Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.40; H, 6.03.

p-Phenylphenacyl O-Methyl-L-lactate from L-(*dextro*)-Lactic Acid (V).—An authentic sample of L-(*dextro*)-lactic acid[15] was converted to the p-phenylphenacyl ester (m. p. 139–140°[16]) and 0.76 g. of this ester, 7.5 g. of silver oxide and 20 ml. of methyl iodide were shaken mechanically at room temperature for four hours. The silver salts were removed by filtration and washed with warm methanol. The filtrate and washings were concentrated to a crystalline residue under reduced pressure; yield 0.70 g., m. p. 70–73°, $[\alpha]^{22}D$ −15.5° (c 3, benzene). Recrystallization from ethanol–water yielded pure material with constants unaltered by further crystallization or by chromatographic purification effected as described above; yield 0.54 g., m. p. 74–75°, $[\alpha]^{22}D$ −16.2° (c 3, benzene).

Anal. Calcd. for $C_{18}H_{18}O_4$: C, 72.47; H, 6.08. Found: C, 72.49; H, 6.06.

Summary

1. Reductive desulfurization of tetraacetyl-2-methyl-D-glucose diethyl thioacetal (I) yielded tetraacetyl-2-methyl-1-desoxy-D-glucitol (II) which on deacetylation (III) and periodate cleavage with subsequent oxidation produced an O-methyllactic acid (IV) whose p-phenylphenacyl ester was identical with that obtained by esterification and methylation of L-(*dextro*)-lactic acid (V). This effects a direct chemical correlation of L-(*levo*)-glyceraldehyde with L-(*dextro*)-lactic acid.

2. Tetraacetyl-2-methyl-*aldehydo*-D-glucose is described.

COLUMBUS, OHIO RECEIVED MAY 31, 1949

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[15] A product of high purity made by the fermentation of carbohydrate material and for which we are indebted to the Clinton Industries, Inc., Clinton, Iowa.

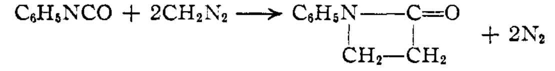
[16] N. L. Drake and J. Bronitsky, THIS JOURNAL, **52**, 3715 (1930), record 145° as the melting point of the p-phenylphenacyl ester of lactic acid (presumably D,L).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, MASSACHUSETTS INSTITUTE OF TECHNOLOGY]

The Reaction of Diazomethane with Isocyanates and Isothiocyanates

BY JOHN C. SHEEHAN AND PATRICK T. IZZO[1]

In a recent communication from this Laboratory the action of diazomethane on phenyl isocyanate was reported.[2] In a reaction analogous to the formation of cyclobutanone from ketene and diazomethane, the β-lactam of N-phenyl-β-alanine is formed.



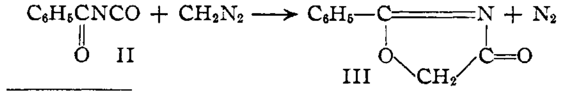
$$C_6H_5NCO + 2CH_2N_2 \longrightarrow \begin{array}{l} C_6H_5N\text{——}C{=}O \\ \quad\ \ | \qquad\ \ | \\ \quad CH_2\text{—}CH_2 \end{array} + 2N_2$$

I

The preparation of this same β-lactam, 1-phenyl-2-azetidinone (I), by cyclization of an ester of N-phenyl-β-alanine with a Grignard reagent has since been described.[3] Phenyl isocyanate and diazomethane were reported by v. Pechmann[4] to yield an oily product which was not further characterized.

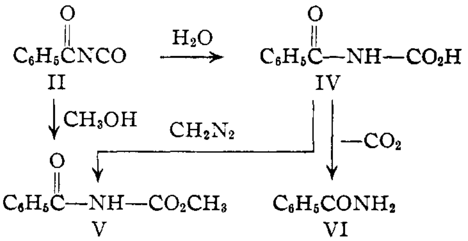
With p-bromophenyl isocyanate a β-lactam also is obtained. Under similar conditions no β-lactam was isolated from the treatment with diazomethane of α-naphthyl, p-nitrophenyl, benzyl and benzoyl isocyanates, or methyl and phenyl isothiocyanates.

