for thirty minutes and the solid product filtered—after cooling—washed with water and recrystallized from glacial acetic acid; m. p. 293.5° (dec.). *Anal.* Calcd. for $C_{10}H_{20}O_4N_2$: C, 67.0; H, 5.8; N, 8.2. Found: C, 66.7; H, 5.5; N, 8.1.

4,4'-Dinitrodiphenylacetic Acid.—A mixture of 31 g. of the ester (I), 150 cc. of glacial acetic acid and 15 cc. of 25% sulfuric acid was refluxed for four hours. After dilution with water, the free acid crystallized upon standing. Recrystallization from 50% acetic acid gave transparent prisms, m. p. 174° (dec.); yield 95%. *Anal.* Calcd. for $C_{14}H_{10}O_8N_2$: mol. wt., 302. Found: mol. wt., 301 (by titration). The crystalline **acid chloride** was obtained in quantitative yield, when the acid (6.5 g.) was refluxed (six hours) with thionyl chloride (25 cc.); recrystallized from a mixture of benzene and petroleum ether, it melted at 142–143°. *Anal.* Calcd. for $C_{14}H_8O_6N_2Cl$: C, 52.5; H, 2.8; N, 8.7. Found: C, 52.5; H, 2.6; N, 9.0.

4,4'-Diaminodiphenylacetic Acid (II).—(a) A solution of 3 g. of 4,4'-dinitrodiphenylacetic acid in 50 cc. of glacial acetic acid was hydrogenated in presence of a palladium-barium sulfate catalyst; the required amount of hydrogen was absorbed in fifteen minutes. The filtered solution was evaporated and the oily residue triturated with isopropyl alcohol; from butanol, yellowish prisms of m. p. 204.5° (dec.); yield, 71%.

(b) A solution of 0.5 g. of the diamino ester in a mixture of 10 cc. of water and 3 cc. of glacial acetic acid was refluxed for twelve hours and then brought to dryness. Recrystallization of the residue from butyl alcohol gave crystals of m. p. 204.5° (dec.), which were identical with the above product.

DANIEL SIEFF RESEARCH INSTITUTE
REHOVOTH, ISRAEL RECEIVED JANUARY 31, 1949

The Bromination of ϵ-Benzoylaminocaproic Acid

BY E. E. HOWE AND E. W. PIETRUSZA

One of the most acceptable syntheses of lysine is that of Eck and Marvel[1] which involves the bromination of ϵ-benzoylaminocaproic acid with bromine and red phosphorus. In a recent communication Galat[2] has observed that this bromination is not easily effected and that the yields are extremely erratic. He has circumvented this undesirable reaction and improved the synthesis of lysine by chlorinating ϵ-benzoylaminocaproic acid with sulfuryl chloride. The excellent yield of α-chloro-ϵ-benzoylaminocaproic acid more than compensates for the somewhat lower yield obtained in the subsequent amination step.

Although Eck and Marvel[1] insist on the use of dry reagents and take precautionary measures to prevent access of moisture to the bromination mixture, we have found that in the presence of a small amount of water the reaction proceeds smoothly with yields consistently above 95%. This innovation leads to the preparation of a compound of sufficiently high purity that it may be used in the succeeding step of the lysine synthesis without the additional recrystallization used by Eck and Marvel. It is our hope that this information may be of value to others who wish to brominate similar compounds.

(1) Eck and Marvel, "Org. Syn." Coll. Vol. II (1943), pp. 74, 76, 374.

(2) Galat, THIS JOURNAL, 69, 86 (1947).

Experimental

An intimate mixture of 37.5 g. (0.16 mole) of ϵ-benzoylaminocaproic acid and 5.45 g. (0.176 mole) of red phosphorus was placed in a 250-cc. 3-necked flask fitted with a dropping funnel, a mechanical stirrer and a reflux condenser. In addition, a thermometer was suspended in the flask through the condenser. To the contents of the flask were added 100 cc. of carbon tetrachloride and 1.16 cc. of distilled water. The mixture was agitated for a short time after which 70.4 g. (0.44 mole) of bromine was slowly added (seventy-five minutes) while the temperature was maintained below 50° by means of an ice-bath. The resultant dark red solution was stirred vigorously for one hour after which the solvent was removed by attaching a down condenser and heating the mixture under reduced pressure.

To the red, viscous mass 25.6 g. (0.16 mole) of bromine was added in thirty minutes with agitation. Again the temperature was kept below 50° during this addition but immediately afterward it was gradually raised to and maintained at 100° for one hour. After the reaction mixture had cooled to 70°, an additional 4.8 g. (0.03 mole) of bromine was added followed by a thirty-minute heating period at 100°.

