Synthesis of [1]Benzothiopyrano[4,3,2-*de*]quinoline

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[1]Benzothiopyrano[4,3,2-*de*]quinoline (**13**), a novel tetracyclic compound without substituents on the ring has been synthesized from 1-amino-9*H*-thioxanthen-9-one (**4**) *via* 1-ethoxycarbonylacetamido)-9*H*-thioxanthen-9-one (**7**) in six steps.

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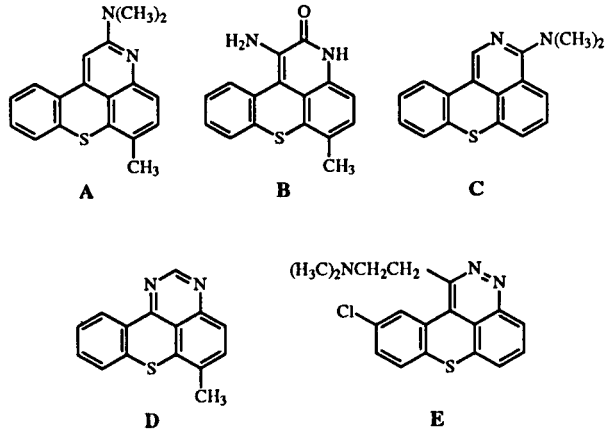
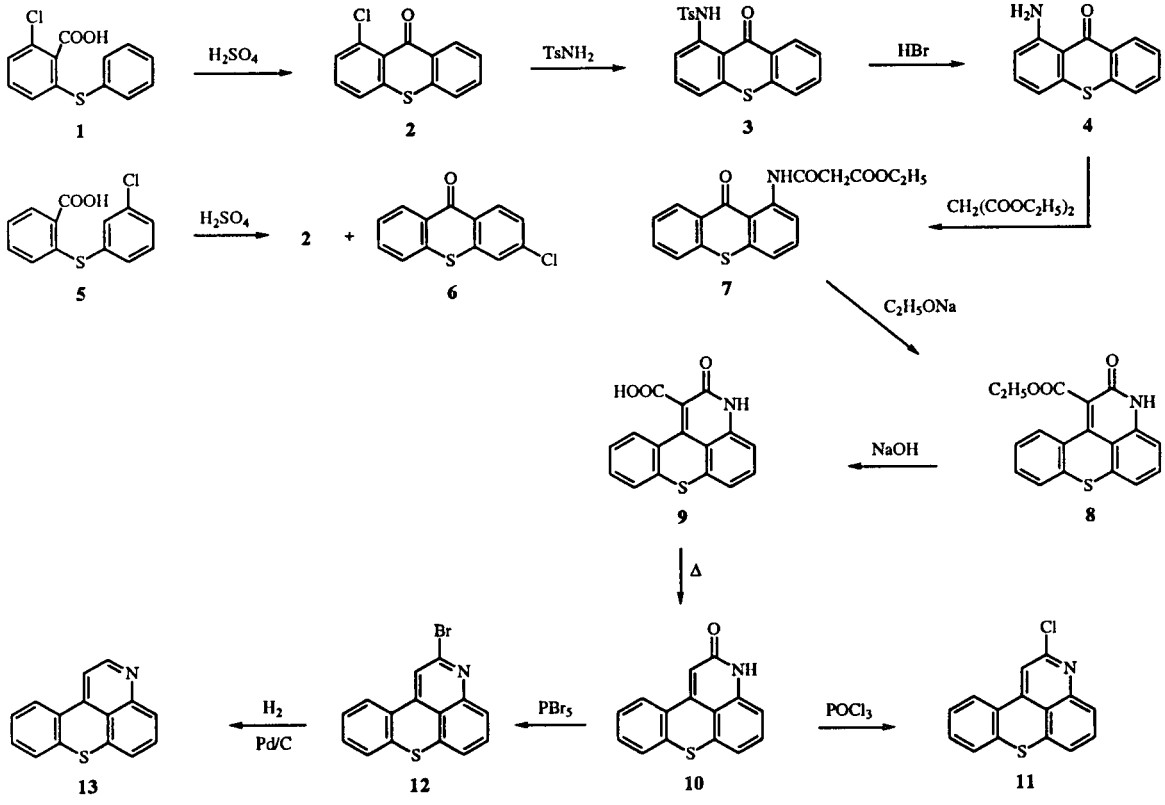
Various tetracyclic quinoline, isoquinoline, quinazoline and cinnoline derivatives condensed with [1]benzothiopyran ring, such as 2-dimethylamino-6-methyl[1]benzothiopyrano[4,3,2-*de*]quinoline (**A**) [1], 1-amino-6-methyl[1]-benzothiopyrano[4,3,2-*de*]quinoline-2(3*H*)-one (**B**) [2], 3-dimethylamino[1]benzothiopyrano[4,3,2-*de*]isoquinoline (**C**) [3], 6-methyl[1]benzothiopyrano[4,3,2-*de*]quinazoline (**D**) [4], and 1-[2-(dimethylamino)ethyl]-10-chloro-[1]benzothiopyrano[4,3,2-*de*]cinnoline (**E**) [5] have been prepared, and their pharmacological activities examined. Unexpectedly no report, however, has yet appeared on the synthesis of unsubstituted tetracyclic quinoline condensed with [1]benzothiopyran ring. In this paper, we report the synthesis of [1]benzothiopyrano[4,3,2-*de*]quinoline (**13**) using 1-amino-9*H*-thioxanthen-9-one (**4**) as a starting material.



