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Benzo[b]thiophene Derivatives. VIII.

Benzo[b]thiophene-3-carboxaldehyde and Derivatives (1)

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A procedure for the preparation of benzo[b]thiophene-3-carboxaldehyde from 3-methylbenzo[b]thiophene is reported. This aldehyde behaves as a typical reactive aromatic aldehyde with respect to oxidation, reduction, the mixed Cannizzaro reaction, reductive amination and acyloin and other condensation reactions.

Thiophene-3-carboxaldehyde (3-8) and many of its derivatives (9) have been extensively discussed in the literature. However, relatively few derivatives of the higher ring homolog, benzo[b]thiophene-3-carboxaldehyde (I), have been reported. In a continuation of our studies (10-17) of benzo[b]thiophene as a source of compounds of potential biological interest, aldehyde I and certain new derivatives were prepared.

Compound I was originally prepared (18) in poor yields by the reaction of the Grignard reagent derived from 3-bromobenzo[b]thiophene with either ethyl orthoformate (17% yield) or ethoxymethyleneaniline (25% yield). Although two groups were unsuccessful in attempts to obtain I by direct formylation (19,20), other workers (21,22) were able to obtain 7 to 9% yields of I by treating benzo[b]thiophene with *N*-methylformanilide and phosphorus oxychloride. Compound I has also been prepared in moderate yields through the Rosenmund reduction of 3-benzo[b]thenoyl chloride and by the McFadyen-Stevens reaction (23). The most convenient preparation of I appears to be the Blanc chloromethylation of benzo[b]thiophene (20,24,25) followed by the Sommelet reaction (20,22). In our hands, benzo[b]thiophene was converted in 78% yield to 3-benzo[b]thenylhexamethylenetetramine chloride and this hydrolyzed in dilute acetic acid to give I in 67% yield.

A shortage of benzo[b]thiophene caused us to investigate alternate intermediates in the preparation of I. The ready availability of 3-methylbenzo[b]thiophene (II) through the cyclization of phenylthiopropanone (17,26) made it appear as an accessible and inexpensive starting material for the preparation of the desired aldehyde. Gaertner (27) has demonstrated that treatment of 2-bromo-3-methylbenzo[b]thiophene with *N*-bromosuccinimide in the presence of peroxide provides a high yield of 2-bromo-3-bromomethylbenzo[b]thiophene, while others (28) have obtained side-chain halogenation of the isoelectronic compound 1-methylnaphthalene under similar conditions.

