[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF PENNSYLVANIA]

Synthesis of Benzimidazolylmethyl Analogs of Thiamine

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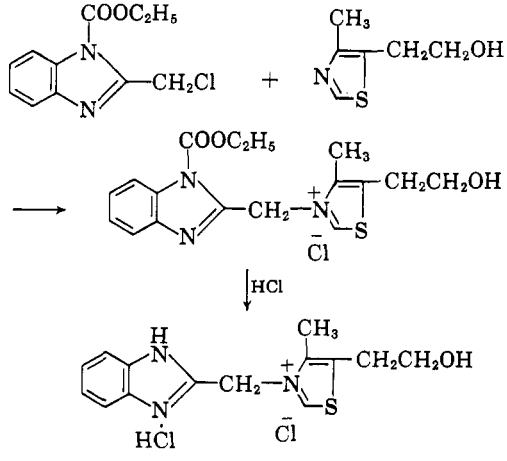
Some benzimidazolylmethyl analogs of thiamine have been prepared. Substituents have been placed in the 5 and/or 6 positions of the benzimidazole nucleus.

The first analog of thiamine reported to have antagonistic action was pyrithiamine,[1] 1-(2-methyl-4-amino-5-pyrimidylmethyl)-2-methyl-3-(β-hydroxyethyl) pyridinium bromide, which was shown to antagonize the growth of *Staphylococcus aureus*, as well as *Escherichia coli*.[2]

Recently, additional analogs of thiamine were reported and some were found to be inhibitory antagonists of thiamine for *E. coli*.[3]

Since the benzimidazole nucleus has been shown to inhibit the growth of certain yeasts and bacteria[4] as well as to possess some anti-vitamin B_{12} and anti-viral[5] activity, the syntheses of benzimidazole analogs of thiamine appeared to be a worthwhile project.

The syntheses of the benzimidazolyl analogs of thiamine involved five steps: (1) preparation of 2-hydroxymethylbenzimidazoles; (2) preparation of 2-chloromethylbenzimidazoles; (3) preparation of 1-carbethoxy-2-chloromethylbenzimidazoles; (4) condensation of 1-carbethoxy-2-chloromethylbenzimidazoles with 4-methyl-5-β-hydroxyethyl thiazole; (5) finally, the removal of the carbethoxy group.



The 2-hydroxymethylbenzimidazoles were prepared from the appropriate *o*-phenylenediamine and glycolic acid by heating in 4*N* hydrochloric solution[6] or by fusing the reagents together. The hydroxy compounds were then converted to the corresponding chloro compounds by treatment with thionyl chloride and the resulting hydrochloride salt was neutralized with a saturated sodium bicarbonate solution at 0°.

The 1-carbethoxy-2-chloromethylbenzimidazoles were prepared by the reaction of ethylchloroformate with the appropriate chloromethyl compound. The condensations were carried out in anhydrous dioxane using two moles of the chloromethylbenzimidazole and one mole of ethylchloroformate, (Table I). It was necessary to block the 1-position of the chloromethylbenzimidazoles in order to prevent self-condensation.[7]

The quaternizations between the 1-carbethoxy-2-chloromethylbenzimidazoles and 4-methyl-5-β-hydroxyethyl thiazole were carried out in absolute ethanol, (Table II). 1-Carbethoxy-2-chloromethyl-5, 6-dimethoxybenzimidazole was the only compound which would not quaternize under these conditions.

The carbethoxy group was removed by refluxing the 1-carbethoxy-2-benzimidazolylmethyl-(4-methyl-5-β-hydroxyethyl)thiazolium chlorides in absolute ethanol which previously had been saturated with anhydrous hydrogen chloride. The removal of the group was verified by infrared spectra and analyses (Table III).

EXPERIMENTAL

All of the melting points reported were taken in an apparatus similar to the one described by Wagner and Meyer.[8] The values are uncorrected.

