1,4-Benzodioxanes. I. A Synthesis Involving the Reaction of α-Halo Michael Acceptors with Catechol

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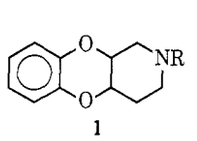
α-Halo Michael acceptors react with catechol in aprotic solvents in the presence of potassium carbonate to form 2-substituted 1,4-benzodioxanes. Cis β-alkyl and β-alicyclic α-halo Michael acceptors yield primarily cis 2,3-disubstituted 1,4-benzodioxanes, whereas trans 2,3-disubstituted isomers predominate when catechol is treated with trans β-alkyl α-halo Michael acceptors. It is therefore inferred that the reaction proceeds *via* a cis Michael addition of catechol monoanion, followed by intramolecular nucleophilic displacement of halide from the newly generated sp^3 α carbon by the remaining catechol oxygen. Ethyl 1,4-bromobut-2-enoate, formed by isomerization of ethyl 2-bromobut-2-enoate during the course of the reaction of the latter with catechol, is believed to be the source of the isomeric ethyl 1,4-benzodioxanyl-2-acetate isolated as a minor product.

2-Substituted 1,4-benzodioxanes represent a series of compounds of considerable medicinal importance.[1-5] As a part of a program directed toward investigation of relationships between conformational and pharmacological properties of this class of compounds, the preparation of tricyclic derivatives of types **1** and **2** was desired. General methods for the synthesis of 1,4-benzodioxanes, *e.g.*, reaction of catechol with vicinal dibromide[6] or an epihalohydrin,[7] did not appear to be efficient procedures for preparing tricyclic analogs. Hence, the reactions of catechol with α-halo Michael acceptors **3**–**7** were investigated.[8] In this report the scope, stereochemical consequences, and probable mechanism of this general reaction are described.

Some time ago, Koo, *et al.*,[6a] reported the "condensation" of catechol with ethyl 2,3-dibromopropanoate (**8**) in the presence of anhydrous potassium carbonate to form ethyl 1,4-benzodioxane-2-carboxylate (**10**). Similarly, a mixture of **12a** and **12b** of undetermined isomer composition was later obtained from the reaction of catechol with ethyl 2,3-dibromobutanoate (**9**).[6b] It seemed likely to us that, under the conditions employed for these reactions (K_2CO_3, 55°, 16 hr), elimination of hydrogen bromide from **8** and **9** to give the α-bromo olefinic esters **3** and **5** would occur more rapidly than would nucleophilic displacement of bromide ion by catechol monoanion. Indeed, when **8** (a mixture of diastereoisomers) was allowed to react under the above conditions for 12 hr in the absence of catechol, ethyl *cis*-2-bromobut-2-enoate (**5a**) was obtained in good yield. Less than 5% of the trans isomer **5b** was obtained. Thus, it is very probable that **10** and **12** are formed from the α-halo Michael acceptors **3** and **5a**, respectively, in the reactions reported by Koo, *et al.*



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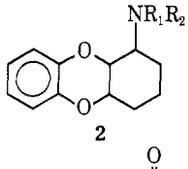

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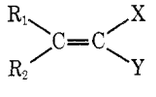
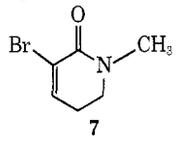
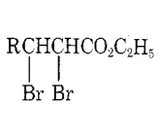
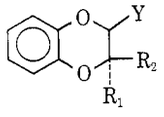


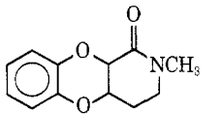


7

3, $R_1 = R_2 = H$; X = Br; Y = CO_2Et
4, $R_1 = R_2 = H$; X = Cl; Y = CN
5a, $R_1 = H$; $R_2 = CH_3$; X = Br; Y = CO_2Et
b, $R_1 = CH_3$; $R_2 = H$; X = Br; Y = CO_2Et
6, $R_1 = R_2 = CH_3$; X = Br; Y = CO_2Et