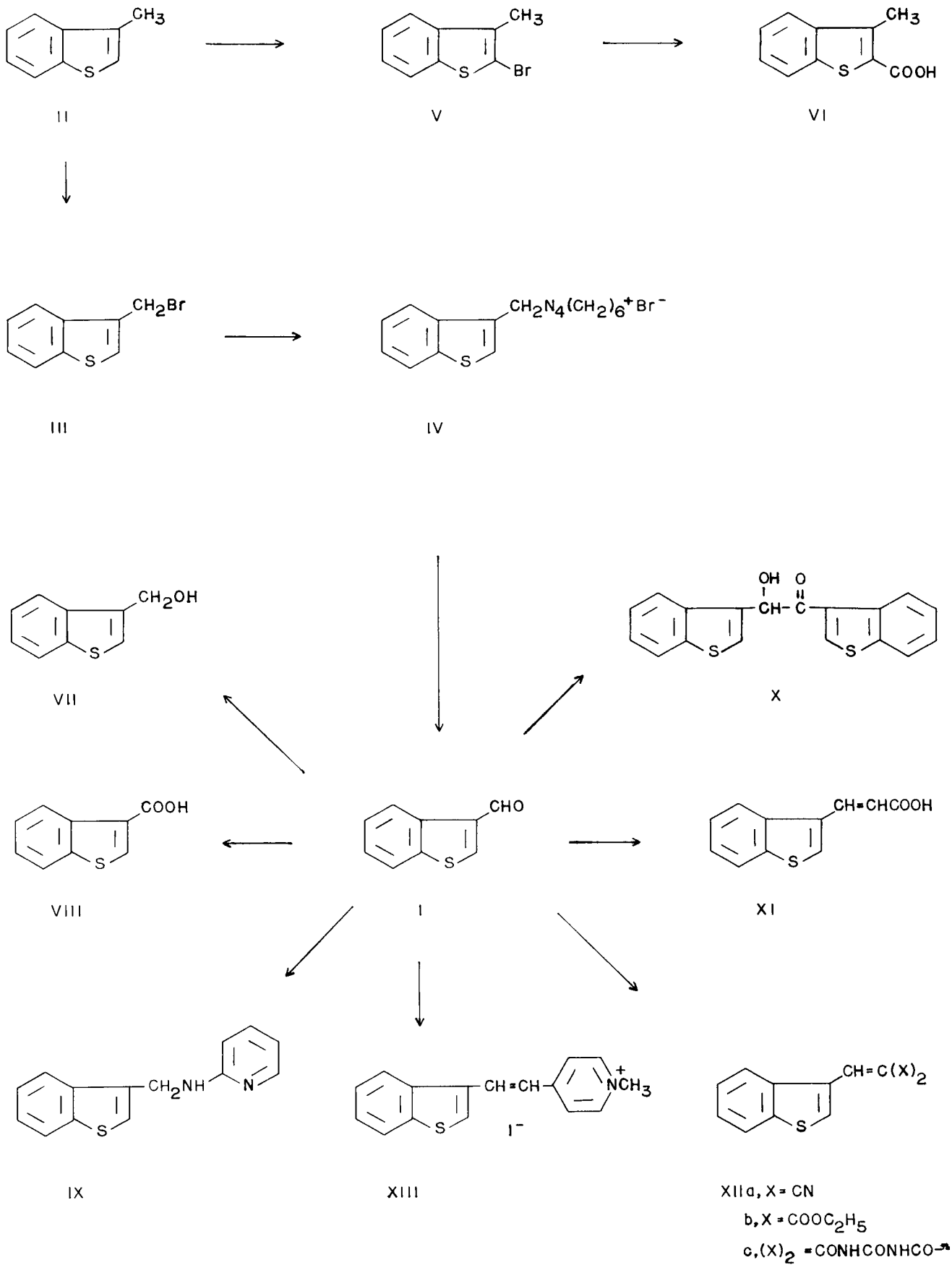
When II was treated in a similar reaction we obtained a 62% yield of 3-bromomethylbenzo[b]thiophene (III) which was isolated as the stable hexamethylenetetramine salt (IV) together with a 12% yield of the nuclear substituted isomer, 2-bromo-3-methylbenzo[b]thiophene (V). Since the completion of this work, others (33) have reported an 82% yield of III through the use of illumination in addition to peroxide in a modification of the reaction, but made no mention of the side-product V. The presence of 2-bromo-3-methylthiophene as a side-product in the bromination of 3-methylthiophene by *N*-bromosuccinimide in the presence of benzoyl peroxide has been clearly established (3,29). The structure of V was established by formation of the Grignard reagent and reaction with carbon dioxide to form the known compound 3-methylbenzo[b]thiophene-2-carboxylic acid (VI). This reaction together with the nuclear magnetic resonance spectrum of V support the assigned structure. The methyl group of V appears in the N.M.R. spectrum as a singlet at 7.71 τ units, whereas the methyl group of II is split into a doublet at 7.66 τ units (17).

Compound V was also prepared in high yield by treatment of II with *N*-bromosuccinimide in the absence of added peroxide. As in our earlier work (3) and that of others (29) the presence of peroxides appears mandatory to achieve a significant degree of side-chain bromination. When the peroxide was omitted, gas chromatography of the crude product failed to indicate the presence of III.

Compound III was unstable, but its hexamine salt (IV) provided an acceptable analysis. Refluxing IV in dilute acetic acid hydrolyzed it to I in good yield. This sequence provides about a 48% conversion of III to I and is of significant value when the parent heterocycle is unavailable or when a more electrophilic moiety than the chloromethyl-group (33) is desired.