The contents of the flask were cooled to 50°, whereupon with vigorous agitation and with cooling to maintain the temperature below 50°, 100 cc. of water was added to the acyl halide in the course of one and one-half hours. This reaction is extremely exothermic, consequently it must be carried out with great caution. The mixture was cooled to 0° and transferred to a mortar where the crystalline product was pulverized and stirred with small amounts of sodium bisulfite to remove unreacted bromine. The acid was removed by filtration and was treated in 50 cc. of water with bisulfite until it assumed a yellowish-white color. It was then collected on a funnel, washed three times with ice water, and dried at 50–60°. The yield was 47.4 g. (95%) of α-bromo-ϵ-benzoylaminocaproic acid melting at 153–161°.

By the procedure of Eck and Marvel[1] 42.3 g. of the acid obtained as described above was aminated to yield 25.6 g. (76%) of benzoyllysine which melted as did that prepared by the earlier workers at 265–270°.

Acknowledgment.—The authors are indebted to Dr. Max Tishler for helpful advice throughout the course of this investigation.

RESEARCH LABORATORIES
MERCK & CO., INC.
RAHWAY, NEW JERSEY RECEIVED MARCH 9, 1949

2-Nitro-4-furaldehyde Semicarbazone, an Isomer of Furacin[1]

BY KENYON HAYES

The general *in vitro* antibacterial activity of α-nitrofuran derivatives has been reported previously from these Laboratories.[2,3] For *in vivo* activity it has been found that a negatively substituted hydrazone of an α′ formyl or acyl group must also be present on the α-nitrofuran.[4,5] The compound of this class most thoroughly studied is 5-nitro-2-furaldehyde semicarbazone, Furacin (I). This compound is active against many gram-positive and gram-negative organisms

(1) Furacin is the Eaton Laboratories brand of nitrofurazone N. N. R.

(2) Dodd and Stillman, *J. Pharmacol. Exptl. Therap.*, **82**, 11 (1944).

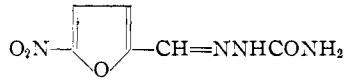
(3) Stillman, Scott and Clampit, U. S. Patent 2,319,481 (1943).

(4) Stillman and Scott, U. S. Patents 2,416,233 through 2,416,239 (1947).

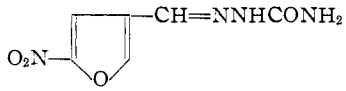
(5) Dodd, Cramer and Ward, to be published.

and has shown marked chemotherapeutic activity in experimental animal infections.[6]

In a study of the effect of structure on antibacterial activity in the nitrofuran series, the isomer of I, 2-nitro-4-furaldehyde semicarbazone (II), was of interest. In II the conjugated system present in I is interrupted and II might be expected to behave differently in the bacterial metabolic processes.



I



II

II was readily prepared from 2-nitro-4-furaldehyde diacetate, derived from 3-furoic acid by the method of Gilman and Burtner,[7] by heating in aqueous acid in the presence of semicarbazide hydrochloride. The solubility of II in water at room temperature is only 90 mg. per liter compared to a solubility of 212 mg. per liter for I.

The *in vitro* antibacterial activity of II was determined by serial dilutions and compared with the activity of I. The maximum concentration tested was 1:14000 due to the low solubility of II. At this level II showed no antibacterial action in Difco brain-heart infusion broth using small inocula of six hour cultures of *S. aureus*, *Strep. hemolyticus*, *E. coli*, *E. typhosa* or *Ps. aeruginosa*. As was shown by Dodd and Stillman[2] most nitrofurans are more active when tested in a synthetic medium. II was tested against *E. coli* in synthetic medium and it was observed that a concentration of 1:200,000 inhibited growth to 50% of controls for twenty-four hours and 1:100,000 prevented all growth for four days. Thus II has a low order of activity, particularly in broth, being less effective than the parent member of the series, 2-nitrofuran,[2] and very much less active than the isomer I. Because of the low antibacterial activity of II, when considered in the nitrofuran series, it was not tested chemotherapeutically in experimental animal infections.

Experimental[8]

3-Furaldehyde.—The preparation by a Rosenmund reduction of 3-furoyl chloride as briefly described by Gilman and co-workers[7,9] required modification to give a satisfactory yield. The hydrogenation of 0.050 mole of 3-furoyl chloride in 50 ml. of sodium-dried xylene with 3.75 g. of Schmidt[10] 5% palladium on barium sulfate, heated at 125°, required six to eight hours for the evolution of hydrogen chloride to be complete and little or no 3-furaldehyde could be isolated. Titration of the hydrogen chloride evolved with standard alkali, at intervals, showed that 80% of the reaction was complete in eighty minutes and that the reduction became very slow beyond this point. Working up the reaction at 80% of completion gave a yield of 50–52%. The yield in this Rosenmund reduction was improved to give 60–62% of the desired aldehyde by the use of finely powdered thiourea (5 mg. per gram of 5% palladium on barium sulfate) as a catalyst poison. Weygand, *et al.*,[11] reported thiourea to be an effective catalyst modifier when employing Adams platinum oxide in the Rosenmund reduction. The time required for 73–76% hydrogen chloride elimination was increased to two hours and the reaction was worked up at this point.

