B. 1,4-Bis(2-indol-3-ylethyl)piperidine.—A mixture of 4-[2-(indol-3-yl)ethyl]piperidine[2] (15 g) and finely powdered $Na_2CO_3 \cdot H_2O$ (15 g) in *i*-PrOH (100 ml) was stirred and refluxed while 3-(2-bromoethyl)indole (15 g) in *i*-PrOH (100 ml) was added dropwise during 1 hr. Stirring and refluxing were continued for 18 hr, then the mixture was evaporated to dryness *in vacuo*. The residue was triturated under $CHCl_3$ several times and an insoluble white solid was filtered off. Evaporation of the filtrate and recrystallization of the residue from AcMe–H_2O gave 13.5 g (53%) of product, mp 145–147°.

C. 1-(2-Indol-3-ylethyl)-4-[2-(2-methylindol-3-yl)ethyl]piperidine.—A mixture of 4-[2-(2-methylindol-3-yl)ethyl]pyridine (23.6 g) and 3-(2-bromoethyl)indole (22.4 g) in absolute EtOH (500 ml) was kept at room temperature in the dark for 1 week. The resultant solution of quaternary salt was hydrogenated at 50° and 28.12 kg/cm² in the presence of PtO_2 (2.0 g) for 18 hr. The product precipitated and was filtered off along with the catalyst. Separation from catalyst was achieved by stirring with $AcNMe_2$ and filtering. H_2O was added to the filtrate until crystallization commenced to give 15.9 g (35%) of product hydrobromide, mp 242–243°.

D. 1,4-Bis[2-(1-methylindol-3-yl)ethyl]piperidine.—1,4-Bis(2-indol-3-ylethyl)piperidine (2.0 g) was added portionwise to $NaNH_2$ in liquid NH_3 prepared from 248 mg of Na. After stirring for 1 hr, MeI (1.56 g) in Et_2O (10 ml) was added dropwise and stirring was continued for 2 hr. NH_3 was allowed to evaporate and the residue was stirred with Et_2O (100 ml) and H_2O (100 ml). Evaporation of the dried ($MgSO_4$) ether layer and recrystallization of the solid residue from AcMe–H_2O provided colorless needles (1.2 g), mp 123–124°.

Derivatives of 9-Thioxanthenecarbonitrile

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Since the discovery of methadone, the analgetic first synthesized by Bockmühl and Ehrhart,[1] the medicinal chemist has found 3,3-diphenylpropylamines in general to be a fertile source of diverse biological activities.[2] Our brief excursion into this area was directed toward amalgamation of the analgetic properties of the diphenylpropylamines with the antianxiety properties of the thioxanthene-9-alkylamines by attempting to prepare the thioxanthene analog (**9**) of methadone and some of its congeners.

Application of the classic methadone synthetic scheme[1] to the thioxanthene ring system embraced two problems: (1) preparation of 9-thioxanthenecarbonitrile (**3**) in adequate yield for use as an intermediate, and (2) conversion of a crowded nitrile to the corresponding ethyl ketone.

Preparation of **3a** from thioxanthen-9-ol (**1a**), obtained by $NaBH_4$ reduction of thioxanthen-9-one,[3] was accomplished in 61% over-all yield by treating intermediate 9-chlorothioxanthene (**2a**)[4] with CuCN. (Scheme I). Conversion of **1a** to other reactive intermediates, *e.g.*, bromide, tosylate, or mesylate, in each case produced markedly inferior results, even when a variety of CN^- sources was employed. This is not unreasonable in the light of our experience with chloride **2a** which is rapidly converted to **1a** and thioxanthen-9-one in the presence of air. Thus the yield of nitrile depends upon the care exercised in isolation of the intermediate.

Alkylation of the Na derivative of **3a** with 2-chloro-*N*,*N*-dimethylethylamine proceeds smoothly to **4a**, which reacts with EtMgBr at 0°. The ketimine is completely hydrolyzed to the corresponding ketone (**5a**) after 30 min at reflux in dilute aqueous acid. By the same scheme 2-chlorothioxanthen-9-ol (**1b**)[5] is converted to **5b**. In each case temperature control during the Grignard addition is critical, since the Mg derivative of the ketimine is unstable above 25°. In fact, if **4b** and the Grignard reagent are heated to 100° before hydrolysis, no **5b** can be detected. The major product, **6**, apparently arises by fragmentation of the Mg adduct driven by the propensity of the thioxanthene system to delocalize anionic charge at C-9.