Benzoyl isocyanate (II) reacted very rapidly at ice-bath temperature to give, in 68–70% yield, 2-phenyl-4-oxazolone (III). Unlike the formation of the β-lactam in the case of phenyl isocyanate, benzoyl isocyanate added only one methylene group, bridging its two reactive carbonyl groups.



$$C_6H_5\underset{\underset{\displaystyle O}{\|}}{C}NCO \ (II) + CH_2N_2 \longrightarrow \begin{array}{l} C_6H_5\text{—}C\text{=====}N \\ \qquad\ \ | \qquad\quad\ \ | \\ \qquad\ O \diagdown \ \ \diagup C{=}O \\ \qquad\quad\ CH_2 \end{array} \ (III) + N_2$$

The structure of 2-phenyl-4-oxazolone was proved by cleavage with boiling water. Hydrolysis took place at the carbon–nitrogen double bond, forming benzoylglycolic acid amide, which was identified by comparison with an authentic sample.[5] About 10–15% of the total reaction products was found to be N-benzoyl methyl carbamate (V), which was also obtained by interaction of methanol and benzoyl isocyanate. Absorption of a small amount of moisture during the addition of diazomethane to benzoyl isocyanate would explain the formation of this compound. A portion of the unstable N-benzoylcarbamic acid (IV) formed by the addition of water to the isocyanate presumably was methylated by diazomethane, and thus its decarboxylation to benzamide (VI) was prevented. However, some decomposition to VI apparently took place as benzamide was found in small amounts among the reaction products.



Phenyl isothiocyanate and diazomethane have been reported by v. Pechmann[4] to form an equimolar adduct, m. p. 172.5°, in unspecified yield. We obtained the addition product in 60% yield,

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[1] Swift Postdoctoral Fellow, 1947–1948. Present address: American Cyanamid Company, Linden, New Jersey.

[2] J. Sheehan and P. Izzo, THIS JOURNAL, **70**, 1985 (1948).

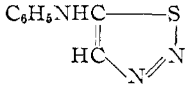
[3] Clarke, Johnson and Robinson, "The Chemistry of Penicillin," Princeton University Press, Princeton, N. J., 1949, p. 977.

[4] H. v. Pechmann, *Ber.*, **28**, 861 (1895).

[5] Aloy and Ch. Rabaut, *Bull. soc. chim.*, **13**, 458 (1913).

m. p. 179–180°, with decomposition. The addition was first assumed by v. Pechmann to have taken place in either of two ways to the nitrogen–carbon double bond of phenyl isothiocyanate. Failure to convert the supposed thiocarbonyl group to a carbonyl by treatment with mercuric oxide (confirmed by us) later led v. Pechmann[6] to formulate the reaction as proceeding by addition of diazomethane across the thiocarbonyl group of phenyl isothiocyanate to produce a sulfur-containing ring.

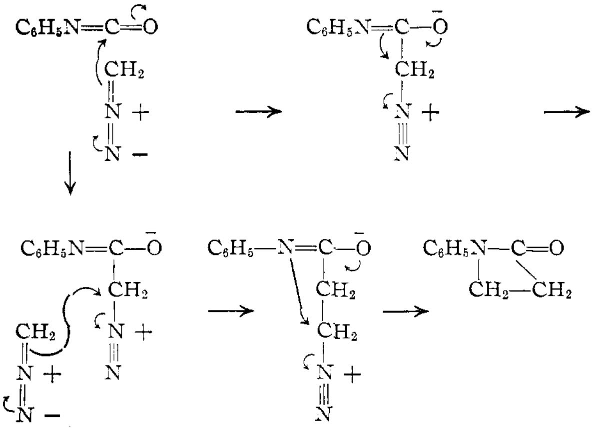
Of the two possible formulas v. Pechmann favored 5-anilino-1,2,3-thiadiazole (VII) or the tautomeric 5-phenylimino-1,2,3-thiadiazoline.



