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The Ethylthiocodides[1]

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The alkylthiocodides of the general formula $C_{18}H_{20}O_2NSR$ result from the action of mercaptans on α- or β-chlorocodides and bromocodide. Four supposedly isomeric ethylthiocodides were described by Pschorr and Rollet,[3] who believed the bases to be related as are the four isomeric codeines. An examination of Pschorr's evidence shows this concept, however, to be untenable, expecially in view of the peculiarities exhibited by β-ethylthiocodide.[4] The present study was initiated to determine the true relationship of the ethylthiocodides and to demonstrate the nature of the "sulfur-free ketone," $C_{18}H_{21}O_3N$, an isomer of metathebainone.[4,5]

α-Ethylthiocodide—α-Ethylthiocodide is prepared by treatment of β-chlorocodide or bromocodide with mercaptan in aqueous alkali at 100°. The process may be regarded as a mercaptolysis taking a course parallel to the hydrolysis and alcoholysis of these halogenocodides. Without regard, however, to this analogy, and independent of any assumption concerning the location of the halogen atom in the two halogenocodides concerned[6] it is apparent that the thioethyl group in α-ethylthiocodide can scarcely be attached at any point other than C-6 (Formula I). Only thus is it possible to explain in a reasonable way the rearrangement of α- to β-ethylthiocodide (Formula II). The presence of an alicyclic unsaturation as required by the empirical formula cannot be demonstrated directly, for catalytic hydrogenation of α-ethylthiocodide involves an immediate liberation of sufficient mercaptan to destroy the activity of the catalyst. Reduction of α-ethylthiocodide by means of sodium and alcohol leads to the same dihydrothebainol (m. p. 142°) as results from the parallel (sodium amalgam) reduction of dihydrothebainone[7] or dihydrocodeinone.[8] While dihydrothebainol unquestionably has the alcoholic hydroxyl group on C-6[9] the appearance of the compound in the reduction under consideration constitutes valid evidence for the location of the thioethyl group in α-ethylthiocodide only as far as has already been claimed through the relationship of the latter substance to β-ethylthiocodide; the conditions prevailing in the sodium and alcohol reduction are exactly those which favor transformation of α-ethylthiocodide to β-ethylthiocodide. There can be little question that this rearrangement is the primary step in the process, and is followed by reductive conversion of β-ethylthiocodide to dihydrothebainol.

The structural concept advanced above for α-ethylthiocodide, which depicts it as the sulfur analog of codeine (or isocodeine) ethyl ether, rests largely upon the hypothesis that the change from α-ethylthiocodide to β-ethylthiocodide consists in the shift of a hydrogen atom from C-6 to the ether oxygen, with creation of a new double bond and a phenolic hydroxyl group. This mechanism finds full support in the experiment which it suggested: codeine methyl ether (III) (but not isocodeine methyl ether), under the conditions imposed in the ethylthiocodide rearrangement, is converted to a phenolic enol ether (IV) which can be hydrolyzed with great ease into thebainone (V).[10]

β-Ethylthiocodide.—This base is formed from the α-compound by a rearrangement brought about by heating the latter with sodium ethylate; it is therefore the main product obtained when bromocodide reacts with mercaptan in the presence of sodium ethylate. The structural formula II which we propose for β-ethylthiocodide is based upon the following considerations. The substance contains a phenolic hydroxyl group, as is shown not only by the ferric chloride reaction, but by alkali-solubility. The phenolic group is, however, so weakly acidic that Pschorr failed to recognize its presence. He prepared an acetyl derivative, which could be saponified to yield the starting material; he noted further the fact that

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[1] The work reported in this paper is part of a unification of effort of a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia and the University of Michigan.

[2] Mallinckrodt Fellow in Alkaloid Chemistry.

[3] Pschorr and Rollet, *Ann.*, **373**, 1 (1910).

[4] Pschorr, *ibid.*, **373**, 15 (1910).

[5] Small and Morris, THIS JOURNAL, **54**, 2122 (1932).

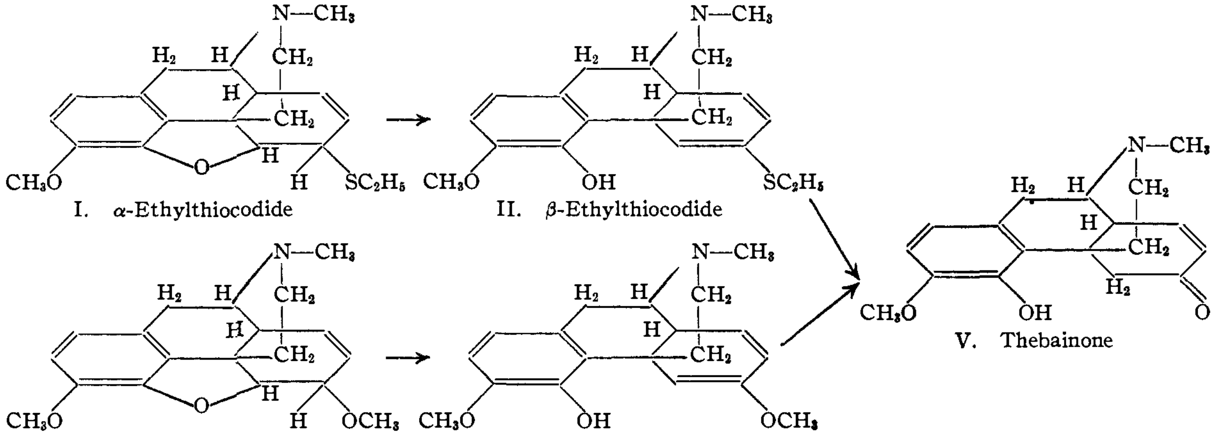
[6] This question will be considered in a later publication from this Laboratory.

[7] Kondo and Ochiai, *J. Pharm. Soc. Japan*, **538**, 99 (1926); *Ann.*, **470**, 246 (1929).

[8] Ochiai, *J. Pharm. Soc. Japan*, **568**, 91 (1929).

