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

Cinchona Alkaloids in Pneumonia. V. Alkyl Ethers of Apocupreine

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The marked antipneumococcic activity of ethyl apocupreine has been discussed in a previous communication from this Laboratory.[1] Investigation of the higher alkyl ethers of apocupreine is a part of our program of research in this field and the present paper consists of a brief report on the preparation and properties of compounds in this series through the butyl ethers, with the exception of the tertiary butyl derivative. The ethers were conveniently prepared by alkylation of apocupreine with the appropriate alkyl *p*-toluenesulfonate, as described below.

Experimental

Reagents.—*n*-Propyl and *n*-butyl *p*-toluenesulfonates were purchased from Eastman Kodak Company, Rochester, N. Y. *i*-Propyl, *i*-butyl and *s*-butyl *p*-toluenesulfonates were prepared from the corresponding alcohols by reaction with *p*-toluenesulfonyl chloride at 0–5° in pyridine solution.[7] The esters were found to be suitable as alkylating reagents after thorough washing.

Anal. *i*-Propyl *p*-toluenesulfonate. Calcd. for $C_{10}H_{14}O_3S$: S, 14.95. Found: S, 14.5. Butyl *p*-toluenesulfonates. Calcd. for $C_{11}H_{16}O_3S$: S, 14.0. Found: S, *i*-butyl ester 13.8; *s*-butyl ester, 13.9.

Alkyl Ethers of Apocupreine.—Two-tenths molar quantities of apocupreine were converted to potassium salt in immediate practical use, the results are believed to be of value as a guide in the preparation of further antipneumococcic substances which may have lower toxicity. Attempts to detoxify these higher apocupreine ethers by hydroxylation[2] are in progress.

TABLE I

SOME PHARMACOLOGICAL PROPERTIES OF APOCUPREINE ETHERS

Apocupreine ether dihydrochloride	*In vitro*[3] prevents growth of pneumococcus in concn. of	Toxicity (20 g. mice) deaths at dosages of— 2 mg.	3 mg.	4 mg.	5 mg.	6 mg.	Visual disturbance (dogs)[4]
Ethyl	1:1,600,000	...	1/30	5/30	22/30	28/30	+
n-Propyl[5]	1:1,600,000	1/30	23/30	10/10	30/30	...	+
i-Propyl[6]	1:1,600,000	...	...	15/30	30/30	15/15	+
n-Butyl[5]	1:400,000	10/30	29/30	30/30	30/30	...	Not done
i-Butyl	1:1,600,000	22/30	29/30	30/30	...	...	Not done
s-Butyl	1:800,000	0/30	12/30	30/30	...	...	Not done

TABLE II

ALKYL ETHERS OF APOCUPREINE. MELTING POINTS, SPECIFIC ROTATIONS[a] AND ANALYSES

Ether	M. p., °C.	Specific rotation bases[b]	Salt used in purification formula	Specific rotation salt	Yield, %	Analyses, % Calcd. N, %	Calcd. Cl, %	Found N, %	Found Cl, %
n-Propyl	169	−197°	$C_{22}H_{28}O_2N_2 \cdot 2HCl$	−240°	40	6.6	16.7	6.4	16.4
i-Propyl	133	−185°	$C_{22}H_{28}O_2N_2 \cdot 2HCl$	−234°	66	6.6	16.7	6.6	16.6
n-Butyl	161–163	−180°	$C_{23}H_{30}O_2N_2 \cdot 2HCl$	−236°	45	6.4	16.1	6.3	15.7
i-Butyl	180	−183°	$C_{23}H_{30}O_2N_2 \cdot 2HCl$	−234°	36	6.4	16.1	6.4	15.9
s-Butyl	Amorph.	....	$C_{23}H_{30}O_2N_2 \cdot 0.5H_2SO_4$[b]	−156°	25	6.7 SO_4	11.6	6.7 SO_4	11.5

[a] $c = 1$; $l = 1$; in water except as noted. [b] Solvent, alcohol.

These substances all have strong action against the pneumococcus and enhanced mouse toxicity over ethylapocupreine. The propyl derivatives share with ethylapocupreine the property of causing visual disturbance in dogs; the butyl ethers have not yet been tested for this effect. The properties of toxicity and visual effect shown in Table I indicate that the unmodified apocupreine ethers in general, may not be suitable for trial in human pneumonia.

The wide range of pneumococcicidal activity in this series is of considerable interest. Although the alkyl ethers themselves may not be of any

(1) Butler, Renfrew, Souther and Cretcher, THIS JOURNAL, **59**, 227 (1937).

(2) Butler, Nelson, Renfrew and Cretcher, *ibid.*, **57**, 575 (1935).

(3) Maclachlan, Permar, Johnston and Kenney, *Am. J. Med. Sci.*, **188**, 699 (1934); *ibid.*, in press.

(4) Dawson, Permar, Johnston and Maclachlan, *ibid.*, **193**, 543 (1937).

