

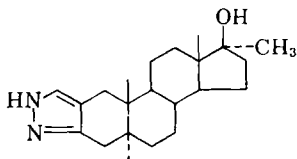
Steroids IX

Synthesis of Some Thiazolosteroids

By NORMAN J. DOORENBOS and CONRAD P. DORN, Jr.†

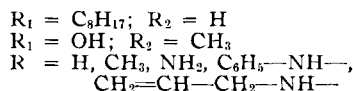
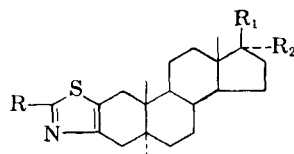
The synthesis of thiazolo[d-3,2]-5 α -cholest-2-ene, and thiazolo[d-3,2]-17 α -methyl-5 α -androst-2-en-17 β -ol, and eight of their 2'-derivatives is reported. These derivatives include the 2'-methyl, 2'-amino, 2'-allylamino, and 2'-phenylamino substituted thiazolosteroids. Preliminary data indicate that 2'-methylthiazolo[d-3,2]-17 α -methyl-5 α -androst-2-en-17 β -ol is a good anabolic agent.

IN RECENT years the search for an effective anabolic agent possessing only low androgenic activity has been markedly intensified. Many modifications of the basic androstane nucleus have been made with moderate success. Recently, however, the Sterling-Winthrop Research Institute announced that a pyrazole derivative, namely, pyrazolo[c-3,2]-17 α -methyl-5 α -androst-17 β -ol has 35 times the anabolic potency and only one-fourth the androgenic potency of methyltestosterone (1).



The structural features by which this molecule differs from methyltestosterone include: hydrogenation of the Δ^4 double bond with trans-fusion of rings A and B, a nitrogen atom attached to carbon 3 in place of oxygen, and a heterocyclic ring system fused to ring A between positions 2 and 3. It appears that the above modifications of the steroid nucleus increase the anabolic/androgenic ratio of the compound.

With the above facts in mind, we sought to prepare a series of thiazolosteroids in the cholestane and androstane series. These compounds have the following structure



The cholestane derivatives were prepared as a means of perfecting our synthetic methods before we began working with the more expensive androstane compounds. We were also hopeful that the thiazolocholestanes would have some interesting biological activity, perhaps that of inhibiting cholesterol biosynthesis.

A preliminary report (2) of the thiazolo-androstanes was made following a communication (3) from Syntex describing the independent synthesis of two of these compounds, XI and XII.

The synthesis of thiazole compounds may be accomplished by the method of Hantzsch (4). This method involves the reaction of an α -halo carbonyl compound with a thioamide. By using the proper combination of reactants, compounds may be prepared with alkyl, aryl, or other groups attached to the three carbons of the thiazole nucleus.

We prepared the α -halo carbonyl compound, 2 α -bromo-5 α -cholestan-3-one (II) according to the method of Fieser and Dominguez (5). This procedure entails the bromination of 5 α -cholestan-3-one (I) in glacial acetic acid in the presence of hydrobromic acid to give 2 α -bromo-5 α -cholestan-3-one (II) in a 44% yield. The carbonyl group of the brominated ketone absorbs at 5.77 μ compared to 5.86 μ in the nonbrominated ketone. This hypsochromic shift indicates that the bromine atom is equatorial and in the 2 α -position (6).

The first step in the preparation of the thiazolo-androstanes was the reduction of 17 α -methyl-

Received April 28, 1961, from the School of Pharmacy, University of Maryland, Baltimore 1.

Accepted for publication July 19, 1961.

Abstracted from a thesis submitted by Conrad P. Dorn, Jr., to the Graduate Faculty of the University of Maryland, School of Pharmacy, in partial fulfillment of the requirements for the degree of Master of Science.

This work was supported in part by Research Grant CY-4132 from the National Cancer Institute, U. S. Public Health Service.

For paper VIII in this series see Doorenbos, N. J., and Singh, H., *THIS JOURNAL*, **50**, 628(1961).

Appreciation is expressed to Smith Kline & French Laboratories for the optical rotational data.

Presented to the Scientific Section, A.P.R.A., Chicago meeting, April 1961.

† American Foundation for Pharmaceutical Education Fellow (1959-1960); National Science Foundation Fellow (1960-1961).

testosterone (VIII). This reaction was carried out in liquid ammonia in the presence of lithium metal according to the procedure which Weisenborn and Applegate (7) used for the reduction of testosterone. This procedure, when used for the reduction of 17 α -methyltestosterone (VIII), gave 17 α -methyl-5 α -androst-17 β -ol-3-one (IX) in a 90% yield. The melting point was in agreement with that previously reported for the 5 α -isomer (8).