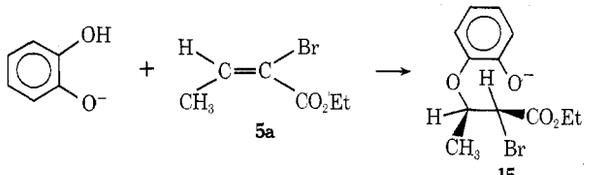


8, R = H
9, R = CH_3

10, $R_1 = R_2 = H$; Y = CO_2Et
11, $R_1 = R_2 = H$; Y = CN
12a, $R_1 = H$; $R_2 = CH_3$; Y = CO_2Et
b, $R_1 = CH_3$; $R_2 = H$; Y = CO_2Et
13, $R_1 = R_2 = CH_3$; Y = CO_2Et

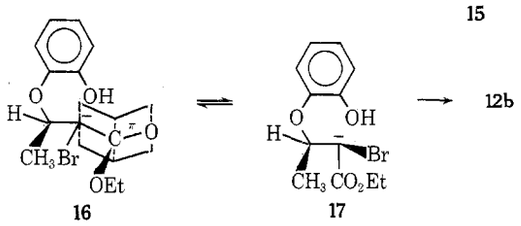
14a, cis
b, trans

Reference to per cent yield data (Table I) provides an indication of the scope of the title reaction. Increasingly poorer yields were obtained as the size and number of β substituents in the α-halo Michael acceptor were increased. Of perhaps greater interest are the stereochemical consequences of the reaction investigated by nmr analysis of product ratios (Table I) obtained from the reactions of catechol with **5a**, **5b**, and **7**. It is noted that reactions of the cis Michael acceptors **5a** and **7** with catechol yield predominantly the thermodynamically less stable *cis*-1,4-benzodioxanes **12a** and **14a**, respectively, while the trans isomer **5b** gives primarily the *trans*-1,4-benzodioxane **12b**. These observations best support the hypothesis that the reaction proceeds primarily by a cis Michael addition of catechol anion (*e.g.*, to **5a**) to form the intermediate **15**, wherein a proton (from catechol) is added from the same side, followed by intramolecular nucleophilic displacement of bromide ion to form **12a** as shown. Inversion of the intermediate carbanion (**16** → **17**), prior to proton attack, accounts for the **12b** formed.



5a

15



16 **17**

The analogous reaction of catechol with the ring compound **7**, wherein the barrier to inversion of the intermediate carbanion should be much higher than in the acyclic case, favors the cis isomer over the trans isomer **14b** by a 20:1 ratio. Comparatively few studies relevant to stereochemical aspects of the Michael reaction have been reported.[9] The general consensus of those investigations involving six-membered ring Michael acceptors[9-12] supports

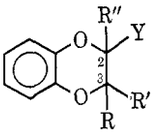
Table I
1,4-Benzodioxanes. Yields and Product Ratios

Michael acceptor	Principal product(s)	Yield, %
3	**10**	74
4	**11**	86
5a	60% **12a**, 40% **12b**	28
5b	28% **12a**, 72% **12b**	32
6	**13?**	<5
7	95% **14a**, 5% **14b**	17

overlap should otherwise be greater in **19** than in **18**), thus reducing the contribution of maximal overlap to stabilizing the intermediate carbanion.

In addition to **12a** and **12b**, relatively small amounts (10–20%) of the isomeric ester **20** (*m/e* 222) were isolated in reactions of catechol with either **5a** or **5b**. It is assumed that **20** arises from the reaction of catechol with ethyl 4-bromo-2-butenoate (**21a**), the latter being formed by aniontropic 1,3 shift of halide involving **21b**,[17] formed by tautomerism of **5a** (or **5b**).[18] Not surprisingly, **20** became

Table II
Nmr Data for 1,4-Benzodioxane Ring Protons (in $DCCl_3$)



10, R = R′ = H; Y = CO_2Et $\delta H_2 = 4.50$ $J = 3.5$ Hz; $\delta H_3 = 4.06$

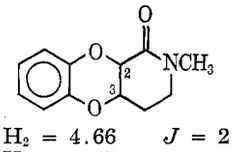
11, R = R′ = H; Y = CN $\delta H_2 = 4.91$ $J_{trans} = 3.8$ Hz; $\delta H_3 = 4.33$ $J_{cis} = 2.7$ Hz; $J_{3,3'} = -11.8$ Hz

