[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

Steroidal Sapogenins. LIV. Effect of Amines on the Catalytic Hydrogenation of the Spiroketal Side Chain and of 3,5-Cyclosapogenins[2,3]

BY MONROE E. WALL, THEODORE PERLSTEIN AND SAMUEL G. LEVINE

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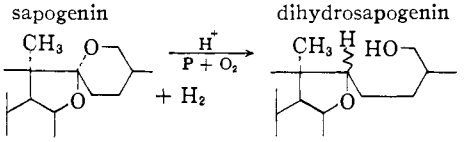
Several sapogenylamines were prepared by sodium reduction of the corresponding oxime or ammonolysis of diosgenyl *p*-toluenesulfonate. It was found that catalytic hydrogenation of the ring F side chain of natural sapogenins or of the 3,5-cyclo- moiety in glacial acetic acid was markedly inhibited in the presence of these sapogenylamines or of *n*-propylamine. The Δ^5-double bond is readily reduced under these conditions. The significance of these findings in regard to the mechanism of catalytic hydrogenation of the sapogenin side chain is discussed in some detail.

It is well known that catalytic hydrogenation of the steroidal sapogenin side chain to give dihydrosapogenins occurs only under acid conditions,[4] thus implying the participation of a *protonated* spiroketal system in the reduction process.



Reasoning, then, that the presence of a more easily protonated group in the same molecule might influence the course or rate of these reactions, we undertook a study of the catalytic hydrogenation of certain amino-sapogenins.

Catalytic hydrogenation of tigogenin acetate (I) in glacial acetic acid in the presence of Adams catalyst at room temperature and 3 atmospheres pressure occurs rapidly. The reaction is complete in 30 minutes. It was observed that under similar conditions, 12β-aminotigogenin (II)[5] was recovered unchanged after 3 hours. To study the effect of an amine moiety at a site more distant from the side chain a 3-aminosapogenin was prepared. Reduction of tigogenone oxime[6a] with sodium in alcohol produced 3β-tigogenylamine[6b] which was characterized as the corresponding acetyl derivative V. Catalytic hydrogenation of 3β-tigogenylamine for 3 hours under the conditions described above resulted in only 5–10% conversion to the corresponding dihydro compound and 60% conversion in 17 hours. Similar 3-hour hydrogenation of the less basic 3β-tigogenylacetamide resulted in complete hydrogenation of the side chain, whereas with 3β-tigogenyl amine hydrochloride there was virtually no side chain opening after a 3-hour hydrogenation. A similar hydrogenation of the latter compound in ethanol containing 5% hydrochloric acid (v./v.) resulted in complete conversion to dihydro-3β-tigogenylamine hydrochloride indicating that the inhibition of side chain hydrogenation by the amine group was ineffective in the presence of a large excess of acid.

Another series of experiments indicated that side chain hydrogenation of non-basic sapogenins could be effectively inhibited by the presence of an amino sapogenin or a simple amine in the reduction system. Hydrogenation of equal quantities of tigogenin acetate and 3β-tigogenylamine followed by acetylation and chromatography resulted in complete separation of the amino- and non-aminosapogenins and demonstrated that no attack on the spiroketal side chain had occurred on either compound. Substitution of diosgenin acetate for tigogenin acetate gave similar results except that the hydrogenation product was *tigogenin acetate*, indicating that there was no inhibition of the hydrogenation of the *double bond* in diosgenin. In a similar experiment *n*-propylamine completely inhibited the hydrogenolysis of tigogenin or diosgenin acetates. In the latter case the reduction product was again tigogenin acetate. In order to study the hydrogenation of a compound with amine and double bond moieties in one molecule we prepared 3β-diosgenylamine (VI) by ammonolysis of 3β-diosgenyl *p*-toluenesulfonate (VII)[7] following the preparation of 3β-cholesterylamine.[8a,b] As was previously found in the cholesterol series,[8a,b] the diosgenylamine isolated as the hydrochloride was a mixture which could be separated into ether-insoluble (A) and soluble (B) fractions. Both fractions were then converted to the free bases and for characterization purposes a portion of each was acetylated. The diosgenylacetamide from fraction A was a mixture which could be easily separated by crystallization or chromatography into high melting (m.p. 255–257°) and lower melting (m.p. 199–202°) isomers, C and D respectively, with distinct differences in their infrared spectra (*cf.* Experimental section). Both, however, were acetamides showing typical N–CO bands[9] at 1680–1685 cm.$^{-1}$, spiroketal bands,[10a] and two bands at 840 and 810 cm.$^{-1}$ indicative of Δ^5- double bonds.[10a,b] The latter assignment was strongly reinforced by the high negative rotation of both compounds C and D with respect to 3β-tigogenylacetamide.[11] Catalytic hydrogenation of fraction