[9] The preparation of this dihydrothebainol and its higher-melting (167.5°) diastereomer by these and other methods which further substantiate this view has been verified repeatedly in this Laboratory.

[10] The details of this reaction and the theoretical significance of thebainone methyl enolate will be discussed in our next publication.



I. α-Ethylthiocodide

II. β-Ethylthiocodide

III. Codeine Methyl Ether

IV. Thebainone Methyl Enolate

V. Thebainone

β-ethylthiocodide methiodide was freely alkali-soluble, and could be converted to a phenol-betaine by treatment with strong alkali, observations which were explained by the assumption that the 4,5-ether bridge was opened by the reagents employed but necessitated the further hypothesis of a most improbable reformation of the ether linkage during saponification of the acetyl derivative.

The empirical formula and phenolic nature of β-ethylthiocodide point to the existence of two double linkages in ring III, an assumption which is justified by the results of catalytic hydrogenation. β-Ethylthiocodide takes up two molecules of hydrogen to form a tetrahydro derivative, without elimination of the thioethyl group. An arrangement of the double bonds other than in conjugation scarcely comes into question, and the addition reactions of β-ethylthiocodide point plainly to the presence of a conjugated system. The position of one double bond is evident from the results of hydrolysis: β-ethylthiocodide is converted with extreme ease (in cold 0.1 *N* hydrochloric acid) to the "sulfur-free ketone" described by Pschorr. This substance we have found to be identical with the true thebainone (V) which was recently described by Schöpf.[11]

The conception that β-ethylthiocodide has its double bonds at C-5, C-6 and C-7, C-8 and is the ethylthioenolate of thebainone is supported not only by the analogy with the rearrangement product from codeine methyl ether cited above, but by the relationship of β-ethylthiocodide to ethylthiodihydrothebainone VII (Pschorr's "thioketone") and to dihydro-β-diethyldithiocodide VI (Pschorr's "diethyldithiocodide"). When β-ethylthiocodide is allowed to stand cold with 0.1 *N* hydrochloric acid, an equimolecular mixture of thebainone and dihydro-β-diethyldithiocodide is obtained.[4] The reaction proceeds through hydrolysis of a portion of the β-ethylthiocodide to thebainone, and addition of the mercaptan thus liberated to the remainder of the β-ethylthiocodide. This is supported by the fact that pure β-ethylthiocodide adds mercaptan to give dihydro-β-diethyldithiocodide.

When the acid solution of β-ethylthiocodide is allowed to stand for a longer period, or is warmed gently, dihydro-β-diethyldithiocodide itself is hydrolyzed at the ethylthio-enolic group, yielding ethylthiodihydrothebainone. The mercaptan liberated from this hydrolysis adds to the thebainone present, giving a second molecule of ethylthiodihydrothebainone, which therefore appears as the only end-product. The hydrolysis of dihydro-β-diethyldithiocodide to ethylthiodihydrothebainone, and the addition of mercaptan to thebainone to give the same compound can both be realized independently.

The addition of mercaptan to thebainone in the 1,4-manner to give ethylthiodihydrothebainone is analogous to the addition of isoamyl or phenyl mercaptan to unsaturated ketones of the type of benzalacetone, which Ruhemann[12] considered most reasonably explained as a 1,4-process. The transformation of ethylthiodihydrothebainone to dihydro-β-diethyldithiocodide may take place through an intermediate mercaptal by addition of mercaptan to the carbonyl and ensuing loss of water, or through condensation of mercaptan with the enol form (VIIa) of ethylthiodihydrothebainone. Either mechanism leads to the same

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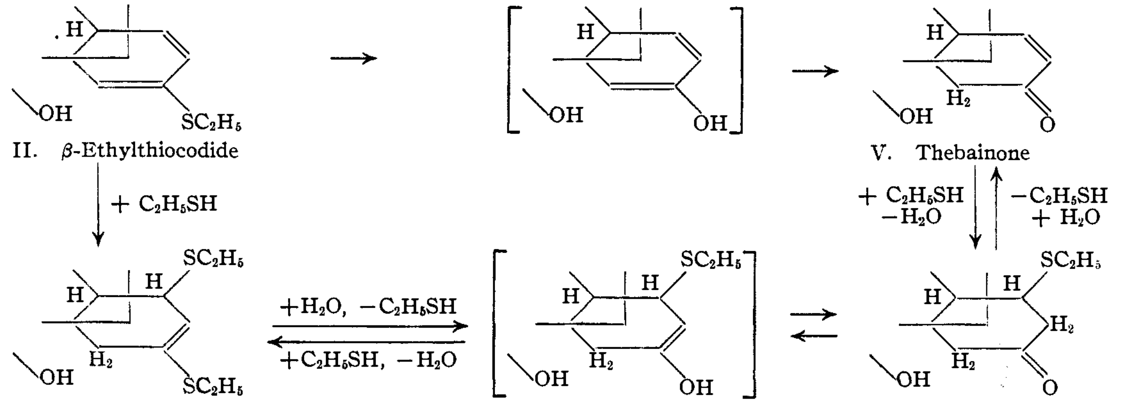
(11) Schöpf and Hirsch, *Ann.*, **489**, 224 (1931). We wish to acknowledge the kindness of Professor Schöpf in supplying us with samples of thebainone and its salts for comparison.

(12) Ruhemann, *J. Chem. Soc.*, **87**, 17, 461 (1905).