12a, R = H; R′ = CH_3; Y = CO_2Et $\delta H_2 = 4.67$ $J = 2.6$ Hz; $\delta H_3 \cong 4.5$

12b, R = CH_3; R′ = H; Y = CO_2Et $\delta H_2 = 4.41$ $J = 5.5$ Hz; $\delta H_3 \cong 4.5$

20, R = R′ = H; Y = CH_2CO_2Et $\delta H_2 = 4.62$ $J_{2,3} = 7.08$ Hz; $\delta H_3 = 4.01$ $J_{2,3'} = 2.21$ Hz; $\delta H_3' = 4.31$ $J_{3,3'} = -12.53$ Hz

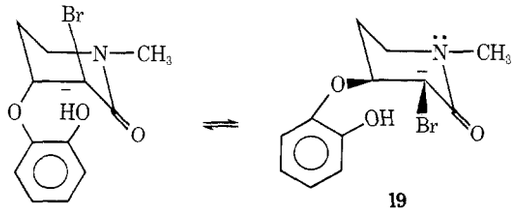
22, R = R′ = H; R″ = CH_3; Y = CH_2CO_2Et $\delta H_3 = 3.78$ $J_{3,3'} = 11.4$ Hz; $\delta H_{3'} = 4.11$



14a $H_2 = 4.66$ $J = 2.8$ Hz; $H_3 = 4.57$

14b $H_2 = 4.35$ $J = 9.5$ Hz; $H_3 = 4.18$

the view that the reaction is characterized by a trans antiparallel attack of the donor to the predominant conformation of the Michael acceptor, wherein both the attacking nucleophile and the proton enter from the axial side. It must be emphasized that in each of these cases the reactions were performed in protic solvents. Thus, the addition of a proton (from solvent) occurs most favorably from the least hindered axial side. Michael reactions involving diprotic donors (*e.g.*, catechol) carried out in aprotic solvents (*e.g.*, acetone, dioxane) appear to represent a special case in which the intramolecular addition of the proton to the equatorial face of the intermediate carbanion is favored. In the case of **7**, equatorial attack of a proton to conformer **18** would be favored over axial attack to conformer **19**, since the latter is destabilized by steric and dipo-



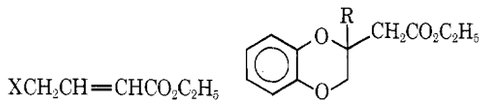
18 **19**

lar 1,2 interaction[13,14] of the carbonyl oxygen and the equatorial bromine atoms and (possibly) a 1,3 interaction between the carbanion and nitrogen lone pairs.[15,16] Furthermore, amide resonance may effectively compete with delocalization of the carbanion into the carbonyl group (π

the major product when either potassium iodide or bromide were added to the reaction mixture. Furthermore, direct reaction of catechol with **21a** gave good yields of **20**. Similarly, the isomeric ester **22** (not the expected **13**) was obtained when catechol was treated with ethyl 2-bromo-3-methyl-2-butenoate in the presence of K_2CO_3 and KI (thus, the reported preparation of **13** *via* the reaction of catechol with ethyl α,β-dibromovalerate by Augstein, *et al.*,[4] is no doubt in error).

Yet a fourth compound, the lactone **23**, was obtained as the major product when catechol was treated with **5a** or **5b** at 25° with KI present. No **23** was isolated when the halide was omitted from the reaction. It was concluded, therefore, that halide ion facilitates isomerization of the double bond to the β,γ position to give **21b**. Nucleophilic attack at the highly activated α carbon by catechol, followed by intramolecular transesterification of the carbethoxy group by the remaining catechol oxygen and migration of the double bond into conjugation with the lactone carbonyl group, then provides **23** (it is entirely possible that transesterification precedes double-bond migration and nucleophilic attack, of course). The geometry of **23**, which according to its nmr spectrum, melting point, and tlc behavior appears to be a single compound, has not been established. Catalytic reduction of **23** gave 3-ethyl-2-oxo-1,4-benzodioxane, confirming that **23** is not the isomeric seven-membered ring isomer.

Proton magnetic resonance data for the 1,4-dioxane ring protons of the compounds prepared are listed in Table II.

