and antimony are intermediate between those calculated for the monomeric monosodium salt and free acid.

The viscosity of aqueous solutions increases with time, up to the formation of stiff, thixotropic gels. For example, a 3% solution of the polymer in 4% urea solution, showed four hours after preparation a relative viscosity of 1.8, the solvent at the same temperature being taken as unity. The relative viscosity of a solution of the crystalline stibonate of equal antimony content was less than 1.05.

A 2% aqueous solution of the polymer shows strong flow birefringence when observed between crossed nicols. An analogous solution of the crystalline sodium salt is optically inactive.

Comparison of Prophylactic Effect of Polymerized Sodium *p*-Melaminylphenylstibonate and Naphuride in the T. equiperdum Infection of the Mouse.—(See Table II.) Mice were treated with a single i. p. dose of the drug and after an interval of two months injected with a suspension of virulent *T. equiperdum*. Daily blood examinations were then carried out. Animals found to be negative after thirty-seven days were then re-infected, controlled by daily blood examinations for two months, and then submitted to a third test infection. The test infection killed untreated control animals within three to five days.

Summary

1. A crystalline sodium salt of *p*-melaminylphenylstibonic acid has been prepared. It cures the experimental *T. equiperdum* infection of the mouse with a therapeutic index of 3, but has no appreciable prophylactic effect.

2. The crystalline *p*-melaminylphenylstibonate has been polymerized. In comparison with the crystalline stibonate, the polymer has a 4-fold increased trypanocidal activity and a 17-fold decreased toxicity, corresponding to a therapeutic index of 200 in the *T. equiperdum* infection of the mouse.

3. In the *T. equiperdum* infection of the mouse, the polymerized product has a very pronounced prophylactic effect. The duration of this effect is significantly longer than with comparable doses of Naphuride.

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[CONTRIBUTION FROM THE DEPARTAMENTO DE QUÍMICA DA FACULDADE DE FILOSOFIA, CIÊNCIAS E LETRAS DA UNIVERSIDADE DE SÃO PAULO]

Some Steroid Mercaptols

BY HEINRICH HAUPTMANN

There appears to have been no attempt to prepare steroid mercaptols since Mylius[1] let thiophenol react with dehydrocholic acid (3,7,12-triketocholanic acid). As previously reported[2] we began an investigation of these substances, first studying the behavior of 4-cholesten-3-one with different mercaptans. While in this case we observed no reaction with thiophenol and could not isolate any crystallized product except diphenyl disulfide, we were able to prepare a mercaptol by the reaction of 4-cholesten-3-one and benzylmercaptan in the presence of anhydrous zinc chloride and sodium sulfate. 4-Cholesten-3-one dibenzylmercaptol melts at 126.5–127°, $[\alpha]^{27}D$ + 128 ± 1°. It crystallizes so well that it can be used for the identification of 4-cholesten-3-one. With tetranitromethane it turns brown. When refluxed with Raney nickel[3] in dioxane and water it is transformed into 4-cholestene which we identified by its m. p. of 79–80°, specific rotation $[\alpha]^{27}D$ 64.6 ± 1°, and its dibromide with the m. p. 115.5–116.5°. That means that there is no addition of the mercaptan to the conjugated double bonds. This observation is surprising in view of the studies by Posner,[4] Ruhemann[5] and Nicolet[6] of the behavior of α,β-unsaturated ketones with mercaptans, as well as the papers of Diels and Abderhalden,[7] Ruzicka[8] and Grasshoff[9] on 4-cholesten-3-one as an α,β-unsaturated ketone. We attempted to bring the double bond to reaction using piperidine as a catalyst, instead of zinc chloride and sodium sulfate. According to Ruhemann[5] this greatly favors the addition of mercaptan to the double bond instead of the condensation to mercaptol. We were unable, however, to isolate any reaction product containing sulfur, except dibenzyl disulfide. In addition to small quantities of unchanged 4-cholesten-3-one, we obtained a few milligrams of a sulfur-free substance, m. p. 146–150°, which with tetranitromethane gave a strong brown color. We believed that *allo*- and *epi-allo*-cholesterol might have been formed by reduction, possibly mixed with other secondary reaction products. According to Schoenheimer and Evans[10] those two substances form a molecular compound of the m. p. 141°. The lack of reaction with trichloroacetic acid, which according to these investigators[10] is characteristic of these unsaturated steroid alcohols or their dehydration products, seems to exclude the presence of both the *allo*-cholesterols. We must postpone clarification of this question until we have greater quantities of this sulfur-free substance.

