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UNITED STATES PATENT OFFICE

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STEROIDAL HORMONE INTERMEDIATES AND THEIR PREPARATION

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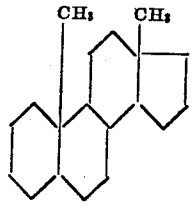
No Drawing. Application November 6, 1941, Serial No. 418,076

14 Claims. (Cl. 260—397.4)

This invention relates to steroidal hormone intermediates and their preparation.

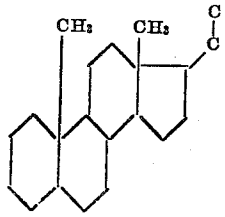
In particular, this invention relates to steroidal hormone intermediates which are useful for the preparation of hormones of the androstane series.

Many of the steroidal hormones, including most of the male sex hormones such as testosterone and androsterone, are steroids of 19 carbon atoms content having the following skeleton:



This skeleton is known as the androstane skeleton or sometimes as the etio-cholane skeleton.

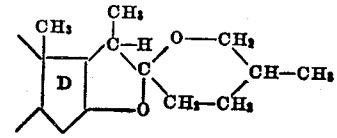
According to the present invention new improved methods are provided for passing to the androstane series from the pregnane series, the pregnane series being represented by the following skeleton:



The terms androstane and pregnane as used in this specification and in the appended claims are to be understood as comprehending steroids of 19 and 21 carbon atoms respectively, regardless of the particular stereo-chemical configuration in the nucleus. For example, the term androstane compound is to be understood to include compounds having the "allo-" configuration at C_5 such as androsterone, or steroids having the "regular" configuration at C_5 such as etio-cholanol-3(β)-one-17, as well as ring-unsaturated steroids such as testosterone.

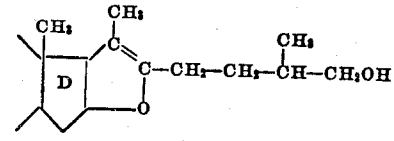
In the past androstane compounds have been prepared by the degradation of the side chain of steroids or bile acids. However, these processes are extremely inefficient and wasteful of material. Thus the yield of androstane compound from the oxidation of cholesterol is only of the order of 1–2%. This low yield makes it necessary to process very large amounts of cholesterol in very large scale equipment in order to get useful amounts of the androstane compound.

Recently a method has been developed for the obtainment of pregnane compounds in high yields from the steroidal sapogenins [J. Am. Chem. Soc. 62, 3350 (1940)]. This method consists in converting a steroidal sapogenin into the corresponding pseudosapogenin and oxidizing the latter to a Δ^{16}-unsaturated-20-keto-pregnane compound. This sequence of transformations is illustrated below, where only the essential changes in the molecule, which occur in ring D, are shown:



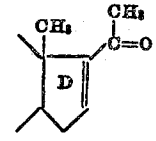
steroidal sapogenin

Ac_2O, 200°, 10 hrs.; alcoholic KOH



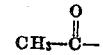
pseudosapogenin

CrO_3—HOAc; hydrolysis

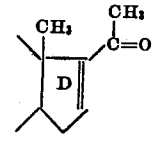


S_{16}-unsaturated-20-keto-pregnane compound

where A^c represents



Because of these recent developments, Δ^{16}-unsaturated-20-keto-steroids, which have in ring D the structure,



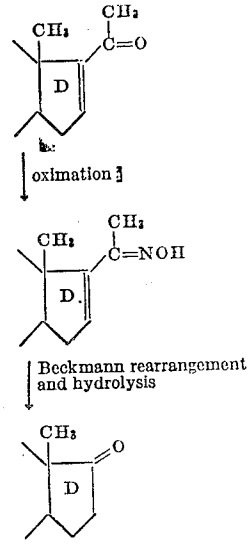
are now available cheaply and in quantity; hence this class of compounds must be considered to be potentially the most satisfactory source for the preparation of androstane compounds.

While methods for the obtainment of androstane compounds from pregnane compounds have been described in the past, these methods have proved to be impractical in commercial operation.

Consequently, an object of this invention is to provide a practical method for preparing androstane compounds from pregnane compounds.

