for the same compound which he prepared by heating benzyl chloride with phenothiazine. This compound was shown to be different from that obtained in our experiment by a mixed melting point determination. We were also unable to prepare N-benzylphenothiazine from N-lithiophenothiazine and benzyl chloride.

### Experimental

In most of the experiments the reagents were stirred for 48 hours in a nitrogen atmosphere at a bath temperature of 170–180°. After cooling the mixture was shaken with ether, which precipitated most of the 2-hydroxyquinoline if it were present in appreciable amounts. The ether was then extracted with 5% aqueous sodium hydroxide to remove any residual 2-hydroxyquinoline which was recovered by acidification of these extracts with hydrochloric acid and concentration by evaporation. The ether layer was dried over sodium sulfate, and after filtration the ether was removed by distillation. From the residue the other cleavage products and unreacted starting materials were obtained by vacuum distillation or by recrystallization. In Table I we have listed the pertinent data for the various experiments.

**Attempt to Prepare N-Benzylphenothiazine.**—N-Lithiophenothiazine was prepared by adding 0.11 mole of phenyllithium in 20 ml. of dry ether to 5.0 g. (0.025 mole) of phenothiazine in 200 ml. of dry benzene. As this mixture gave a blue-green color which resembled Color Test I,[6] the time at which the phenyllithium was used up could not be noted, so the mixture was stirred at room temperature for 48 hours. A solution of 4.0 g. (0.03 mole) of benzyl chloride in 75 ml. of dry ether was then added, and the stirring was continued at room temperature for 24 hours. After refluxing for one hour, the volatile solvents were removed by distillation. This left a gummy residue which was extracted with 95% ethanol. No crystalline material could be obtained from these extracts.

**Preparation of N-Benzylbenzenesulfonamide.**—A modification of Hinsberg's method[7] was used in this preparation. The addition of 17.6 g. (0.1 mole) of benzenesulfonyl chloride and 40 ml. of 10% sodium hydroxide in small portions, with shaking, to 10.7 g. (0.1 mole) of benzylamine resulted in a brown oil. The mixture was shaken with an additional 400 ml. of 10% sodium hydroxide before filtering. After standing for two days it was filtered again and then acidified with hydrochloric acid. This yielded a white precipitate which was washed with water and dried. The yield was 17.3 g. (70%) of N-benzylbenzenesulfonamide (m.p. 87–89°). Attempts to recrystallize the material from aqueous ethanol, as recommended by Hinsberg, yielded a tan material with a lower melting point (about 80°).

**Acknowledgment.**—The authors are grateful to Dr. Gabriello Illuminati for generous assistance.

(6) H. Gilman and F. Schulze, THIS JOURNAL, **47**, 2002 (1925).
(7) O. Hinsberg, *Ann.*, **265**, 178 (1891).

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## Steroid Mercaptols. II[1]

BY H. HAUPTMANN AND M. MOURA CAMPOS

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Some years ago[1] it was found that 7- and 12-ketosteroids form mercaptols only with dithiols, whereas the carbonyl groups in the 3-, 16[2] and 17-positions react also with monothiols. Recently, we examined cholestanol-3-one-6, whose keto group is generally more reactive than those in the 7- and 12-positions.[3] However, in the mercaptol formation under the usual conditions cholestanol-3-one-6 behaves in the same manner as the 7- and 12-ketosteroids in that it does not form a mercaptol with ethanethiol but reacts with ethanedithiol.

The 11-ketosteroids are known for their low reactivity. Accordingly ethyl 11-keto-3-hydroxyetiocholanate did not react with ethanedithiol[4] but was recovered almost completely. Similar observations have recently been made on 7,11-diketones derived from ergosterol and cholanic acid.[5]

A survey of the results obtained makes it obvious that all keto groups which form mercaptols with monothiols as well as with dithiols are in rings A and D, whereas those which give no mercaptols with monothiols are in rings B and C. Among these the 11-keto group shows a special behavior, since it is even inert to dithiols.

Studies on Stuart–Fischer–Hirschfelder models show that the 11-position is the only one in which a hemimercaptol cannot be constructed since there is not enough space around the carbon atom for both an alkylmercapto and a hydroxy group. This might explain why even with a dithiol no mercaptol is formed. However, more evidence will be necessary before a definite explanation of the behavior of the different keto groups can be given.

**Acknowledgment.**—We are indebted to the Rockefeller Foundation for a grant supporting this work. One of us (H. H.) wishes to express his thanks to Dr. L. F. Fieser for granting facilities at his laboratory and to the Rockefeller Foundation for a special fellowship.

### Experimental

**Treatment of Cholestanol-3-one-6 with Ethanethiol.**—Dry hydrogen chloride was passed for two hours through a mixture of 450 mg. of cholestanol-3-one-6 and 4 ml. of ethanethiol cooled in an ice-bath. After standing overnight at room temperature, the mixture was kept in a vacuum desiccator over potassium hydroxide until all hydrogen chloride and ethanethiol had been removed. The residue was recrystallized twice from methanol, giving 400 mg., m.p. 142–144°, undepressed by admixture of starting material.