The aldehyde I has been characterized as its semicarbazone, phenylhydrazone, *p*-nitrophenylhydrazone (18) and oxime (30). Its reaction with Grignard reagents, 2,4,6-trinitrotoluene (31), and a variety of arylacetonitriles (31,32) and α-keto methylene groups (30,23) has been reported. In this work I was further characterized as a thiosemicarbazone and 2-naphthylhydrazone.

Compound I was readily oxidized with freshly prepared silver oxide to benzo[b]thiophene-3-car-


CH3
S
II
CH3
S
Br
V
CH3
S
COOH
VI
CH2Br
S
III
CH2N4(CH2)6+Br−
S
IV
CH2OH
S
VII
OH O
CH-C
S
S
X
COOH
S
VIII
CHO
S
I
CH=CHCOOH
S
XI
CH2NH
N
S
IX
CH=CH
+
NCH3
S
I−
XIII
CH=C(X)2
S
XIIa, X = CN
b, X = COOC2H5
c, (X)2 = CONHCONHCO

boxylic acid (VIII) and alkaline sodium borohydride reduced it to 3-hydroxymethylbenzo[b]thiophene (VII) in good yield. It was demonstrated to undergo the mixed Cannizzaro reaction and to form a *bis*-azomethane derivative with hydrazine. The aldehyde was further shown to react in an acyloin condensation to form 3,3'-benzo[b]thenoin (X) which was then oxidized to 3,3'-benzo[b]thenil which formed a quinoxaline derivative with *o*-phenylenediamine.

Compound I underwent reductive alkylation with 2-aminopyridine to yield the amine IX, and formed condensation products with a variety of active methylene containing compounds. In all of these reaction the carboxaldehyde group of I has been observed to behave as a typical reactive aromatic aldehyde and as a convenient intermediate in these syntheses.

EXPERIMENTAL

Melting points were taken on a Mel-Temp capillary melting point apparatus and are corrected. The microanalyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. Infrared spectra were determined with a Perkin-Elmer Model 137 Infracord Spectrophotometer and N.M.R. spectra were taken with a Varian A-60 instrument employing tetramethylsilane as an internal reference. Gas chromatography was performed with an F. and M. Scientific Corporation Model 500 Gas Chromatograph using a 6 foot Diethyleneglycol adipate column at 200° with a helium flow rate of 68 ml./min.

Benzo[b]thiophene-3-carboxaldehyde (I).

A solution consisting of 148.2 g. (1.0 mole) of 3-methylbenzo[b]-thiophene (II) (17,26) and 2 g. of benzoyl peroxide in 400 ml. of anhydrous benzene was heated to a vigorous reflux in a 2 liter flask fitted with a stirrer and two reflux condensers. A mixture of 178 g. (1.0 mole) of *N*-bromosuccinimide and 2 g. of benzoyl peroxide was added to this in small portions as fast as the violent foaming would permit. After the addition, the reaction mixture was allowed to reflux for an additional 30 minutes and then cooled (ice-bath) and filtered. The collected succinimide was washed with two 50 ml. portions of dry benzene and filtrate and washings were combined and treated with anhydrous sodium carbonate. The inorganic material was filtered, the solvent removed under reduced pressure and the residue distilled. The first fraction consisted of 19 g. of unchanged II which was followed by 155 g. (78%) of a pale yellow oil which boiled over the range 131-151°/5 mm. This oil was slowly added to a boiling solution of 122 g. (0.872 mole) of hexamethylenetetramine in 900 ml. of dry chloroform. After 3 hours of refluxing, the reaction mixture was kept at 5° overnight and the white salt was collected and washed with 50 ml. portions of cold chloroform. In this manner 199 g. (62%) of 3-benzo[b]thenylhexamethylenetetramine bromide (IV) was obtained. An analytical sample was recrystallized twice from ethanol to yield fine white needles which began to darken at 175° and melted with decomposition at 183-185°.