We have found that a very satisfactory procedure for preparing a 17-keto-steroid comprises oximating a Δ^{16}-unsaturated-20-keto-steroid, subjecting the resulting oxime to Beckmann rearrangement and hydrolizing the rearrangement product.

The transformation involved may be represented as follows:



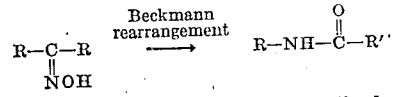
Here only the essential changes, occurring in ring D, have been shown.

The first step, comprising the oximation of the Δ^{16}-unsaturated-20-keto-steroid, can be accomplished by reacting the ketone with hydroxylamine or an acid addition salt thereof.

The step of rearrangement of the oxime can be effected in a great many ways according to methods which are generally employed for effecting the Beckmann rearrangement. We have found that the rearrangement proceeds in an especially satisfactory manner when the oxime in a tertiary amine is treated with an acid halide and preferably with an aromatic sulfonyl halide.

The Beckmann rearrangement product thus obtained is then hydrolyzed, e. g., by treatment with a diluted strong acid. It is unnecessary to isolate the Beckmann rearrangement product, instead it is sufficient to hydrolyze the crude reaction mixture.

It will be noted that the above outlined process represents a novel application of the Beckmann rearrangement, for as ordinarily employed the Beckmann rearrangement transforms a ketoxime into a N-substituted amide as follows:

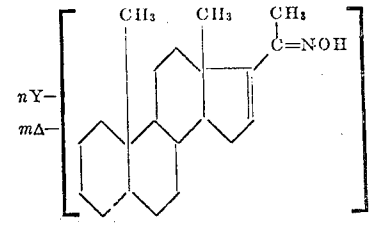


where R and R' are alkyl or aryl radicals or the like. The amides thus obtained are usually relatively resistant to hydrolysis, but when hydrolyzed, yield amines of the formula RNH_2.

In contrast, our process yields an intermediate which is readily hydrolyzed to yield a 17-keto-steroid.

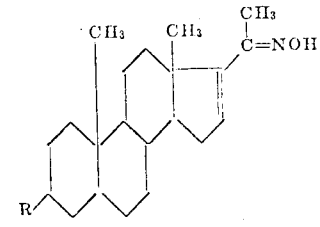
It will also be noted that our new process does not require the use of strong oxidizing agents, and accordingly, pregnane derivatives unsaturated at other positions in the ring system in addition to at Δ^{16} may be degraded to the corresponding nuclearly unsaturated androstane derivatives without protection of double bonds. Hence our process provides a simple practical process for obtaining nuclearly unsaturated androstane compounds in high yields.

The oximes of Δ^{16}-unsaturated-20-keto-steroids formed as intermediates in our process constitute a valuable class of steroidal hormone intermediates. A particularly useful group of these oximes is representable by the formula:

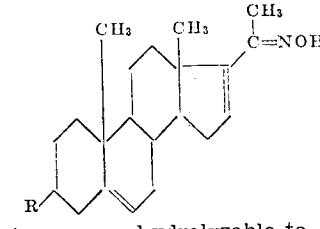


where nY represents n substituents hydrolyzable to —OH in the rings-A-B portion of the steroid skeleton, n having one of the values 0, 1 and 2, and where $m\Delta$ represents m double bonds in the rings-A-B portion of the steroid skeleton, m having one of the values 0, 1 and 2, the sum $n+m$ not exceeding the value 3. This class of substances includes: $\Delta^{4,16}$-pregnadienone-20 oxime; $\Delta^{5,16}$-pregnadienone-20 oxime; $\Delta^{5,16}$-pregnadienol-3(β)-one-20 acetate oxime; 3-chloro-$\Delta^{5,16}$-pregnadienone-20 oxime; Δ^{16}-allo-pregnenediol-3(β),-6-one-20 diacetate oxime; $\Delta^{4,16}$-pregnendiol-3,6-one-20 diacetate oxime; $\Delta^{5,16}$-pregnenediol-3,4-one-20 dibenzoate oxime; and the like.

Certain subclasses of this group of new steroidal hormone intermediates have been found to be particularly useful. These have the formulae



and



where R is a group hydrolyzable to —OH, such as halogen, or acyloxy groups. Of these, the compounds where R is acyl—O— are preferred because of their ease of preparation and conversion into intermediates suitable for the preparation of testosterone.

