[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY AND PHYSICS OF THE PENNSYLVANIA STATE COLLEGE]

Sterols. LXVI. Reactions of Tigogenin

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The work of Tschesche and Hagedorn[1] on the degradation of tigogenin through the C_{22} lactone to *etio-allo*-bilianic acid has established the nuclear configuration of the substance beyond any doubt. However, in view of our recent work concerning sarsasapogenin,[2] their formulation of the side chain of the substance is open to question.

We have extended the reactions characteristic of sarsasapogenin to tigogenin. While the results obtained indicate that the substances are similar and undoubtedly contain the same type of structure in the side chain, there are some interesting differences. Unfortunately our supply of tigogenin is very limited and we have not been able to extend these reactions as far as would be desirable.

Tigogenin resembles sarsasapogenin in that upon catalytic hydrogenation in acidic medium it gives a dihydrotigogenin. This substance was further characterized by its formation of a dibenzoate and by its oxidation under mild conditions with chromic anhydride to yield an acid of the same carbon content. Tigogenin acetate reacts slightly less readily with bromine than does sarsasapogenin acetate to yield bromotigogenin acetate. Reduction of the bromo compound with sodium and ethanol readily gave tigogenin. Dihydrotigogenin showed no tendency to react with bromine. Tigogenin acetate and tigogenin readily gave a red precipitate when heated with selenium dioxide in acetic acid solution. Both bromotigogenin acetate and dihydrotigogenin were inert to this reagent.

Attempts to reduce tigogenin by the Clemmensen method under the conditions described for the reduction of sarsasapogenin to tetrahydrosarsasapogenin[2] were unsuccessful. When the reduction was carried out over a longer period a poor yield of a product of the probable composition $C_{27}H_{46}O_2$ was obtained. The substance was unsaturated to bromine but would not undergo catalytic reduction with Adams catalyst in neutral medium. An attempt to prepare a crystalline acetate was unsuccessful.

Tigogenone on Clemmensen reduction in ethanol solution with unamalgamated zinc yielded a desoxy compound, $C_{27}H_{44}O_2$, m. p. 174°. Tigogenin upon similar treatment was recovered unchanged, indicating that the desoxy compound is not an isomerization product. This desoxy compound is evidently different from the desoxy compound, m. p. 267°, which Jacobs and Fleck[3] obtained by the Clemmensen reduction of tigogenone using amalgamated zinc in acetic acid solution.

The work of Tsukamoto, Ueno and Ota[4] on the unsaturated sapogenin, diosgenin, $C_{27}H_{42}O_3$, should prove of great interest in connection with future studies on tigogenin since the unsaturated substance upon catalytic hydrogenation gives a substance designated as dihydrodiosgenin which from all available published data appears to be identical with tigogenin. A comparison of the chromic anhydride oxidation products of tigogenin and dihydrodiosgenin shows an especially striking similarity. Evidently their catalytic reduction of diosgenin was carried out in neutral medium and their dihydro compound should not be confused with our dihydro compounds.

From all of the available published data dioscoreasapogenin,[5] $C_{27}H_{42}O_3$, appears to be identical with or at least very closely related to diosgenin.

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Experimental Part

The tigogenin was isolated from *Chlorogalum pomeridianum* by the method described by Liang and Noller[6] with the exception that ethanol was used in place of isopropanol for the separation of the tigogenin from the other sapogenins present.

Tigogenin, when heated on the steam-bath in acetic acid solution with selenium dioxide, readily yielded the red precipitate characteristic of selenium dioxide oxidations. The reaction was not investigated further.

(1) Tschesche and Hagedorn, *Ber.*, **68**, 1412 (1935).

(2) Marker and Rohrmann, THIS JOURNAL, **61**, 846 (1939).

(3) Jacobs and Fleck, *J. Biol. Chem.*, **88**, 545 (1930).

(4) Tsukamoto, Ueno and Ota, *C. A.*, **31**, 3493 (1937); Tsukamoto, Ueno and Ota, *ibid.*, **32**, 2537 (1938); Tsukamoto and Ueno, *ibid.*, **32**, 7470 (1938).

(5) Huzii and Matukawa, *ibid.*, **33**, 640 (1939).

(6) Liang and Noller, THIS JOURNAL, **57**, 525 (1935).

Dihydrotigogenin.—A mixture of 3 g. of tigogenin, 1 g. of Adams catalyst and 100 cc. of glacial acetic acid was shaken with hydrogen at 3 atmospheres pressure at 70° for twenty hours. The mixture was filtered and the acetic acid removed *in vacuo*. The residual sirup after refluxing for twenty minutes with an excess of ethanolic potassium hydroxide was diluted with water and the precipitated solid taken up in ether. Evaporation of the ether gave a product which crystallized from acetone as white plates, m. p. 167–168°.

Anal. Calcd. for $C_{27}H_{46}O_3$: C, 77.4; H, 11.1. Found: C, 77.3; H, 11.0.