Preparation of 2-hydroxymethylbenzimidazoles. These compounds were prepared from the corresponding *o*-phenylenediamines and glycolic acid. The following were made by Phillips method[6]: 2-hydroxymethylbenzimidazole,[7] 2-hydroxymethyl-5-chlorobenzimidazole,[9] 2-hydroxymethyl-5-

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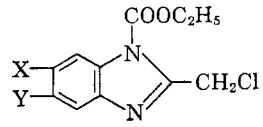
TABLE I

1-CARBETHOXY-2-CHLOROMETHYLBENZIMIDAZOLES

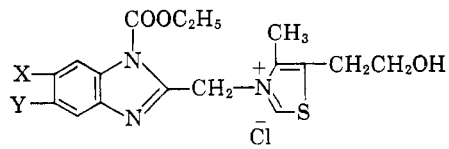


Compound	X	Y	Yield, %	M.P.	Calcd. C	H	N	Cl	Found C	H	N	Cl
I	H	H	82	82–83	55.35	4.65	11.74	14.86	55.50	4.48	11.41	14.62
II[a]	H	Cl	59	84–110								
III	H	CH_3	64	78–91	57.03	5.18	11.09	14.03	57.10	5.09	10.91	13.90
IV	H	CH_3O	38	97–105	53.64	4.88	10.43	13.20	53.90	5.09	10.43	12.96
V	H	$COOC_2H_5$	94	91–104	54.11	4.86	9.02	11.41	54.35	5.01	9.02	11.26
VI	CH_3	CH_3	82	150–151	58.53	5.67	10.50	13.29	58.56	5.87	10.59	13.10
VII	CH_3O	CH_3O	42	144–145	52.26	5.06	9.38	11.87	52.08	5.17	9.60	11.94

[a] Private communication B. Dittmar, research assistant, University of Pennsylvania.

TABLE II

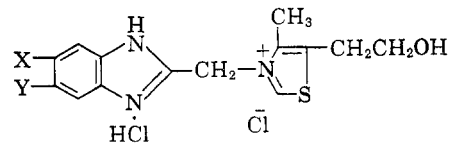
1-CARBETHOXY-2-BENZIMIDAZOLYLMETHYL-(4-METHYL-5-β-HYDROXYETHYL)THIAZOLIUM CHLORIDES



Compound	X	Y	Yield, %	M.P., °C. dec.	Calcd. C	H	N	Cl	S	Found C	H	N	Cl	S
VIII	H	H	29	163–164	53.46	5.28	11.00	9.28	8.40	53.69	5.47	11.04	9.47	8.34
IX	H	Cl	23	155–156	49.04	4.60	10.09	17.03	7.70	48.81	4.84	9.84	17.14	7.60
X	H	CH_3	11	169–170	54.60	5.60	10.61	8.96	8.10	54.78	5.64	10.67	9.02	8.19
XI	H	CH_3O	8	129.5–131	52.48	5.38	10.20	8.61	7.78	52.46	5.44	10.32	8.39	7.95
XII	H	$COOC_2H_5$	11	138–139.5	52.91	5.33	9.26	7.81	7.06	53.00	5.28	9.18	7.94	7.02
XIII	CH_3	CH_3	10	157.5–159	55.67	5.90	10.25	8.65	7.82	55.48	5.91	10.10	8.49	7.72

TABLE III

2-BENZIMIDAZOLYLMETHYL-(4-METHYL-5-β-HYDROXYETHYL)THIAZOLIUM CHLORIDE HYDROCHLORIDES



Compound	X	Y	Yield, %	M.P., °C. dec.	Calcd. C	H	N	Cl	S	Found C	H	N	Cl	S
XIV	H	H	80	194–195	48.56	4.95	12.13	20.48	9.26	48.54	4.93	11.96	20.52	9.11
XV	H	Cl	25	220.5–222	44.16	4.24	11.04	27.94	8.42	44.40	4.44	11.16	28.12	8.32
XVI	H	CH_3	42	194–196	50.00	5.32	11.66	19.68	8.90	50.23	5.14	11.40	19.47	9.06
XVII	H	CH_3O	45	189–190.5	47.87	5.09	11.17	18.84	8.52	48.01	5.13	11.03	18.87	8.76
XVIII	H	$COOC_2H_5$	44	189.5–191	48.80	5.06	10.04	16.95	7.67	48.78	4.94	9.89	16.75	7.45
XIX	CH_3	CH_3	48	219–220	51.33	5.66	11.22	18.94	8.57	51.35	5.88	11.08	18.72	8.62

methylbenzimidazole,[10] 2-hydroxymethyl-5-methoxybenzimidazole, 2-hydroxymethyl-5,6-dimethylbenzimidazole,[9] and 2-hydroxymethyl-5,6-dimethoxybenzimidazole.[11] Phillips method proved to be an excellent method for the preparation of all but one of the above compounds. The yields were in the range of 78–94%.

