A[18] and perhaps larger weight of PAC, based upon its relative non-dialyzability.[19]

It has been pointed out[5] that since other inert analogs of pantothenic acid have in general differed from the vitamin in the hydroxy acid moiety, an attachment through the moiety is also required for the complete coupling of the vitamin molecule to its apoenzyme. Analogs which differ in the β-alanine portion of the molecule, on the other hand, are almost without exception competitive inhibitors of pantothenic acid, and it has been assumed that this moiety is involved (presumably through the carboxyl group) in metabolic reactions. This view has been strengthened by the findings[20,21] that coenzyme A and the pantothenic acid conjugate (PAC) described in this Laboratory are hydrolyzed by the combined action of a pigeon liver enzyme preparation and a phosphodiesterase, thus releasing the free vitamin for *L. arabinosus* activity. This relatively stable attachment to phosphorus would presumably occur through hydroxyl groups. Thus, although it is still not possible to obtain a detailed picture of the combination of the vitamin within the cell, on the basis of present evidence it seems plausible to suppose that connections between the vitamin and other units in the respective coenzyme molecules are normally made through hydroxy and amide nitrogen linkages.

Acknowledgment.—The authors wish to express their thanks to Marjorie McCanse for carrying out the microbiologic assays.

Summary

A new analog of pantothenic acid (α,γ-dihydroxy-β,β-dimethylbutyryl-β'-N-methyl alanide) has been prepared and tested for growth effects upon *A. suboxydans*, *L. arabinosus* and LM yeast. The compound has no activity for *L. arabinosus* or LM yeast and from 5–18% activity for *A. suboxydans*. On the basis of evidence obtained it appears that N-methylpantothenic acid does not combine with cellular enzymes in *L. arabinosus*. The amide group may therefore be considered a point of attachment, either directly to the apoenzyme or through some other group which does not involve the functional metabolic role of the vitamin.

CORVALLIS, OREGON RECEIVED MAY 19, 1949

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[18] G. D. Novelli, R. M. Flynn and F. Lipmann, *J. Biol. Chem.*, **177**, 493 (1949).

[19] T. E. King, I. G. Fels and V. H. Cheldelin, THIS JOURNAL, **71**, 131 (1949).

[20] T. E. King and V. H. Cheldelin, unpublished results.

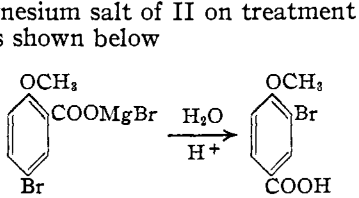
[21] F. Lipmann, N. O. Kaplan and G. D. Novelli, *Federation Proc.*, **6**, 272 (1947).

[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF NORTHWESTERN UNIVERSITY]

The Reaction of Magnesium with 2,4-Dibromoanisole

BY ALLEN S. HUSSEY AND I. J. WILK

It has been reported that the reaction of magnesium with 2,4-dibromoanisole (I) in equimolar quantities involves primarily the bromine atom ortho to the methoxyl group.[1] The isolation of 65% of 4-bromoanisole on hydrolysis and 30% of 4-bromo-2-hydroxyanisole on oxidation of the magnesium derivative of I was cited as evidence, although carbonation did not give the expected 5-bromo-2-methoxybenzoic acid (II), but gave instead 3-bromo-4-methoxybenzoic acid (III) in 60% yield.[1b–d] This unexpected result was explained to arise from a rearrangement of the bromomagnesium salt of II on treatment with dilute acid, as shown below



III (1)

As proof for (1), synthetic II was reported to rearrange to III, and 5-bromosalicylic acid (IV) to rearrange to 3-bromo-4-hydroxybenzoic acid (V), when treated with ethylmagnesium bromide followed by dilute acid.[1b–e] The magnesium derivative of 2-bromo-4-chloroanisole (VI) was reported to give the rearranged acid, 3-chloro-4-methoxybenzoic acid (VII) by an analogous mechanism.[1d]

We have investigated these reactions and our results lead to an entirely different interpretation. The monomagnesium derivative of I is actually a mixture in which the isomer para to the methoxyl group is the major one; thus no rearrangement need be postulated to explain the formation of III on carbonation and acidification.