(1) F. Mylius, *Ber.*, **20**, 1968 (1887).

(2) H. Hauptmann, *Anais assoc. quim. Brasil*, **3**, 231 (1944); *C. A.*, **40**, 569 (1946).

(3) (a) J. Bougault, E. Cattelain and P. Chabrier, *Compt. rend.*, **208**, 615 (1939); *C. A.*, **33**, 485 (1940); *Bull. soc. chim.*, [5] **6**, 34 (1939); **7**, 781 (1940); *C. A.*, **36**, 2198 (1942); (b) R. Mozingo, D. E. Wolf, S. A. Harris and K. Folkers, THIS JOURNAL, **65**, 1477 (1943); (c) M. L. Wolfrom and J. V. Karabinos, *ibid.*, **66**, 909 (1944).

(4) Th. Posner, *Ber.*, **33**, 3165 (1900).

(5) S. Ruhemann, *Proc. Chem. Soc.*, **20**, 251 (1904); *Chem. Zentr.*, I, 443 (1905); *Proc. Chem. Soc.*, **21**, 123 (1905); *Chem. Zentr.*, I, 1466 (1905); *J. Chem. Soc.*, **87**, 17, 461 (1905); *Chem. Zentr.*, I, 741, 1640 (1905).

(6) B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(7) O. Diels and E. Abderhalden, *Ber.*, **37**, 3099 (1904).

(8) L. Ruzicka, *Helv. Chim. Acta*, **17**, 1414 (1934).

(9) H. Grasshoff, *Z. physiol. Chem.*, **223**, 250 (1934).

(10) R. Schoenheimer and E. A. Evans, *J. Biol. Chem.*, **174**, 567 (1936); E. A. Evans and R. Schoenheimer, THIS JOURNAL, **58**, 182 (1936).

In the same way as benzylmercaptan, ethanedithiol reacts with 4-cholesten-3-one, yielding a 4-cholesten-3-one-ethylene-mercaptol which melts at 106–107°, $[\alpha]^{27}D$ + 119 ± 1°. The ethylene double bond does not react under these conditions either, as we can establish beyond doubt by the same reactions used in case of the dibenzylmercaptol.

We examined the behavior of dehydrocholic acid, or its ethyl ester, with several mercaptans in order to check the general applicability of the reaction to the hydrocyclopentanophenanthrene series, and especially in order to determine whether the position of the keto group in the steroid skeleton has any decisive influence. When we attempted the reaction of dehydrocholic acid with thiophenol using gaseous hydrochloric acid as a catalyst, as described by Mylius,[1] we were unable either to observe the great solubility of the acid in the mercaptan, mentioned by this author, or to isolate the product he describes. Under milder conditions, however, *i. e.*, in glacial acetic acid and with concentrated aqueous hydrochloric acid as a catalyst, we obtained a compound of a m. p. 215–216°, $[\alpha]^{27}D$ + 48.5 ± 2°, which evidently is identical with Mylius' product. Its constitution was clarified by the result of its desulfuration with Raney nickel by means of which 7,12-diketocholanic acid was formed. This latter was identified by transformation into the methyl ester[11] and its dioxime.[11] Thus Mylius' compound is the dehydrocholic acid 3-diphenylmercaptole.[12]

Similarly, by reaction of dehydrocholic acid ethyl ester with ethyl mercaptan we have so far isolated the ethyl dehydrocholate 3-diethylmercaptol. It melts at 119–120.5°, $[\alpha]^{27}D$ + 34.1 ± 2° and by desulfuration with Raney nickel it was transformed into the ethyl ester of the 7,12-diketocholanic acid,[13] which was characterized by its dioxime. In view of the great reactivity of the ethyl mercaptan with carbonyl groups[14] it is surprising that here too only a mono-mercaptol could be isolated.

That is why we must emphasize the importance of our finding that under identical conditions, *i. e.*, in the presence of gaseous hydrochloric acid at low temperature, ethanedithiol reacts easily with all three of the keto-groups of dehydrocholic acid ethyl ester. As a result dehydrocholic acid ethyl ester triethylenemercaptol of the m. p. 181.5°, $[\alpha]^{27}D$ + 69.9 ± 3° is formed, which can be saponified to the corresponding acid by means of alcoholic sodium hydroxide solution. This acid melts at 198–200°, solidifies again at about 210° and melts definitively at 276–278°. Its specific rotation is $[\alpha]^{27}D$ + 75.6 ± 3°. During the desulfuration with Raney nickel all the carbon–sulfur bonds are hydrogenolyzed and cholanic acid ethyl ester is formed from the ethyl ester.

