Reactions of Enamines. X. Methylene Bases in the Benzothiazole Series as Enamines[1]

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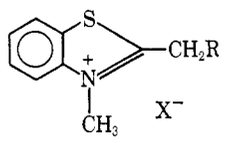
The methylene base 2-benzylidene-3-methylbenzothiazoline (**7**, R = H) has been shown to undergo alkylation, acylation, and reaction with trichloroacetic acid. The products are those characteristic of the reaction of **7** (R = H) as an enamine. 2-Diphenylmethylene-3-methylbenzothiazoline (**7**, R = C_6H_5), a methylene base disubstituted on the methylene carbon, proved to be unreactive compared with **7** (R = H).

The methylene bases derived from the quaternary salts of various nitrogen heterocyclic compounds have been shown to undergo many reactions characteristic of enamines.[1,2] In the case of the methylene base[3] derived from 2,3-dimethylbenzothiazolium salts (**1**, R = H), elucidation of the course of its reactions has been complicated by the fact that it exists as a dimer.[4] The correct structure **2** of this dimer was first proposed by Larive and Dennilauler[5] on the basis of chemical evidence and was later confirmed by nuclear magnetic resonance spectroscopy.[6] Many reactions of the dimer



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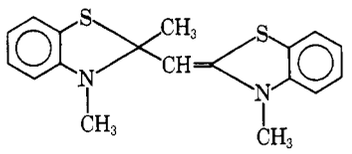

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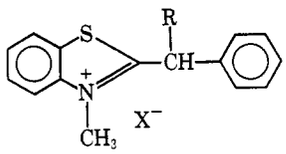
2 with electrophilic reagents have been reported.[4-12] These reactions are best rationalized on the basis of reaction at sulfur[13] of the mesomeric form **3** rather than reactions at the enamine carbon of **2**. Very little is recorded in the literature about the reactions of monomeric methylene bases in the benzothiazole series. The methylene base **4** is reported to acylate with boiling acetic anhydride[14] to give reaction at the enamine carbon. The methylene base **5** derived from 2-ethyl-3-methylbenzothiazolium iodide (**1**, R = CH_3; X = I) has been prepared and shown to be monomeric.[6] Alkylation of **5** with methyl iodide is reported[15] to give 2-isopropyl-3-methylbenzothiazolium iodide. It seemed of interest, therefore, to prepare a monomeric methylene base in the benzothiazole series and investigate its reactions as an enamine.

2-Benzylbenzothiazole[16] was converted into 2-benzyl-3-methylbenzothiazolium tosylate (**6**, R = H; X = tosyl) by reaction with methyl *p*-toluenesulfonate. Treatment of **6** (R = H; X = tosyl) with sodium methoxide in methanol gave the methylene base **7** (R = H) as a crystalline solid. The compound **7** (R = H) had



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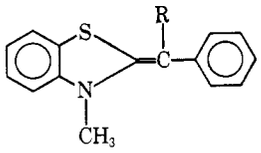

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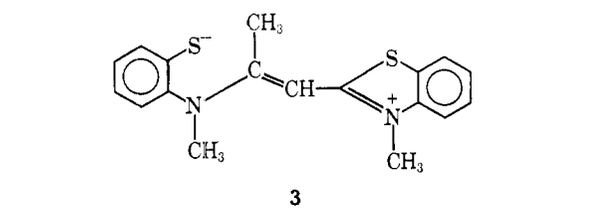
the correct elemental analysis and the nuclear magnetic resonance spectrum was consistent with the assigned structure showing a vinyl proton at τ 4.46. The nmr spectrum and a molecular weight determination showed **7** (R = H) to be monomeric.

Alkylation of **7** (R = H) with excess methyl iodide or *p*-nitrobenzyl bromide gave the expected products (**6**, R = CH_3; X = I) and (**6**, R = $CH_2C_6H_4NO_2$; X = Br) in high yield, respectively. Alkylation of **7** (R = H) with 2,4-dinitrofluorobenzene, however gave the new methylene base **7** (R = $C_6H_3(NO_2)_2$). Evidently **7** (R = H) was a stronger base and removed the elements of hydrofluoric acid from the intermediate **6** (R = $C_6H_3(NO_2)_2$; X = F). In support of this, a salt was isolated from the reaction mixture which on treatment with sodium iodide was found to be **6** (R = H; X = I).

