrous benzene, and three drops of piperidine was heated under reflux for 24 hours, employing a Dean-Stark water separator. At that time, no separation of water had occurred and a probe of the reaction mixture showed that no reaction had taken place. Ten drops of piperidine were then added and the heating under reflux was continued for an additional 4 hours; however, no reaction had occured at this point, either. To the mixture was then added 0.10 g. of benzoic acid and the heating under reflux continued for 20 hours; at the completion of that time, *ca.* 0.2 ml. of water had been separated. Concentration, *in vacuo*, gave 3.90 g. of an orange-colored residue; this was recrystallized from 400 ml. of 2-propanol to give 2.30 g. (62% yield) of the orange, crystalline **4d**, m.p. 209-211°, ir (mull): ν 1600 (s), 1610 (s), 1600 (s), 1590 (s), 1580 (s), 1500 (s), 1470 (s), 1460 (s), 1450 (s) cm^{-1}; uv λ max (methanol): 215, 252, 303, 338 mμ (ε 52,300, 22,000, 32,500, 35,000); pmr (deuteriochloroform): δ 3.90 (s, 9H, 3 OCH_3), 5.0 (s, 2H, NCH_2), 5.37 (s, 2H, OCH_2), 6.68-7.60 (m, 7H, 7-Ar-*H*), 7.98 (s, 1H vinylic-*H*), 8.00-8.40 (m, 1H, Ar-*H* at position-4).

Anal. Calcd. for $C_{27}H_{22}F_3NO_5$: C, 65.18; H, 4.46; N, 2.82; F, 11.46. Found: C, 65.30; H, 4.54; N, 2.68; F, 11.22.

11-(Trifluoromethyl)-2-(3,4,5-trimethoxybenzyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**3e**); Preparation by Isomerization **4d**.

To an orange-colored solution of 0.60 g. (0.0012 mole) of **4d** in 50 ml. of absolute ethanol was added 0.2 g. of powdered sodium hydroxide adn the whole heated to reflux; within 5 minutes, the color became a pale yellow and remained that color during the remaining 25 minutes of heating. Concentration of the solution, *in vacuo*, gave 1.0 g. of a solid residue. This was dissolved in 30 ml. of boiling benzene, the solution was filtered, and the filtrate cooled. The solid that separated was filtered to give 0.22 g. of unchanged **4d**, m.p. 208-211°. When the benzene filtrate was diluted with hexane, an off-white solid separated. This was filtered to give 0.55 g. of crude **3e**, m.p. 143-145°. Recrystallization from 100 ml. of diisopropyl ether gave 0.36 g. (60% yield) of colorless, crystalline **3e**, m.p. unchanged at 143-145°, ir (mull): ν 1633 (s), 1618 (s), 1610 (s), 1590 (s), 1570 (m), 1515 (m), 1500 (s), 1477 (s), 1460 (s), 1445 (s) cm^{-1}; uv λ max (methanol): 248, 278 (sh), 293 (sh), 343, 353 mμ (ε 27,500, 8600, 6100, 18,200, 18,400); pmr (deuteriochloroform): δ 3.80 [s, 9H, 3 OCH_3], 3.90 (s, 2H, $CH_2C_6H_2$), 5.36 (s, 2H, OCH_2), 6.61 (s, 2H, 2 Ar-*H* remaining in $CH_2C_6H_2$), 7.30-7.80 (m, 6H, 5 Ar-*H* plus *H* at position-1), 8.41-8.71 (m, 1H, Ar-*H* at position-4).

Anal. Calcd. for $C_{27}H_{22}F_3NO_5$: C, 65.18; H, 4.46; N, 2.82. Found: C, 65.25; H, 4.53; N, 2.94.

2-Benzyl-11-(trifluoromethyl)-3*H*,7*H*-quino[8,1-*cd*][1,5]benzoxazepin-3-one (**3a**). Preparation by Isomerization of **4a**.

A solution of 0.030 g. of **4a** 0.010 g. of powdered sodium hydroxide, and 10 ml. of absolute ethanol was heated under reflux for 2.5 hours. The solution was concentrated to dryness *in vacuo*, the solid residue washed with two 5 ml. portions of water, and recrystallized from 1.5 ml. of absolute ethanol to give 0.020 g. (66% yield) of **3a**, m.p. 200-201°; a mixture m.p. with **3a**, prepared as described above, was 201-202°, and their pmr and ir spectra were superimposable.

Attempted Isomerizations.

(a) Of **4a** by UV Irradiation.

A solution of 0.25 g. of **4a** in 20 ml. of anhydrous Reagent grade benzene in a quartz tube was irradiated at room temperature for 12 hours with a Hanovia 450 W mercury lamp contained in an immersible quartz housing that was surrounded by a Corex filter. A probe of the solution after the completion of the experiment was shown by tlc to contain only unchanged **4a**.

(b) Of **4a**, Thermally.

A solution of 0.25 g. of **4a** in 5 ml. of diethylbenzene was heated in a nitrogen atmosphere for 6 hours; tlc of a probe showed only unchanged **4a**.

(c) Of **3b** to the 2-*trans*-(*p*-Chlorobenzylidene) Derivative.

To a solution of 0.500 g. of **3b** in 30 ml. of anhydrous benzene was added 4 drops of piperidine and 30 mg. of benzoic acid. Subsequently, the mixture was stirred and heated under reflux for 22 hours. No change in color was observed. Workup of the reaction mixture gave only **3b**, identified by m.p. mixture m.p., and ir spectrum.