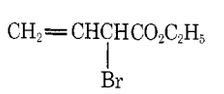


$XCH_2CH{=}CHCO_2C_2H_5$

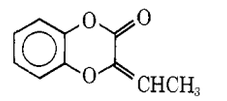
21a, X = Br or I

20, R = H

22, R = CH_3



21b



23

Although approximate coupling constants for the tricyclic isomers **14a** and **14b** had previously been obtained from Eu(fod)$_3$-shifted 60-MHz spectra,[19] accurate $J_{2,3}$ and δ values required the use of 220-MHz spectra for resolution of 2 H and 3 H resonances. $J_{2,3}$ values for **14a** and **14b** provide a reasonable standard for J_{ae} (average) and J_{aa} in 1,4-benzodioxanes and are in good agreement with values reported by previous workers.[20-23] Mixtures of 2-carbethoxy-3-methyl-1,4-benzodioxanes **12a** and **12b** were not separated, but their ratios were estimated by both integration of the ring methyl protons in Eu(fod)$_3$-shifted spectra and the sums of peak heights for the 2 H ring doublets. The ring protons of **20** form the AA'B part of an AA'BXX' spectrum. This five-spin system was subjected to computer analysis using the LAOCOON III program.

Experimental Section

Nmr spectra were determined on Varian T-60 and HA-100 spectrometers and, in the case of **12a** and **12b** (mixtures), **14a**, and **14b**, an HR-220 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Melting points were obtained using a Thomas-Hoover melting point apparatus and are corrected.

Ethyl *cis*-2-bromobut-2-enoate (5a) was obtained by refluxing a mixture of 27.4 g (0.1 mol) of ethyl 2,3-dibromobutanoate and 41.4 g (0.3 mol) of anhydrous K_2CO_3 in dry acetone under a stream of N_2 for 12 hr. After removal of the acetone (aspirator), water and methylene chloride were added to the residue. The methylene chloride was then separated and extracted, in turn, with 5% NaOH, 5% HCl, and saturated NaCl solutions, dried over anhydrous Na_4SO_4, and evaporated. Vacuum distillation of the residue gave 13.9 g (79%) of **5a**: bp 83–84° (20 mm) [lit.[24] bp 82–83° (20 mm)]; nmr ($CDCl_3$) δ 5.66 (q, 1, J = 7.1 Hz, CH=C), 4.43 (q, 2, J = 8.4 Hz, OCH_2), 1.93 (d, 3, J = 7.1 Hz, C=CCH_3), 1.33 (t, 3, J = 8.4 Hz, CH_3).

Ethyl *trans*-2-bromobut-2-enoate (5b) was prepared by refluxing 27.4 g (0.1 mol) of ethyl 2,3-dibromobutanoate and 12.7 g (0.15 mol) of freshly distilled pyridine in 100 ml of dry toluene for 8 hr. The mixture was cooled and fitered, and the filtrate was evaporated to remove the toluene and excess pyridine. The residue was taken up in methylene chloride, extracted with 5% HCl and saturated NaCl solutions, and dried over anhydrous Na_2SO_4, the methylene chloride was evaporated, and the residue was distilled, giving 2.5 g (14%) of **5b**, bp 67–70° (14 mm), and 12.8 g (72%) of **5b**: bp 78–79° (14 mm) [lit.[25] bp 78–79° (14 mm)]; nmr ($CDCl_3$) δ 6.60 (q, 1, J = 7.8 Hz, CH=C), 4.25 (q, 2, J = 7.4 Hz, OCH_2), 1.93 (d, 3, J = 7.8 Hz, C=CCH_3), 1.33 (t, 3, J = 7.4 Hz, CH_3).

1-Methyl-2-piperidone was obtained by treating the sodium salt of 2-piperidone (formed by reaction of 2-piperidone with an equimolar quantity of sodium hydride) with a 10% excess of methyl iodide.

3,3-Dibromo-1-methyl-2-piperidone was prepared by treating 1-methyl-2-piperidone with bromine in the presence of phosphorus pentachloride and zinc chloride according to the procedure of Wineman, *et al.*,[26] for the α,α-dibromination of ϵ-caprolactam. Combustion data indicated that the product, mp 74–75° after several recrystallations (95% ethanol), was contaminated with traces of α-chlorinated product. It was not purified further. *Anal.* Calcd for $C_6H_9Br_2NO$: C, 26.56; H, 3.32; Br, 59.04; N, 5.16. Found: C, 28.09; H, 3.17; Br, 52.86; N, 5.42.