Acylation of **7** (R = H) with benzoyl chloride gave **8a** together with an equimolar amount of **6** (R = H; X = Cl). The formation of **6** (R = H; X = Cl) could be prevented and the yield of **8a** increased by adding triethylamine as base. In this way, **7** (R = H) was acylated by acetyl, *p*-nitrobenzoyl, and 3,4-dichlorobenzoyl chlorides to give **8b**, **c**, and **d**, respectively.



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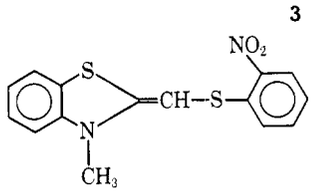

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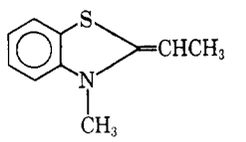

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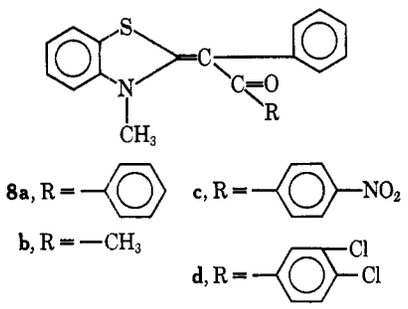
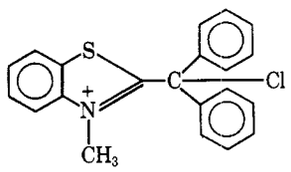
(1) Part IX: G. H. Alt, *J. Org. Chem.*, **31**, 2384 (1966).
(2) M. Coenen, *Angew. Chem.*, **61**, 11 (1949).
(3) W. König and W. Meier, *J. Prakt. Chem.*, **109**, 324 (1925).
(4) O. Mumm, H. Hinz, and J. Diederichsen, *Ber.*, **72**, 2107 (1939).
(5) H. Larive and R. Dennilauler, *Chimia*, **15**, 115 (1961).
(6) J. Metzger, H. Larive, E. Vincent, and R. Dennilauler, *J. Chem. Phys.*, **60**, 944 (1963).
(7) A. I. Kiprianov and F. S. Babichev, *J. Gen. Chem. USSR*, **20**, 145 (1950).
(8) F. S. Babichev, *ibid.*, **20**, 1904 (1950).
(9) V. I. Dénes, M. Fărcăsan, and G. Ciurdaru, *Ber.*, **97**, 1246 (1964); see also V. I. Dénes and M. Fărcăsan, *J. Gen. Chem. USSR*, **32**, 119, 654 (1962).
(10) L. M. Yagupolsky and M. S. Marenets, *ibid.*, **23**, 481 (1953).
(11) M. Coenen, *Ann.*, **633**, 78 (1960).
(12) M. T. LeBris, *Ann. Chim.* (Paris), [13] **1**, 328 (1956), and references there cited.
(13) In cases where the products from **2** are those which would be expected from the monomeric methylene base [*e.g.*, L. G. S. Brooker and F. L. White, U. S. Patent 2,112,139 (1938)], they are formed from the primary products by an intermolecular rearrangement under the reaction conditions (see ref 9).
(14) V. I. Dénes, M. Fărcăsan, and G. Ciurdaru, *Ber.*, **96**, 174 (1963).
(15) Unpublished work at Kodak-Pathé, Vincennes, France; see ref 5.
(16) F. L. Hamer, *J. Chem. Soc.*, 1487 (1956).



8a, R =
c, R =
b, R = —CH_3
d, R =

The disubstituted methylene base **7** (R = C_6H_5) was also prepared from the corresponding salt **6** (R = C_6H_5; X = tosyl) and shown to be monomeric. The compound **7** (R = C_6H_5) proved to be unreactive compared with **7** (R = H) owing to steric hindrance at the enamine carbon and/or to the electron withdrawing effect of the phenyl groups. However, **7** (R = C_6H_5) could be converted into **6** (R = C_6H_5; X = I) by treatment with hydriodic acid and was chlorinated[17] by chlorine in carbon tetrachloride to the salt **9**.



