Asymmetric Thiazolium Salt Catalysis of the Benzoin Condensation

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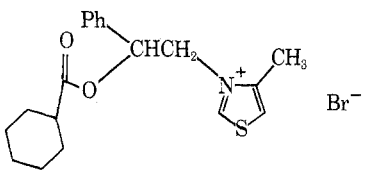
Starting from optically active α-substituted ethylamines, salts of the following thiazolium ions have been synthesized: (*R*)-(−)-3-α-benzylethyl-4-methylthiazolium (**4a**): (*R*)-(−)- and (*S*)-(+)-4-methyl-3-α-(1-naphthyl)ethylthiazolium (**4b**); and (*S*)-(+)-4-methyl-3-α-phenylethylthiazolium (**4c,d**). Asymmetric induction of the benzoin condensation using these thiazolium salts as catalysts has been studied. Optical purities as large as 51% were observed.

Although there have been various reports of reactions with asymmetric induction,[2] relatively few examples of homogeneous asymmetric catalysis are known. The benzoin condensation and related condensations catalyzed by thiazolium salts constitute unique examples of homogeneous catalysis by a relatively simple organic compound of a type of reaction which does not proceed otherwise (except by use of cyanide ion) in finite time. Benzoin is not produced from benzaldehyde by acid or base catalysis, or under thermal or free-radical conditions. Some years ago, a homogeneous, asymmetric benzoin condensation was reported[3] using optically active thiazolium salt **1** as catalyst. The product obtained had an optical purity as high as 22%. This type of reaction provides a good model for the mode of action of thiamine pyrophosphate (TPP) in enzymatic reactions. TPP is required as coenzyme in such systems as the decarboxylation of pyruvate to acetaldehyde and the formation of acetoin or α-acetolactate from pyruvate.[4] The present study elucidates the stereochemical course of the asymmetric thiazolium salt catalysis of the benzoin condensation (Scheme I).



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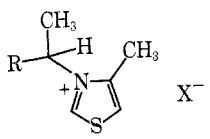
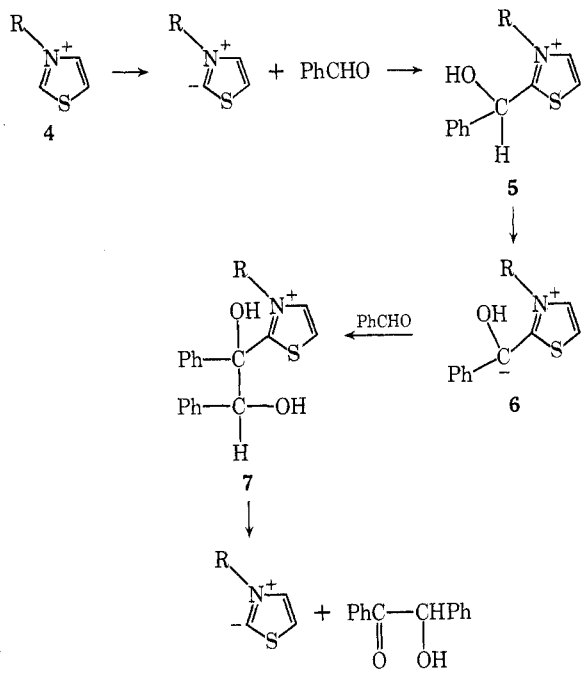
Synthesis of the Catalysts. The following considerations led to the synthesis of 4-methyl 3-α-substituted ethylthiazolium salts **4a–d** as asymmetric catalysts: (a) location of the asymmetric center next to the reacting site, and (b) the high yields of benzoin obtained with 3-benzyl- or 3-phenethylthiazolium salts.[5,6] The higher yields observed suggest an advantage in having a phenyl group in the α or β position of the N substituent.



