This invention relates to an improvement in the method of introducing a carbon-carbon double bond into a steroid nucleus by the removal of nuclear vicinal chlorine and bromine atoms by interaction with iodide ions, and is more particularly concerned with such process whereby the iodide ions are furnished by quaternary ammonium iodides. The term "vicinal" as herein employed, has the meaning customarily attributed thereto in organic chemistry, viz., adjacent, neighboring, or consecutively positioned.

Many transformations of cyclopentanopyrrole hydrocarbons require the protection of nuclear double bonds. The addition of chlorine or bromine to the nuclear double bond, prior to the transformation, is a standard method for accomplishing such protection. After the desired transformation or reaction has been completed, it becomes necessary to introduce a carbon-carbon double bond into the steroid nucleus to complete the synthesis, and this is accomplished by removal of the halogens which have been introduced previously for protective purposes. Such reaction has been accomplished in the art by use of zinc in acetic acid or alcohol, by the use of chromous chloride (United States Patent 2,374,683), and by the use of alcoholic sodium iodide (J. Biol. Chem. 110, (1935); United States Patents 2,203,611 and 2,319,801).

The use of sodium iodide has been found effective, according to the references mentioned above, in the removal of vicinal chlorine and bromine from relatively simple and stable steroid compounds. However, sodium iodide and other similar alkali metal iodides have not been found to be useful in the dehalogenation of highly substituted or unstable steroid molecules, especially those sensitive to heat.

Moreover, the process employing the use of sodium iodide or other similar alkali metal iodides has the further inherent disadvantage of producing yields which are much less than desirable. For example, when the dehalogenation is conducted with the employment of sodium iodide and a steroid dihalide to which the sodium iodide dehalogenation process can be safely applied, the yield of desired unsaturated steroid product is generally at best no greater than sixty percent of the theoretical. Since the cost of the starting materials is considerable, it is obvious that a process producing yields no greater than sixty percent of the theoretical leaves much to be desired from an economical, and hence also from a commercial standpoint.

It is, therefore, an object of the present invention to provide a superior method of dehalogenating vicinally nuclearly dihalogenated steroids. A further object of the present invention is the provision of a process for the dehalogenation of vicinally nuclearly dihalogenated steroids which involves the employment of a quaternary ammonium iodide as the dehalogenating agent. Other objects of the invention will be apparent hereinafter.

It has now been found that quaternary ammonium iodides are superior process dehalogenating or dechlorinating agents as compared with the previously-employed alkali metal iodides. Yields of pure unsaturated product are considerably higher than attained by employment of the previously-used dehalogenating agents, in some instances being practically quantitative. The crude product, obtained by the method of the present invention, is generally sufficiently pure to be used without additional purification in subsequent chemical reactions. While debranumation and decoloration with the agents of this invention can, if desired, be carried out at elevated temperatures, such as the boiling point of the reaction solvents, these agents are sufficiently powerful so that the dehalogenation can be carried out at room temperature in a reasonable length of time, which is another obviously important advantage of the process.

The method of the invention can be carried out by mixing a solution of the selected nuclearly dihalogenated steroid, in a suitable solvent, with a solution of a quaternary ammonium iodide, and allowing the mixture to stand under room conditions until the chlorine or bromine has been removed, which period of standing may conveniently be overnight. The time required to accomplish the dehalogenation will vary considerably with the temperature of the reaction, the particular halogen to be removed, the position of the vicinal halogens in the steroid nucleus, and the general character of the steroid molecule. However, the proper length of time for any specific dehalogenation reaction can be determined readily by standard procedure, as by titrating the elemental iodine released during the reaction with a suitable reagent, such as sodium thiosulfate. When an aliquot portion of the reaction mixture shows that about one-hundred percent of the theoretical quantity of elemental iodine has been formed, the reaction is complete and the desired
product can be isolated. This time is usually from one to twenty-four hours within the broader temperature ranges, and ordinarily between about twelve and twenty-four hours.

Temperatures useful in the method of this invention are between about ten degrees and about one-hundred degrees centigrade, with temperatures between about twenty and forty degrees centigrade being preferred.