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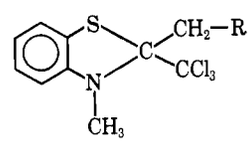

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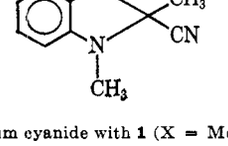
Enamines have been shown to add trichloroacetic acid to give α-trichloromethyl amine derivatives.[18] In the same way **7** (R = H) reacts with trichloroacetic acid to give the trichloromethyl derivative **10** (R = C_6H_5). The latter compound has an interesting nuclear magnetic resonance spectrum. The benzyl protons are in different environments due to the asymmetry of the molecule and appear as two doublets centered at τ 6.30 with J = 16 cps and at 6.55 with J = 16 cps. This reaction must have involved protonation of the methylene base **7** (R = H) to give **6** (R = H; X = Cl_3COO^-), followed by decarboxylation of the trichloroacetate anion to give trichloromethyl anion. Addition of the latter to the cation of **6** (R = H) then affords the observed product **10** (R = C_6H_5).

As the dimer **2** is reconverted to the benzothiazolium salt **1** (R = H) on protonation,[4] the dimer **2** was also subjected to reaction with trichloroacetic acid.[19] Reaction of **2** in benzene solution with trichloroacetic acid gave **10** (R = H). Compound **17** was characterized by elemental analysis, and had a nuclear magnetic resonance spectrum consistent with the assigned structure.

(17) Enamines have been shown to chlorinate [A. J. Speziale and L. R. Smith, *J. Org. Chem.*, **28**, 3492 (1963)] and brominate [(a) R. L. Pedersen, J. L. Johnson, R. P. Holysz, and A. C. Ott, *J. Amer. Chem. Soc.*, **79**, 1115 (1957); (b) M. E. Kuehne, *ibid.*, **83**, 1492 (1961)], to give β-haliminium salts.

(18) G. H. Alt and A. J. Speziale, *J. Org. Chem.*, **31**, 1340 (1966).

(19) H. Wahl and J. J. Vorsanger [*Bull. Soc. Chim. Fr.*, 3359 (1965)] have isolated



from the reaction of sodium cyanide with **1** (X = $MeSO_4^-$).

In summary, it may be concluded that methylene bases in the benzothiazole series undergo reactions characteristic of enamines. Only when the methylene base exists as a dimer are anomalous reactions encountered and these are best rationalized as reactions on sulfur of a species such as **3**. The initially formed products from **3** occasionally undergo intermolecular rearrangements under the conditions of the reaction resulting in products which would be expected from the monomeric methylene base.

Experimental Section[20]

2-Benzylbenzothiazole.—This compound was prepared by the method of Hamer,[16] bp 165–170° (1.4 mm) [lit.[16] bp 157–163° (0.5 mm)]; $n^{24}D$ 1.6415; nmr, τ 5.79 (s, 2, CH_2Ph), 1.9–3.1 (m, 9, aromatic H).

2-Benzyl-3-methylbenzothiazolium Tosylate (6, R = H; X = tosyl).—2-Benzylbenzothiazole (11.3 g, 0.05 mol) and methyl *p*-toluenesulfonate (9.3 g, 0.05 mol) were heated at 180° for 3 hr. The solid residue was triturated with ether and filtered to give 20.5 g (99%) of crude product. Two recrystallizations from 2-propanol gave analytically pure **6** (R = H; m = tosyl), mp 175–177°.

Anal. Calcd for $C_{22}H_{21}NO_3S_2$: C, 64.20; H, 5.14; N, 3.40; S, 15.58. Found: C, 64.44; H, 5.21; N, 3.47; S, 15.74.

2-Benzyl-3-methylbenzothiazolium Iodide (6, R = H; X = I).—2-Benzylbenzothiazole (3.0 g; 0.013 mol) was dissolved in excess methyl iodide (10 ml) and heated at the reflux temperature overnight. On cooling, ether was added and the precipitate filtered. Recrystallization from ethanol gave **6** (R = H; X = I) as fine needles, mp 208–209° dec.

Anal. Calcd for $C_{15}H_{14}INS$: C, 49.05; H, 3.84; I, 34.56; N, 3.82; S, 8.73. Found: C, 49.04; H, 3.79; I, 34.65; N, 4.02; S, 8.75.

2-Benzylidene-3-methylbenzothiazoline (7, R = H).—Sodium methoxide solution (10 ml of 1.02 *N*; 0.01 mol) was added dropwise to an ice-cold solution of 2-benzyl-3-methylbenzothiazolium tosylate (4.1 g, 0.01 mol) in methanol (10 ml). The product separated as an oil which solidified on addition of water (30 ml). Recrystallization from ethanol gave 1.5 g (63%) of yellow needles: mp 74–75°; nmr, τ 6.87 (s, 3, CH_3N), 4.46 (s, 1, CH=C), 2.6–3.6 (m, 9, aromatic H).

