anol solution with a view to obtaining 3-aza-3-methylbicyclo [3,3,1] nonan-9-one (III). When relatively concentrated solutions of the reactants in methanol were employed, instead of the desired cyclic product III, I was isolated. Replacement of cyclohexanone with 3-methylcyclohexanone and 4-methylcyclohexanone gave the corresponding bis derivatives. When condensations were effected in dilute solutions in methanol so as to favor the formation (intramolecular rather than bis formation) of III, no crystalline products were isolated.

EXPERIMENTAL[4]

Reaction 1: methyl-bis(2-cyclohexanonylmethyl)amine (I). To 3.88 g. of 40% methylamine (4.4 ml., 0.05 mole) in 15 ml. methanol was added dropwise, with agitation, at 15–18°, 7.5 ml. 37% formaldehyde (0.1 mole) dissolved in 10 ml. methanol. A solution of 9.8 g. of cyclohexanone (10.4 ml., 0.1 mole) in 25 ml. methanol was added with shaking, followed by the dropwise addition of 4.2 ml. 37% hydrochloric acid (0.05 mole). The flask was stoppered, shaken well for 2 min. and set aside at room temperature (25–28°) for 22 hr. The solution was decanted to a beaker and placed under a hood for 24 hr. The remaining liquid was treated with 25 ml. water and extracted with two 25 ml. portions of ether. The ether extracts were distilled at 34–35°, 755 mm. pressure, leaving only a trace of higher boiling material. To the aqueous extract after cooling on an ice bath was added 3.05 g. monoethanolamine (3 ml., 0.05 mole). A cloudiness appeared and after 3 hr. standing 4.78 g. white product, m.p. 152–161°, was removed by filtration. An additional 0.9 g. was obtained from the filtrate. The total crude yield was 45.2%. After five recrystallizations from ethyl acetate the compound melted at 163.5–164°.

Anal. Calcd. for $C_{15}H_{25}NO_2$: C, 71.64; H, 10.01; N, 5.57. Found: C, 71.52; H, 9.71; N, 5.60.

When reaction 1 was repeated using 4.9 g. cyclohexanone (0.05 mole) instead of 0.1 mole, 2.49 g., 39.6% yield, of I was obtained. When the latter condensation was repeated using a total of 500 ml. methanol instead of 50 ml., no crystalline product was isolated.

When reaction 1 was repeated using 3.38 g. methylaminehydrochloride (0.05 mole) in lieu of the 40% methylamine and hydrochloric acid, 2.38 g. of I, 18.9% yield, was isolated.

When reaction 1 was repeated but omitting the addition of 4.2 ml. 37% hydrochloric acid, no crystalline product was isolated.

When reaction 1 was repeated using 0.05 mole quantities of methylamine, formaldehyde, cyclohexanone, and hydrochloric acid, 1.94 g. of I, 30.9% yield, was obtained. When the latter reaction was repeated using 0.1 mole quantities of methylamine, formaldehyde, and hydrochloric acid, and 0.05 mole cyclohexanone, 3.48 g. of I, 55.4% yield, was secured.

Reaction 2: Methyl-bis(4-methyl-2-cyclohexanonylmethyl)-aminehydrochloride (IV). To 7.78 g. of 40% methylamine (8.8 ml., 0.1 mole) in 60 ml. of methanol at 15–18° was added 8.36 ml. 37% hydrochloric acid (0.1 mole). Over a period of 3 min. 15 ml. 37% formaldehyde (0.2 mole) was added with agitation. After adding 22.4 g. 4-methylcyclohexanone (24.6 ml., 0.2 mole), the resulting solution was gently refluxed for 2 hr. on a water bath. The solution was decanted to a beaker and placed under a hood to remove the solvents. The resulting solution was treated with 40 ml. water and 16.7 ml. concentrated hydrochloric acid. Small particles of white solid began to separate. After standing for 3 hr. 3.11 g., m.p. 185–187°, white solid was removed by filtration. The filtrate was extracted with three 15 ml. portions of ether, which after drying and distillation gave but a trace of high boiling material. The aqueous extracts after standing 2 days gave an additional 2.18 g. white solid, m.p. 185–187°. The total crude yield was 5.29 g. or 16.9%. Upon two recrystallizations from *n*-butyl alcohol, the hydrochloride melted at 193–195°.

