6α-Fluoro-17α-acetoxyprogesterone (V).—Anhydrous hydrogen chloride was bubbled steadily through a suspension of the fluoro-hydrin IV (1.6 g.) in acetic acid (350 cc.) at 15–18° for 2 hours. The flask was then stoppered and kept at room temperature for a further 3 hours. The solution was then poured onto an excess of ice-water and the product was isolated with ether. The ether solution was washed with a saturated salt solution (4 × 150 cc.), an excess of 5% sodium bicarbonate solution and finally water. Removal of the ether and crystallization of the product from benzene–hexane afforded 6α-fluoro-17α-acetoxyprogesterone (V) (1.2 g.), m.p. 243–246°, raised by several crystallizations from benzene–hexane to 255–257°, $[\alpha]_D$ +54°, λ_{max}^{EtOH} 236 mμ, ε 15,900; λ_{max}^{KBr} 1745, 1720, 1670, 1630 cm.$^{-1}$; rotatory dispersion curve (*c* 0.067, dioxane): $[\alpha]_{700}$ +54°, $[\alpha]_{589}$ +63°, $[\alpha]_{397.5}$ +167.5°, $[\alpha]_{370}$ +16°, $[\alpha]_{307.5}$ +3220, $[\alpha]_{300}$ +2560.

Anal. Calcd. for $C_{23}H_{31}O_4F$: C, 70.74; H, 8.00; F. 4.86. Found: C, 70.82; H, 8.16; F, 4.76.

Compound V was recovered unchanged after treatment with dry hydrogen chloride in acetic acid for 3 hours at 15°.

6α-Fluoro-Δ^{1,4}-pregnadiene-17α-ol-3,20-dione 17-Acetate (VI).—Selenium dioxide (0.52 g.) was added to a solution of 6α-fluoro-17α-acetoxyprogesterone (V) (1.0 g.) in *t*-butyl alcohol (45 cc.) containing pyridine (0.143 cc.) and heated under reflux for 18 hours in an atmosphere of nitrogen. The solution was then filtered through Celite to remove the precipitated selenium and evaporated to dryness on the steam-bath. The residue was triturated with water, filtered, dissolved in acetone and boiled with a little carbon and then crystallized from acetone–hexane to afford 6α-fluoro-Δ^{1,4}-pregnadiene-17α-ol-3,20-dione 17-acetate (VI) (460 mg.), m.p. 255–260°, raised by several crystallizations from acetone–hexane to 258–261°, $[\alpha]_D$ +19°, λ_{max}^{EtOH} 240–242 mμ, ε 15,900; λ_{max}^{KBr} 1735, 1718, 1660, 1625, 1605 and 1250 cm.$^{-1}$; rotatory dispersion curve (*c* 0.055, dioxane); $[\alpha]_{700}$ −7°, $[\alpha]_{589}$ −25°, $[\alpha]_{310}$ +1885°, $[\alpha]_{300}$ +1192°.

Anal. Calcd. for $C_{23}H_{29}O_4F$: C, 71.08; H, 7.52; F, 4.89. Found: C, 71.34; H, 7.50; F, 4.77.

Δ^{4,6}-Androstadiene-17β-ol-3-one Acetate.—Chloranil (10.0 g.) was added to a solution of testosterone acetate (5.0 g.) in ethyl acetate (250 cc.) containing acetic acid (50 cc.) and heated under reflux for 8 hours in an atmosphere of nitrogen. After cooling to room temperature the excess of reagent was removed by filtration and washed with a little cold ethyl acetate. The filtrate was diluted with ethyl acetate (500 cc.) and washed with sodium hydroxide solution (5%) until the alkaline wash was no longer highly colored. It was then washed with water and dried over sodium sulfate. Removal of the solvent afforded a product which was chromatographed over alumina to afford Δ^{4,6}-androstadiene-17β-ol-3-one acetate (3.24 g.), m.p. 136–142°, raised by one crystallization from acetone–hexane to 141–143° undepressed on admixture with an authentic sample[27]; λ_{max}^{EtOH} 284 mμ, ε 27,600. The infrared spectra were identical.

6-Fluoro-Δ^{4,6}-pregnadiene-17β-ol-3,20-dione 17-Acetate (VII).—Chloranil (8.0 g.) was added to a solution of 6α-fluoro-17α-acetoxy-progesterone (V) (4.0 g.) in *n*-amyl acetate (110 cc.) containing glacial acetic acid (22 cc.) and heated under reflux in an atmosphere of nitrogen for 9 hours. After cooling to room temperature the solution was filtered from the excess of reagent. The filtrate was then diluted with ethyl acetate (250 cc.), washed with 5% sodium hydroxide solution (4 × 500 cc.) and then with water until the washings were neutral. Removal of the solvent *in vacuo* afforded a product which was adsorbed from benzene onto alumina (200 g.). Elution with benzene–ether (90:10, 1.25 l.) afforded 6-fluoro-Δ^{4,6}-pregnadiene-17β-ol-3,20-dione 17-acetate (VII) (1.51 g.), m.p. 222–225°, raised by several crystallizations from acetone–hexane to 226–228°, $[\alpha]_D$ −53°, λ_{max}^{EtOH} 282-284 mμ, ε 24,500; λ_{max}^{KBr} 1740, 1720, 1660, 1650, 1620 and 1600 cm.$^{-1}$; rotatory dispersion curve (*c* 0.054, dioxane): $[\alpha]_{700}$ −57°, $[\alpha]_{589}$ −54°, $[\alpha]_{392.5}$ +832, $[\alpha]_{332.5}$ −2300, $[\alpha]_{315}$ −1490.