**Reaction of Cholestanol-3-one-6 Acetate with Ethanedithiol.**—Cholestanol-3-one-6 acetate (200 mg.) and 1.5 ml. of ethanedithiol were cooled in an ice-bath and treated with a stream of dry hydrogen chloride for two hours. After standing for several hours the reaction mixture was dissolved in ether, the ether solution washed with water, 5% sodium hydroxide and with water again, dried with calcium chloride and evaporated to dryness. The residue after several recrystallizations from acetone yielded the mercaptol, m.p. 148–151°, yield 190 mg. (80%).

*Anal.* Calcd. for $C_{31}H_{52}O_2S_2$: S, 12.31. Found: S, 12.13.

**Treatment of 11-Keto-3-hydroxyetiocholanate with Ethanedithiol.**—A stream of dry gaseous hydrogen chloride was allowed to pass through a mixture of 500 mg. of ethyl 11-keto-3-hydroxyetiocholanate and 2 ml. of ethanedithiol, cooled in an ice-bath. After 15 minutes the mixture was warmed to about 40° in order to dissolve the suspended ester. Passing of hydrogen chloride was continued at room temperature for half an hour, and 3 ml. of ethanedithiol was added when precipitation occurred again. After leaving the reaction mixture at room temperature for several hours the hydrogen chloride was removed in a vacuum desiccator over potassium hydroxide. The precipitate was separated by filtration, washed with petroleum ether and recrystal-

(1) H. Hauptmann, THIS JOURNAL, **69**, 562 (1947).
(2) M. N. Huffmann and M. H. Lott, *ibid.*, **69**, 1835 (1947).
(3) L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," Reinhold Publishing Corp., New York, N. Y., 1949.
(4) This experiment was performed in the Converse Memorial Laboratory, Harvard University.
(5) H. Heusser, Y. Eichenberger, P. Kurath, H. R. Dallenbach and O. Jeger, *Helv. Chim. Acta*, **34**, 2106 (1951).

lized from a mixture of benzene and ligroin, giving 465 mg. of colorless crystals, m.p. 159–161°, undepressed by admixture of starting material.

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## N-Substituted Colchiceinamides

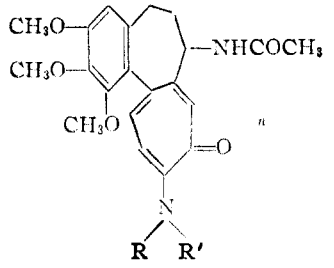
BY JONATHAN L. HARTWELL, M. V. NADKARNI[1] AND J. LEITER

RECEIVED JANUARY 24, 1952

Since certain N-substituted colchiceinamides[2] have been reported to inhibit cell mitosis[3] and growth[4] in certain tumors, we have prepared a series of these derivatives as listed in the table, for screening against Sarcoma 37 in mice. Six of the fourteen compounds are new; of the other eight, analyses are not given in the literature for six, the melting points for two are not listed, and the melting points reported for three others are widely different from those reported here. It was therefore thought desirable to bring all the characterizing data together.

With the exception of the β-chloroethyl derivative, all the compounds were prepared generally according to the method of Zeisel[5] by heating colchicine with a 10% alcoholic solution of the appropriate amine in 50% excess in a sealed tube at 120° (100° for colchiceinamide itself) for varying lengths of time depending on the amine. The reaction mixtures were evaporated to dryness and the products crystallized from suitable solvents.

