structure factors remain essentially constant). The values in Table I show that the melting points decrease markedly with increasing size of the alkyl groups.

TABLE I

MELTING POINTS OF VARIOUS ALKYLATED AMINO NITRO COMPOUNDS

Substance	M. p., °C.
Nitroaminodurene	161
Nitrodimethylaminodurene	90
1-Amino-4-nitronaphthalene	191
1-Methylamino-4-nitronaphthalene	184
1-Ethylamino-4-nitronaphthalene	176
1-Benzylamino-4-nitronaphthalene	156
1-Dimethylamino-4-nitronaphthalene[a]	65
1-Diethylamino-4-nitronaphthalene[a]	Liquid

[a] There is no chance for a preferred position of the alkyl groups in this case.

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RECEIVED MAY 16, 1940

THE BIOLOGICAL ACTIVITY OF SYNTHETIC PANTOTHENIC ACID

Sir:

The lactone of the "acid fragment" of pantothenic acid has been identified as α-hydroxy-β,β-dimethylbutyrolactone by Stiller, Keresztesy and Finkelstein.[1] The coupling of the synthetic *dl*-lactone with β-alanine in 50% yields, as determined by microbiological assay, and assuming the inactivity of one isomer, has been reported by Weinstock and co-workers.[2] In the present investigation the yield from the coupling reaction was 88%, and definite evidence was found for the inertness of the unnatural isomer.

When equimolecular amounts of 1 *N* sodium hydroxide, β-alanine and the lactone[3] are mixed at 0°, 50% coupling takes place almost immediately as determined by a Sörensen formol titration for free amino nitrogen. Upon standing no further coupling occurs. Instead, the remaining hydroxide ion disappears during the course of an hour, due probably to the saponification of the uncoupled lactone. If instead of equimolecular amounts, the ratio of lactone to β-alanine to 1 *N* sodium hydroxide is made 3:1:1, a 55% coupling occurs immediately, again followed by the disappearance of hydroxide ion. If now to this same solution an amount of 10 *N* sodium hydroxide equivalent to the amount of free β-alanine remaining is added, 51% of this remainder likewise couples. Upon repetition of the procedure, the % of the remainder of the β-alanine which couples falls off rapidly. The results of a typical experiment are summarized in Table I.

(1) As reported by Williams and Major, *Science*, **91**, 246 (1940).
(2) Weinstock, Arnold, May and Price, *ibid.*, **91**, 411 (1940).
(3) Prepared according to the directions of Kohn and Neustadter, *Monatsh.*, **39**, 295 (1918).

TABLE I

	Milliequivalents of				Total % conversion
	β-alanine	hydroxide ion	Lactone	*dl*-pantothenic acid	
Present at start	540	540	1680	0	..
Present after 1 hr.	235[a]	< 1[b]	..	305[c]	55
Added at end of 1 hr.	0	235	0	0	..
Present at end of 2 hr.	115[a]	< 1[b]	..	425[c]	79
Added at end of 2 hr.	0	115	0	0	
Present at end of 3 hr.	78[a]	< 1[b]	..	462[c]	85
Added at end of 3 hr.	0	100	0	0	
Present at end of 4 hr.	68[a]	< 1[b]	..	472[c]	88

[a] By Sörensen formol titration. [b] Acid to phenolphthalein. [c] By difference.

At the end of the experiment, the solution was biologically assayed with chicks,[4] and found to contain 3,680,000 chick filtrate factor units, corresponding to 36 units per mg. of *dl*-pantothenic acid. Natural pantothenic acid has been stated to contain 71 chick units per mg.[5] This points to the inactivity of one enantiomorph in the synthetic preparation.

At the same time a mixture of 10 g. of the *dl*-lactone and 7 g. of β-alanine was incorporated in 1000 g. of heated diet and biologically assayed. Slight but definite activity was observed, calculated to correspond roughly to a coupling *in vivo* of 0.06% of the mixture. This indicates that none of the activity of the pantothenic acid solution at the level fed (corresponding to 2.1 mg. of *dl*-pantothenic acid per 100 g. of diet) may be attributed to the presence of unchanged starting materials.

(4) Jukes, *J. Biol. Chem.*, **117**, 11 (1937).
(5) Jukes, *ibid.*, **129**, 225 (1939).

