TABLE I

PHYSICAL AND ANALYTICAL DATA FOR SUBSTITUTED BENZOIC ACIDS

R	M. p., °C.[a]	Yield, %	Analyses, % Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
H-	120–121	94.0	68.85	68.65	4.90	4.88
p-Chloro-	237–238	93.9	53.79	53.66	3.19	3.41
m-Chloro-	154–156	95.6	53.79	53.70	3.19	3.29
o-Chloro-	140–141	95.0	53.79	53.73	3.19	3.32
m-Nitro-	139–140	70.6	50.33	50.39	3.01	3.23
m-Amino-	173–174	72.2	61.32	61.41	5.15	5.01
m-Hydroxy-	Ca. 200	79.2	60.81	60.69	4.03	3.81
2-Chloro-5-nitro-	165–166	83.0	41.52	41.71	1.99	2.11
3-Nitro-4-chloro-	180–182	87.3	41.52	41.80	1.99	2.17

[a] All melting points are uncorrected.

Trifluoromethylaryls.—With the exception of *m*-hydroxybenzotrifluoride, all trifluoromethylaryls were obtained through the courtesy of the Hooker Electrochemical Company and were used without further purification. The *m*-hydroxybenzotrifluoride was easily prepared by conversion of *m*-aminobenzotrifluoride through the diazonium transformation.

Hydrolysis of Benzotrifluoride.—A mixture of 36.5 g. (0.25 mole) of benzotrifluoride and 28 g. of 100% sulfuric acid was heated cautiously until the evolution of hydrogen fluoride began as could be detected by its etching of the glass walls of the reaction vessel. The heat source then was withdrawn and reapplied intermittently until the benzotrifluoride layer disappeared. After the evolution of hydrogen fluoride had ceased, the reaction mixture was poured, with stirring, into 1 l. of ice-water, the resultant precipitate sucked dry, and finally washed thoroughly with cold water. The crude product was purified through its sodium salt using Norit, and the free acid was recrystallized from hot water.[7] This procedure is typical for the series investigated.

Using 80% sulfuric acid the starting material is recovered unchanged after refluxing for several hours, while with 20–30% fuming sulfuric acid small amounts of sulfones and sulfonic acids are formed. Prolonged or excessive heating gives rise to tars. Occasionally it is difficult to initiate the reaction. In these cases, the addition of small amounts of 20–30% oleum portionwise is effective. *m*-Nitrobenzotrifluoride in particular is subject to this difficulty and with it 15% oleum must be used for the reaction to take place.

Since 65% fuming sulfuric acid is required to effect satisfactory sulfonation of trifluoromethylaryls,[8] probably because of the strong inductive effect of the meta-directing CF_3– group, it is apparent that the rate of sulfonation is far slower than attack of the CF_3– group. This competitive situation accounts for the appearance of sulfur-containing by-products only at the higher concentrations of sulfur trioxide.

Acknowledgments.—The author expresses appreciation to Dr. K. M. Seymour and Mr. P. G. Scheurer for their helpful suggestions.

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[7] Only traces of fluorine and no sulfur or chlorine could be detected by the usual qualitative tests.

[8] Zitscher, U. S. Patent 2,141,893 (Dec. 27, 1938).

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Steroidal Sapogenins. 174. 17-Hydroxy-20-ketopregnanes from Steroidal Sapogenins

BY RUSSELL E. MARKER[1]

In the synthesis of cortisone and its analogs the introduction of a hydroxyl group on the C-17 carbon of the pregnanes is quite complicated and involved leading to low yields. A new and very simple reaction has now been found in which this can be accomplished in high yield from naturally occurring steroidal sapogenins containing ketonic groups on C-12. As sapogenins occur widely distributed in nature, they now present a large potential source of material for this synthesis.

Treatment of the oxidation product of the diacetate of pseudobotogenin with a dilute methanolic solution of potassium carbonate gives an immediate precipitation of the acetate of 16-dehydropregnen-5-ol-3-dione-12,20 removing it from further action with the alkaline solution.[2] A small amount of a secondary product resulting from this reaction was further studied. It has now been found that this new material is the major product of the hydrolysis if alcoholic potassium hydroxide is employed instead of dilute methanolic potassium carbonate. In this case the product does not precipitate during the reaction. The same product was obtained when 16-dehydropregnen-5-ol-3-dione-12,20 acetate was treated with alcoholic potassium hydroxide. The new product analyzes for a pregnendioldione, containing two hydroxyl groups, only one of which acetylates with boiling acetic anhydride. It is recovered unchanged when shaken with hydrogen and palladium catalyst, showing that it does not contain the conjugated double bond system. These reactions indicate that the new hydroxyl group was introduced in the 17-position as a tertiary carbinol. A secondary hydroxyl group on C-16 would readily form an acetate under the conditions employed. Whether the formation of a 17-hydroxyl group in the conjugated ketone system by alkali is characteristic only of pregnenes containing a ketone group in the beta-position at C-12 has not been determined but present indications are that the addition of water to the 16-double bond is influenced by the presence of a C-12 ketone in the molecule. In the strong alkaline hydrolysis of the oxidation product, the first product formed is probably the expected 16-dehydropregnene which then hydrates under the influence of alkali to give the 17-hydroxy compound.

