

Novel Derivatives of 4-Keto-1,2,3,4-tetrahydrodibenzothiophene (1)

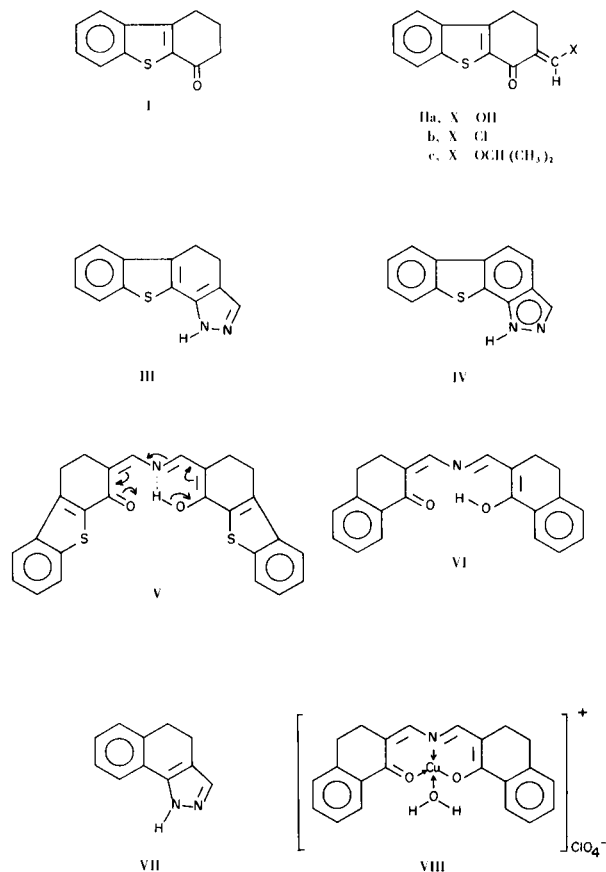
E. Campaigne, D. McClure and John Ashby

The Chemistry Laboratories of Indiana University

Cagniant (2) has prepared 4-keto-1,2,3,4-tetrahydrodibenzothiophene (I) in 16% overall yield by Friedel-Craft succinylation of benzo[*b*]thiophene with succinic anhydride, followed by reduction of the keto-acid and intramolecular cyclization. We experienced great difficulty in repeating the initial Friedel-Craft reaction, maximum yields for this step being *ca.* 30%. A modified approach to the synthesis of I was therefore devised. Benzo[*b*]thiophene reacts with β -carbomethoxypropionyl chloride under Friedel-Craft conditions to yield a keto-ester (3). Wolff-Kishner reduction of the ketone moiety caused hydrolysis of the ester function, yielding the intermediate γ -3-benzo[*b*]thienylbutyric acid, which readily cyclized to I (overall yield 30%).

Treatment of I with sodium hydride and methyl formate gave 3-formyl-4-keto-1,2,3,4-tetrahydrodibenzothiophene (IIa). Compound IIa was converted to the corresponding vinyl chloride (IIb) and this in turn to the isopropyl ether (IIc). The keto-aldehyde (IIa) reacted with hydrazine to yield the pyrazole (III), which upon aromatization yielded pyrazolo[4,3-*c*]dibenzothiophene (IV).

Reaction of IIa with ammonium acetate in acetic acid gave an orange-red powder formulated at V on the basis of elemental analysis, mass spectrum (MW 441) and reactions to be discussed below. The formation of V is envisaged as imine formation between two molecules of IIa and one molecule of ammonia. Basic hydrolysis of V regenerated IIa. Thus upon refluxing V with hydrazine and base the previously synthesized pyrazole (III) was formed. The sensitivity of V to base was demonstrated during its preparation from IIa in ethanol with ammonia gas. During the first few seconds of gas addition the solution turned bright red and a small amount of V precipitated; however, as the basicity of the solution increased the precipitate redissolved. Upon making the solution acidic with a few drops of hydrochloric acid, V was again precipitated and shown to be identical with the previously prepared sample. The hydrogen bonded, resonance stabilized form of V, as shown, is consistent with the high melting point (278°) and the intense color of the product. In view of the unusual nature of V, the corresponding α -tetralone derivative (VI) was prepared from 2-formyl-1-keto-1,2,3,4-tetrahydronaphthalene (4). Compound VI formed rust-colored needles and behaved like V; for example treatment with hydrazine and alkali gave the benz[*g*]indazole (VII) in high yield. Reaction of VI with cupric perchlorate