The bromination of 17 α -methyl-5 α -androst-17 β -ol-3-one (IX) was accomplished by the use of pyridine hydrobromide perbromide as the brominating agent (9). Tetrahydrofuran was used as the solvent for this reaction to absorb the hydrogen bromide evolved and thus prevent dehydration at position 17. This procedure gave 2 α -bromo-17 α -methyl-5 α -androst-17 β -ol-3-one (X) in a 41% yield. Once again the shift in the carbonyl absorption from 5.85 μ to 5.76 μ indicates that the bromine is equatorial or in the 2 α -position.

The substituted thiazole compounds were prepared by refluxing the steroid bromoketones with the appropriate thioamide in ethanol or a mixture of ethanol and chloroform for 3 to 6 hours. Isolation of the free thiazolosteroid was accomplished by treating the hydrobromide salt with base. No difficulty was encountered when the thioamide was thioacetamide, thiourea, N-phenylthiourea, or N-allylthiourea. 2 α -Bromo-5 α -cholestan-3-one (II) reacted with thioacetamide to yield 22% of 2'-methylthiazolo[d-3,2]-5 α -cholest-2-ene (IV); with thiourea to yield 79% of 2'-aminothiazolo[d-3,2]-5 α -cholest-2-ene (V); with N-phenylthiourea to yield 45% of 2'-phenylaminothiazolo[d-3,2]-5 α -cholest-2-ene (VI); and with N-allylthiourea to yield 50% of 2'-allylaminothiazolo[d-3,2]-5 α -cholest-2-ene (VII). Likewise, 2 α -bromo-17 α -methyl-5 α -androst-17 β -ol-3-one (X) reacted with thioacetamide to yield 49% of 2'-methylthiazolo[d-3,2]-17 α -methyl-5 α -androst-2-en-17 β -ol (XII); with thiourea to yield 57% of 2'-aminothiazolo[d-3,2]-17 α -methyl-5 α -androst-2-en-17 β -ol (XIII); with N-phenylthiourea to yield 35% of 2'-phenylaminothiazolo[d-3,2]-17 α -methyl-5 α -androst-2-en-17 β -ol (XIV); and with N-allylthiourea to yield 71% of 2'-allylaminothiazolo[d-3,2]-17 α -methyl-5 α -androst-2-en-17 β -ol (XV).

The preparation of the unsubstituted thiazole derivatives, however, presented a problem. Thioformamide is unstable and must be prepared just prior to use, usually by reacting formamide with phosphorus pentasulfide. We attempted the synthesis of the unsubstituted thiazole

in the cholestane series by two methods. The first was a modification of the procedure suggested by Schwartz (10) for the synthesis of 2,4-dimethylthiazole from chloroacetone, acetamide, and phosphorus pentasulfide. We first treated formamide with phosphorus pentasulfide in dry benzene for 1 hour and then added the steroid bromoketone. This procedure gave a product which was extremely difficult to purify. In addition the yield of thiazolo[d-3,2]-5 α -cholest-2-ene (III) was only 3.5%.

The method recommended by Cerecedo and Tolpin (11) for the synthesis of thioformamide was then tried. The crude thioformamide was prepared by the addition of phosphorus pentasulfide to formamide which have been covered with anhydrous ether. This mixture was allowed to stand overnight in an ice bath and was then shaken for 15 hours. The ether layer was separated and evaporated at reduced temperature and pressure to yield the crude thioformamide. The thioformamide was added in generous excess to a solution of 2 α -bromo-5 α -cholestan-3-one (II) in a mixture of chloroform and ethanol. The reaction mixture was stored in the refrigerator for 4 days and allowed to stand at room temperature for 2 weeks. The yield of thiazolo[d-3,2]-5 α -cholest-2-ene (III) was 48%. Similarly, 2 α -bromo-17 α -methyl-5 α -androst-17 β -ol-3-one (X) when allowed to react with crude thioformamide for 5 days in the cold and 6 weeks at room temperature yielded 33% of thiazolo[d-3,2]-17 α -methyl-5 α -androst-2-en-17 β -ol (XI).