Anal. Calcd. for $C_{17}H_{30}ClNO_2$: C, 64.64; H, 9.57; Cl, 11.22; N, 4.43. Found: C, 64.65; H, 9.69; Cl, 11.10; N, 4.22.

Repetition of reaction 2 in which the reactants were allowed to stand 46 hr. at 25–28° instead of refluxing for 2 hr. gave 6.17 g. of IV or 19.7% yield.

Methyl-bis(5-methyl-2-cyclohexanonylmethyl)amine or methyl-bis(3-methyl-2-cyclohexanonylmethyl)amine. (The structure of the compound is being investigated.) Repetition of reaction 1 using 0.1 mole of 3-methylcyclohexanone in lieu of 0.1 mole of cyclohexanone gave 1.45 g. white product, m.p. 164.5–166°, 10.5% yield.

Anal. Calcd. for $C_{17}H_{29}NO_2$: C, 73.07; H, 10.45; N, 5.01. Found: C, 72.80; H, 10.33; N, 5.15.

Each of the condensations mentioned above has been repeated at least five times with essentially the same yields.

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(4) Melting points are uncorrected.

2-Keto-1-methyl-$\Delta^{1(8)}$-tetrahydroindan[1]

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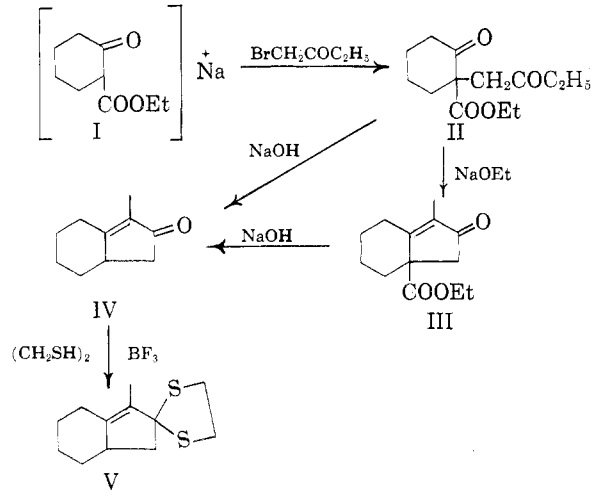
A synthesis of 2-keto-$\Delta^{1(8)}$-tetrahydroindan has been described in which sodio-2-carbethoxycyclohexanone (I) was alkylated with propargyl bromide, the triple bond hydrated, and the resulting diketoester cyclized and decarboxylated to yield the ketone in a 45% over-all yield.[2] This three step synthesis was evidently necessary as the authors reported that chloroacetone would not alkylate I. In an attempt to prepare the corresponding 1-methyl homolog (IV) it was found that 1-bromobutan-2-one was reactive enough toward I to give the diketoester (II) which was converted to the desired ketone (IV) in an over-all yield of 42%. The diketoester (II) was also cyclized with sodium ethoxide to the unsaturated ketoester (III) and then saponified and decarboxylated to give IV.

(1) This work was supported by institutional grants to the Detroit Institute of Cancer Research from the American Cancer Society, Inc., The American Cancer Society, Southeastern Michigan Division, and the Kresge Foundation.

(2) A. M. Islam and R. A. Raphael, *J. Chem. Soc.*, 4086 (1952).

Attempts to convert the carbonyl function of IV into a methylene group were unsuccessful by the attempted desulfurization of the ethylene thioketal (V) with various activities of Raney nickel. The ketone (IV) was reduced with lithium aluminum hydride without dehydration but attempts to prepare either the mesylate or tosylate (−20°) gave dark brown intractable tars.



EXPERIMENTAL[3]

2-(2'-Oxo-1'-butyl)-2-carbethoxycyclohexanone (II). To a stirred suspension of 10.4 g. (0.45 mole) of sodium hydride in 400 cc. of dry benzene under an atmosphere of nitrogen and at room temperature, was added dropwise 85 g. (0.5 mole) of 2-carbethoxycyclohexanone. After 2 hr. additional stirring, 68 g. (0.45 mole) of 1-bromobutan-2-one[4] was added dropwise and the mixture stirred overnight. Since there had been no appreciable thinning of the paste, the temperature of the mixture was raised to 80° for 22 hr. The product was worked up with ice and acetic acid and isolated by ether extraction. The dried residual brown oil was distilled through a Vigreux column (14 × 1 cm.) and *ca.* 10 cc. of unreacted keto ester was collected at 110–113°, and 20 mm. The product (II) distilled as a light yellow oil, b.p. 125–130° at 0.4 mm.; yield, 55 g. (57%). A center cut was redistilled for analysis, b.p. 115–117° at 0.2 mm., and was nearly colorless; n_D^{25} 1.4711; $\lambda_{max}^{CHCl_3}$ 5.80 and 5.86 μ.