VII

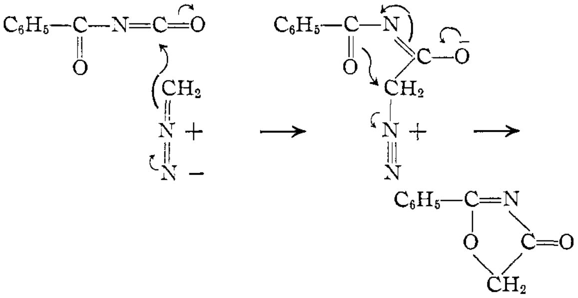
Our degradation studies confirm this structure. Hydrolysis with 10% sodium hydroxide produced a soluble sodium salt, but no sulfide ion was liberated. Reflux with 20% sulfuric acid yielded hydrogen sulfide and aniline (identified by the benzenesulfonamide and the phenylthiourea), but the adduct was essentially resistant to prolonged heating in boiling water. No methylaniline was found and no formaldehyde could be detected by the sensitive dimedon method. These results tend to rule out any structures having a thiocarbonyl group or a methylene unattached to carbon.

Although diazomethane reacts with phenyl isocyanate, benzoyl isocyanate and phenyl isothiocyanate to give three distinctly different types of products, related electronic interpretations can be made. The formation of a β-lactam may be explained by the successive addition of two methylene groups to the polarized carbonyl double bond of phenyl isocyanate.

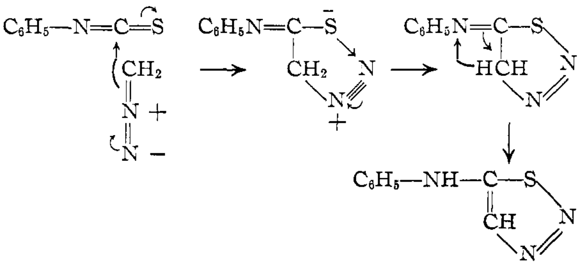


Apparently the addition of one methylene group leads to an electronic structure which is either unable to form a stable three-membered ring (an α-lactam), or such a substance may actually be formed but combines immediately with another molecule of diazomethane to enlarge the ring to the more stable four-membered ring (a β-lactam).

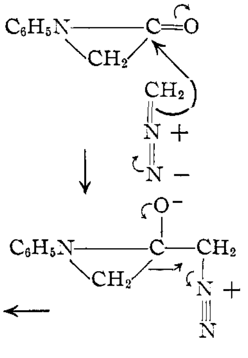
An electronic representation of the reaction with benzoyl isocyanate is similar. However, the presence of a neighboring carbonyl group changes the course of the reaction after the addition of one methylene group. The intermediate is so constituted that a stable five-membered oxazoline ring is preferentially formed, and the addition of a second methylene group does not take place.



The formulation of the phenyl isothiocyanate–diazomethane addition product as 5-anilino-1,2,3-thiadiazole receives further support from the following electronic interpretation of the addition mechanism.



In this case also structural differences in the isocyanate alter the course of the reaction. A molecule of diazomethane adds to the thiocarbonyl group, but the nucleophilicity of the neighboring sulfur atom makes possible ring closure to a stable five-membered ring at a faster rate than nitrogen is eliminated.



In each of the three cases the methylene portion of diazomethane first adds to the polarized carbonyl bond of the isocyanate (or isothiocyanate); the subsequent sequence of reactions is determined by structural characteristics of the particular isocyanate or isothiocyanate.

Diazomethane reacted vigorously with α-naphthyl, p-nitrophenyl and benzyl isocyanates,

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[6] H. v. Pechmann and A. Nold, *Ber.*, **29**, 2588–2593 (1896).

but no well-defined monomeric products were isolated. Methyl isothiocyanate and diazomethane did not react appreciably at room temperature in ether; both starting materials were recovered in good yield.

Experimental[7]

β-Lactam of N-(*p*-Bromophenyl)-β-alanine.—Two grams (0.01 mole) of *p*-bromophenyl isocyanate was dissolved in 25 ml. of anhydrous ether and 35 ml. of a 0.49 *M* sodium-dried ether solution of diazomethane was added in small portions with shaking. A reaction set in immediately with brisk evolution of nitrogen and simultaneous precipitation of an amorphous, orange powder. After allowing the mixture to stand overnight, the clear ethereal solution was separated from the solid by decantation. The solid weighed 0.5 g. and gave positive tests for halogen.