hexahydrate gave a monohydrated copper complex salt formulated as VIII, consistent with the hydrogen bonded structure for both V and VI. The formation of metal chelates with these bis(keto-aldehyde)imides offers an interesting area for further investigation.

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are corrected. The infrared spectra were measured as potassium bromide discs on a Perkin Elmer Infracord Spectrometer. Ultraviolet spectra, taken in absolute ethanol were measured on a Bausch and Lomb Spectronic 505 Spectrometer. For 60 MHz nmr spectra of Varian A-60 machine was used, and the 100 MHz spectra were determined on a Varian HA-100 spectrometer. In reporting the nmr spectra the following abbreviations have been used: s = singlet; d = doublet; m = multiplet (δ values refer to the center of the resonance). Anhydrous magnesium sulfate was used throughout as drying agent.

Methyl β (3-Benzothienyl)propionate.

β -Carbomethoxypropionyl chloride (5) could be used in this reaction, or more conveniently made *in-situ* as described below. To methyl hydrogen succinate (6) (10.35 g., 0.0783 mole) was added, slowly, phosphorus pentachloride (16.56 g., 0.079 mole) and the mixture warmed on a steam bath for 1.5 hours. To this solution (or to 11.8 g. of pure β -carbomethoxypropionyl chloride) was added benzo[*b*]thiophene (10 g., 0.074 mole) in dry benzene (50 ml.) and the mixture cooled in an ice bath with efficient stirring. To the mixture was added stannic chloride (17.8 ml., 0.15 mole) keeping the reaction temperature at 0°. The mixture was kept at 0° with stirring for 2 hours and then at room temperature overnight. The reaction mixture was hydrolyzed with ice (60 g.) and hydrochloric acid (55 ml.) and allowed to stand for 2 hours. The benzene layer (augmented by 200 ml. benzene) was separated and dried. Reduction in volume of the benzene gave crystals (6.8 g.). The filtrate on standing gave further crystals (2.5 g.) (combined yield 55%). Crystallization from benzene gave the pure product m.p. 94.5-95° (Lit. (3) m.p. 95°); ν 5.75 (CO₂CH₃), 5.95 (C=O).

Anal. Calcd. for C₁₃H₁₂O₃S: C, 62.9; H, 4.9; S, 12.9. Found: C, 62.9; H, 5.0; S, 13.0.

 γ (3-Benzothienyl)butyric acid.

A mixture of the previously described keto-ester (3 g., 0.0122 mole), sodium hydroxide (1.85 g.) and hydrazine hydrate (85% solution, 1.85 ml.) in diethylene glycol (25 ml.) was refluxed for 1.5 hours. The condenser was removed and the temperature allowed to rise to 200°. The solution at 200° was refluxed again for 3 hours. The mixture was added to ice (200 g.), and hydrochloric acid (4*N*) added dropwise to the rapidly stirred solution, yielding the product as a cream-colored solid. Crystallization from benzene gave needles (2 g., 68%), m.p. 104.5-107.5° (Lit. (2) m.p. 109-110°); ν 6.0 (COOH).

4-Keto-1,2,3,4-tetrahydrodibenzothiophene (I).

A mixture of γ -3-benzo[*b*]thienylbutyric acid (15.4 g., 0.07 mole) and phosphorus pentachloride (12.7 g.) in benzene (150 ml.) was swirled in a conical flask until dissolved. The flask was allowed to stand for 40 minutes, then cooled in ice and stannic chloride (13 ml. 0.1095 mole) added with swirling in one portion. After standing for a further 40 minutes the solution was decomposed by pouring into a mixture of ice (50 g.) and hydrochloric acid (100 ml.). The benzene layer was washed with a solution of sodium carbonate and dried. Concentration of the solvent gave the product (11.10 g., 78%), m.p. 111-112° (Lit. (2) m.p. 112°); ν 6.05 (C=O).