It is interesting that the condensation of dehydrocholic acid with ethanedithiol produces the trimercaptol without difficulty only in the presence of hydrochloric acid. With anhydrous zinc chloride and sodium sulfate even when heating to 100° one obtains mixtures which according to the analytical results (28% sulfur) contain trimercaptol mixed with lower condensation products. By heating the reaction mixtures to 50° we isolated, by means of repeated recrystallizations, small quantities of di-mercaptols[15] which, however, were too small for a determination of structure by desulfuration.

Our experiments show that the ethanedithiol condenses with carbonyl groups of dehydrocholic acid, which do not react under comparable conditions with the monovalent mercaptans which we examined. We believe that the possibility of formation of a ring facilitates the formation of mercaptols.

On the other hand, the behavior of dehydrocholic acid with monovalent mercaptans shows that here, too, the keto group of the carbon atom 3 is the most reactive. This is understandable in the light of the general behavior of the ketosteroids. This behavior, however, reduces the possibilities of using the mercaptols as intermediate products of partial reduction of the ketosteroids, since usually the reduction of this group is not desired, *e.g.*, in the preparation of lithocholic acid. For this purpose we used 3-hydroxy-7,12-diketocholanic acid, whose ethyl ester condenses easily with two moles of ethanedithiol forming ethyl 3-α-hydroxy-7,12-diketocholanate diethylenemercaptol, m. p. 191–193°, $[\alpha]^{22}D$ 73.5 ± 2°. It can be saponified with alcoholic solution of sodium hydroxide to the corresponding acid of the m. p. 230–231°, $[\alpha]^{27}D$ + 69.6 ± 3°. During the ethyl ester's desulfuration with Raney nickel the ethyl lithocholate was formed. It did not crystallize, and was therefore first saponified for purification to free lithocholic acid, which in turn was transformed into its methyl ester[16] and the acetate of the methyl ester[17] in order to identify it.

Furthermore, we let estrone acetate react with ethanedithiol in the presence of gaseous hydrochloric acid and obtained estroneacetate ethylene mercaptol, m. p. 141.5–142°, $[\alpha]^{27}D$ + 20.2 ± 2°.

(11) R. Tschesche, *Z. physiol. Chem.*, **203**, 263 (1932).

(12) In "The Chemistry of the Steroids," Baltimore, 1938, p. 416, H. Sobotka assigns to the compound the structure we proved for it, but he does not indicate the source, and we were not able to detect it either.

(13) W. Borsche, *Ber.*, **52**, 1363 (1901).

(14) Th. Posner, *ibid.*, **34**, 2643 (1901).

(15) We referred to one of these products in our preliminary communication[2] indicating that under mild conditions two keto groups of the dehydrocholic acid react with ethanedithiol.

(16) (a) F. Borsche, O. Weikert and F. Hallwass, *Ber.*, **55**, 3224 (1922); (b) L. Ruzicka and M. W. Goldberg, *Helv. Chim. Acta*, **18**, 668 (1935); (c) F. Reindel and K. Niederlaender, *Ber.*, **68**, 1969 (1935).

(17) (a) S. Bergstroem and G. A. D. Haslewood, *J. Chem. Soc.*, 540 (1939); (b) R. Grand and T. Reichstein, *Helv. Chim. Acta*, **28**, 344 (1945).

We therefore made sure that the keto group at the carbon atom 17 of the steroid skeleton also reacts under these conditions. Even estrone itself condensed with ethanedithiol, but the reaction product was difficult to purify. So, in order to prove the condensation, we acetylated the product according to Butenandt[18] obtaining the above mentioned acetate.

The keto group at the carbon atoms 3, 7, 12 and 17, where oxygen atoms are found most frequently in natural steroids, all form easily cyclic mercaptols with ethanedithiol. It should be of special interest to examine the unreactive keto group[19] at the carbon atom 11, for its faculty to form mercaptols.[20]

