tremely sensitive to the position of the halogen in the aromatic rings. Some dicarbamates and -urethans derived from 2,2-dialkyl-1,3-propanediols display sedative and antispasmodic properties.[4]

This paper reports the synthesis of the title urethans derived from 1,1-dimethylol-3-cyclopentene for screening as possible antispasmodics and anticonvulsants. N.m.r. evidence is presented which unequivocally establishes the position of the cyclopentene double bond.

Experimental Section[5]

1,1-Dimethylol-3-cyclopentenedi-N-phenylurethan.—The diol (0.5 g., 0.004 mole) was dissolved in 10 ml. of dry benzene. Phenyl isocyanate (1.0 g., 0.008 mole) was then added, and the solution was boiled under reflux for 5 hr. During this time the clear solution began to deposit colorless needles. The solvent was removed by a stream of dry nitrogen. The residue was recrystallized from 95% ethanol affording 0.97 g. (68%) of pale yellow needles, m.p. 186–188°. A small sample was recrystallized from aqueous ethanol yielding an analytically pure product, m.p. 186.5–187°. The infrared spectrum (KBr disk) shows bands at 3230 (N–H) and 1690 cm.$^{-1}$ (C=O).

Anal. Calcd. for $C_{21}H_{22}N_2O_4$: C, 68.84; H, 6.05; N, 7.65. Found: C, 69.17; H, 6.09; N, 7.45.

Because of the lengthy period of heating in this reaction there was some concern about positional isomerization of the double bond in the cyclopentene ring. That this did not occur is shown by the n.m.r. spectrum of the product. It shows the following singlet absorptions given in parts per million relative to tetramethylsilane: 2.27, 4 protons (ring methylene hydrogens); 4.08, 4 protons ($-CH_2-O-$); 5.60, 2 protons (vinyl hydrogen); and 8.66, 2 protons (N–H). In addition a 10-proton multiplet is found centered at 7.24 (aromatic region). The specific proton assignments were made by consideration of chemical shifts and relative integrated areas and by comparison with the spectrum of the diol. The method used for distinguishing the two sets of methylene protons has previously been discussed.[6]

1,1-Dimethylol-3-cyclopentenedi-N-(α-naphthyl)urethan.—To 0.5 g. (0.004 mole) of the diol in 10 ml. of dry benzene was added 1.35 g. (0.008 mole) of α-naphthyl isocyanate. The solution was boiled under reflux for 10 hr. The solvent was removed by evaporation using dry nitrogen. The residual solid was recrystallized from ethanol and benzene affording 1.1 g. (61%) of fine white needles, m.p. 208–210°. A small amount was recrystallized again giving the pure product, m.p. 208.5–209.5°. The infrared spectrum (KBr disk) shows bands at 3200 (N–H) and 1680 cm.$^{-1}$ (C=O). The n.m.r. spectrum was obtained as a 1% solution in deuterioacetone containing tetramethylsilane as an internal standard. The chemical shifts for the various protons in the di-α-naphthylurethan listed in the same order as for the di-N-phenylurethan are 2.32, 4.18, 5.60, 8.56, and 7.26.

Anal. Calcd. for $C_{29}H_{26}N_2O_4$: C, 74.66; H, 5.62; N, 6.00. Found: C, 75.00; H, 5.67; N, 6.28.

(4) F. M. Berger, *J. Pharmacol. Exptl. Therap.*, **112**, 413 (1954); (b) J. Lincoln, British Patent 894,434 (April 18, 1962); (c) E. Rosenberg, British Patent 904,410 (Aug. 29, 1962).

(5) Melting points are corrected. Infrared spectra were determined on a Perkin-Elmer Infracord recording spectrophotometer. The n.m.r. spectra were determined on a Varian Model A-60 spectrometer. Spectra were obtained by Mr. Robert Steed. The analyses were performed by C. F. Geiger.

(6) E. J. Grubbs and D. J. Lee, *J. Org. Chem.*, **29**, 3105 (1964).

Syntheses of 3-Cyano-3-methyl-4-thiochromanone and 3-Carbomethoxy-3-methyl-4-thiochromanone

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In attempted synthesis of thia steroid analogs, the compounds were synthesized as intermediary models. The method of synthesis is analogous to the route used by Bachmann, *et al.*,[1] and Johnson, *et al.*,[2] for the preparation of equilenin.