Anal. Calcd. for $C_{15}H_{19}BrN_4S$: C, 49.10; H, 5.22; Br, 21.80; N, 15.25. Found: C, 49.27; H, 5.29; Br, 22.53; N, 15.05.

The combined chloroform filtrate and washings were concentrated to 200 ml. and extracted serially with two 100 ml. portions of water, 10% hydrochloric acid solution and again with water. The organic phase was dried with anhydrous sodium sulfate, filtered and the solvent was distilled. Fractionation of the residual oil under reduced pressure gave 23.6 g. (12%) of a colorless liquid which distilled at 121-124°/3 mm. The infrared spectrum of this liquid was identical to that of 2-bromo-3-methylbenzo[b]thiophene (V) (*vide infra*) and identity was further confirmed by augmentation of the gas chromatograph signal for authentic V. The n.m.r. spectrum of V in deuterochloroform exhibited a methyl singlet at 7.71 τ (integrating for 3H) and an aromatic multiplet at 2.31-2.89 τ (4H).

One-hundred and sixty grams (0.436 mole) of the salt IV was added to 800 ml. of 50% acetic acid solution and allowed to reflux for 2.5 hours. Then 200 ml. of 6 *N* hydrochloric acid solution was added and the mixture was boiled for a further 10 minutes. After cooling at 5° overnight, the solidified aldehyde (I) was collected and the acid solution was extracted with three 150 ml. portions of ether. The solid I was dissolved in ether and the ether solutions combined and washed with two 100 ml. portions of salt water, two 100 ml. portions of 10% sodium bicarbonate solution and again with 100 ml. of salt water. After drying with sodium sulfate the ether was removed and the residue was distilled to yield 54 g. (76.5%) of I boiling at 125-128°/2 mm. This represents a 47.6% conversion of II to I. After recrystallization from ethanol, white crystals were obtained which melted at 57.5-58.5°. The reported melting point of I is 58° (20); λ max (KBr), 3.28 μ (=C-H), 3.53 μ (C-H), 5.96 μ (C=O).

Anal. Calcd. for C_9H_6OS: C, 66.63; H, 3.73; S, 19.75. Found: C, 66.70; H, 3.70; S, 19.34.

A thiosemicarbazone derivative of I was prepared by the usual procedure (27) as tiny white plates which melted at 221-222° after recrystallization from ethanol.

Anal. Calcd. for $C_{10}H_9N_3S_2$: C, 50.75; H, 4.26; S, 27.10. Found: C, 50.54; H, 4.52; S, 27.14.

The 2-naphthylhydrazone of I was prepared by adding 0.81 g. of I in 10 ml. of ethanol to 0.97 g. of 2-naphthylhydrazine in 30 ml. of hot ethanol. The yellow product was collected and recrystallized from ethanol to yield yellow crystals which melted at 170-171°.

Anal. Calcd. for $C_{19}H_{14}N_2S$: N, 9.26. Found: N, 9.20.

Similarly, the dropwise addition of ethanolic hydrazine to I dissolved in ethanol gave bis-3-benzo[b]thenylidine azine as yellow crystals which melted at 166-168° after recrystallization from isoamyl alcohol.

Anal. Calcd. for $C_{18}H_{12}N_2S_2$: N, 8.43. Found: N, 8.56.

2-Bromo-3-methylbenzo[b]thiophene (V).

A mixture of 29.6 g. (0.2 mole) of 3-methylbenzo[b]thiophene (II), and 33 g. (0.185 mole) of *N*-bromosuccinimide in 80 ml. of dry chloroform was allowed to reflux for 22 hours. The succinimide was filtered from the cooled reaction mixture and the solvent was removed from the filtrate under reduced pressure. Gas chromatography of the residual oil demonstrated only two peaks with retention times of 7 and 18.4 minutes. The earlier component formed 9.2% of the mixture and was shown to be residual II by the augmentation of the signal upon addition of II to a sample of the crude product. The major peak (90.8% of the crude product) was attributed to V. Fractionation of the oil gave 35.5 g. (78%) of V as a colorless liquid which boiled at 129-130°/4.5 mm. (35). Compound V did not give a positive halogen test with silver nitrate solution, but the presence of the aromatic halogen substituent was demonstrated after sodium fusion. The observed spectral and chromatographic properties of V were identical to those of the minor product obtained when II was treated with *N*-bromosuccinimide in the presence of peroxide.

