DECARBOXYLATION AND RECONSTITUTION OF LINOLEIC ACID[1]

Sir:

In search of an approach to the preparation of isotope-labelled linoleic acid more promising than those suggested by recently reported total syntheses of this physiologically and commercially important unsaturated fatty acid,[2,3,4] we have succeeded in showing that the carboxyl group of linoleic acid isolated from natural sources can be removed and replaced, the sensitive and synthetically-imposing unsaturated hydrocarbon moiety being protected during this process by bromination. Starting with the readily purified 115°-9,10,12,13-tetrabromostearic acid (I) (in which form linoleic acid is most commonly isolated from certain saponified seed oils), the process involves the following steps

$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7COOH$ I

↓

$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7COOAg$ II

↓

$C_5H_{11}(CHBr)_2CH_2(CHBr)_2(CH_2)_7Br$ III

↓

$C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_7Br$ IV

↓

$C_5H_{11}CH{=}CHCH_2CH{=}CH(CH_2)_7MgBr$

↓

linoleic acid

Treatment of an absolute methanol solution of the ammonium salt of I with another of silver nitrate in the same solvent gives the corresponding silver salt (II). Addition of dry II to a solution of bromine in carbon tetrachloride results in the loss of carbon dioxide and the formation of the 1,8,9,11,12-pentabromoheptadecane III, m.p. 62–64° (*Anal.* Calcd. for $C_{17}H_{31}Br_5$: C, 32.15; H, 4.92; Br, 62.93. Found: C, 32.22; H, 4.89; Br, 62.90). The action of zinc on III results in the regeneration of the *cis,cis*-1,4-diene grouping originally present in the linoleic acid, while the isolated terminal bromine atom is unaffected; the product, 8,11-heptadecadienyl bromide (IV), is a colorless oil, b.p. 131° at 0.15 mm., $n^{25}D$ 1.4810, d^{26} 1.02145, M_D 87.86 (theory 87.56) (*Anal.* Calcd. for $C_{17}H_{31}Br$: C, 64.75; H, 9.91; Br, 25.34. Found: C, 64.87; H, 9.91; Br, 25.17). The Grignard reagent prepared from IV, on treatment with carbon dioxide, regenerates linoleic acid, identified by virtue of the fact that its infrared absorption spectrum was essentially identical with that of an authentic sample and by the melting point and mixed melting point of the tetrabromostearic acid (I) prepared from it.

Since linoleic acid is reconstituted (by replacement of the carboxyl group as carbon dioxide) in the high-yield last step of the series, this procedure seems ideally suited to the preparation of the carboxyl-labelled substance. Moreover, there seems to be no reason why the method should not be applicable with equal success to other unsaturated fatty acids whose carboxyl labelling would be desirable.

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(1) This paper is based on work performed under Contract AT-04-1-GEN-12 between the Atomic Energy Commission and the University of California at Los Angeles.

(2) R. A. Raphael and F. Sondheimer, *J. Chem. Soc.*, 2100 (1950).

(3) H. M. Walborsky, R. H. Davis and D. R. Howton, THIS JOURNAL, **73**, 2590 (1951).

(4) W. J. Gensler and G. R. Thomas, *ibid.*, **73**, 4601 (1951).

THE SYNTHESIS OF MORPHINE

Sir:

Racemic β-Δ⁶-dihydrodesoxycodeine methyl ether[1] yields with L(+)-dibenzoyltartaric acid only the salt of the *d* base (monohydrate), m.p. 162.5–163°, found C, 65.60; H, 6.07; $[\alpha]^{27}D$ +44.5° (*c* 1.53, chf.) whose mixed m.p. with natural *d*-β-Δ⁶-dihydrodesoxycodeine methyl ether L(+)-dibenzoyltartrate monohydrate of m.p. 163–163.5°, $[\alpha]^{27}D$ +48° (*c* 1.80 chf.) was not depressed. The infrared spectra of these salts are indistinguishable. Similarly with D(−)-dibenzoyltartaric acid, only the salt of the *l* base, m.p. 161.5–162°, found C, 66.09; H, 6.45, $[\alpha]^{27}D$ −44° (*c* 1.94 chf.), is obtained. Equal amounts of synthetic *l* salt and natural *d* salt yield inactive β-Δ⁶-dihydrodesoxycodeine methyl ether dibenzoylracemate (anhydrous), m.p. 182°, found C, 67.37; H, 6.05, identical in m.p. and mixed m.p. with the product of the synthetic racemic base and dibenzoylracemic acid.

The *d* salt with ammonia yields the *d* base, found C, 76.40; H, 8.51; $[\alpha]^{27}D$ +80° (*c* 1.24, alc.) m.ps. 43.5–44° and 57.5–58°, dimorphous, whose mixed m.ps. with natural β-Δ⁶-dihydrodesoxycodeine methyl ether, found C, 76.49; H, 8.61; $[\alpha]^{27}D$ +80 (*c* 1.55, alc.) which also exhibits these m.ps., were undepressed. The infrared spectra of these bases are indistinguishable. Confirmation of this identity was obtained through the methiodide, synthetic *d*, m.p. 186.5–188°, natural, 188–189°, mixture undepressed, found C, 54.33; H, 6.51; and the picrate, m.p. synthetic *d*, 227.5–228.5°, natural 230–231°, mixture undepressed, found C, 56.88; H, 5.67.

d-β-Δ⁶-Dihydrodesoxycodeine methyl ether on hydration with dilute sulfuric acid yields β-dihydrothebainol methyl ether, m.p. 152–153°, methiodide, m.p. 243–244°, mixed m.ps. with authentic samples[1] not depressed. The infrared spectrum of the base is indistinguishable from that of an authentic sample. On vigorous treatment of this substance with potassium hydroxide in diethylene glycol, demethylation takes place, and from the resulting mixture β-dihydrothebainol, m.p. 165.5–166.5°, methiodide m.p. 266–268°, mixed m.p.s with authentic samples[1] undepressed, can be isolated. Oxidation of this substance by the potassium *t*-butoxide–benzophenone system[2] gives β-dihydrothebainone,[3] perchlorate, m.p. 265–268°, oxime, m.p. 223–226°, mixed m.ps. undepressed.

β-Dihydrothebainone on bromination with two moles of bromine followed by treatment with 2,4-

(1) M. Gates and G. Tschudi, THIS JOURNAL, **72**, 4839 (1950).

(2) R. B. Woodward, N. L. Wendler and F. V. Brutschy, *ibid.*, **67**, 1425 (1945); H. Rapoport, *et al.*, *J. Org. Chem.*, **15**, 1103 (1950).

(3) L. F. Small and G. L. Browning, *J. Org. Chem.*, **3**, 618 (1939).

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.

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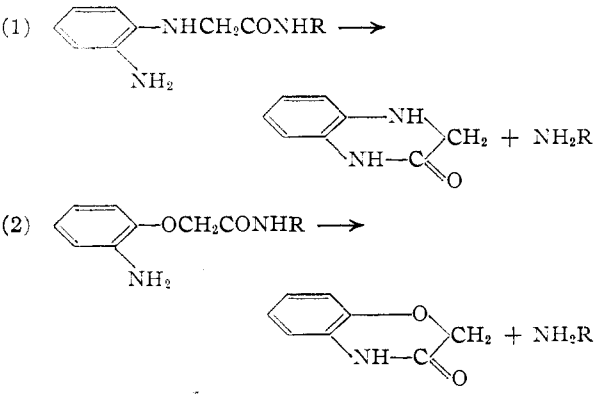
LACTAM FORMATION FROM AMINO ACID AMIDES: APPLICATIONS IN PEPTIDE CHEMISTRY

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.*, **54**, 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.