TABLE I

5,5-DISUBSTITUTED-2,4-DITHIOHYDANTOINS AND 5,5-DISUBSTITUTED-2,4,6-TRITHIOBARBITURATES

Substituents	M. p., °C. (cor.)	Yield, %	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
Methyl Methyl DTH[a]	147.5–148.0	30					17.48	17.30	40.01	39.93
Phenyl Methyl DTH	176.5–177.0	61	54.02	54.18	4.53	4.64	12.60	12.47	28.84	29.85
Phenyl Ethyl DTH	174.5–175.0	55	55.90	55.84	5.11	5.26	11.85	11.68	27.13	28.14
Phenyl Phenyl DTH	260.0–261.0 (dec.)	18	63.37	63.35	4.25	4.52	9.85	9.76	22.55	23.43
Phenyl Ethyl TTB[b]	175.0–177.0	22					10.00	9.81	34.30	34.45
Ethyl Ethyl TTB	196.5–197.0	56	41.34	41.25	5.20	5.49	12.05	12.28	41.39	41.77

[a] Refers to 2,4-dithiohydantoin. [b] Refers to 2,4,6-trithiobarbiturates.

for fifteen minutes, crystals formed, whereupon 200 cc. of water was added, the mixture was chilled and the crystalline material was filtered. Recrystallization was made from diluted alcohol and from benzene.

The trithiobarbiturates are more soluble in hot benzene than are the dithiohydantoins, otherwise these derivatives possess similar solubility in the usual organic solvents. Data for melting points, yields and analyses are to be found in Table I.

Hydrolysis of 5,5-Diethyl-2,4,6-trithiobarbituric Acid.—Under the conditions of the interaction of the hydantoins or barbiturates with phosphorus trisulfide, it was conceivable that structural rearrangement might have occurred. Hence, 3 g. of the trithiobarbiturate was heated under a reflux condenser with 60 cc. of a 5% solution of sodium hydroxide for twenty-four hours on a steam-bath. The solution was treated with norite, filtered and heated until ammonia ceased to be evolved. Dilute hydrochloric acid was added to cause evolution of hydrogen sulfide and the solution was evaporated to dryness. The residue was extracted with four 20-cc. portions of ether, the extract evaporated to dryness, and the residue suspended in absolute ether; the unchanged trithiobarbiturate passed into solution and was removed by filtration. The residue was again suspended in ether, filtered and dried; m. p. 222–222.5° (cor.) without decomposition. This melting point is in good agreement with that reported for the diamide of diethylmalonic acid[15]; therefore, no rearrangement had taken place during the replacement of oxygen atoms by sulfur atoms.

Summary

1. The replacement of all carbonyl oxygen atoms in certain selected 5,5-disubstituted hydantoins and barbiturates has been accomplished by heating the latter in tetralin solution with phosphorus trisulfide.

2. The six thio compounds prepared in this study do not possess analgesic, hypnotic or anticonvulsant activity.

(15) Fischer and Dilthey, *Ber.*, **35**, 854 (1902); Conrad and Zart, *Ann.*, **340**, 339 (1905).

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[CONTRIBUTION FROM THE DEPARTMENT OF RESEARCH IN PURE CHEMISTRY, MELLON INSTITUTE OF INDUSTRIAL RESEARCH]

Cinchona Alkaloids in Pneumonia. XI. Some Ethers of Apocupreine

BY R. STUART TIPSON, MARY A. CLAPP AND LEONARD H. CRETCHER

In previous communications of this series, a number of ethers of apocupreine have been described. We had observed that, on passing from the methyl to the *n*-butyl ether of 6′-(β-thiolethyl)-apocupreine, there was a progressive increase[1] both in bacteriostatic activity *versus* the pneumococcus and in toxicity to mice, concomitant with a uniform change in certain physical properties. For comparison, a number of corresponding ethers of 6′-(β-hydroxyethyl)-apocupreine have now been prepared.

Some of the properties of the bases and their dihydrochlorides are given in Table I, from which it may be seen that, as the length of the aliphatic side-chain at position 6′ is increased, the melting point and specific rotation of the bases get lower, although the molecular rotations remain approximately constant. In addition, it was found that with each increase in length of the side-chain there was an increase in solubility of the resulting free base in certain organic solvents. The same general conclusions had previously been found[1] to apply to the alkylthio-ethyl ethers.