Anal. Calcd. for C_9H_7BrS: C, 47.59; H, 3.11; Br, 35.19. Found: C, 47.66; H, 3.13; Br, 35.42.

3-Hydroxymethylbenzo[b]thiophene (VII).

A. By the sodium borohydride reduction of I.

To 16.2 g. (0.1 mole) of I stirred in 100 ml. of methanol was added dropwise a solution of 2 g. of sodium borohydride in 20 ml. of 0.2 *N* sodium hydroxide solution. The reaction mixture was cooled to maintain a reaction temperature of 20-25°. After the addition, the mixture was boiled on the steam bath to remove the methanol and then 100 ml. of water was added. The basic solution was extracted with two 100 ml. portions of ether and the combined organic phase was dried with anhydrous magnesium sulfate. Removal of the ether and distillation of the residue gave 14.2 g. (86.7%) of a colorless liquid which boiled at 141-144°/1.5 mm. Upon trituration and recrystallization from ethanol white crystals were obtained which melted at 43-44°, λ max (KBr), 3.05 μ (-OH, bonded). Compound VII has been reported to boil at 124-125°/1.5 mm., but no melting point was given (39).

Anal. Calcd. for C_9H_8OS: C, 65.82; H, 4.91; S, 19.50. Found: C, 65.98; H, 4.88; S, 19.35.

B. By the crossed Cannizzaro reaction of I.

Into a three necked flask equipped with a stirrer, dropping funnel and thermometer were placed 10 g. (0.0617 mole) of I, 20 ml. of methanol and 10 ml. of 37% formaldehyde solution. The mixture was stirred and heated on the steam bath to 65-70° and then a solution of 12 g. of sodium hydroxide in 12 ml. of water was added dropwise with cooling to maintain the reaction temperature in the range 60-75°. After a further hour at 65-70° the solution was allowed to reflux for 20 minutes. The dark reaction mixture was diluted with 50 ml. of water and extracted with three 30 ml. portions of benzene. The benzene solutions were combined and washed with two 25 ml. portions of 10% sodium bicarbonate solution and with water and was dried over anhydrous magnesium sulfate. Removal of the solvent under reduced pressure and distillation of the residue provided 4.5 g. (45.6%) of the colorless carbinol boiling at 136-139°/1 mm. The infrared spectrum of this product was identical to that of VII obtained as indicated above. A mixture melting point determination was undepressed (43-44°).

Benzo[b]thiophene-3-carboxylic acid (VIII).

The procedure of Campaigne and LeSuer (3) for the oxidation of 3-thenaldehyde was used with appropriate modification. A solution of 42.4 g. (0.25 mole) of silver nitrate in 100 ml. of water was added with efficient stirring to a solution of 20 g. (0.5 mole) of sodium hydroxide in 100 ml. of water. To this brown, semisolid silver oxide mixture was added 16.2 g. (0.1 mole) of I in small portions with stirring and cooling. After the addition, the mixture was stirred for an additional 0.5 hour at room temperature and the black silver suspension was separated by aspirator filtration and washed with two 100 ml. portions of hot water. The combined filtrate and washings were treated with Norit, boiled and filtered hot. The alkaline filtrate was cooled, acidified with 6 *N* hydrochloric acid, and the white precipitate collected and recrystallized from boiling benzene to yield 15.6 g. (87.5%) of VIII as white needles which melted at 175-176° after a further recrystallization. This acid is reported to melt at 174-175° (18,36) and 179-180° (23,37).

Anal. Calcd. for $C_9H_6O_2S$: C, 60.65; H, 3.39; S, 17.98. Found: C, 60.82; H, 3.53; S, 17.97.

2-(3-Benzo[b]thenyl)aminopyridine (IX).

