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20-DIMETHYLAMINO-PREGNENES AND THEIR QUATERNARY HALIDES

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5 Claims. (Cl. 260—397.5)

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The present invention relates to the production of dimethylamino steroid compounds and their quaternary ammonium salts, and particularly to those characterized by the presence of a dimethylamino group at the 17 position of the steroid nucleus or in a group attached to the 17 position.

As yet no one has attempted to degrade the steroid molecule via the quaternary ammonium derivatives of tertiary dimethylamines of the cyclopentanopolyhydrophenanthrene series. The discovery of new methods of steroid degradation has been a challenge in view of the need for efficient means for the production of therapeutically active materials. Certain of the quaternary ammonium compounds have been found useful in steroid degradation, thus any method for the preparation of the tertiary dimethylamines is of value and, indeed, a method which possesses a certain degree of specificity is of considerable importance. Furthermore, it has been stated that quaternary ammonium halides of 7-amino-steroids could not be formed (H. Eckhardt, Ber., 71, 461 (1938)), but we have found that all amines studied by our methods have led to such quaternary compounds.

It is accordingly an object of the present invention to provide a method for the production of tertiary dimethylamines in the steroid series.

A further object is to provide a method for the production of quaternary ammonium compounds in the steroid series.

Another object is to produce quaternary ammonium compounds from tertiary dimethylamines of the steroid series.

An additional object is to produce tertiary dimethylamines in the steroid series.

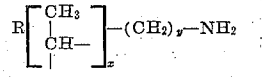
Still another object is to produce quaternary ammonium compounds in the steroid series.

Other objects will be apparent to those skilled in the art from the following description.

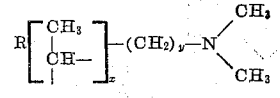
It has been found that steroid amines containing an amino group either at the 17 position of the nucleus or in a group attached to the 17 position of the nucleus may be converted to the dimethylamines by reductive methylation

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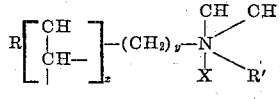
through treatment with formaldehyde and formic acid. Thus, amines of the type



where R is the cyclopentanopolyhydrophenanthrene nucleus, x equals 0 or 1, and where y equals 0 when x equals 0 and where y equals 0, 1 or 2 when x equals 1, may all be readily methylated to compounds of the type