We also take this occasion to describe an improved method for the preparation of hydroxyethylapocupreine. One method described previously[2] consists in the hydrolysis of the benzyl group from benzyloxyethylapocupreine. It is

(1) Tipson and Cretcher, THIS JOURNAL, **64**, 1162 (1942).

(2) Butler and Renfrew, *ibid.*, **60**, 1473 (1938).

now found that under the same conditions one of its homologs, α-phenylethoxyethyl-apocupreine, is completely hydrolyzed to hydroxyethyl-apocupreine in approximately one-sixth the time, with consequent lessening of decomposition to a negligible amount and with isolation of very pure product in practically quantitative yield.

For comparison with the properties[2] of β,β′-dihydroxyisopropyl-apocupreine, we have now prepared β,γ-dihydroxy-*n*-propyl-apocupreine. This was accomplished by alkylation of apocupreine with α-tosyl-β,γ-isopropylidene glycerol to give the crystalline 6′-(isopropylidene-β,γ-dihydroxy-*n*-propyl) ether, from which the alkali-stable acetone residue was readily hydrolyzed off by means of dilute mineral acid. The specific rotations of the isomers were practically identical.

Experimental

Apocupreine was purified as previously described.[1]

β,γ-Isopropylidene glycerol was prepared by the method of Hibbert and Morazain.[3] It boiled at 73–74° at 10 mm. (bath temp., 81–86°) and had $n^{20}D$ 1.4346.

Esters of *p*-Toluenesulfonic Acid.—These were prepared by the action of *p*-toluenesulfonyl chloride upon the appropriate alcohol, in pyridine at −5°. **α-Phenylethoxyethyl *p*-toluenesulfonate** was obtained in 93% yield by tosylation of α-phenylethoxyethanol ("methyl benzyl cellosolve"[4]). It was recrystallized from 95% alcohol (10 g. in 20 cc.) and then had m. p. 34–35°.

Anal. Calcd. for $C_{17}H_{20}O_4S$: S, 10.01. Found: S, 10.07.

β-Phenylethoxyethyl *p*-toluenesulfonate was prepared in 73% yield by tosylation of β-phenylethoxyethanol ("phenyl ethyl cellosolve"[4]). It was recrystallized from dry ether by the addition of pentane and then had m. p. 39–40°.

Anal. Calcd. for $C_{17}H_{20}O_4S$: S, 10.01. Found: S, 9.87.

α-Tosyl-β,γ-isopropylidene glycerol was prepared essentially by the method of Freudenberg and Hess[5] but the product was isolated by extraction with chloroform, giving practically the theoretical yield. It was recrystallized by dissolving 10 g. in 250 cc. of pentane plus 25 cc. of dry ether (by boiling under reflux) and then cooling. It had $[\alpha]^{20}D$ zero (c = 1, in absolute ethanol), m. p. 49–50°.

Anal. Calcd. for $C_{13}H_{18}O_5S$: C, 54.51; H, 6.3; S, 11.2. Found: C, 54.65; H, 6.3; S, 10.9.

α-Tosyl Glycerol.—Hydrochloric acid (150 cc. of 0.5 *N*) was added to 10 g. of α-tosyl-β,γ-isopropylidene glycerol and the suspension heated under reflux in a bath at 90° during forty-five minutes. The solution was then cooled and barium carbonate added until the solution was neutral. The mixture was filtered and the filtrate evaporated

(3) Hibbert and Morazain, *Can. J. Research*, **2**, 35 (1930); Reichstein, *et al.*, *Helv. Chim. Acta*, **18**, 598 (1935).

(4) Kindly presented by the Carbide and Carbon Chemicals Corporation.

(5) Freudenberg and Hess, *Ann.*, **448**, 121 (1926).