Anal. Calcd. for $C_{23}H_{29}O_4F$: C, 71.03; H, 7.52; F, 4.89. Found: C, 71.09; H, 7.50, F, 4.36.

6-Fluoro-Δ^{1,4,6}-pregnatrien-17α-ol-3,20-dione Acetate (VIII).—Selenium dioxide (200 mg.) was added to a solution of 6-fluoro-Δ^{4,6}-pregnadien-17α-ol-3,20-dione acetate (VII) (400 mg.) in *t*-butyl alcohol (36 cc.) containing pyridine (0.055 cc.) and heated under reflux in an atmosphere of nitrogen for 36 hours. Ethyl acetate (50 cc.) was added and the solution filtered through a layer of Celite to remove the precipitated selenium. The solvent was then removed *in vacuo* and the semi-solid residue was triturated with water, filtered, dried and then adsorbed from benzene onto alumina (30 g.). Elution with benzene–ether (90:10, 400 cc.) afforded 6-fluoro-Δ^{1,4,6}-pregnatrien-17α-ol-3,20-dione (VIII) (170 mg.), m.p. 202–206° raised by crystallizations from acetone–hexane to 204–206°, $[\alpha]_D$ −123°; λ_{max}^{EtOH} 225, 254 and 298 mμ; ε 10,580, 10,000 and 10,230, respectively; λ_{max}^{KBr} 1745, 1720, 1665, 1620, 1585 and 1255 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{27}O_4F$: C, 71.52; H, 7.04; F, 4.91. Found: C, 71.28; H, 7.07; F, 4.81.

---

[27] C. Djerassi, G. Rosenkranz, J. Romo, St. Kaufmann and J. Pataki, This Journal, **72**, 4534 (1950).

Mexico, D. F., Mexico

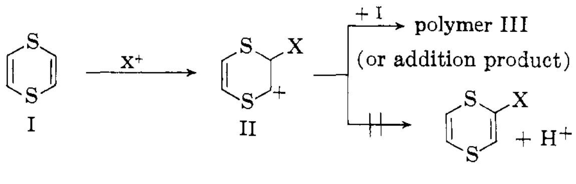
[Contribution from the School of Chemistry of the University of Minnesota]

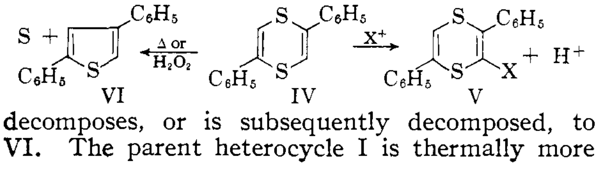
Heterocyclic Vinyl Ethers. XVI. 2,5-Dimethyl-1,4-dithiadiene[1]

By William E. Parham, Gwendolyn L. O. Mayo[2] and Brian Gadsby

Received May 6, 1959

2,5-Dimethyl-1,4-dithiadiene, the first example of an alkyl dithiadiene, has been prepared, and its chemical behavior compared with that of 1,4-dithiadiene and 2,5-diphenyl-1,4-dithiadiene.





A comparison of the chemical behavior of 1,4-dithiadiene (I) with that of 2,5-diphenyl-1,4-dithiadiene (IV) reveals rather marked dissimilarities.[3,4] The latter readily undergoes certain electrophilic substitution reactions (IV → V), decomposes at 180° to give the diphenylthiophene VI and sulfur, and is converted to a monosulfoxide which readily decomposes, or is subsequently decomposed, to VI. The parent heterocycle I is thermally more

---

[1] This work was supported by the Office of Ordnance Research, Contract No. DA-11-022-Ord-2616.

[2] In part from the Ph.D. thesis of G. L. O. Mayo, University of Minnesota, 1958.

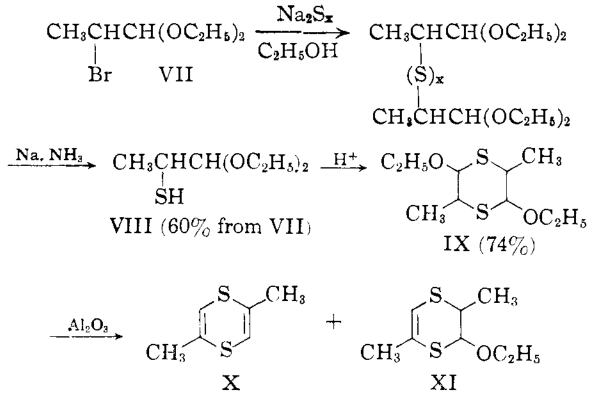
[3] W. E. Parham, B. Gadsby and R. A. Mikulec, *J. Org. Chem.*, **24**, in press (1959).

[4] "Organic Sulfur Compounds," editor N. Kharasch, Pergamon Press, Inc., New York 22, N. Y., in press, Vol. I, Ch. 8, W. E. Parham.

stable, apparently does not give thiophene upon thermal decomposition, is readily oxidized with hydrogen peroxide to a mono- or disulfone, and has not successfully been substituted by an electrophilic reagent. It has been postulated that the ion II, formed with electrophilic reagents, reacts preferentially with 1,4-dithiadiene to give telomers or polymer (III), rather than eliminating a proton as required for substitution.