It is desirable for optimum yields to remove the elemental iodine from the mixture before isolating the reaction product. This can be accomplished by converting the iodine to iodide ion with a bisulfite solution or other equivalent procedure known in the art. The isolation of the steroid product can be carried out, in any case, by known procedure. The reaction of the present invention is believed to proceed according to the equation:

\[
\text{C}_9\text{H}_{11}\text{Br} + \text{I}_2 \rightarrow \text{C}_9\text{H}_{11}\text{I} + 2\text{Br}^{-}
\]

wherein the vicinal bromine atoms are a part of a steroid ring system, although it is to be understood that the invention is not to be limited by any such theory of reaction mechanism.

Solvents suitable for the method of the invention are those organic solvents commonly used for such purposes, and include the liquid aliphatic and aromatic hydrocarbons, lower aliphatic alcohols, glycols, and their ethers, and numerous others.

Various substituents may be present in the steroid nucleus, such as carbonyl, acyl, acyloxy, alkyl, and ether groups. The preferred embodiment of this invention contemplates that the halogens to be removed be present in the 5,6-positions of the steroid nucleus. Substituents, other than the halogen atoms in the 5,6-positions, are preferably in the 3-position, in the 10,13 positions, in the 3,11 positions, and in the 17 position, but the process is not limited other than it relates to the removal of vicinal nuclear chlorine or bromine atoms from a steroid compound.

The quaternary ammonium iodides suitable for use in the process of this invention should not contain substituent groups which would react with any functional group present in the steroid molecule or cause decomposition of the molecule. Therefore, the quaternary ammonium iodide suitable for use in the process of the invention does not appear to be critical and any quaternary ammonium iodide may be employed. The preferred quaternary ammonium iodides are those without additional functional groups, for example, aliphatic hydrocarbon quaternary ammonium iodides, such as tetramethyl ammonium iodide and methytrityethyl ammonium iodide; mixed aliphatic-cycloaliphatic hydrocarbon ammonium iodides, such as cyclohexyltrimethyl ammonium iodide and mixed aliphatic-aromatic quaternary ammonium iodides, such as phenyltrimethyl ammonium iodide, and tolyltripropyl ammonium iodide; alkyllaralkyl quaternary ammonium iodides, such as benzyltrimethyl ammonium iodide; and heterocyclic quaternary ammonium iodides, such as pyridine methiodide, lutidine ethiodide, dimethyl piperidinium iodide, methyl morpholinium iodide, and diethyl pyrrolidinium iodide. In addition to the above, other equivalent quaternary ammonium iodides, obvious to one skilled in the art, may also be employed.

The following examples illustrate the method of the present invention but are not to be construed as limiting.

**Example 1.** 23-Dibromostigmasteryl acetate

A solution of 0.95 parts of methyltributyl ammonium iodide in 6.5 parts of alcohol was added to one part of stigmasteryl acetate, 5.6 dibromomethiodide dissolved in thirteen parts of benzene and allowed to stand at room temperature for eighteen hours at which time an iodine determination with sodium thiosulfate showed 52 percent of the theoretical amount of iodine, based on the presence of four bromine atoms and been liberated. The reaction mixture was then diluted with an equal volume of water and shaken with solid sodium bisulfite until the iodine color disappeared. The two layers were then separated and the organic layer washed three times with equal volumes of water, dried and concentrated to forty percent of its original volume. The hot, concentrated solution was diluted with 19.5 parts of alcohol, cooled, and the resulting crystals collected and dried. There was thus obtained 0.665 parts (92.5 percent of theory) of 22,23-dibromostigmasteryl acetate which melted at 203 to 206 degrees centigrade.

**Example 2.**

A solution of 1.41 parts of benzyltrimethyl ammonium iodide in 8.5 parts of alcohol was added to one part of cholesteryl acetate, 5.6-dibromomethiodide dissolved in seventeen parts of benzene and the mixture stirred at room temperature for twenty-one hours, at which time an iodine determination with sodium thiosulfate showed 96 percent of the theoretical amount of iodine had been liberated. By a procedure essentially that described in Example 1, 0.588 parts (82.5 percent of theory) of recrystallized cholesterol acetate, which melted at 111 to 114 degrees centigrade, was isolated from the reaction mixture.

**Example 3.**

By a procedure essentially that described in Example 2, there was obtained from one part of cholesterol acetate, 5.6-dibromide and 1.64 parts of pyridine methiodide, 0.71 part 88 percent of theory of recrystallized cholesterol acetate, which melted at 111 to 114 degrees centigrade.