II. β-Ethylthiocodide

V. Thebainone

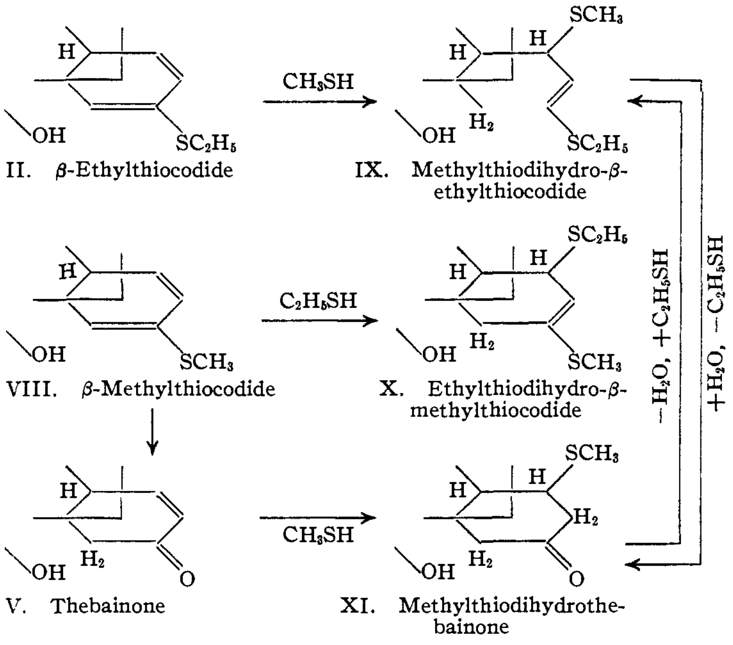
VI. Dihydro-β-diethyldithiocodide

VIIa

VII. Ethylthiodihydrothebainone

formula for dihydro-β-diethyldithiocodide, a formula which is furthermore concordant with our conception that formation of dihydro-β-diethyldithiocodide directly from β-ethylthiocodide and mercaptan takes place through a 1,4-addition of the latter reagent.

$$\begin{tikzcd}
\underset{\text{II}}{(C_{18}H_{20}O_2N)SC_2H_5} \arrow[r, "CH_3SH"] & \underset{\text{IX}}{(C_{18}H_{21}O_2N)(SCH_3)(SC_2H_5)} \\
\underset{\text{VIII}}{(C_{18}H_{20}O_2N)SCH_3} \arrow[r, "C_2H_5SH"] \arrow[dr, "\text{hydrolysis}"'] & \underset{\text{X}}{(C_{18}H_{21}O_2N)(SCH_3)(SC_2H_5)} \\
 & \underset{\text{XI}}{(C_{18}H_{22}O_3N)CH_3S} \arrow[uu, bend right, "C_2H_5SH"']
\end{tikzcd}$$


II. β-Ethylthiocodide

IX. Methylthiodihydro-β-ethylthiocodide

VIII. β-Methylthiocodide

X. Ethylthiodihydro-β-methylthiocodide

V. Thebainone

XI. Methylthiodihydrothebainone

The formulas which we proposed for β-ethylthiocodide and for alkylthiodihydrothebainones permit a structural interpretation of Pschorr's experiments on the dihydro-β-dialkyldithiocodides which furnish additional evidence concerning the mechanism of additions to thebainone and to β-ethylthiocodide. When β-*ethyl*-thiocodide is treated with *methyl* mercaptan, the product is methylthiodihydro-β-ethylthiocodide IX; when β-*methyl*-thiocodide (VIII) is treated with *ethyl* mercaptan, an isomer, ethylthiodihydro-β-methylthiocodide X results. If β-methylthiocodide is hydrolyzed, the product is methylthiodihydrothebainone XI, which condenses with ethyl mercaptan to give not X but IX.

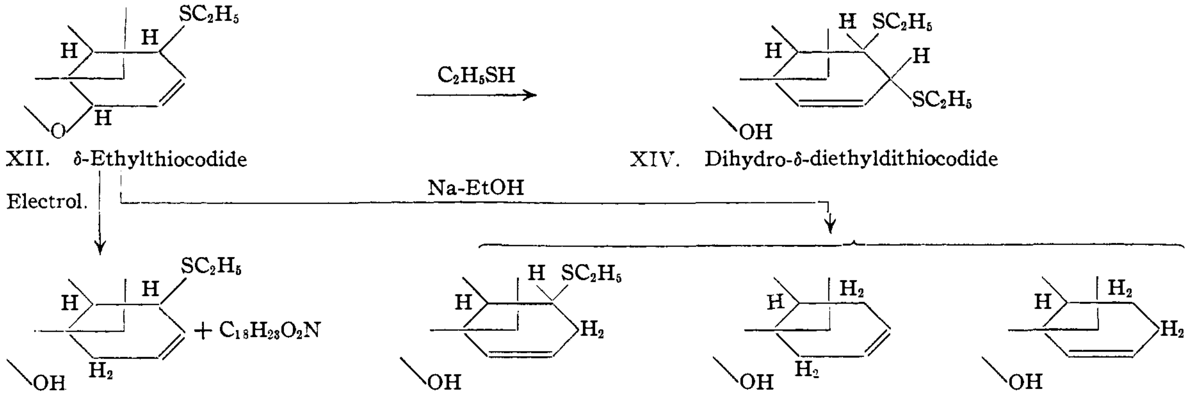
This shift of the thiomethyl group in the change VIII ⟶ XI ⟶ IX which mystified Pschorr has its explanation in the formulas below; the transformation VIII ⟶ V ⟶ XI is parallel to that demonstrated above for β-ethylthiocodide (II ⟶ V ⟶ VII).

It follows therefore: (1) that the thioalkyl group introduced into thebainone by addition of RSH appears at a point different from that occupied by the thioethyl group in β-ethylthiocodide (V ⟶ XI ⟶ IX), (2) that the addition of RSH to alkylthiodihydrothebainones (XI ⟶ IX) takes place in a different manner, such that the new thioalkyl group goes to the position which the thioethyl group has in β-ethylthiocodide (IX from II and from XI); conversely, the ketone group generated in the hydrolysis of the dialkyldithiocodides (IX ⟶ XI) and therefore the ketone group in thebainone (since V ⟶ XI) has the position of the thioethyl group in β-ethylthiocodide.