The procedure of Kaye and Kogan (38) was used with appropriate modification. A solution of 8.1 g. (0.05 mole) of I and 4.75 g. (0.05 mole) of 2-aminopyridine in 50 ml. of cumene was allowed to reflux for 3 hours during which time azeotroped water was separated in a Dean-Stark trap. Then 6 ml. of 90% formic acid was added to the hot solution and rapid evolution of gas was observed. The solution was refluxed for a further 19 hours after which the cumene and excess formic acid were removed under reduced pressure. The solid residue was recrystallized (Norit) from a benzene-hexane mixture to yield 8.6 g. (70%) of light yellow crystals which melted at 102-103°. This compound was previously prepared (25) from 3-chloromethylbenzo[b]-thiophene and 2-aminopyridine and is reported to melt at 101-103°.

Anal. Calcd. for $C_{14}H_{12}N_2S$: C, 69.96; H, 5.04; N, 11.63. Found: C, 69.60; H, 5.18; N, 11.80.

3,3'-Benzo[b]thenoin (X).

To 6 g. (0.037 mole) of I in 20 ml. of 95% ethanol was added a solution of 1 g. of potassium cyanide dissolved in 5 ml. of water and the reaction mixture was allowed to reflux for 3 hours. After cooling overnight the reaction mixture was treated with several drops of acetic acid and the dark precipitate was collected. Recrystallization from ethanol (Norit) and then from hexane, gave 4.4 g. (73.5%) of tiny yellow needles which melted at 179.5-180°, λ max (KBr), 2.90 μ (-OH, intramolecular H bonded), 6.0 μ (C=O), 7.40 μ, 9.58 μ (C-O).

Anal. Calcd. for $C_{18}H_{12}O_2S_2$: S, 19.77. Found: S, 19.89.

3,3'-Benzo[b]thenil.

Six grams of copper sulfate, 5 g. of pyridine and 5 ml. of water was heated on the steam bath and stirred until all of the copper sulfate dissolved. Then two grams of X was added and the mixture was warmed and stirred for 2 hours. Upon pouring the warm reaction mixture into 100 ml. of cold water a yellow precipitate separated which was recrystallized first from ethanol and then from hexane to yield 1.7 g. (88%) of yellow crystals which melted at 165-166°, λ max (KBr), 3.28 μ (=C-H), 6.05 μ (C=O).

Anal. Calcd. for $C_{18}H_{10}O_2S_2$: S, 19.88. Found: S, 19.57.

2,3-Bis-(3-benzo[b]thienyl)quinoxaline.

A mixture of 3.22 g. (0.01 mole) of 3,3-benzo[b]thenil was refluxed with 1.08 g. (0.01 mole) of *o*-phenylenediamine in 70 ml. of ethanol for 2 hours. The ethanol was then reduced to about 20 ml. and the reaction mixture was diluted with 50 ml. of water. The dark precipitate was collected and recrystallized from ethanol (Norit) and then from hexane to yield 2.1 g. (53%) of yellow crystals which melted at 168-169°. A mixture melting point with the thenil was depressed to 133-141°.

Anal. Calcd. for $C_{24}H_{14}N_2S_2$: C, 73.07; H, 3.58; N, 7.10. Found: C, 73.20; H, 3.76; N, 6.92.

β-3-Benzo[b]thienylacrylic acid (XI).

A mixture of 20.2 g. (0.125 mole) of I, 26 g. (0.25 mole) of malonic acid, 100 ml. of dry pyridine and 1 ml. of piperidine were heated gently to initiate an exothermic reaction. After the initial vigorous refluxing had subsided, the reaction mixture was allowed to reflux on the steam bath for 2 hours. The cooled reaction mixture was poured into 200 ml. of cold water and acidified by the slow addition of 6 *N* hydrochloric acid with cooling. The white precipitate was collected and recrystallized from a large volume of ethanol to yield 23.5 g. (92%) of small white needles which melted at 221-222°. Further recrystallization did not change the melting point, λ max (KBr), 3.3-4 μ (bonded O-H), 5.98 μ (α,β-unsaturated C=O), 6.18 μ (aromatic conjugated C=C).