TABLE I

MELTING POINTS, SPECIFIC ROTATIONS AND ANALYSES OF SOME APOCUPREINE ETHERS

Apocupreine ether	Yield of crude ether (in g.) from 10 g. of apocupreine	Vol. (in cc.) of acetone for recryst. of 10 g.	Bases: M. p., °C.	Sp. rot.[a]	Mol. rot. × 10^{-2}	Formula	Analyses, %: Calculated C	H	N	Found C	H	N	Dihydrochlorides: Sp. rot.[b]	Analyses, %: Calculated N	Cl	Found N	Cl
Methoxyethyl	8.5	180	156	−184°	−678	$C_{22}H_{28}O_4N_2$	71.69	7.7	7.61	71.52	8.2	7.3	−223°	6.35	16.07	6.20	15.82
Ethoxyethyl	9.0	50	111–2	−179°	−684	$C_{23}H_{30}O_4N_2$	72.20	7.9	7.33	72.16	7.9	7.31	−197°[c,d]	5.50[e]	13.93[e]	5.40	13.91
n-Propoxyethyl	10.2	20	100–102	−173°	−686	$C_{24}H_{32}O_4N_2$	72.68	8.1	7.07	72.34	8.1	7.16	−213°	5.97	15.11	5.82	14.75
n-Butoxyethyl	11.25	20	98–99[e]	−165°	−677	$C_{25}H_{34}O_4N_2$	73.12	8.4	6.83	72.67	8.3	6.96					
α-Phenylethoxyethyl	9.1	540	170–1	−132°	−605	$C_{28}H_{34}O_4N_2$			6.11			6.10	−160°				
Isopropylidene β,γ-dihydroxy-*n*-propyl	7.0	20	186–8	−169°	−717	$C_{28}H_{32}O_4N_2$	70.71	7.6	6.60	70.48	7.9	6.43					
β,γ-Dihydroxy-*n*-propyl			amorph.	−167°[f]	−642	$C_{22}H_{28}O_4N_2$	68.71	7.4	7.29	68.54	7.7	7.26	−202°[g,h]	5.7[g]	14.4[g]	5.5	14.0
Lauryl	12.3	127	−145°	−694		$C_{41}H_{86}O_2N_2$			5.86			5.98	−156°[a,i]	5.08	12.86	5.22	11.50

[a] 1% solution in absolute ethanol. [b] 1% solution in water. [c] For substance containing $3H_2O$. [d] −220° calculated for anhydrous substance. [e] Compare Butler, *et al.*, THIS JOURNAL, **59**, 227 (1937). [f] −266° for 1% solution in 0.1 *N* hydrochloric acid. [g] For substance containing $2H_2O$. [h] −218° calculated for anhydrous substance. [i] −129° for 1% solution in 0.1 *N* hydrochloric acid.

to dryness under diminished pressure. The product was extracted repeatedly with boiling chloroform under reflux, and the chloroform extracts united and evaporated to dryness. The resulting colorless sirup was dissolved in dry ether and a few cc. of pentane added. On standing overnight in the refrigerator the product settled in colorless crystals. It had m. p. 54°. For *l*-α-tosyl glycerol, Fischer, *et al.*,[6] report m. p. 63–64°.

Anal. Calcd. for $C_{10}H_{14}O_6S$: C, 48.75; H, 5.7; S, 13.02. Found: C, 48.68; H, 5.9; S, 12.81.

Alkylation of apocupreine (dried at 110°) was accomplished by means of these esters as described for the preparation of benzyloxyethyl-apocupreine,[2] except that the reaction time was extended to three hours, chloroform was substituted for ether in the extraction of alkylation product, and unchanged apocupreine was recovered. In the case of the **isopropylidene β,γ-dihydroxy-*n*-propyl ether** the reaction time was extended to twelve hours. Even so, about 50% of the apocupreine and 20 to 30% of crystalline tosyl acetone glycerol were recovered unchanged.

Crystallization and Properties of the Bases.—All but one of the bases were isolated as colorless crystals and were recrystallized from acetone (Table I) or as follows.

Lauryl.—From absolute ethanol (10 g. in 20 cc.) and then from heptane (10 g. in 40 cc.).

Isopropylidene β,γ-Dihydroxy-*n*-propyl.—After recrystallization from acetone it was recrystallized twice from absolute ethanol (10 g. in 60 cc.).

6′-(β,γ-Dihydroxy-*n*-propyl).—This was liberated from its crystalline dihydrochloride dihydrate by means of aqueous sodium hydroxide solution. It could not be obtained in crystalline form but was a colorless, amorphous powder which was dried at 110° (20 mm.). It is fairly soluble in boiling water.

Crystallization and Properties of the Dihydrochlorides.—The dihydrochlorides were prepared in the usual manner and isolated as colorless crystals as follows.

Methoxyethyl.—From absolute ethanol (10 g. in 20 cc.).

Ethoxyethyl.—From absolute ethanol (10 g. in 20 cc.) on addition of dry ether (50 cc.) to the cold solution. After drying in the vacuum desiccator it contained 3 moles of water of crystallization.

Anal. Calcd. for $C_{23}H_{30}O_3N_2 \cdot 2HCl \cdot 3H_2O$: H_2O, 10.61. Found: H_2O, 10.62.