3-Formyl-4-keto-1,2,3,4-tetrahydrodibenzothiophene (IIa).

A mixture of I (4.9 g., 0.0243 mole) and sodium hydride (1.2 g., 50% dispersion, 0.025 mole) in dry benzene (100 ml.) was refluxed for 5 hours. To the cooled light brown solution was added methyl formate (2 ml.) and the resultant green solution stirred overnight at room temperature. The benzene solution was extracted with 2% sodium hydroxide until the benzene layer was almost colorless. Acidification of the alkaline solution gave the impure product which was extracted with chloroform. This solution was dried and evaporated to yield a yellow semisolid, which crystallized from ethyl acetate (4.1 g., 73%), m.p. 126-127°; ν 2.95 (OH), 6.2 (C=O).

Anal. Calcd. for C₁₃H₁₀O₂S: C, 67.8; H, 4.4; S, 13.9. Found: C, 67.8; H, 4.6; S, 13.7.

3-Chloromethylene-4-keto-1,2,3,4-tetrahydrodibenzothiophene

(IIb).

A solution of IIa (2.5 g., 0.0108 mole) in thionyl chloride (5.8 ml.) was slowly brought to reflux. The solution was cooled and the excess thionyl chloride removed under reduced pressure. The solid was dissolved in toluene and treated with charcoal. On cooling, the product was collected as colorless needles (1.72 g., 62%), m.p. 134-135°; ν 6.1 (C=O).

Anal. Calcd. for C₁₃H₉ClOS: C, 62.8; H, 3.65; Cl, 14.3. Found: C, 63.0; H, 3.73; Cl, 14.5.

3-Isopropoxymethylene-4-keto-1,2,3,4-tetrahydrodibenzothiophene (IIC).

Isopropyl iodide (freshly distilled b.p. 86-88°, 4.8 ml.) was added to a solution of IIa (1.304 g., 0.0056 mole) in DRY acetone (100 ml.). To this solution was added freshly fused potassium carbonate (8 g.) and the mixture refluxed for 72 hours. The solvent was removed and the resultant solid distributed between benzene (100 ml.) and water (100 ml.). The benzene solution was separated and the water extracted with a further 50 ml. of benzene. The combined extracts were dried and the solvent removed yielding a yellow oil (1.73 g.). The oil was extracted with boiling petroleum (b.p. 30-60°) (80 ml.). Upon cooling the extract the product separated as yellow needles (0.7 g.). The filtrate was used to extract a further 0.18 g. of product, (total yield 0.88 g. 57%), m.p. 90-94°. Recrystallization from light petroleum raised the m.p. to 106.5-107.5°; ν 3.35 (CH), 6.1 (C=O); nmr (deuteriochloroform) δ 7.15-7.8 (m, aromatic), 4.2 (septet; J 7.5 Hz; isopropyl H), 2.85 (s, aliphatic), 1.33 and 1.3 (d,d; isopropyl CH₃, intensity 1:4 due to *cis-trans* configuration; J 7.5 Hz).

Anal. Calcd. for C₁₆H₁₆O₂S: C, 70.6; H, 5.9; S, 11.8. Found: C, 70.5; H, 5.9; S, 11.7.

4,5-Dihydropyrazolo[4,3-*c*]dibenzothiophene (III).

(a) From IIa.

Hydrazine hydrate (0.082 ml.) was added to a solution of IIa (0.285 g., 0.00124 mole) in methanol (25 ml.) and the resultant solution kept at room temperature for 1 hour. Removal of the solvent gave an orange solid which was dissolved in methanol. Addition of water to the methanolic solution gave the product as crystals (0.174 g., 53%) m.p. 210-211.5°. An analytical sample from ethanol had m.p. 213-214°; ν 3.16 (NH), 3.4 (CH), 13.4 (*ortho* fused benzene); ν (EtOH) 233 (4.04), 248 (3.75), 257 (3.91), 266 (3.97), 308.5 (4.15), 323.5 (4.07) with an inflection at 299 μ (4.07); nmr (deuteriochloroform) δ 7.8 and 7.3 (m, aromatic), 7.55 (s, pyrazolo H), 3.0-3.7 (m, aliphatic), 3.3 (s, NH, concentration dependant). The peak at δ 3.3 collapsed on the addition of deuterium oxide.