(1) Eastern Utilization Research and Development Division, Agricultural Research Service, U. S. Department of Agriculture.

(2) Previous paper in this series, Steroidal Sapogenins, LIII. Monroe E. Wall, *et al.*, *J. Org. Chem.*, **24**, 741 (1959).

(3) Presented at 136th National Meeting, Atlantic City, N. J., September, 1959.

(4) R. E. Marker, *et al.*, THIS JOURNAL, **69**, 2167 (1947).

(5) R. Anliker, O. Rohr and H. Heusser, *Helv. Chim. Acta*, **38**, 1175 (1955).

(6) W. A. Jacobs and E. E. Fleck, *J. Biol. Chem.*, **88**, 545 (1930).

(7) M. E. Wall and S. Serota, THIS JOURNAL, **78**, 1747 (1956).

(8) (a) P. L. Julian, A. Magnani, E. W. Meyer and W. Cole, *ibid.*, **70**, 1834 (1948); (b) R. D. Haworth, J. McKenna and R. G. Rowell, *J. Chem. Soc.*, 1110 (1953).

(9) L. J. Bellamy, "The Infrared Spectra of Complex Molecules," John Wiley and Sons, Inc., New York, N. Y., 1954.

(10) (a) C. R. Eddy, M. E. Wall and M. K. Scott, *Anal. Chem.*, **25**, 266 (1953); (b) P. Bladon, J. M. Fabian, H. B. Henbest, A. B. Koch and G. W. Wood, *J. Chem. Soc.*, 2402 (1951).

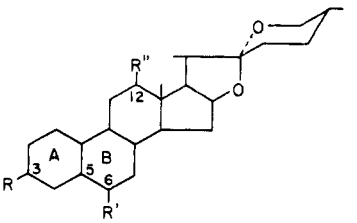
(11) MD fraction C − MD tigogenylacetamide = −279. D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948), give −298 as the average molecular rotation contribution of a 5,6-double bond.

C in ether containing 5% acetic acid gave 3β-tigogenylacetamide identical to the product previously prepared *via* reduction of tigogenone oxime. Therefore fraction C must be 3β-diosgenylacetamide (VIII) and by analogy with the comparable cholesterol series[12] fraction D must be 3α-diosgenylacetamide (IX). This assignment of structure is strengthened by the fact that hydrogenation of D in ether containing 5% acetic acid gave a saturated compound, presumably 3α-tigogenylacetamide (X). The molecular rotation differences between 3β-tigogenylacetamide and the presumed 3α-tigogenylacetamide were comparable to the known molecular rotation differences of 3β- and 3α-cholestanylacetamides.[12,13] The acetamide (E) prepared from the ether-soluble hydrochloride (B) had infrared absorption bands showing the presence of an amide group and spiroketal bands of the 25D-series. In addition there was a well defined weak band at 3060 cm.$^{-1}$ present in the spectrum of 3,5-cyclodesoxydiosgenin,[7] and the 835–840 cm.$^{-1}$ band indicative of Δ^5-unsaturation[10a,b] was absent although a band near 810 cm.$^{-1}$ was present. The latter assignment was supported by the fact that acetamide E had a much more positive optical rotation than those of the Δ^5-isomers C or D.[14] From the above data and from a close analogy with the cholesterol series[8a,b,12] we assign to fraction E the structure 3,5-cyclo-6β-diosgenylacetamide (XI), the free amine having the corresponding structure XII.