Lauryl.—From alcohol–dry ether, m. p. 134°. It is insoluble in water but soluble in 0.1 *N* hydrochloric acid (1 g. in 100 cc.). The specific rotation of the resulting solution is less negative than that of a solution in absolute ethanol.

β,γ-Dihydroxy-*n*-propyl.—5.5 g. of recrystallized β,γ-"acetoneglyceryl"-apocupreine was suspended in 100 cc. of absolute ethanol and concentrated hydrochloric acid was added dropwise until all the material had dissolved and the solution was very slightly acid to congo red. It was then evaporated to dryness and dissolved in absolute ethanol (2 volumes). The colorless product rapidly crystallized. It was recrystallized from absolute ethanol (6 volumes). The partial hydrolysis of the isopropylidene group, which took place during formation of the dihydrochloride, was completed during this recrystallization. After drying in the vacuum desiccator it contained 2 moles of water of crystallization.

Anal. Calcd. for $C_{22}H_{28}O_4N_2 \cdot 2HCl \cdot 2H_2O$: C, 53.53; H, 7.0; H_2O, 7.31. Found: C, 53.16; H, 6.8; H_2O, 7.49.

We were unable to isolate in crystalline form the dihydrochlorides of ***n*-propoxyethyl-** and **α-phenylethoxyethyl-apocupreine.**

It is of interest that, unlike quinine,[7] the **dihydrochlorides** of methoxyethyl, ethoxyethyl, *n*-propoxy-ethyl and dihydroxy-*n*-propyl ethers each displayed a rich blue fluorescence in aqueous solution. They also possessed a very bitter taste.

Hydrolysis of α-Phenylethoxyethyl-apocupreine.—The specific rotation of pure, crystalline hydroxyethyl-apocupreine dihydrochloride is $[\alpha]^{26}D$ −228° (*c* = 1, in water) and −192° (*c* = 1, in 3 *N* hydrochloric acid).

The course of hydrolysis, in a sealed tube at 100°, of a 1% solution of benzyloxyethyl-apocupreine in 3 *N* hydrochloric acid was studied polarimetrically. Under these conditions, the initial specific rotation of the solution ($[\alpha]^{26}D$ −167.5°) showed a smooth change as follows: −177.2° (one hr.), −179.5° (two hours), −183.2° (four hours), constant thereafter. Recalculated as hydroxyethyl-apocupreine dihydrochloride, the final specific rotation is $[\alpha]^{26}D$ −191°.

Under the same conditions a 1% solution of recrystallized α-phenylethoxyethyl-apocupreine in 3 *N* hydrochloric acid, having an initial specific rotation of $[\alpha]^{26}D$ −146°, showed a smooth change as follows: −182.6° (fifteen min.), −187.4° (thirty min.), −189.3° (one hour), constant thereafter. Recalculated as hydroxyethyl-apocupreine-dihydrochloride, the final specific rotation is $[\alpha]^{26}D$ −203°.

Accordingly, 3.3 g. of recrystallized α-phenylethoxyethyl apocupreine was dissolved in 330 cc. of 3 *N* hydrochloric acid and the solution heated under reflux in a boiling water-bath during sixty minutes. The opalescent solution was then cooled and extracted with three 100-cc. portions of ether to remove α-phenethyl chloride. The aqueous solution was evaporated to dryness, giving a practically quantitative yield of pale yellow, crystalline dihydrochloride. This was recrystallized from absolute ethanol (7 volumes) yielding 2.5 g. of pure, colorless hydroxyethyl-apocupreine dihydrochloride.

It may be noted that hydrolysis of β-phenylethoxyethyl-apocupreine by means of 3 *N* hydrochloric acid, under the conditions originally given[2] for hydrolysis of benzyloxyethyl-apocupreine, resulted in a yield of pure crystalline hydroxyethyl-apocupreine dihydrochloride amounting to only 15% of the theoretical.

Summary

1. Some new ethers of apocupreine have been prepared and certain of their chemical and physical properties are described.

2. New methods for (a) hydroxyethylation and (b) polyhydroxyalkylation are given.

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(6) Fischer and Baer, *Naturwissenschaften*, **25**, 588 (1937); Sowden and Fischer, THIS JOURNAL, **64**, 1291 (1942).

(7) Stokes, *Trans. Roy. Soc. London*, **142**, 541 (1852); Rabe and Marschall, *Ann.*, **382**, 360 (1911); Jette and West, *Proc. Roy. Soc.* (London), **A121**, 299 (1928).