The differences noted in chemical behavior of I and IV can, in part, be rationalized in terms of steric and electrical effects of the attached phenyl groups in IV. This report describes the synthesis of 2,5-dimethyl-1,4-dithiadiene and a comparison of its chemical behavior with that of I and IV.

2,5-Dimethyl-1,4-dithiadiene (X) was prepared as summarized by the equations



The cyclization of diethyl α-mercaptopropional (VIII) was accomplished in 74% yield in a refluxing benzene solution containing *p*-toluenesulfonic acid. The mixture of stereoisomeric 2,5-dimethyl-3,6-diethoxy-1,4-dithianes (IX), produced in this manner, was used successfully in the next step. One crystalline isomer of IX (α-isomer, m.p. 119–120°) was obtained in a pure state. Oxidation of the mixture of isomers of IX with potassium permanganate in acetic acid afforded a mixture from which a single pure disulfone was isolated in 17% yield.

Dealkoxylation of IX with phosphorus pentoxide at 160° gave ethanol and the monoölefin, 3-ethoxy-2,5-dimethyl-1,4-dithiene-5 (XI), in 44% yield (n^{25}D 1.543). Attempts to prepare 2,5-dimethyl-1,4-dithiadiene by further dealkoxylation of XI with phosphorus pentoxide were unsuccessful.

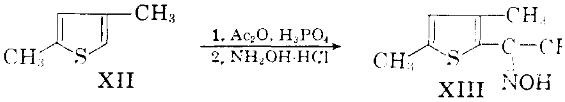
2,5-Dimethyl-1,4-dithiadiene (X) was successfully prepared by dealkoxylation of IX (mixture of isomers) over preconditioned alumina at 204–280°. The yields of X and XI were quite varied (14–38% and 15–64%, respectively) and, although the reaction was performed a total of twenty times, conditions could not be found that would give reproducible results. At higher temperatures (>290°) considerable decomposition occurred and the formation of hydrogen sulfide was noticeable.

3-Ethoxy-2,5-dimethyl-1,4-dithiene-5 (XI), prepared by pyrolysis of IX on alumina, was obtained analytically pure by chromatography and subsequent distillation. The boiling point and infrared spectrum of this product were identical to those of the product obtained by dealkoxylation of IX with phosphorus pentoxide; however, the refractive indices of the two materials were different (n^{25}D 1.5383 and 1.5437, respectively). It is probable that the two procedures afford different ratios of stereoisomers of XI. The monoene XI from the alumina reactions gave 2,5-dimethyl-1,4-dithiadiene (X) in 35–45% yields by further reaction on alumina at 245–255°.

2,5-Dimethyl-1,4-dithiadiene (X) was purified, with little loss, by chromatography on alumina and subsequent distillation. Pure X has a "questionably" pleasant odor, and the following physical properties: b.p. 61–62° (2.0 mm.), n^{26}D 1.5754. The diene is pale yellow in color and has absorption peaks in the ultraviolet spectrum at λ_{max} 262 (*E* 4131) and λ_{max} 269 (*E* 4102). This compares[5] to λ_{max} 262 (*E* 5400) and λ_{max} 266–270 (*E* 5280) for 1,4-dithiadiene (I).

Oxidation of 2,5-dimethyl-1,4-dithiadiene with hydrogen peroxide (30%) in glacial acetic acid at 70° afforded an almost quantitative yield of the corresponding disulfone, 2,5-dimethyl-1,4-dithiadiene-1,1,4,4-tetroxide. Thus the oxidation of X proceeds in a manner analogous to that of I.

The variable yields obtained in the thermal conversion of IX to X suggested that 2,5-dimethyl-1,4-dithiadiene is thermally less stable than the parent heterocycle, 1,4-dithiadiene, and this was shown to be the case. A sample of X was heated in an atmosphere of nitrogen until reflux began (approximately 204°). At this point the liquid decomposed and a colorless material (b.p. 90–138°, n^{27}D 1.5057) distilled. The amount of distillate was small (approx. 20% by wt.) and most of the material remained as a black solid residue. The volatile distillate was a mixture which was not resolved. The infrared spectrum of this product suggested 2,4-dimethylthiophene[6] (XII) (b.p. 138°, n^{24}D 1.5120) as a component, but was not conclusive. The presence of 2,4-dimethylthiophene was confirmed in the following way. A sample of the crude distillate in benzene was treated with acetic anhydride and orthophosphoric acid. The crude ketonic material that resulted was treated with hydroxylamine hydrochloride to give a mixture of oximes which melted at 55–68° (55–118° in a second experiment). Sublimation of this solid afforded a small quantity of XIII (m.p. 65°), identical to an authentic sample derived from 2,4-dimethylthiophene.[6,7] Recrystallization of the crude oxime from alcohol–water afforded a higher melting product (m.p. 118–123°) which was not identified.



The reaction of 2,5-dimethyl-1,4-dithiadiene with aluminum chloride in petroleum ether gave a tarry product containing an amorphous insoluble gray solid with the composition calculated for polymeric X $(C_6H_8S_2)_x$. The reaction of 2,5-dimethyl-1,4-dithiadiene with bromine, chlorine, nitric acid, acetic anhydride and phosphoric acid, mercuric ion,

---

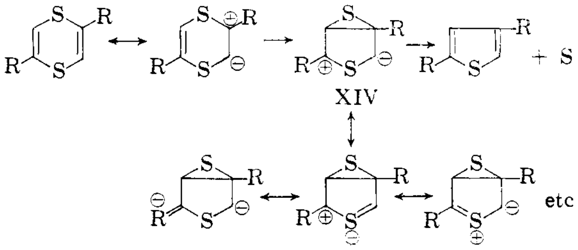
[5] W. E. Parham, H. Wynberg and F. Ramp, This Journal, **75**, 2065 (1953).