Because of the significance of this reaction in the preparation of cortisone or its analogs from steroidal sapogenins, it has been applied to kammogenin, another possible starting material for the antiarthritic hormone. This sapogenin is now known to occur in many plants and new sources for it and the other steroidal sapogenins will be reported at a later date.

Pseudokammogenin triacetate[3] was oxidized as described for pseudobotogenin diacetate.[2] Treatment of the oxidation product with alcoholic potassium hydroxide gave a diketopregnene containing three hydroxyl groups, only two of which are acetylatable. The product cannot be

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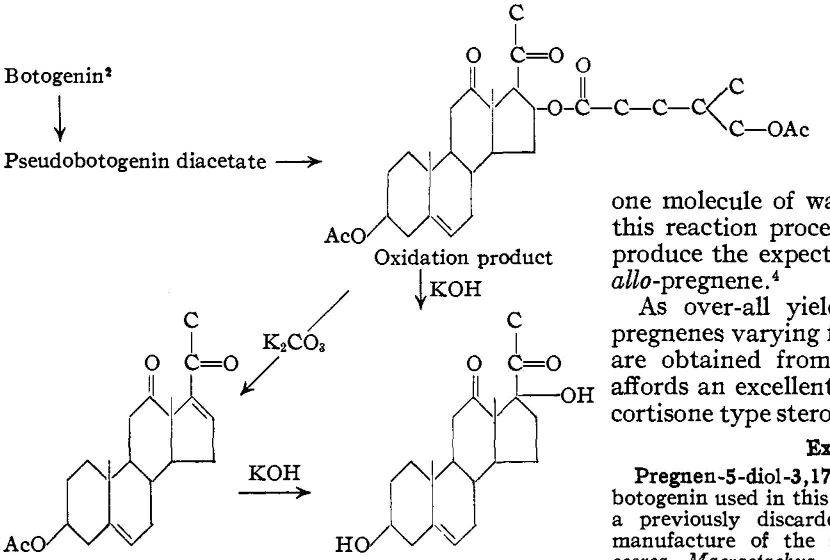
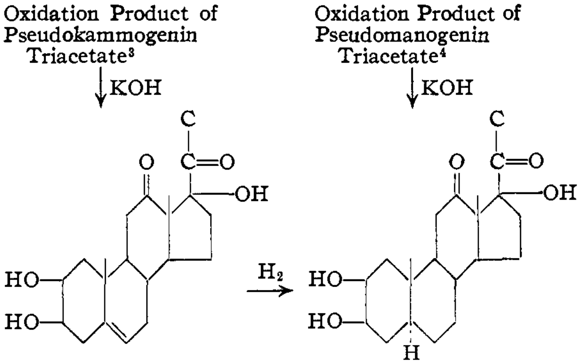
[1] Present address: Hotel Geneve, Mexico City, Mexico.

[2] Marker, THIS JOURNAL, 71, 2656 (1949).

[3] Marker and Lopez, *ibid.*, 69, 2373, 2375 (1947).



reduced by hydrogen using palladium catalyst, indicating absence of the C-16 double bond and that a new hydroxyl group was introduced as described above to form pregnen-5-triol-2,3,17-dione-12,20. Mild catalytic reduction using hydrogen and platinum oxide catalyst saturated the double bond in the 5-position. This product was identical with the product obtained by the alkali treatment of the oxidation product of the triacetate of pseudomanogenin followed by acetylation, which also contains a hydroxyl group that does not form an acetate.



It was previously reported[2] that *allo*-pregnantrione-3,12,20 was formed by the reduction of pregnen-5-ol-3-dione-12,20 (erroneously this should have read *16-dehydro*-pregnen-5-ol-3-dione-12,20) followed by mild oxidation.[2] The material actually used was the alcoholic potassium hydroxide hydrolysis product of the acetate of 16-dehydropregnen-5-ol-3-dione-12,20, which has now been shown to give the 17-hydroxypregnene instead of the expected 16-dehydropregnene. Analysis of the triketone produced in this reaction shows it to be 17-hydroxy-*allo*-pregnantrione-3,12,20 containing a tertiary hydroxyl group which does not acetylate. This product is identical with the triketone produced from the oxidation product of pseudohecogenin followed by strong alkaline hydrolysis. Previously it was assumed from the analysis that this was a triketone containing one molecule of water of crystallization and that this reaction proceeded in its normal manner to produce the expected 16-dehydro-3,12,20-triketo-*allo*-pregnene.[4]

As over-all yields of the 17-hydroxy-20-keto-pregnenes varying from 40–55% on a weight basis are obtained from the 12-keto-sapogenins, this affords an excellent method for the production of cortisone type steroids.

