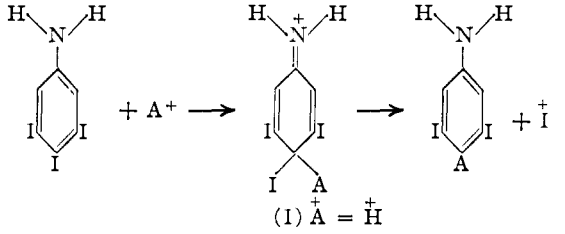
stannous chloride obviates the effects due to resubstitution and oxidation.

The results shown in Table I demonstrate the expected deactivation by *m*-halogen substituents. However, the introduction of one *o*-iodine atom increases the reactivity and a second *o*-iodine brings about a further increase in reactivity. The authors have considered that a plausible reason for the unexpected activation lies in the steric repulsion between adjacent halogens, which in turn favors the formation of intermediate (I).



(I) $\overset{+}{A} = \overset{+}{H}$

In the intermediate (I) A and iodine are not in the plane of the benzene ring. It is interesting to note in this connection that in *o*-dichloro- and *o*-dibromobenzene there is a 15° angle between the plane of the ring and the carbon–halogen bonds. However *p*-dibromobenzene is coplanar.[4]

The present authors believe that a steric activation by ortho halogens might also be of some importance in nucleophilic displacements, although in this case the steric effect is difficult to single out from other factors. Previous work[1] with piperidine as the nucleophilic reagent has shown steric deactivation due to steric hindrance of reagent approach. With a smaller entering group, steric deactivation would become less and electronic effects and steric activation (if any) would become important. However, the last two effects cannot be separated.[5]

### Experimental

**Materials.**—3,4,5-Triiodoaniline,[6] m.p. 175°, 3,4-diiodoaniline,[7] m.p. 75°, *p*-iodoaniline,[8] m.p. 62–63°, and 2,6-dibromo-4-iodoaniline,[9] m.p. 147–148°, were prepared without difficulty and in good yield.

**Reaction with Hydrochloric Acid and Stannous Chloride.**—The method employed was similar to the one used by Nicolet[3a] and co-workers for the determination of so-called "positive" halogen. It was essential that the acid concentrations should be the same for all runs, since it is known that the rate of halogen removal is directly proportional to the acid concentration but is independent of the stannous chloride concentration.

In this work 0.001 mole of compound was dissolved in a boiling mixture of 50 cc. of glacial acetic acid and 10 cc. of concentrated hydrochloric acid. To this was added 0.025 mole of stannous chloride and the solution was refluxed for 15 minutes. On boiling, some hydrogen chloride was lost. However, since all experiments were carried on as nearly as possible under the same conditions, no attempt was made to avoid this loss.

After refluxing, the reaction mixture was made alkaline, extracted with carbon tetrachloride and steam distilled. The reaction mixture thus freed from organic material was acidified with sulfuric acid and treated with excess ferric chloride. The liberated iodine was steam distilled into a cold solution of potassium iodide in water, and was then titrated with standard sodium thiosulfate. The percentage of iodine removed for each compound is shown in Table I. The authors make no claim to great quantitative accuracy.

TABLE I

| | Substance | *p*-Iodine removed by $HCl-SnCl_2$, % |
|---|---|---|
| I | 2,6-Dibromo-4-iodoaniline[a] | 23 |
| II | *p*-Iodoaniline | 41 |
| III | 3,4-Diiodoaniline[b] | 52 |
| IV | 3,4,5-Triiodoaniline[c] | 99 |

[a] 2,4,6-Triiodoaniline was not used because *o*-iodine is also displaced. [b] *m*-Iodoaniline was isolated as the acetyl derivative, m.p. 119–120°. [c] 3,5-Diiodoaniline, m.p. 105°, recovered.

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(4) O. Bastiansen and O. Hassel, *Acta Chem. Scand.*, *I*, 489 (1947); *C. A.*, **42**, 2484 (1948).

(5) In the careful work by Spitzer and Wheland, THIS JOURNAL, **62**, 2995 (1940), it has been shown that in the reactions with piperidine the ratio of the velocity constants for *p*-nitrobromobenzene and 2-bromo-5-nitro-*m*-xylene is about 160:1, while, in the reactions with hydroxide ion, the ratio is only about 11:1. Thus the total deactivation due to the two methyl groups ortho to the bromine atom has been reduced by the use of the smaller reagent molecule.

(6) L. Kalb, F. Schweizer, H. Zellner and E. Berthold, *Ber.*, **59**, 1860 (1926).