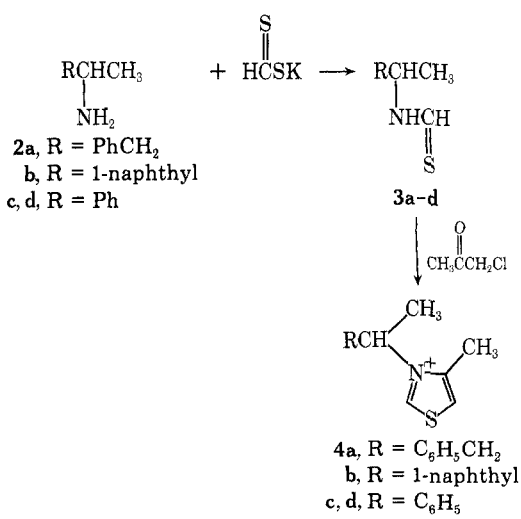
4a, R = $PhCH_2$; X = Cl
b, R = 1-naphthyl; X = Br
c, R = Ph; X = (+)-3-bromocamphor 9-sulfonate
d, R = Ph; X = (−)-3-bromocamphor 9-sulfonate

The crystalline thiazolium salts (*R*)-(−)-**4a**, (*R*)-(−)-**4b**, (*S*)-(+)-**4b**, and (*S*)-(+)-**4c,d** were synthesized according to the procedure of Götze[7] as outlined in Scheme II. Treatment of aqueous solutions of crude thiazolium chlorides with fluoroboric acid gave the thiazolium tetrafluoroborates. The tetrafluoroborate salts were used for purification since the chloride salts could not be recrystallized effectively. The halide salts were regenerated by use of an ion-exchange resin.

Scheme I



Scheme II



Thiazolium Salt Catalysis. Most reactions were carried out in methanol and triethylamine.[5] The benzoin produced was isolated by column chromatography on silicic acid. The results of the benzoin condensation reactions are compiled in Table I. Optically active benzoin was obtained by the catalysis of optically active **4b**, **4c**, and **4d**, but not by **4a**, indicating that the effective steric bulk of the benzyl group is considerably smaller than that of the phenyl group in this reaction. The similar optical

Table I
Thiazolium Salt Catalysis of the Benzoin Condensation

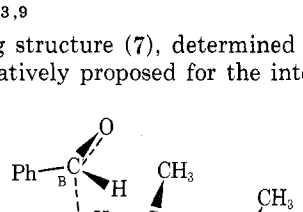
Salt	Reaction conditions,[a] solvent, base, time in hr	Yield,[b] %	Optical rotation[c] $[\alpha]_{436}$ Temp, °C	$[\alpha]$	c	Optical purity,[d] %
(*R*)-(−)-**4a**	MeOH, Et_3N 6	12	23	0	0.92	0
(*S*)-(+)-**4b**	MeOH, Et_3N 6	6.1	21	+221	0.46	51.5
(*R*)-(−)-**4b**	MeOH, Et_3N 24	21	23	−165	1.03	38.5
		17	20.5	−161	0.86	37.5
	MeOH, Et_3N 48	26	25	−126	1.03	29.4
	MeOH–H_2O, NaOH 24	22	23	−133	1.06	31.0
(*S*)-(+)-**4c**	MeOH, Et_3N 25	78	25	+33.6	1.01	7.8
(*S*)-(+)-**4d**	MeOH, Et_3N 25	68	20	+30.4	1.03	7.1

[a] Bath temperature, 30°. [b] Based on benzoin isolated by chromatography on silicic acid. [c] In methanol. [d] Calculated based on the following rotation of (−)-benzoin:[8] $[\alpha]_{436}^{20}$ −429 (*c* 1.01, MeOH).

purities of the benzoins obtained with **4c** and **4d** confirm that the chiral anion of the salt does not participate in the asymmetric induction.

Catalysis by **4b** afforded benzoin of fairly high optical purity but low yield. The opposite is found with **4c** and **4d**. These observations indicate that, in the case of 4-methyl 3-α-substituted thiazolium salts, as one group on the asymmetric carbon atom becomes larger the catalytic activity of the salt decreases, presumably owing to steric effects. In addition, the optical purity of the isolated benzoin decreases with increasing time (**4b**). Moreover, it has been shown that benzoin does not racemize detectably under the conditions of the reaction in the absence of a thiazolium salt.[3,9]

The following structure (**7**), determined with the aid of models, is tentatively proposed for the intermediate leading to the predominant product. The criteria used are those established by conformational analyses of transition states by Cram[10] and Prelog.[11] Thus the steric interactions of the various groups help to determine the chirality of the product benzoin, although electronic effects are possible and have been minimized in this discussion. The main assumptions are that the anion formed by addition of benzaldehyde (A) to the thiazolium ion is basically planar and that approach of a second molecule of benzaldehyde (B) should be from the side opposite the bulky group R. The conformation of the chiral carbon of benzoin (B) is formed in such a way as to minimize the steric interactions of the groups attached to carbons A and B.