"γ-Ethylthiocodide."—As a by-product from the preparation of β-ethylthiocodide, Pschorr isolated an amorphous base which he designated as γ-ethylthiocodide. We have verified the existence of the base and its methiodide; analysis of the latter shows it to contain, however, one oxygen atom more than required for the formula of an ethylthiocodide methiodide. The nature of "γ-ethylthiocodide" became clear when we found that it no longer was formed if the preparation of β-ethylthiocodide was carried out in a hydrogen atmosphere. It is a sulfoxide of β-ethylthiocodide, and can be prepared directly from β-ethylthiocodide by shaking an alcoholic solution of the latter with oxygen.

δ-Ethylthiocodide.—The fourth member of the thiocodide series of Pschorr is obtained in good yield when α-chlorocodide is treated with mercaptan and alcoholic or aqueous alkali. δ-Ethylthiocodide is of the pseudocodeine type, that is, carries the thioethyl group in position-8 and the double bond at 6–7, as we have demonstrated by the addition and reduction reactions characteristic of this structure.

When δ-ethylthiocodide, which has no phenolic hydroxyl, is treated with mercaptan at room temperature, the product is a phenolic base containing one molecule of mercaptan more than the starting material, and isomeric with dihydro-β-diethyldithiocodide. The appearance of the phenolic hydroxyl in dihydro-δ-diethyldithiocodide as a result of scission of the ether bridge in the mercaptan addition has its parallel in the addition of mercaptan and of the Grignard reagent[13] to such a typical pseudocodeine structure as desoxycodeine-C.



XII. δ-Ethylthiocodide

XIV. Dihydro-δ-diethyldithiocodide

XIII. Dihydro-δ-ethylthiocodide-A

XV. Dihydro-δ-ethylthiocodide-B

Dihydrodesoxycodeines-B and -C

While the decisive test of catalytic hydrogenation is not applicable to δ-ethylthiocodide because of the ease with which mercaptan is eliminated, other reduction reactions present a parallelism with pseudocodeine and pseudocodeine methyl ether[14] which is so striking as to leave no doubt concerning the nature of the structure involved. By the electrolytic process, δ-ethylthiocodide is converted to a phenolic dihydro derivative, dihydro-δ-ethylthiocodide-A; in the same reduction a portion of the material suffers loss of the thioethyl group, yielding a dihydrodesoxycodeine which has the properties of dihydrodesoxycodeine-C, but whose degradation product depresses the melting point of des-N-methyldihydrodesoxycodeine-C.

Reduction of δ-ethylthiocodide with sodium and alcohol, on the other hand, gives an isomeric phenolic dihydrothio compound, dihydro-δ-ethylthiocodide-B, together with a considerable amount of the constant-proportion mixture of dihydrodesoxycodeines-B and -C which was shown by Small and Lutz[15] to compose the so-called dihydrodesoxycodeine-A. This reduction recalls that of pseudocodeine or pseudocodeine methyl ether to the corresponding phenolic dihydro derivatives and to dihydrodesoxycodeines-B and -C for which the explanation of competing 1,4- and 1,6-addition of hydrogen has already been suggested.[14]

Pseudocodeine Systems.—The structural conclusion drawn from the appearance of a phenolic mercaptan addition product of δ-ethylthiocodide involves the assumption that the allyl ether system present in pseudocodeine types will add mer-

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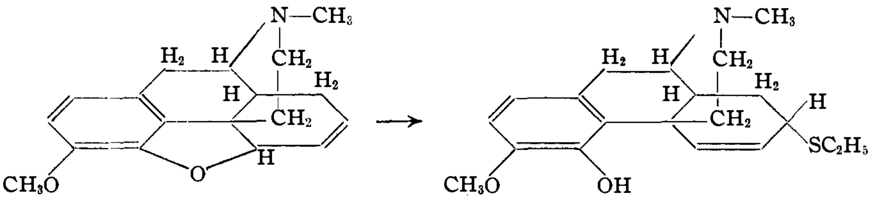
(13) Small and Yuen, unpublished results.

(14) Lutz and Small, THIS JOURNAL, **56**, 1741 (1934).

(15) Small and Lutz, *ibid.*, **56**, 1738 (1934).

captan in a manner involving scission of the ether linkage. Pschorr mentioned briefly a phenolic substance formed by the action of mercaptan on pseudocodeinone, a result which we have verified. To test this addition, however, we have selected a pseudocodeine system offering the least possibility of complications, namely, desoxycodeine-C. The structure of desoxycodeine-C has been amply demonstrated through the method of preparation and by reduction reactions typical of pseudocodeine types.[16] As would be predicted, desoxycodeine-C reacts with mercaptan to give a phenolic ethylthiodihydrodesoxycodeine. No method of showing the location of the thioethyl group, and hence the mode of addition, appears to be open. In analogy with the addition of organomagnesium halides to desoxycodeine-C, which is probably a 1,4-process, we assume the thioethyl group to be in position-7.



XVI. Desoxycodeine-C XVII. Ethylthiodihydrodesoxycodeine

Pseudocodeine likewise reacts with mercaptan, but with much greater reluctance; the phenolic product could not be isolated in a pure state. Pseudocodeine methyl ether, even after prolonged treatment, was recovered unchanged.

Experimental

α-Ethylthiocodide (I).—This base was prepared according to the directions of Pschorr.[3] We find it to exist in a low-melting form, m. p. 77–79°, $[\alpha]^{28}_{\mathrm{D}}$ −340.7° (95% alcohol, c = 0.945), which changes at its m. p. to the more stable known form of m. p. 86–87°, for which we find $[\alpha]^{27}_{\mathrm{D}}$ −344.6° (95% alcohol, c = 0.959). After the high-melting form is obtained the low-melting form can be isolated only with difficulty. Both forms crystallize from petroleum ether, isopropyl ether or dilute alcohol; no color reaction with ferric chloride.

Anal. Calcd. for $C_{20}H_{25}O_2NS$: C, 69.93; H, 7.34. Found (low-melting form): C, 69.84; H, 7.33.

α-Ethylthiocodide sulfate crystallizes from water in white prismatic needles of m. p. 185–190°; $[\alpha]^{26}_{\mathrm{D}}$ −276.6° (water, c = 1.119).