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2-Hydroxymethyl-5-carbethoxybenzimidazole was prepared by fusing ethyl 3,4-diaminobenzoate with glycolic acid. The yield was 50%.[12]

2-Hydroxymethyl-5-methoxybenzimidazole. This compound was recrystallized from ethanol-water with the aid of decolorizing carbon, yield 81%, m.p. 190–191°.

Anal. Calcd. for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.66; N, 15.72. Found: C, 60.53; H, 5.51; N, 15.81.

Preparation of 2-chloromethylbenzimidazoles. These compounds were prepared from the reactions of thionyl chloride, in chloroform, with the corresponding hydroxymethylbenzimidazoles. The following compounds were prepared: 2-chloromethylbenzimidazole,[7] 2-chloromethyl-5-chlorobenzimidazole,[8] 2-chloromethyl-5-methylbenzimidazole,[13] 2-chloromethyl - 5 - methoxybenzimidazole, 2 - chloromethyl-5,6-dimethylbenzimidazole,[9] 2-chloromethyl-5,6-dimethoxybenzimidazole,[11] and 2-chloromethyl-5-carbethoxybenzimidazole. The compounds were isolated as their hydrochlorides and neutralized at 0° with sodium carbonate solution. In two cases, the 5-methoxy and 5,6-dimethoxy compounds, the free bases could not be obtained in solid form. The yields for the hydrochlorides were in the 82–99% range and for the free bases in the 70–91% range.

2-Chloromethyl-5-carbethoxybenzimidazole. The hydrochloride was washed with ether and recrystallized from dry ethanol-ether with the aid of decolorizing carbon, yield 82%, m.p. 220–222° dec.

Anal. Calcd. for $C_{11}H_{12}N_2Cl_2O_2$: C, 48.02; H, 4.40; N, 10.18; Cl, 25.77. Found: C, 48.07; H, 4.18; N, 10.22; Cl, 25.75.

The free base was obtained by dissolving the hydrochloride in cold water, stirring with decolorizing carbon, filtering, and slowly neutralizing the filtrate at 0° with sodium bicarbonate solution. The product separated as a gum which solidified on continuous trituration at 0°. It was recrystallized from benzene–petroleum ether, yield 70%, m.p. 132–133°.

Anal. Calcd. for $C_{11}H_{11}N_2ClO_2$: C, 55.35; H, 4.65; N, 11.74; Cl, 14.86. Found: C, 55.24; H, 4.68; N, 11.62; Cl, 14.58.

2-Chloromethyl-5-methoxybenzimidazole hydrochloride. The crude product was washed with dry ether and recrystallized from 2-propanol, yield 86%, m.p. 210–212° dec.

Anal. Calcd. for $C_9H_{10}N_2Cl_2O$: C, 46.37; H, 4.32; N, 12.02; Cl, 30.42. Found: C, 46.26; H, 4.36; N, 12.14; Cl, 30.50.

Numerous attempts to convert the hydrochloride to the free base failed to produce a solid product.

Preparation of 1-carbethoxy-2-chloromethylbenzimidazoles. The 1-carbethoxybenzimidazoles were prepared by either of two different methods depending on whether the free base or the hydrochloride of the 2-chloromethylbenzimidazole was available.

Method A. Preparation of 1-carbethoxy-2-chloromethylbenzimidazole (I). 2-Chloromethylbenzimidazole (18.7 g., 0.113 mole) was suspended in 175 ml. of dry dioxane. Ethyl chloroformate (6.2 g., 0.057 mole) was added gradually, the mixture was stirred at room temperature for 2–3 hr. and then refluxed for 1 hr. After cooling, 2-chloromethylbenzimidazole hydrochloride was removed by filtration. The recovery was usually complete. The filtrate was evaporated to give an oil. Two or three evaporations with dry ether caused the oil to solidify. The crude product was recrystallized from ethanol. The following compounds were prepared by this method: 1-carbethoxy-2-chloromethyl-5(6)-chlorobenzimidazole (II), 1-carbethoxy-2-chloromethyl-5(6)-methylbenzimidazole (III), 1,5-dicarbethoxy-2-chloromethylbenzimidazole (V), and 1-carbethoxy-2-chloromethyl-5,6-dimethylbenzimidazole (VI). The compounds were recrystallized from hexane.

