The derivatives tabulated below were obtained merely by shaking the corresponding amine with slightly more than a molar equivalent of benzyl-chlorocarbonate in the presence of excess 10% sodium hydroxide solution. The product solidified in a few minutes, was filtered and then recrystallized from ethyl alcohol. The yields of recrystallized material were between 60 and 90% of the theoretical amount.

Product, carbonate	M. p., °C.	Nitrogen, % Calculated	Found
N-Phenyl-benzyl	77	6.16	6.11
N-*p*-Tolyl-benzyl	83	5.81	5.64
N-*o*-Tolyl-benzyl	83.5	5.81	5.62
N-*p*-Methoxy-phenyl-benzyl	98.0	5.83	5.65
N-*m*-Bromophenyl-benzyl	58.0	4.58	4.45

Orthoanisidine produced a liquid derivative which was not further investigated. Three of the above compounds have been prepared previously by the isocyanate method: N-phenyl-benzyl carbamate,[3] N-*o*-tolyl-benzyl carbamate,[4] and N-*p*-methoxyphenyl-benzyl carbamate.[5] The remaining two benzyl carbamates have not previously been reported. Nitrogen analyses were made by the Dumas method. Carbobenzoxy chloride was prepared by the method of Bergmann and Zervas.[2]

The low melting points and low melting point spread of these derivatives indicate that they would be of little value in the identification of the amines investigated. On the other hand they are prepared in excellent yield and seem to offer a convenient method for "masking" amino groups.

(3) Soden and Rojahn, *Ber.*, **34**, 2809 (1901).
(4) Gattermann and Cantzler, *ibid.*, **25**, 1807 (1892).
(5) Brunner and Wohol, *Monatsh.*, **63**, 374 (1930).

DEPARTMENT OF CHEMISTRY
WORCESTER POLYTECHNIC INSTITUTE
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Percain Analogs. The Preparation of β-Diethylaminoethoxyethyl 2-Alkoxy-cinchonates

BY CHI-CHIEK CHANG AND NENG-YÜAN WOO

Most 2-alkoxy-cinchonic acid derivatives exhibit a local anesthetic effect. In a series of β-diethylaminoethylamides of this acid prepared by Aeschlimann,[1] percain, the butoxy derivative, is the strongest, being ten times as active as cocaine, and is used in medicine.

Luré[2] showed that in a series of amino esters of these acids the anesthetic effect was to some extent dependent on the nature of the alkoxy group in the 2-position, but more on the side chain in the 4-position, the effect increasing with the increase of the number of the carbon atoms.

In a series of a different type of amides of these acids Magidson[3] proved that an increase in the number of the hydroxyl groups in the side chain in the 4-position decreases the anesthetic effect.

With these views in mind, we prepared a series of β-diethylaminoethoxyethanol esters of 2-alkoxy-cinchonic acids containing an O-atom in the side chain in the 4-position, and studied the change in the local anesthetic effect when the alkoxy group in the 2-position was varied.

β-Diethylaminoethoxyethanol was prepared by the method of Horne and Shriner.[4] 2-Chlorocinchonic acid was prepared by the method of Aeschlimann[1] or Thielepape,[5] and it was converted into a series of 2-alkoxycinchonic acids by the action of sodium alcoholate in the corresponding alcohols. From these, the acid chlorides, the esters, and finally the ester hydrochlorides were prepared.

2-Alkoxy-cinchonic Acid Chloride.—This was prepared by the action of thionyl chloride on a solution of the corresponding alkoxy-cinchonic acid[1,5] in benzene following the procedure of Gardner and Hammel.[6] In several repetitions of this procedure we found the yield to be dependent on the time of heating, as follows

Time of heating, min.	Amount of 2-alkoxy-cinchonic acid used, g.	Amount of acid recovered, g.
10	0.38	0.30
35	1.20	.25
60	1.40	.19

β-Diethylaminoethoxyethyl 2-Alkoxy-cinchonate Hydrochloride.—To a solution of the alkoxy-cinchonate chloride in about ten times its weight of benzene was added a slight excess of β-diethylaminoethoxyethanol. The mixture was heated at 60° for fifteen minutes. After cooling, the benzene solution was extracted with dilute hydrochloric acid. The ester was precipitated by neutralizing the acid solution with sodium carbonate, and was extracted with benzene. The benzene solution was dried with anhydrous sodium sulfate and treated with the calculated amount of hydrogen chloride gas. The mixture was allowed to stand for several hours and the precipitate was filtered off, washed with benzene, and dried in a desiccator. Yields and melting points are given in the table.