Anal. Calcd. for C₁₃H₁₀N₂S: C, 69.0; H, 4.45; N, 12.4; M.W. 226.0564. Found: C, 68.9; H, 4.65; N, 12.2; M.W. (mass spectrum) 226.0556.

(b) From V.

A mixture of V (7.38 g., 0.0167 mole), sodium hydroxide (4.14 g.), and hydrazine hydrate (4.14 ml., 85%) in diethylene glycol (54 ml.) was refluxed gently for 1.5 hours. The solution was poured slowly into water and the resultant solid collected and air dried. The product was crystallized from benzene (4.7 g., 73%) m.p. 213-214°. The product was shown to be identical to a sample prepared as in part (a), by ν and mixture m.p.

Pyrazolo[4,3-*c*]dibenzothiophene (IV).

A mixture of III (1.5 g., 0.564 mmole) and 30% palladium on carbon (1 g.) in decalin (60 ml.) was refluxed for 4 hours. The

solution was cooled and the solid filtered. Extraction of the solid with acetone and removal of the solvent gave the product which crystallized from benzene as long needles (1.02 g., 68%) m.p. 242-243°. An analytical sample from benzene had m.p. 244°; $\text{ir } \mu$ 3.1 (NH) and 13.6; uv (EtOH), 249 (4.70), 295 (4.3), 319 (4.16), 333 (4.17).

Anal. Calcd. for $\text{C}_{13}\text{H}_8\text{N}_2\text{S}$: C, 69.6; H, 3.6; N, 12.5. Found: C, 69.4; H, 3.8; N, 12.8.

Bis(3-formyl-4-keto-1,2,3,4-tetrahydrodibenzothiophene)imine (V).

A mixture of IIa (0.57 g., 0.025 mole) and ammonium acetate (0.5 g.) was stirred in glacial acetic acid (9 ml.) at 100° for 35 minutes. Water (20 ml.) was added to the orange suspension and the resultant precipitate was filtered, washed with dilute sodium hydroxide (25 ml., 10%), water (15 ml.) and air dried, producing a gleaming red solid, (0.51 g., 87%) m.p. 277-278°; $\text{ir } \mu$ 6.1 (C=O), 6.4, 13.2 and 13.75 (unassigned).

Anal. Calcd. for $\text{C}_{26}\text{H}_{19}\text{NO}_2\text{S}_2$: C, 70.7; H, 4.3; N, 3.2; S, 14.5; M.W. 441. Found: C, 71.0; H, 4.4; N, 3.1; S, 14.4; M.W. 441 (mass spectrum).

Alkaline Hydrolysis of V to IIa.

A solution of V (0.15 g., 0.00034 mole) in a saturated solution of ethanolic potassium hydroxide (25 ml.) was heated on a steam bath for 1 hour. The solution turned deep purple immediately. Aqueous sodium hydroxide (100 ml., 10%) was added and the solution extracted with chloroform until the aqueous layer was almost colorless. The basic extract was then acidified with hydrochloric acid and the solution again extracted with chloroform. This extract was dried and evaporated to yield a yellow semisolid. Recrystallization from a 4:1 mixture of cyclohexane and tetrahydrofuran yielded IIa (0.072 g., 48%), m.p. and mixed m.p. 126-127°.

V from IIa and Ammonia.

When IIa (0.4 g., 0.0174 mole) was stirred in warm ethanol with the slow addition of ammonia gas, an orange-yellow precipitate formed, but dissolved with further addition of ammonia gas. The mixture was then made slightly acidic with the dropwise addition of hydrochloric acid. The orange-red precipitate which formed was filtered and recrystallized from tetrahydrofuran yielding red crystals of V (0.34 g., 82%), m.p. 278-278.5°. Bis(2-formyl-1-keto-1,2,3,4-tetrahydronaphthalene)imine (VI).