1-Methyl-3-bromo-1,2,5,6-tetrahydro-2(2*H*)-pyridone (7) was obtained by heating a mixture of impure 1-methyl-3,3-dibromo-2-piperidone and an equimolar quantity of anhydrous calcium carbonate in dimethylformamide at 80–85° for 20 hr. The majority of the dimethylformamide was removed by vacuum distillation at 10–15 mm and the residue was taken up in methylene chloride and extracted with water. The combined methylene chloride extracts were washed with 5% HCl and saturated NaCl solutions and dried over anhydrous Na_2SO_4. After removal of the solvent, distillation of the residue gave **7**, bp 94–95° (2 mm), which solidified on standing to give brownish plates, mp 44–47° (aqueous ethanol). Combustion analysis indicated the presence of impurity, assumed to be 1-methyl-3-chloro-1,2,5,6-tetrahydro-2(2*H*)-pyridone (based on the nmr spectrum), which could not be separated by attempted fractional distillations and recrystallizations. The nmr spectrum ($CDCl_3$) of the mixture gave δ 7.01 (t, 0.67, J = 4.3 Hz, BrC=CH), 6.67 (t, 0.33, J = 4.6 Hz, ClC=CH), 3.53 (t, 2, J = 7.4 Hz, NCH_2), 3.01 (s, 3, NCH_3), 2.5 (m, 2, CH_2). *Anal.* Calcd for a mixture containing 67% C_6H_8BrNO and 33% C_6H_8ClNO: C, 41.72; H, 4.54; N, 8.11. Found: C, 41.55; H, 4.78; N, 8.29.

Reactions of catechol with α-halo Michael acceptors were carried out using essentially identical procedures in every case. *Therefore, one representative example will be described in detail* and only physical data for the remaining compounds will be described.

Ethyl 1,4-Benzodioxane-2-carboxylate (10). A mixture of 12 g (0.11 mol) of catechol, 17.9 (0.1 mol) of ethyl 2-bromopropenoate (**3**), and 41.4 g (0.3 mol) of anhydrous K_2CO_3 was refluxed in 200 ml of dry acetone for 18 hr. After the acetone was removed (aspirator) the residue was taken up in methylene chloride, extracted (in turn) with water, 5% NaOH, 5% HCl, and saturated NaCl solutions, and dried over anhydrous Na_2SO_4. Evaporation of the solvent and distillation of the residue afforded 15.4 g (74%) of **10**: bp 106–108° (0.14 mm) [lit.[6a] bp 105–107° (0.15 mm)]; nmr ($CDCl_3$) δ 6.84 (m, 4, aromatic), 4.50 (t, 1, J = 3.5 Hz, ring OCH), 4.06 (d, 2, J = 3.5 Hz, ring OCH_2), 4.23 (q, 2, J = 7.0 Hz, ester OCH_2), 1.28 (t, 3, J = 7.0 Hz, CH_3).

2-Cyano-1,4-benzodioxane (11) was obtained from the reaction of catechol with α-chloroacrylonitrile (**4**) in 86% yield as a solid: mp 57° (toluene–petroleum ether) [lit.[20] bp 93–94° (0.2 mm)]; nmr ($CDCl_3$) δ 6.90 (s, 4, aromatic), 4.91 (t, 1, J_{trans} = 7.8, J_{cis} = 2.7, $J_{3,3}$ = −11.8 Hz, OCH), 4.33 (d, 2, J_{trans} = 3.8, J_{cis} = 2.7, $J_{3,3}$ = −11.8 Hz, OCH_2).