Proof of the thiazole structures was based on elemental analyses and infrared spectral data. Randall, *et al.* (12), report that thiazoles show characteristic absorption at 6.12–6.37 μ (thiazole I) and 6.50–6.70 μ (thiazole II). All of our compounds with the exception of the methyl thiazoles absorbed in these regions. The methyl compounds had the thiazole II peak at approximately 6.40 μ . In addition, the characteristic absorptions of hydroxyl, amino, phenyl, and allyl groups were observed in the appropriate spectra.

EXPERIMENTAL¹

Thiazolo[d-3,2]-5 α -cholest-2-ene (III).—(*Method A*).—Formamide, 1.8 Gm., and 1.8 Gm. of phosphorus pentasulfide were heated for 1 hour in dry benzene on a steam bath. To this mixture was added a solution of 9.3 Gm. of 2 α -bromo-5 α -cholestan-3-one (II) dissolved in 100 ml. of dry benzene. The reaction mixture was refluxed 5 hours and filtered

¹ All melting points are uncorrected and were determined with either a Fisher Johns or a Thomas Hoover melting point apparatus. The infrared spectra were prepared on a Perkin Elmer Infracord recording spectrophotometer. The specific rotations were determined by the analytical section of Smith Kline & French Laboratories.

while hot to remove the insoluble impurities. The benzene solution was evaporated to dryness and yielded a yellow-white mass. This material was dissolved in 500 ml. of ethanol and, upon the addition of 2 Gm. of potassium hydroxide, turned orange-red. The solution was heated 30 minutes and the solvent evaporated. Ether was added to the solid material and the ether solution washed well with water. The ether solution was evaporated and the noncrystallizable mass was treated with anhydrous ether saturated with hydrogen bromide in an attempt to isolate the hydrobromide salt. The colloidal precipitate could not be filtered and the ether suspension was evaporated to dryness. The resulting brown mass was washed with dry acetone and yielded a white precipitate. This precipitate was dissolved in ethanol and 2 Gm. of potassium hydroxide was added. The solution was refluxed 30 minutes, cooled, and water added to precipitate the product. This dirty white powder was treated with charcoal in ethanol, filtered while hot, and cooled. The steroid was precipitated by the addition of water. This crude material (m.p. 163–170°) was recrystallized from methanol-water and finally from dimethylformamide to yield 300 mg. (3.5%) of thiazolo[d-3,2]-5 α -cholest-2-ene (III) as yellow-white crystals; m.p. 163.5–165°.

Anal.—Calcd. for $C_{28}H_{46}NS$: C, 78.63; H, 10.60; N, 3.27. Found: C, 78.67; H, 10.60; N, 3.09.

(*Method B*).—To 5.0 Gm. of 2 α -bromo-5 α -cholestan-3-one (II), dissolved in 50 ml. of chloroform-ethanol (1:1), was added 5.0 Gm. of crude thioformamide (11) dissolved in 50 ml. of chloroform-ethanol (1:1). The solution was placed in the refrigerator for 4 days and then allowed to stand at room temperature for 2 weeks. The reaction mixture was made alkaline by the addition of methanolic potassium hydroxide and washed well with water. The organic solution was dried over sodium sulfate and evaporated to dryness. The yellow solid obtained was recrystallized from dimethylformamide-acetone (1:1) to yield 2.2 Gm. (48%) of thiazolo[d-3,2]-5 α -cholest-2-ene (III) as fine yellow-white needles; m.p. 166–168°; $[\alpha]_D^{25} +55.3^\circ$ (c, 0.7 chloroform); λ_{max}^{KBr} , 6.12 and 6.42 μ .

Anal.—Calcd. for $C_{28}H_{46}NS$: C, 78.63; H, 10.60; N, 3.27. Found: C, 78.72; H, 10.64; N, 3.21.

2'-Methylthiazolo[d-3,2]-5 α -cholest-2-ene (IV).—2 α -Bromo-5 α -cholestan-3-one (II), 2.0 Gm., and 0.5 Gm. of thioacetamide were refluxed 5 hours in 200 ml. of chloroform-ethanol (1:1). The solvent was evaporated and the hydrobromide salt washed with a small amount of ether. The solid material was dissolved in 25 ml. of boiling ethanol. The solution was made alkaline by the addition of potassium hydroxide and refluxed for 30 minutes. The solution was cooled and the precipitated thiazole collected by filtration. The precipitate was washed with 50 ml. of cold acetone and yielded 800 mg. (22%) of 2'-methylthiazolo[d-3,2]-5 α -cholest-2-ene (IV) as a white powder; m.p. 168.5–169.5°; $[\alpha]_D^{25} +52.9^\circ$ (c, 0.81 chloroform); λ_{max}^{KBr} , 6.12 and 6.41 μ .