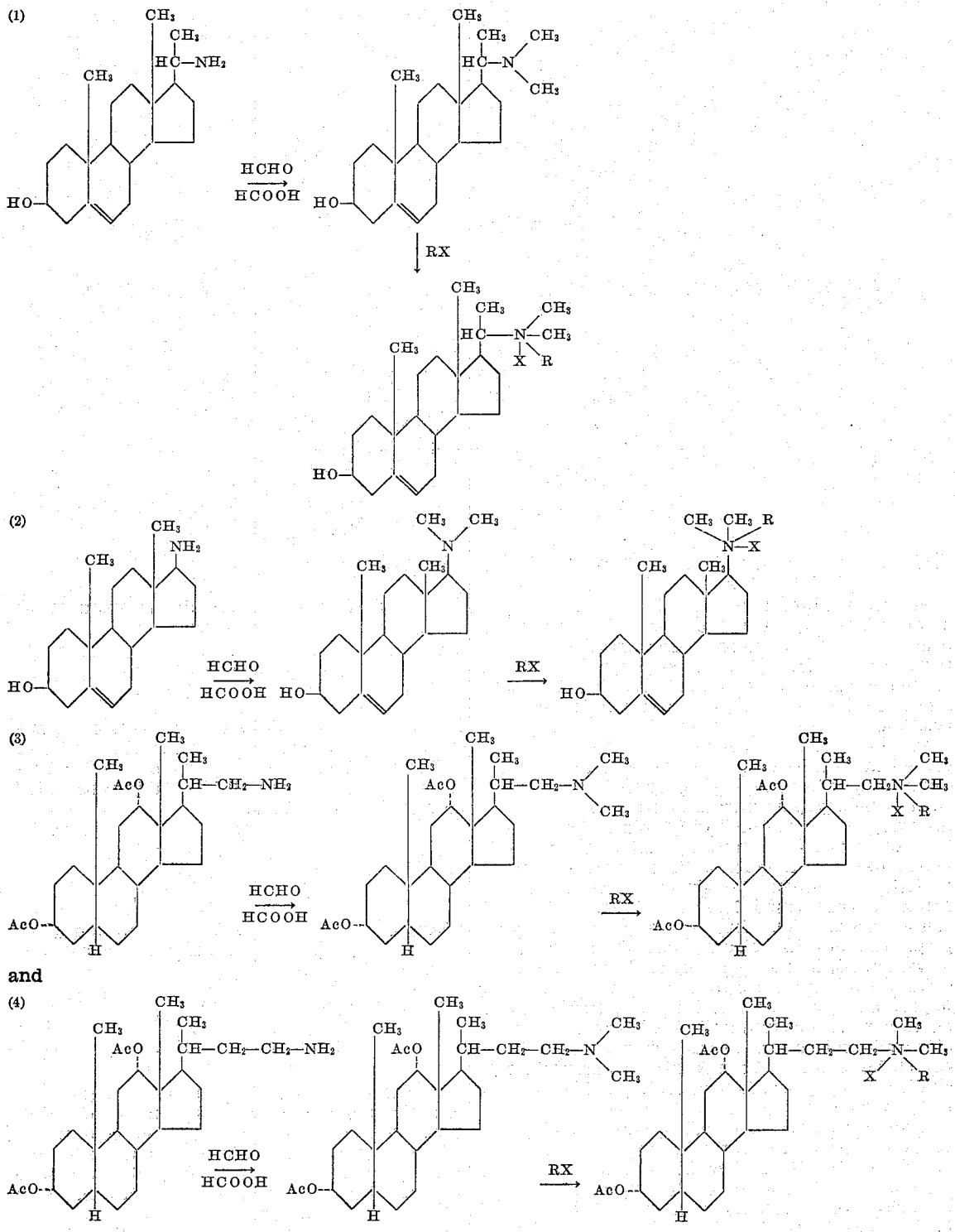


where R, x, and y have the connotation given above, and converted to the quaternary ammonium derivatives of the type



where R, x, and y are as previously designated and where R' is alkyl or aralkyl and Z is chlorine, bromine, iodine or hydroxyl. This type of methylation is not sufficiently drastic to cause any extensive or uncertain alteration of other labile functional groups. These dimethylamines may be converted to the quaternary ammonium halide salts by treatment of the dimethyl tertiary amines with alkyl and aralkyl halides. These quaternary ammonium compounds are valuable in the synthesis of therapeutically active steroids. The dimethylamines, in addition to their being useful for the preparation of the quaternary ammonium compounds, may themselves prove to have valuable therapeutic properties since certain other steroid amines have been recorded in the literature as being bacteriostatic agents.

These reactions involved in the reductive methylation and formation of the quaternary ammonium salts may be illustrated by the following equations, employing typical amines of the steroid series.



EXAMPLE I

3-hydroxy-5-ternorcholenyldimethylamine

6.34 g. of 3-hydroxy-5-ternorcholenylamine was dissolved with gentle warming in 6.24 g. of 90% formic acid. After the addition of 3.77 g. of 35% aqueous formaldehyde solution, the mixture was refluxed for four hours. CO_2 was liberated during this period. The mixture was then suspended in water-ether and shaken out with dilute hydrochloric acid. The aqueous layer containing suspended insoluble hydrochloride was separated and made alkaline with dilute sodium carbonate solution. The alkaline suspension was extracted with ether and the ether layer was washed several times with water and dried. The ethereal solution was concentrated to about 30 cc. volume, chilled and the crystalline solid separated by filtration. A second crop of crystalline material was obtained by concentration of the mother-liquor. The product, 5.8 g. of 3-hydroxy-5-ternorcholenyldimethylamine, melted at 167–171° C. Recrystallization from ether gave purer material melting at 169.5–171.5° C.

EXAMPLE II

3-acetoxy-5-ternorcholenyldimethylamine

A mixture of 3.59 g. of 3-acetoxy-5-ternorchol-

enylamine, 3.57 g. of 90% formic acid and 35% aqueous formaldehyde solution was heated on the steam bath under reflux for four hours. The mixture was then chilled, made basic with dilute sodium carbonate solution and extracted with ether. The ether extract was washed with water several times and dried. The white crystalline residue remaining after removal of solvent was recrystallized from ether-petroleum ether. There resulted 2.1 g., first crop, of crude 3-acetoxy-5-ternorcholenyldimethylamine. More of the amine may be obtained by concentration of the mother-liquor. The amine when purified by further recrystallization melts at 184.5–187.5° C.