Anal. Calcd. for $(C_{20}H_{25}O_2NS)_2H_2SO_4$: S, 12.26. Found: S, 12.35.

α-Ethylthiocodide in alcoholic solution forms with silver nitrate a double compound which can be recrystallized from absolute alcohol. Attempts to reduce I with sodium or aluminum amalgam under various conditions gave only unchanged material. In prolonged electrolytic reduction some mercaptan was liberated, but I was recovered to the extent of 90%. With a palladium catalyst, hydrogenation starts, but is stopped by the mercaptan evolved. Reduction of 1 g. of I with 5 g. of sodium in 30 cc. of boiling absolute alcohol gave 0.3 g. of dihydrothebainol, m. p. 137–138°, $[\alpha]^{29}_{\mathrm{D}}$ −50.1°; sulfur-free, no depression in mixed melting point with an authentic sample, ferric chloride reaction blue-green to brown, then red-brown, like dihydrothebainol.

β-Ethylthiocodide (II).—This base could be prepared from rearrangement of α-ethylthiocodide by Pschorr's method in 75% yield; m. p. 144–146°, $[\alpha]^{28}_{\mathrm{D}}$ −45.5°. Pschorr's preparation from bromocodide was improved by working in a hydrogen atmosphere both during the preparation and recrystallization; oxidation of β-ethylthiocodide to the material designated by Pschorr as γ-ethylthiocodide was thus avoided: yield, 90%, m. p. 146–148°. Under similar conditions, β-chlorocodide of $[\alpha]^{24}_{\mathrm{D}}$ −8.4° and m. p. 151–152° gave 80% yield of II. Contrary to Pschorr's statements, the rotation is reproducible and constant, $[\alpha]^{28}_{\mathrm{D}}$ −47.1, −49.9, −49.8° (alcohol, c = 1.19) for different preparations.

Anal. Calcd. for $C_{20}H_{25}O_2NS$: C, 69.91; H, 7.34. Found: C, 70.05; H, 7.41.

β-Ethylthiocodide sublimes readily at 125–150° and 0.001 mm. pressure; the melting point is unchanged. Its phenolic nature is shown by the ferric chloride reaction: red-brown, becoming rapidly brownish-black; further, by its alkali-solubility. When solutions of II in acid are made alkaline, a momentary cloudiness is seen, followed by complete solubility. The amount in alkaline solution precipitable by carbon dioxide is 0.31 g. per liter. This figure for the solubility in alkali is the same as that determined for tetrahydrodesoxycodeine by the same method. Diazomethane reacts with II, but a crystalline product could not be obtained.

Reduction of β-Ethylthiocodide.—(1) Catalytic, to tetrahydro-β-ethylthiocodide. One gram of II in alcoholic solution with palladium-barium sulfate catalyst was shaken under hydrogen. Several 2-g. portions of catalyst were added from time to time until the addition of fresh catalyst caused no further absorption. Calcd. for 2 moles, 152 cc.; observed, 160 cc. Tetrahydro-β-ethylthiocodide is a pale yellow oil and was purified by several distillations in high vacuum; in alcohol, $[\alpha]^{26}_{\mathrm{D}}$ +15.3° (c = 1.044).

Anal. Calcd. for $C_{20}H_{29}O_2NS$: C, 68.94; H, 8.54. Found: C, 69.12; H, 8.41.

(2) Sodium and alcohol, to dihydrothebainol. One gram of β-ethylthiocodide of $[\alpha]^{28}_{\mathrm{D}}$ −49.9° was reduced with sodium and alcohol as described under the α-isomer. The product was 0.55 g. of sulfur-free crystals of m. p. 138–139° (143° with rapid heating), giving no depression in mixed melting point with dihydrothebainol obtained from dihydrothebainone reduction. Further identifica-

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(16) Small and Cohen, THIS JOURNAL, **53**, 2214 (1931); Small and Morris, *ibid.*, **55**, 2874 (1933).

tion was made through the rotation, $[\alpha]^{28}_{D}$ −49.9°, ferric chloride reaction, and the fact that, as with dihydrothebainol, two crystalline forms can be obtained: from alcohol, six-sided plates, not soluble directly in alkali; from ethyl acetate, diamond-plates, alkali-soluble.

(3) Electrolytic. Reduction of II in dilute sulfuric acid on a lead cathode gave a sulfur-free oily base, which yielded no crystalline salts.

Thebainone (V).—A solution of 10 g. of β-ethylthiocodide in 75 cc. of 2 *N* hydrochloric acid was boiled until the evolution of mercaptan ceased (one hour). Addition of 30 g. of potassium iodide caused separation of an oily hydriodide, which soon became crystalline. After two recrystallizations from water, the hydriodide melted at 262–264°, yield 9.5 g. Thebainone precipitated in crystalline form when dilute (1:12) ammonia was added to a solution of the hydriodide, and was purified from ethyl acetate. It had the m. p. 144–146°, $[\alpha]^{28}_{D}$ −46.4, −46.9° (95% alcohol, c = 1.163). Its hydriodide melted at 160–165°, solidified and remelted at 258–261°. Its methiodide melted at 249–251°. A sample of thebainone from Professor C. Schöpf had the m. p. 145–147°, $[\alpha]^{26}_{D}$ −45.7°; hydriodide, m. p. 163–165°, solidifying and remelting at 257–260°; methiodide, m. p. 250–251°. Mixed melting points of these with the samples from β-ethylthiocodide hydrolysis showed no depression. Schöpf's error in comparison of the melting point of thebainone hydriodide with the "sulfur-free ketone" hydriodide arises from the fact that the hydrated, lower-melting, hydriodide is obtained only when crystallization is carried out in very dilute solution. Thebainone is also formed when β-ethylthiocodide stands for eighteen hours in cold 0.1 *N* hydrochloric acid, but is accompanied by ethylthiodihydrothebainone and diethyldithiocodide.