Anal. Calcd for $C_{15}H_{13}NS$: C, 75.27; H, 5.47; N, 5.85; S, 13.40; mol wt, 239.32. Found: C, 75.31; H, 5.57; N, 5.78; S, 13.46; mol wt, 240.

2-α-Methylbenzyl-3-methylbenzothiazolium Iodide (6, R = CH_3; X = I).—2-Benzylidene-3-methylbenzothiazoline (1.2 g, 0.005 mol) was refluxed in methyl iodide (20 ml) for 18 hr. The methyl iodide was then removed *in vacuo*, and the residue was triturated with ether and filtered to give 1.7 g (89%) of a white salt. One recrystallization from ethanol gave pure material, mp 176–178° dec.

Anal. Calcd for $C_{16}H_{16}INS$: C, 50.40; H, 4.23; I, 33.29; N, 3.67. Found: C, 50.22; H, 4.24; I, 33.47; N, 3.66.

2-α-(*p*-Nitrobenzyl)benzyl-3-methylbenzothiazolium Bromide (6, R = $CH_2C_6H_4NO_2$; X = Br).—A mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and *p*-nitrobenzyl bromide (4.3 g, 0.02 mol) was refluxed in benzene (50 ml) for 2 hr. Cooling and filtering gave 1.4 g of pale yellow solid. The benzene mother liquors were returned to reflux for 18 hr from which a further 1.8 g of solid was obtained. The two portions were combined and purified by slurrying in hot acetone, to give 3.0 g of a pale yellow solid, mp 190° dec.

Anal. Calcd for $C_{22}H_{19}BrN_2O_2S$: C, 58.02; H, 4.21; Br, 17.55; N, 6.15. Found: C, 57.89; H, 4.31; Br, 17.81; N, 5.92.

2-α-(2,4-Dinitrophenyl)benzylidene-3-methylbenzothiazoline [7, R = $C_6H_3(NO_2)_2$].—2-Benzylidene-3-methylbenzothiazoline (1.2 g, 0.05 mol) and 2,4-dinitrofluorobenzene (0.9 g, 0.05 mol)

(20) Melting points were taken with a Mel-Temp capillary melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin-Elmer Infracord Model 137 in chloroform solution. Nmr spectra were taken with a Varian A-60 instrument in deuteriochloroform solution using tetramethylsilane as an internal standard. Elemental analyses and molecular weights (by differential osmometry) were carried out by Galbraith Laboratories.

were refluxed in benzene (25 ml) for 1 hr. The deep purple mixture was cooled and filtered, and the filtrate was evaporated to dryness, giving a dark resin, which was chromatographed on 60 g of Woelm neutral alumina (grade I) in benzene. Elution with benzene afforded the product as 0.6 g, (28%) of dark purple solid. One recrystallization from ethanol gave pure material as dark purple, nearly black, crystals, mp 184–185°.

Anal. Calcd for $C_{21}H_{15}N_3O_4S$: C, 62.21; H, 3.73; N, 10.36. Found: C, 62.03; H, 3.82; N, 10.25.

The residue from the filtration above was taken up in a little hot ethanol and treated with a solution of sodium iodide in ethanol. On cooling, a salt, mp 207–209° dec, crystallized which was identified as **6** (R = H; X = I) by mixture melting point.

2-α-Benzoylbenzylidene-3-methylbenzothiazoline (8a). A.—Benzoyl chloride (1.4 g, 0.01 mol) in benzene (20 ml) was added dropwise to a solution of **7** (R = H) (4.8 g, 0.02 mol) in benzene (75 ml). The reaction mixture was heated at the reflux temperature for 3 hr, cooled, and filtered. The solid had mp 223–224° dec and the analysis fits the formula for **6** (R = H; X = Cl).

Anal. Calcd for $C_{15}H_{14}ClNS$: C, 65.32; H, 5.12; Cl, 12.86; N, 5.08; S, 11.63. Found: C, 65.38; H, 5.20; Cl, 13.03; N, 4.96; S, 11.62.

On treatment with aqueous sodium hydroxide **6** (R = H; X = Cl) gave **7** (R = H), mp 72–74° not depressed in admixture with authentic material. The filtrate above was evaporated to dryness under reduced pressure and the residue (2.0 g, 52.5%) recrystallized from ethanol to give **8a**, mp 208–210°, not depressed in admixture with the material below.