Finally we wish to point out that the desulfuration of mercaptols represents a convenient and mild method of preparative reduction of steroid ketones. Wolfrom and Karabinos[3c] were the first to use this method for transforming diethylmercaptols of aliphatic and aromatic ketones into the corresponding hydrocarbons, and to prove the applicability of the method for transformation of the carbonyl into the methylene group of the sugar series. Our experiments show that in the steroid series the ethylenemercaptols are obtained with good yields, and that their desulfuration under mild conditions substitutes the thioketal groups by hydrogen, a process which in its final effects equals a substitution of ketonic oxygen by hydrogen. The two methods of reduction most frequently applied to ketosteroids are those of Clemmensen and Wolff–Kishner. The desulfuration method is superior to that of Clemmensen. In the first place the double bonds α, β to the keto group, which by the Clemmensen reduction may be altered, are left intact. Secondly, none but mercaptol groupings are hydrogenolyzed. Therefore 3-α-hydroxy-7,12-diketocholanic acid is reduced to lithocholic acid instead of cholanic acid formed by the Clemmensen method. On the other hand, the Wolff–Kishner method is not superior to that of desulfuration, in spite of the fact that incomplete reduction to secondary hydroxyl groups can be avoided[21] and that the application of pressure is unnecessary.[22] In any case, under the condition of hydrogenolysis of the mercaptols there is no danger of epimerization of secondary alcohol groups, which may be present, a risk that can never be entirely neglected during the reduction according to the method of Wolff-Kishner.[18b,19b,23]

When this paper had already been received by the Editor there appeared a publication by S. Bernstein and L. Dorfmann, THIS JOURNAL, **68**, 1152 (1946), who studied some steroid monomercaptols and the hydrogenolytic desulfuration with Raney nickel, and who found results analogous to those obtained by ourselves.

Acknowledgment.—I wish to express my thanks to my assistants and doctoral candidates for their aid in preparing reagents and substances for comparison and to Dr. F. Berti and Mr. W. Rzeppa of the Instituto Butantan for the microanalyses. Acknowledgment is also made to the Rockefeller Foundation for the laboratory material granted to the Department of Chemistry of the Faculdade de Filosofia Ciências e Letras da Universidade de São Paulo, part of which we used for this work, and to the Instituto Butantan, the Endochimica S. A., the Instituto Hormoterapico Nacional and the I. R. F. Matarazzo for estrone, bile acids and other drugs, which they kindly furnished.

Experimental

All rotations were measured in 2 cc. of chloroformic solution with a tube of 1-dm. length. The Raney nickel was prepared from nickel aluminum alloy according to the procedure of Mozingo and his colleagues.[3b]

4-Cholesten-3-one Dibenzylmercaptol.—Two cc. of benzyl mercaptan was added slowly with ice-cooling to a mixture of 1 g. of freshly fused zinc chloride, 1 g. of anhydrous sodium sulfate and 0.8 g. of 4-cholesten-3-one. The mixture was maintained at room temperature for three days, whereupon it was extracted with ether. The ethereal solution was evaporated and the excess of benzyl mercaptan removed *in vacuo*. The residue consisting of mercaptol was recrystallized from a mixture of absolute alcohol and benzene 4:1, m. p. 126.5–127°, yield 1.2 g. (94%).

Anal. Calcd. for $C_{41}H_{58}S_2$: S, 10.43. Found: S, 10.16, 10.31; rotation for 17.5 mg. was $\alpha^{27}D$ +1.12 ± 0.01° $[\alpha]^{27}D$ +128 ± 1°.

Desulfuration of 4-Cholesten-3-one Dibenzylmercaptol.—Fifty-five hundredths gram of 4-cholesten-3-one dibenzylmercaptol was dissolved in 30 cc. of water and after adding about 5 g. of Raney nickel refluxed during seven hours. At the end of this period the residue of a filtered test portion of the solution was free from sulfur. The Raney nickel was filtered off and washed several times with ether. The combined filtrates were evaporated in the water-bath and dried *in vacuo*. By recrystallization from ether–methanol mixture we obtained a substance with m. p. 79–80°, yield 280 mg. (92%). Rotation for 22.6 mg. was $\alpha^{26}D$ +0.73 ± 0.01°, $[\alpha]^{26}D$ 64.6 ± 1°; the recorded constants[24] for 4-cholestene are m. p. 78–79°, $[\alpha]D$ +64.9°. To 50 mg. of the desulfuration product in ether a 2% solution of bromine in glacial acetic acid was added and the colorless precipitate recrystallized from a mixture of benzene and absolute alcohol, m. p. 115.5–116.5°, yield 63 mg. (86.6%). The recorded melting point[24a] of the dibromocholestane is 116–117°.

Reaction of Benzylmercaptan with 4-Cholesten-3-one in Presence of Piperidine.—A mixture of 2.5 g. of 4-cholesten-3-one, 7.5 g. of benzylmercaptan and 1 g. of piperidine was allowed to stand for five days at room tem-

(18) A. Butenandt, *Z. physiol. Chem.*, **191**, 140 (1930).