Thebainone hydrochloride was prepared in absolute alcohol with alcoholic hydrogen chloride. It melts at 254–256° (red) with copious gas evolution; $[\alpha]^{30}_{D}$ −24.6° (water, c = 1.627).

Anal. Calcd. for $C_{18}H_{22}O_3NCl$: Cl, 10.57. Found: Cl, 10.88.

The reaction of β-ethylthiocodide with methyl iodide in aqueous alcohol which Pschorr was unable to explain consists only of a simultaneous hydrolysis and methiodide formation. One gram of β-ethylthiocodide in 25 cc. of 75% alcohol with 0.5 cc. of methyl iodide was heated at 100° for one hour in a sealed tube. The product was 0.75 g. of thebainone methiodide, m. p. 247–249°, $[\alpha]^{27}_{D}$ −11.1° (water, c = 0.901). It gave no depression in melting point when mixed with thebainone methiodide of m. p. 249–251° and $[\alpha]^{27}_{D}$ −10.4°. Thebainone methiodide could not be degraded to a crystalline product with alkali or by the thallous hydroxide method.

An attempt to reduce thebainone by the Wolff–Kishner method with hydrazine hydrate at 120–160° yielded a crystalline product of m. p. 220–222°; it was presumably a ketazine or hydrazone and was not further investigated. The same reaction carried out at 170° for five hours gave an amorphous base which could not be distilled at 190° and 0.001 mm. Thebainone reacts with diazomethane to give a small yield (90 mg. from 1 g. of thebainone) of a crystalline product which can be isolated by high-vacuum sublimation. It sinters at 125°, melts unsharply at 142–144°. The methoxyl determination does not decide between thebainone methyl ether and the possible thebainone methyl ether-6-ethylene oxide.

Anal. Calcd. for $C_{19}H_{23}O_3N$: $2OCH_3$, 19.81. Calcd. for $C_{20}H_{25}O_3N$: $2OCH_3$, 18.96. Found: OCH_3, 19.46.

Ethylthiodihydrothebainone (VII).—Pschorr's "thioketone" was prepared by heating 20 g. of β-ethylthiocodide in 150 cc. of 2 *N* hydrochloric acid at 70° for eighty minutes (complete solubility in 2.5 *N* sodium hydroxide). The resulting yellow solution was cooled, treated with 100 cc. of satd. sodium carbonate solution and filtered. The base was purified from acetone; after the first crystallization the less soluble, anhydrous form was obtained. The yield was 7 g. of ketone, m. p. 181–182° and $[\alpha]^{26}_{D}$ +55.4° (acetone, c = 1.111); from the mother liquors 8 g. more was recovered. The thioketone dissolves slowly in 2.5 *N* sodium hydroxide and is precipitated by ammonium chloride; the ferric chloride reaction is intense blue-green. Ethylthiodihydrothebainone absorbed no hydrogen in 95% alcohol with platinum.

A solution of 1 g. of ethylthiodihydrothebainone in 50 cc. of 20% sodium hydroxide was extracted with 50 cc. of chloroform, and the chloroform solution then shaken out with two portions of sodium hydroxide. The residue from distillation of the chloroform crystallized on addition of ethyl acetate. The product was a mixture of ethylthiodihydrothebainone and thebainone, from which 0.12 g. of the latter, m. p. 143–145°, $[\alpha]_D$ −46.9°, was obtained through crystallizations from ethyl acetate.

Methylthiodihydrothebainone (XI).—Preparation of this compound by hydrolysis of β-methylthiocodide according to Pschorr's method gave a monohydrate which sintered at 90° and melted at 95–97°, foaming at 110°.

Anal. Calcd. for $C_{19}H_{25}O_3NS + H_2O$: H_2O, 4.95. Found: H_2O, 5.98.

On long standing in alcohol at 0° the hydrate was converted to the anhydrous form of Pschorr, m. p. 138–140°. A second anhydrous form of m. p. 164–166° is obtained when the hydrate is dried at 110° in high vacuum and crystallized from dry benzene.

The hydrolysis of methylthiodihydro-β-ethylthiocodide (IX) was accomplished by warming at 80° for fifteen minutes with 2 *N* hydrochloric acid. The hydrolysis product was identical with XI described above, and likewise existed in three forms which give no melting point depression with those of XI from β-methylthiocodide.

The Supposed γ-Ethylthiocodide Methiodide. β-Ethylthiocodide Sulfoxide Methiodide.—The oily base was isolated as described by Pschorr from the mother liquors of the β-ethylthiocodide preparation carried out in contact with air; when the preparation and purification of β-ethylthiocodide was done under hydrogen, the so-called γ-ethylthiocodide could not be found. The base was converted to the methiodide and the latter purified from water; white leaflets, m. p. 259–260° (dec.), $[\alpha]^{26}_{D}$ −116.2° (water, c = 0.254). Pschorr gives the m. p. 265–266° and $[\alpha]_D$ −119.2°.

Anal. Calcd. for γ-ethylthiocodide methiodide $C_{21}H_{28}O_2NIS$: C, 51.94; H, 5.82; I, 26.16; S, 6.61. Calcd. for β-ethylthiocodide sulfoxide methiodide $C_{21}H_{28}O_3NIS$: C, 50.28; H, 5.63; I, 25.32; S, 6.40. Found: C, 50.05; H, 5.56; I, 25.10; S, 6.33.

The above analysis indicates the presence of a new oxygen atom. This was verified by direct oxidation of β-ethylthiocodide. One gram of β-ethylthiocodide (m. p. 146–148°, $[\alpha]^{26}_{D}$ −47.1°) in 50 cc. of alcohol was shaken under oxygen at 38–40°. The experiment was stopped after thirty-two hours when 46.2 cc. (1.3 atoms) of oxygen had been taken up (absorption still proceeding). A total of 0.3 g. of methiodide or 21% of the theoretical was obtained. It melted at 259–260° and had $[\alpha]^{26}_{D}$ −115.1°, and gave no depression in melting point with the material isolated from β-ethylthiocodide preparation. The low yield is not remarkable, for it could be shown that oxidation goes further.