B.—Benzoyl chloride (1.4 g, 0.01 mol) in benzene (25 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) in benzene (75 ml) at 25°. The mixture was then refluxed 2 hr. On cooling, the triethylamine hydrochloride was filtered off, the filtrate was evaporated to dryness, and the residue was crystallized from ethanol, affording the product as 2.2 g, (65%) of yellow prisms, mp 209–211°. The material showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{22}H_{17}NOS$: C, 76.93; H, 4.99; N, 4.08. Found: C, 76.78; H, 4.94; N, 4.13.

2-α-Acetylbenzylidene-3-methylbenzothiazoline (8b).—Acetyl chloride (0.8 g, 0.01 mol) in benzene (20 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) in benzene (70 ml) at 25°, stirred for 1 hr, then refluxed 1 hr. The mixture was then cooled and filtered. The filtrate was evaporated and the residue was crystallized from ethanol, giving 1.5 g (63%) of off-white solid, mp 154–157°. Two recrystallizations from aqueous methanol afforded pure material as yellow plates, mp 157–158°. The material showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{17}H_{15}NOS$: C, 72.56; H, 5.37; N, 4.98. Found: C, 72.37; H, 5.31; N, 5.19.

2-α-(*p*-Nitrobenzoyl)benzylidene-3-methylbenzothiazoline (8c).—*p*-Nitrobenzoyl chloride (0.9 g, 0.005 mol) in benzene (25 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (1.2 g, 0.005 mol) and triethylamine (0.5 g, 0.005 mol) and triethylamine (0.5 g, 0.005 mol) at 25°. The mixture became quite dark on addition, but on refluxing for 3 hours turned bright orange. After this time, the mixture was filtered hot, and the filtrate concentrated to *ca.* 60 ml. On cooling, the product separated as 1.5 g (67%) of orange crystals, mp 247–249°. Recrystallization from chloroform–methanol gave bright orange plates, mp 249–250°. The material showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{22}H_{16}N_2O_3S$: C, 68.02; H, 4.15; N, 7.21. Found: C, 67.87; H, 4.17; N, 7.16.

2-α-(3,4-Dichlorobenzoyl)benzylidene-3-methylbenzothiazoline (8d).—3,4-Dichlorobenzoyl chloride (2.1 g, 0.01 mol) in benzene (20 ml) was added dropwise to a mixture of 2-benzylidene-3-methylbenzothiazoline (2.4 g, 0.01 mol) and triethylamine (1.0 g, 0.01 mol) and benzene (100 ml) at 25°. After refluxing for 3 hr, the mixture was filtered hot, the filtrate was evaporated, and the greenish residue was crystallized from benzene–methylcyclohexane. This material was washed well with hot ethanol, then recrystallized from chloroform–methanol to afford the pure product as 1.5 g (37%) of bright-yellow needles, mp 194–196°. The compound showed no carbonyl absorption below 6.0 μ in the infrared spectrum.

Anal. Calcd for $C_{22}H_{15}Cl_2NOS$: C, 64.08; H, 3.97; Cl, 17.20. Found: C, 64.26; H, 3.75; Cl, 17.15.

2-Diphenylmethylbenzothiazole.—Diphenylacetyl chloride (46.0 g, 0.2 mol) was added to *o*-aminothiophenol (25.0 g, 0.2 mol). The reaction mixture was heated to 90° and phosphorus pentoxide (9.5 g) was added portionwise with stirring. On completion of the addition the mixture was heated to 200° for 15 min. The reaction mixture was cooled to 100° and 10% sodium hydroxide solution (160 ml) was added. The reaction mixture was extracted with ether. The ethereal solution was dried ($MgSO_4$) and evaporated to give 57 g of crude product. Vacuum distillation afforded 37 g (61%) of product, bp 215–220° (1.0 mm). Crystallization from methanol gave 2-diphenylmethylbenzothiazole as prisms: mp 89–91°; nmr, τ 4.11 [s, 1, **CH**$(Ph)_2$], 1.9–3.05 (m, 14, aromatic H).

Anal. Calcd for $C_{20}H_{15}NS$: C, 79.70; H, 5.02; N, 4.65; S, 10.64. Found: C, 79.52; H, 5.01; N, 4.63; S, 10.91.