(19) M. Steiger and T. Reichstein, *Helv. Chim. Acta*, **20**, 817 (1937); **21**, 828 (1938); C. W. Shoppee, *ibid.*, **23**, 740 (1940); C. W. Shoppee and T. Reichstein, *ibid.*, **24**, 351 (1941); A. Lardon and T. Reichstein, *ibid.*, **26**, 747 (1943); C. Kendall, H. L. Mason, W. M. Hoehn and B. F. McKenzie, *J. Biol. Chem.*, **120**, 719 (1937); H. L. Mason and W. M. Hoehn, THIS JOURNAL, **60**, 2566 (1938).

(20) We hope soon to be able to report on our experiments referring to this.

(21) J. D. Dutcher and O. Wintersteiner, THIS JOURNAL, **61**, 1992 (1939).

(22) M. D. Soffer, M. B. Soffer and K. W. Sherk, THIS JOURNAL, **67**, 1485 (1945); C. H. Herr, F. C. Whitmore and R. W. Schiessler, *ibid.*, **67**, 2061 (1945).

(23) A. Windaus and C. Uibrich, *Ber.*, **48**, 857 (1915); A. Windaus, *ibid.*, **49**, 1724 (1916).

(24) (a) J. Mauthner, *Monatsh.* **28**, 1113 (1907); *Chem. Zentr.*, II, 1597 (1907); (b) J. M. Heilbronn and W. A. Sexton, *J. Chem. Soc.*, 47 (1928); *Chem. Zentr.*, I, 2507 (1928); (c) O. Stange, *Z. physiol. Chem.*, **223**, 245 (1934).

perature. At the end of this period a precipitate formed, which was filtered off, m. p. 60–130°. It was recrystallized from alcohol yielding some needles, m. p. 145–150°, after two recrystallizations from alcohol 146–150°. This substance did not contain sulfur, developed a dark brownish yellow coloration with tetranitromethane, and gave a colorless solution with 90% trichloroacetic acid. From the alcoholic mother liquors colorless needles, m. p. 70°, were precipitated by crystallization.

Anal. Calcd. for $C_{14}H_{14}S_2$: S, 26.04. Found: S, 25.87.

4-Cholesten-3-one-ethylenemercaptol.—The compound was prepared in the manner described above for the dibenzylmercaptol from 0.9 cc. of ethanedithiol, 0.9 g. of 4-cholesten-3-one, 1 g. of freshly fused zinc chloride and 1 g. of anhydrous sodium sulfate. After recrystallization from acetone the melting point of the mercaptol was 106–107°, yield 0.8 g. (73.5%).

Anal. Calcd. for $C_{29}H_{48}S_2$: S, 13.92; mol. wt., 460.5. Found: S, 13.80; mol. wt., 470.0; rotation for 15.3 mg. was $\alpha^{27}D$ +0.91 ± 0.01°; $[\alpha]^{27}D$ +119 ± 1°.

Refluxed with about 5 g. of Raney nickel in 90% alcoholic solution for six hours, 0.6 g. of the mercaptol yielded 0.35 g. (69%) of 4-cholestene which was identified as described above.

Dehydrocholic Acid 3-Diphenylmercaptol.—A solution of 4 g. of dehydrocholic acid and 7 cc. of thiophenol in a mixture of 25 cc. of glacial acetic acid and 0.2 cc. of concentrated hydrochloric acid was allowed to stand for twenty hours in the ice-box. At the end of this period a crystalline precipitate had formed which was recrystallized several times from glacial acetic acid yielding 0.8 g. (13.4%) of the mercaptol, m. p. 215–216°.

Anal. Calcd. for $C_{36}H_{44}O_4S_2$: S, 10.61. Found: S, 10.46; rotation 21.0 mg. $\alpha^{27}D$ +0.51 ± 0.02°; $[\alpha]^{27}D$ +48.5 ± 2°.