The 3β- and 3α-diosgenylamines were difficult to separate except as their acetamide derivatives, which in turn gave poor yields of the free amine because of the drastic hydrolytic conditions required. Therefore these amines were hydrogenated as a mixture (approximately 1:1) under our standard conditions. Infrared analysis of the acetylated hydrogenation product showed complete reduction of the Δ^5- double bond and only slight side chain attack (<10%), thus demonstrating inhibition of side chain hydrogenation and non-inhibition of double bond hydrogenation on the same molecule and in addition showing that the stereochemistry of the amine at C_3 is not a factor in the inhibition of the side chain hydrogenation. Under our experimental conditions the mixture of 3α- and 3β-diosgenylamine hydrochlorides were resistant to side chain hydrogenation, only the C_5-double bond being reduced. The pure 3α- and 3β-diosgenylacetamides were completely hydrogenated under our standard conditions.

Some years ago Schmid and Kagi[15] found that 3,5-cyclocholestane on hydrogenation in glacial acetic acid in the presence of platinum oxide gave a compound whose structure was designated as 3β-methyl-A-nor-5β-cholestane.[16] It became of interest to study the catalytic hydrogenation of some available 3,5-cyclosapogenins. Catalytic hydrogenation of 3,5-cyclodesoxydiosgenin (XIII)[7] in 5% acetic acid in ethyl acetate resulted in complete recovery of starting material. Hydrogenation of XIII in glacial acetic acid gave a crystalline compound with an infrared spectrum that showed presence of a hydroxyl group and absence of both the characteristic spiroketal bands[10a] and of the band at 3060 cm.$^{-1}$ characteristic of 3,5-cyclosteroids[17] which was present in the spectrum of compound XIII. The hydrogenation product of XIII was non-identical to 3-desoxydihydrotigogenin, a crystalline compound obtained by catalytic hydrogenation of 3-desoxytigogenin.[7] We tentatively assign to the former the structure 26-hydroxy-3β-methyl-A-nor-5β,22ξ-furostane based on analogy to the compound obtained by catalytic hydrogenation of 3,5-cyclocholestane.[15,16] Catalytic hydrogenation of XIII in glacial acetic acid in the presence of propylamine resulted in complete recovery of starting material showing inhibition by the amine of hydrogenation of both the spiroketal and 3,5-cyclo-moieties. Similar hydrogenation of 3,5-cyclo-6β-diosgenylamine (XII) or its hydrochloride also resulted in recovery of starting material, whereas the corresponding 6β-acetamide on hydrogenation showed complete hydrogenation of the spiroketal and almost complete hydrogenation of the 3,5-cyclo groups.

Any of the amines mentioned above would exist predominantly as the conjugate acid in acetic acid solution and, on adsorption, would produce a positive charge on the catalyst surface. The repulsion of solvated protons from such a surface



I. R = 3β – OAc, R′ = R″ = H, A/B = 5α
II. R = 3β – OH, R′ = H, R″ = 12β – NH_2, A/B = 5α
III. R = = NOH, R′ = R″ = H, A/B = 5α
IV. R = 3β – NH_2, R′ = R″ = H, A/B = 5α
V. R = 3β – NHAc, R′ = R″ = H, A/B = 5α
VI. R = 3β – NH_2, R′ = R″ = H, A/B = Δ^5
VII. R = 3β – OTs, R′ = R″ = H, A/B = Δ^5
VIII. R = 3β – NHAc, R′ = R″ = H, A/B = Δ^5
IX. R = 3α – NHAc, R′ = R″ = H, A/B = Δ^5
X. R = 3α – NHAc, R′ = R″ = H, A/B = 5α
XI. R = R′ = H, R′ = 6β – NHAc, A/B = 3,5-cyclo
XII. R = R″ = H, R′ = 6β – NH_2, A/B = 3,5-cyclo
XIII. R = R′ = R″ = H, A/B = 3,5-cyclo
XIV. R = R′ = R″ = H, A/B = 5α

(12) J. H. Pierce, H. C. Richards, C. W. Shoppee, R. J. Stephenson and G. H. R. Sommers, *J. Chem. Soc.*, 644 (1955).

(13) M_D 3β-cholestanylacetamide-M_D 3α-cholestanylacetamide = −58[12]; M_D 3β-tigogenylacetamide-M_D 3α-tigogenylacetamide = −32.