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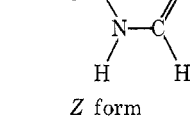
Intermediate **7** subsequently collapses to regenerate the thiazolium ion and an optical isomer of benzoin. If the thiazolium salt has the *S* configuration, the predominant benzoin isomer predicted according to this model also has the *S* configuration. It has been shown[12] that (+)-benzoin and (−)-benzoin are *S* and *R*, respectively, by synthesis from (*S*)-(+)- and (*R*)-(−)-mandelic acids. Thus the observed results are in agreement with the model presented.

Experimental Section

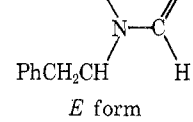
General. Melting points were determined on a Fisher-Johns hot-stage apparatus and are corrected. Microanalyses were performed by Galbraith Laboratories, Inc., Knoxville, Tenn. Infrared spectra were recorded on a Perkin-Elmer 237 spectrophotometer; only significant maxima are listed. Nuclear magnetic resonance spectra were obtained on a Varian T-60 spectrometer with tetramethylsilane as internal standard. Optical rotations were measured at 436, 546, and 578 mμ on a Zeiss photoelectric precision polarimeter, and the values at 589 mμ (D line) were obtained by using the equation

$$X = \frac{\alpha_{578}}{\alpha_{546} - \alpha_{578}} \qquad \alpha_D = \frac{X(\alpha_{456})}{X + 1.37}$$

Salts of (*R*)-(−)-3-α-Benzylethyl-4-thiazolium Ion (4a). (*R*)-α-Benzyl-*N*-thioformylethylamine (3a). To a stirred solution of (*R*)-(−)-α-benzylethylamine (**2a**)·½H_2SO_4, $[\alpha]^{21}D$ −22.3° (*c* 0.51, H_2O) [lit.[13] $[\alpha]^{20}D$ −24.57° (*c* 2.00, H_2O)] (2.77 g, 7.52 mmol) in 40 ml of water was added crude dithioformate (prepared[14] from 11.5 g of 86.5% KOH) in 15 ml of water. The reaction proceeded with evolution of a gas. The mixture was stirred at room temperature for 21.5 hr. After the remaining gas was removed by evacuation at 30 mm, the reaction mixture was extracted with two 50-ml portions of ether, and the combined extracts were washed with three 10-ml portions of aqueous NaCl solution and dried over sodium sulfate. The crude material (2.50 g) obtained on evaporation of the solvent was chromatographed on silicic acid with methylene chloride as eluent, and 2.38 g of purified compound **3a** was obtained as an oil: tlc two spots, R_f 0.28 and 0.18 (silica gel, CH_2Cl_2); ir (neat) 3180 (s, broad, -NH-), 1540 (s), and 1450 cm^{-1} (s, C=S); nmr (CCl_4) δ 9.15 (2 H, m, NH and CHS), 7.27 (5 H, Ph), 4.86 (0.64 H, septet, m, $-CH(Z)CH_3$), 3.81 (0.36 H, m, $-CH(E)CH_3$), 3.22–2.52 (2 H, m, $-CH_2Ph$), 1.30 (d, *J* = 5.2 Hz, $-CH_3(E)$), 1.20 (d, *J* = 6.6 Hz, $-CH_3(Z)$).