Desulfuration of Dehydrocholic Acid 3-Diphenylmercaptol.—Forty-five hundredths gram of the dehydrocholic acid 3-diphenylmercaptol was desulfurated in the manner described above for fourteen hours. The colorless oil resulting from the evaporation of the filtered alcoholic solution was dissolved in ether and treated with an excess of diazomethane for two hours in the cold. At the end of this period the excess of diazomethane was destroyed by adding some drops of glacial acetic acid. From the concentrated and cooled solution crystallized colorless needles, which after three recrystallizations from methanol–water showed the m. p. 133°, yield 210 g. (72%); rotation 16.2 mg.; $\alpha^{24}D$ +0.29 ± 0.01°; $[\alpha]^{24}D$ +35.8 ± 1°. The recorded constants[11] for methyl 7,11-diketocholanate are: m. p. 136°; $[\alpha]D$ +15.5°. A methyl 7,12-diketocholanate which was prepared according to the procedure of Borsche, melted at 134–135°; rotation for 25.0 mg. was $\alpha^{27}D$ +0.27 ± 0.03°; $[\alpha]^{27}D$ +21.6 ± 3°. Its mixed melting point with the desulfuration product was 133–135°. Eleven mg. of the desulfuration product, 50 mg. of hydroxylaminechlorhydrate and 50 mg. of sodium acetate in 15 cc. of methanol were refluxed for two and one-half hours. Upon addition of water a crystalline solid precipitated which after recrystallization melted at 235°. A sample prepared in the same manner from methyl 7,12-diketocholanate melted at 234.5–235° and the mixture of both products at the same temperature. The recorded m. p. is 235°.[11]

Dehydrocholic Acid Ethyl Ester 3-Diethylmercaptol.—Through a mixture of 2.2 g. of dehydrocholic acid and 3.1 cc. of ethylmercaptan, cooled with ice–salt mixture, a current of gaseous hydrogen chloride was passed for three minutes. After remaining in the ice box for fourteen hours the excess of ethyl mercaptan was removed in a vacuum desiccator in the presence of sodium hydroxide. The slightly brownish residue was recrystallized from methanol until it showed the m. p. 119–120.5°, yield 1.48 g. (54%).

Anal. Calcd. for $C_{30}H_{48}O_4S_2$: S, 11.95. Found: S, 11.56; rotation for 24.0 mg. was $\alpha^{27}D$ +0.41 ± 0.02°; $[\alpha]^{27}D$ +34.1 ± 2°.

Desulfuration of Dehydrocholic Acid Ethyl Ester 3-Diethylmercaptol.—Five hundred and fifty mg. of dehydrocholic acid ethyl ester 3-diethylmercaptol was desulfurated as described above. The product obtained was recrystallized from methanol, m. p. 148.5–150°; rotation for 23.1 mg. was $\alpha^{24}D$ +0.31 ± 0.01°; $[\alpha]^{24}D$ +26.8 ± 1°, yield 389 mg. (91%). The recorded m. p.[14] is 153–155°. A sample prepared according to the procedure of Borsche showed: m. p. 150–152°, rotation 20.8 mg., $\alpha^{24}D$ +0.21 ± 0.01°; $[\alpha]^{24}D$ +20.2 ± 1°. Its mixture with the desulfuration product melted at 148.5–150°. The dioxime prepared from the desulfuration product as described above melted at 244–246°, that from the ethyl 7,11-diketocholanate prepared according to Borsche[13] at 244–246° and the mixture of both products showed the same melting point.

Dehydrocholic Acid Ethyl Ester Triethylenemercaptol.—Through a mixture of 2 g. of dehydrocholic acid ethyl ester and 3 cc. of ethanedithiol cooled with ice water a slow current of gaseous hydrogen chloride was passed during two hours. At the end of this period the hydrogen chloride was removed in a vacuum desiccator in the presence of sodium hydroxide, and the excess of ethanedithiol was removed by washing with cold petroleum ether. The residue melted after several recrystallizations from acetone at 181–182.5°, yield 2.4 g. (77.5%).

Anal. Calcd. for $C_{32}H_{30}O_2S_6$: S, 29.2; mol. wt., 658.8. Found: S, 29.41; mol. wt., 635.7; rotation for 21.5 mg. was $\alpha^{27}D$ +0.75 ± 0.03°; $[\alpha]^{27}D$ +69.9 ± 3°.

Desulfuration of Dehydrocholic Acid Ethyl Ester Triethylenemercaptol.—One gram of dehydrocholic acid ethyl ester triethylenemercaptol dissolved in 25 cc. of dioxane and 100 cc. of 90% alcohol was desulfurated as described above for fourteen hours. The residue obtained by evaporation of the filtered solution was dissolved in hot absolute alcohol. After adding a drop of water colorless needles were obtained, which after two more recrystallizations melted at 91–92°; rotation for 23.2 mg. was $\alpha^{27}D$ +0.25 ± 0.01°; $[\alpha]^{27}D$ +21.6 ± 1°. The recorded constants for cholanic ethyl ester[25] are: m. p. 92, 93–94°; rotation $[\alpha]D$ +20.6, +21.6°.