Alkylation of the Na derivative of **3a** with 2-(dimethylamino)isopropyl chloride provides the two expected isomers **7** and **8**, which can be separated on alumina. Structural assignments are based upon several bits of data: (1) relative chemical shifts of the N-Me and C-Me protons based on models reported by Casy,[6] (2) isomer **7** runs faster than **8** on both alumina and silica gel, and (3) relative reactivity toward the Grignard reagent. Neither isomer reacts with EtMgBr at room temperature. Isomer **8** is consumed only at temperatures above 100°, but after aqueous acid treatment no ketonic material can be detected by ir analysis of the total product. Isomer **7** reacts at *ca.* 50–60° with similar results. Apparently steric hindrance by the α-Me is sufficient to preclude attack of the reagent at a temperature compatible with adduct stability. Further studies indicate that variation of the solvent and or the halogen has no influence on the temperature requirement. The utility of EtLi has not yet been explored.

The intermediates **4**–**8** were devoid of activity at 10 mg/kg (administered subcutaneously) when subjected to three well-known laboratory methods for evaluating analgetic activity: the hot plate method,[7] the tail flick method,[8] and the phenylbenzoquinone writhing method.[9]

Experimental Section

Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values. Melting points (Thomas–Hoover capillary melting point apparatus) are uncorrected. The ir spectra were measured with a Perkin-Elmer Model 21 spectrophotometer, uv spectra with a Cary Model 11 recording spectrometer, and nmr spectra with a Varian A-60 spectrometer with Me_4Si as an internal standard.

9-Thioxanthenecarbonitrile (3a).—A suspension of thioxanthen-9-ol[3] (21.4 g, 0.100 mole) in 200 ml of anhydrous Et_2O under N_2 was treated carefully with $SOCl_2$ (8.0 ml) with stirring at 0–5°. The alcohol dissolved before a white solid began to separate. After 1 hr at 25°, the solvent was removed *in vacuo*, 100 ml of anhydrous C_6H_6 added, and the solution again evaporated. All manipulations were performed with rigorous exclusion of air. Anhydrous C_6H_6 (100 ml) and CuCN powder

(1) M. Bockmühl and G. Ehrhart, *Ann. Chem.*, **561**, 52 (1949).

(2) P. A. J. Janssen, "Synthetic Analgesics. Part 1. Diphenylpropylamines," Pergamon Press, Inc., New York, N. Y., 1960.

(3) C. C. Price, M. Hori, T. Parasaran, and M. Polk, *J. Amer. Chem. Soc.*, **85**, 2278 (1963).

(4) T. P. Hilditch and S. Smiles, *J. Chem. Soc.*, **99**, 145 (1910).

(5) J. O. Jilek, M. Rajsner, J. Pomykacek, and M. Protiva, *Cesk. Farm.*, **14**, 294 (1965); *Chem. Abstr.*, **65**, 2212g (1966).

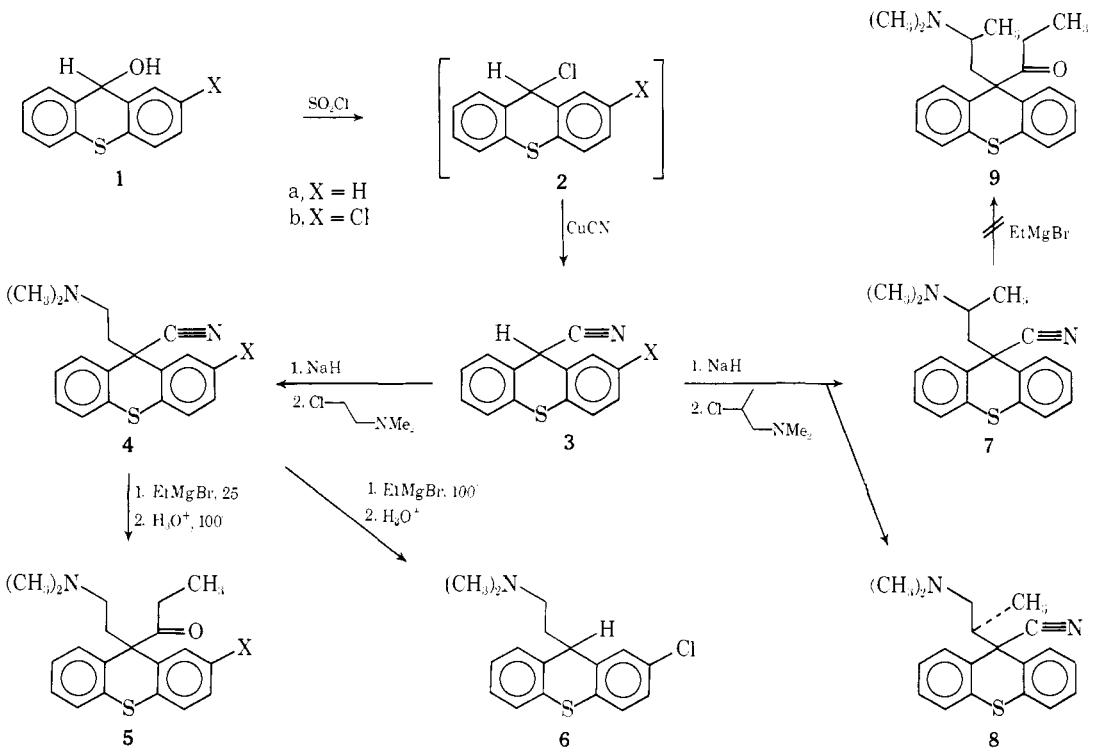
(6) A. F. Casy, *J. Chem. Soc. B* 1157 (1966).