Our invention may be illustrated further by the following examples:

Example 1

(A) To a solution of 13.0 grams of Δ^{16}-pregnenol-3(β)-one-20 acetate in 350 cc. of 95% alcohol is added a solution of 13 grams of hydroxylamine hydrochloride and 20 grams of sodium acetate in 25 cc. of water. The mixture is stoppered and allowed to stand with occasional shaking at room temperature for four days. Then the mixture is concentrated in vacuo on a water bath at 40° C. until the volume of the residue is about 100 cc. Then this residue is diluted with about two liters of water and the precipitate col-

lected and washed with water. The crude product thus obtained is recrystallized from methanol to give Δ^{16}-pregnenol-3(β)-one-20 acetate oxime of M. P. 197–205° C. (dec.).

(B) Five grams of the above oxime are dissolved in 25 cc. of dry pyridine, cooled in an ice bath, and 5 grams of p-toluene-sulfonyl chloride added. After one hour, the mixture is removed from the ice bath and allowed to stand at room temperature for four hours. Then the dark red solution is poured into an excess of 10% aqueous sulfuric acid. The reaction flask is rinsed with alcohol and with ether, and the alcohol and ether washings added to the aqueous acidic mixture. After this mixture has stood overnight at room temperature, the hydrolysis is essentially complete. Then the mixture is extracted with ether and the ethereal extract washed thoroughly with dilute sulfuric acid, dilute sodium carbonate solution and water. The ether is removed on a steam bath and the residual solid crystallized from acetone containing a small amount of water. Thus there is obtained etio-cholanol-3(β)-one-17 acetate of M. P. 157–158° C.

Instead of using p-toluenesulfonyl chloride in the above Beckmann rearrangement, other sulfonyl halides may be used, such as benzenesulfonyl chloride, benzenesulfonyl bromide, methanesulfonyl chloride, anthraquinonesulfonyl chloride, p-nitrobenzenesulfonyl chloride, naphthalene-β-sulfonyl chloride, and the like. Likewise, instead of using pyridine, other tertiary amines may be used, such as dimethylaniline, tributylamine, N-ethylmorpholine, quinoline, or the like.

Again, instead of using Δ^{16}-pregnenol-3(β)-one-20 acetate, other Δ^{16}-unsaturated-20-keto-steroids may be used. Thus the following transformations can be effected, following the procedure outlined in the above example:

Starting material	Final product
Δ^{16}-Pregnenol-3(α)-one-20 propionate.	Etio-cholanol-3(α)-one-17 propionate.
Δ^{16}-Allo-pregnenol-3(β)-one-20 benzoate.	Etio-allo-cholanol-3(β)-one-17 benzoate.
Δ^{16}-Allo-pregnenol-3(α)-one-20 butyrate.	Etio-allo-cholanol-3(α)-one-17 butyrate.
3-chloro-Δ^{5}-[^{16}-pregnadienone-20	3-chloro-Δ^{5}-androstenone-17.
$\Delta^{5,16}$-pregnadienone-20	Δ^{5}-Androstenone-17.
Δ^{16}-Allo-pregnenediol-3(β),6-one-20 diacetate.	Androstanediol-3(β),6-one-17 diacetate.
Δ^{16}-Allo-pregnenone-20	Androstanone-17.
$\Delta^{4,16}$-Pregnadienone-20	Δ^{4}-Androstenone-17.

The starting materials required above can be obtained from the corresponding pseudo-sapogenins which in turn are readily prepared from the corresponding sapogenins themselves all according to the copending application of Marker, Serial No. 393,667, filed May 15, 1941.

Example 2

(A) To a solution of 15 grams of $\Delta^{5,16}$-pregnadienol-3(β)-one-20 acetate in 500 cc. of warm alcohol are added 15 grams of hydroxylamine hydrochloride in 25 cc. of water and 22 grams of sodium acetate in 25 cc. of water. The mixture is allowed to stand at room temperature with occasional shakings for four days. The mixture is evaporated to a small volume in vacuo on a water bath at 40° C. and then diluted with two liters of water. The precipitated crude oxime is collected on a Buchner funnel, washed with water and dried. After crystallization from alcohol, it yields $\Delta^{5,16}$-pregnadienol-3(β)-one-20 acetate oxime of M. P. 210–215° C. (with decomposition).