(7) P. Brenans, *Compt. rend.*, **136**, 1077 (1903).

(8) R. Q. Brewster, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., 1943, p. 347.

(9) J. J. Sudborough and J. V. Lakhumalani, *J. Chem. Soc.*, **111**, 41 (1917).

## Steroidal Sapogenins. IV.[1] Hydrolysis of Steroidal Saponins[2]

BY EDWARD S. ROTHMAN, MONROE E. WALL AND HENRY A. WALENS

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Steroidal sapogenins are recognized as excellent sources for sex hormones and may be important precursors for cortisone synthesis.[3] The sapogenins are not found free, but occur in a combined glucosidal form which can be cleaved by the use of strong hydrochloric acid. Consequently, the yield of sapogenin depends on the completeness of the acid hydrolysis of the precursor saponins. The question of yield has not been clearly elucidated by previous workers. Jurs and Noller[4] hydrolyzed a purified saponin precursor of tigogenin (isoallospirostan-3$\beta$-ol) using 1.4 *N* hydrochloric acid for 72 hours. Marker, *et al.*,[5] hydrolyzed crude alcoholic plant extracts with 2 *N* hydrochloric acid for 2–3 hours. In neither case was it shown that the hydrolysis conditions were optimal.

We have studied the acid hydrolysis of a number of different saponins. The results are summarized in Table I. Several important facts can be deduced from the data. All the saponins tested were rapidly hydrolyzed with 4 *N* hydrochloric acid, yielding in most cases 90% of the total sapogenin found, in 1–2 hours. Hydrolysis occurred very rapidly when 6 *N* acid was used, cleavage taking place within 10 minutes with the two saponins tested.

Hydrolysis of the different saponins with 2 *N* acid resulted in variable hydrolysis rates. In all cases, the time to reach 90% hydrolysis was much

(1) Paper III, E. S. Rothman, M. E. Wall and C. R. Eddy, THIS JOURNAL, **74**, 4013 (1952).

(2) Not copyrighted.

(3) For pertinent references of papers by Marker, *et al.*, THIS JOURNAL, (1940–1947), and Djerassi, Rosenkranz, *et al.*, THIS JOURNAL, (1950–1952).

(4) P. C. Jurs and C. R. Noller, *ibid.*, **58**, 1251 (1936).

(5) R. E. Marker, *et al.*, *ibid.*, **69**, 2167 (1947).

TABLE I

ACID HYDROLYSIS OF STEROIDAL SAPONINS

| Saponin and derived sapogenin | Hydrochloric acid normality | Percentage of total sapogenin (based on 4 $N$) Time (hours) 1/6 | 1/2 | 1 | 2 | 3 | 4 | 5 | 6 | 8 | 72 | Time for 90% hydrolysis, hours |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sarsasaponin spirostan-3$\beta$-ol | 1 | | | | 27 | 47 | 53 | 60 | 67 | | | >6 |
| | 2 | | | 47 | 73 | 87 | 93 | | 93 | | | 3–4 |
| | 4 | | 80 | 87 | 93 | 93 | 93 | | 100 | | | 1–2 |
| Dioscin $\Delta^5$-isospirosten-3$\beta$-ol | 1 | | | 13 | 17 | | 17 | 26 | | | | >5 |
| | 2 | | | 9 | 35 | 70 | 74 | 78 | | | | >5 |
| | 4 | | 74 | | 83 | 91 | 100 | 100 | | | | 3 |
| Chloronin isoallospirostan-3$\beta$,6$\alpha$-diol | 2 | | | | | | 41 | | | 57 | 99 | >8 |
| | 4 | | | | 93 | | 98 | | | 100 | | 1–2 |
| | 6 | 93 | | | | | 61 | | | 63 | | <1 |
| Digitonin isoallospirostan-2,3$\beta$,15(?)-triol | 1 | | | | 12 | 18 | 30 | 35 | | | | >5 |
| | 2 | | | | 47 | 65 | 80 | 84 | | | | >5 |
| | 4 | | | 89 | 91 | 100 | 100 | 100 | | | | 1/2–1 |
| Gitonin isoallospirostan-2$\alpha$,3$\beta$-diol | 2 | | | 82 | 89 | | 94 | | | | | 2 |
| | 4 | | | 89 | 98 | | 100 | | | | | 1 |
| | 6 | 100 | 77 | | | | | | | | | <1 |

longer than the comparable 4 $N$ period, and as shown in Table I, the times varied from 2 hours to more than 8 hours.