REFERENCES

(1) For Paper XI in this series, see, *J. Heterocyclic Chem.*, In Press.

(2) To whom all correspondence should be addressed.

(3) Present address: Rohm and Haas Co., Research Division, Spring House, Pa., 19477.

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

(5) The reaction is frequently described as the Claisen-Schmidt condensation. Relevant literature references are disclosed below.

(6) H. Rapoport and D. M. Bowman, *J. Org. Chem.*, **24**, 324 (1959) reported that piperidine catalyzed the reaction between 5,6-dihydro-4*H*-pyrido[3,2,1-*jk*]carbazol-4-one and benzaldehyde to give the 5,6-dihydro-5-benzylidene derivative (the *exo*cyclic α,β-unsaturated ketone) (a) and that (a) was rapidly isomerized (10 minutes, reflux temperature in ethanolic potassium hydroxide) to 5-(benzyl)-4*H*-pyrido[3,2,1-*jk*]carbazol-4-one, the *endo*cyclic α,β-unsaturated ketone).

(7) In the earlier literature, it was noted that two isomeric derivatives were obtained from the base or the acid catalyzed reactions of a fused polycyclic ketone and an aromatic aldehyde, *i.e.*, the melting points and the colors of the crystalline products were significantly different. The conclusions drawn were that these were *cis*- and *trans*- isomers of the *exo*cyclic derivatives, although, in no instance, was the proof of structure presented, nor, was there any effort made to assign the appropriate stereochemistry. This work has been reviewed by H. Rapoport and D. M. Bowman (6) and by H. Rapoport and J. R. Tretter, *ibid.*, 23, 248 (1958), who then showed that the two products were, in reality, simply *exo*- and *endo*-isomeric α,β-unsaturated ketones, and, in addition, that the *exo*-derivative was rapidly rearranged by ethanolic sodium hydroxide to the *endo*-isomer. The latter, however, did not under-

go the reverse rearrangement of the carbon-carbon double bond. Rapoport and his co-workers also observed that in their ir spectra, the carbonyl absorption moved, invariably from *ca.* 1660 cm^{-1} in the *exo-* to *ca.* 1630 cm^{-1} in the *endo-* derivative, and attributed this phenomenon to the enhancement of aromaticity in the *endo*-cyclic unsaturated-2-benzyl substituted derivative. Furthermore, the carbonyl absorption in the latter now coincided with that seen in the more fully aromatized, but benzyl-unsubstituted, parent ketone. In addition, in the 310-160 mμ region of their uv spectra, the rearranged products showed higher extinction coefficients, ranging from two- to five-fold, than seen in the fully saturated parent ketone. That these conclusions by Rapoport and his co-workers were correct, was shown by D. N. Kevill, E. D. Weiler, and N. D. Cromwell [*ibid.*, 29, 1276 (1964)]. These workers were able to demonstrate that the initially obtained *exo*-cyclic Claisen-Schmidt reaction products have the *trans*-stereochemistry (the vinylic proton of the arylidene group is *cis-* to the carbonyl oxygen atom), and that when the *trans*-derivatives were rearranged to the *cis* stereoisomers, the latter showed, in their ir spectra, carbonyl absorptions that represented a 3 to 10 cm^{-1} shift, *either upfield or downfield,* from the reference carbonyl absorptions of the *trans*-isomers, while in their uv spectra, the extinction coefficients in the 310-360 mμ region *either did not change, or, decreased by 25-35%* from the reference values in the *trans*-derivatives. The most recent work has utilized the pmr spectra of the Claisen-Schmidt products and has served to confirm the conclusions of Rapoport and Cromwell and their co-workers; see, for example D. N. Kevill, E. D. Weiler, and N. D. Cromwell (*vide supra*); A. Hassner and T. C. Mead, *Tetrahedron*, 20, 2201 (1964); D. D. Keane, K. G. Marathe, W. I. O'Sullivan, E. M. Philibin, R. M. Simons, and P. C. Teague, *J. Org. Chem.*, 35, 2286 (1970); R. E. Harmon, H. N. Subbarao, S. K. Gupta, and G. Slomp, *Synthetic Commun.*, 1, 117 (1971); M. Hooper and W. N. Pitkethly, *J. Chem. Soc., Perkin I*, 1607 (1972); and, P. Bennett, J. A. Donnelly, D. C. Meany, and P. O'Boyle, *ibid.*, 1554 (1972). See, also, H. O. House, "Modern Synthetic Reactions," W. H. Benjamin, Inc., N.Y., N.Y., 1965, p. 220.

(8) L. M. Jackmann and S. Sternhell, "Applications of Nuclear Magnetic REsonance Spectroscopy in Organic Chemistry," Pergamon Press, N.Y., N.Y., 2nd Ed., 1969, pp. 111-113, 246-248. A comparison of the deuteriochloroform spectrum with that obtained in perdeuteriobenzene shows striking alterations: the proton at position-4 and the benzyl methylene protons are shifted *downfield* by 0.30 and 0.20 ppm. respectively; the aromatic envelope was segmented broadly *upfield*, in part almost 1 ppm, but the singlet contributed by the five phenyl protons moved *upfield* only 0.12 ppm; and, significantly, the signal for the methylene protons at position-7 was shifted upfield by 0.74 ppm.

(9a) $Eu(fod)_3$ = Tris-1,1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedione Europium chelate; (b) H. L. Yale, B. Toeplitz, J. Z. Gougoutas, and M. Puar, *J. Heterocyclic Chem.*, 10, 123 (1973).

(10) The decoupling and shift reagent studies were performed by Dr. M. Puar.