The ether solution was evaporated to dryness, leaving 1.5 g. of a soft, brown semi-solid. This material was triturated with anhydrous acetone, which dissolved the larger part but left undissolved a white, pulverulent substance insoluble in the common organic solvents. This material was not further investigated.

The acetone solution was evaporated to dryness at reduced pressure and the brown, viscous residue was subjected to a slow evaporative distillation. A colorless, crystalline product (0.25 g., m. p. 110–118°) sublimed at 120–130° and 0.05 mm. After one recrystallization from benzene–ligroin, glistening platelets were obtained which melted at 126–127°.

Anal. Calcd. for C_9H_8ONBr: C, 47.82; H, 3.56; N, 6.19. Found: C, 47.86; H, 3.68; N, 6.28.

The compound hydrolyzed with dilute sodium hydroxide, but the hydrolysis did not proceed as readily as in the case of the simpler unhalogenated β-lactam, already reported.

2-Phenyl-4-oxazolone.—To a solution of 3.12 g. (0.021 mole) of benzoyl isocyanate[8] in 10 ml. of absolute ether, was added slowly from a buret a 0.23 *N* sodium-dried ethereal solution of diazomethane. Since the reaction was extremely vigorous, care was necessary to prevent violent bubbling and ejection of the reaction mixture from the flask. The diazomethane reacted instantaneously with the isocyanate without any discoloration of the solution and with simultaneous deposition of the colorless, crystalline oxazolone. The isocyanate solution could be "titrated" with the diazomethane to the appearance of the yellow color. The color did not appear until 88 ml. of the diazomethane solution had been added. The theoretical amount required on the basis of mole-for-mole reaction is 90 ml. Ten milliliters of diazomethane solution was added in excess and the reaction mixture was allowed to stand for one hour at room temperature and then overnight at 0–5°.

The colorless, crystalline mass was separated from the solution by filtration. This material weighed 2.30 g. (68%) and melted at 154–156°. Recrystallization from benzene lowered the m. p. to 150–152° dec.

Anal. Calcd. for $C_9H_7O_2N$: C, 67.07; H, 4.37; N, 8.68; mol. wt., 161.2. Found: C, 67.14; H, 4.35; N, 8.36; mol. wt., 185 (Rast, using camphor as a solvent).

Hydrolysis of 2-Phenyl-4-oxazolone.—To 0.5 g. of the oxazolone was added 40 ml. of water and the mixture was refluxed for two and one-half hours. Solution took place immediately upon warming; no ammonia was evolved. The cooled, clear solution was evaporated to dryness at reduced pressure, leaving a colorless oil which soon crystallized (m. p. 60–80°). After two recrystallizations from hot water, the compound melted constantly at 121–122° (0.23 g.). This product was insoluble in sodium bicarbonate solution and dissolved very slowly in hot 10% sodium hydroxide with evolution of ammonia. The melting points of mixtures with benzoic acid and benzamide showed a depression, but the melting point of a mixture with an authentic sample[6] of benzoyl glycolic acid amide (m. p. 120–121°) showed no depression.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82; mol. wt., 179.2. Found: C, 60.12; H, 5.29; N, 8.09; mol. wt., 190 (Rast, using camphor as a solvent).

N-Benzoyl Methyl Carbamate.—On standing in the cold, a second crop of crystals (0.6 g., m. p. 110–118°) separated from the concentrated ethereal mother liquor from the 2-phenyl-4-oxazolone preparation. After two recrystallizations from benzene, this compound melted constantly at 118–119°. The analytical data indicated an hydrolysis product of 2-phenyl-4-oxazolone. The melting point of a mixture with benzoyl glycolic acid amide was depressed.

Anal. Calcd. for $C_9H_9O_3N$: C, 60.33; H, 5.06; N, 7.82. Found: C, 60.47; H, 5.27; N, 7.90.