Mixtures of ethyl *cis*- and *trans*-3-methyl-1,4-benzodioxane-2-carboxylate (12a and 12b) and ethyl 1,4-benzodioxanyl-2-acetate (20) were obtained under the conditions described above as follows: from ethyl 2,3-dibromobutyrate (**9**), 53% **12a**, 38% **12b**, and 9% **20** (30% yield); from ethyl *cis*-2-bromobut-2-enoate (**5a**), 54% **12a**, 36% **12b**, and 10% **20**; and from ethyl *trans*-2-bromobut-2-enoate (**5b**), 26% **12a**, 66% **12b**, and 8% **20**. Chromatography of the mixture obtained from **5b** on neutral alumina with benzene–dichloromethane separated **20** out as a pure fraction, but failed to separate **12a** and **12b**. Distillation of the mixture of **12a** and **12b** gave a colorless oil, bp 96–98° (0.1 mm) [lit.[6b] bp 96–97° (0.1 mm)]. In the 220-MHz nmr spectrum of the mixture, doublets were observed at δ 1.40 (J = 7.1 Hz) and 1.36 ppm (J = 7.2 Hz), respectively. Resonances of the C-3 OCH, aromatic, and ester protons for the two isomers overlapped.

Ethyl 1,4-Benzodioxanyl-2-acetate (20). A. From 5b. When catechol was treated with **5b** (or **5a**) in the presence of an equimolar quantity of KI, a 30% yield of **12a**, **12b**, and **20** was obtained in a ratio of 20% **12a** and **12b** to 80% **20**.

B. From Ethyl 4-Bromo-2-butenoate (21a). Reaction of catechol with **21a** gave an 82% yield of **20**: bp 108–110° (0.1 mm) [lit.[27] bp 168–171° (7 mm), lit.[28] mp 100–101°]; acid mp 100–101°; nmr ($CDCl_3$) δ 6.84 (m, 4, aromatic), 4.62 (m, 1, $J_{2,3}$ = 7.08, $J_{2,3}$ = 2.21, $J_{2\alpha}$ = 6.32, $J_{2\alpha}$ = 6.89 Hz, OCH), 4.01, 4.31 (m, $J_{2,3}$ = 7.08, $J_{2,3}$ = 2.21, $J_{3,3}$ = −12.53 Hz, OCH_2), 2.63, 2.77 (m, 2, $J_{2\alpha}$ = 6.32, $J_{2\alpha}$ = 6.89, $J_{\alpha,\alpha}$ = −16.03 Hz, CH_2CO), 4.21 (q, 2, J = 7.2 Hz, CH_2CH_3), 1.28 (t, 3, J = 7.2 Hz, CH_3).

Ethyl 3,3-Dimethyl-1,4-benzodioxane-2-carboxylate (13). The nmr spectrum of the residue obtained from the work-up of the reaction of catechol with ethyl 3-methyl-2-bromo-2-butenoate showed less than 5% of **13** (from aromatic and ring CH_3 absorptions). Further purification was not attempted.

Ethyl 2-Methyl-1,4-benzodioxanyl-2-acetate (22). A. From Ethyl *cis*-2-Bromobut-2-enoate (5a). Reaction of **5a** with catechol in the presence of an equimolar amount of KI gave **22** (26%), bp 120–122° (0.2 mm).

From the reaction of ethyl 4-bromo-3-methyl-2-butenoate[26] with catechol, a 78% yield of **22** was obtained: bp 121–122° (0.2 mm); nmr ($CDCl_3$) δ 3.94 (q, 2, J = −11.5 Hz, ring CH_2), 2.52 (s, 2, CH_2CO), 1.29 (s, 3, CH_3), 1.08 (t, 3, J = 7.2 Hz, ester CH_3), 0.00 (m, 4, aromatic). *Anal.* Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83. Found: C, 65.92; H, 6.60.

3-Ethylidino-2-oxo-1,4-benzodioxane (23). Reaction of catechol with **5b** at 25° for 72 hr in the presence of KI gave **23** (18% yield): mp 74–75° (95% ethanol); nmr ($CDCl_3$) δ 6.99 (s, 4, aromatic), 6.29 (q, 1, J = 7.6 Hz, CH=), 1.88 (d, 3, J = 7.6 Hz, CH_3). *Anal.* Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.54. Found: C, 67.96; H, 4.51. The nmr spectrum of the crude reaction mixture indicated the presence of about 20–25% of a mixture of **12a** and **12b** and 30% of unreacted **5b**, which were removed by fractional distillation.

