dinitrophenylhydrazine yields a dinitrophenylhydrazone, m.p. 207–208°, found C, 51.69; H, 4.45; $[\alpha]^{27}D$ −1307° (*c* 1.63, chf.), $\lambda_{max}^{chf.}$ 379 mμ, log ε 4.49, which also results from β-thebainone *or from thebainone* by the action of dinitrophenylhydrazine in acetic acid followed by bromination. That this remarkable reaction[4] has produced epimerization at C_{14} (*trans* → *cis* ring fusion of rings II and III) is clearly shown by cleavage of the dinitrophenylhydrazone with acetone and acid to produce 1-bromothebainone, m.p. 198.5–199.5°, found, C, 57.45; H, 5.31; $[\alpha]^{32}D$ −74° (*c* 0.89, chf.) identical in m.p., mixed m.p. and infrared spectrum with the monobromination product of thebainone. This substance is converted by catalytic hydrogenation over palladium on barium carbonate to dihydrothebainone hydrate,[5] m.p. 123–152°, purified through its hydriodide,[5] m.p. 277–278.5° and characterized through its oxime,[5] m.p. 252–253.5° and oxime hydrochloride,[5] m.p. >300°. The hydriodide and oxime showed no m.p. depressions with authentic samples, and the infrared spectrum of the base was indistinguishable from that of an authentic sample, m.p. 124–152°.

Bromination of dihydrothebainone in acetic acid with three moles of bromine followed by treatment with 2,4-dinitrophenylhydrazine produces 1-bromocodeinone dinitrophenylhydrazone in low yield, m.p. 224–225°, found C, 52.07; H, 4.23; $[\alpha]^{27}D$ −1940° (*c* 1.81, chf.), $\lambda_{max}^{chf.}$ 377 mμ, log ε 4.51, identical in m.p., mixed m.p. and infrared spectrum with the dinitrophenylhydrazone prepared directly from *l*-bromocodeinone. It can be cleaved, although with difficulty and in poor yield, to 1-bromocodeinone, m.p. 202.5–203.5°, mixed m.p. and infrared spectrum identical with those of 1-bromocodeinone, found C, 57.55; H, 5.22; $\lambda_{max.}^{alc.}$ 288 mμ, log ε 3.33; $[\alpha]^{32}D$ −164° (*c* 1.23, chf.) prepared by Oppenauer oxidation[6] of 1-bromocodeine.[7]

1-Bromocodeinone is converted by lithium aluminum hydride in refluxing tetrahydrofuran directly into codeine, m.p. 156.5–158°, undepressed by admixture with an authentic sample. The infrared spectra of the two were indistinguishable. A strong depression in m.p. occurred on admixture of 1-bromocodeine, m.p. 161–163°.

The cleavage of codeine to morphine has recently been described by Rapoport and his coworkers,[8] and we have confirmed their report. With this, the first synthesis of morphine is complete.

We wish to acknowledge the generous financial help of Merck and Co., Inc., and the Research Corporation, as well as gifts of material through the courtesy of Drs. Karl Pfister and Max Tishler of Merck and Co., Inc., Dr. V. H. Wallingford of the Mallinckrodt Chemical Works, and Dr. Lyndon F. Small, The National Institutes of Health.

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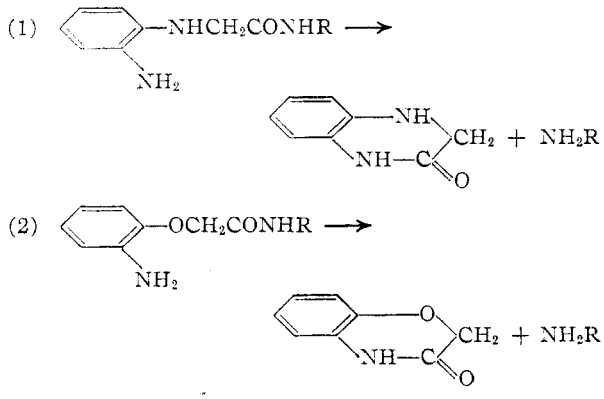
LACTAM FORMATION FROM AMINO ACID AMIDES: APPLICATIONS IN PEPTIDE CHEMISTRY

Sir:

Though most γ- and δ-amino acids must be subjected to dehydration conditions to obtain the lactams, a few, for example *o*-aminophenylglycine[1] and *o*-aminophenoxyacetic acid,[2] lactamize so readily that the free amino acids have never been obtained. We have found that lactam formation also takes place readily in the case of the amino acid amides [3] (equations (1) and (2)). Since other amide linkages are not affected, this reaction has applications in peptide chemistry.