Dehydrocholic Acid Triethylenemercaptol.—One gram of dehydrocholic acid ethyl ester triethylenemercaptol was dissolved in 10 cc. of dioxane and 15 cc. of 0.5 *N* sodium hydroxide solution was added. After refluxing for one and one-half hours, the acid was precipitated with dilute sulfuric acid and recrystallized first from ethyl acetate and then from toluene, m. p. 200°, resolidification at 210°; there was definite melting at 276–278°, yield 0.87 g. (91%).

Anal. Calcd. for $C_{30}H_{46}O_2S_6$: S, 30.50. Found: 30.37; rotation for 14.7 mg. was $\alpha^{27}D$ +0.56 ± 0.02°; $[\alpha]^{27}D$ +75.6 ± 2°.

Ethyl 3α-Hydroxy-7,12-diketocholanate Diethylenemercaptol.—One gram of ethyl 3α,7,12-diketocholanate and 1.9 cc. of ethanedithiol were treated in the manner described for dehydrocholic ethyl ester. The mercaptol was recrystallized from acetone, m. p. 191–195°, yield 1.2 g. (77%).

Anal. Calcd. for $C_{30}H_{48}O_3S_4$: S, 21.93. Found: S, 21.64; rotation for 18.5 mg. was $\alpha^{22}D$ +0.68 ± 0.02°; $[\alpha]^{22}D$ +73.5 ± 2°.

Desulfuration of Ethyl 3α-Hydroxy-7,12-Diketocholanate Diethylenemercaptol.—One gram of the mercaptol was treated in the manner described for dehydrocholic acid ethyl ester triethylenemercaptol. The sulfur-free oil, 690 mg. (99%) did not crystallize and was therefore saponified and the acid obtained (430.5 mg., m. p. 175–182° after several recrystallizations from dilute acetic acid) treated with diazomethane as described above. By two recrystallizations from dilute acetone needles were obtained which melted at 124–126°, yield 402 mg. (60% calculated upon the applied mercaptole); rotation for 20.1 mg. was $\alpha^{27}D$ +0.34 ± 0.03°; $[\alpha]^{27}D$ +33.7 ± 3°.

(25) H. Wieland and W. Boersch, *Z. physiol. Chem.*, **106**, 109 (1919); H. Wieland and F. J. Weil, *ibid.*, **80**, 287 (1912).

The recorded m. p.[16] for methyl lithocholate are 125–126, 125–127 and 130°. By acetylation with acetic anhydride in pyridine and recrystallization from methanol the methyl 3α-acetoxycholanate was obtained, m. p. 129–130°. The recorded m. p. are 128–130 and 129–131°.[19]

Saponification of Ethyl 3α-Hydroxy-7,12-diketocholanate Diethylenemercaptol.—One gram of the mercaptol was saponified in the manner described for dehydrocholic acid ethyl ester triethylenemercaptol. After recrystallization from methanol 3α-hydroxy-7,12-diketocholanic acid diethylenemercaptol melted at 230–231° (Kofler block); yield 0.89 g. (94%).

Anal. Calcd. for $C_{28}H_{44}O_3S_4$: S, 23.04. Found: S, 23.07; rotation for 21.0 mg. was $\alpha^{27}D$ +0.74 ± 0.03°; $[\alpha]^{27}D$ +69.6 ± 3°.

Estrone Acetate Ethylenemercaptol.—28.5 mg. of estrone acetate and 100 mg. of ethanedithiol were treated in the manner described for dehydrocholic acid ethyl ester. After recrystallization from acetone the mercaptol melted at 141.5–142°, yield 35 mg. (94%).

Anal. Calcd. for $C_{22}H_{18}O_2S_2$: S, 16.44. Found: S, 16.14; rotation for 16.9 mg. was $\alpha^{27}D$ +0.17 ± 0.02°; $[\alpha]^{27}D$ +20.2 ± 2°.

Summary

1. The following compounds have been prepared and characterized: 4-cholesten-3-one dibenzylmercaptol, 4-cholesten-3-one ethylenemercaptol, dehydrocholic acid 3-diphenylmercaptol, dehydrocholic acid ethyl ester 3-diethylmercaptol, dehydrocholic acid 3,7,12-triethylenemercaptol and its ethyl ester, 3α-hydroxy-7,12-diketocholanic acid and its ethyl ester, estrone acetate 17-ethylenemercaptol.

