region around 400 mμ disappears as one goes from dioxane to butanol, to ethanol, to water and to the albumin-bound form of dinitrophenol. The direction of this shift is in accord with the findings of Ungnade[26] for monosubstituted benzene derivatives with electron donor substituents in a variety of solvents. This seems to indicate hydrogen bond formation between dinitrophenol and serum albumin through the oxygen atom of dinitrophenol.

Competitive Binding.—As shown in Figs. 1 and 2, chloride ion at 0.16 *M* concentration inhibits the interaction of bovine serum albumin with dinitrophenol. As non-ionized dinitrotoluene also interferes with the binding of dinitrophenol (see below), it is apparent that both ionic and non-ionic interactions are effective in forming a stable complex of serum albumin with an ionic compound such as dinitrophenol. The binding of dinitroaniline was not affected by the presence of chloride ion at the concentration used. It is of interest that Klotz and Ayers[3] reported displacement of aminoazobenzene from bovine serum albumin by SCN^- ion but not by Cl^- ion. The small effect of chloride ion on the binding of dinitrophenol and the lack of an effect on the binding of dinitroaniline is at least partly due to the small affinity of bovine serum albumin for Cl^- ion. It might also indicate that chloride ion is bound to sites in the protein other than those involved in the interaction with an organic molecule.

In order to test whether there are structural differences among the binding sites in the protein with regard to organic anions and organic molecules, an experiment was set up in which dinitrophenol and dinitrotoluene were equilibrated simultaneously with serum albumin. It can be seen from Fig. 1 that dinitrophenol and dinitrotoluene compete for some common albumin sites, since the amount of dinitrophenol bound is reduced in the presence of dinitrotoluene. At the same free dinitrophenol concentration the total number of moles of dinitrophenol + dinitrotoluene bound exceeds the number of moles of dinitrophenol bound in the absence of dinitrotoluene, until 6 moles is bound (Table IV).

TABLE IV

EFFECT OF DINITROTOLUENE (61.6×10^{-5} *M*) ON THE BINDING OF DINITROPHENOL BY BOVINE SERUM ALBUMIN IN 0.05 *M* PHOSPHATE BUFFER, *p*H 7.4, 25°

Free concn. of dinitrophenol, $c \times 10^5$	A[a] Dinitrophenol in the absence of dinitrotoluene	B Dinitrophenol in the presence of dinitrotoluene	C[b] Dinitrotoluene in the presence of dinitrophenol
71.1	6.20	5.40	1.0
31.4	4.90	4.24	2.0
21.6	4.44	3.91	2.1
12.7	3.69	3.26	2.4
9.1	3.39	3.00	2.5
3.13	2.52	2.03	2.8
1.07	1.60	1.19	3.3
0.427	.86	.64	3.4
0.344	.70	.51	3.7

[a] Interpolated from binding curve (see Fig. 1). [b] The values in this column are subject to error ranging from 10% at low values of *c* to 35% at high values of *c*. Nevertheless, even with this error, the sum of B + C exceeds A for all free concentrations of dinitrophenol up to 31.4×10^{-5} *M*.

This finding suggests that, on the average, some of the sites preferentially bind dinitrophenol while others preferentially bind dinitrotoluene. It may be inferred, therefore, that some specific differences occur in the binding sites of bovine serum albumin despite its great adaptability in the binding of molecules and ions of varying structures.

Acknowledgment.—We wish to thank Dr. Fred Karush for stimulating discussions and Dr. Norton Nelson for his helpful interest during the course of this work.

NEW YORK, N. Y.

(26) H. E. Ungnade, THIS JOURNAL, **75**, 432 (1953).

[CONTRIBUTION FROM THE RESEARCH DIVISION, ELECTROCHEMICALS DEPARTMENT OF E. I. DU PONT DE NEMOURS AND COMPANY]

A New Synthesis of the Thiazole Fragment of Vitamin B_1[1]

BY THOMAS E. LONDERGAN, NORMAN L. HAUSE AND WILLIAM R. SCHMITZ

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The thiazole fragment of vitamin B_1, 4-methyl-5-(β-hydroxyethyl)-thiazole, has been prepared by a new 4-step synthesis from 2-methylfuran.