We have found that the monobromoanisole product obtained on hydrolysis consists of a mixture of 68–72% 2-bromoanisole and 28–32% 4-bromoanisole as indicated by ultraviolet absorption and refractive index. Furthermore, we have not been able to rearrange II to III, nor IV to V, although we varied conditions widely in attempts to do so. In addition, when the magnesium derivative of I was added to a large excess of ethyl carbonate[2] we were able to isolate only III in 55–60% yield (either as the free acid or its ethyl ester).

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[1] (a) Paty, *Compt. rend.*, **214**, 910 (1942); (b) Paty and Quelet, *Bull. soc. chim.*, **8**, 55 (1942); (c) *Compt. rend.*, **217**, 229 (1943); (d) *Bull. soc. chim.*, **11**, 505 (1944); (e) *Compt. rend.*, **220**, 324 (1945).

[2] Whitmore and Loder, "Organic Synthesis," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 282.

The bromomagnesium salt of II cannot be an intermediate in this preparation.

When the magnesium derivative was carbonated with a stream of dry carbon dioxide at −15°, or by filtering the ether solution onto powdered Dry Ice, only III and traces of 4-methoxyisophthalic acid, m. p. 258–261°,[3] could be isolated. However, when carbonated by slow addition to a well-stirred slurry of Dry Ice in anhydrous ether at −80°, 7–8% of 4-methoxyisophthalic acid and 17–18% of II in addition to 54–57% of III were isolated from the acidic products. The remainder of I could be accounted for as monobromoanisole (8–9%) and recovered I (5–6%). When similarly treated, carefully purified VI gave 85–87% of 5-chloro-2-methoxybenzoic acid, m. p. 96.2–7.2°,[4] and a small amount of 4,4′-dichloro-2,2′-dimethoxybenzophenone (VIII), m. p. 108.8–109.6°, but no VII at all.

A reason for the failure to isolate II from carbonations by the usual procedures or from the reaction with ethyl carbonate is suggested by a further experiment with the magnesium derivative of VI. When this was carbonated on powdered Dry Ice, 13–15% of the benzophenone VIII was isolated, and in one experiment, in which the addition was made more rapidly, 26% of VIII was obtained. Considerable non-distillable neutral material was observed when I was carbonated by the usual procedures, or with ethyl carbonate. Although we have not been able to identify this material, it seems likely that it is formed by secondary condensations which are particularly important when the bromomagnesium function or the carboxylate group is ortho to the methoxyl group. We have observed this same trend, in a qualitative way, during the carbonation of the magnesium derivatives of 2-bromo- and 4-bromoanisole.

Experimental[5]

5-Bromosalicylic Acid (IV).—The product from the reaction of 64.0 g. of bromine in glacial acetic acid with 55.2 g. of salicylic acid in glacial acetic–sulfuric acid[6] at 40–50° was isolated by removal of most of the acetic acid under reduced pressure. Recrystallization from dilute alcohol gave 62.0 g. of IV (71%), m. p. 165.4–166.2°.

5-Bromo-2-methoxybenzoic Acid (II).—Dimethyl sulfate (34.0 cc., 0.2 mole), was added dropwise to a well-stirred solution of 21.7 g. (0.1 mole) of IV and 11.2 g. of potassium hydroxide in 70 cc. of water cooled to below 5°. After two hours, the mixture was warmed to room temperature and stirred for twelve hours, with periodic additions of alkali to keep the solution basic. After refluxing for two hours, the solution was cooled and acidified. One recrystallization from hot water gave 19.0 g. (82%) of II, m. p. 118–119°; from dilute alcohol, m. p. 120.0–120.8°.[7]

3-Bromo-4-hydroxybenzoic Acid (V).—The bromination of 27.6 g. of *p*-hydroxybenzoic acid in glacial acetic–sulfuric acid as described above gave 22.0 g. (55%), of product after one recrystallization from acetic acid, m. p. 163.8–165.0°. After sublimation at 1 mm., V melted at 164.8–165.4°[8]; mixed with IV, depression to 140–152°. The identity of this compound was demonstrated by means of the methyl[9] and ethyl[8b] esters, m. p. 105.3–107.0° and 102.2–103.1°, respectively, once recrystallized from Skellysolve B.