(B) A solution of 6 grams of the above $\Delta^{5,16}$-pregnadienol-3(β)-one-20 acetate oxime in 30 cc. of dry pyridine is cooled in an ice bath while 6 grams of p-toluenesulfonyl chloride are added. After one hour, the mixture is removed from the ice bath and allowed to stand for four hours at room temperature. The reaction mixture is poured into an excess of dilute aqueous sulfuric acid, the material adhering to the sides of the reaction flask being transferred to the aqueous liquor with the aid of alcohol and ether. Then the hydrolyzing mixture is allowed to stand for three days at room temperature, after which it is extracted with ether. The ethereal extract is washed with dilute sulfuric acid, water, dilute sodium hydroxide, and again with water, and the ether is removed on a steam bath to leave a crystalline residue. This is recrystallized from dilute acetone to yield Δ^{5}-etio-cholenol-3(β)-one-17 acetate of M. P. about 169° C.

Instead of using the acetate of $\Delta^{5,16}$-pregnadienol-3(β)-one-20 in the above example, there may be used other esters, such as the propionate, butyrate, benzoate, naphththoate, palmitate, and the like.

Example 3

To a solution of 1 gram of $\Delta^{5,16}$-pregnadienol-3(β)-one-20 acetate in 10 cc. pyridine are added 0.22 gram of hydroxylamine hydrochloride, and the mixture is allowed to stand at room temperature for four days. Then the mixture is cooled in an ice bath while 2.4 grams of benzenesulfonyl chloride are slowly added. After the mixture has stood for six hours, about 20 cc. of water are added dropwise with shaking to hydrolyze the reaction mixture. The hydrolysis is completed by pouring the mixture into a mixture of 20 cc. concentrated sulfuric acid, 100 cc. of ice, and 100 cc. of ether. This mixture is shaken thoroughly and then allowed to stand overnight. The next morning the aqueous layer is discarded, and the ethereal layer is filtered from a small amount of brown, insoluble impurity. The ethereal extract is washed with water, dilute sodium hydroxide and water, and evaporated to leave a residue which, after crystallization from methanol, gives Δ^{5}-etio-cholenol-3(β)-one-17 acetate of M. P. 169° C. This substance is frequently called dehydroisoandrosterone acetate.

Example 4

One gram of $\Delta^{5,16}$-pregnadienol-3(β)-one-20 acetate oxime is dissolved in 30 cc. of hot dioxan, and then the solution is cooled in an ice bath until about one-half of the dioxan has solidified. Then 1 g. of phosphorus pentachloride is added and the mixture is shaken until all the dioxan has melted. The mixture is maintained at 35° C. for seventy-five minutes, then an excess of ice is added and the solution is again allowed to stand at 35° C. After about thirty minutes, a solution of 5 cc. of concentrated hydrochloric acid in 10 cc. of water is added, and the mixture is diluted with water, extracted with ether and the ethereal extract washed with dilute sodium hydroxide solution. The ether is removed on a steam bath and the residue is worked up to yield dehydroisoandrosterone.

The isolation of the dehydroisonandrosterone is best accomplished as follows: The crude residue obtained above is refluxed for thirty minutes with 5 cc. of acetic anhydride. Then the excess acetic anhydride is removed in vacuo and the residue is crystallized from dilute methanol

and finally from pure methanol to obtain dehydroisonandrosterone acetate of M. P. 165° C.

The yield by this procedure is considerably less than by the procedure of Example 3.

The above examples are subject to numerous variations with regard to the methods of conducting the reactions and isolating the products. Furthermore, the process is generally operable on Δ^{16}-unsaturated-steroidal-20-ketoximes, regardless of the structural features present in rings A, B, and C. However, it will be appreciated that transformations of these structural features in rings A, B, and C may occur during the process. For example, the application of our process to Δ^{16}-pregnenedione-3, 20 dioxime gives a 17-ketoandrostane derivative in which ring A has been transformed into a lactam ring. In general, it has been found that the presence in rings A, B, and C of acyloxy groups, halogens, and/or double bonds does not complicate the process, for these groups remain unaffected during the transformations of our process. On the other hand, ketone or hydroxyl groups are transformed in our process; so that steroids containing nuclear ketone groups, after oximation, rearrangement, and hydrolysis, yield ring-lactams; while nuclearly hydroxylated steroids are frequently esterified or dehydrated during the rearrangement process.