N-Benzoyl methyl carbamate was prepared from benzoyl isocyanate and absolute methanol in anhydrous ether. After two recrystallizations from ethanol, the compound melted constantly at 118.6–120°. The melting point of a mixture with the above compound showed no depression.

The ethereal mother liquor was evaporated to dryness, leaving a brown, oily residue (0.35 g.) which crystallized on standing. Evaporative distillation of this material gave a good recovery of colorless crystals, m. p. 80–90°. Two recrystallizations from benzene gave a compound melting constantly at 127–128°. The melting point of a mixture with benzamide showed no depression.

5-Anilino-1,2,3-thiadiazole.—To 2.70 g. (0.02 mole) of phenyl isothiocyanate in 10 ml. of absolute ether was added 35 ml. of cold 0.65 *M* sodium-dried ethereal solution of diazomethane. Evolution of nitrogen did not immediately set in, but soon the solution turned deep amber and a crystalline product began to precipitate. After allowing the mixture to stand at room temperature for one hour, during which time a substantial amount of nitrogen was evolved, the reaction was stored overnight at 0–5°. The tan crystals were separated by filtration (1.7 g.) and the mother liquor was concentrated to about one-half its volume and allowed to stand in the cold for a few hours, giving a second crop of crystals (0.4 g.). The total yield of crystalline compound amounted to 2.1 g. (60%). This crude material turned to a black mass at 120° and decomposed at 168°. For purification, the crystals were first quickly triturated with cold acetone, which dissolved most of the dark-colored impurities. The solid residue was dissolved in hot absolute alcohol and decolorized (Norit). The compound crystallized in long, nearly colorless needles. A further recrystallization yielded a product with a faintly yellow cast, which darkened slightly at 170° and melted with decomposition at 179–180° (reported,[4] m. p. 172.5°).

Anal. Calcd. for $C_8H_7N_3S$: C, 54.22; H, 3.98; N, 23.71; mol. wt., 177.2. Found: C, 54.55; H, 4.12; N, 24.10; mol. wt., 205.3 (Rast, using camphor as a solvent).

The adduct was hydrolyzed by boiling with 20% sulfuric acid. After basification, a small amount of an amine was isolated by ether extraction. This was identified as aniline by the preparation of two derivatives and comparison with authentic samples: the benzenesulfonamide, m. p. 109–111°, and the phenyl thiourea, m. p. 152–153°. No formaldehyde could be detected (dimedon).

A portion (0.25 g.) of 5-anilino-1,2,3-thiadiazole was refluxed for three and one-half hours with 20 ml. of 10% sodium hydroxide solution. The compound dissolved completely as the solution warmed. The resulting water-clear solution was tested frequently with lead acetate paper; all tests were negative.

Summary

Diazomethane has been found to undergo three entirely different types of reaction with various

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[7] All melting points are corrected.

[8] O. Billeter, *Ber.*, **36**, 3218 (1903).

isocyanates and isothiocyanates. Phenyl isocyanate and *p*-bromophenyl isocyanate interact with diazomethane in cold ethereal solution to form the β-lactams of N-phenyl-β-alanine and N-(*p*-bromophenyl)-β-alanine.

Benzoyl isocyanate reacts vigorously with diazomethane to give in 68–70% yield 2-phenyl-4-oxazolone. With phenyl isothiocyanate, diazomethane forms a crystalline equimolar addition product, 5-anilino-1,2,3-thiadiazole. An electronic interpretation of the reactions is presented.

CAMBRIDGE 39, MASS. RECEIVED JUNE 8, 1949

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

The Metalation of Some Sulfur-Containing Organic Compounds[1a]

BY HENRY GILMAN AND F. J. WEBB[1b]

Methyl phenyl sulfide was shown to undergo exclusive lateral metalation[2] with *n*-butyllithium in diethyl ether.

$$C_6H_5SCH_3 + n\text{-BuLi} \xrightarrow[\text{HOH}]{\text{CO}_2} C_6H_5SCH_2COOH$$

Under corresponding conditions nuclear metalation[3] is effected with both diethylbarium and diethylstrontium to give metalation products which yield on carbonation, *o*-methylmercaptobenzoic acid. Metalations of methyl phenyl sulfide with other reagents are now reported. To determine the generality of the lateral metalation with *n*-butyllithium, a number of aryl methyl sulfides and higher-alkyl aryl sulfides were studied.