EXAMPLE III

3-acetoxy-5-ternorcholenyldimethylamine

A mixture of 20.5 g. of 3-acetoxy-5-ternorcholenylamine acetate, 17.85 g. of 90% formic acid and 35% aqueous formaldehyde was heated on a steam bath for five hours. Carbon dioxide was liberated at the beginning of the heating period. The mixture was diluted with water. After the addition of ether and dilute hydrochloric acid, the mixture was shaken and the aqueous layer containing suspended insoluble hydrochloride was separated. The aqueous suspension was made alkaline with dilute sodium carbonate solution and extracted with ether. The extract was washed with water and dried. Upon removal of solvent, there remained 17.8 g. of crude 3-acetoxy-5-ternorcholenyldimethylamine, M. P. 153–175° C. Recrystallization from ether gave pure material melting at 184.5–187.5° C.

EXAMPLE IV

3-hydroxy-5-androstene-17-dimethylamine

25 g. of 3-hydroxy-5-androstene-17-amine was added with cooling and shaking to 24 cc. of 90% formic acid. The slurry became brown. Then 17 cc. of 35–38% aqueous formaldehyde was added and the mixture was heated for four hours under reflux on the steam cone. The solid dissolved with copious evolution of CO_2. The solution was concentrated in vacuo to a thick sirup which was taken up in a mixture of ether and 5% aqueous hydrochloric acid. The acidic layer was made basic with 10% sodium hydroxide and the amine extracted with ether. The ether solution was washed several times with water, dried and concentrated to about 150 cc. After chilling, the separated solid was filtered and washed with petroleum ether. Another crop was obtained from the mother-liquor. There resulted 19.0 g. of white crystalline 3-hydroxy-5-androstene-17-dimethylamine, M. P. 208–213° C.

EXAMPLE V

3-acetoxy-allo-ternorcholanyldimethylamine

4.2 g. of 3-acetoxy-allo-ternorcholanylamine acetate was mixed with 3 g. of 90% formic acid and 2 g. of 35% aqueous formaldehyde solution and heated on a steam bath for four hours. The solution was then concentrated in vacuo, diluted with 5% hydrochloric acid and extracted with ether. The acidic aqueous layer was made alkaline with 10% sodium hydroxide solution and extracted with ether. The ether extract was washed with water and dried. The residue remaining after removal of solvent was crystallized from benzene. The crude 3-acetoxy-allo-ternorcholanyldimethylamine melted at 147–153° C.

EXAMPLE VI

3(α),12(α)-diacetoxy-ternorcholanyldimethylamine

The acid chloride was prepared from 7.2 g. of 3(α),12(α)-diacetoxy-bisnor-cholanic acid and 4.2 cc. of thionyl chloride in 20 cc. of dry benzene–40 cc. of dry ether. After one hour the solvent was removed and the acid chloride was dissolved in 130 cc. of acetone. This solution was treated, dropwise, at 0–5° C. with a solution of 2.3 g. of sodium azide in 10 cc. of water. The mixture was stirred for twenty minutes and the azide precipitated by the addition of 200 cc. of cold water. The solid azide was separated, suspended in 130 cc. of 80% aqueous acetic acid and decomposed by heating to 50–60° C. for one hour. The clear solution was steam distilled, neutralized with dilute sodium carbonate solution and extracted with ether. The washed and dried ether solution gave upon concentration 6.2 g. of crude 3(α),12(α)-diacetoxy - ternorcholanylamine (acetamide derivative, M. P. 220–221° C.).

The crude amine was methylated by heating 5.2 g. in 6 cc. of 90% formic acid and 4 cc. of 35% aqueous formaldehyde on the steam bath under reflux for four hours. The orange liquid was poured into cold dilute sodium hydroxide and extracted with ether. The ether solution was washed with water, dried and concentrated in vacuo. The resulting amorphous material (5.5 g.) was crystallized from petroleum ether (B. P. 35–60° C.) yielding small needles of 3(α), 12(α) - diacetoxy-ternorcholanyldimethylamine melting at 134–137° C.

Treatment of the ternorcholanyldimethylamine with methyl iodide in boiling benzene under reflux gave the ether insoluble, solid quaternary methiodide.

EXAMPLE VII

A solution of 3.6 g. of 3-keto-5-androstene-17-amine acetate in 3.6 g. of formic acid and 2.6 g. of 35% aqueous formaldehyde was heated on the steam bath under reflux for four hours. Carbon dioxide was liberated. The liquid was diluted with sodium carbonate solution and extracted with benzene-chloroform. The extract was washed with water followed by dilute hydrochloric acid. The acidic extract was made alkaline with sodium carbonate solution and extracted with benzene-chloroform. The extract was then washed with water and dried. Concentration gave the crude 3-keto - 5 - androstene- 1 -dimethylamine. This material can be crystallized from ether-petroleum ether (B. P. 35–60° C.) after treatment with activated alumina.