2-Diphenylmethyl-3-methylbenzothiazolium Tosylate (6, R = C_6H_5; X = Tosyl).—2-Diphenylmethylbenzothiazole (6.0 g, 0.02 mol) and methyl *p*-toluenesulfonate (3.7 g, 0.02 mol) were heated at 200° for 2 hr. The solid residue was triturated with ether and filtered to give 9.7 g (99%) of crude product. Two recrystallizations from 2-propanol gave analytically pure **6** (R = C_6H_5; X = tosyl), mp 181–182° dec.

Anal. Calcd for $C_{28}H_{25}NO_3S_2$: C, 68.96; H, 5.17; N, 2.87; S, 13.15. Found: C, 68.78; H, 5.40; N, 2.76; S, 12.95.

2-Diphenylmethyl-3-methylbenzothiazolium Iodide (6, R = C_6H_5; X = I). A.—The tosylate **6** (R = C_6H_5; X = tosyl) (2.45 g, 0.005 mol) in hot 50% aqueous ethanol (10 ml) was treated with 57% hydriodic acid (2 ml). The precipitated solid was filtered and recrystallized twice from methanol to give **6** (R = C_6H_5; X = I), mp 222–224° dec.

Anal. Calcd for $C_{21}H_{18}INS$: C, 56.89; H, 4.09; I, 28.63; N, 3.16; S, 7.23. Found: C, 56.83; H, 4.11; I, 28.51; N, 3.07; S, 7.16.

B.—Hydriodic acid, (0.1 ml of 57% aqueous acid, 0.0032 mol) was added to a warm solution of 2-diphenylmethylene-3-methylbenzothiazoline (0.1 g, 0.0032 mol) in ethanol (7 ml). On cooling, 0.1 g (71%) of colorless prisms formed, mp 222–224° dec, not depressed in admixture with authentic material above.

2-Diphenylmethylene-3-methylbenzothiazoline (7, R = C_6H_5).—Sodium methoxide solution (10 ml of 1.02 *N*, 0.01 mol) was added to an ice-cold solution of **6** (R = C_6H_5; X = tosyl) (4.9 g, 0.01 mol) in methanol (10 ml). The precipitated product was filtered to give 3.0 g (95%) of crude **7** (R = C_6H_5). One recrystallization from 2-propanol, then two from hexane, gave the product as bright yellow needles: mp 130–131°; nmr, τ 7.17 (s, 3, CH_3N), 2.6–3.6 (m, 14, aromatic H).

Anal. Calcd for $C_{21}H_{17}NS$: C, 79.96; H, 5.43; N, 4.44; S, 10.17; mol wt, 315.42. Found: C, 80.09; H, 5.56; N, 4.26; S, 10.44; mol wt, 330.

2-(Diphenylchloromethyl)-3-methylbenzothiazolium Chloride (9).—A carbon tetrachloride solution of chlorine (25 ml of 0.168 *M* solution, 0.0042 mol) was added dropwise to an ice-cold solution of 2-diphenylmethylene-3-methylbenzothiazoline (1.3 g, 0.0042 mol) in carbon tetrachloride. A salt immediately precipitated. Filtration and recrystallization from acetonitrile–ethyl acetate gave 0.6 g (37%) of almost colorless prisms, mp 163–165° dec.

Anal. Calcd for $C_{21}H_{17}Cl_2NS$: C, 65.28; H, 4.44; Cl, 18.35; N, 3.63; S, 8.30. Found: C, 65.09; H, 4.66; Cl, 18.57; N, 3.57; S, 8.14.

2,3-Dimethyl-2-(trichloromethyl)benzothiazoline (10, R = H).—To a solution of the dimer **2**[5] (3.26 g, 0.01 mol) in boiling benzene (50 ml) was added a solution of trichloroacetic acid (3.30 g, 0.02 mol) in benzene (25 ml). The reaction mixture was heated at the reflux temperature for 1.5 hr. The benzene was removed under aspirator vacuum. The residue was recrystallized twice from aqueous acetone to give **17**: mp 75–77° (4.0 g, 71%); nmr, τ 7.83 (s, 3, C-**CH**$_3$), 6.86 (s, 3, N-**CH**$_3$), 2.8–3.7 (m, 4, aromatic H).

Anal. Calcd for $C_{10}H_{10}Cl_3NS$: C, 42.49; H, 3.57; Cl, 38.64; N, 4.96. Found: C, 42.33; H, 3.51; Cl, 37.81; N, 5.05.