TABLE I

METALATION OF METHYL PHENYL SULFIDE

Metalating agent[a]	Time, hr.	Temp., °C.	Solvent	Acid[b] yield, %	Thiophenol yield, %	Recovered sulfide, %
Sodium	18	25–28	Ether	3.9	20.9	52.4
Sodium	18	25–28	Benzene	Trace[c]	Trace[c]	87.5
Mercuric acetate	9.5	95–100		36.6[d]		
n-Butylmagnesium bromide	2	135–140	None[e]	42.0[f]	Trace[c]	63.0
	5	150–155	None	0.2[g]		67.0
Methyllithium	20	34	Ether	0.12		84.0
n-Butyllithium	20	28–38	Pet. ether	Trace[c]		91.5
n-Butyllithium	168	28–38	Pet. ether	3.6	2.27	31.7
n-Butyllithium	3	130–150	None	Trace[c]	22.7	29.0
n-Butyllithium	1	To 150[h]	None	21.2	10.0	52.2
Phenyllithium	16	34	Ether	9.2		37.0
Phenylsodium	5	Room	Benzene	8.9		44.4
Phenylcalcium iodide	46	34	Ether	[i]		78.5
	3.5	150–160	None	[i]	13.0	58.8

[a] The mole ratio of metalating agent to sulfide was 1:1. [b] Phenylmercaptoacetic acid was isolated unless otherwise specified. The yield was calculated on sulfide introduced. [c] Traces were not identified. [d] The product was *p*-acetoxymercuriphenyl methyl sulfide. [e] The ether was distilled, prior to addition of the sulfide, until the desired temperature was reached, as measured by a thermometer in the liquid. [f] Valeric acid only was isolated. [g] The product was *o*-methylmercaptobenzoic acid. [h] The sulfide was added to the cooled residue, after distillation of the ether. The mixture was heated to 150° during thirty minutes and cooled during the next thirty minutes. [i] Benzoic acid only was isolated.

Metalation of Methyl Phenyl Sulfide.—The position substituted was conditioned by the metalating agent employed rather than by solvent or temperature. Methyl- and phenyllithium in ether, *n*-butyllithium in petroleum ether (b. p. 28–38°) and phenylsodium in benzene gave lateral metalation (Table I). The rate of reaction was especially slow in petroleum ether. Lateral metalation also occurred with *n*-butyllithium at 150° in the absence of solvent. Under corresponding conditions at 150–155°, *n*-butylmagnesium bromide gave a nuclear metalation since *o*-methylmercaptobenzoic acid was isolated subsequent to carbonation. Thus, ortho-nuclear substitution was effected by metalating agents of the Group II metals, magnesium, barium[3] and strontium[3] but lateral metalation by the metalating agents of the Group I metals, lithium and sodium. Anisole also gives ortho-nuclear metalation with Grignard reagents.[4] Phenylcalcium iodide failed to metalate methyl phenyl sulfide in ether or at 150–160° in the absence of solvent. This reagent did not metalate phenyl sulfide[5] but did metalate dibenzothiophene in the 3-position.[6] Mercuric acetate gave

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[1a] Paper LXVI in the Series: "The Relative Reactivities of Organometallic Compounds"; the preceding paper with Gainer is in THIS JOURNAL, **71**, 2327 (1949).

[1b] Present address: Firestone Tire and Rubber Co., Akron, Ohio.

[2] Gilman and Webb, THIS JOURNAL, **62**, 987 (1940).

[3] Gilman, Haubein, O'Donnell and Woods, *ibid.*, **67**, 922 (1945).

[4] Challenger and Miller, *J. Chem. Soc.*, 894 (1938).

[5] Gilman and Bebb, THIS JOURNAL, **61**, 109 (1939).

[6] Gilman, Jacoby and Pacevitz, *J. Org. Chem.*, **3**, 120 (1938).