3-Bromo-4-methoxybenzoic Acid (III).—Bromination of 6.0 g. of anisic acid in glacial acetic–sulfuric acid at 70–90° gave 4.5 g. (50%) of III after one recrystallization from alcohol–water, m. p. 216.7–217.8°.[10] Recrystallization from alcohol raised the m. p. to 221.5–222.6°.

2,4-Dibromoanisole (I).—To a well-stirred solution of 196 g. of purified anisole in 400 cc. of glacial acetic acid and 600 cc. of concd. sulfuric acid was added dropwise, with occasional warming on the steam-bath, 580 g. of bromine in 300 cc. of acetic acid. After five hours, the mixture was poured onto ice, the excess bromine was destroyed with bisulfite and the product was filtered and dissolved in ether. After washing with 10% potassium hydroxide and water, the ether was removed and the product vacuum distilled; yield 350 g. (72%) of I, b. p. 101–106° at 1 mm. After two recrystallizations from Skellysolve B, 301 g. (62%) of I, m. p. 61.5–62.3°,[11] was obtained.

2-Bromo-4-chloroanisole (VI).—Dry chlorine was bubbled through 346 g. (3.2 moles) of purified anisole without addition of heat until the gain in weight was 121 g. After washing with water, the product was vacuum distilled at 17 mm. to yield 265 g. of product (58%) boiling at 85–90°, n^{25}D 1.5354. The 4-chloroanisole thus obtained was warmed in 1000 cc. of equal volumes of glacial acetic and sulfuric acids while 290 g. (1.8 moles) of bromine was added dropwise with stirring over five hours. After pouring onto ice, destroying the unreacted bromine and extracting with ether, phenolic material was removed by washing with sodium hydroxide (20%) and then with water. After removal of the ether, the product was vacuum distilled at 125–30° at 11 mm. to give 270 g. (66%) of VI, f. p. 19.8–24.5°. The product was purified by freezing 80% of it, filtering and recrystallizing the material from Skellysolve B to constant m. p. 28.6–29.1°[12]; yield 171 g. (24%, from anisole).

2-Bromoanisole.—Eastman Kodak Co. 2-bromoanisole was fractionally crystallized four times and distilled; b. p. 124° at 40 mm.; f. p. 2.49–2.51°; $n^{25.0}$D 1.5717; molar extinction coefficient (ϵ) in 95% alcohol 344 at 245 mμ, 651 at 240 mμ.

4-Bromoanisole.—Eastman Kodak Co. 4-bromoanisole was purified in the same way: b. p. 124° at 40 mm.; f. p. 13.39–13.41°; $n^{25.0}$D 1.5617; ϵ in 95% alcohol 1240 at 245 mμ, 3160 at 240 mμ. The refractive index–composition curve for 2-bromoanisole and 4-bromoanisole is linear.

Reaction of Ethylmagnesium Bromide with II and IV.—In a typical experiment, the reagent from 2.3 g. of ethyl bromide and 0.50 g. of magnesium was added dropwise to a stirred solution of 4.6 g. of II in absolute ether. After fifteen minutes, the solution was acidified with ice-cold, dilute hydrochloric acid and the ether layer was washed with water. Acidification of alkaline extracts of the ether layer gave 4.5 g. of recovered II, m. p. 119.6–120.4°. In other experiments, variations in the amount and concentration of mineral acid and temperature of neutralization gave the same results. The use of excess Grignard reagent resulted in a decreased recovery of II and produced neutral material (not identified).

When 2.3 g. of IV was similarly treated, but with two equivalents of Grignard reagent, 2.0–2.2 g. of material, m. p. 155–158°, was obtained. Mixed m. p. experiments with IV and V showed this to be recovered IV. One re-

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(3) Schall, *Ber.*, **12**, 828 (1879).

(4) Gilman, Langham and Moore, THIS JOURNAL, **62**, 2327 (1940).

(5) All m.p.'s corrected unless otherwise specified.

(6) Hewitt, Kenner and Silk, *J. Chem. Soc.*, **85**, 1228 (1904).

(7) Peratoner, *Gazz. chim. ital.*, **16**, 407 (1886).