Experimental Section

3-Hydroxymethylene-4-thiochromanone (I).—To a suspension of 10.8 g. of sodium methoxide in 30 ml. of benzene was added a solution of 15.2 g. of ethyl formate in 70 ml. of benzene. To the ice-cooled mixture was added a solution of 16.4 g. of 4-thiochromanone[3] in 100 ml. of benzene with stirring. A pink precipitate gradually formed, and after 4 hr. at room temperature it was hydrolyzed with 70 ml. of water. The organic layer was extracted with water and with 10% NaOH solution. The aqueous portions were combined, washed with ether, and acidified with HCl with cooling. The separated oil was extracted with ether. The extract was washed with water, dried, and concentrated to give 18.0 g. (94%) of crude I which was satisfactory for the next step. Distillation of the crude product gave a light yellow oil, b.p. 157–158° (4 mm.), accompanying decomposition.

Anal. Calcd. for $C_{10}H_8O_2S$: C, 62.50; H, 4.20. Found: C, 62.83; H, 4.31.

When the condensation was carried out by using sodium ethoxide, the yield of I dropped to 85%.

Reaction of I with Hydroxylamine.—A solution of 8.0 g. of I in 80 ml. of acetic acid was stirred for 8 hr. at 85–90° with 6.0 g. of powdered hydroxylamine hydrochloride. Most of the acetic acid was removed under reduced pressure, and the residue was diluted with water and extracted with benzene and ether. The combined organic layer was washed with saturated $NaHCO_3$ solution and with water. Evaporation of the dried solution gave 8.0 g. (quantitative yield) of a dark reddish viscous condensation product (II) which was directly isomerized as described below.

3-Cyano-4-thiochromanone (III).—A solution of 13.0 g. of II in 100 ml. of benzene was added to a cooled solution of 2.5 g. of sodium in 30 ml. of methanol. After stirring for 1.5 hr. at room temperature, the mixture was treated with 80 ml. of water and extracted with 5% NaOH solution. Acidification of the combined aqueous solutions with HCl gave 8.8 g. (68%) of III as tan needles, m.p. 92–95°. Recrystallization from aqueous ethanol gave a pure sample of m.p. 101.5–102°.

Anal. Calcd. for $C_{10}H_7NOS$: C, 63.49; H, 3.73. Found: C, 63.68; H, 3.79.

3-Cyano-3-methyl-4-thiochromanone. A. Directly from II.—A solution of 16.0 g. of II in 150 ml. of benzene was added to a cold solution of 3.4 g. of sodium in 50 ml. of methanol. After stirring for 30 min. at room temperature, the mixture was refluxed for 10 min. and cooled. The mixture was treated with 10 ml. of methyl iodide and allowed to stir at room temperature for 30 min. An additional 6 ml. of methyl iodide was added, and after 30 min. at room temperature, the mixture was refluxed for 4 hr. The solvents were largely removed at reduced pressure; the residue was taken up in benzene, washed with dilute NaOH solution and with water, dried, and concentrated. Distillation of the residue gave 9.3 g. (53%) of the product, b.p. 154–156° (2 mm.), as light yellow viscous oil.

Anal. Calcd. for $C_{11}H_9NOS$: C, 65.02; H, 4.46. Found: C, 65.21; H, 4.74.

The 2,4-dinitrophenylhydrazone formed small orange crystals from ethyl acetate, m.p. 195–196°.

Anal. Calcd. for $C_{17}H_{13}N_5O_4S$: C, 53.26; H, 3.42. Found: C, 53.04; H, 3.12.

B. From III.—A solution of 6.5 g. of III in 60 ml. of warm benzene was added to a solution of 2.9 g. of sodium in 50 ml. of methanol. The mixture was then refluxed for 20 min. To the cooled mixture was added 4.0 ml. of methyl iodide and the resulting mixture was allowed to stir at room temperature for 45 min. An additional 4 ml. of methyl iodide was then added, and after 30 min. 2 ml. of methyl iodide was introduced and the mixture was refluxed for 2.5 hr. The product was isolated as described above; yield 2.4 g. (34%). Unchanged III (1.5 g.) was recovered from the alkaline washings.

(1) W. E. Bachmann, W. Cole, and A. L. Wilds, *J. Am. Chem. Soc.*, **62**, 824 (1940).