(5) Liebetruth, *A. Immunitätsforschung*, **84**, 445 (1935).

(6) Ishizaka, Okamoto, Miura, Matsuda and Shako, *Jap. J. Med. Sci. IV Pharmacol.*, **7**, 42 (1933).

(7) Patterson and Frew, *J. Chem. Soc.*, **89**, 332 (1906); Sekera and Marvel, THIS JOURNAL, **55**, 345 (1933).

alcoholic solution and digested with equivalent amounts of alkyl toluenesulfonates for two hours on a water-bath. The alkylated products were worked up in the usual way and purified in all cases but one by recrystallization of the dihydrochloride from alcohol or a mixture of alcohol and ether. *s*-Butylapocupreine was best purified by crystallization of the monosulfate from alcohol.

The bases were recovered from the purified salts. The *n*-propyl, *i*-propyl and *n*-butyl derivatives were crystallized from ether, the *i*-butyl from acetone and the *s*-butyl failed to crystallize from all the ordinary solvents.

Summary

Some alkyl ethers of apocupreine have been prepared and some of their pharmacological properties have been briefly presented.

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Isolation of Pure Isomeric Hexanes from Natural Gas, Including the Determinations of their Physical Properties and the Phase-Equilibrium Diagram of the Condensed System *n*-Heptane–2-Methylpentane[1]

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In addition to the normal hexane there are four theoretically possible isomers of this hydrocarbon. Three of these isomeric hexanes were reported isolated from a mid-continent petroleum by two of the authors[2] while connected with the American Petroleum Institute Project No. 6 at the National Bureau of Standards. While the purity of the isolated isomeric hexanes appeared to be fairly high, and at the time of publication of the paper equal to the purest reported synthetic samples of these isomers, the authors have felt that considerable improvement could be made in their purification. Since the separating power of our present day stills is between 500 and 1000% as great as that of the stills used eight years ago, the present investigation was undertaken partly in order to determine whether it would be possible to isolate isomeric hexanes in a very much purer form than hitherto and with only a very small fraction of the effort previously required (20 to 25 distillations) for the isolation of even relatively impure compounds.

Experimental

The raw material consisted of a commercial cut from natural gas boiling between 55 and 65° and originating from the Clendenin Gas Field in West Virginia.

The preliminary distillation was done at a rate of 1 to 2 ml. per minute with a 12:1 reflux ratio in a 52-plate, all glass bubble-cap column made in 4-cm. sections. As indicated in Figs. 1 and 2, most of the other distillations were done in a 100-plate column made in 2-cm. sections at low rates of distillation (0.1 to 0.3 ml. per minute) and high reflux ratios (20:1 to 50:1). A complete description of the distillation equipment used may be found in previous publications from this Laboratory.[3,4]

The 3-methylpentane was isolated in a pure condition after two distillations (see Curve C-100 Plate). The 2-methylpentane required three distillations (see Curves B-52 Plate and E-100 Plate), and in the case of 2,3-dimethylbutane a total of five distillations was necessary to produce a compound of high purity (see Curves A-52 Plate, D-100 Plate, F-100 Plate, and G-100 Plate). As a result of these distillations three groups of fractions were obtained, each of which is represented by the flat portion of its distillation curve, G-100 Plate (pure 2,3-dimethylbutane), E-100 Plate (pure 2-methylpentane), and C-100 Plate (pure 3-methylpentane). The extreme boiling point differences found between the last and first fraction in each of these groups varied between 0.03 and 0.07° when carefully determined in the Cottrell boiler. The individual best fractions selected from each group had a boiling point spread in the 100-plate column of 0.01°, or less.

In reference to Fig. 2, it is noted that as soon as the 60% point had been passed in Curve C-100 Plate the material remaining in the still consisted largely of 3-methylpentane. Hence a constant boiling range was obtained. During the first part of the distillation (between the 5 and 35% points) the effect of the partial vapor pressure of the higher boiling 3-methylpentane, which was present in large amounts, prevented the 2-methylpentane from distilling at a constant or narrow boiling range.

Generally speaking, however, it may be stated that it is considerably easier to isolate a pure compound by distillation from a mixture containing, for instance, 10% of low boiling impurities than from a mixture containing the same amount (10%) of high boiling impurities, assuming, of course, that the difference in vapor pressure between the high boiling impurity and the compound is about the same as that between the compound and the low boiling

(1) Presented before the Symposium on Characteristic Properties of Hydrocarbons and their Derivatives as Related to Structure, of the 94th meeting of the American Chemical Society at Rochester, New York, Sept. 6–10, 1937.

(2) Bruun and Hicks-Bruun, *Bur. Standards J. Research*, **5**, 933–942 (1930).

(3) Bruun, *Ind. Eng. Chem., Anal. Ed.*, **8**, 224 (1936).

(4) Bruun and Faulconer, *ibid.*, **9**, 192 (1937).