Anal.—Calcd. for $C_{29}H_{48}NS$: C, 78.84; H, 10.73; N, 3.17. Found: C, 78.58; H, 11.02; N, 3.21.

2'-Aminothiazolo[d-3,2]-5 α -cholest-2-ene (V).—2 α -Bromo-5 α -cholestan-3-one (II), 2.0 Gm., and 5.0 Gm. of thiourea were refluxed for 5 hours in 75 ml. of chloroform-ethanol (1:1). A white precipitate formed after about 1 hour. The reaction mixture

was evaporated to dryness. The solid residue was redissolved in 250 ml. of ethanol and made alkaline with potassium hydroxide. The solution was cooled and the precipitate collected by filtration. The crude thiazolosteroid was recrystallized from ethanol to yield 1.5 Gm. (79%) of 2'-aminothiazolo[d-3,2]-5 α -cholest-2-ene (V) as fluffy white crystals; m.p. 271–271.5°; $[\alpha]_D^{25} +58.3^\circ$ (c, 0.78 chloroform); λ_{max}^{KBr} , 2.82–3.02, 3.13–3.25, 6.10, and 6.53 μ [reported m.p. 266°; $[\alpha]_D^{25} +64.4^\circ$ (c, 0.49 chloroform)] (13).

Anal.—Calcd. for $C_{28}H_{46}N_2S$: C, 75.97; H, 10.47; N, 6.32. Found: C, 75.88; H, 10.47; N, 6.32.

2'-Phenylaminothiazolo[d-3,2]-5 α -cholest-2-ene (VI).—2 α -Bromo-5 α -cholestan-3-one (II), 4.0 Gm., and 1.5 Gm. of N-phenylthiourea were refluxed for 6 hours in 400 ml. of ethanol. The reaction mixture was made alkaline with methanolic potassium hydroxide and concentrated until crystals began to appear. The solution was cooled and the precipitate collected. The crude product was recrystallized from ethanol to yield 2.0 Gm. (45%) of 2'-phenylaminothiazolo[d-3,2]-5 α -cholest-2-ene (VI) as white needles; m.p. 194.5–195.5°; $[\alpha]_D^{25} +62.9^\circ$ (c, 0.99 chloroform); $\lambda_{max}^{CHCl_3}$, 2.93, 6.21, 6.50, and 6.67 μ .

Anal.—Calcd. for $C_{31}H_{50}N_2S$: C, 78.70; H, 9.71; N, 5.40. Found: C, 78.68; H, 9.47; N, 5.34.

2'-Allylaminothiazolo[d-3,2]-5 α -cholest-2-ene (VII).—2 α -Bromo-5 α -cholestan-3-one (II), 5.0 Gm., and 2.0 Gm. of N-allylthiourea were refluxed 3 hours in ethanol. The solution was made alkaline with methanolic potassium hydroxide, concentrated, and the precipitate collected by filtration. The crude product was recrystallized from chloroform-methanol to give 2.6 Gm. (50%) of 2'-allylaminothiazolo[d-3,2]-5 α -cholest-2-ene (VII) as white granules; m.p. 189.5–192°; $[\alpha]_D^{25} +57.4^\circ$ (c, 1.03 chloroform); $\lambda_{max}^{CHCl_3}$, 2.92, 6.07, 6.30, and 6.49 μ .

Anal.—Calcd. for $C_{31}H_{50}N_2S$: C, 77.13; H, 10.44; N, 5.80. Found: C, 76.63; H, 10.30; N, 5.91.

17 α -Methyl-5 α -androstan-17 β -ol-3-one (IX).—17 α -Methyltestosterone (VIII), 5.0 Gm., was dissolved in 120 ml. of 50:50 dry dioxane-ether. This solution was added, dropwise, with stirring to a solution of 1.0 Gm. of lithium metal in approximately 500 ml. of liquid ammonia. Thirty minutes after the addition was completed the blue color of the ammonia solution was discharged by the cautious addition of ammonium chloride. The ammonia was evaporated and the solid material taken up in chloroform and washed well with water. The chloroform solution was dried over sodium sulfate and evaporated to dryness. The residue was crystallized from methanol to yield 4.5 Gm. (90%) of 17 α -methyl-5 α -androstan-17 β -ol-3-one (IX) as white granular crystals; m.p. 192–194°; $\lambda_{max}^{CHCl_3}$, 2.76, and 5.85 μ (reported m.p. 193°) (8).