(14) M_D 3,5-cyclodiosgenin − M_D diosgenin = +424[7]; M_D 3,5-cyclo-6β-diosgenylacetamide − M_D 3β-diosgenylacetamide = +320.

(15) H. Schmid and K. Kagi, *Helv. Chim. Acta*, **33**, 1582 (1950).

(16) The structural assignment was based on the logical assumption that the strained substituted cyclopropane ring would rupture on hydrogenolysis and the fact that other logical structures such as 5α-cholestane, 5β-cholestane, 3α-methyl-A-nor-5β-cholestane and 3β-methyl-A-nor-5α-cholestane were rigidly excluded by the experimental data. Shoppee and Sommers, *J. Chem. Soc.*, 2528 (1952), in a reinvestigation of the problem agreed with the assignment of Schmid and Kagi. The latter workers, it should be pointed out, did not regard their structure as rigidity established. They did not consider one other possibility, *i.e.*, fission of the 3,4-bond to give A-nor-5β-methylcholestane, a structure wihich cannot be excluded by any of the data presently available.

(17) A. H. R. Cole, *J. Chem. Soc.*, 3807, 3810 (1954).

might be expected to retard acid-catalyzed hydrogenolysis.[18]

It might be argued that the observed inhibitions of catalytic hydrogenation arise from the equivalent of acetate ion formed by protonation of the amines. These ions in turn by common ion effect would greatly reduce the concentration of protonated spiroketal side chain (or protonated 3,5-cyclo group). Our data clearly show that such a process does not account for the observed inhibition of hydrogenation. In the first place the hydrochlorides of compounds IV, VI and XII are as resistant to hydrogenation as the corresponding free amines and in this case there is no increase in acetate ion concentration. Even more conclusively, catalytic hydrogenation of diosgenin acetate in the presence of an 8 *M* excess of potassium acetate resulted in complete conversion to dihydrotigogenin-3 monoacetate.

The inhibition of catalytic hydrogenation of the spiroketal side chain by propylamine is of some preparative interest. Nuclear double bonds are best hydrogenated in glacial acetic acid. For example, diosgenin can be rapidly converted to tigogenin in glacial acetic acid. The reaction proceeds sluggishly under less acidic conditions. Addition of propylamine to the reaction medium will permit facile reduction of nuclear double bonds in sapogenins without appreciable side chain attack. Similar considerations apply to the protection of the 3,5-cyclo moiety.

Experimental[19]

3β-Tigogenylamine (IV).—Tigogenone was treated with hydroxylamine hydrochloride by the procedure of Jacobs and Fleck[6] to give tigogenone oxime (III),[5] m.p. 254–256° (lit.[6] gives m.p. 256–258°) infrared spectrum (chloroform, concn. 25.0 g./l.) shows weak bands at 3570 and 3260 cm.$^{-1}$ (unassociated and associated OH stretching bands), weak band at 1655 cm.$^{-1}$ (C = N[9]) and typical 25D spiroketal side chain bands.[10a] A solution of tigogenone oxime, 1.0 g. in 120 ml. of ethanol, was heated to boiling and treated with 5.7 g. of sodium added in small portions over a 1–2-hour period. The solution then was refluxed 3 hours. Dilution with water followed by benzene extraction and chromatography on Florisil gave 0.7 g. of crude tigogenylamine which on crystallization from methanol gave 0.4 g. of crystals, m.p. 174–177°. The amine was characterized as the acetamide prepared in the usual manner by acetylation at room temperature with acetic anhydride in pyridine. After the usual work-up, methanol crystallization gave 3β-tigogenylacetamide (V), irregular plates, m.p. 282–285°, with sublimation at 200–220°, $[\alpha]^{25}D$ −68.0°, infrared spectrum shows bands at 3500 cm.$^{-1}$ (N-H stretching[9]), 1680 cm.$^{-1}$ (−C(=O)−NH[9]) and typical 25D spiroketal bands.[10a]

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.19; H, 10.35; N, 3.07. Found: C, 76.10; H, 10.43; N, 3.10.