In a study of derivatives of furfural, a new and improved synthesis of 4-methyl-5-(β-hydroxyethyl)-thiazole (V) has been developed. 2-Methylfuran (I), which was employed as the starting material for this route, can be obtained in high yield by the hydrogenation of furfural.[2-4] The thiazole moiety of vitamin B_1 was obtained from I by the four-step synthesis shown below.

2-Methylfuran (I) has previously been converted to 5-hydroxy-2-pentanone (II) by a process equivalent to partial hydrogenation followed by hydrolysis.[4-6] Significant improvement in yields of II was obtained through a detailed study of reaction variables. We have developed a continuous process for the cyclodehydration of II in the presence of acid catalysts to give III in reproducible yields of 86% or more. Although high yields of III had been reported by distillation of II,[4] we

(1) Presented at the 122nd Meeting of the American Chemical Society, Atlantic City, New Jersey, 1952.

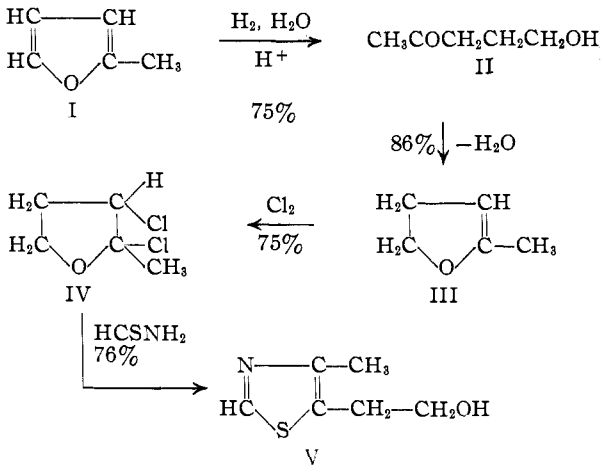
(2) W. A. Lazier, U. S. Patent 2,077,422 (April 20, 1937).

(3) L. W. Burnette, *Iowa State Coll. J. Sci.*, **19**, 9 (1944).

(4) L. E. Schniepp, H. H. Geller and R. W. Von Korff, THIS JOURNAL, **69**, 672 (1947).

(5) K. Topchiev, *Comp. rend. acad. sci. U.R.S.S.*, **19**, 497 (1938); [*C.A.*, **32**, 8411 (1938)].

(6) S. Swadesh, S. Smith and A. P. Dunlop, *J. Org. Chem.*, **16**, 477 (1951).



found that different samples of II gave erratic yields upon distillation. These results agreed with recent work[6] in which it was noted that pure II did not dehydrate when distilled, and that traces of acidic catalysts were required for the dehydration.

Good yields of IV were obtained by a chlorination procedure similar to that recently reported.[7]

4-Methyl-5-(β-hydroxyethyl)-thiazole (V) has been prepared by the reaction of thioformamide with a variety of reagents.[8-11] The reaction of IV with thioformamide, however, provided a new preparation of V. The solvent used in the reaction was an important variable and best results were obtained using technical 88–90% formic acid. It was rather surprising that a high yield of V was obtained with formic acid as solvent since thioformamide generally decomposes rapidly in an acidic medium.[12] There was some evidence for the formation of a small amount of the formate ester of V, but this ester could be readily hydrolyzed to V by heating with water.