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RECEIVED MAY 20, 1940

NAPHTHOQUINONE OXIDES

Sir:

Since 2-methyl-1,4-naphthoquinone oxide can be converted very easily and efficiently [Fieser, *J. Biol. Chem.*, **133**, 391 (1940)] into the isomer phthiocol, it was somewhat surprising to discover

that the substance surpasses phthiocol by far in vitamin K activity. The observation that the pure oxide [Fieser, Campbell, Fry and Gates, THIS JOURNAL, **61**, 3216 (1939)] is fully effective in the chick assay at a dosage of 5 γ prompted the investigation of other oxides of 2-alkyl and 2,3-dialkyl 1,4-naphthoquinones, and it was found that the hydrogen peroxide procedure [Fieser, *et al.*, *loc. cit.*] provides a convenient route to a number of substances of both types. Farnesylnaphthoquinone oxide [found: C, 78.88; H, 8.16] and phytylnaphthoquinone oxide [found: C, 79.91; H, 9.76] were obtained as nearly colorless oils showing, respectively, very weak and weak (500 γ) antihemorrhagic activity. These substances are cleaved by alkali to a mixture of 2-hydroxy-1,4-naphthoquinone and its 3-alkyl derivative. Crystalline oxides were obtained from 2,3-dimethyl-1,4-naphthoquinone [m. p. 104–104.5°, found: C, 71.26; H, 5.09; active at 25 γ] and 2-methyl-3-cinnamyl-1,4-naphthoquinone [m. p. 85–86°, found: C, 78.94; H, 5.47].

Vitamin K_1 was converted in nearly quantitative yield into the 2,3-oxide, which was obtained as an almost colorless oil [found: C, 79.85; H, 9.69]. Any uncertainty as to the structure is eliminated by the observation that the absorption spectrum corresponds closely with that of 2,3-dimethyl-1,4-naphthoquinone oxide. The K_1 oxide shows antihemorrhagic activity of about the same order as the vitamin (1.5 γ) and gives no purple-blue color with alcoholic alkali. The properties of the oxide are of interest in connection with the reports of Fernholz, Ansbacher and coworkers [THIS JOURNAL, **61**, 1613 (1939); *Proc. Soc. Exptl. Biol. Med.*, **42**, 655 (1939)] stating that they have isolated from alfalfa concentrates a nearly colorless substance of high potency which does not give the Dam–Karrer color test characteristic of vitamins K_1 and K_2. However, in our hands, there is no great difference in the ratio of the effective dose of the oxide and of vitamin K_1 when assayed by the six and eighteen hour method.

We have found that the oxides of vitamin K_1 and of methylnaphthoquinone can be reduced smoothly to vitamin K_1 hydroquinone and methylnaphthohydroquinone with sodium hydrosulfite in aqueous alcohol, even at room temperature. This lends plausibility to the hypothesis that the high potency of the oxides is due to a reduction in the organism to the corresponding quinones or hydroquinones; possibly the 2-methyl oxide is converted in part into the comparatively inactive phthiocol.

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RECEIVED APRIL 20, 1940

MISCIBILITY OF CARBON DIOXIDE AND WATER UNDER HIGH PRESSURE

Sir:

Wiebe and Gaddy [THIS JOURNAL, **62**, 815 (1940)] report the solubility of carbon dioxide in water and make the following statement: "The compositions of the gas and liquid phases at 12° and 600 atm. were identical." My understanding of the behavior of carbon dioxide–water systems is that compression at 12° to about 47.7 atm. will change the phases from a gas (predominantly carbon dioxide) and liquid (mostly water) to a gas (mostly carbon dioxide), a liquid (mostly carbon dioxide), and a liquid (mostly water). Further attempts to compress the system will cause the gas phase to change to a liquid (mostly carbon dioxide) phase and leave at its disappearance two liquids, one predominantly water and the other predominantly carbon dioxide.

Their data show that compression of the two phases increases the carbon dioxide content of the water phase only from 0.03 mole fraction to less than 0.04 mole fraction. Lowry and Erickson [*ibid.*, **49**, 2729 (1927)] indicated that the water concentration in the liquid carbon dioxide was much lower than the above concentration of carbon dioxide in the water phase. Wiebe and Gaddy [*ibid.*, **61**, 315 (1939)] state the mutual solubility of water and carbon dioxide as liquid–liquid system is affected by pressure to only a slight extent.

These statements appear contradictory to the above quotation of identical phases. Any critical phenomena in this region would be of the liquid–liquid critical solution type and not of the type reported by Kuenen [*Commun. Phys. Lab. Univ. Leiden*, **4** (1892)] for the carbon dioxide–methyl chloride system. To become mutually soluble, it is normally expected that the two phases approach each other in composition. A consideration of the probable behavior of these two phases upon compression indicates a possible explanation of the above contradictions. At 10 to 20°,