3β-Tigogenylamine Hydrochloride.—The free amine, 0.2 g., in 200 ml. of ether was shaken with 25 ml. of 1.2 *N* hydrochloric acid. The crystalline precipitate which formed was filtered and recrystallized from ethanol–water (1–1 v./v.) giving 0.1 g. of plates, m.p. 244–246°, $[\alpha]^{25}D$ ethanol −42.0°.

3β-Diosgenylamine (VI).—Following procedures described for the ammonolysis of 3β-cholesteryl *p*-toluenesulfonate,[8a,b] 20.0 g. of 3β-diosgenyl *p*-toluenesulfonate (VII)[7] was heated with 150 ml. of liquid ammonia in a steel bomb for 72 hours at 100°. The bomb was cooled, opened, and the ammonia allowed to evaporate. The residue was dissolved in 500 ml. of ether, shaken with dilute hydrochloric acid, and the voluminous precipitate (fraction A) filtered and washed with ether giving 4.0 g. of insoluble hydrochloride A which was then taken up in aqueous ethanol, made alkaline and the free amine extracted with ether. The ether was allowed to evaporate and the crude diosgenylamine used for hydrogenation experiments. The crude amine mixture was purified and characterized by conversion to the acetamide in the usual manner. A sample of crude acetamide, 0.3 g., was crystallized from methanol giving 0.08 g. of a high melting, 251–257° (fraction C) and 0.22 g. of a lower melting fraction 187–204° (D). The high melting acetamide VIII (fraction C) was further purified by several crystallizations from methanol and *n*-heptane to give rods, m.p. 255–257°, $[\alpha]^{25}D$ −129°; infrared spectrum shows bands at 3440, 1688 cm.$^{-1}$, typical 25D-spiroketal bands, and bands at 836, 812 and 796 cm.$^{-1}$ (Δ^5-moiety in diosgenin[10a]).

Anal. Calcd. for $C_{29}H_{45}O_3N$: C, 76.43; H, 9.96; N, 3.07. Found: C, 76.50; H, 10.12; N, 3.14.

Conversion of 3β-Diosgenylacetamide (Fraction C) to 3β-Tigogenylacetamide.—A sample, 0.07 g., of fraction C in 40 ml. of ethanol containing 5% acetic acid was catalytically hydrogenated in the presence of 0.07 g. of Adams catalyst for 16 hours at 3 atmospheres pressure. The catalyst was removed, the solvent evaporated *in vacuo* and the residue crystallized from *n*-heptane giving 0.05 g. of 3β-tigogenylacetamide, m.p. 280–281°, with infrared spectrum identical with that of a specimen prepared from tigogenin oxime.

3α-Diosgenylacetamide (IX).—The low melting acetamide fraction D was purified by chromatography on Florisil. The fractions elutable with benzene were combined and crystallized repeatedly from *n*-heptane giving fine needles, m.p. 199–202°, $[\alpha]^{25}D$ −136°. Infrared spectrum shows all the basic features described for the 3β- isomer; however, the "fingerprint" region of the 3β- and 3α-isomers were completely different.

Anal. Calcd. for $C_{29}H_{45}O_3N$: C, 76.43; H, 9.96; N, 3.07. Found: C, 76.68; H, 10.21; N, 3.12.

3α-Tigogenylacetamide (X).—A sample of 0.1 g. of 3α-diosgenylacetamide was hydrogenated as described for 3β-diosgenylacetamide. The hydrogenation was crystallized from *n*-heptane giving 0.09 g. of needles, m.p. 278–280° with sublimation at 200–235°, $[\alpha]^{25}D$ −61°; infrared spectrum shows general bands similar to 3β-tigogenyl acetamide but a "fingerprint" spectrum markedly different from the latter.

Anal. Calcd. for $C_{29}H_{47}O_3N$: C, 76.19; H, 10.35; N, 3.06. Found: C, 75.92; H, 10.58; N, 3.01.