Experimental Part

Pregnen-5-diol-3,17-dione-12,20 from Botogenin.—The botogenin used in this work was prepared from ricogenin,[5] a previously discarded by-product in the commercial manufacture of the steroidal sex hormones from *Dioscorea Macrastachya* in Mexico. The crude oxidation product of pseudobotogenin diacetate, prepared from 5 g. of botogenin acetate[2] was refluxed for thirty minutes with 500 cc. of 3% alcoholic potassium hydroxide. Water was added and the product was extracted with a large volume of ether. Upon concentration to a small volume the material crystallized. It was recrystallized from ether, m. p. 258–260°; yield 2.7 g.

Acetylation with boiling acetic anhydride followed by crystallization from ether gave a mono-acetate, m. p. 232–234°. Mixed with the acetate of 16-dehydro-pregnen-5-ol-3-dione-12,20 it gave a depression of 15–22°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.1; H, 8.3. Found: C, 71.4; H, 8.7.

Hydrolysis of the acetate with alcoholic potassium hydroxide followed by crystallization from ether gave the above unacetylated product, m. p. and mixed m. p. 258–260°.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.8. Found: C, 72.6; H, 8.7.

A solution of 1 g. of the acetate of 16-dehydro-pregnen-5-ol-3-dione-12,20 in 100 cc. of 3% alcoholic potassium hydroxide was refluxed for one hour. The product was crystallized from ether to give pregnen-5-diol-3,17-dione-12,20, m. p. and mixed m. p. with the above product, 258–260°. Acetylation of this product followed by crystallization from ether gave the 3-acetate of pregnen-5-diol-3,17-dione-12,20, m. p. and mixed m. p. with the above mono-acetate, 232–234°.

Anal. Calcd. for $C_{23}H_{32}O_5$: C, 71.1; H, 8.3. Found: C, 71.4; H, 8.5.

***allo*-Pregnanol-17-trione-3,12,20.**—The preparation of this product was previously reported[2] but erroneously the starting material used in the experiment should have read *16-dehydro*-pregnen-5-ol-3-dione-12,20. This was prepared by alcoholic potassium hydroxide hydrolysis of the acetate of 16-dehydro-pregnen-5-ol-3-dione-12,20 which has now been shown to add water to its 16-double bond to form a new C-17 tertiary hydroxyl group. It melted at 262–264° and gave no depression in melting point when mixed with the same product prepared by alcoholic potassium hydroxide hydrolysis of the oxidation product of pseudohecogenin as previously described.[4] It is unaffected by boiling acetic anhydride.

Anal. Calcd. for $C_{21}H_{30}O_4$: C, 72.8; H, 8.8. Found: C, 72.8; H, 8.6.

Pregnen-5-triol-2,3,17-dione-12,20 from Kammogenin.—To a solution of 2 g. of pseudokammogenin triacetate[3]

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[4] Marker and co-workers, THIS JOURNAL, **69**, 2167 (1947).

[5] Marker, *ibid.*, **71**, 3856 (1949).

in 100 cc. of glacial acetic acid was added a solution of 800 mg. of chromic anhydride in 10 cc. of 90% acetic acid keeping the temperature at 20°. After standing thirty minutes water was added and the product was extracted with ether. The solvent was removed and the residue was refluxed for thirty minutes with 100 cc. of 3% alcoholic potassium hydroxide. Water was added, the solution was neutralized and the product was filtered and washed with water. It was recrystallized from ether, m. p. 275–278°, yield 0.9 g.

Anal. Calcd. for $C_{21}H_{30}O_5$: C, 69.6; H, 8.4. Found: C, 70.0; H, 8.6.

Acetylation with boiling acetic anhydride followed by crystallization from ether gave a diacetate, m. p. 264–265°. Upon shaking with hydrogen and palladium catalyst in ethyl acetate the product was recovered unchanged.

Anal. Calcd. for $C_{25}H_{34}O_7$: C, 67.1; H, 7.7. Found: C, 67.4; H, 7.8.