Using the type of reaction shown in equation (1), a stepwise degradation of peptides has been developed according to the following equations. The final reaction, lactam formation from the amino acid amide, is complete in 5 hours at 25° or in 15 minutes at 70° in aqueous solution. Glycylglycylglycine, glycyl-L-alanyl-L-leucine, and L-phenylalanyl-L-leucine have been degraded. The accumulation of salts and by-products was prevented by isolation of the 4-carbomethoxy 2-nitrophenylpeptides (I). The lactams (II) crystallized, leaving the peptide or amino acid (III) in solution. The average yield per amino acid residue was 84%. The lactams, II (7-carbomethoxy-3,4-dihydro-2-(1*H*)-quinoxalones), were identical with samples prepared from the amino acids: from glycine, R = H, m.p. 292–294°.[4] (*Anal.* Calcd. for $C_{10}H_{10}N_2$-

(4) The 2,4-dinitrophenylhydrazone of β-thebainone, m.p. 224–225° dec., found C, 60.08; H, 5.14; $[\alpha]^{27}D$ +13.5° (*c* 1.85, chf.) is so easily epimerized at C_{14} that it can be obtained only under special conditions which minimize contact with acids. The abnormally high rotation of 1-bromothebainone dinitrophenylhydrazone appears to be a property of Δ^7-6-ketone dinitrophenylhydrazones of the *cis* series (thebainone dinitrophenylhydrazone −1370°, codeinone dinitrophenylhydrazone −1910°, 1-bromocodeinone dinitrophenylhydrazone −1940°) but not of the *trans* series (1-bromo-β-thebainone dinitrophenylhydrazone −76.4°).

(5) (a) M. Freund, E. Speyer and E. Guttmann, *Ber.*, **53**, 2250 (1920); (b) A. Skita, F. F. Nord, J. Reichert and P. Stukart, *ibid.*, **64**, 1560 (1921); (c) C. Schöpf and L. Winterhalder, *Ann.*, **452**, 232 (1927).

(6) We are indebted to Drs. A. H. Homeyer and George DeLaMater of the Mallinckrodt Chemical Works for details of this oxidation as applied to codeine and for a generous sample of methoxycyclohexanone.

(7) E. Speyer and H. Rosenfeld, *Ber.*, **58**, 1110 (1925).

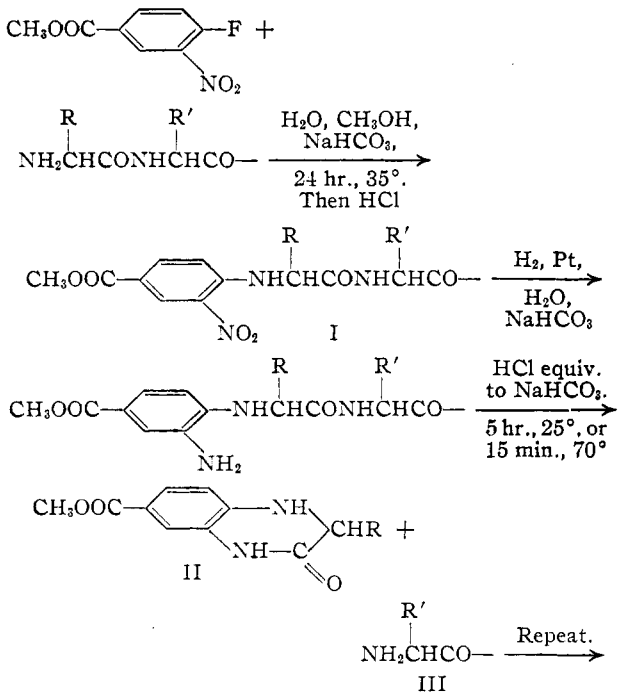
(8) H. Rapoport, Calvin H. Lovell and Bert M. Tolbert, THIS JOURNAL, **73**, 5900 (1951).

(1) J. Plöchl, *Ber.*, **19**, 6 (1886).

(2) A. Thate, *J. prakt. Chem.*, [2] **29**, 178 (1884).

(3) W. A. Jacobs and M. Heidelberger, THIS JOURNAL, **39**, 2418 (1917), obtained the lactam of *o*-aminophenoxyacetic acid from an attempted preparation of *o*-aminophenoxyacetamide.

(4) All melting points were determined on a microscope hot stage and are corrected.