Cyclization of 2-chloro-6-(phenylthio)benzoic acid (**1**) gave 1-chloro-9*H*-thioxanthen-9-one (**2**), which was converted to 1-(*p*-toluenesulfonamido)-9*H*-thioxanthen-9-one (**3**) [6] by treatment with *p*-toluenesulfonamide, followed by hydrolysis [7] with 47% hydrobromic acid in the pres-



ence of phenol to give 1-amino-9*H*-thioxanthen-9-one (**4**) in good yield.

As an alternative starting material of **4**, 2-[(3-chlorophenyl)thio]benzoic acid (**5**) was prepared according to the similar literature procedure [8] *via* the copper-catalyzed coupling of 2-mercaptobenzoic acid and 1-bromo-3-chlorobenzene in 90% yield. The yield was higher than that (61%) by the method [9] through the Ullmann reaction from 2-chlorobenzoic acid and 3-chlorobenzenethiol. Cyclization [6] of **5** gave a mixture of **2** and 3-chloro-9*H*-thioxanthen-9-one (**6**); these were not easily separated on a preparative scale. The mixture, however, was useful for the preparation of **4**, since on reaction with *p*-toluenesulfonamide, only the chlorine at the 1-position, which is at an *ortho* activated position, underwent reaction, and separation of product **3** and the unreacted **6** was easy.

Reaction of **4** with diethyl malonate gave 1-(ethoxycarbonylacetamido)-9*H*-thioxanthen-9-one (**7**) in 79% yield. Cyclization of **7** was achieved using sodium ethoxide to afford ethyl [1]benzothiopyrano[4,3,2-*de*]quinolin-2(3*H*)-one-1-carboxylate (**8**) in 85% yield, which was saponified to the carboxylic acid **9** by treatment with aqueous sodium hydroxide. When **9** was heated at 310° or refluxed in pyridine decarboxylation was caused to give [1]benzothiopyrano[4,3,2-*de*]quinolin-2(3*H*)-one (**10**) in 98% yield, which was converted to 2-chloro[1]benzothiopyrano[4,3,2-*de*]quinoline (**11**) by reaction with phosphoryl chloride in 81% yield. The 2-bromo analog **12** was obtained by treatment of **10** with phosphorus pentabromide. Compound **12** was debrominated by catalytic hydrogenation to give a tetracyclic quinoline, [1]benzothiopyrano[4,3,2-*de*]quinoline (**13**) in 97% yield. Catalytic debromination of compound **12** was accomplished with 10% Pd/C in a solution of anhydrous sodium acetate and acetic acid under a hydrogen atmosphere for 1 hour at 60°. Compound **11** was unfavorable as a starting material of **13**, since catalytic hydrogenation of **11** afforded a mixture of **13** and the unreacted **11** under the reaction conditions described above.