***cis*- and *trans*-1-methyl-1,2,3,4,5,6-hexahydrobenzo[*b*]-*p*-dioxino[3,4-*e*]pyrid-2(2*H*)-one (14a and 14b)** were prepared by treating catechol with 1-methyl-3-bromo-1,2,5,6-tetrahydro-2(2*H*)-pyridone (**7**) in the usual manner. Column chromatography of the residue following work-up on neutral alumina with benzene–dichloromethane gave **14b**: mp 218° after recrystallizations from acetone; 220-MHz nmr ($CDCl_3$) δ 6.93 (m, 4, aromatic), 4.35 (d, 1, J = 9.4 Hz, C-2 OCH), 4.18 (m, 1, C-3 OCH), 3.39 (m, 2, NCH_2), 2.99 (s, 3, NCH_3), 2.45, 2.13 (m, 2, CH_2). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.97; N, 6.87. Found: C, 65.67; H, 5.92; N, 6.66.

Subsequent fractions gave **14a**: mp 136–137° after recrystallizations from benzene; nmr ($CDCl_3$) δ 6.93 (m, 4, aromatic), 4.66 (d, 1, J = 2.8 Hz, C-2 OCH), 4.57 (m, 1, C-3 OCH), 3.62, 3.25 (m, 2, NCH_2), 2.93 (s, 3, NCH_3), 2.37, 2.38 (m, 2, CH_2). *Anal.* Calcd for $C_{12}H_{13}NO_3$: C, 65.75; H, 5.97; N, 6.87. Found: C, 65.76; H, 5.96; N, 6.29.

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Registry No.—**3**, 5459-35-8; **4**, 920-37-6; **5a**, 51263-38-8; **5b**, 51263-39-9; **7**, 51263-41-3; **9**, 609-11-0; **10**, 4739-94-0; **11**, 1008-92-0; **12a**, 51263-58-2; **12b**, 51263-59-3; **14a**, 35528-83-7; **14b**, 35528 84-8; **20**, 51263-60-6; **21a**, 6065-32-3; **22**, 51263-61-7; **23**, 51263-62-8; 2-piperidone, 675-20-7; 1-methyl-2-piperidone, 931-20-4; 3,3-dibromo-1-methyl-2-piperidone, 49785-78-6; 1-methyl-3-chloro-1,2,5,6-tetrahydro-2(2*H*)-pyridone, 51263-48-0; catechol, 120-80-9; ethyl 4-bromo-2-methyl-2-butenoate, 51263-63-9.