(2) W. S. Johnson, J. W. Petersen, and C. D. Gutsche, *ibid.*, **69**, 2942 (1947).

(3) F. Krollpfeiffer and H. Schultze, *Ber.*, **56**, 1821 (1923).

Methyl 4-Thiochromanone-3-glyoxalate (IV).—A mixture of sodium methoxide (prepared from 2.6 g. of sodium) and 13.5 g. of dimethyl oxalate in 80 ml. of benzene was refluxed for 10 min. in order to dissolve most of the solid. To the cooled solution was added a solution of 9.8 g. of 4-thiochromanone in 50 ml. of benzene and the mixture was stirred at room temperature for 3 hr. to give a light yellow solution. The mixture was hydrolyzed with 150 ml. of water and a small amount of NaOH solution was added. After drawing off the aqueous layer, the benzene solution was extracted with 2% NaOH solution and the combined aqueous solution was acidified with dilute HCl. The yellow crystalline glyoxalate was filtered off, dried, and recrystallized from methanol to give 12.0 g. of IV. Additional 1.5 g. of IV was isolated from the mother liquor. The total yield of IV, m.p. 92–94°, was 13.5 g. (90%).

An analytically pure sample, m.p. 96–97°, was obtained as stout yellow fine needles by further recrystallization from methanol.

Anal. Calcd. for $C_{12}H_{10}O_4S$: C, 57.60; H, 4.03. Found: C, 57.77; H, 4.13.

3-Carbomethoxy-4-thiochromanone (V).—A mixture of 11.0 g. of IV and 5.5 g. of powdered glass was heated at 180° for 30 min. A vigorous evolution of CO took place, all of the gas being evolved in 10 min. After cooling, the dark product was dissolved in acetone and the solution was decanted from the glass and allowed to evaporate. Distillation of the residue gave 7.9 g. (81%) of V, b.p. 158–160° (3 mm.), m.p. 45–47°.

Anal. Calcd. for $C_{11}H_{10}O_3S$: C, 59.46; H, 4.54. Found: C, 59.87; H, 4.62.

3-Carbomethoxy-3-methyl-4-thiochromanone.—To a solution of 3.2 g. of sodium in 50 ml. of methanol was added a solution of 6.0 g. of V in 60 ml. of benzene. The mixture was refluxed for 1 hr., cooled, and treated with 8 ml. of methyl iodide. After 30 min. at room temperature, an additional 8 ml. of methyl iodide was added. The orange solution was stirred at room temperature for 30 min., then refluxed for 2 hr., cooled, neutralized with acetic acid, and evaporated nearly to dryness. The residue was treated with benzene and water, and the organic solution after separating was washed with dilute NaOH solution and with water, dried, and evaporated. Recrystallization of the residue from methanol gave 5.0 g. (78%) of the product, m.p. 82–84°. Further recrystallizations from methanol gave a pure sample, m.p. 85–86°.

Anal. Calcd. for $C_{12}H_{12}O_3S$: C, 61.01; H, 5.12. Found: C, 61.59; H, 5.39.

The Partial Synthesis of 1,2,3,4,4aα,9,10,10aβ-Octahydro-1α-(2-hydroxyethyl)-7-methoxy-2β-methyl-2α-phenanthrenecarboxylic Acid δ-Lactone[1]