Z form



E form

(*R*)-(−)-3-α-Benzylethyl-4-methylthiazolium Tetrafluoroborate (4a·BF_4^-). To a stirred solution of (*R*)-**3a** (2.35 g, 0.013 mol) in 20 ml of benzene was added chloroacetone (1.22 g, 0.013 mol) dissolved in 10 ml of benzene, and the mixture was stirred at room temperature overnight and in an oil bath at 75–80° for 15 min. The upper benzene layer was removed from the cooled reaction mixture with a pipette, and the residual gummy material was partitioned between water (30 ml) and methylene chloride (20 ml). The aqueous layer was extracted with four 20-ml portions of methylene chloride, evacuated on a rotary evaporator to remove traces of methylene chloride, and then treated with 49% fluoroboric acid (1.8 ml) by dropwise addition. The precipitated, colorless solid was collected on a filter, washed with water, and dried over phosphorus pentoxide to give 2.05 g (52%), mp 136–

136.5°. Recrystallization from 1,2-dichloroethane gave 1.46 g of crystals, mp 136.8–137.2°, $[\alpha]^{21.5}D$ −104° (*c* 0.48, MeOH), and recrystallization of the material obtained by evaporating the mother liquor gave 0.38 g of crystals, mp 136.2–137°, $[\alpha]^{21}D$ −103° (*c* 0.625, MeOH). An analytical sample was obtained by additional recrystallization of the first crop: mp 138–139°; ir (KBr) 1573 (s, thiazolium ring), 1120–1020 cm^{-1} (very s, broad, BF_4^-); nmr (CD_2Cl_2) δ 9.96 (1 H, d, *J* = 2.8 Hz, $^+$N=CHS–), 7.61 (1 H, m, –SCH=C), 7.35–6.94 (5 H, m, C_6H_5–), 4.93 (1 H, m, $CHCH_3$), 3.29–3.15 (2 H, AB of ABX, $C_6H_5CH_2$–), 2.27 (3 H, s, $-CH_3$ on the thiazolium ring), 1.74 (3 H, d, *J* = 6.9 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{16}BF_4NS$: C, 51.16; H, 5.29; F, 24.91; N, 4.59; S, 10.51. Found: C, 51.46; H, 5.24; F, 24.85; N, 4.58; S, 10.70.

(*R*)-(−)-3-α-Benzylethyl-4-methylthiazolium Chloride (4a·Cl⁻). A solution of the tetrafluoroborate salt (*R*)-(−)-**4a**·BF_4^- (2.23 g, 7.32 mmol) in 50 ml of methanol was applied to a column of anion exchange resin (Dowex 2-X8, chloride form, 20–50 mesh, 50 ml, *ca.* 66 mequiv) and 100 ml of methanol was used to elute the last portion of the solution. The eluent was evaporated to dryness to give 1.99 g of a glass, which slowly crystallized overnight, mp 149–150°, insoluble in acetone, CCl_4, and Et_2O and moderately soluble in $Cl(CH_2)_2Cl$. Recrystallization from $Cl(CH_2)_2Cl$–acetone gave 1.41 g of prisms, mp 150–151°, $[\alpha]^{23}D$ −131° (*c* 1.40, EtOH). An analytical sample was obtained by additional recrystallization: mp 150–151°; $[\alpha]^{21}D$ −130° (*c* 1.12, EtOH); ir (KBr) 1569 cm^{-1} (s, thiazolium ring); nmr ($CDCl_3$) δ 11.90 (1 H, d, *J* = 2.8 Hz, $^+$N=CHS–), 8.19 (1 H, –SCH=C), 7.17 (5 H, m, C_6H_5–), 4.94 (1 H, m, $CHCH_3$), 3.79–3.13 (2 H, eight lines, AB of ABX, $C_6H_5CH_2$–), 2.30 (3 H, s, $-CH_3$ on the thiazolium ring), 1.91 (3 H, d, *J* = 7.0 Hz, $CHCH_3$).

Anal. Calcd for $C_{13}H_{16}ClNS$: C, 61.51; H, 6.36; Cl, 13.97. Found: C, 61.27; H, 6.43; Cl, 13.97.