The dihydro compound showed no evidence of oxidation when heated at 95° for one hour with selenium dioxide in acetic acid solution. The substance showed no tendency to absorb bromine in acetic acid solution in the presence of a trace of hydrobromic acid. Dihydrotigogenin readily gives a precipitate with an alcoholic solution of digitonin.

Dibenzoate of Dihydrotigogenin.—To a solution of 200 mg. of dihydrotigogenin in 10 cc. of dry pyridine was added approximately 0.25 cc. of benzoyl chloride. After standing at 25° for twenty-four hours the mixture was heated at 95° for one hour and then the product was freed from pyridine and acidic products and the material after treatment with Norite was crystallized from aqueous acetone as white plates, m. p. 110–112°.

Anal. Calcd. for $C_{41}H_{54}O_5$: C, 78.55; H, 8.7. Found: C, 78.5; H, 8.7.

Oxidation of Dihydrotigogenin.—To a solution of 700 mg. of dihydrotigogenin in 75 cc. of glacial acetic acid was added a solution of 1 g. of chromic anhydride in 10 cc. of 80% acetic acid. The mixture was allowed to stand at 25° for one hour, after which it was diluted with water. The precipitated solid was taken up with ether and the ethereal extract washed with 5% sodium carbonate solution. The sodium carbonate washings was acidified with hydrochloric acid and the precipitated solid extracted with ether and crystallized from ether–pentane to give white crystals, m. p. 192°. The substance gave a positive Zimmermann test.

Anal. Calcd. for $C_{27}H_{42}O_4$: C, 75.3; H, 9.6. Found: C, 75.2; H, 9.9.

Bromotigogenin Acetate.—To 200 mg. of tigogenin acetate in 30 cc. of glacial acetic acid containing two drops of 48% hydrobromic acid was added at room temperature 0.5 cc. of 1.05 *M* bromine in glacial acetic acid. The bromine was taken up rather slowly and hydrogen bromide was liberated. The solution was diluted with water and the white precipitate collected, washed with water and dried. The material was crystallized from acetone to give white needles, m. p. 223° dec.

Anal. Calcd. for $C_{29}H_{45}O_4Br$: C, 64.7; H, 8.4. Found: C, 64.5; H, 8.4.

The substance showed no evidence of oxidation when heated for twenty minutes at 90°, with selenium dioxide in acetic acid.

To a boiling solution of 50 mg. of bromotigogenin acetate in 50 cc. of absolute ethanol was added 2 g. of sodium over a period of forty-five minutes. The solution was diluted with water, and the precipitated solid taken up in ether and crystallized from methanol as small white plates, m. p. 202–203°. This gave no depression with a sample of tigogenin.

Clemmensen Reduction of Tigogenone.—To a boiling mixture of 250 mg. of tigogenone, 80 cc. of 95% ethanol and 10 g. of zinc (20-mesh) was added 10 cc. of concentrated hydrochloric acid over a period of three hours. The solution was decanted into water and the precipitated solid taken up with ether and crystallized from acetone to give white plates, m. p. 173–174°. This gave no appreciable depression with a sample of desoxychlorogenin, m. p. 172°.

Anal. Calcd. for $C_{27}H_{44}O_2$: C, 80.9; H, 11.1. Found: C, 80.6; H, 11.0.

Tigogenin when treated in a similar manner was recovered unchanged.

Dihydrodesoxytigogenin.—A mixture of 100 mg. of desoxytigogenin, 500 mg. of Adams catalyst, 75 cc. of glacial acetic acid and 25 cc. of 99% ethanol was shaken with hydrogen at three atmospheres pressure at 25° for fourteen hours. The product was worked up as described for dihydrotigogenin. After treatment with Norite it was crystallized from aqueous acetone as small white plates, m. p. 92.5°.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.5; H, 11.5. Found: C, 80.5, 80.5; H, 11.1, 11.6.

Clemmensen Reduction of Tigogenin.—To a boiling solution of 300 mg. of tigogenin in 100 cc. of 95% ethanol with 20 g. of amalgamated zinc (20-mesh) was added over a period of thirty-five hours 35 cc. of concentrated hydrochloric acid. The solution was decanted into water and the resulting mixture extracted with ether. Evaporation of the ether gave a residue which crystallized from acetone as compact white crystals, m. p. 152°; yield 25 mg.

Anal. Calcd. for $C_{27}H_{46}O_2$: C, 80.5; H, 11.5. Found: C, 80.7; H, 11.5.

The substance gave a precipitate with a solution of digitonin in 80% ethanol. The product rapidly absorbed bromine in acetic acid solution. However, an attempt to reduce the substance with Adams catalyst in ether solution gave only unchanged material. An attempt to prepare a crystalline acetate by refluxing with acetic anhydride was unsuccessful, a non-crystalline gum resulting.

Summary

Tigogenin appears to have a ketone spiro acetal group in the side chain. The substance differs from sarsasapogenin in its behavior toward Clemmensen reduction.

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