[6] J. Sice, *J. Org. Chem.*, **19**, 70 (1954).

[7] H. D. Hartough, This Journal, **73**, 4033 (1951).

and dimethylformamide in phosphorus oxychloride, were carried out under conditions previously described for similar reactions with 2,5-diphenyl-1,4-dithiadiene (IV) and 1,4-dithiadiene. In a number of cases some 2,5-dimethyl-1,4-dithiadiene was recovered unchanged; however, amorphous polymeric-like materials generally resulted, and in no case was an isolable derivative obtained.

In its chemical behavior 2,5-dimethyl-1,4-dithiadiene resembles the parent heterocyclic 1,4-dithiadiene and not the diaryl dithiadienes, which readily undergo electrophilic substitution reactions. The thermal instability of 2,5-dimethyl-1,4-dithiadiene and 2,5-diaryl-1,4-dithiadiene contrast sharply with the greater stability of the parent heterocycle. The available data suggest that: (a) the greater stability of the diaryl dithiadienes toward electrophilic reagents is due to the electrical effects of the attached phenyl groups, and (b) that groups in the 2,5-position of 1,4-dithiadiene, which can stabilize the intermediate XIV, decrease the thermal stability of the ring system and promote decomposition to thiophenes.


XIV

Experimental

Diethyl α-Mercaptopropional (VIII).—Sodium sulfide enneahydrate (559 g., 2.33 moles) was dissolved in boiling 95% ethanol (2800 ml.). Powdered sulfur (149 g., 4.66 g. atoms) was added and the resulting mixture was heated at the reflux temperature for 10 minutes. The source of heat was removed, and diethyl α-bromopropional (prepared in 61–72% yield by the procedure of Williams and Woodward[8]) (654 g., 3.10 moles) was added at a rate sufficient to maintain reflux. The resulting mixture was heated for three hours at the reflux temperature, 500 ml. of solvent was then removed, and sodium bicarbonate (135 g.) was added as a buffer. The distillation was continued until a total of 2.6 liters of solvent was collected. The residue was cooled, water (1500 ml.) was added, and the mixture then extracted with ether. The organic extract was washed, in turn, with water, dilute sodium hydroxide, water, and saturated aqueous sodium chloride, and was then dried over anhydrous potassium carbonate. After removal of ether by distillation, the residue was heated on a steam-cone at reduced pressure (water-pump) until the residue reached essentially a constant weight. A nearly black oil (n^{26}D 1.50, 525–555 g.) remained (*ca.* 90% yield calculated as tetrasulfide).

Liquid ammonia (5 liters) was added to the polysulfide (538 g., 1.38 moles) dissolved in absolute ether (500 ml.). The flask was immersed in a Dry Ice–acetone-bath (once the stirrer was started it was not allowed to stop until the ammonia had been removed by distillation). Sodium metal (200 g., 8.7 g. atoms) was added in small lumps over a period of one hour. (The work was carried out in a hood and care was exercised during the addition of sodium to avoid rapid evolution of ammonia). After the sodium was added, about 500 ml. of liquid ammonia was added to replace that lost by distillation. The blue solution was stirred for 30–40 minutes and 200 g. of ammonium chloride carefully added in small portions. The cooling bath was replaced with a water-bath into which steam could be introduced, and the ammonia was distilled with stirring. When most of the ammonia had been removed the residue became gummy, and the stirrer was stopped. The reaction mixture was allowed to stand overnight (*ca.* 32°), then one liter of ice-water was added. The resulting mixture was stirred, and concentrated hydrochloric acid was added until a *p*H of 8 to 8.5 was obtained (*p*H meter). The *p*H was lowered to 7.8 to 8.0 by the addition of carbon dioxide. The organic layer was removed, and the aqueous phase extracted with ether. The combined organic material was washed with water and saturated aqueous sodium chloride, and then dried over anhydrous potassium carbonate. The resulting ethereal solution was distilled to give diethyl α-mercaptopropional (VIII, 300 g., 66% yield, b.p. 60–78° (9 mm.), n^{27}D 1.436–1.437). This material was redistilled (b.p. 62° (10 mm.), $n^{25.5}$D 1.4371) for analysis.

Anal. Calcd. for $C_7H_{16}SO_2$: C, 51.18; H, 9.82. Found: C, 51.18; H, 10.16.

The 2,4-dinitrophenylhydrazone of α-*n*-butylthiopropionaldehyde was prepared from VIII (1.5 g.), sodium ethoxide (from 0.23 g. atom of sodium) in ethanol (10 ml.) and *n*-butyl bromide (1.5 ml.). This mixture was heated at the reflux temperature for 90 minutes. The resulting mixture was acidified with concentrated hydrochloric acid, and then treated with 2,4-dinitrophenylhydrazine in the usual way. The hydrazone was recrystallized from 95% ethanol and melted at 110–111°.

Anal. Calcd. for $C_{13}H_{18}SO_4H_4$: C, 47.84; H, 5.56; N, 17.17. Found: C, 47.54; H, 5.38; N, 17.14.

