Spirans XVII. Spirans Derived from 4-Chromanone (1)

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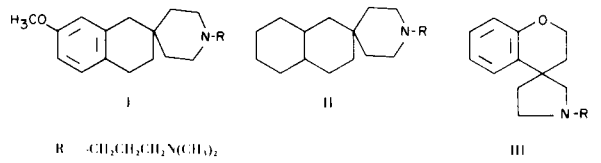
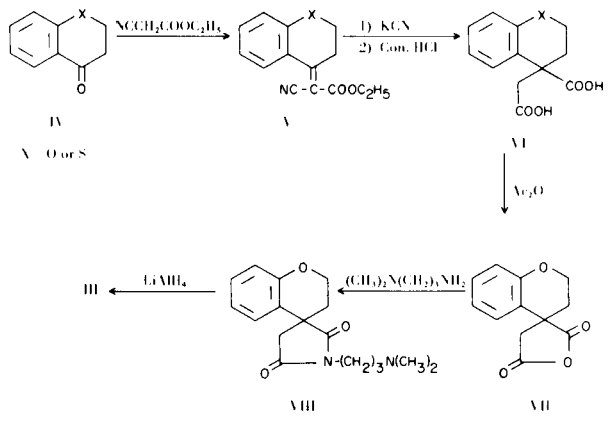
As part of a continuing program on the synthesis of various azaspiroalkanes and related compounds derived from some heterocyclic systems, we wish to report our research with 4-chromanone and 4-thiochromanone and to ascertain the structure of III. Compounds previously prepared from β-tetralone (I) (2) and β-decalone (II) (3) are closely related and exhibited a high degree of inhibition of the growth of KB cell cultures.



The starting point in our synthesis was 4-chromanone (IV), (X = O or S) which was subjected to the reaction sequence as follows:



The ketones IV (X = O or S) were converted by a modified Cope procedure (4) into their corresponding cyanoalkylidene esters in yields of 33% and 37% respectively. The addition of potassium cyanide across the double bond of V produced a potassium salt with a series of color changes from yellow to red and then orange to yellow. The hydrolysis of the dried salt with concentrated hydrochloric acid provided the acids VI (X = O or S). The yield of acid VI (X = O) was 55.4% whereas the yield of acid VI (X = S) was only 4.1%. The acid VI (X = O) was converted into its anhydride VII with acetic anhydride. This anhydride was allowed to react with 3-dimethylaminopropylamine to give the amic acid which upon further heating was cyclized to the corresponding imide VIII. An azaspirochroman (III) was obtained by reducing VIII with lithium aluminum hydride, which was converted to its dihydrochloride.

In an effort aimed at an alternate synthesis, the Wittig reaction using triethyl phosphonoacetate on ketones IV failed to give the 4-chromanylidene or 4-thiochromanylidene esters. These ketones also failed to undergo the Guareschi reaction. Compound III inhibited the growth of KB tissue culture at 4-6 ug./ml. which is lower activity than that exhibited by either compound I or II.

EXPERIMENTAL

All melting points (Thomas-Hoover capillary-type) are corrected. Elemental microanalysis were performed by Schwarzkopf Microanalytical Laboratory, Woodside, New York. The infrared spectra of all compounds corresponded with assigned structures.

Ethyl α-Cyano-α-(4-chromanylideneyl)acetate (V, X = O).

To 51.0 g. (0.21 mole) of 4-chromanone dissolved 50 ml. of benzene was added 23.8 g. (0.21 mole) of ethyl cyanoacetate, 16 g. acetic acid, and 5 g. of ammonium acetate. The mixture was refluxed with a Dean-Stark water trap attached until water ceased to be collected. The reaction mixture was treated with 500 ml. of water and extracted with three 200 ml. portions of ether. After washing the ethereal extract (saturated sodium bicarbonate, saturated salt) and drying (sodium sulfate), the ether was removed *in vacuo* and the product was distilled, 27.5 g. (33%) b.p. 137-139° at 0.02 mm.