β-DIETHYLAMINOETHOXYETHYL 2-ALKOXY-CINCHONATE HYDROCHLORIDES

Alkoxy	Yield, %	M. p., °C.	Formula	Percentage composition Nitrogen Calcd.	Nitrogen Found	Chlorine Calcd.	Chlorine Found
-ethoxy-	64	80	$C_{20}H_{33}O_4N_2Cl$	7.02	7.10	8.94	9.03
-isopropoxy-	68	75	$C_{21}H_{35}O_4N_2Cl$	6.95	6.94	8.64	8.72
-butoxy-	66	108	$C_{22}H_{37}O_4N_2Cl$	6.72	6.77	8.35	8.50
-pentoxy-	66	78	$C_{23}H_{39}O_4N_2Cl$	6.50	6.53	8.08	8.12

These compounds, in 1% aqueous solution, produce a local anesthetic effect when tested by the tongue, but the pharmacological properties will be further investigated.

(4) Horne and Shriner, THIS JOURNAL, **54**, 2925–2930 (1932).
(5) Thielepape, *Ber.*, **55**, 133–134 (1922).
(6) Gardner and Hammel, THIS JOURNAL, **58**, 1360–1361 (1936).

DEPARTMENT OF CHEMISTRY
NATIONAL CHEKIANG UNIVERSITY
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Derivatives of Phenothiazine

BY STEWART E. HAZLET AND CHARLOTTE E. RODERUCK

In connection with other investigations[1] at this institution, several new derivatives of pheno-

(1) Aeschlimann, *J. Chem. Soc.*, 2906 (1926).
(2) Luré, *J. Gen. Chem.* (U. S. S. R.), **9**, 287 (1938).
(3) Magidson, *ibid.*, **9**, 2097–2103 (1939).

(1) Nicholson and McCulloch, *J. Am. Vet. Med. Assoc.*, **101** (No. 786), 205 (1942).

thiazine[2] have been prepared. Methods used were similar to those which had been employed for the acylation of phenols. Acetyl derivatives were prepared by the use of acetic anhydride.[3] Other acylations were effected by permitting the materials to react in pyridine solution,[4] but no heating was required.

Phenothiazine.—"Phenothiazine (Regular) Lot 18-10402-1-769" was generously provided by E. I. du Pont de Nemours & Company. Recrystallizations from benzene yielded a product melting at 179°.

Nitro Derivatives.[5]—3-Nitrophenothiazine-5-oxide and 3,7-dinitrophenothiazine were prepared by recorded methods; 3,7-dinitrophenothiazine-5-oxide was obtained as a by-product in the preparation of the mononitro oxide.

Acyl Derivatives of Phenothiazine and Substituted Phenothiazines

(A) **10-Benzenesulfonylphenothiazine:** glistening, colorless needles from ethanol, 30% yield, m. p. 170–170.5°. *Anal.* Calcd. for $C_{18}H_{13}O_2NS_2$: S, 18.87. Found: S, 19.0.

(B) **10-Acetyl-3-nitrophenothiazine-5-oxide:** dark red irregular crystals from nitrobenzene (precipitated by the addition of 90–120° ligroin), 90% yield, sublimes *ca.* 250°, dec. above 360°. *Anal.* Calcd. for $C_{14}H_{10}O_4N_2S$: S, 10.59. Found: S, 9.6.

(C) **10-Benzoyl-3-nitrophenothiazine-5-oxide:** dark red irregular crystals from nitrobenzene (precipitated by the addition of 90–120° ligroin), crude yield nearly quantitative, sublimes *ca.* 270°, dec. above 360°. *Anal.* Calcd. for $C_{19}H_{12}O_4N_2S$: S, 9.14. Found: S, 9.12.

(D) **10-Benzenesulfonyl-3,7-dinitrophenothiazine:** as small red irregular platelets from nitrobenzene (precipitated by the addition of benzene), 40% yield, dec. above 300°. *Anal.* Calcd. for $C_{18}H_{11}O_6N_3S_2$: S, 14.94. Found: S, 14.96.

(2) In this report the nomenclature system listed recently by *Chemical Abstracts* [**37**, 7807 (1943)] and used by Gilman and Shirley [THIS JOURNAL, **66**, 888 (1944)] has been followed.

(3) Hazlet and Kornberg, THIS JOURNAL, **61**, 3037 (1939).

(4) Hazlet, *ibid.*, **59**, 287 (1937).

(5) Kehrmann and Nossenko, *Ber.*, **46**, 2809 (1913).