2,5-Dimethyl-3,6-diethoxy-1,4-dithiane (IX).—*p*-Toluenesulfonic acid monohydrate (1.0 g.) was dissolved in thiophene-free benzene and the water of crystallization was removed by azeotropic distillation. Diethyl α-mercaptopropional (49.2 g., 0.30 mole) was added, and the mixture was heated at the reflux temperature for two hours. The cooled benzene solution was extracted with three 25-ml. portions of 10% aqueous sodium hydroxide, washed with saturated aqueous sodium chloride, dried (magnesium sulfate) and distilled. There was obtained 26.2 g. (74% yield) of IX, b.p. 82–87° (0.35 mm.), n^{25}D 1.5012. The dithiane was a white semi-solid mixture of isomers. The solid portion (α-isomer), recrystallized from 95% ethanol, was obtained as colorless cubic crystals melting at 119–120°.

Anal. Calcd. for $C_{10}H_{20}SO_2$: C, 60.81; H, 8.53. Found (mixture): C, 50.77; H, 8.64. Found (solid): C, 51.07; H, 8.45.

2,5-Dimethyl-3,6-diethoxy-1,4-dithiane-1,1,4,4-tetroxide.—Powdered potassium permanganate (47.4 g., 0.30 mole) was added in small portions to a solution of IX (mixture of isomers, 23.6 g., 0.10 mole) in glacial acetic acid (162 g.). After three days at room temperature the acetic acid was removed by distillation, water (160 ml.) was added, and the manganese dioxide was removed by the addition of sulfur dioxide. The tarry yellow semi-solid was separated, dried *in vacuo*, and extracted with ethyl acetate in a Soxhlet extractor. The solid, obtained from the ethyl acetate extract, was recrystallized from 95% ethanol, affording 5.22 g. (17% yield) of white disulfone melting at 183–185°. After recrystallization of this product from absolute ethanol, the disulfone was obtained as white needles melting, with sublimation, at 190–191°.

Anal. Calcd. for $C_{10}H_{20}S_2O_6$: C, 39.98; H, 6.71. Found: C, 40.01; H, 6.66.

The Reaction of 2,5-Dimethyl-3,6-diethoxy-1,4-dithiane (IX) with Phosphorus Pentoxide. 3-Ethoxy-2,5-dimethyl-1,4-dithiene-5 (XI).—A mixture of IX (12.00 g., 0.051 mole) and phosphorus pentoxide (0.1 g.) was heated at 160°. Ethyl alcohol (1.93 g., 0.042 mole, 82%) distilled and was collected over a two-hour period. The residue was cooled, diluted with ether, and washed three times with 2% aqueous sodium hydroxide. The resulting ethereal solution was washed with water, dried (magnesium sulfate) and distilled. 3-Ethoxy-2,5-dimethyl-1,4-dithiene-5 (XI, 4.24 g., 44% yield, n^{25}D 1.544) was collected, boiling at 104–110° (7 mm.). This product was fractionated, with little loss, through an 8-inch spiral wire column for analysis. Pure XI was collected at 104–105° (5.3 mm.), b.p. 60–62° (0.25 mm.), $n^{26.5}$D 1.5437, as a nearly colorless oil.

Anal. Calcd. for $C_8H_{14}S_2O$: C, 50.48; H, 7.42. Found: C, 50.45; H, 7.37.

The solid α-isomer of IX (3.66 g.) gave XI (1.03 g.) in 35% yield under identical conditions.

---

[8] A. H. Williams and F. M. Woodward, *J. Chem. Soc.*, 40 (1948).

2,5-Dimethyl-1,4-dithiadiene (X). A. From 2,5-Dimethyl-3,6-diethoxy-1,4-dithiane (IX).—Alumina pellets (60 g., Harshaw 1/8″) were heated in a vertical tube (2 cm. in diameter, 25 cm. high) at 260° for 40–48 hours under a flow of nitrogen (Linde). The tube was cooled to 213° and absolute alcohol (5 ml.) was passed through the tube at the rate of 10–12 drops per minute (nitrogen flow about 0.5 liter per minute). 2,5-Dimethyl-3,6-diethoxy-1,4-dithiane (IX, 30 g.) dissolved in absolute alcohol (25 ml.) was then added, at the same rate, and finally absolute ethanol (10 ml.). The pyrolysate, collected in a Dry Ice–acetone condenser, was dissolved in ether, and the solution was washed once with 2% sodium hydroxide, twice with saturated aqueous sodium chloride, dried (magnesium sulfate), and distilled through a 12-inch spiral wire column. The material boiling from 72–78° (2.8 mm.) (6.9 g., 38%) was 2,5-dimethyl-1,4-dithiadiene (X, n^{25}D 1.56); the material boiling from 91–106° (2.0 mm.) was 3-ethoxy-2,5-dimethyl-1,4-dithiadiene-5 (XI, 8.2 g., 34% yield, $n^{26.5}$D 1.5329–1.5258).

The dealkoxylation of IX (25 g.), by itself,[9] or dissolved in ethanol (25 ml.), was carried out essentially as described above a total of 20 times. The alumina was conditioned at temperatures ranging from 316–360°, the rate of flow of nitrogen was varied from 0.3 to 0.5 liter/minute, and the reaction temperature from 204–310°. The yield of X and XI varied from 0–38% and 0–64%, respectively, and reproducible results were not obtained. Neither X nor XI could be isolated when the reaction temperature was higher than 270°.