The oximation of the Δ^{16}-unsaturated-20-keto-steroid may be accomplished by reacting the keto-steroid in alcohol solution with hydroxylamine acetate, free hydroxylamine or with the combination of a hydroxylamine acid addition salt and a dehydrohalogenating agent, such as sodium acetate, or a tertiary amine, such as pyridine. In general, we have found it best to conduct the oximation under relatively mild conditions, so as to minimize the possibility of adding hydroxylamine to the Δ^{16} double bond.

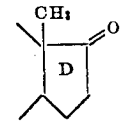
The Beckmann rearrangement of the Δ^{16}-unsaturated-steroidal-20-ketoxime may be accomplished by a host of different methods, such as are generally employed for effecting the Beckmann rearrangement. These methods are described, for example, in Houben, Die Methoden der organischen Chemie, second edition, volume 4, pages 356 ff. Thus the rearrangement may be effected by acidic agents or by agents which are reactive with water to form strong acids. Such reagents include hydrochloric acid, sulfuric acid, phosphorus pentachloride, thionyl chloride, antimony pentachloride, benzenesulfonyl chloride, benzoyl chloride and the like. The use of a diluent, such as acetic acid, dioxan, ether, benzene, or pyridine, is usually advisable to secure optimum yields. We have obtained especially satisfactory results by using diluents in which the oxime is reasonably soluble. Among such diluents, the most satisfactory appear to be tertiary amines. We prefer to use tertiary amines which contain no free hydroxyl groups or primary or secondary amino groups, i. e. tertiary amines which are not permanently attacked by acid halides. Tertiary amines containing hydroxyl groups, etc., may react at the hydroxyl groups, etc., with the acid halide; so the use of such substituted tertiary amines is often uneconomical.

We have obtained especially good results by the following simple procedure: The Δ^{16}-unsaturated-20-keto-steroid in a tertiary amine, such as pyridine, is treated with a hydroxylamine acid addition salt, preferably the sulfate or the hydrochloride, thereby forming the oxime. Without isolating this oxime, it is rearranged in the tertiary amine diluent by adding an acid halide, preferably an aromatic sulfonyl chloride. After some standing, the reaction mixture is hydrolyzed by treatment with a diluted strong acid and the 17-keto-steroid isolated and purified.

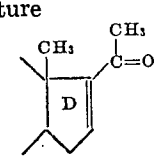
What we claim as our invention is:

1. The process for preparing a 17-keto-steroid which comprises oximating a Δ^{16}-unsaturated-20-keto-steroid, subjecting the resulting oxime to Beckmann rearrangement and hydrolyzing the rearrangement product.

2. The process for preparing a steroid having in ring D the formula

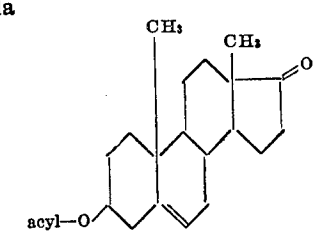


which comprises oximating a steroid having in ring D the structure

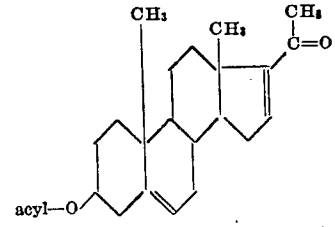


subjecting the resulting oxime to Beckmann rearrangement and hydrolyzing the rearrangement product.

3. The process for preparing a steroid having the formula



which comprises reacting a steroid having the formula



in a tertiary amine with a hydroxylamine acid addition salt, reacting the resulting oxime with an aromatic sulfonyl halide, and hydrolyzing the rearrangement product by treatment with a diluted strong acid.

4. The process for preparing a lower fatty acid ester of dehydroisoandrosterone, which comprises reacting a lower fatty acid ester of $\Delta^{5,16}$-pregnadienol-3 (β)-one-20 in a tertiary amine with a hydroxylamine acid addition salt, reacting the resulting oxime with an aromatic sulfonyl halide and hydrolyzing the rearrangement product with a diluted strong acid.