EXPERIMENTAL

Melting points were determined on a Yanagimoto micro-melting point apparatus and are uncorrected. The ir spectra were recorded with a Hitachi 260-10 spectrophotometer in potassium bromide disks. The ^{1}H nmr spectra were obtained on a JEOL JNM-FX 200 spectrometer in deuteriochloroform with tetramethylsilane as an internal standard. The mass spectra were measured with a Hitachi RMU-7MG double focusing spectrometer. Wakogel (C-200) was employed for silica gel column chromatography. Merck plate precorted with Kieselgel 60F_{254} was employed for preparative thin-layer chromatography.

1-(Ethoxycarbonylacetamido)-9*H*-thioxanthen-9-one (**7**).

A solution of **4** (4.55 g, 20 mmoles) in diethyl malonate (45 ml) was boiled for 20 minutes, then the ester was removed by distillation under reduced pressure. Recrystallization of the residue from ethanol gave **7** (5.40 g, 79%) as yellow needles, mp 106-107°; ir: 1730, 1670, 1585, 1440, 1265, 1175 cm^{-1}; ^{1}H nmr: δ 1.34 (3H, t, J = 8 Hz, CH_3), 3.60 (2H, s, $COCH_2$), 4.30 (2H, q, J = 8 Hz, CH_2CH_3), 7.30 (1H, d, J = 8 Hz, 4-H), 7.49 (1H, t, J = 8 Hz, 7-H), 7.55 (1H, d, J = 8 Hz, 5-H), 7.58 (1H, t, J = 8 Hz, 3-H), 7.64 (1H, t, J = 8 Hz, 6-H), 8.58 (1H, d, J = 8 Hz, 8-H), 8.80 [10] (1H, d, J = 8 Hz, 2-H); ms: m/z 341 ($M^{+\cdot}$).

Anal. Calcd. for $C_{18}H_{15}NO_4S$: C, 63.33; H, 4.43; N, 4.10. Found: C, 63.43; H, 4.39; N, 4.10.

Ethyl [1]Benzothiopyrano[4,3,2-*de*]quinolin-2(3*H*)-one-1-carboxylate (**8**).

A solution of sodium ethoxide from sodium (0.6 g) in ethanol (20 ml) was added dropwise to a boiling suspension of **7** (3.41 g, 10 mmoles) in ethanol (60 ml). The mixture was boiled for additional 15 minutes. After cooling, the solid product was stirred for some time with dilute hydrochloric acid, then washed and dried to give **8** (2.74 g, 85%). Recrystallization from aqueous dioxane afforded small yellow needles, mp 276-278°; ir: 1720, 1630, 1580, 1190, 1093, 750 cm^{-1}; ^{1}H nmr: δ 1.29 (3H, t, J = 8 Hz, CH_3), 4.43 (2H, q, J = 8 Hz, CH_2), 6.96-7.44 (6H, m, ArH), 7.98 (1H, d, J = 8 Hz, 11-H); ms: m/z 323 ($M^{+\cdot}$).

Anal. Calcd. for $C_{18}H_{13}NO_3S$: C, 66.86; H, 4.05; N, 4.33. Found: C, 66.72; H, 3.99; N, 4.26.

[1]Benzothiopyrano[4,3,2-*de*]quinolin-2(3*H*)-one-1-carboxylic Acid (**9**).

Compound **8** (3.23 g, 10 mmoles) was refluxed with 5% aqueous sodium hydroxide (300 ml) for 5 hours. The solution was acidified with dilute hydrochloric acid, and the product was recrystallized from acetic acid to give **9** (2.50 g, 85%) as orange needles; it began to lose carbon dioxide and change its appearance at 250°; the melting point of the yellow residue was over 300°; ir: 1715, 1630, 1567, 760 cm^{-1}; ^{1}H nmr: δ 7.10-7.60 (6H, m, ArH), 8.11 (1H, d, J = 8 Hz, 11-H); ms: m/z 295 ($M^{+\cdot}$).

Anal. Calcd. for $C_{16}H_9NO_3S$: C, 65.08; H, 3.07; N, 4.74. Found: C, 64.88; H, 3.31; N, 4.51.

[1]Benzothiopyrano[4,3,2-*de*]quinolin-2(3*H*)-one (**10**).

a) Compound **9** (2.95 g, 10 mmoles) was heated at 310°. The product (2.46 g, 98%) was sublimed to afford yellow needles (1.88 g, 75%), mp > 300°; ir: 1647, 1585, 753 cm^{-1}; ^{1}H nmr: δ 7.00-7.60 (7H, m, ArH), 8.22 (1H, d, J = 8 Hz, 11-H), 8.29 (1H, s, OH); ms: m/z 251 ($M^{+\cdot}$).