The olefins X and XI were further purified by passing a solution of either X or XI (*ca.* 5 g.) in 1:1 ether–petroleum ether over a chromatography column containing 20 g. of alumina, with subsequent distillation of the eluate.

2,5-Dimethyl-1,4-dithiadiene (b.p. 61–62° (2.0 mm.), n^{26}D 1.5754) was obtained as a pale yellow oil; ultraviolet absorption: $\lambda_{\max}$ 262 (E 4131) and $\lambda_{\max}$ 269 (E 4102).

Anal. Calcd. for $C_6H_8S_2$: C, 50.00; H, 5.60. Found: C, 50.42; H, 5.82.

3-Ethoxy-2,5-dimethyl-1,4-dithiene-5 (b.p. 90–92.5° (2.4 mm.), $n^{26.9}$D 1.5383) was obtained as an almost colorless oil; ultraviolet absorption: $\lambda_{\max}$ 232 (E 4300), $\lambda_{\max}$ 268 (E 4000). The infrared and ultraviolet spectra of this material were essentially identical to that obtained by reaction of IX with phosphorus pentoxide.

Anal. Calcd. for $C_8H_{14}S_2O$: C, 50.48; H, 7.42. Found: C, 50.50; H, 7.51.

B. From 3-Ethoxy-2,5-dimethyl-1,4-dithiene-5.—3-Ethoxy-2,5-dimethyl-1,4-dithiene-5 (22.5 g., 0.118 mole, b.p. 87–93° (2.5 mm.), n^{26}D 1.536) was added to a column of alumina pellets (60 g., conditioned at 360°) at 227°. The apparatus, rate of flow, etc., was as described under A, above. Some dithiene (XI, 7.1 g., 32%, n^{26}D 1.534) was recovered; the yield of 2,5-dimethyl-1,4-dithiadiene (X) was 5.0 g. (44% conversion, n^{26}D 1.568).

2,5-Dimethyl-1,4-dithiadiene-1,1,4,4-tetroxide.—Aqueous hydrogen peroxide (2.5 ml. of a 30% solution) was added over a 90-minute period to a hot (70°) solution of 2,5-dimethyl-1,4-dithiadiene (0.400 g., 2.8 mmoles) in glacial acetic acid. The mixture was maintained at 70° for 18 hours and then at 10° for one hour. The large crystals of disulfone (0.35 g., 61% yield) were removed, then washed with water and cold alcohol. The filtrate was evaporated to dryness and the residue was dissolved in acetic acid (2 ml.). A few drops of 30% hydrogen peroxide was added and the resulting solution was heated on a steam-cone for 30 minutes. Additional disulfone (0.22 g., 38%) was isolated from the cold acetic acid solution and the combined product (0.57 g., 99% yield) was recrystallized twice from 95% alcohol for analysis, m.p. 218–221° with sublimation.

Anal. Calcd. for $C_6H_8S_2O_4$: C, 34.60; H, 3.87; S, 31.51. Found: C, 34.59; H, 4.07; S, 31.15.

Thermal Decomposition of 2,5-Dimethyl-1,4-dithiadiene. 2,4-Dimethylthiophene.—A sample of 2,5-dimethyl-1,4-dithiadiene (4.35 g., 0.30 mole, b.p. 62–64° (2.3 mm.), $n^{27.3}$D 1.5702) was placed in a small flask fitted with a 12″ spiral wire column. The system was flushed well with dry nitrogen, a nitrogen flow was maintained and the flask was then heated with a flame to the reflux temperature. As soon as reflux began (*ca.* 204°) the residue decomposed, and a colorless, vile smelling liquid (b.p. 90–138°) was collected over a one-hour period. Attempted distillation of the residue afforded a small additional quantity of colorless liquid (0.27 g., n^{27}D 1.5218, b.p. to 55° (2 mm.)), together with a solid black residue (2.13 g.). The colorless distillate (0.88 g., $n^{27.3}$D 1.5057) had an infrared spectrum similar to that of authentic 2,4-dimethylthiophene (b.p. 137°, n^{25}D 1.511)[6]; however, the spectral analysis was not conclusive.

Four drops of 85% orthophosphoric acid was added to a hot (60°), stirred solution prepared from benzene (1.0 ml.), acetic anhydride (1.36 g.) and the above distillate (0.75 g.). The resulting mixture was heated at the reflux temperature for 2.5 hours, then cooled; water (2.5 ml.) was added and the mixture allowed to stand overnight. The mixture was extracted with ether, and the ether extract then washed with 10% sodium carbonate until basic, with water, and finally was dried (magnesium sulfate). To the crude ketonic product, resulting on evaporation of ether, was added hydroxylamine hydrochloride (1 g.), pyridine (5 ml.) and absolute alcohol (5 ml.). The mixture was heated at the reflux temperature for two hours and the solvents then evaporated from the reaction mixture under reduced pressure at room temperature. The resulting oil was triturated with water (5 ml.) and crystallized slowly. This product, dissolved in 95% alcohol, was then treated with decolorizing charcoal. When water was added to the ethanolic solution, a solid, m.p. 55–68°, separated. This material was a mixture containing a solid melting near 65° and another near 120°. Attempts to resolve the mixture by chromatography on alumina were unsuccessful (product m.p. 58–118°). A sample of this mixture was placed in a sublimator and left at room temperature and atmospheric pressure for 14 days. A small amount of material sublimed and this was shown to be the oxime of 2,4-dimethylthiophene (m.p. and mixed m.p. with an authentic specimen 65°).[6,7] Repeated crystallization of the crude oxime from water–alcohol afforded an unidentified product melting at 118–123°.