O_3: C, 58.24; H, 4.89; N, 13.59. Found: C, 58.44; H, 4.73; N, 13.31.) From L-alanine, R = CH_3, m.p. 216.5–218°, $[\alpha]^{24}D$ +17° (*c*, 1.1; methanol). (*Anal.* Calcd. for $C_{11}H_{12}N_2O_3$: N, 12.7. Found: N, 13.1). From L-leucine, R = $(CH_3)_2CHCH_2$, m.p. 212–215°, $[\alpha]^{26}D$ +20° (*c*, 1.1; methanol). (*Anal.* Calcd. for $C_{14}H_{18}N_2O_3$: N, 10.7. Found: N, 10.5.) From L-phenylalanine, R = $C_6H_5CH_2$, m.p. 197–201° (transition 190–192°), $[\alpha]^{22}D$ −99° (*c*, 0.5; methanol). (*Anal.* Calcd. for $C_{17}H_{16}N_2O_3$: N, 9.46. Found: N, 9.79). The extension of this degradation to more complex peptides, such as those containing cystine and lysine, may require modification of the present procedure. This is now under investigation.

Using the reaction shown in equation (2), the *o*-nitrophenoxyacetyl group can be removed from N-*o*-nitrophenoxyacetylpeptides by catalytic reduction of the nitro group followed by lactam formation, which is complete in 30 to 120 minutes at 100° in aqueous solution. Similarly, the chloroacetyl group can be removed from N-chloroacetylpeptides by reaction with *o*-phenylenediamine in aqueous solution for 30 to 120 minutes at 100°, the reaction presumably proceeding by way of equation (1). The yields of once-recrystallized peptides prepared from their *o*-nitrophenoxyacetyl and chloroacetyl derivatives, respectively, and identical with authentic samples, were: glycylglycine 73%, 76%; glycylglycylglycine 76%, 68%; glycyl-L-alanyl-L-leucine 65%, 59%; and L-phenylalanyl-L-leucine 70%, 31%. These reactions suggest the use of the *o*-nitrophenoxyacetyl and chloroacetyl groups as protecting groups during peptide synthesis. In preliminary experiments, using the *o*-nitrophenoxyacetyl group and the Curtius azide procedure,[5] L-phenylalanyl-L-leucine ($[\alpha]^{22}D$ −21° (*c*, 1; 1% sodium bicarbonate solution)), identical with material prepared by the carbobenzoxy method, was synthesized in 31% yield[6] (from L-phenylalanine ethyl ester hydrochloride). With the chloroacetyl as the protecting group, glycylglycylglycine was synthesized from glycylglycine in 18% yield using the method of Boissonnas.[7]

(5) T. Curtius, *Ber.*, **35**, 3226 (1902).

(6) C. S. Smith and A. E. Brown, THIS JOURNAL, **63**, 2605 (1941), synthesized D-phenylalanyl-D-leucine from D-phenylalanine in 12% yield by the carbobenzoxy method. B. F. Erlanger and E. Brand, THIS JOURNAL, **73**, 3508 (1951), report yields of 30 to 35% for six dipeptides, which is more representative of the method.

(7) R. A. Boissonnas, *Helv. Chim. Acta*, **34**, 874 (1951).

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RECEIVED DECEMBER 19, 1951

ON A PHOSPHO-TRI-ANHYDRIDE FORMULA FOR THE NUCLEIC ACIDS

Sir:

In a recent issue of this Journal[1] a hypothetical structure for desoxyribonucleic acid is proposed, having as its core a polymer chain of phosphorus atoms held together by oxygen atoms. In formulating a hypothetical structure for a substance one must take care that the structural elements of which use is made are reasonable ones, for which some precedent exists, or one must show that there is an overwhelming necessity for a radical proposal. In the proposed structure for the nucleic acids each phosphorus atom has five oxygen atoms attached to it, three of which bind it to adjacent phosphorus atoms, and two of which are in a hydroxyl group and a sugar ester group, respectively. There is, however, no precedent for a structure in which phosphorus is bonded to five oxygen atoms. Of the scores of phosphorus compounds that have been subjected to complete structural investigation, the phosphorus atom is surrounded by four oxygen atoms in every compound in which it has oxidation number +5.

The proposer of this extraordinary formula for the nucleic acids has not quoted any significant evidence in support of it. The ligation of five oxygen atoms about each phosphorus atom is such an unlikely structural feature that the proposed phospho-tri-anhydride formula for the nucleic acids deserves no serious consideration.

(1) E. Ronwin, THIS JOURNAL, **73**, 5141 (1951).

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RECEIVED JANUARY 24, 1952

THE MOLECULAR WEIGHT OF AMYLOPECTIN[1]

Sir:

Potter and Hassid[2] have reported measurements of the molecular weights of acetylated starch fractions by osmotic methods. We here report the results of light-scattering measurements of one of their acetylated amylopectins, Easter Lily sample L-3-B, in nitromethane solution at 25°. The apparatus and procedures used have previously been

(1) This work was supported by the Office of Naval Research.

(2) A. L. Potter and W. Z. Hassid, THIS JOURNAL, **70**, 3774 (1948).