N-SUBSTITUTED COLCHICEINAMIDES




| Substituent | Reaction time, hr. | Appearance, crystallizing solvent | M.p., °C. cor. | Yield, % Crude | Yield, % Pure | Empirical Formula | Analyses,[k,l] % Methoxyl Calcd. | Methoxyl Found | Nitrogen Calcd. | Nitrogen Found |
|---|---|---|---|---|---|---|---|---|---|---|
| None[a,b] | 4 | Prisms, alc. | 261–262 | 82 | 63 | $C_{21}H_{24}N_2O_5$ | 24.2 | 24.0 | 7.3 | 7.0 |
| Methyl[b,c] | 20 | Prisms, EtOAc | 230–232 (softens 185) | 85 | 66 | $C_{22}H_{26}N_2O_5$ | 23.4 | 23.1 | 7.0 | 6.8 |
| Ethyl[b,d] | 20 | Needles, EtOAc | 200–210 (softens 94) | 87 | 82 | $C_{23}H_{28}N_2O_5$ | 22.6 | 22.2 | 6.8 | 6.8 |
| *n*-Propyl[b,e] | 18 | Prisms, alc. | 162–165 | .. | 61 | $C_{24}H_{30}N_2O_5$ | 21.8 | 22.5 | 6.6 | 6.3 |
| *n*-Butyl[b,f] | 18 | Prisms, alc. | 192–193 | 87 | 75 | $C_{25}H_{32}N_2O_5$ | 21.1 | 20.7 | 6.4 | 6.3 |
| *n*-Amyl | 18 | Prisms, alc. | 189–194 | .. | 98 | $C_{26}H_{34}N_2O_5$ | 20.5 | 20.5 | 6.2 | 6.0 |
| *n*-Hexyl | 18 | Needles, benz. | 164–166 (softens 157) | 90 | .. | $C_{27}H_{36}N_2O_5$ | 19.9 | 20.5 | 6.0 | 6.0 |
| *n*-Heptyl | 18 | Amorphous[i] | 131 (softens 94) | 83 | .. | $C_{28}H_{38}N_2O_5$ | 19.3 | 19.4 | 5.8 | 5.8 |
| *n*-Octyl | 18 | Amorphous[i] | 121 (softens 85) | 77 | .. | $C_{29}H_{40}N_2O_5$ | 18.7 | 18.6 | 5.6 | 5.8 |
| β-Hydroxyethyl[g] | 20 | Prisms, EtOAc | 225–226 (softens 185) | 86 | 51 | $C_{23}H_{28}N_2O_6$ | 21.7 | 21.2 | 6.5 | 6.5 |
| β-Chloroethyl | .. | Amorphous | ... | 94 | .. | $C_{23}H_{27}ClN_2O_5 \cdot 2H_2O$ | 18.3 | 18.8 | [m] | |
| Dimethyl[h] | 20 | Amorphous | 203–205 (foams 145) | 89 | 68 | $C_{23}H_{28}N_2O_5$ | 22.6 | 22.6 | 6.8 | 6.6 |
| Diethyl[i] | 26 | Needles, EtOAc & pet. ether | 209–211 | 86 | 75 | $C_{25}H_{32}N_2O_5$ | 21.1 | 21.4 | 6.4 | 6.1 |
| Bis-(β-hydroxy)-ethyl | 26 | Amorphous | ... | 47 | 34 | $C_{25}H_{32}N_2O_7$ | 19.7 | 19.5 | 5.9 | 6.2 |

[a] Reference 1; dimorphic crystals from ethanol analyzing for 0.5 mole ethanol of crystallization. No m.p. given. [b] H. Lettré, *Naturwissenschaften*, **33**, 75 (1946). No m.p. or anal. given. [c] May and Baker, Ltd., *et al.*, British Patent 577,606 (1946); prisms from ethanol–ether, m.p. 173–174°. No anal. given. [d] See ref. [c]; prismatic needles from ether, m.p. 160–162°. No anal. given. [e] See ref. [c]; prisms from ether, m.p. 164°. No anal. given. [f] See ref. [c]; prisms from benzene–ether, m.p. 196°. No anal. given. [g] See ref. [c]; amorphous. No m.p. or anal. given. [h] See ref. [c]; micro crystals, m.p. 204–206°. No anal. given. More recently this compound has been described by H. Rapoport and A. R. Williams, THIS JOURNAL, **73**, 1896 (1951), as having m.p. 174–176°, and its constitution was confirmed by analysis. [i] See ref. [c]; prisms from alcohol–ether, m.p. 207°. No anal. given. [j] Further treatment by chromatography in chloroform solution over activated alumina did not yield a crystalline product. [k] By the Microanalytical Laboratory, National Institutes of Health, in charge of Dr. W. C. Alford. [l] Difficulty was experienced in burning most of these compounds in order to obtain C and H percentages. Since colchicine itself, which would be the expected impurity, has the calculated values $OCH_3$, 31.1 and N, 3.5, methoxyl and nitrogen analyses represent valid criteria of purity. [m] Chlorine analysis: calcd., 7.5; found 7.4. [n] This formula is based on what is regarded as the most likely structure for colchicine. As an alternative, the substituents in the "C" ring may be reversed, with appropriate shifts of the double bonds.

The β-chloroethyl derivative was prepared from the β-hydroxyethyl derivative by the action of thionyl chloride. While nearly all the compounds were obtained crystalline, it was found that these crystals gave erratic analytical results, probably due to retention of small amounts of solvent,

(1) Post-doctorate Research Fellow of the National Cancer Institute.

(2) Colchiceinamide has been more usually called colchicamide and colchicinamide. It seemed to us more logical to base the name on the "acid" colchiceine rather than on colchicic acid, a name which has been given to two compounds, or on the "ester" colchicine.

(3) H. Lettré, *Die Chemie*, **55**, 265 (1942); H. Lettré and H. Fernholz, *Z. physiol. Chem.*, **278**, 175 (1943).

(4) H. Lettré, *Z. Krebsforsch.*, **57**, 1 (1950).

(5) S. Zeisel, *Monatsh.*, **9**, 1 (1888).