Salts of 4-Methyl-3-α-(1-naphthyl)ethylthiazolium Ion (4b). (*R*)-(+)-α-(1-Naphthyl)-*N*-thioformylethylamine [(*R*)-(+)-3b]. To a cold, stirred solution of (*R*)-(+)-α-(1-naphthyl)ethylamine (**2b**, 5.13 g, 0.030 mol) in 30 ml of methanol was added dropwise crude potassium dithioformate (22.2 g, prepared[14] from 23 g of 86.5% KOH) dissolved in 30 ml of water, and the mixture was stirred at room temperature overnight. The precipitated solid was collected and washed three times by trituration with water to give 6.0 g (93%), mp 96–101°. The crude product was recrystallized from EtOH–H_2O (2:1) to give 4.32 g of crystals, mp 114.5–115.5°. An analytical sample was obtained by an additional recrystallization: mp 116.5–117.5°; $[\alpha]^{20.5}D$ +505° (*c* 1.47, EtOH); ir (KBr) 3195 (s, broad, NH), 1519 (s), 1510 (shoulder), 1458 (s), and 1440 cm^{-1} (s, NC=S); nmr (CD_2Cl_2) δ 9.14 (1 H, d, *J* = 6.9 Hz, –CHS), 8.2–7.1 (7 H, m, $C_{10}H_7$), 6.41 (1 H, m, $-CHCH_3$), 1.65 (3 H, d, *J* = 6.4 Hz, $-CH_3$). When the solution was shaken with D_2O, the doublet at δ 9.14 and the quintet at δ 6.41 collapsed to a singlet and a quartet, respectively.

Anal. Calcd for $C_{13}H_{13}NS$: C, 72.50; H, 6.08; N, 6.51; S, 14.89. Found: C, 72.87; H, 6.09; N, 6.39; S, 14.50.

(*R*)-(−)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Tetrafluoroborate [(*R*)-(−)-4b·BF_4^-]. The compound was obtained from 1.08 g (5.0 mmol) of (*R*)-(+)-**3b** according to the method described for (*R*)-(−)-**4a**·BF_4^- to give 0.45 g (26.4%) of crude product insoluble in $CHCl_3$, CH_2Cl_2, and acetone, mp 170.5–173°. An analytical sample was obtained by recrystallizing twice from $Cl(CH_2)_2Cl$–EtOH (10:1): mp 178–179° dec (corrected); $[\alpha]^{23.5}D$ −121° (*c* 1.11, DMSO); ir (KBr) 1480 (s, thiazolium ring), 1160–1000 cm^{-1} (very s, broad, BF_4^-); nmr (DMSO-d_6) δ 10.36 (1 H, d, *J* = 2.7 Hz, $^+$N=CHS–), 8.2–7.07 (8 H, –SCH=C and $C_{10}H_7$–), 6.91 (q, *J* = 6.5 Hz, $-CHCH_3$), 2.38 (3 H, s, $-CH_3$ on the ring), 2.10 (3 H, d, *J* = 6.5 Hz, $-CHCH_3$).

Anal. Calcd for $C_{16}H_{16}BF_4NS$: C, 56.33; H, 4.73; F, 22.27; N, 4.11; S, 9.40. Found: C, 56.91; H, 4.64; F, 22.47; N, 4.25; S, 9.08.

(*R*)-(−)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Bromide [(*R*)-(−)-4b·Br⁻]. The tetrafluoroborate (*R*)-(−)-**4b**·BF_4^- (1.61 g, 4.72 mmol) was converted to the bromide with anion-exchange resin (Dowex 2-X8, bromide form) as described for **4a**·Cl. The crude compound (1.56 g) showed mp 177–182° dec. After recrystallization from ethanol, 1.20 g of crystals were obtained: mp 178–182° dec; $[\alpha]^{22}D$ −116° (*c* 1.18, MeOH); ir (KBr) 1479 cm^{-1} (s, thiazolium ring); nmr (DMSO-d_6) δ 10.52 (1 H, d, *J* = 2.4 Hz, $^+$N=CHS–), 8.3–6.8 (9 H, –SCH=C, $C_{10}H_7$–, and $CHCH_3$), 2.38 (3 H, s, $-CH_3$ on the thiazolium ring), 2.08 (3 H, *J* = 7.1 Hz, $CHCH_3$).

Anal. Calcd for $C_{16}H_{16}BrNS$: C, 57.49; H, 4.83; Br, 23.90; N, 4.19. Found: C, 57.24; H, 4.88; Br, 23.76; N, 4.04.