Anal. Calcd. for $C_{11}H_8O_2S$: C, 64.68; H, 3.94; S, 15.64. Found: C, 65.04; H, 4.01; S, 15.64.

α-Cyano-β-(3-benzo[b]thienyl)acrylonitrile (XIIa).

A mixture of 12 g. (0.074 mole) of I, 4.9 g. (0.074 mole) of malononitrile, 1 g. of ammonium acetate, 4 ml. of acetic acid and 50 ml. of benzene was refluxed for 14 hours while water was collected in a Dean-Stark trap. The benzene was evaporated and the yellow crystalline residue was recrystallized twice from an ethanol acetone mixture to yield 14.5 g. (93.5%) of bright yellow needles which melted at 203-204°, λ max (KBr), 3.26 μ (=C-H), 4.55 μ (-CN), 6.29 μ, 6.40 μ (C=C).

Anal. Calcd. for $C_{12}H_6N_2S$: N, 13.32. Found: N, 13.58.

Ethyl 3-Benzo[b]thenalmalonate (XIIb).

A mixture of 16.2 g. (0.1 mole) of I, 16 g. (0.1 mole) of ethyl malonate, 2.5 ml. piperidine, 0.35 g. of benzoic acid and 80 ml. of dry benzene were refluxed for 8 hours in a flask fitted with a Dean-Stark water trap and condenser. After cooling, the benzene solution was washed with water, 10% hydrochloric acid solution, 20% sodium bicarbonate solution and again with water. The organic phase was dried with anhydrous sodium sulfate, filtered and distilled. The solid yellow residue was recrystallized from 70% ethanol to give 25.2 g. (83%) of white crystals which melted at 59-60° after a further recrystallization from ethanol.

Anal. Calcd. for $C_{16}H_{16}O_4S$: C, 63.13; H, 5.29; S, 10.53. Found: C, 63.25; H, 5.33; S, 10.40.

5-(3-Benzo[b]thenylidene)barbituric acid (XIIc).

Six and one-half grams (0.0507 mole) of barbituric acid was stirred in one liter of water at room temperature for 30 minutes, then 8.1 g. (0.05 mole) of finely powdered I was added and vigorous stirring was resumed. Within 5 minutes a yellow suspension formed, but stirring was continued for 12 hours to insure complete reaction, after which 125 g. of sodium chloride was added and the suspension stirred a further hour. After storage for 6 hours at 5° the yellow product was collected, washed with three 100 ml. portions of water and two 25 ml. portions of cold ether and then recrystallized from glacial acetic acid to yield 12.2 g. (89.6%) of yellow crystals which melted at 302-303.5°. The melting point was unchanged after further recrystallization.

Anal. Calcd. for $C_{13}H_8N_2O_3S$: C, 57.32; H, 2.96; N, 10.29. Found: C, 57.07; H, 3.15; N, 10.67.

N-Methyl-4-(3-Benzo[b]thienylethenyl)pyridinium iodide (XIII).

A solution of 11.25 g. (0.05 mole) of *N*-methyl-4-picolinium iodide, 8.1 g. (0.05 mole) of I, 15 drops of piperidine and 250 ml. of methanol was heated at reflux on the steam bath for 16 hours. After 5 minutes of heating a yellow precipitate began to separate from the green solution. The reaction mixture was concentrated to one-half its volume and cooled at 5° overnight. The yellow crystals were collected, washed with 50 ml. of ether and recrystallized from 600 ml. of methanol to yield 13.9 g. (73%) of yellow needles which melted at 292-293°.

Anal. Calcd. for $C_{16}H_{14}INS$: C, 50.65; H, 3.72; I, 33.46. Found: C, 50.34; H, 3.74; I, 33.81.

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(1) Contribution No. 1347. This work was supported in part by Public Health Service Research Grant GM-10366 to Indiana University.

(2) National Institutes of Health Predoctoral Fellow, 1961-1964, under Grant MH-14,696.

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Received December 29, 1965 Bloomington, Indiana 47401