The 3-furaldehyde was isolated by extraction from the xylene with 30% aqueous sodium bisulfite, rather than by distillation because of the proximity of the boiling points. The aqueous solution of the sodium bisulfite addition product was washed with ether, the aldehyde regenerated with alkali and extracted repeatedly with ether. The ether solution was dried, the ether distilled off and the residual oil vacuum distilled. The observed boiling points were 66–68° (39 mm.) and 71–73° (53 mm.).

The 3-furaldehyde gave a semicarbazone from aqueous ethanol, in the form of white needles, of m. p. 210–211° uncor., which was unchanged by recrystallization from 20% aqueous ethanol.

3-Furaldehyde Diacetate.—This was prepared in the same manner and in the same yield as reported by Gilman and Burtner.[7] The observed boiling point was 118–119° (15 mm.); m. p. 46–47°. *Anal.* Calcd. for $C_9H_{10}O_5$: C, 54.26; H, 5.02. Found: C, 54.64; H, 5.10.

2-Nitro-4-furaldehyde Diacetate.—The nitration of 3-furaldehyde diacetate was accomplished by the usual procedure employing fuming nitric acid in acetic anhydride at −5 to −10°.[7] The mixture was poured over ice and after hydrolysis of the acetic anhydride was complete the nitration intermediate was extracted with ether. The ether extract was washed free of acid with 5% sodium bicarbonate and water. Partial evaporation of the ether produced a small amount of crystalline, white nitration intermediate. This was filtered and after recrystallization from ether had a melting point of 133–134°. This crystalline nitration intermediate had the expected composition, representing 2-nitro-4-furaldehyde diacetate plus the elements of acetic acid. *Anal.* Calcd. for $C_{11}H_{13}O_9N$: C, 43.55; H, 4.32. Found: C, 43.70; H, 4.45.

Complete removal of the ether from the solution of nitration intermediate on the steam-bath left the major portion of this material in the form of an oil. This oily nitration intermediate was converted to 2-nitro-4-furaldehyde diacetate by heating with excess pyridine at 60° for forty minutes. The pyridine mixture was dissolved in ether, after cooling, and the pyridine salts and base were removed by washing with dilute sulfuric acid and water. The red ether solution was treated with Darco and dried over Drierite. Removal of the ether on the steam-bath gave crude 2-nitro-4-furaldehyde diacetate as a light yellow oil. This was used in the next reaction without further purification.

2-Nitro-4-furaldehyde Semicarbazone (II).—The 2-nitro-4-furaldehyde diacetate was refluxed with excess semicarbazide hydrochloride in 10% sulfuric acid containing 20% ethanol. Within five minutes a yellow precipitate of 2-nitro-4-furaldehyde semicarbazone formed. The suspension was cooled after thirty minutes and the fine yellow needles filtered, washed well with water and alcohol, and dried *in vacuo*. From 7.70 g. of 3-furaldehyde diacetate there was obtained 1.05 g. of crystalline nitration intermediate (8.9%), together with 3.25 g. of II (42.2%). No satisfactory solvent was found for recrystallization of II; m. p. 215°, dec. uncor. *Anal.* Calcd. for $C_6H_6O_4N_4$: C, 36.35; H, 3.06; N, 28.28. Found: C, 36.56; H, 3.15; N, 27.90. The ultraviolet absorption spectrum in 20% ethanol showed two peaks,

(6) Dodd, *J. Pharmacol. Exptl. Therap.*, **86**, 311 (1946).
(7) Gilman and Burtner, THIS JOURNAL, **55**, 2903 (1933).
(8) All melting points are corrected, unless otherwise indicated.
(9) Gilman, Burtner and Smith, THIS JOURNAL, **55**, 403 (1933).
(10) Schmidt, *Ber.*, **52**, 409 (1919).
(11) Weygand and Meusel, *Ber.*, **76**, 503 (1943).

$\lambda_{max.}$ 250.0 mμ, log E_M 4.146 and $\lambda_{max.}$ 347.5 mμ, log E_M 4.014.

Acknowledgment.—I am indebted to Mr. G. Gever, of these Laboratories, for the supply of 3-furoic acid used in this synthesis, and to Mr. C. Piepoli for permission to use the data on the antibacterial activity, determined in the Bacteriology Division of Eaton Laboratories.