2. The constitution has been proved by hydrogenolitic desulfuration with Raney nickel.

3. Ethanedithiol condenses with the keto group at the carbon atoms 3, 7, 12 and 17 of the steroid skeleton, while monothiols only react with that at the carbon atom 3.

4. The desulfuration of mercaptols represents a convenient method for preparative reduction of ketosteroids.

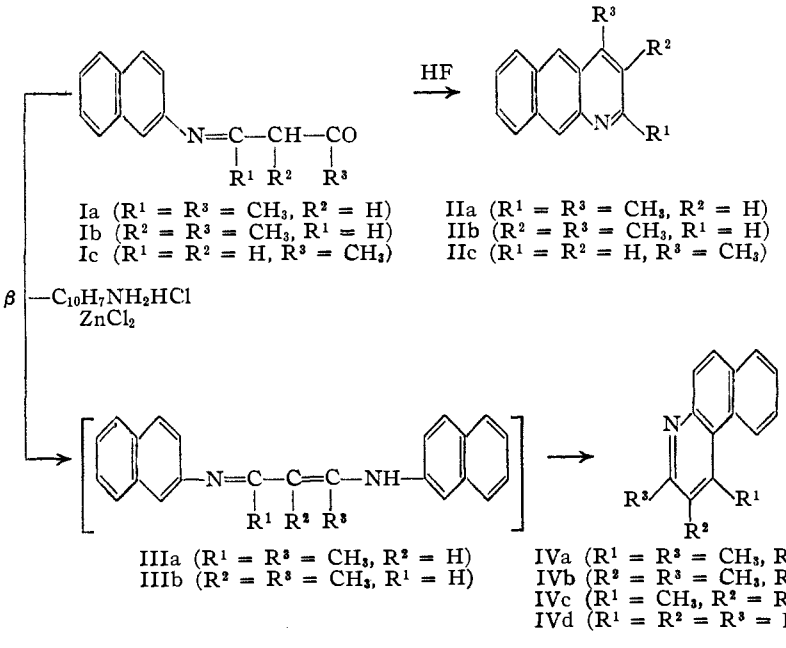
SÃO PAULO, BRASIL RECEIVED JUNE 15, 1946

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Cyclization Studies in the Benzoquinoline and Naphthoquinoline Series. II

BY WILLIAM S. JOHNSON, EUGENE WOROCH AND FREDERICK J. MATHEWS[1]

In the first communication of this series[2] it was shown that 4-(2-naphthylimino)-pentanone-2, Ia, is cyclized by hydrogen fluoride in almost quantitative yield to 2,4-dimethylbenzo[*g*]quinoline, even though the latter was unhindered—not only was quite unexpected[3] but was, to our knowlege, without precedent. In the present work we are reporting the results of some further studies of this type of cyclization as well as some investigations on directing the cyclization into the 1-position.



Ia (R^1 = R^3 = CH_3, R^2 = H)
Ib (R^2 = R^3 = CH_3, R^1 = H)
Ic (R^1 = R^2 = H, R^3 = CH_3)

IIa (R^1 = R^3 = CH_3, R^2 = H)
IIb (R^2 = R^3 = CH_3, R^1 = H)
IIc (R^1 = R^2 = H, R^3 = CH_3)

IIIa (R^1 = R^3 = CH_3, R^2 = H)
IIIb (R^2 = R^3 = CH_3, R^1 = H)

IVa (R^1 = R^3 = CH_3, R^2 = H)
IVb (R^2 = R^3 = CH_3, R^1 = H)
IVc (R^1 = CH_3, R^2 = R^3 = H)
IVd (R^1 = R^2 = R^3 = H)

Angular cyclization of Ia has now been realized to give the previously known[4] 1,3-dimethylbenzo[*f*]quinoline, IVa. The method of ring closure involved heating the anil Ia in alcoholic solution with β-naphthylamine hydrochloride and zinc chloride according to the procedure of Petrow.[5] Since the reaction appears to involve the anilino anil IIIa as an intermediate it may be considered a modification of König's quinoline synthesis.[6] This angular cyclization of Ia suggests that the ring closure of 3-(2-naphthyl IIa. This exclusive preference for linear cyclization into the 3- rather than into the 1-position—

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(2) Johnson and Mathews, THIS JOURNAL, **66**, 210 (1944).

(3) See footnote 7 of ref. 2.

(4) Reed, *J. prakt. Chem.*, [2] **35**, 298 (1887).

(5) Petrow, *J. Chem. Soc.*, 693 (1942).

(6) König, *Ber.*, **56**, 1853 (1923).