(8) (a) Paal, *Ber.*, **28**, 2411 (1895); (b) Meyer, *Monatsh.*, **22**, 438 (1901); (c) Robertson, *J. Chem. Soc.*, **81**, 1483 (1902); (d) Commanducci and Marcello, *Gazz. chim. ital.*, **33** [1], 69 (1903) report m. p. between 148 and 159° for this compound while (e) Leulier and Pinet [*Bull. soc. chim.*, **41**, 1369 (1927)] report 177°.

(9) Auwers and Reis, *Ber.*, **29**, 2360 (1896).

(10) Salkowski, *ibid.*, **7**, 1013 (1874).

(11) Korner, *Ann.*, **137**, 206 (1866).

(12) Brand and Pabst, *J. prakt. Chem.*, [2] **120**, 199 (1928).

crystallization from alcohol-water raised the m. p. to 163.4–165.7°.

Reaction of Magnesium with 2,4-Dibromoanisole.—A solution of 53.2 g. of dibromoanisole and 21.8 g. of ethyl bromide[13] in 500 cc. of absolute ether was added with stirring over two hours to 9.7 g. of magnesium turnings in a system kept under dry, oxygen-free nitrogen. The mixture was refluxed for two hours longer, at which time nearly all of the magnesium had disappeared. Usually, but not always, the solution separated into two phases at this point, but failure to do so did not seem to cause different results when treated as below.

Hydrolysis.—The filtered solution of the magnesium derivative of I from above was hydrolyzed by the addition of cold, dilute hydrochloric acid and washed with water. On distillation, 2.8 g. (13%) of anisole (b. p. 57–60° at 20 mm.), 29.1 g. (74%) of monobromoanisole (b. p. 96–99° at 12 mm.), and 3.5 g. (6.5%) of unreacted I, (b. p. 102–105° at 1 mm.), were isolated. The monobromoanisole fraction was further purified by distillation at 40 mm. where both isomers distil at 124°. In this way, 25.6 g. of monobromoanisole was obtained and analyzed by refractive index (D, 25.0°) and ultraviolet absorption at 245 mμ and 240 mμ in 95% ethyl alcohol. All samples thus obtained had refractive indices between 1.5685 and 1.5689 (68–72% 2-bromoanisole). At 245 mμ, the molar extinction coefficients of the samples were between 602 and 625 (69–71% 2-bromoanisole); at 240 mμ between 1370 and 1400 (70–71% 2-bromoanisole).

Anal. Calcd. for C_7H_7OBr: C, 44.94; H, 3.78; Br, 42.72. Found: C, 45.2, 45.5; H, 3.8, 3.9; Br, 42.9.

Ethyl 3-Bromo-4-methoxybenzoate.—The filtered solution of the magnesium derivative of I from above was added over one hour to a well-stirred solution of 190 g. (threefold excess) of purified ethyl carbonate[2] in 200 cc. of absolute ether. After hydrolysis with dilute hydrochloric acid and washing with water, ether, ethyl propionate and unreacted ethyl carbonate were removed at the water-pump and the residue was then vacuum distilled. There was obtained 3.2 g. of unreacted I, b. p. 97–99° at 0.8 mm., and 29.6 g. (57%) of ethyl 3-bromo-4-methoxybenzoate, b. p. 114–118° at 0.6 mm. After one crystallization from Skellysolve B, this melted at 69.9–71.6°.[14] Saponification of 5.0 g. of the ester gave 4.3 g. of III, m. p. 219.5–220.7°.

No ethyl 5-bromo-2-methoxybenzoate could be found in the reaction product, but considerable (13–16 g.) unidentified high-boiling material (above 150° at 0.6 mm.) was observed in each of several experiments. No single pure material could be isolated from this mixture.

In one experiment III was isolated directly from the reaction mixture by saponification with potassium hydroxide, extraction with water and acidification. In this way, 26.5 g. (57%) of III, m. p. 217.8–219.7°, was obtained. No II could be isolated by fractional crystallization.