DEPARTMENT OF CHEMISTRY
STATE COLLEGE OF WASHINGTON
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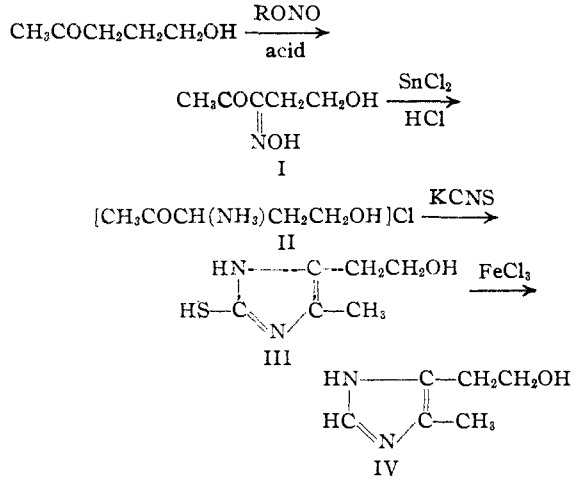
Thiamin Analogs. IV.[1] 4(5)-Methyl-5(4)-(β-hydroxyethyl)-imidazole

BY SIDNEY W. FOX,[2] HERBERT SARGENT AND EDWIN R. BUCHMAN

This communication deals with the synthesis of (IV), the imidazole[3] analog of the vitamin B_1 thiazole. Its preparation was accomplished by the following steps, which are based on reactions well known in the field of imidazole chemistry.[4]



Studies carried out at this Institute by Dr. James Bonner show that (IV) is unable to function as the vitamin thiazole in supporting growth of either pea roots or *Phycomyces Blakesleeanus*.

Experimental[5]

3-Oximinopentanol-5-one-2 (I).[6]—To a mixture of 58 g. of γ-acetopropanol[7] and 1.8 cc. of concentrated hydrochloric acid, 45 g. of butyl nitrite was added over a period of fifteen minutes, with the temperature maintained at 45–50° by means of an ice-bath. After the addition the mixture was allowed to stand for an additional fifteen minutes; 50 g. of ice and 48 g. of 33% sodium hydroxide solution were then added and the mixture stirred for one-half hour. The aqueous layer was separated and extracted twice with ether, after which it was brought to *p*H 6 by addition of dilute sulfuric acid while the temperature was kept below 10° by external cooling. The resulting mixture was continuously extracted with ether and the ether extract evaporated *in vacuo;* from the residual sirup 7 g. (9% from acetopropanol) of crude (I) crystallized on standing; m. p. 91.5° after recrystallization from ethyl acetate.

Anal. Calcd. for $C_5H_9NO_3$: C, 45.79; H, 6.92; N, 10.68. Found: C, 45.97; H, 6.94; N, 10.33.

The mother liquors containing additional amounts of (I) were utilized without further purification for conversion to (IV); attempts to distill them led to extensive decomposition.

3-Aminopentanol-5-one-2 Hydrochloride (II).[8]—In a flask surrounded by a bath at −15° was placed 75 g. of stannous chloride, 100 cc. of concentrated hydrochloric acid and 180 g. of mossy tin. To this was added 14. g. of (I) at such a rate that the reaction temperature did not rise above 0° (about ten minutes). The resulting mixture was allowed to stand at room temperature for one-half hour and then heated to boiling for several minutes. The liquid was decanted, the tin was washed with water and the combined aqueous solutions, after diluting to about 1300 cc., treated with hydrogen sulfide until precipitation of tin

(1) Paper XXIV in the R. R. Williams series.

(2) Present address: Chemistry Department, Iowa State College, Ames, Iowa.

(3) Tracy and Elderfield (*Science*, **92**, 180 (1940); *J. Org. Chem.*, **6**, 54 (1941)) have prepared the pyridine analog of thiamine; see Robbins, *Proc. Natl. Acad. Sci.*, **27**, 419 (1941); also Finkelstein and Elderfield, *J. Org. Chem.*, **4**, 365 (1939); Schmelkes, *Science*, **90**, 113 (1939); Schmelkes and Joiner, THIS JOURNAL, **61**, 2562 (1939); Baumgarten and Dornow, *Ber.*, **73**, 44 (1940); Dornow, *ibid.*, **73**, 156, 353 (1940). A pyrimidine analog has been synthesized (Tota and Elderfield, *J. Org. Chem.*, **7**, 309 (1942); see Robbins, *Proc. Natl. Acad. Sci.*, **28**, 352 (1942)) and attempts to prepare a pyrazine analog have been recorded (*J. Org. Chem.*, **7**, 313 (1942)). Schultz (*Z. physiol. Chem.*, **256**, 113 (1940)) has reported on the physiological activity of the selenazole analog.

(4) Compare, for instance, Garforth and Pyman, *J. Chem. Soc.*, 489 (1935).

(5) All melting points are corrected.

(6) The structure of this compound is based on analogy; see Gabriel and Posner, *Ber.*, **27**, 1040 (1894); Fileti and Ponzio, *ibid.* **28R**, 555 (1895). Its preparation directly from α-acetobutyrolactone will be discussed in another connection.

(7) Knunyantz, Chelintzev and Osetrova, *Compt. rend. acad. sci.*, (U. R. S. S.), [N. S.] **1**, 312 (1934); *C. A.*, **28**, 4382 (1934).

(8) Compare Künne, *Ber.*, **28**, 2036 (1895); Gabriel and Pinkus, *ibid.*, **26**, 2199 (1893).