3,5-Cyclo-6β-diosgenylacetamide (XI) (E).—The ether-soluble amine hydrochloride (fraction B) precipitated on partial concentration of the ethereal solution. The precipitate was dissolved in aqueous ethanol, the solution made alkaline and extracted with benzene giving 1.43 g. of crude amine. Standard acetylation gave the acetamide E (XI), small rods from *n*-heptane, m.p. 203–205°, $[\alpha]^{25}D$ −59°. The infrared spectrum showed all the general bands described for the 3β- and 3α-diosgenylacetamides, except that the 836 cm.$^{-1}$ band indicative of Δ^5-unsaturation was absent and a distinct resolved peak at 3060 cm.$^{-1}$ was present.[17]

Anal. Calcd. for $C_{29}H_{45}O_3N$: C, 76.43; H, 9.96; N, 3.07. Found: C, 76.26; H, 10.24; N 3.15.

26-Hydroxy-5α,22ξ-furostane (26-Hydroxy-3-desoxydihydrotigogenin).—A solution of 0.3 g. of 3-desoxytigogenin (XIV) in 100 ml. of glacial acetic acid was hydrogenated for 3 hours at 3 atmospheres pressure in the presence of 0.3 g. of platinum oxide. After filtration of the catalyst, the solvent was evaporated *in vacuo* and the residue crystallized from petroleum ether, b.p. 30–60°, to give a crystalline product, m.p. 85–90°; infrared spectrum shows presence of a hydroxyl group and absence of spiroketal bands. The compound is not pure.

26-Hydroxy-3β-methyl-A-nor-5β,22ξ-furostane?—A sample of 0.3 g. of 3,5-cyclodiosgenin (XIII) was hydrogenated in manner described above. The reaction product was crystallized from petroleum ether to give 0.15 g., m.p. 66–75°; infrared spectrum shows presence of hydroxyl bands, absence of 3,5-cyclo band at 3060 cm.$^{-1}$ and absence of spiro-

(18) In the case of the inhibition of side chain hydrogenation of the 12β-aminosapogenin (11) or of the 3,5-cyclo group in the 6β-aminosapogenin (XII) we do not rule out the operation of a direct field effect in inhibiting the hydrogenolysis.

(19) Infrared spectra were obtained in carbon bisulfide solution and optical rotations in chloroform unless otherwise stated. All melting points were obtained with a Kofler micro melting point apparatus. We wish to thank C. T. Leander for infrared spectra, S. Serota for optical rotations, and R. H. Campbell for compound analyses.

ketal bands. The compound is probably impure. The fingerprint region of the infrared spectrum was quite different from the hydrogenation product of XIV.

Hydrogenation Experiments.—The standard reaction conditions involved shaking a solution of 0.1 g. of steroidal sapogenin plus 0.1 g. of steroidal amine or *n*-propylamine in 30 ml. of glacial acetic acid, or 0.1 g. of steroidal amine in 15 ml. of glacial acetic acid, with an equal weight of platinum oxide at room temperature and 3 atmospheres pressure for 3 hours or 25 hours. The catalyst was then removed and the solvent evaporated *in vacuo*. The residue was acetylated in the usual manner with pyridine and acetic anhydride and after standard work up the infrared spectrum of the total sample was obtained. Then in the case of mixtures of steroidal sapogenins and steroidal amines a sharp separation between the sapogenin acetate and the sapogenin acetamide could be obtained by chromatography on Florisil, the sapogenin acetate being much more easily eluted than the acetamide. In cases in which only the steroidal amine was hydrogenated, all pertinent data could be obtained from the infrared spectrum of the acetylated total reaction product. In this case absorption bands at 1735 cm.$^{-1}$ can come only from the acetylated C_{26}-hydroxyl formed as a consequence of side-chain opening. Since the O-acyl and N-acyl bands are well separated (1735 *vs.* 1680-1685 cm.$^{-1}$, respectively) the intensity of O-acyl bands can be estimated with reasonable accuracy. The intensity of the 1735 cm $^{-1}$ band of 3-desoxydihydrotigogenin acetate was used as a standard and the degree of side chain hydrogenation calculated from the intensity ratios. In cases involving only sapogenin acetates or mixtures in which the sapogenin had been previously separated from the amine by chromatography, the degree of side chain attack could be estimated by the decrease in intensity of the strong 982–985 cm.$^{-1}$.[10a] In the case of the 3,5-cyclosapogenins, all of the compounds studied, without regard to the nature of the 6β-substituent, had an infrared absorption band at 3060 cm.$^{-1}$ characteristic of methylene groups in the cyclopropane ring and found in all steroids with such structure.[17] Presence or absence of this infrared band provided a simple means of determining whether the 3,5-cyclo group had been hydrogenated. Other features of the molecule could be examined as described previously.