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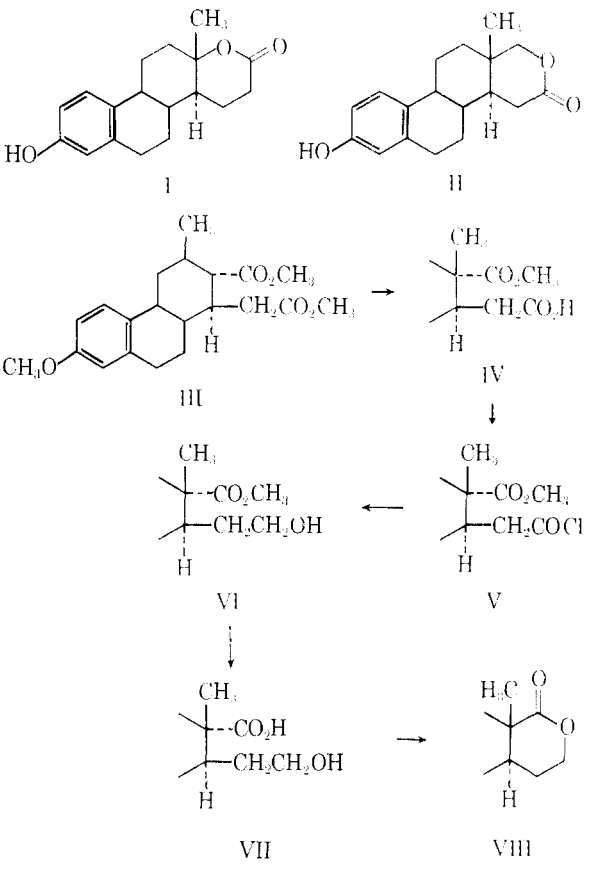
Interest in steroidal lactones was stimulated by the recent effective use of the spirolactones in adrenal pathology. Two different ring D lactones (I and II) derived from estrone are known (see Scheme I).[2] This paper describes the preparation of the methyl ether of a third one (VIII).

The infrared spectra[3] for the three lactone methyl ethers were different in that the carbonyl band of Westerfeld's lactone I (as the methyl ether) was at 1717 cm.$^{-1}$, or 7 cm.$^{-1}$ lower than the new lactone methyl ether VIII. This may be due to the increased strain in the ring of this lactone VIII caused by interaction between the 17-ester group and the C-18 methyl group. The methyl ether of Huffman's lactone II absorbed 9 cm.$^{-1}$ lower in the carbonyl region. In this lactone there would be even less interaction of the type mentioned above than in the methyl ether of estrolactone I.

The n.m.r. spectrum[4] for methyl ether VIII showed τ values of 2.83, 3.11, and 3.37 for the aromatic protons; 6.23 for the methoxy protons; 8.76 for the C-18 methyl protons; and 5.57 (multiplet) for the structure CH_2OCO, as expected. The spectrum for estrolactone 7-methyl ether had values of 2.83, 3.11, and 3.38 for the aromatic protons; 6.24 for the methoxy protons; and 8.65 for the C-18 methyl protons. The absence of the 5.57 band in the spectrum of estrolactone 7-methyl ether is in agreement with structure I since it does not have the group CH_2OCO. The τ-value for the C-18 methyl protons of Δ^1-testolactone (lactone structure corresponds to that of estrolactone) is 8.60. Therefore, the shift to 8.65 for estrolactone 7-methyl ether (I) may be expected.

SCHEME I



Experimental Section[5]

Hemimethyl Ester (IV).—7-Methoxydimethyl marrianolate[6] (1.08 g.) (III), in 20 ml. of methanol (refluxing), was treated with 0.04 *M* K_2CO_3 in 5-ml. aliquots every 15 min. for 4–5 hr. Faster addition of the carbonate tended to cause precipitation. The alcohol was evaporated, and the concentrate was transferred to a separatory funnel with carbonate, washed well with ether, and acidified to pH 1 with concentrated HCl. The precipitated oil was extracted with ether. The ether was washed with water and evaporated to give 1.0 g. of IV which melted at 90–92° after crystallization from aqueous acetone.

Anal. Calcd. for $C_{20}H_{26}O_3$: C, 69.34; H, 7.56; neut. eq., 346. Found: C, 69.11; H, 7.50; neut. equiv., 330.

(1) Supported in part by U. S. Public Health Service Grant HD-01199 and Research Career Development Award AM-14,013.

(2) W. W. Westerfeld, *J. Biol. Chem.*, **143**, 177 (1942); R. P. Jacobsen, *ibid.*, **171**, 61 (1947); M. Keller and J. Weiss, *J. Chem. Soc.*, 1247 (1951); M. N. Huffman, M. H. Lott, and J. Ashmore, *J. Biol. Chem.*, **196**, 367 (1952).

(3) Infrared spectrophotometry was performed on a Perkin-Elmer 421 instrument using KBr pellets.

(4) Performed through the courtesy of Dr. Edward Becker, Squibb Institute for Medical Research; $CDCl_3$ was used as solvent.

(5) All melting points were taken on a Fisher-Johns apparatus, uncorrected.

(6) J. C. Touchstone, W. H. Elliott, S. A. Thayer, and E. ... *Am. Chem. Soc.*, **77**, 3562 (1955).