2-Benzyl-2-trichloromethyl-3-methylbenzothiazoline (10, R = C_6H_5).—A dried solution of 2-benzylidene-3-methylbenzothiazoline (1.0 g, 0.0042 mol) in benzene (20 ml) was added to a hot, anhydrous solution of trichloroacetic acid (0.7 g, 0.0042 mol) in benzene (20 ml). The mixture was refluxed 1.5 hr. Removal of the solvent *in vacuo* and recrystallization from ethanol afforded the product as 0.8 g (54%) of pale yellow needles: mp 104–105°; nmr, τ 6.87 (s, 3, N-**CH**$_3$), 6.55 (d, 1, J = 16 Hz, benzyl H), 6.00 (d, 1, J = 16 Hz, benzyl H), 2.8–3.7 (m, 9, aromatic H).

Anal. Calcd for $C_{16}H_{14}Cl_3NS$: C, 53.57; H, 2.93; Cl, 29.65; N, 3.91; S, 8.94; mol wt, 358.71. Found: C, 53.51; H, 3.92; Cl, 29.60; N, 3.70; S, 8.92; mol wt, 370.

Registry No.—**6** (R = H; X = tosyl), 16622-37-0; **6** (R = H; X = I), 16622-21-2; **6** (R = CH_3; X = I), 16622-22-3; **6** (R = $CH_2C_6H_4NO_2$; X = Br), 16622-23-4; **6** (R = H; X = Cl), 16622-24-5; **6** (R = C_6H_5; X = tosyl), 16622-25-6; **6** (R = C_6H_5; X = I), 16622-26-7; **7** (R = H), 16622-27-8; **7** [R = $C_6H_3(NO_2)_2$], 16622-28-9; **7** (R = C_6H_5), 16622-29-0; **8a**, 16622-30-3; **8b**, 16622-31-4; **8c**, 16622-32-5; **8a**, 16638-70-3; **9**, 16622-33-6; **10** (R = H), 16622-34-7; **10** (R = C_6H_5), 16622-35-8; 2-diphenylmethylbenzothiazole, 16622-36-9.

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Synthesis of 11H-Indeno[1,2-c]isoquinoline Compounds Related to Chelerythrine

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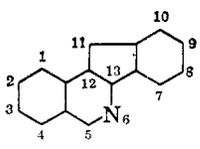
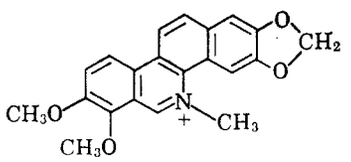
Reactions leading to the 11H-indeno[1,2-c]isoquinoline nucleus are described. 7,8-Dimethoxyisoquinoline was obtained by an acid-catalyzed cyclization of 2,3-dimethoxybenzylaminoacetal to 4-hydroxy-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline followed by dehydration and dehydrogenation. Reductive condensation of the methiodide of 7,8-dimethoxyisoquinoline with benzaldehyde gave 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline in low yield. The Bobbitt process, by which a benzylaminoacetal is condensed with an aromatic aldehyde, was employed effectively in producing several 4-benzylisoquinolines. Reduction of the corresponding methiodides with lithium aluminum hydride gave 1,2-dihydroisoquinolines, which cyclized under the proper acid conditions to give tetrahydro-11H-indeno[1,2-c]isoquinolines. Dehydrogenation with iodine completed the synthesis. In this way, 3,4-dimethoxy-6-methyl-8,9-methylenedioxy-11H-indeno[1,2-c]isoquinolinium iodide and 3,4,8,9-tetramethoxy-6-methyl-11H-indeno[1,2-c]isoquinolinium iodide—both related to chelerythrine—were prepared.

The authors wish to report a new synthesis for the little known 11H-indeno[1,2-*c*]isoquinoline system **1**.[1,2] The general purpose was to open a convenient way to compounds of this class; the particular purpose was to synthesize structural variations of the Sanguinaria alkaloids,[3] *e.g.*, chelerythrine (**2**).