(7) N. B. Eddy and D. Leimbach, *J. Pharmacol. Exp. Therap.*, **107**, 385 (1953).

(8) L. B. Witkin, M. Maggio, and W. E. Barrett, *Proc. Soc. Exp. Biol. Med.*, **101**, 377 (1959).

(9) E. Siegmund, R. Cadmus, and G. Lu, *ibid.*, **95**, 729 (1957).

SCHEME I



(17.9 g, 0.20 mole) were added and the suspension was stirred at reflux under N_2 for 4 hr. Before cooling the mixture was filtered, the solids were washed with hot C_6H_6, and the filtrate was evaporated to yield a crystalline residue (20.6 g), mp 85–89°, containing thioxanthene and thioxanthen-9-one, as well as the desired nitrile (tlc). One recrystallization from hexane removed thioxanthene and one recrystallization from *i*-PrOH removed most of the thioxanthen-9-one to provide 13.6 g (61%) of **3a**, mp 92.5–95°, which was pure enough to be used as a synthetic intermediate. Three additional recrystallizations from *i*-PrOH provided pure **3a**: mp 97–98°, ir (KBr) C≡N stretching either weak or absent; uv max (EtOH) 262 mμ (log ε 4.0). *Anal.* ($C_{14}H_9NS$) C, H, N.

2-Chloro-9-thioxanthenecarbonitrile (**3b**) was prepared by the same procedure in 64% yield, mp 134–136° (Me_2CO–hexane), ir (KBr) 4.49 μ (C≡N, very weak), uv max (EtOH) 266 mμ (log ε 4.1). *Anal.* ($C_{14}H_8ClNS$) C, H, N.

Method A. 9-[2-(Dimethylamino)ethyl]-9-thioxanthenecarbonitrile (**4a**).—A solution of **3a** (11.2 g, 0.050 mole) in 50 ml of anhydrous DMF under N_2 was treated with 49% NaH in oil (2.5 g, 0.050 mole). After *ca.* 10 min H_2 evolution subsided and 2-chloro-N,N-dimethylethylamine (8.5 g, 0.070 mole) was added to the deep red carbanion solution. The mixture was stirred at 95° for 15 min during which time the color discharged. After dilution by 2 vol of H_2O, the products were extracted into EtOAc. The EtOAc extracts were washed twice with H_2O, then extracted by three 30-ml portions of 1 *N* aqueous HCl. The combined acidic extracts were treated with 10 *N* aqueous NaOH to pH 11 and the product was extracted with EtOAc.

The residue dissolved in Et_2O afforded a crystalline salt upon treatment with HCl–Et_2O. One recrystallization from *i*-PrOH provided 10.0 g (60%) of pure **4a**,HCl, mp 232–234°, uv max (EtOH) 265 mμ (log ε 4.1). *Anal.* ($C_{18}H_{18}N_2S$·HCl) C, H, N.