Carbonation.—The filtered solution of the magnesium derivative of I from above was added dropwise over two hours with stirring to a slurry of powdered Dry Ice in anhydrous ether and the mixture was allowed to stand overnight. After hydrolysis with dilute hydrochloric acid, the ether layer was separated and the aqueous layer was washed twice with ether and subjected to continuous ether extraction for two days. The combined ether solutions were extracted with several portions of 15% potassium hydroxide. After removal of the ether, 3.3 g. (8.9%) of monobromoanisole (b. p. 93–95° at 10 mm.) and 2.7 g. (5.1%) of I (b. p. 100–102° at 1 mm.) were obtained on vacuum distillation. Acidification of the alkaline washings furnished 33.8 g. of crude acids. An additional 4.2 g. of acid was obtained by a continuous ether extraction of the filtrate; total yield, 82% (calculated as bromomethoxybenzoic acid). Fractional crystallization of the acidic product using acetone, ethanol, benzene and ethanol-water in sequence gave 2.9 g. (7.4%) of 4-methoxyisophthalic acid,[3] m. p. 263–264° (uncor.), (neut. equiv. 102), 25.1 g. (54%) of III, m. p. 218.2–219.4°,[10] and 8.5 g. (18%) of II, m. p. 119.8–120.6°.[7]

When the solution was carbonated by filtering onto powdered Dry Ice and the reaction mixture worked up as above, 25–30 g. of III (54–65%) was obtained in several experiments. From the neutral material, 5–8% of I could be recovered by distillation, with 8–12 g. of non-distillable residue. No II could be isolated by fractional crystallization, but in two experiments, a small amount of 4-methoxyisophthalic acid, m. p. 258–261° (uncor.) was isolated.

5-Chloro-2-methoxybenzoic Acid.—An ether solution of 49.7 g. (0.224 mole) of 2-bromo-4-chloroanisole (VI) and 24.5 g. (0.224 mole) of ethyl bromide was added to 10.9 g. (0.450 mole) of magnesium turnings over one hour and the mixture refluxed two hours longer. The filtered solution was carbonated with Dry Ice in ether as described previously for 2,4-dibromoanisole. There was thus obtained 36.4 g. (87%) of 5-chloro-2-methoxybenzoic acid, m. p. 94.2–96.0°. This melted at 96.2–97.2° when recrystallized from Skellysolve B.[4]

In addition, 0.5 g. of crystalline neutral material, m. p. 108.8–109.6° (from ethyl acetate), was isolated from the ether solution. This material formed a 2,4-dinitrophenylhydrazone, m. p. 221.2–222.0° (from ethanol-pyridine). The analyses were in good agreement with the calculated value for 4,4′-dichloro-2,2′-dimethoxybenzophenone (VIII), a compound not previously described.

Anal. Calcd. for $C_{15}H_{12}O_3Cl_2$: C, 57.89; H, 3.89. Found: C, 57.4, 57.8; H, 3.9, 3.8. Calcd. for $C_{21}H_{16}O_6N_4Cl$: N, 11.41. Found: N, 11.3.

When the magnesium derivative of VI was carbonated by filtering onto powdered Dry Ice, the yield of acid in two experiments was 31–32 g. (74–76%). From the ether solutions could be recovered 4.0–4.6 g. (13–15%) of benzophenone, VIII. In another experiment, the solution was added more rapidly to powdered Dry Ice. The yield of acid was only 24.2 g. (58%), whereas 8.2 g. (26%) of benzophenone, VIII, was isolated.

Summary

The monomagnesium derivative of 2,4-dibromoanisole is a mixture consisting of 68–72% of the 4-isomer and 28–32% of the 2-isomer. On hydrolysis, it yields a mixture of 2- and 4-bromoanisole. On carbonation with Dry Ice in ether at −80°, 3-bromo-4-methoxybenzoic acid and 5-bromo-2-methoxybenzoic acid can be isolated.

Carbonation of the magnesium derivative of 2-bromo-4-chloroanisole gives 4-chloro-2-methoxybenzoic acid. A new compound, 4,4′-dichloro-2,2′-dimethoxybenzophenone, has been isolated as a by-product.

EVANSTON, ILLINOIS RECEIVED MARCH 16, 1949

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(13) Grignard, *Compt. rend.*, **198**, 625 (1934).

(14) Balbiano, *Gazz. chim. ital.*, **11**, 406 (1881).