In the preparation of thioformamide by the reaction of formamide with phosphorus pentasulfide, better yields were obtained with tetrahydrofuran as solvent than without a diluent[12] or with ether.[13]

Experimental[14]

5-Hydroxy-2-pentanone (II).—A 300-ml. citrate bottle containing 100 g. (1.22 moles) of 2-methylfuran (I), 100 g. of acetone, 35 ml. of 0.2 *N* hydrochloric acid and 2.0 g. of 5% palladium-on-carbon catalyst was connected to a Parr shaker apparatus. The system was flushed first with nitrogen and then three times with hydrogen. The hydrogenation which was conducted under 42–15 lb./sq. in. pressure required the absorption of one mole of hydrogen during a period of seven hours. After the catalyst was removed by filtration, the filtrate was neutralized to a *p*H of 7 by stirring rapidly with sodium carbonate for about 30 minutes. The acetone, water and low-boiling by-products were removed by distillation at atmospheric pressure. The residue was distilled through a six-inch Vigreux column to give 93 g. (75%) of 5-hydroxy-2-pentanone (II), b.p. 78–80° (5–7 mm.). A sample was redistilled to give pure II, b.p. 74–75° (3 mm.), $n^{20}D$ 1.4360.

Other organic solvents such as dioxane, methanol, ethanol, tetrahydrofuran and formic acid were used, but acetone and ethanol gave the best results. A disadvantage of ethanol was that 2-ethoxytetrahydro-2-methylfuran was formed as a by-product. The amount of solvent was important. Best yields were obtained using equal parts by weight of solvent and I.

4,5-Dihydro-2-methylfuran (III).—A 50-ml. portion of a solution containing 300 g. (2.94 moles) of II and 4 ml. of 0.3 *N* phosphoric acid was placed in a 200-ml., three-necked flask, equipped with a separatory funnel and thermometer and set for distillation through a 1.5 × 45 cm., jacketed Vigreux column. The column was heated to 80°. When the pot temperature reached 175°, cyclodehydration began. The solution of II and phosphoric acid was fed into the distillation pot at the same rate as the dihydromethylfuran–water mixture distilled at the column head. In this manner, polymerization of II and formation of by-products were held to a minimum since II was not subjected to prolonged heating as was the case in batch distillations. The head temperature remained between 85 and 97°, and during the distillation the pot temperature rose slowly from 175 to 195°. After all of the 5-hydroxy-2-pentanone solution had been added, the pot temperature rose gradually to 260°. Two hundred twelve grams (86%) of 4,5-dihydro-2-methylfuran (III) and 61 ml. of water were collected. The water was separated, and the product dried over anhydrous potassium carbonate. Twenty-six grams of residue remained in the pot. A sample of the product after drying over sodium had b.p. 79–80°, $n^{20}D$ 1.4312.

A non-volatile acid catalyst was essential in this dehydration since a volatile acid catalyzed the hydration of III in the column and receiver. The type and size of column affected both the rate of dehydration and yield of III. Optimum specifications for the column were not established, but a Vigreux column was preferable to one with packing. In several experiments, little if any of III was obtained with various sizes of columns packed with glass helices or Berl Saddles. The cyclodehydration was also carried out under reduced pressure (4–15 mm.) and yields comparable to those obtained at atmospheric pressure were obtained, but the rate was much slower.

2,3-Dichlorotetrahydro-2-methylfuran (IV).—In a 3-liter, three-necked flask equipped with a good mechanical stirrer, thermometer, chlorine inlet-tube and dropping funnel was placed 2000 g. of methylene chloride. After the methylene chloride had been cooled to −78°, 504 g. (6.0 moles) of III was added dropwise during one hour and fifty minutes while 505 g. (7.1 moles) of chlorine was added during two hours. The reactants were added simultaneously with III in slight excess until all of III had been added. Maximum temperature during the chlorination was −58°.[15] The reaction mixture was stirred for five minutes after the addition of chlorine was complete. After the solvent had been removed by distillation under 20–30 mm. pressure, the residue was distilled through an 18-cm. Vigreux column to give a small forerun (15 g.), and 691 g. (74.5%) of IV, b.p. 55–65° (7–15 mm.), $n^{20}D$ 1.4795. A pot residue of 180 g. remained. A sample of IV was carefully fractionated and a fraction, b.p. 49–51° (15 mm.) and $n^{20}D$ 1.4780, was analyzed.

Anal. Calcd. for $C_5H_8OCl_2$: C, 38.72; H, 5.17. Found: C, 38.99; H, 4.99.