Method B. Preparation of 1-carbethoxy-2-chloromethyl-5(6)-methoxybenzimidazole (IV). A mixture of 2-chloromethyl-5-methoxybenzimidazole hydrochloride (9.3 g., 0.04 mole), triethylamine (4.05 g., 0.04 mole) and 100 ml. of dry dioxane was stirred at room temperature for 30 min. Ethyl chloroformate (4.4 g., 0.04 mole) was added followed by the addition of 4.05 g. (0.04 mole) of triethylamine. The mixture was stirred for 1 hr. and then stirred and refluxed for 3 hr. The mixture was filtered while hot and the filtrate evaporated to dryness. Dry ether was added, the mixture cooled, and the solid removed by filtration. It was recrystallized from hexane.

1-Carbethoxy-2-chloromethyl-5,6-dimethoxybenzimidazole (VII) was also prepared by this method.

Preparation of 1-carbethoxybenzimidazolyl analogs of thiamine. General method. Preparation of 1-carbethoxy-2-benzimidazolylmethyl-(4-methyl-5-β-hydroxyethyl)thiazolium chloride (VIII). A solution of 1-carbethoxy-2-chloromethylbenzimidazole (2.6 g., 0.011 mole), 4-methyl-5-β-hydroxyethylthiazole (1.6 g., 0.011 mole), and 20 ml. of dry ethanol was refluxed for 20–48 hr. The reaction mixture was cooled to room temperature, petroleum ether (30–60°) was added, and the solution cooled. The solid was removed by filtration. Petroleum ether was added to the filtrate and on cooling more solid was obtained. The solid portions were combined and recrystallized from dry ethanol–petroleum ether (30–60°) with the aid of decolorizing carbon. In some cases, the addition of petroleum ether to the reaction mixture produced an oil. The oil was extracted with hot benzene or hexane to remove starting material and then triturated with dry ethanol at 0° until solidification occurred. 1-Carbethoxy-5-chloro-2-benzimidazoylmethyl - (4 - methyl - 5 - β - hydroxyethyl)-thiazolium chloride (IX), 1-carbethoxy-5-methyl-2-benzimidazolylmethyl - (4 - methyl - 5 - β - hydroxyethyl)thiazolium chloride (X), 1-carbethoxy-5-methoxy-2-benzimidazolylmethyl - (4 - methyl - 5 - β - hydroxyethyl)thiazolium chloride (XI), 1,5 - dicarbethoxy - 2 - benzimidazolylmethyl-(4 - methyl - 5 - β - hydroxyethyl)thiazolium chloride (XII) and 1 - carbethoxy - 5,6 - dimethyl - 2 - benzimidazolylmethyl - (4 - methyl - 5 - β - hydroxyethyl)thiazolium chloride (XIII) were prepared by this method.

Preparation of the thiazolium chloride hydrochlorides. 2-Benzimidazolylmethyl - (4 - methyl - 5 - β - hydroxyethyl)-thiazolium chloride hydrochloride (XIV). Compound VIII (790 mg., 0.0021 mole) was added to 20 ml. of ethanol which had been previously saturated with dry hydrogen chloride. The reaction mixture was refluxed for 4 hr. After cooling, the product was removed and recrystallized from dry ethanol–petroleum ether (30–60°). The addition of dry ether facilitates the separation of the hydrochloride from the reaction mixture. In a few cases the hydrochloride separated as an oil. The oil was converted to a solid either by drying in vacuo or by dissolving in dry ethanol and removing the ethanol by distillation. 5-Chloro-2-benzimidazoylmethyl-(4-methyl-5-β-hydroxyethyl)thiazolium chloride hydrochloride (XV), 5-methyl-2-benzimidazolylmethyl-(4-methyl-5-β-hydroxyethyl)thiazolium chloride hydrochloride (XVI), 5-methoxy - 2 - benzimidazolylmethyl - (4 - methyl - 5 - β-hydroxyethyl)thiazolium chloride hydrochloride (XVII), 5 - carbethoxy - 2 - benzimidazolylmethyl - (4 - methyl - 5-β-hydroxyethyl)thiazolium chloride hydrochloride (XVIII) and 5,6 - dimethyl - 2 - benzimidazolylmethyl - (4 - methyl-5 - β - hydroxyethyl)thiazolium chloride hydrochloride (XIX) were prepared by this method.

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