(*S*)-(−)-α-(1-Naphthyl)-*N*-thioformylethylamine [(*S*)-(−)-3b]. Compound **3b** was made from (*S*)-(−)-α-(1-naphthyl)ethylamine (**2b**), $[\alpha]^{20.5}D$ −90.7° (*c* 1.84, benzene), as described for (*R*)-(+)-**3b**. The product was recrystallized from EtOH–H_2O to give mp 115.5–116.5°.

Anal. Calcd for $C_{13}H_{13}NS$: C, 72.50; H, 6.08; N, 6.51. Found: C, 72.63; H, 6.10; N, 6.39.

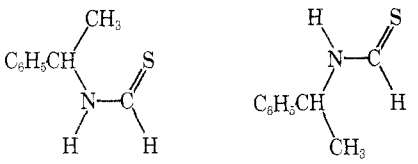
(*S*)-(+)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Tetrafluoroborate [(*S*)-(+)-4b·BF_4^-]. The compound was obtained from 5.50 g (25.6 mmol) of (*S*)-(−)-**3b** as described for (*R*)-(+)-**4b**·BF_4^- to give 2.93 g (34%) of crude product. Recrystallization from $Cl(CH_2)_2Cl$–EtOH gave 2.14 g of crystals, mp 170–174° dec, $[\alpha]^{21}D$ +118° (*c* 1.03, DMSO); recrystallization of the material obtained on evaporation of the mother liquor gave a second crop, mp 169–172° dec, $[\alpha]^{23}D$ +118° (*c* 0.99, DMSO).

Anal. (first crop). Calcd for $C_{16}H_{16}BF_4NS$: C, 56.33; H, 4.73; N, 4.11. Found: C, 56.09; H, 4.75; N, 4.09.

(*S*)-(+)-4-Methyl-3-α-(1-naphthyl)ethylthiazolium Bromide [(*S*)-(+)-4b·Br⁻]. The compound was obtained from (*S*)-(+)-**4b**·BF_4^- as described for (*R*)-(−)-**4b**·Br^-, mp 184.5–186.5°, $[\alpha]^{20}D$ +121° (*c* 0.98, MeOH). Spectra are identical with those of (*R*)-(−)-**4b**·Br^-.

Anal. Calcd for $C_{16}H_{16}BrNS$: C, 57.49; H, 4.83; N, 4.19. Found: C, 57.68; H, 4.68; N, 3.96.

Salts of 4-Methyl-3-α-phenylethylthiazolium Ion (4c). (*S*)-α-Phenyl-*N*-thioformylethylamine (3c) was prepared as described for **3b** starting with (*S*)-(−)-α-phenylethylamine (**2c**), $[\alpha]^{20.5}D$ −37.6° (neat) [lit.[15] $[\alpha]^{22}D$ −40.3° (neat)]. However, as the product was separated from the reaction mixture as an oil, it was extracted with ether. The crude product obtained from 1.82 g (0.015 mol) of (*R*)-**2c** was chromatographed on silicic acid (70 g) with methylene chloride, giving 1.93 g of purified compound as an oil: tlc two spots (silica gel, CH_2Cl_2), R_f 0.34 and 0.24; ir (neat) 3080 (s, broad, NH), 1524 and 1439 cm^{-1} (s, C=S); nmr (CCl_4) δ 7.27 (5 H, $-C_6H_5$), 5.72 (0.75 H, m, $-CH(Z)CH_3$), 4.69 (0.25 H, m, $-CH(E)CH_3$), 1.52 (3 H, d, *J* = 7.0 Hz, $-CH_3(Z)$ and $-CH_3(E)$).



Z form *E* form

(*S*)-(+)-4-Methyl-3-α-phenylethylthiazolium Iodide (4c·I⁻). To a stirred solution of (*S*)-**3c** (3.81 g, 0.231 mol) in benzene (50 ml) was added chloroacetone (2.14 g, 0.23 mol) dissolved in 5 ml of benzene, and the mixture was stirred at room temperature overnight and in an oil bath at 70° for 0.5 hr. The upper benzene layer was removed from the cooled reaction mixture with a pipette, and the residual gummy material was partitioned between water (80 ml) and benzene (50 ml). The aqueous layer was washed with four 50-ml portions of methylene chloride and then treated with potassium iodide (15 g) by portionwise addition. Immediate separation of an oil was observed. The mixture was extracted with two 70-ml portions of methylene chloride, and the combined extracts were washed with water (20 ml), dried over sodium sulfate, and evaporated to dryness to give 3.50 g (46%) of an oil, which failed to crystallize, although the ir spectrum suggested high purity, ir spectrum (neat) 1570 cm^{-1} (s, thiazolium ring).