2 α -Bromo-17 α -methyl-5 α -androstan-17 β -ol-3-one (X).—17 α -Methyl-5 α -androstan-17 β -ol-3-one (IX), 6.0 Gm., was dissolved in 500 ml. of tetrahydrofuran. To this solution was added, portionwise, 6.4 Gm. of pyridine hydrobromide perbromide. The mixture was allowed to stand overnight at room temperature and then poured into 200 ml. of water. This mixture was extracted well with ether and the ether solution dried over sodium sulfate and evaporated to dryness. The residue was crystallized from ethyl acetate-petroleum ether to yield 3.1 Gm. (41%)

of 2 α -bromo-17 α -methyl-5 α -androstan-17 β -ol-3-one (X) as tan crystals; m.p. 185–187°; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.76 and 5.76 μ (reported m.p. 196–198°) (3).

Anal.—Calcd. for $\text{C}_{20}\text{H}_{31}\text{BrO}_2$: C, 62.66; H, 8.15; Br, 20.84. Found: C, 62.54; H, 8.14; Br, 21.30.

Thiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XI).—2 α -Bromo-17 α -methyl-5 α -androstan-17 β -ol-3-one (X), 5.0 Gm., was dissolved in 100 ml. of chloroform. To this solution was added 10 Gm. of crude thioformamide (11) dissolved in 50 ml. of chloroform-ethanol (1:1). The reaction mixture was stored in the refrigerator for 5 days and then allowed to stand at room temperature for 6 weeks. The reaction mixture was then made alkaline and washed well with water. The chloroform solution was dried over sodium sulfate and evaporated to yield a dark oil. The oil was dissolved in a minimum of dimethylformamide and allowed to stand at room temperature. After a week, oily crystals appeared and were collected by filtration. The crude material was recrystallized from anhydrous ether-petroleum ether to yield 1.5 Gm. (33%) of thiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XI) as salmon colored granules; m.p. 177–179°; $[\alpha]_D^{25} +48.8^\circ$; $\lambda_{\text{max}}^{\text{EtOH}}$ 251 μ , $\log \epsilon$ 3.64; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.75, 3.00–3.05, and 6.40 μ (reported m.p. 192–193°; $[\alpha]_D^{25} +33^\circ$; $\lambda_{\text{max}}^{\text{EtOH}}$ 252 μ , $\log \epsilon$ 3.61) (3).

Anal.—Calcd. for $\text{C}_{21}\text{H}_{31}\text{NOS}$: C, 73.02; H, 9.04; S, 9.53. Found: C, 72.66; H, 9.01; S, 9.53.

2'-Methylthiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XII).—2 α -Bromo-17 α -methyl-5 α -androstan-17 β -ol-3-one (X), 1.5 Gm., and 1.5 Gm. of thioacetamide were refluxed 5 hours in ethanol. The reaction mixture was made alkaline with methanolic potassium hydroxide. Ether (150 ml.) was added and the resulting solution washed well with water. The organic layer was dried over sodium sulfate and evaporated to dryness. The crude material was recrystallized twice from acetone to yield 700 mg. (49%) of 2'-methylthiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XII) as yellow-white needles; m.p. 198–199.5°; $[\alpha]_D^{25} +35.6^\circ$; $\lambda_{\text{max}}^{\text{EtOH}}$ 253 μ , $\log \epsilon$ 3.72; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.76, and 6.40 μ (reported m.p. 212–215°; $[\alpha]_D^{25} +47^\circ$; $\lambda_{\text{max}}^{\text{EtOH}}$ 254 μ , $\log \epsilon$ 3.76) (3).

Anal.—Calcd. for $\text{C}_{22}\text{H}_{33}\text{NOS}$: C, 73.48; H, 9.25; N, 3.90; S, 8.92. Found: C, 73.42; H, 9.23; N, 4.12; S, 9.04.

2'-Aminothiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XIII).—2 α -Bromo-17 α -methyl-5 α -androstan-17 β -ol-3-one (X), 5.0 Gm., and 3.0 Gm. of thiourea were refluxed 5 hours in ethanol. The reaction mixture was then made alkaline with methanolic potassium hydroxide and concentrated until the crude product precipitated. This precipitate was filtered and recrystallized from methanol-water to yield 2.7 Gm. (57%) of 2'-aminothiazolo-

[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XIII) as white plates; m.p. 270–272°; $[\alpha]_D^{25} +45.0^\circ$; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.76, 2.86, 2.94, 6.25, and 6.57 μ .