In all the experiments, use of 1 $N$ hydrochloric acid was ineffective, as was also hydrolysis with 1 and 2 $N$ sulfuric acid (not shown in table). Destruction of sapogenins with excess heating time apparently occurred only when 6 $N$ hydrochloric acid was used.

The limited data indicate that the structure of the steroidal aglucone portion of the molecule does not influence the rate of hydrolysis (*i.e.*, isomerism at $C_5$ or $C_{22}$ or number of hydroxyl groups). This is best shown by the data obtained with 2 $N$ acid hydrolysis. Sarsasaponin, yielding spirostan-3$\beta$-ol and gitonin, the precursor of isoallospirostan-2$\alpha$,3$\beta$-diol, are the most rapidly hydrolyzed saponins. Dioscin, yielding $\Delta^5$-isospirosten-3$\beta$-ol, and digitonin forming isoallospirostan-2,3$\beta$,15(?)-triol, were more resistant to hydrolysis. Chloronin, forming isoallospirostan-3$\beta$,6-diol, was the most difficultly hydrolyzable saponin tested.

The results discussed above suggest that the routine use of 2 $N$ hydrochloric acid for the hydrolysis of *unknown saponins* in crude plant extracts can result in *low sapogenin yields*. Crude plant extracts such as those used by Marker, *et al.*,[5] contain proteins and sugars. It is not surprising therefore, that when we attempted to hydrolyze such extracts with 4 $N$ acid, large quantities of tar were produced, from which little sapogenin could be isolated. Subsequently, a procedure was developed at this Laboratory[6] in which saponins could be routinely separated from proteins and carbohydrates by extraction from the aqueous phase with butanol. After this treatment, the saponin preparations could be hydrolyzed by refluxing with 4 $N$ acid for 3–4 hours with little tar formation. The sapogenins thus formed are readily isolated. A number of experiments comparing the direct 2 $N$ hydrolysis[5] with the butanol purified 4 $N$ hydrolysis[6] have invariably shown that the latter procedure gives 25–100% higher yields of sapogenin.

(6) Paper I, M. E. Wall, M. M. Krider, E. S. Rothman and C. R. Eddy, *J. Biol. Chem.*, in press.

### Experimental

Purified saponin preparations were prepared as described previously[1,6] with the exception of digitonin, which was obtained from a commercial source. The saponin yielding isoallospirostan-3$\beta$,6$\alpha$-diol was obtained from bulbs of *Chlorogalum pomeridianum;* the saponin yielding $\Delta^5$-isospirosten-3$\beta$-ol was obtained from rhizomes of *Dioscorea composita;* the saponin yielding isoallospirostan-2$\alpha$,3$\beta$-diol[7] was obtained from leaves of *Yucca gloriosa;* and the saponin yielding spirostan-3$\beta$-ol was obtained from the leaves of *Yucca baccata*.[8]

Stock solutions of saponins were prepared in 1:1 ethanol-water (by volume) so that 3.34-ml. aliquots contained 100 mg. of saponin. To the aliquots were added sufficient concentrated hydrochloric acid, water and alcohol to bring the final volume of 5.00 ml. to the desired normality. Two ml. of benzene, previously equilibrated with an equal volume of 1:1 ethanol–water was added, and the hydrolyses were conducted at reflux temperature in centrifuge tubes immersed in a water-bath at 75–78° as described previously[9] and the sapogenins, as acetates, were assayed by the infrared method,[9,10] or in some cases gravimetrically.

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(7) A small quantity of isoallospirostan-3$\beta$-ol was also present.

(8) We wish to thank C. O. Erlanson, D. S. Correll and H. S. Gentry of the Division of Plant Exploration and Introduction, Bureau of Plant Industry, Soils, and Agricultural Engineering for procuring the various plant specimens.

(9) Paper II, M. E. Wall, C. R. Eddy, M. L. McClennan and M. E. Klumpp, submitted to *Anal. Chem.*

(10) The infrared assays were conducted by C. R. Eddy and M. E. Klumpp.

(11) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. This work was done as part of a coöperative arrangement between the Bureau of Plant Industry, Soils and Agricultural Engineering and the Bureau of Agricultural and Industrial Chemistry, United States Department of Agriculture, and the National Institutes of Health, Federal Security Administration.

## Fluorination of Carbon Disulfide and Carbonyl Sulfide

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The fluorination of methyl mercaptan or carbon disulfide has been shown under certain conditions to produce trifluoromethylsulfur pentafluoride, $CF_3SF_5$.[1] A continuation of the study of fluorina-

(1) G. A. Silvey and G. H. Cady, THIS JOURNAL, **72**, 3624 (1950).