(*S*)-(+)-4-Methyl-3-α-phenylethylthiazolium (+)-3-Bromocamphor-9-sulfonate [(*S*)-(+)-4c·(+)-CSA]. To a stirred solution of (*S*)-(+)-**4c**·I^- (1.20 g, 3.63 mmol) in ethanol (30 ml) was added powdered silver (+)-3-bromocamphor-9-sulfonate monohydrate[16] (1.58 g, 3.63 mmol), and the mixture was stirred at room temperature overnight and heated at reflux with stirring for 0.5 hr. The cooled reaction mixture was filtered to remove AgI, and the filtrate was evaporated to dryness to give 1.83 g of crude compound as a slightly yellow solid. After recrystallization from $Cl(CH_2)_2Cl$, the product showed mp 168–170.5°. An analytical sample was prepared by repeated recrystallization from $Cl(CH_2)_2Cl$: mp 173.5–175°; $[\alpha]^{25}D$ +94° (*c* 0.50, EtOH); ir (KBr) 1750 (s, C=O), 1573 (m, thiazolium ring), ~1200 and 1038 cm^{-1} (s, SO_2); nmr (DMSO-d_6) δ 10.54 (1 H, d, *J* = 3.0 Hz, $^+$N=CHS–), 8.14 (1 H, –SCH=C), 7.43 (5 H, C_6H_5–), 6.11 (1 H, q, C_6H_5CH), 4.97 (1 H, d, *J* = 4.5 Hz, CHBr), 1.98 (3 H, d, *J* = 7.1 Hz, $CHCH_3$), 1.12 (3 H, s, $-CH_3$ of the anion), 0.83 (3 H, s, $-CH_3$ of the anion).

Anal. Calcd for $C_{22}H_{28}BrNS_2O_4$: C, 51.34; H, 5.48; Br, 15.53; N, 2.72; S, 12.46. Found: C, 51.72; H, 5.67; Br, 15.39; N, 2.76; S, 12.47.

(*S*)-(+)-4-Methyl-3-α-phenylethylthiazolium (−)-3-Bromo-

camphor-9-sulfonate [(S)-(+)-4c·(−)-CSA]. The compound was prepared from (S)-(+)-4c·I⁻ and silver (−)-3-bromocamphor-9-sulfonate monohydrate as described for (S)-(+)-4c·(+)-CSA⁻. The crude solid was recrystallized twice from $Cl(CH_2)_2Cl$ to give colorless crystals: mp 179°; $[\alpha]^{20.5}D$ −25.2° (c 0.522, EtOH); ir (KBr) 3500 (s), 3450 (s), 1747 (s, C=O), 1649 (m), 1572 (m, thiazolium ring), ~1200 (s), and 1040 cm^{-1} (s, SO_2).

Anal. Calcd for $C_{22}H_{28}BrNS_2O_4$: C, 51.34; H, 5.48; N, 2.72; S, 12.46. Found: C, 51.11; H, 5.49; N, 2.78; S, 12.28.

Benzoin Condensation Catalyzed by Thiazolium Salts. The molar ratio of benzaldehyde:triethylamine:catalyst was 10:1:~0.95. The concentrations of the reaction mixtures ranged from 0.19 to 0.35 millimoles of catalyst/milliliters of solvent. In all reactions benzaldehyde was added to a solution of the catalyst in methanol (methanol-H_2O, 0.98:2.3 v/v) under nitrogen. A methanolic solution of triethylamine was added dropwise with stirring. After stirring for 24 hr at 30° the reaction mixture was evaporated to dryness and the residue was chromatographed on silicic acid with chloroform. After unreacted benzaldehyde, benzoin was eluted. When the initial separation of benzoin was incomplete, the overlapped portion was rechromatographed with chloroform–benzene (70:30).