The crude amine gave an ether insoluble quaternary iodide when treated with methyl iodide in boiling benzene. It is soluble in water.

EXAMPLE VIII

3-hydroxy-5-ternorcholenyltrimethylammonium iodide

A solution of 2.0 g. of 3-hydroxy-5-ternorcholenyldimethylamine in 25 cc. of dry benzene was treated with 4 cc. of methyl iodide. After refluxing for an hour, the solid was filtered and washed with dry ether. The 3-hydroxy-5-ternorcholenyltrimethylammonium iodide weighed 2.3 g.

EXAMPLE IX

3-acetoxy-5-ternorcholenyltrimethylammonium iodide

A solution of 17.8 g. of 3-acetoxy-5-ternorcholenyldimethylamine in 200 cc. of dry benzene was treated with 12 cc. of methyl iodide. After refluxing for three hours, the semi-solid mass was filtered and washed with anhydrous ether. The mother-liquor was retreated with 5 cc. of methyl iodide for an additional crop. There resulted 20.7 g. of 3-acetoxy-5-ternorcholenyltrimethylammonium iodide; M. P. of crude, 260–270° C. with decomposition.

EXAMPLE X

3-hydroxy-5-etiocholenyltrimethylammonium iodide

A solution of 3.2 g. of 3-hydroxy-5-androstene-17-amine in 90 cc. of dry benzene was treated with 15 cc. of methyl iodide. The mixture was refluxed until it was thick with crystalline solid material. After chilling, the solid was filtered and washed with anhydrous ether. The product, 3-hydroxy - 5 - etiocholenyltrimethylammonium iodide, weighed 4.0 g. Recrystallization from methanol gave 3.5 g. of pale yellow needles.

EXAMPLE XI

3-acetoxy-allo-ternorcholanyltrimethylammonium bromide

A solution of 0.5 g. of 3-acetoxy-allo-ternorcholanyldimethylamine in 10 cc. of benzene was mixed with a solution of 5 g. of methyl bromide in 5 cc. of benzene. The mixture was refluxed for five hours. As heating progressed the solution became cloudy and then a solid separated. After dilution with ether, the white solid was separated and washed well with ether. The product, 3 - acetoxy - allo - ternorcholanyltrimethyl - ammonium bromide, weighed 0.4 g. The material is quite soluble in methanol but may be recrystallized from a cold, concentrated solution.

EXAMPLE XII

3-acetoxy-5-ternorcholenyldimethylbenzylammonium chloride

A solution of 1.0 g. of 3 - acetoxy - 5 - ternorcholenyldimethylamine in 10 cc. of benzyl-chloride was refluxed for 20 minutes. The chilled mixture was diluted with ether and the white solid was filtered. This material, 0.4 g., was quite soluble in methanol but almost insoluble in ether. It is recrystallized from ether-methanol. The fine crystals of 3-acetoxy-5-ternorcholenyldimethylbenzylammonium chloride decomposed slightly when heated to 285° C. but did not melt. They proved to be partially soluble in water; the aqueous solution forming a white precipitate upon the addition of silver nitrate solution.

EXAMPLE XIII

3-hydroxy-5-etiocholenyldimethylisoamylammonium bromide

A solution of 1.0 g. of 3-hydroxy-5-androstene-17-dimethylamine in 10 cc. of isoamyl bromide was refluxed for one hour. After chilling the mixture was diluted with ether and the solid was filtered. The crystalline solid, 0.5 g., was poorly soluble in ether and slightly soluble in water. It may be recrystallized from methanol. This material, 3 - hydroxy - 5 - etiocholenyldimethyl - isoamylammonium bromide does not meet below 250° C.

EXAMPLE XIV

3(α),12(α)-diacetoxy-bisnorcholanyldimethylamine

The acid chloride was prepared from 9.2 g. of 3(α), 12(α)-diacetoxy-norcholanic acid and 4.8 cc. thionyl chloride in 20 cc. dry benzene and 40 cc. dry ether. After 1½ hours the solvent was removed and the acid chloride was dissolved in 160 cc. distilled acetone. This solution was treated at 10° C. with a solution of 2.8 g. sodium azide in 12 cc. water, added dropwise in 10 minutes. The azide was precipitated with 300 cc. cold water as a gum, which was extracted with alcohol-free ether. The ethereal solution was washed, dried, concentrated in vacuo. The residual solid was dissolved in 160 cc. 80% acetic acid and decomposed by heating one hour at 150°±10° F. The solution was steam distilled, made alkaline with sodium carbonate, extracted with ether, and the ethereal solution shaken out with 10% hydrochloric acid. The acid washes were made alkaline with sodium carbonate solution, the amine extracted with ether, washed, and dried. On concentration 8.0 g. amine was obtained (acetamide derivative M. P. 215° C.).