**Example 4.**

By a procedure essentially that described in Example 2, there was obtained from 1.21 parts of N-ethyl-N-methyl-morpholinium iodide and one part of cholesterol acetate, 5.6-dibromide, 0.605 parts 83 percent of theory of recrystallized cholesterol acetate, which melted at 113 to 114 degrees centigrade.

**Example 5.**

5-Androstene-3-beta-ol - 17-one, 3-acetate

In a manner essentially that described in Example 1, there was obtained from 1.47 parts of methyltributyl ammonium iodide and one part of 5.6 dibromomadrostane - 3 - beta-ol-17-one, 3-acetate dissolved in 10 parts of alcohol and 20.5 parts of benzene, 0.656 parts (97 percent of theory) of 5-androstene-3-beta-ol-17-one, 3-acetate, which melted at 158 to 165 degrees centigrade.

It is to be understood that the present invention is not to be construed as limited to the exact details of operation or exact compounds shown or described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only as defined by the appended claims.
We claim:
1. A method for the introduction of a nuclear double bond into a steroid molecule comprising: contacting in the presence of an organic solvent at a temperature between about ten and about one-hundred degrees centigrade, a vicinally nuclear-di-halogenated steroid, said halogen being a member of the group consisting of chlorine and bromine, and a quaternary ammonium iodide, until about the theoretical quantity of elemental iodine, as determinable by standard procedures, has been released, and isolating the nuclearly-ununsaturated steroid thus formed.
2. A method for the introduction of a nuclear double bond into a steroid molecule comprising: contacting in the presence of an organic solvent, a vicinally nuclear-di-halogenated steroid, said halogen being a member of the group consisting of chlorine and bromine, and a quaternary ammonium iodide, at a temperature between about ten and about one-hundred degrees centigrade for a period of from about one to about twenty-four hours, and isolating the nuclearly-ununsaturated steroid thus formed.
3. A method for the introduction of a nuclear double bond into a steroid molecule comprising: contacting in the presence of an organic solvent, a vicinally nuclear-di-halogenated steroid, said halogen being a member of the group consisting of chlorine and bromine, with a quaternary ammonium iodide at a temperature between about twenty and about forty degrees centigrade for a period of from about twelve to about twenty-four hours, and isolating the nuclearly-ununsaturated steroid thus formed.
4. A method for the introduction of a 5,6-double bond into a steroid molecule comprising: contacting in the presence of an organic solvent, at a temperature between about ten and about forty degrees centigrade, a 5,6-di-halogen steroid, said halogen being a member of the group consisting of chlorine and bromine, with a quaternary ammonium iodide until about the theoretical quantity of elemental iodine, as determinable by standard procedure, is released, and isolating the 5,6-unsaturated steroid thus formed.
5. The process of claim 4, wherein the temperature is between about twenty and forty degrees centigrade.
6. The process of claim 4, wherein the time of reaction is between about one and twenty-four hours.
7. The process of claim 4, wherein the time of reaction is between about twelve and twenty-four hours.
8. The process of claim 4, wherein the starting steroid is 5,6-dibromoandrostane-3-ol-17-one,3-acetate, and the unsaturated product is 5-androsten-3-ol-17-one,3-acetate.
9. The process of claim 4, wherein the starting steroid is cholesteryl acetate, 5,6-dibromide, and the unsaturated product is cholesteryl acetate.
10. The process of claim 4, wherein the starting steroid is stigmasteryl acetate, 5,6,22,23-tetra-bromide, and the unsaturated product is 22,23-dibromostigmasteryl acetate.
11. The process of claim 4, wherein the starting steroid is 5,6-dibromoandrostane-3-ol-17-one,3-acetate, the unsaturated product is 5-androsten-3-ol-17-one,3-acetate, and the quaternary ammonium iodide is methyltriethyl ammonium iodide.
12. The process of claim 4, wherein the starting steroid is cholesteryl acetate, 5,6-dibromide, the unsaturated product is cholesteryl acetate, and the quaternary ammonium iodide is pyridine methiodide.
13. The process of claim 4, wherein the starting steroid is stigmasteryl acetate, 5,6,22,23-tetra-bromide, the unsaturated product is 22,23-dibromostigmasteryl acetate, and the quaternary ammonium iodide is methyltriethyl ammonium iodide.

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