Anal. Calcd. for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 64.86; H, 8.38.

The crude *bissemicarbazone* melted at 195–200°. It was recrystallized from dimethylformamide, washed with ether and vacuum dried, m.p. 198.8–200.0°.

Anal. Calcd. for $C_{15}H_{26}N_6O_4$: C, 50.83; H, 7.40; N, 23.72. Found: C, 50.91; H, 7.64; N, 23.84.

2-Keto-1-methyl-$\Delta^{1(8)}$-tetrahydroindan (IV). A mixture of 10 g. of II, 30 cc. of ethanol and 50 cc. of 5% sodium hydroxide was refluxed under nitrogen overnight. After cooling and neutralization the product was taken up in ether and washed well with water to remove excess alcohol. The dried residual oil was distilled through a micro column (32 × 1 cm.) and, after a few drops of a forerun, the product (IV) distilled at 74–81° and 1 mm.; yield, 4.60 g. (74%). A center cut exhibited n_D^{25} 1.5168; $\lambda_{max}^{alc.}$ 239 mμ, ϵ 18,150; $\lambda_{max}^{CHCl_3}$ 5.90 and 6.08 μ (reported,[2] for 2-keto-$\Delta^{1(8)}$-tetrahydroindan, $\lambda_{max}^{alc.}$ 228 mμ, ϵ 16,500).

Anal. Calcd. for $C_{10}H_{14}O$: C, 79.95; H, 9.39. Found: C, 79.63; H, 9.40.

The *2,4-dinitrophenylhydrazone* recrystallized from ethyl acetate–ethanol as red plates, m.p. 195.2–196.0° dec.

Anal. Calcd. for $C_{16}H_{18}N_4O_4$: C, 58.17; H, 5.49; N, 16.96. Found: C, 58.58; H, 5.58; N, 17.24.

The *semicarbazone* was recrystallized from ethanol to give stout needles, m.p. 204.6–206.0° dec.

Anal. Calcd. for $C_{11}H_{17}N_3O$: C, 63.74; H, 8.27; N, 20.27. Found: C, 63.63; H, 8.25; N, 20.52.

9-Carbethoxy-2-keto-1-methyl-$\Delta^{1(8)}$-tetrahydroindan (III). The addition of 47 g. of II to a solution prepared by dissolving 6.8 g. of sodium in 300 cc. of absolute ethanol gave a cherry red color. After 2 hr. at room temperature, the mixture was decomposed with acetic acid and the product taken up in ether. Washing with water and then saturated bicarbonate solution removed 13 g. (30–35%) of some acidic material. The dried neutral fraction on concentration weighed 28 g. (65%) and was distilled through the Vigreux column described above. The first fraction consisted primarily of the ketone IV as judged by its boiling point and infrared spectrum, b.p. 70–75° at 0.4 mm.; yield, 1.1 g. (4%). Fraction two, b.p. 75–130° at 0.4 mm., consisted mostly of the unsaturated ketoester (III); yield, 16.2 g. (39%). A third fraction, b.p. 135–140° at 0.4 mm., was recovered II; yield, 8.41 g. (18%).

The second fraction was redistilled as a very light yellow oil and a center cut taken for analysis, b.p. 105–107° at 0.3 mm.; n_D^{25} 1.5018; $\lambda_{max}^{alc.}$ 239 mμ, ϵ 13,940; $\lambda_{max}^{CHCl_3}$ 5.80, 5.88 and 6.05 μ.

Anal. Calcd. for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16. Found: C, 69.85; H, 8.34.

Saponification with 5% sodium hydroxide in 50% aqueous ethanol gave IV, n_D^{25} 1.5171. The 2,4-dinitrophenylhydrazone was identical with the one prepared above as judged by a mixture melting point determination, which was not depressed.

No further attempt was made to improve the yield of IV from III as a satisfactory yield may be obtained directly from II as described above.