A mixture of 2-hydroxymethylene-1-tetralone (4) (4.33 g., 0.0218 mole) and ammonium acetate (5 g.) in glacial acetic acid (75 ml.) was warmed to 75° for 15 minutes when a deep red solution had formed. The solution was poured into ice water (750 ml.) and the resultant solid filtered, dissolved in acetone and treated with activated charcoal. The acetone solution was evaporated to yield a red solid which recrystallized from ethanol as needles (3.01

g., 56%), m.p. 160-165°. An analytical sample from ethanol had m.p. 177-178°; $\text{ir } \mu$ 6.05 (C=O), 6.3, 6.4, 8.3, 10.9 and 13.6 (unassigned).

Anal. Calcd. for $\text{C}_{22}\text{H}_{19}\text{NO}_2$: C, 80.2; H, 5.8; N, 4.28; M.W. 329. Found: C, 80.3; H, 5.9; N, 4.33; M.W. 329 (mass spectrum).

4,5-Dihydro-1H-benz[*g*]indazole (VII).

A mixture of crude VI (0.652 g., 0.00198 mole) sodium hydroxide (0.46 g.) and hydrazine hydrate (85%, 0.46 ml.) in diethylene glycol (6 ml.) was refluxed gently for 1.5 hours. The resultant cherry-red solution was added dropwise to 60 ml. of rapidly stirred water. The colorless precipitate was collected and dried (0.52 g., 95%), m.p. 122-123°. An analytical sample from benzene had m.p. 123-124°; $\text{ir } \mu$ 3.25 (NH), 3.5 (CH), 13.2 μ (*ortho* fused benzene); uv (EtOH) 223 (inf) (3.95), 250 (3.80), 260 (3.47) 268 (3.97), 285 (3.68) and 294 μm (3.57); nmr (acetone) δ 7.18 (m) and 7.8 (m, aromatic), 7.25 (s, pyrazolo H), 2.8-3 (m, aliphatic and NH). Addition of deuterium oxide reduced the integral of the δ 2.8-3.0 multiplet from 5 to 4 protons.

Anal. Calcd. for $\text{C}_{11}\text{H}_{10}\text{N}_2$: C, 77.6; H, 5.9; N, 16.4. Found: C, 77.4; H, 5.9; N, 16.5.

Cupric Bis(1-formyl-1-keto-1,2,3,4-tetrahydronaphthalene)imine Perchlorate Monohydrate (VIII).

Cupric perchlorate hexahydrate (870 mg., 2.37 mmoles) in ethanol (5 ml.) was added to a hot solution of VI (780 mg., 2.37 mmoles) in ethanol (60 ml.) and the mixture allowed to cool to room temperature. Water (50 ml.) was then added causing the product to crystallize as fine coppery needles (900 mg., 75%), m.p. 239-240°. Crystallization from ethanol-water raised the m.p. to 240-241°. If crystallization was allowed to occur slowly long purple needles m.p. 240-241° were formed.

Anal. Calcd. for $\text{C}_{22}\text{H}_{20}\text{ClCuNO}_7$: C, 51.9; H, 3.96; Cl, 6.96; N, 2.75. Found: C, 51.9; H, 4.08; Cl, 6.79; N, 2.62.

REFERENCES

- (1) Contribution No. 1729, supported by a Public Health Service Grant GM-10366 to Indiana University.
- (2) P. Cagniant and N. P. Buu-Hoi, *Chem. Ber.*, 76, 1269 (1943).
- (3) P. Cagniant and Mme. P. Cagniant, *Bull. Soc. Chim. France*, 5, 336 (1952).
- (4) K. N. Campbell, A. Schrage and B. K. Campbell, *J. Org. Chem.*, 15, 1135 (1950).
- (5) J. Cason, *J. Am. Chem. Soc.*, 64, 1106 (1942).
- (6) Organic Syntheses, Coll. Vol. III, 169.

Received July 22, 1969

Bloomington, Indiana, 47401