References and Notes

(1) E. Fourneau and D. Bovet, *Arch. Int. Pharmacodyn. Ther.*, **46**, 178 (1933).
(2) R. Landi-Vittroy, M. A. Iorio, F. Fraschetti, and S. Chiavarelli, *Gazz. Chim. Ital.*, **93**, 38 (1963).
(3) M. W. Baines, D. B. Cobb, R. J. Eden, R. Fielden, J. N. Gardner, A. M. Roe, W. Tertiuk, and J. L. Willey, *J. Med. Chem.*, **8**, 81 (1965).
(4) J. Augstein, S. M. Green, A. M. Monro, G. W. H. Potter, C. R. Worthing, and T. I. Wrigley, *J. Med. Chem.*, **8**, 446 (1965); A. M. Monro, G. W. H. Potter, and M. J. Sewell, *ibid.*, **10**, 880 (1967).
(5) R. Howe, B. S. Rao, and M. S. Chodnekar, *J. Med. Chem.*, **13**, 169 (1970).
(6) (a) J. Koo, S. Avakian, and G. J. Martin, *J. Amer. Chem. Soc.*, **77**, 5373 (1955); (b) J. Koo, *J. Org. Chem.*, **26**, 339 (1961).
(7) O. Stephenson, *J. Chem. Soc.*, 157 (1954).
(8) An attempt to synthesize **2** by Michael addition of catechol to 2-bromo-2-cyclohexenone followed by reductive amination is in progress. It is anticipated that **1** will be prepared from **14** by diborane reduction.
(9) P. Chamberlain and G. H. Whitham, *J. Chem. Soc., Perkin-Trans*, 2, 130 (1972), and references cited therein.
(10) W. E. Truce and A. J. Levy, *J. Amer. Chem. Soc.*, **72**, 5529 (1950).
(11) R. A. Abramovitz and D. L. Struble, *Tetrahedron*, **24**, 357 (1968).
(12) N. L. Allinger and C. K. Riew, *Tetrahedron Lett.*, 1269 (1966).
(13) E. J. Corey, *J. Amer. Chem. Soc.*, **75**, 3201 (1953).
(14) N. L. Allinger, J. Allinger, L. A. Freiberb, R. F. Cjaja, and N. A. Lebel, *J. Amer. Chem. Soc.*, **82**, 5976 (1960).
(15) R. O. Hutchins, L. D. Kopp, and E. Eliel, *J. Amer. Chem. Soc.*, **90**, 7174 (1968).
(16) R. A. Y. Jones, A. R. Katritzky, and M. Snarey, *J. Chem. Soc. B*, 131 (1970).
(17) It is, of course, also possible that **20** is formed from **21b** or a common ion-paired intermediate of **21a** and **21b**.
(18) The formation of α-methoxycrotonic acids from α-bromocrotonic acids has been explained on the basis of similar tautomerism: L. N. Owen, *J. Chem. Soc.*, 385 (1945); 1030 (1947); 3089 (1949); 236 (1949).
(19) J. F. Caputo and A. R. Martin, *Tetrahedron Lett.*, 4547 (1971).
(20) M. J. Cook, A. R. Katritzky, and M. J. Sewell, *J. Chem. Soc. B*, 1207 (1970).
(21) G. Pfundt and S. Farid, *Tetrahedron*, **22**, 2237 (1966).
(22) R. Berthold, P. Niklaus, A. P. Stoll, and F. Troxlen, *Helv. Chim. Acta*, **53**, 1128 (1970).
(23) V. Rosnati, F. Sannicolo, and G. Zecchi, *Gazz. Chim. Ital.*, **201**, 344 (1971).
(24) H. Moureau, P. Chovin, M. Garcin, and J. Ventrillard, *Bull. Soc. Chim. Fr.*, 296 (1952).
(25) G. W. Stacy and G. D. Wagner, *J. Amer. Chem. Soc.*, **74**, 909 (1952).
(26) R. J. Wineman, E.-P. T. Hsu, and C. F. Anagnostopoulos, *J. Amer. Chem. Soc.*, **80**, 6233 (1958).
(27) M. Sasamoto, *Chem. Pharm. Bull.*, **8**, 324 (1960).
(28) C. Milani, R. Landi-Vittory, and G. B. Marini-Bettolo, *Rend. Ist. Super. Sanita (Ital. Ed.)*, **20**, 201 (1959); *Chem. Abstr.*, **54**, 1523a (1960).

1,4-Benzoxathians. 1. Reactions of *o*-Mercaptophenol with α-Halo Michael Acceptors

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α-Halo Michael acceptors react with *o*-mercaptophenol in the presence of potassium carbonate to form substituted 1,4-benzoxthians, wherein the S atom may be α or β to the activating function. α-S substitution predominates when there are β-alkyl substituents present in the α-halo Michael acceptor, while β-S substitution occurs when the α carbon is unsubstituted. Both α- and β-S-substituted products were obtained in the reaction of *o*-mercaptophenol with 3-bromo-1,2,5,6-tetrahydro-2(2*H*)-pyridone, the α-S-substituted product having a trans configuration and the β-S-substituted product a cis configuration.

As part of a continuing investigation of the base-catalyzed (anhydrous K_2CO_3) reactions of dibasic nucleophiles with α- and γ-halo Michael acceptors,[1,2] reactions of *o*-mercaptophenol with **1–5** were examined. Because of the greater nucleophilicity of sulfur as compared with oxygen and the greater acidity of thiophenols as compared with phenols,[3,4] it was anticipated that the thiophenolate anion generated in an alkaline medium would preferentially attack the double bond of an α-halo Michael acceptor. This would be followed by nucleophilic displacement of halide at the newly generated sp^3-hybridized α carbon to yield, preferentially, 1,4-benzoxathians wherein the S atom is β to the activating group. This prediction is supported by the work of Tsai, *et al.*,[5] who recently reported