Ethylenethioketal of 2-keto-1-methyl-$\Delta^{1(8)}$-tetrahydroindan (V). To a mixture of 10.0 g. of IV and 25 cc. of ethanedithiol, at room temperature, was added 3 cc. of boron trifluoride ethereate which produced an immediate discoloration. After 2 days the tan two-phase mixture was diluted with ether, washed with water, saturated sodium bicarbonate, saturated sodium chloride solution, dried over magnesium sulfate and concentrated. The excess of ethanedithiol was removed *in vacuo* at about 40° and the yellow residual oil was frozen on dry ice. Trituration with dry ether and filtration gave the crude thioketal (V) as a colorless solid, m.p. 60–65°; yield, 8.85 g. (59%). A second crop, m.p. 57–59°, weighed 2.2 g. (15%) and a third crop, m.p. 62–67°, weighed 0.85 g. (5%) and brought the total yield to 79%.

The analytical sample was recrystallized from methanol as large plates, m.p. 66.0–67.4°.

Anal. Calcd. for $C_{12}H_{18}S_2$: C, 63.61; H, 8.01; S, 28.32. Found: C, 63.63; H, 8.13; S, 28.07.

Refluxing overnight 6.7 g. of V with ca. 50 g. of freshly prepared W-2 Raney nickel in 300 cc. of acetone, filtration, and concentration gave a brown oil, 4.6 g. An attempted distillation gave only a few drops of an oil, b.p. 56–60° at 15 mm., with decomposition of the pot residue. Other

(3) The melting points of the analytical samples were taken with uncalibrated Anschutz thermometers. The crude melting points and boiling points are not corrected. Analyses by Micro-Tech Laboratories, Skokie, Ill. The infrared spectra were determined in chloroform using a Perkin-Elmer, Model 21, spectrophotometer.

(4) J. R. Catch, D. F. Elliott, D. H. Hey, and E. R. H. Jones, *J. Chem. Soc.*, 272 (1948). The bromination of methyl ethyl ketone gave a mixture of primary and secondary bromides. For this work, the mixture was separated by fractionation through a Widmer column to give the desired isomer. The b.p., 104–108° at 140 mm., was 15° above that of the secondary bromide.

Raney nickels of different activity either returned crystalline V or resulted in complete decomposition.

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Steroidal Sapogenins. XLI. Willagenin, a New 12-Keto Sapogenin[1,2]

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In the course of our investigations of the plant kingdom for steroidal sapogenins[3a,b,c] we have isolated a new sapogenin in low yield from *Yucca filifera*.[4] We wish to call this sapogenin willagenin.[5] This paper describes our investigations on the structure of willagenin.[6]

Extraction of the saponins from *Yucca filifera* sawdust[4] by our usual procedure[7] followed by acid hydrolysis gave a crude sapogenin mixture. Infrared analysis indicated that the chief constituent was sarsasapogenin and that there was also a minor ketonic impurity. Treatment of the sapogenin mixture with Girard's reagent T resulted in isolation of the ketonic fraction, willagenin, in pure form. Treatment with acetic anhydride gave a mono-acetate with a carbon and hydrogen analysis corresponding to $C_{29}H_{44}O_5$.

The infrared spectrum of willagenin acetate, shown in Fig. 1, gave valuable clues to the structure of this sapogenin. Thus the bands at 986(S), 919(S), 895(W) and 850 cm.$^{-1}$(M) showed that the sidechain was in the 22b (25L) series.[8,9] The split bands at 1252 cm.$^{-1}$ and 1234 cm.$^{-1}$ indicated that willagenin might have the ring A/B *cis* fusion in conjunction with a 3β-acetate.[10] The two strong bands at 1735 and 1708 cm.$^{-1}$ showed, respectively, a monoacetate and a ketone, possible at C_{12}.[11]

Wolff-Kishner reduction of willagenin gave sarsasapogenin (20α,22a,25L-spirostan-3β-ol), confirming the structural considerations deduced from the infrared data. All the structural features of willagenin were now clarified except for the location of the carbonyl group.