5. A process according to claim 1 in which the oximation of the Δ^{16}-unsaturated-20-keto-steroid is accomplished by reacting said keto-steroid in a tertiary amine with a hydroxylamine acid addition salt.

6. A process according to claim 1 in which the Beckmann rearrangement is accomplished by treating the oxime in a tertiary amine with an acid halide.

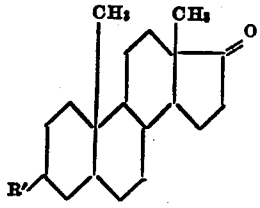
7. A process according to claim 1 in which the Beckmann rearrangement is accomplished by reacting the oxime in a tertiary amine with an aromatic sulfonyl halide.

8. A process according to claim 1 in which the Beckmann rearrangement product is hydrolyzed by treatment with a diluted strong acid.

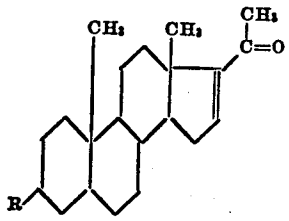
9. A process according to claim 1 in which the Beckmann rearrangement is accomplished by reacting the oxime in a tertiary amine with an aromatic sulfonyl chloride.

10. The process for preparing a 17-keto-steroid which comprises subjecting a Δ^{16}-unsaturated-steroidal-20-ketoxime to Beckmann rearrangement and hydrolyzing the rearrangement product.

11. The process for preparing a steroid having the formula

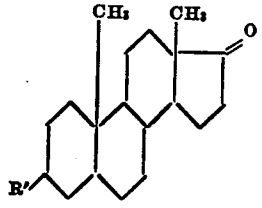


where R' is a member of the class consisting of —OH and groups hydrolyzable to —OH, which comprises oximating a steroid having the formula

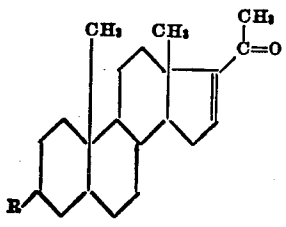


where R is a member of the class consisting of —OH and groups hydrolyzable to —OH, subjecting the resulting oxime to Beckmann rearrangement and hydrolyzing the rearrangement product.

12. The process for preparing a steroid having the formula

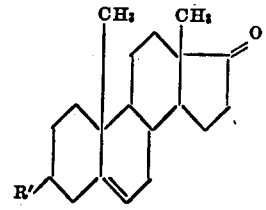


where R' is a member of the class consisting of —OH and groups hydrolyzable to —OH, which comprises reacting a steroid having the formula

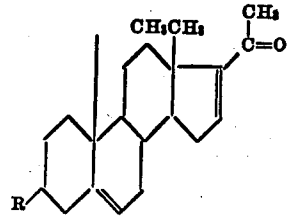


where R is a member of the class consisting of —OH and groups hydrolyzable to —OH, in a tertiary amine with a hydroxyl amine acid addition salt, reacting the resulting oxime with an acid halide and hydrolyzing the rearrangement product with a diluted strong acid.

13. The process for preparing a steroid having the formula

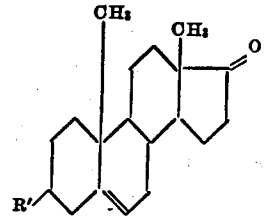


where R' is a member of the class consisting of —OH and groups hydrolyzable to —OH, which comprises oximating a steroid having the formula

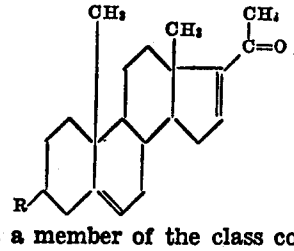


where R is a member of the class consisting of —OH and groups hydrolyzable to —OH, subjecting the resulting oxime to Beckmann rearrangement and hydrolyzing the rearrangement product.

14. The process for preparing a steroid having the formula



where R' is a member of the class consisting of —OH and groups hydrolyzable to —OH, which comprises reacting a steroid having the formula



where R is a member of the class consisting of —OH and groups hydrolyzable to —OH, in a tertiary amine with a hydroxyl amine acid addition salt, reacting the resulting oxime with an acid halide and hydrolyzing the rearrangement product with a diluted strong acid.

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