Anal.—Calcd. for $\text{C}_{21}\text{H}_{32}\text{N}_2\text{OS}$: C, 69.95; H, 8.95; N, 7.77. Found: C, 69.80; H, 9.26; N, 7.47.

2'-Phenylaminothiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XIV).—2 α -Bromo-17 α -methyl-5 α -androstan-17 β -ol-3-one (X), 3.0 Gm., and 3.0 Gm. of N-phenylthiourea were refluxed 3 hours in ethanol. The reaction mixture was made alkaline with methanolic potassium hydroxide and concentrated until the crude product precipitated. This material was filtered and recrystallized from ethanol to yield 1.2 Gm. (35%) of 2'-phenylaminothiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XIV) as white plates; m.p. 250–252°; $[\alpha]_D^{25} +46.0^\circ$; $\lambda_{\text{max}}^{\text{EtOH}}$ 298 μ , $\log \epsilon$ 4.21; $\lambda_{\text{max}}^{\text{KBr}}$ 2.76, 2.90, 2.06, 6.19, 6.48, and 6.64 μ .

Anal.—Calcd. for $\text{C}_{27}\text{H}_{36}\text{N}_2\text{OS}$: C, 74.27; H, 8.31; N, 6.42. Found: C, 74.61; H, 8.41; N, 6.14.

2'-Allylaminothiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XV).—2 α -Bromo-17 α -methyl-5 α -androstan-17 β -ol-3-one (X), 5.0 Gm. and 2.0 Gm. of N-allylthiourea were refluxed 3 hours in ethanol. The reaction mixture was made alkaline by the addition of methanolic potassium hydroxide and concentrated until the crude product precipitated. This material was filtered and recrystallized from ethanol-water to yield 3.7 Gm. (71%) of 2'-allylaminothiazolo[d-3,2]-17 α -methyl-5 α -andro-2-en-17 β -ol (XV) as white needles; m.p. 232–234°; $[\alpha]_D^{25} +50.5^\circ$; $\lambda_{\text{max}}^{\text{EtOH}}$ 266 μ , $\log \epsilon$ 3.93; $\lambda_{\text{max}}^{\text{CHCl}_3}$ 2.76, 2.90, 6.07, 6.27, and 6.49 μ .

Anal.—Calcd. for $\text{C}_{25}\text{H}_{36}\text{N}_2\text{OS}$: C, 71.96; H, 9.06; N, 6.99. Found: C, 71.96; H, 9.13; N, 7.15.

REFERENCES

- (1) Clinton, R. O., Manson, A. J., Stonner, F. W., Boyler, A. L., Potts, G. O., and Arnold, A., *J. Am. Chem. Soc.*, **81**, 1513 (1959).
- (2) Doorenbos, N. J., and Dorn, C. P., Jr., *THIS JOURNAL*, **50**, 271 (1961).
- (3) Zderic, J. A., et al., *Chem. & Ind. London*, **1960**, 1625.
- (4) Hantzsch, et al., *Ann.*, **249**, 1 (1888).
- (5) Fieser, L. F., and Dominguez, X. A., *J. Am. Chem. Soc.*, **75**, 1704 (1953).
- (6) Jones, R. N., Ramsay, D. A., Herling, F., and Dobriner, K., *ibid.*, **74**, 2828 (1952).
- (7) Weisenborn, F. L., and Applegate, H. E., *ibid.*, **81**, 1960 (1959).
- (8) Ruzicka, L., Goldberg, M. W., and Meyer, G., *Helv. Chim. Acta*, **18**, 210 (1935).
- (9) Djerassi, C., and Scholz, C. R., *J. Am. Chem. Soc.*, **70**, 417 (1948).
- (10) Schwartz, G., *Org. Syntheses*, **25**, 35 (1945).
- (11) Cerecedo, L. R., and Tolpin, J. G., *J. Am. Chem. Soc.*, **59**, 1660 (1937).
- (12) Randall, H. M., Fuson, N., Fowler, R. G., and Dangi, J. R., "Infrared Determination of Organic Structures," D. Van Nostrand Co., Inc., New York, N. Y., 1960, p. 20.
- (13) Antaki, H., and Petrow V. J., *J. Chem. Soc.*, **1951**, 901.