The dichloro compound was a vesicant and darkened on standing at room temperature. On storage at −20° to −40°, however, it solidified and remained colorless over a period of several months.

4-Methyl-5-(β-hydroxyethyl)-thiazole (V).—In a 500-ml. three-necked flask equipped with a mechanical stirrer and thermometer were placed 155 ml. of 88% formic acid and 77.5 g. (0.5 mole) of IV. With stirring, 79 g. (1.0 mole) of pyridine was added at room temperature followed by 61 g. (1.0 mole) of thioformamide. The reaction mixture was stirred at 55–60° for 20 hours. After the excess formic acid had been removed under reduced pressure, 250 ml. of water was added and the reaction mixture was stirred at 95–100° for two hours to hydrolyze a small amount of the formate ester of V which was present. Non-basic material was ex-

(7) R. Paul and S. Tchelitcheff, *Bull. soc. chim. France*, 520 (1950).
(8) E. R. Buchman, THIS JOURNAL, **58**, 1803 (1936).
(9) J. R. Stevens and G. A. Stein, *ibid.*, **62**, 1045 (1940).
(10) A. Wenz, German Patent 664,789 (Sept. 5, 1938).
(11) German Patent 663,305 (August 3, 1938).
(12) R. Willstätter and T. Wirth, *Ber.*, **42**, 1911 (1909).
(13) S. Gabriel, *ibid.*, **49**, 1115 (1916).
(14) Melting points are corrected and boiling points are uncorrected.
(15) The yields obtained at various temperatures were: 65–75% at −58 to −40°, 50% at −20° and 32% at 20°.

tracted with two 100-ml. portions of methylene chloride, and the combined methylene chloride extracts were washed with two 50-ml. portions of 10% hydrochloric acid. The wash solutions along with the original aqueous solution were made basic with sodium carbonate, then extracted with five 100-ml. portions of methylene chloride. After the combined methylene chloride extracts were dried over anhydrous sodium sulfate, the solvent was removed by distillation. The residue, which contained both pyridine and thiazole, was distilled through a six-inch Vigreux column under reduced pressure. Pyridine was collected at 2–4 mm. in a receiver cooled with Dry Ice while 54 g. (76%) of 4-methyl-5-(β-hydroxyethyl)-thiazole (V) was collected at 110–116° (0.7 mm.), $n^{20}D$ 1.5470. A pot residue of 7 g. remained.

When the reaction was conducted in the same manner as described above except that 68 g. (1.0 mole) of sodium formate was used in place of pyridine, the yield of thiazole was 68%.

A sample of V was redistilled, and a center cut boiling at 99–100° (0.20 mm.), $n^{20}D$ 1.5477, was analyzed.

Anal. Calcd. for C_6H_9NOS: C, 50.32; H, 6.33; N, 9.78. Found: C, 50.46; H, 6.36; N, 9.59.

Melting points of the **picrate**, m.p. 164–164.8°, and the ***p*-nitrobenzoate** of V, m.p. 124 to 125°, agreed with values previously reported in the literature.[8]

Thioformamide.—In a 5-l., three-necked flask equipped with a mechanical stirrer and thermometer were placed 3 l. of tetrahydrofuran and 300 g. (6.67 moles) of technical formamide. This solution was rapidly stirred while 330 g. (1.49 moles) of phosphorus pentasulfide was added in portions of about 50 g. during a period of one and one-half hours at 30–35°. During the addition and for a short time thereafter, it was occasionally necessary to cool the flask in an ice-bath in order to maintain this temperature. After the reaction mixture had been stirred at room temperature for six hours, a sticky solid which gradually formed in the reaction mixture was collected on a filter and discarded. Tetrahydrofuran was stripped from the filtrate under reduced pressure to leave a residue containing thioformamide, formamide and polymer. The residue was shaken with an equal part by weight of ether to dissolve thioformamide, leaving formamide and polymer undissolved. The ether solution was separated and concentrated under reduced pressure to give 201 g. (50%) of thioformamide.