Anal. Calcd. for $C_8H_{11}SON$: C, 56.77; H, 6.55. Found: C, 55.58; H, 6.57.

Reaction of 3-Ethoxy-2,5-dimethyl-1,4-dithiene-5 with *n*-Butyl Alcohol. 3-*n*-Butoxy-2,5-dimethyl-1,4-dithiene-5.—A mixture containing anhydrous *p*-toluenesulfonic acid (0.2 g.), *n*-butyl alcohol (44.0 g., 0.59 mole) and XI (12.0 g., 0.063 mole, b.p. 85–91° (2.1 mm.), n^{27}D 1.535) was heated at the reflux temperature for 24 hours. Ether (150 ml.) was added to the cooled reaction mixture, and the ethereal solution was extracted with two portions (25 ml.) of 2% aqueous sodium hydroxide, and three portions of saturated aqueous sodium chloride. The ethereal solution was dried (magnesium sulfate) and distilled to yield: (a) recovered XI, 2.5 g., n^{28}D 1.53; and (b) a pale yellow oil, b.p. 81–91° (0.45 mm.), n^{28}D 1.52, 7.3 g. (53% yield calcd. as 3-*n*-butoxy-2,5-dimethyl-1,4-dithiadiene). Redistillation of this product afforded an almost colorless oil, b.p. 80–81° (0.3 mm.), $n^{25.7}$D 1.5266; ultraviolet $\lambda_{\max}$ 232 (E 4330), $\lambda_{\max}$ 286 (E 4080).

Anal. Calcd. for $C_{10}H_{18}S_2O$: C, 54.99; H, 8.31; mol. wt., 218. Found: C, 53.58; H, 8.18; mol. wt. (f.p. benzene), 212.

This material apparently reacts rapidly with oxygen. The sample reported above was analyzed five times over a period of four days. The percentage of carbon and hydrogen decreased on each consecutive analysis, reaching the values C, 50.42, H, 5.30, after the second day and C, 29.25, H, 3.95, after the fourth day.

Reaction of 2,5-Dimethyl-1,4-dithiadiene with Aluminum Chloride.—Anhydrous aluminum chloride (1.75 g., 0.013 mole) was added to a solution of X (1.89 g., 0.013 mole) in petroleum ether (15 ml.). An exothermic reaction occurred and a red gummy oil separated. Water was added and the resulting mixture was stirred overnight. The resulting gray tarry product was triturated with 95% ethanol, leaving a gray solid, m.p. 140–150°, which was insoluble in alcohol and ether.

Anal. Calcd. for $(C_6H_8S_2)_x$: C, 50.00; H, 5.60. Found: C, 49.60; H, 5.82.

Attempted Substitution of 2,5-Dimethyl-1,4-dithiadiene.—Conditions employed were essentially identical to those previously reported for similar reactions with 1,4-dithiadiene or 2,5-diphenyl-1,4-dithiadiene.

---

[9] In the absence of ethanol, it was necessary to preheat the diethoxy-1,4-dithiane (IX) to prevent crystallization of the α-isomer.

1. **Nitration.**[10]—From a mixture of X (1.48 g., 0.01 mole), in acetic anhydride (125 ml.), and nitrating solution (1.3 ml., 0.013 mole) there was obtained: (a) an amorphous brown solid (0.30 g.), insoluble in ether, acetone, ethyl acetate, chloroform and acetic acid. After alcohol extraction (26% loss of weight) the material had the composition: C, 22.9; H, 1.99; N, 3.13; ash, 4.7; (b) a chloroform-soluble oil (1.12 g.) which gave, upon oxidation with hydrogen peroxide in acetic acid, only the disulfone of X.

2. **Chlorination.**[3]—From X (3.2 g., 0.22 mole) in carbon tetrachloride (25 ml.) and chlorine (1.6 g., 0.22 mole) at 0° there was obtained: (a) a chloroform-insoluble black tar, and (b) a chloroform-soluble oil, which, after distillation (b. p. 70(2.2) 86° (0.2 mm.)) rapidly decomposed to black tar and hydrogen chloride.

3. **Bromination.**[11]—From X (1.40 g., 0.01 mole) in acetic anhydride (130 ml.), and bromine (1.6 g., 0.01 mole) there was obtained: (a) A brown amorphous solid (0.36 g., m.p. 40–70°) which was partially soluble in hot acetone and chloroform and insoluble in hot ethanol. *Anal.* Calcd. for $(C_6H_8S_2Br)_x$: C, 32.29; H, 3.16. Found: C, 43.72; H, 4.13. The solid contained bromine but decomposed upon attempted recrystallization. (b) An unidentified ether-soluble oil (0.95 g.) which gave no solid on oxidation with hydrogen peroxide in acetic acid at 70°.

4. **Acylation.**[12]—From X (1.5 g., 0.011 mole), acetic anhydride (1.4 g., 0.014 mole) and 85% phosphoric acid (two drops) at 100°, there was obtained: (a) unchanged X (0.6 g., 40%), (b) an orange oil (0.22 g., n^{25}_{D} 1.5850) which distilled at 0.35 mm. This oil showed carbonyl absorption in the infrared spectrum, although reaction of this product with 2,4-dinitrophenylhydrazine gave a black precipitate; attempts to purify this material by recrystallization were unsuccessful.