PHILADELPHIA 19, PENNA.

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The Chemistry of Polythienyls. II[1-3]

BY HANS WYNBERG AND A. BANTJES

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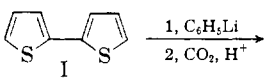
The acylation and metal–hydrogen interchange of 2,2′-bithienyl, 2,3′-bithienyl and 2,2′,5′,2″-terthienyl are described. The structures of the resulting products were determined by reductive desulfurization to aliphatic compounds. A formal total synthesis of *d,l*-muscone is recorded. An attempt is made to evaluate the directive influence of the thiophene ring.

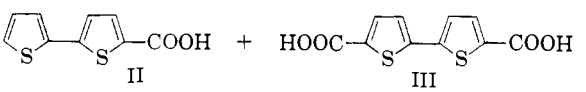
In order to determine the orienting affect of a thiophene ring *as a substituent* upon aromatic substitution reactions it becomes necessary to design a bi- or polyaryl in which the thiophene itself does not undergo substitution. Thus a phenylthiophene would be inadequate since substitution occurs in the thiophene ring.[4,5]

A biaryl possessing the desired characteristics would be a thienylfuran[6] since furan undergoes substitution reactions under milder conditions than those needed with thiophene. In the absence of such a biaryl, the bithienyls appear to be suited for a study of this kind. Consequently we have investigated the behavior of 2,2′-bithienyl (I),2,3′-bithienyl (VIII) and 2,2′,5′,2″-terthienyl (IV) under conditions of electrophilic substitution and of hydrogen–metal interchange.

The results with 2,2′-bithienyl were as expected—both acylation, which had been carried out previously[1], as well as hydrogen–metal interchange occurring in the 5- and 5′-positions, respectively



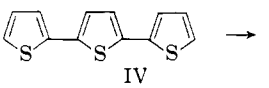
I



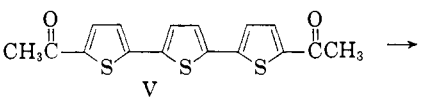
II III

Carbonation followed by acidification of the reaction mixture obtained from phenyllithium and 2,2′-bithienyl furnished the mono- and dicarboxylic acids II and III in high yields. The structures of II and III were proved by their conversion to nonanoic and sebacic acid, respectively.

The acylation of 2,2′,5′,2″-terthienyl (IV) likewise proceeded in a predictable fashion to furnish as major product 5,5″-diacetyl-2,2′,5′,2″-terthienyl(V). This structure was confirmed by desul-



IV



V

VI

furization followed by oxidation to the known[7] 2,15-hexadecanedione (VI), which has been used by Stoll in his synthesis of muscone.

(1) For the first paper in this series see H. Wynberg, A. Logothetis and D. VerPloeg, THIS JOURNAL, **79**, 1972 (1957).

(2) Part of this work was supported by the Office of Ordnance Research, Contract No. DA-01-009-ORD-500.

(3) From the doctoral dissertation of A. Bantjes.

(4) A. Chrzaszczewska, *Roczniki Chem.*, **5**, 1,33 (1925); *C. A.*, **20**, 1078 (1926); A. S. Broun and M. G. Voronkov, *Doklady Akad. Nauk (USSR)*, **59**, 1293 (1941); *C. A.*, **43**, 2614 (1949); W. Steinkopf and H. J. Petersdorff, *Ann.*, **543**, 119 (1940).

(5) Some doubt has been thrown upon the assignment of structures resulting from substitution reactions with phenylthiophenes by I. V. N. Ivanov, *Zhur. Obschei Khim.*, **28**, 1232 (1958).

(6) The preparation of 3-thienylfuran has recently been reported by us (H. Wynberg and G. Schollmann, Abstracts of Papers, Division of Organic Chemistry, 135th National Meeting American Chemical Society Boston, Mass., April 5–10, 1959, p. 75-O).

(7) M. Stoll and A. Rouve, *Helv. Chim. Acta*, **30**, 2019 (1947).