A CONTRIBUTION FROM
EATON LABORATORIES, INC.
NORWICH, NEW YORK RECEIVED FEBRUARY 14, 1949

Sodium Borohydride–Disodium Diborane

BY JOHN S. KASPER, LEWIS V. MCCARTY AND ARTHUR E. NEWKIRK

We have repeated the preparation of disodium diborane as described by Stock and Laudenklos,[1] and find that the resulting product yields an X-ray powder diffraction pattern identical to that given by them, and also identical with that for sodium borohydride as described by Soldate.[2] The other data reported for these two compounds are similar, and it seems probable that the compounds are the same and of the composition $NaBH_4$.

The disodium diborane was prepared by shaking a sodium amalgam in the presence of diborane gas and the course of the reaction was followed by observing the pressure decrease on a manometer attached to the system. As reported by Stock and Laudenklos, the reaction required several days to go to completion, and more diborane was absorbed than that required by the assumption of the simple reaction to form disodium diborane. At the end of ninety-six hours, however, the amalgam was still absorbing diborane. On plotting the logarithm of the pressure against the time a straight line was obtained for the first twenty-four hours. Mercury was distilled from the product of the reaction under vacuum, and the contents transferred in a dry box filled with nitrogen to a sublimer in which the remainder of the mercury was removed. The resulting residue was loaded into fine capillaries for the X-ray diffraction examination.

Using CuK_α radiation, the samples gave excellent patterns which checked completely the data for $NaBH_4$ reported by Soldate. It was evident that the same pattern (sodium chloride-type structure) was present in the photographs of Stock and Laudenklos for "$Na_2B_2H_6$", but, since no data were given by them for the X-ray work, it was necessary for us to measure these photographs. For "$Na_2B_2H_6$" the measured $\sin\theta$ values for all of 16 lines were in agreement, within experimental error, with our values obtained with CuK_α.

Assuming that all photographs given by Stock and Laudenklos are for CuK_α, the following tentative conclusions can be drawn:

(1) The corresponding potassium salts are isomorphous with the sodium compounds. For example, the compound reported as "$K_2(B_2H_6)$" appears then to be KBH_4, with an a_0 about 10% larger than that for $NaBH_4$.

(2) In addition to the BH_4^- salts, there appears to be another substance present among all the various products. The pattern for this material appears especially prominent in the diffraction patterns of "$K_2(B_4H_8)$" and "$K_2(B_5H_8)$."

(3) The sublimates of the various borane salts reported by Stock consist principally of $NaBH_4$ or KBH_4 with some of the unidentified substance as a separate phase.

In view of these findings, it seems to us that a reinvestigation of the reactions of alkali metals with boron hydrides and of the resulting products is called for.

RESEARCH LABORATORY
GENERAL ELECTRIC COMPANY
SCHENECTADY, N. Y. RECEIVED JANUARY 12, 1949

Preparation of Ethyl β-(Bromomethyl)-cinnamate[1a]

BY ALLEN C. MOORE[1b]

The Wohl–Ziegler bromination,[2] which has been applied successfully to several β-alkyl substituted crotonic esters,[2,3,4] appeared to afford a method for the synthesis of β-(bromomethyl)-cinnamic esters. Since the methyl group in β-methylcinnamic ester is attached to a C–C double bond conjugated on either side with an unsaturated group, its bromination by N-bromosuccinimide would not be predicted[3] to occur with ease. Such was shown to be the case. Under the usual reaction conditions,[3] ethyl β-methylcinnamate did not react. Extension of the reaction period to forty-eight hours gave a 39% yield of crude brominated ester. However, addition of catalytic amounts of benzoyl peroxide[5] caused the reaction to occur smoothly, giving a 50% yield of ethyl β-(bromomethyl)-cinnamate in less than eight hours.

Preliminary experiments have indicated that the brominated ester does not react to any significant extent in Reformatsky-type condensations.[6]

Experimental

Ethyl β-methylcinnamate was prepared according to the method of Lindenbaum.[7]

(1) A. Stock and H. Laudenklos, *Z. anorg. allgem. Chem.*, **228**, 178 (1936).

(2) A. M. Soldate, THIS JOURNAL, **69**, 987 (1947).

(1a) This investigation was carried out under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the Government Synthetic Rubber Program.

(1b) Present address: Research Department, Parke, Davis and Co., Detroit 32, Mich.

(2) Djerassi, *Chem. Rev.*, **43**, 271 (1948).

(3) Ziegler, Späth, Schaaf, Schumann and Winkelmann, *Ann.*, **551**, 80 (1942).

(4) Campbell and Hunt, *J. Chem. Soc.*, 1176 (1947).

(5) Schmid and Karrer, *Helv. Chim. Acta*, **29**, 573 (1946).

(6) Ziegler, Schumann and Winkelmann, *Ann.*, **551**, 120 (1942).

(7) Lindenbaum, *Ber.*, **50**, 1270 (1917).