The crude amine was methylated by heating 8.0 g. in 8 cc. 90% formic acid and 6 cc. 38% aqueous formaldehyde for 4 hours under reflux on the steam bath. The solution was diluted with water and 5% hydrochloric acid, shaken out with ether, and the water layer made alkaline with 5% sodium hydroxide. The white precipitate was extracted with ether, washed, dried, concentrated and crystallized from ether-petroleum ether (B. P. 35–60° C.). A total of 5.7 g. amine was obtained. On recrystallization from ether it melted at 168–171° C.

A 2.6 g. sample of the dimethylamine was dissolved in 30 cc. of benzene and treated with 5 cc. of methyl iodide. After refluxing for one-half hour, the quaternary halide, 3(α), 12(α)-diacetoxy - bisnorcholanyltrimethylammonium iodide, was precipitated by the addition of ether. The mixture was chilled, filtered, and the solid washed with ether. The crude quaternary ammonium iodide weighed 3.4 g.

EXAMPLE XV

3(α),12(α)-diacetoxy-norcholanyldimethylamine

The diacetoxy derivative from 20.0 g. of desoxycholic acid was converted to the acid chloride with 13 cc. of thionyl chloride in 100 cc. of dry benezene–200 cc. of dry ether, and one drop 10% pyridine in benzene. After one and one-half hours the solvent was removed in vacuo and the crystalline acid chloride dissolved in 400 cc. of distilled acetone. This solution was cooled to 5° C. and a solution containing 7.0 g. of sodium azide in 30 cc. of distilled water was added during 30 minutes. The reaction was stirred for 30 minutes, then diluted with 600 cc. of cold water, added during one hour. The precipitated azide was filtered and washed with water. The moist azide was decomposed in 400 cc. 80% acetic acid at 70° C. for one hour, then steam distilled for 45 minutes. The reaction was made slightly alkaline with sodium carbonate and extracted with ether. The ethereal extract was washed, shaken out with 10% hydrochloric acid; the acid washes were made alkaline with sodium carbonate, extracted with ether, washed, dried, and concentrated. 15.7 g. of amine portion was obtained.

This crystallized from ether-petroleum-ether (B. P. 35–60° C.) as needles, M. P. 156–158° C.

20 g. of the crude amine was methylated in 20 cc. of 90% formic acid and 15 cc. of 38% aqueous formaldehyde by warming on the steam bath, under reflux, for sixteen hours. The reaction was diluted with water, poured with stirring into sodium carbonate solution and the amorphous solid filtered and washed. It was taken up in ether, the amine shaken out with 10% hydrochloric acid, and the acid washes made alkaline with sodium carbonate. The amine was extracted with ether, washed, dried, and concentrated. The residue weighed 15.5 g. This material was dissolved in 100 cc. of methanol, 50 g. of methyl iodide added, and the solution refluxed for two hours. It was then concentrated, dry ether added, and 12.3 g. of methiodide was obtained as yellow crystals. On recrystallization this melted at 218–220° C.

The foregoing examples are illustrative of the invention, it being understood that various changes and modifications may be made therein without departing from the spirit and the scope of the invention. Thus, other alkyl and aralkyl iodides, bromides and chlorides may be used for the preparation of the quaternary halides.

Reference is made herein to the copending application of two of us, Serial No. 770,336, filed August 23, 1947.

Having described the invention, what is claimed is:

1. Pregnene compounds selected from the class consisting of 20-dimethylamino-5-pregnenes and their quaternary ammonium halides other than quaternary ammonium fluorides.

2. The quaternary ammonium halide compounds of claim 1.

3. The trimethyl ammonium halides of claim 2.

4. 20-dimethylamino-5-pregnenes.

5. 3-acetoxy-20-dimethylamino-5-pregnene.

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REFERENCES CITED

The following references are of record in the file of this patent:

UNITED STATES PATENTS

Number	Name	Date
2,252,863	Raymond et al.	Aug. 19, 1941
2,481,524	MacPhillamy	Sept. 13, 1949