Anal. Calcd. for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.18; H, 5.29; N, 5.66.

Ethyl α-Cyano-α-(4-thiochromanylidenyl)acetate (V, X = S).

This compound was prepared as above in 37% yield, b.p. 148-152° at 0.05 mm.

Anal. Calcd. for $C_{14}H_{13}NO_2S$: C, 64.84; H, 5.05; N, 5.40; S, 12.35. Found: C, 65.00; H, 5.18; N, 5.67; S, 12.08.

Chroman-4-carboxy-4-acetic Acid (VI, X = O).

A solution of 27 g. of VI (X = O) above dissolved in 200 ml. of alcohol was mixed with a solution of 13.5 g. of potassium cyanide

dissolved in 20 ml. of water and 100 ml. of alcohol. The yellow solution changed to red, then orange and after standing 24 hours changed back to yellow. All solvent was removed under reduced pressure and the residue was refluxed for 24 hours with 300 ml. of concentrated hydrochloric acid, cooled and diluted with 300 ml. of water. The crude acid was filtered, dissolved in 10% potassium bicarbonate solution and treated with decolorizing carbon. After filtering, the solution was acidified with hydrochloric acid and filtered, 16.1 g. (55%) m.p. 195-197°. Recrystallization from methanol gave m.p. 199-200°.

Anal. Calcd. for $C_{12}H_{12}O_5$: C, 61.01; H, 5.12. Found: C, 60.87; H, 5.14.

Thiochroman-4-carboxy-4-acetic Acid (VI, X = S).

This acid was prepared as above but the yield was less than 5%, m.p. 164-165° (methanol).

Anal. Calcd. for $C_{12}H_{12}O_4S$: C, 57.13; H, 4.80; S, 12.70. Found: C, 57.04; H, 4.64; S, 12.92.

2′,3′,4′,5′-Tetrahydrospiro[chroman-4,3′-furan]-2′,5′-dione (VII).

The acid VI (X = O) (9 g.) was refluxed with 50 ml. of acetic anhydride for 3 hours and the excess acetic anhydride was removed by vacuum distillation. Distillation of the residual oil (b.p. 129-132°, 0.06 mm.) gave 6 g. of product.

Anal. Calcd. for $C_{12}H_{10}O_4$: C, 66.05; H, 4.62. Found: C, 66.17; H, 4.58.

1′-Dimethylaminopropylspiro[chroman-4,3′-pyrrolidine]-2′,5′-dione (VIII).

Dimethylaminopropylamine (3 g.) was slowly added, with shaking, to 6 g. of finely powdered anhydride VII. The mixture was heated at 180-200° for 1 hour. Cyclization of the amic acid intermediate was completed at the cessation of water evolution. After cooling, the product was distilled, 6 g., b.p. 156-162° (0.05 mm.).

Anal. Calcd. for $C_{17}H_{22}N_2O_3$: C, 67.53; H, 7.33; N, 9.26. Found: C, 67.63; H, 7.48; N, 9.28.

1′-Dimethylaminopropylspiro[chroman-4,3′-pyrrolidine] (III).

Compound VIII (6 g.) dissolved in 60 ml. of anhydrous ether, was slowly added with stirring to a solution of 5 g. of lithium aluminum hydride dissolved in 250 ml. of anhydrous ether. After standing overnight the reaction mixture was decomposed, filtered, and dried over sodium sulfate. The ether was removed *in vacuo* and the product was distilled under reduced pressure to give 5 g., b.p. 120-125° (0.05 mm.). The dihydrochloride was made in absolute alcohol and precipitated with ether, m.p. 255-257°.

Anal. Calcd. for $C_{17}H_{28}Cl_2N_2O$: C, 58.78; H, 8.07; N, 8.13; Cl, 20.42. Found: C, 58.49; H, 8.30; N, 7.90; Cl, 20.37.

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