5. **Mercuration.**[13]—From X (1.00 g., 0.070 mole) and a solution prepared from mercuric chloride (58 g., 0.015 mole), 33% sodium acetate solution (12 g.), and 95% alcohol (54 g.) there was obtained 1.35 g. of solid, m.p. 100–130°, which was insoluble in hot benzene, ether, petroleum ether and nitromethane. A sample was digested with hot ethanol and filtered while hot. The solid (m.p. 85–100°) that crystallized from the ethanol had the composition: C, 13.15; H, 2.06; Cl, 10.95; S, 11.33.

Different products were obtained when the reaction was carried out in the absence of sodium acetate; however, the resulting amorphous solids were not obtained pure. The percentage composition of two products (m.p. >285° and 100–200° dec., respectively) were: C, 7.71; H, 1.09; Cl, 11.09; S, 8.47; and C, 20.89; H, 2.51; Cl, 8.41; S, 16.93.

---

(10) W. E. Parham and V. J. Traynelis, THIS JOURNAL, **77**, 68 (1955).

(11) W. E. Parham, I. Nicholson and V. J. Traynelis, *ibid.*, **78**, 850 (1956).

(12) W. E. Parham, H. Wynberg, W. R. Hasek, P. A. Howell, R. M. Curtis and W. N. Lipscomb, *ibid.*, **76**, 4957 (1954).

(13) W. E. Parham, P. L. Stright and W. R. Hasek, *J. Org. Chem.*, **24**, 262 (1959).

MINNEAPOLIS 14, MINN.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, ARIZONA STATE UNIVERSITY]

Potential Purine Antagonists. XX. The Preparation and Reactions of Some Methylthiopurines[1]

BY C. WAYNE NOELL AND ROLAND K. ROBINS

RECEIVED APRIL 17, 1959

A study has been made of the reaction of chlorine and various methylthiopurines in absolute and aqueous methanol. In aqueous methanol the alkyl sulfone was isolated. In absolute methanol, replacement of the methylthio group by chlorine was observed in positions 6 and 8 of the purine nucleus. Under these conditions the methylthio group in position 2 was converted to the expected methyl sulfone. A possible general mechanism for these reactions is discussed. A preliminary study of the nucleophilic displacement of the methylsulfonyl group in the purine series has been made, and a new synthesis for 2,6,8-purinetrithiol is reported.

The anti-tumor activity reported for 6-methylthiopurine[2] stimulated our interest in the preparation of additional methylthiopurine derivatives. The preparation of 8-methylthiopurine[3] and 2-methylthiopurine[4] have previously been reported. The syntheses of 2,6-bis-methylthiopurine[5] and 6,8-bis-methylthiopurine[6] have also recently been described. The remaining compounds, 2,8-bis-methylthiopurine (II) and 2,6,8-tris-methylthiopurine (VII), were prepared for this study.

When 4,5-diamino-2-pyrimidinethiol[7] was treated with carbon disulfide in pyridine, a good yield of 2,8-purinedithiol (I) was obtained. This preparation proved superior to the cyclization of 4,5-diamino-2-pyrimidinethiol by thiourea fusion. Treatment of 2,8-purinedithiol (I) with 2 moles of methyl iodide in the presence of aqueous potassium hydroxide readily provided the desired 2,8-bis-methylthiopurine, (II). The preparation of 2,6,8-tris-methylthiopurine (VII) was accomplished by methylation of 2-methylthio-6,8-purinedithiol[8] and also by reaction of 6-chloro-2,8-bis-methylthiopurine (VI) with methanethiol in basic solution.

The compound 6-chloro-2,8-bis-methylthiopurine (VI) was prepared readily by chlorination of 6-hydroxy-2,8-bis-methylthiopurine (V) with phosphorus oxychloride. Compound V was obtained from methylation of 6-hydroxy-2,8-purinedithiol (III)[9] which was conveniently obtained by thiourea fusion of 4,5-diamino-6-hydroxy-2-pyrimidinethiol.[10]

The need for large quantities of 2,6,8-tris-methylthiopurine (VII) for this study led to the investigation of a more convenient method of synthesis from 2,6,8-purinetrithiol (IV). Fischer[11] records the preparation of IV from 2,6,8-trichloropurine

---

(1) Supported by Research Contract SA-43-ph-1928 with the Cancer Chemotherapy National Service Center of the National Institutes of Health, U. S. Public Health Service.

(2) G. S. Tarnowsky and C. C. Stock, *Proc. Am. Soc. Cancer Res.*, **51** (1955).

(3) D. J. Brown and S. F. Mason, *J. Chem. Soc.*, 682 (1957).

(4) A. Albert and D. J. Brown, *ibid.*, 2060 (1954).

(5) K. L. Dille and B. E. Christensen, THIS JOURNAL, **76**, 5087 (1954).

(6) R. K. Robins, *ibid.*, **80**, 6671 (1958).

(7) D. J. Brown, *J. Appl. Chem.*, **2**, 239 (1952).

(8) C. W. Noell and R. K. Robins, Part XVII, *J. Org. Chem.*, **24**, 320 (1959).

(9) C. O. Johns and A. G. Hogan, *J. Biol. Chem.*, **14**, 299 (1913).

(10) A. Albert, D. J. Brown and G. Cheeseman, *J. Chem. Soc.*, 474 (1951).

(11) E. Fischer, *Ber.*, **31**, 431 (1898).