A solution of 200 mg. of the above diacetate in 25 cc. of acetic acid containing 100 mg. of platinum oxide catalyst was shaken with hydrogen at 40 pounds pressure for fifteen minutes. After filtration, water was added and the product was extracted and crystallized from ether, m. p. 265–267°. It gave no depression in melting point when mixed with the 2,3-diacetate of *allo*-pregnantriol-2,3,17-dione-12,20 prepared from the potassium hydroxide hydrolysis of the oxidation product of pseudomanogenin triacetate followed by acetylation. Mixtures of both products with the unreduced diacetate from kammogenin gave depressions in melting point of 12–18°.

Anal. Calcd. for $C_{25}H_{36}O_7$: C, 66.8; H, 8.1. Found: C, 67.0; H, 8.4.

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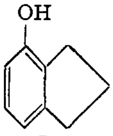
Partition Studies on Phenols. III. Steric Effects

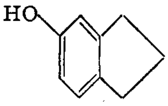
BY MILTON ORCHIN[1] AND CALVIN GOLUMBIC[1]

It has been previously suggested that the partition coefficient of a phenol between water and an organic phase provides a sensitive index of the degree of steric hindrance around the phenolic group.[2] This arises from the fact that an important factor affecting the solubility of a phenol in the aqueous phase often is the degree of hydrogen bonding between the phenol and the water molecules; if the approach to the phenolic group is sterically inhibited, hydrogen bonding and, hence, solubility in water is reduced.

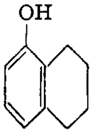
Arnold and co-workers have shown in a series of papers[3] that the relative steric influence of methylene groups in six-membered rings is greater than that of five-membered rings. In the course of our investigations on partition coefficients, we have obtained information on the same subject.



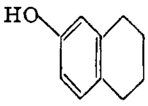
I



II



III



IV

The partition coefficients of the indanols, I and II, and the tetrahydronaphthols, III and IV, were determined in the system cyclohexane–water (Table I). The partition coefficient (*k*) of 5-hydroxy-1,2,3,4-tetrahydronaphthalene, III, is 5.6 times that of 4-indanol, I. It would be expected, of course, that III would have less solubility in water than I solely on the basis of its greater molecular weight, but that III's high partition coefficient is due mainly to steric inhibition of hydrogen bonding is shown by comparison with its isomer IV, the hydroxyl group of which is unhindered. The ratio of partition coefficients of IV/I is only 1.9 as compared to III/I of 5.6. These results agree with Arnold's contention that methylene groups in five-membered rings offer less steric hindrance than those in six-membered rings. Further evidence of the correctness of this view is provided by the infrared specta of I and III in the hydroxyl group region. The spectrum of I shows a rather broad band at 2.93μ, while that of III shows only a weak shoulder at 2.91μ. This significant difference between the two spectra indicates the greater association through hydrogen bonding in the case of 4-indanol.[4] The slightly higher *k* value of I as compared to II indicates some steric interference of hydrogen bonding by the five-membered ring. This is consistent with the fact that I is the lower boiling of the two isomers.

TABLE I

PARTITION COEFFICIENTS AND IONIZATION CONSTANTS OF PHENOLS[a]

Compound	$k(H_2O)$	*m*	*pK*
4-Indanol (I)	4.5	0.98	10.2
5-Indanol (II)	3.7	1.03	10.2
5-Hydroxy-1,2,3,4-tetrahydronaphthalene (III)	25.3	1.04	10.1
6-Hydroxy-1,2,3,4-tetrahydronaphthalene (IV)	8.6	1.08	9.9

[a] Measurements at 25°.

Table I also lists the *pK* values of the four phenolic compounds calculated from observed partition coefficients at various *p*H values in the manner previously described.[2] The slopes (*m*) of the straight lines obtained by plotting the logarithms of the observed partition coefficients against *p*H are also listed in Table I. These values are in good agreement with the theoretical slope of one for monobasic phenols.

Experimental[5]

4-Indanol (I) was isolated by Dr. E. O. Woolfolk from the products of the hydrogenation of coal at the Bureau of Mines. It had a melting point of 47–48°.

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[1] Organic Chemist, Bureau of Mines, Research and Development Branch, Office of Synthetic Liquid Fuels, Pittsburgh, Pa.

[2] Golumbic, Orchin and Weller, THIS JOURNAL, **71**, 2624 (1949).

[3] For the most recent paper in this series see Arnold and Richter, *ibid.*, **70**, 3505 (1948).

[4] We wish to thank Dr. R. A. Friedel, Lois Harnack and Marion Springer for the spectral data. Both spectra were determined in a 7% carbon disulfide solution and will be published in greater detail with other material in another article. We are indebted to George Goldbach for assistance with the experimental work.

[5] All melting points corrected.