1



chelerytarine (**2**)

The plan of synthesis required 4-benzylisoquinolines (specifically **9**) as key intermediates. Such compounds should be accessible by reductively condensing an isoquinoline methiodide (specifically **7**) with an aromatic aldehyde.[4] The resulting 4-benzyltetrahydroisoquinoline products **8** could then be dehydrogenated to produce **9**. For the compounds of interest, this approach required 7,8-dimethoxyisoquinoline (**6**), which was prepared in two ways, both making use of 2,3-dimethoxybenzylaminoacetal (**3**) as the starting material. Treatment of acetal **3** with hydrochloric acid in the presence of hydrogen and a catalyst[5] gave tetrahydroisoquinoline (**5**). Treatment of acetal **3** with hydrochloric acid in the absence of hydrogen and catalyst gave 4-hydroxytetrahydroisoquinoline (**4**).[6] Structure **4** for the hydroxy compound is consistent with its nmr spectrum. Thus, the ratio of methoxy protons to aromatic protons is 6:2 as required, and the two-proton multiplet at 2.98 ppm corresponds to the methylene group at position 3. Formation of a dibenzoyl derivative of compound **4** is also consistent with its assigned structure. Catalytic dehydrogenation converted both tetrahydroisoquinolines **4** and **5** into the same compound, the fully aromatic 7,8-dimethoxyisoquinoline (**6**).[7] The isoquinoline preparation *via* hydroxy compound **4** gave good yields (*ca.* 60%) and was simpler to carry out than the alternate preparation involving **5**. Both methods were far superior to the Pomeranz–Fritsch synthesis.[8] (See Scheme I.)

Attachment of a 4-benzyl group[4] was tried with benzaldehyde itself as the aromatic aldehyde. When a mixture of methiodide **7** and benzaldehyde was exposed to hydrogenation conditions in acid solution, the expected product, 2-methyl-4-benzyl-7,8-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**8**, $R_1 = R_2 = H$), was obtained. However the low yield was discouraging and,

(1) The name and numbering follow the recommendations of "The Ring Index" [L. T. Capell and D. F. Walker, Jr., 2nd Suppl. to 2nd ed, American Chemical Society, Washington, D. C., 1964, p 189] in ring number 10815.

(2) Only three references could be found, *i.e.*, J. N. Chatterjea and H. Mukherjee, *J. Indian Chem. Soc.*, **37**, 379 (1960); S. Wawzonek, J. K. Stowell, and R. E. Karll, *J. Org. Chem.*, **31**, 1004 (1966); S. F. Dyke and D. W. Brown, *Tetrahedron*, **24**, 1455 (1968).

(3) R. H. F. Manske and H. L. Holmes, "The Alkaloids," Academic Press Inc., New York, N. Y., Vol. IV, 1954; p 253; Vol. VII, 1960, p 430.

(4) Method of R. Grewe, W. Krüger, and E. Vangermain, *Chem. Ber.*, **97**, 119 (1964).

(5) J. M. Bobbitt, K. L. Khanna, and J. M. Kiely, *Chem. Ind.* (London), 1950 (1964); J. M. Bobbitt, J. M. Kiely, K. L. Khanna, and R. Ebermann, *J. Org. Chem.*, **30**, 2247 (1965).

(6) In independent work, J. M. Bobbitt and J. C. Sih, utilizing a similar procedure, have isolated several analogous 4-hydroxytetrahydroisoquinolines [*J. Org. Chem.*, **33**, 856 (1968)]. Also *cf.* I. G. Hinton and F. G. Mann, *J. Chem. Soc.*, 599 (1959); T. Kondo and S. Tanaka, *J. Pharm. Soc. Jap.*, **50**, 923 (1930); *Chem. Abstr.*, **25**, 515 (1931).

(7) Related aromatizations of 4-ethoxy-1,2,3,4-tetrahydroisoquinolines have been reported by N. Vinot, *Bull. Soc. Chim. Fr.*, 617 (1960); *Ann. Chim.* (Paris), [13], **3**, 461 (1958).

(8) *Cf.* W. J. Gensler, *Org. Reactions*, **6**, 191 (1951). W. H. Perkin, Jr., and R. Robinson [*J. Chem. Soc.*, **105**, 2376 (1914)], using sulfuric acid in the Pomeranz–Fritsch cyclization of 2,3-dimethoxybenzalaminoacetal obtained 7,8-dimethoxyisoquinoline (**6**) in about 5% yield. C. Djerassi, F. K. Markley, and R. Ehrlich [*J. Org. Chem.*, **21**, 975 (1956)] using polyphosphoric acid brought the yield to 12–17%. In our hands, a variety of conditions produced **6** in yields no better than 8%.