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Registry No.—(R)-**2a**·½H_2SO_4, 51-62-7; (R)-(+)-**2b**, 3886-70-2; (S)-(−)-**2b**, 10420-89-0; (S)-**2c**, 2627-86-3; (R)-**3a**, 50486-64-1; (R)-(+)-**3b**, 50486-65-2; (S)-(−)-**3b**, 50486-66-3; (S)-**3c**, 50486-67-4; (R)-(−)-**4a**·BF_4^-, 50477-40-2; (R)-(−)-**4a**·Cl^-, 50486-68-5; (R)-(−)-**4b**·BF_4^-, 50477-41-3; (R)-(−)-**4b**·Br^-, 50486-69-6; (S)-(+)-**4b**·BF_4^-, 50477-42-4; (S)-(+)-**4b**·Br^-, 50486-70-9; (S)-(+)-**4c**·I^-, 50486-71-0; (S)-(+)-**4c**·(+)-CSA, 50486-72-1; (S)-(+)-**4c**·(−)-CSA, 51064-34-7.

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Stable Carbonium Ions from β-Arylalkyl Derivatives in SbF_5·SO_2. II. Ions Related to Mescaline[1,2]

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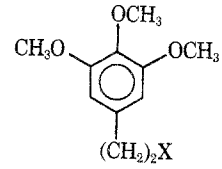
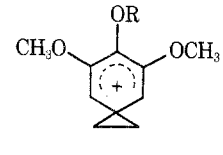
A study of carbonium ions formed from a series of β-di- and trimethoxyphenyl-1-chloroethanes and 2-(*o*-anisyl)-1-chloroethane in either SbF_5·SO_2 or SbF_5·SO_2·BF_3 was carried out. Methoxy-stabilized phenonium ions were generated only from BF_3 complexes of the di- and trimethoxyphenyl-1-chloroethanes in SbF_5·SO_2 wherein the number of ortho and para methoxy groups was greater than the number of meta "destabilizing" methoxys. The 2-(*o*-anisyl)-1-chloroethane gave the oxonium ion **14**, whereas its BF_3 complex gave phenonium ion **15**. In the reaction system SbF_5·SO_2·BF_3, the major reaction competing with phenonium ion formation appeared to be C-protonation by trace amounts of HF. The oxonium ion was obtained from 2-(2′,5′-dimethoxyphenyl)-1-chloroethane in $AgSbF_6$·SO_2 at −20°. No benzylic ion formation was observed in these systems, apparently because the stable ring carbon protonated ions will not readily undergo abstraction of Cl^- by SbF_5.

A variety of ideas have been offered in attempts to correlate physiological activity and structure in mescaline (**1a**), amphetamines, and other hallucinogens.[4]

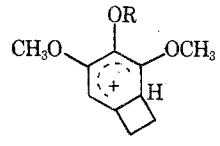
A report[5] that 2-(3′,4′,5′-trimethoxyphenyl)ethanol (**1b**) (a minor rat mescaline metabolite[6c]) or 3′,4′,5′-trimethoxyphenylacetaldehyde produced potent biological effects in rats at significantly lower doses than mescaline, coupled with the isolation of demethylated products[6] from *in vivo* mescaline metabolism [such as 3′,4′-dihydroxy-5′-methoxyphenylacetic acid and 2-(3′-hydroxy-4′,5′-dimethoxyphenyl)ethylamine], suggests the interesting possibility of the intervention of ions or ion pairs such as **2** or **3** at some stage in the biochemistry of mescaline. Such ions seem reasonable, since both alkoxycarbonium ions and the *p*-anisonium ion (**4**) are known to be exceptionally stable, and at least in the case of simple methoxy carbonium ions excellent methylating agents as well.[7,8] Further, Sung and Parker have recently observed a linear correlation between intermolecular charge transfer transition energies and biological activity in mescaline units for a series of psychoac-



1a, X = NH_2
b, X = OH



2
R = H, CH_3



3
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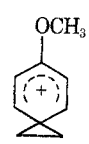

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