Anal. Calcd. for $C_{21}H_{28}O_3NIS$: C, 50.28; H, 5.63. Found: C, 50.17; H, 5.64.

In view of the ease with which β-ethylthiocodide is hydrolyzed, attempts were made to hydrolyze the sulfoxide methiodide to thebainone methiodide in order to demonstrate the position of the new oxygen atom. Sulfur was eliminated, but no crystalline material could be isolated.

δ-Ethylthiocodide (XII).—The preparation of δ-ethylthiocodide was improved by the use of aqueous in place of alcoholic alkali, and by isolation of the product as the perchlorate. From 25 g. of α-chlorocodide of $[\alpha]_{D}$ −386.7°, 24 g. or 74% yield of pure δ-ethylthiocodide perchlorate was obtained. The salt crystallizes best from alcohol; it has the m. p. 223–224° and $[\alpha]^{28}_{D}$ +54.3° (water, c = 0.525) or $[\alpha]^{28}_{D}$ +40.5° (alcohol, c = 0.754).

Anal. Calcd. for $C_{20}H_{26}O_6NClS$: Cl, 7.99. Found: Cl, 7.79.

δ-Ethylthiocodide, liberated from the perchlorate and distilled in high vacuum has the consistency of petrolatum; in alcohol it showed $[\alpha]^{28}_{D}$ +57.7° (c = 1.039).

Anal. Calcd. for $C_{20}H_{25}O_2NS$: C, 69.93; H, 7.43. Found: C, 69.62, 69.96; H, 7.61, 7.62.

To 0.3 g. of the base in 2 cc. of 95% alcohol, 6 cc. of 5% alcoholic silver nitrate solution was added. The double compound which separated became granular on stirring. It was recrystallized from 75 cc. of boiling absolute alcohol, and consisted of thin needles melting with decomposition and gas evolution at 176–180°.

Anal. Calcd. for $C_{20}H_{25}O_2NS\cdot AgNO_3$: Ag, 21.03. Found: Ag, 20.79.

Dihydro-δ-Diethyldithiocodide (XIV).—Two grams of pure δ-ethylthiocodide perchlorate in 25 cc. of 6 *N* hydrochloric acid with 2.5 cc. of mercaptan was shaken for nineteen days at room temperature in a sealed tube. The mixture, which contained an insoluble oil (readily soluble in mercaptan), was treated with excess sodium carbonate and extracted with ether. The crystalline product from ether (89% yield) was purified from ethyl acetate; colorless thin rectangular plates of m. p. 125–126°, $[\alpha]^{25}_{D}$ −100.0° (ethyl acetate, c = 1.03).

Anal. Calcd. for $C_{22}H_{31}O_2NS_2$: C, 65.12; H, 7.79; S, 15.74. Found: C, 65.22; H, 7.73; S, 15.99.

The freshly precipitated base is sparingly soluble in excess of dilute alkali, and is reprecipitated by ammonium chloride.

Dihydro-δ-ethylthiocodide-A (XIII).—The attempted catalytic reduction of δ-ethylthiocodide as the perchlorate or silver nitrate compound failed because of the liberation of mercaptan. For the electrolytic reduction 13 g. of δ-ethylthiocodide perchlorate was treated with sodium carbonate solution, extracted into ether, and the ethereal solution extracted with 160 cc. of 20% sulfuric acid. The acid solution was electrolyzed on a prepared pure lead cathode of 120 sq. cm., at 12–18° with 12 amp. At the end of six hours the mercaptan odor abated, and at eleven hours complete alkali-solubility was attained. After a total of twelve and one-half hours the base was precipitated with carbonate, taken up in 1250 cc. of ether, and the ether removed, the last portion under diminished pressure. The thick yellow oil, in 25 cc. of alcohol, was treated with 5 g. of benzoic acid in 25 cc. of alcohol; the benzoate crystallized completely in twelve hours at 0°, and after five recrystallizations from alcohol was constant in properties. The yield of pure benzoate was 6.1 g.; m. p. 151–154° (gas evolution), $[\alpha]^{26}_{D}$ +119.8° (methanol, c = 1.006).

Anal. Calcd. for $C_{20}H_{27}O_2NS\cdot C_7H_6O_2 + H_2O$: C, 66.76; H, 7.27; S, 6.61. Found: C, 66.63; H, 7.31; S, 6.77.

The hydrate water could not be determined directly because of slight volatility of the salt in vacuum.

The base, prepared in the usual way from the benzoate, consisted of fine white needles, crystallizable from ethyl acetate, acetone or best from alcohol. It sublimed at 130° and 0.001 mm.; m. p. of the sublimate 156–157°, $[\alpha]^{25}_{D}$ +167.6° (alcohol, c = 1.080). It is soluble in alkali when freshly precipitated, and is thrown out of the alkaline solution by ammonium chloride.

Anal. Calcd. for $C_{20}H_{27}O_2NS$: C, 69.50; H, 7.88; S, 9.29. Found: C, 69.53; H, 8.03; S, 9.54.

Dihydrodesoxycodeine.—The evolution of mercaptan noted in the electrolytic reduction of δ-ethylthiocodide is accounted for by the formation of a dihydrodesoxycodeine, as well as of other sulfur-free products which could not be identified. From the mother liquors of the benzoate preparation, a brown oil was obtained, which on high-vacuum distillation (140°) gave 3.2 g. of a pale yellow glass. This was converted to the hydrochloride, and after four recrystallizations 0.15 g. of a dihydrodesoxycodeine hydrochloride was obtained; m. p. 157–159° (foaming), $[\alpha]^{26}_{D}$ +9.6°. This was converted to the base and purified by two sublimations in high vacuum.

Anal. Calcd. for $C_{18}H_{23}O_2N$: C, 75.74; H, 8.12. Found: C, 75.40, 75.34; H, 8.28, 8.17.