Since willagenin reacted with Girard's reagent T and could be reduced by the Huang-Minlon modification[12] of the Wolff-Kishner reduction, the carbonyl could not be C_{11}. The location of the infrared band at 1708 cm.$^{-1}$ narrowed the choice of carbonyl positions to C_1, C_2, C_4, C_6, C_7, and C_{12}.[13]

Using the method of molecular rotation differences[14] the contribution of the ketonic group in willagenin and its acetate was found to be +333 and +314, respectively.[15] The high positive values obtained strongly suggest that the location for the carbonyl group is C_{12}.[16] Thus, willagenin probably has the structure 3β-hydroxy-20α,22a,25L-spirostan-12-one.

The isolation of willagenin adds another link in the biogenetic pattern of steroidal sapogenins in the 5-n, 25L series. The other members in this series are the well known sarsasapogenin, found as a major component in many Yucca species[3a,b,c] and its recently discovered dihydroxy analog, markogenin.[17] The isomeric 5-n, 25D series includes smilagenin (3β-hydroxy), samogenin (2β, 3β-dihydroxy) and mexogenin (2β,3β-dihydroxy-12 ketone). The latter two were discovered in nature by Marker[18] and the location of the 2β-hydroxyl was clarified by Djerassi.[19] The last remaining member in this series (3β-hydroxy-12 ketone) has not

(1) Paper XL, "Simplified Procedure for the Qualitative Detection of Cardiac Glycosides," M. M. Krider, H. A. Monroe, M. E. Wall, and J. J. Willaman; presented at 130th National Meeting, AMERICAN CHEMICAL SOCIETY, Atlantic City, N. J., September 16–21, 1956.

(2) Article not copyrighted.

(3a) M. E. Wall *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 1 (1954); (b) *J. Am. Pharm. Assoc.*, **43**, 503 (1954); (c) *J. Am. Pharm. Chem. Assoc.*, **44**, 438 (1955).

(4) We wish to thank Mr. Rafael Rojas Gutierrez, Director General, Laboratorios Nacionales de Fomento Industrial, Mexico, D. F., for supplying us with plant material. Mr. Rojas informs us that the plant material used in our investigations came from a species identified as *Yucca filifera* Chabaud by Dr. Bassett Maguire, New York Botanical Gardens. *Y. filifera* grows at an altitude of 1000–1500 meters in Mexican arid zones. Dry stems from this species were sawed into chips. The sawdust obtained during the chipping process was the material sent to us for analysis by Mr. Rojas.

(5) In honor of Dr. J. J. Willaman, Head, Biochemical Section, Eastern Regional Research Laboratory, who has initiated and constantly encouraged plant chemical investigations at this laboratory.

(6) On account of the small quantity of pure material available many of the structural assignments were based on physical data.

(7) M. E. Wall, M. M. Krider, E. S. Rothman, and C. R. Eddy, *J. Biol. Chem.*, **198**, 533 (1952).

(8) M. E. Wall, C. R. Eddy, M. L. McClennan, and M. E. Klumpp, *Anal. Chem.*, **24**, 1337 (1952).

(9) R. N. Jones, E. Katzenellenbogen, and K. Dobriner, *J. Am. Chem. Soc.* **75**, 158 (1953).

(10) R. N. Jones, P. Humphries, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, **73**, 3215 (1951).

(11) R. N. Jones, P. Humphries, and K. Dobriner, *J. Am. Chem. Soc.*, **71**, 241 (1949); **72**, 956 (1950).

(12) Huang-Minlon, *J. Am. Chem. Soc.*, **71**, 3301 (1949).

(13) R. N. Jones and F. Herling, *J. Org. Chem.*, 19, 1252 (1954).

(14) D. H. R. Barton and W. Klyne, *Chemistry & Industry*, 755 (1948).

(15) M_D willagenin − M_D sarsasapogenin = +22 − (−312) = +333 M_D willagenin acetate − M_D sarsasapogenin acetate = −5 − (−319) − +314.

(16) Barton and Klyne, reference 14, give the following values for the molecular rotation contributions of ketones: C_1 = +67, C_2 = +98, C_4 = +25, all 5-allo series; C_6 (5n) = −224, C_{12} (5n + 5 allo) = +270.

(17) M. E. Wall, C. R. Eddy, S. Serota, and R. F. Mininger, *J. Am. Chem. Soc.* **75**, 4437 (1953).

(18) R. E. Marker *et al.*, *J. Am. Chem. Soc.*, **69**, 2167 (1947).

(19) C. Djerassi and J. Fishman, *J. Am. Chem. Soc.*, **77**, 4291 (1955).