2-Chloro-9-[2-(dimethylamino)ethyl]-9-thioxanthenecarbonitrile (**4b**) was prepared in 73% yield from **3b** *via* method A: mp 71.5–73° (hexane). The hydrochloride crystallized from *i*-PrOH: mp 260–261.5°, uv max (EtOH) 270 mμ (log ε 4.1). *Anal.* ($C_{18}H_{17}ClN_2S$·HCl) C, H, N.

1-{9-[2-(Dimethylamino)ethyl]thioxanthen-9-yl}-1-propanone (**5a**).—A solution of **4a** (4.1 g, 0.014 mole) in 60 ml of anhydrous C_6H_6 was added to a solution of EtMgBr (from 3.3 g of EtBr, 0.73 g of Mg, and 15 ml of anhydrous Et_2O) under N_2 at such a rate so as to maintain the reaction temperature below 5°. After stirring at 25° for 18 hr, the pale green suspension was treated with 30 ml of 3 *N* aqueous HCl and heated for 0.5 hr on a steam bath while the Et_2O and C_6H_6 were allowed to distil away from the reaction mixture. The mixture was cooled and the oily hydrochloride was extracted into $CHCl_3$. Two recrystallizations from C_6H_6–hexane afforded 3.05 g (50%) of pure **5a**.HCl,[10] mp 178–180°, ir (KBr), 5.81 μ (C=O), uv max (EtOH) 274 mμ (log ε 4.0). *Anal.* ($C_{20}H_{23}NOS$·HCl) C, H, N.

1-(2-Chloro-9-[2-(dimethylamino)ethyl]thioxanthen-9-yl]-1-propanone (**5b**) was prepared in 41% yield from **4b** by the same procedure but was isolated as the maleate salt: mp 188–190°, ir (KBr) 5.85 μ (C=O), uv max (EtOH) 277 mμ (log ε 4.1). *Anal.* ($C_{20}H_{22}ClNOS$·$C_4H_4O_4$) C, H, N.

2-Chloro-N,N-dimethylthioxanthene-9-ethylamine (**6**), the major product if the Grignard mixture is heated to 100° *before* addition of the aqueous HCl, was isolated as the hydrochloride, mp 257–258.5°, uv max (EtOH) 272 mμ (log ε 4.1). *Anal.* ($C_{17}H_{18}ClNS$·HCl) C, H, N.

9-[2-(Dimethylamino)propyl]-9-thioxanthenecarbonitrile (**7**) was prepared from 11.2 g of **3a** and 2-chloro-N,N-dimethylpropylamine by method A. The crude residue (14.8 g) derived from the EtOAc extract was dissolved in hexane and chromatographed on 300 g of neutral Al_2O_3 (Woelm, activity I). Elution with 2% Et_2O–hexane provided 3.0 g of an oil, which was greatly enriched (*ca.* 9:1) in the less polar (LP) isomer. Subsequent elution by Et_2O yielded 8.7 g of a mixture slightly enriched (*ca.* 6:4) in the more polar (MP) isomer. The 90% LP fraction was converted to the hydrochloride salt in Et_2O and twice recrystallized from EtOH to yield 1.2 g of pure **7**·HCl: mp 276–277° dec; nmr ($CDCl_3$) δ 2.42 (broad singlet, $^+NCH_3$), 1.20 (d, 3 H, J = 6 cps, CCH_3). *Anal.* ($C_{19}H_{20}N_2S$·HCl) C, H, N.

9-[1-(Dimethylamino)-2-propyl]-9-thioxanthenecarbonitrile (**8**) was obtained by rechromatographing the above Et_2O eluate on 90 g of neutral Al_2O_3, eluting with C_6H_6 to remove all LP isomer, then eluting the MP isomer with Me_2CO. The Me_2CO eluate was treated with HCl and the insoluble salt was recrystallized from EtOH to afford 1.4 g of pure 8·HCl: mp 241.5–243° dec; nmr ($CDCl_3$) δ 2.46 (sharp singlet, $^+NCH_3$), 1.29 (d, 3 H, J = 7 cps, CCH_3). *Anal.* ($C_{19}H_{20}N_2S$·HCl) C, H, N.

Acknowledgment.—I wish to express my appreciation for the valuable technical assistance contributed by Mr. Hans Wiedermann.

(10) Compound **5a** previously reported is the maleate salt: C. L. Zirkle, U. S. Patent 3,095,425 (1963); *Chem. Abstr.*, **59**, 12842*g* (1963).