The crude thioformamide is of sufficient purity to react satisfactorily with IV but if desired, it can be recrystallized from ethyl acetate at Dry-Ice temperature to give pure thioformamide, m.p. 32.0 to 33.8°.

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NIAGARA FALLS, NEW YORK

[CONTRIBUTION FROM THE LILLY RESEARCH LABORATORIES]

Analgesics: Esters of 4-Dialkylamino-1,2-diphenyl-2-butanols

BY A. POHLAND AND H. R. SULLIVAN

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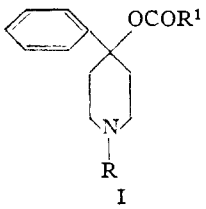
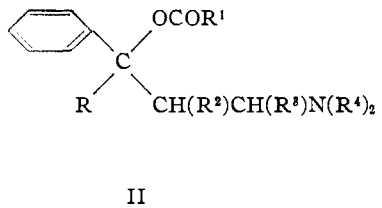
Sixteen amino carbinols of the type $C_6H_5CH_2C(C_6H_5)OHCH(R^1)CH(R^2)N(R^3)_2$ have been prepared and eight of these separated into their diastereoisomeric forms. The carbinols have been converted to esters. Pharmacological studies in animals have shown that a number of these esters possess a high order of analgesic activity.

Acyl derivatives of 4-piperidinols[1,2] have been found to possess significant analgesic properties. These compounds (I) may be considered to be analogs of meperidine in which the ester function



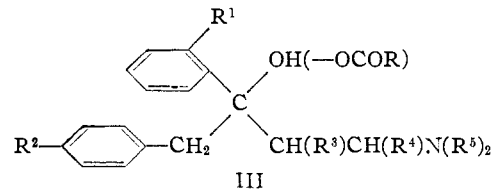
I



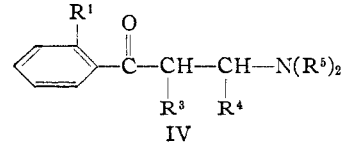
II

is reversed. Similar open chain esters (II) have been prepared by other investigators[3–5] but according to the published pharmacological results, have failed to show any promising analgesic activity.

In our laboratories compounds of the type II have been under investigation as possible analgesic substances. Esters of 3-dialkylamino-1,1-diphenylpropanols were found to exhibit weak analgesic properties. These esters are unstable in aqueous solution, being readily hydrolyzed to the carbinol.[3] It was felt that more stable esters might possibly have greater analgesic activity, since the carbinols are devoid of activity. The present work is concerned with the preparation of 4-dialkylamino-1,2-diphenyl-2-butanols and their esters III.



III



IV

The intermediate β-dialkylaminopropiophenones and α-alkyl-β-dialkylaminopropiophenones (IV where R^1 is H or CH_3, R^3 is H or CH_3 or C_2H_5 and R^4 is H) were prepared by means of the Mannich reaction. The β-dialkylaminobutyrophenones (IV where R^1 and R^3 are H, R^4 is CH_3) were prepared by addition of the secondary amines to phenyl propenyl ketone.[6]

These aminoketones were allowed to react with benzylmagnesium chloride to yield the carbinols (Table I). The ketones containing an asymmetric

(1) K. A. Jensen, F. Lindquist, E. Rekling and C. G. Wolffbrandt, *Dansk Tids. Farm.*, **17**, 173 (1943).

(2) A. Ziering and J. Lee, *J. Org. Chem.*, **12**, 911 (1947).

(3) A. C. Kjaer and P. V. Petersen, *Acta Chem. Scand.*, **5**, 1145 (1951).

(4) J. H. Burckhalter and S. H. Johnson, Jr., THIS JOURNAL, **73**, 4827 (1951).

(5) M. B. Slomka and F. W. Schuller, *J. Am. Pharm. Assoc.*, **41**, 618 (1951).

(6) D. Shapiro, *J. Org. Chem.*, **14**, 839 (1949).