The above-mentioned dihydrodesoxycodeine hydrochloride could not be hydrogenated catalytically, probably because of the presence of traces of sulfur. Degradation of the methiodide by thallous hydroxide and high-vacuum distillation gave a methine base of m. p. 172–174°, which depressed the melting point of des-N-methyldihydrodesoxycodeine C (175–176°) by 15°.

Dihydro-δ-ethylthiocodide-B (XV).—The δ-ethylthiocodide isolated from 13 g. of pure perchlorate was dissolved in absolute alcohol, and the boiling solution treated with 50 g. of sodium during two and one-half hours, more alcohol being added as necessary; at the end of the reaction, the solution was acidified as rapidly as possible. During the entire reduction and acidification a vigorous stream of hydrogen was conducted over the mixture. The acid solution was evaporated nearly to dryness on the water-bath, and the mixture of oily hydrochloride and salt dissolved in a liter of water, from which the base was liberated with carbonate and extracted into 600 cc. of ether. The only crystalline salt obtainable was the malonate. The residue from distillation of the ether was treated with 5 g. of malonic acid in 75 cc. of ether, and the colorless oily malonate washed with a little fresh ether. The malonate in 25 cc. of acetone crystallized completely on standing for twelve hours at 0°. After four crystallizations from water 2.3 g. of pure malonate was obtained, m. p. 170.5–171.5°, $[\alpha]^{22}_{D}$ +91.1° (methanol, c = 1.109). From the mother liquors 0.6 g. more malonate was recovered.

Anal. Calcd. for $C_{20}H_{27}O_2NS \cdot C_3H_4O_4$: C, 61.43; H, 6.96; S, 7.14. Found: C, 61.41; H, 7.00; S, 7.22.

The base obtained from the pure malonate could not be induced to crystallize; it was purified by distillation in high vacuum at 140°. It is sparingly soluble in alkali, and precipitated from alkaline solution by ammonium chloride.

Anal. Calcd. for $C_{20}H_{27}O_2NS$: C, 69.50; H, 7.88; S, 9.29. Found: C, 69.39; H, 7.88; S, 9.38.

"Dihydrodesoxycodeine-A."—As the sulfur-free by-product of the sodium and alcohol reduction of δ-ethylthiocodide, the constant-proportion mixture of dihydrodesoxycodeines-B and -C previously known as α-tetrahydrodesoxycodeine or dihydrodesoxycodeine-A, could be isolated. The acetone mother liquor from the preparation of dihydro-δ-ethylthiocodide-B malonate gave a thick sirup, from which on conversion to the base with carbonate and ether, 5.3 g. of crystalline material was obtained. Repeated crystallization yielded 1.15 g. of pure "dihydrodesoxycodeine-A," m. p. 134–136°, $[\alpha]^{24}_{D}$ −29.3° (alcohol, c = 1.076), and 2.1 g. of the same base, m. p. 128–131°. When seeded with the high-melting form obtained in the desoxycodeine studies of Small and Lutz, the pure base gave an abrupt jump in melting point to 160–161.5° and gave no melting point depression with the authentic sample. Shaken under hydrogen with platinum oxide the base took up 1 mole of hydrogen, giving tetrahydrodesoxycodeine, $[\alpha]^{22}_{D}$ −35.1° (alcohol, c = 0.983). This was converted to the anhydrous form by vacuum sublimation, m. p. 154–156°, mixed melting point with anhydrous tetrahydrodesoxycodeine, 155–156°.

Ethylthiodihydrodesoxycodeine (XVII).—A solution 1.0 g. of desoxycodeine-C ($[\alpha]^{28}_{D}$ −176°) in 25 cc. of 6 *N* hydrochloric acid with 2 cc. of mercaptan was shaken in a sealed tube for seven days. The base isolated by the usual procedure was not crystalline and gave no crystalline salts. In high vacuum at 100° a trace of desoxycodeine-C sublimed out; the residue was then distilled twice at 140° and 0.05 mm. The yield was 0.45 g. of pale yellow oil, which was alkali-soluble, and precipitated from the alkaline solution with ammonium chloride; ferric chloride test negative. The pure distillate had $[\alpha]^{24}_{D}$ −59.8° (alcohol, c = 1.094).

Anal. Calcd. for $C_{20}H_{27}O_2NS$: C, 69.50; H, 7.88; S, 9.29. Found: C, 69.44; H, 8.08; S, 8.93.

The addition of mercaptan to pseudocodeinone already reported by Pschorr was reinvestigated in order to demonstrate that the ether linkage was involved in the reaction; Pschorr reported dihydroethylthiopseudocodeinone methiodide to be alkali-soluble. We confirm Pschorr's observation that addition of mercaptan takes place, and find the sulfur-containing amorphous dihydroethylthiopseudocodeinone base to be slightly soluble in alkali, 1 mg. in 100 cc. of dilute sodium hydroxide. It is difficult to explain why the methiodide should be more soluble; the effect is not due to a water solubility of the methohydroxide.

From reaction of pseudocodeine with mercaptan and hydrochloric acid for fourteen days, 77% of the pseudocodeine was recovered. The remainder, an alkali-soluble oil, was obtained in too small amount to be studied. Pseudocodeine methyl ether, after nineteen days, was recovered to the extent of 70%. No alkali-soluble material could be detected.

Summary

1. The structure of α-ethylthiocodide and the mechanism of its conversion to β-ethylthiocodide is discussed. A parallel conversion of codeine methyl ether to thebainone methyl enolate has been realized.

2. The structure of β-ethylthiocodide is demonstrated through catalytic hydrogenation, through reduction to dihydrothebainol, and through hydrolysis to thebainone.

3. The structural relationsip of β-ethylthiocodide, dihydro-β-diethyldithiocodide, ethylthiodihydrothebainone and thebainone is elucidated.

4. The relationships of the dialkyldithiocodides are shown.

5. The so-called γ-ethylthiocodide is an oxide of β-ethylthiocodide.

6. δ-Ethylthiocodide is shown by reduction and by addition reactions to have a pseudocodeine type of structure.

7. Addition of mercaptan to other pseudocodeine types is described.

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