Anal. Calcd. for $C_{15}H_9NOS$: C, 71.69; H, 3.61; N, 5.57. Found: C, 71.33; H, 3.52; N, 5.44.

b) A mixture of **9** (2.07 g, 7 mmoles) and pyridine (200 ml) was refluxed for 1 hour. After cooling, the mixture was poured into 10% hydrochloric acid, stirred and filtered. The solid (1.72 g, 98%) was sublimated to give yellow needles (1.32 g, 75%), mp >300°. The physical properties were identical with those of a sample obtained by method a).

2-Chloro[1]benzothiopyrano[4,3,2-*de*]quinoline (**11**).

A solution of **10** (2.51 g, 10 mmoles) in phosphoryl chloride (10 ml) was heated on a boiling water-bath for 1 hour, then cooled and poured on ice. The mixture was neutralized and the product was recrystallized from benzene and then aqueous ace-

tone to give **11** (2.17 g, 81%) as yellow needles, mp 187-188°; ir: 1565, 1547, 765 cm^{-1}; ^1H nmr: δ 7.27-7.70 (7H, m, ArH), 7.97 (1H, d, J = 8 Hz, 11-H); ms: m/z 269 ($M^{+\cdot}$).

Anal. Calcd. for $C_{15}H_8ClNS$: C, 66.79; H, 2.99; N, 5.19. Found: C, 66.61; H, 2.91; N, 5.14.

2-Bromo[1]benzothiopyrano[4,3,2-*de*]quinoline (**12**).

A mixture of **10** (0.75 g, 3 mmoles) and phosphorus pentabromide (1.30 g, 3 mmoles) was heated at 80° for 30 minutes and at 130° for 1 hour. To the cooled reaction mixture ice and water were added and the mixture neutralized with aqueous sodium hydroxide. The product was filtered and purified by column chromatography on silica gel using chloroform as an eluent to afford **12** (0.32 g, 34%). Recrystallization from aqueous ethanol gave yellow crystals, mp 173-176°; ir: 1565, 1545, 765 cm^{-1}; ^1H nmr: δ 7.30-7.74 (7H, m, ArH), 7.95 (1H, d, J = 8 Hz, 11-H); ms: m/z 313 ($M^{+\cdot}$).

Anal. Calcd. for $C_{15}H_8BrNS \cdot {}^1/_2H_2O$: C, 55.74; H, 2.81; N, 4.33 Found: C, 56.08; H, 2.77; N, 4.36.

[1]Benzothiopyrano[4,3,2-*de*]quinoline (**13**).

A solution of **12** (220 mg, 0.70 mmole) and anhydrous sodium acetate (58 mg, 0.71 mmole) in acetic acid (30 ml) was stirred with 10% Pd/C (50 mg) under a hydrogen atmosphere for 1 hour at 60°. The resulting mixture was filtered and the filtrate evaporated under reduced pressure. The solid residue was preparative thin-layer chromatographed with chloroform to give **13** (160 mg, 97%) as yellow needles, mp 133-134°; ir: 1565, 765 cm^{-1}; ^1H nmr: δ 7.20-7.40 (4H, m, 5,6,8,9-H), 7.52 (1H, t, J = 8 Hz, 10-H), 7.62 (1H, d, J = 6 Hz, 1-H), 7.74 (1H, d, J = 8 Hz, 4-H), 8.02 (1H, d, J = 8 Hz, 11-H), 8.78 (1H, d, J = 6 Hz, 2-H); ms: m/z 235 ($M^{+\cdot}$).

Anal. Calcd. for $C_{15}H_9NS$: C, 76.57; H, 3.86; N, 5.95. Found: C, 76.61; H, 3.84; N, 5.59.

Acknowledgment.

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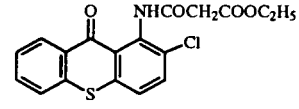
[10] On the ^1H nmr spectrum of compound **7**, a signal at δ 8.80 was assigned to the aromatic proton of the 2-position, because the ^1H nmr spectrum of the 2-chloro derivative **14** corresponding to **7** showed no signal at 8.80.



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