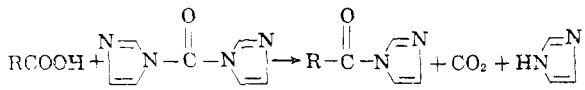
COMMUNICATIONS TO THE EDITOR

N,N'-CARBONYLDIIMIDAZOLE, A NEW REAGENT FOR PEPTIDE SYNTHESIS

Sir:

Wieland and Schneider[1] showed in 1953 that peptide derivatives could be synthesized via acylation of the imidazole ring of methyl N-benzoyl-L-histidinate, but their procedure was not suitable for general use. In seeking a simple method for making N-acylimidazoles, it occurred to us that N,N'-carbonyldiimidazole should be ideal, since elimination of carbon dioxide would be a driving force



Staab[2] has shown recently that N,N'-carbonyldiimidazole is highly reactive to amines and alcohols. We now have found that this compound reacts readily with carboxylic acids to form acyl imidazoles, and subsequent reaction with amines to form amides goes smoothly. Application to peptide synthesis has been highly successful. We encountered difficulties in following Staab's procedure for the preparation of the reagent. These were overcome by preparing the reagent from phosgene and imidazole in rigorously dried benzene. The crude reagent was assayed for carbon dioxide on hydrolysis; the purity was usually 98–100% and the m.p. 113–115°. Adjusting the quantity to give 0.10 mole, the reagent was added to 0.10 mole of an acylamino acid in dry tetrahydrofuran (THF) at room temperature. When the effervescence stopped, the desired amino acid or peptide ester in 0.010 mole quantity then was added, and the reaction was allowed to proceed for 15 minutes or more at room temperature. The product was isolated by removal of the solvent under vacuum followed by washing with *N* acid, saturated bicarbonate and water. Ester hydrochlorides may be used in this reaction as may aqueous solutions of amino acid salts. In the latter case the yields are lower. Examples are ethyl carbobenzoxyglycyl-L-tyrosinate,[3,4] obtained in 83% yield (recrystallized) m.p. 126–127°, $[\alpha]^{25}D$ +18 ±1.0° (*c* 5, EtOH); ethyl *t*-butyloxycarbonyl-L-phenylalanylglycinate[5] 78% yield, m.p. 88–89.5°, $[\alpha]^{25}D$ −4.2 ±1.2° (*c* 2, EtOH); carbobenzoxyglycyl-L-leucinate, via ethyl L-leucinate hydrochloride followed by saponification of the peptide ester (an oil), 68% over-all yield, m.p. 103–104°, $[\alpha]^{25}D$ −18.2 ±0.5° (*c* 5, *N* NaOH); carbobenzoxyglycyl-L-phenylalanine via the sodium salt of phenylalanine, 40% yield, m.p. 126.5–127.5°, $[\alpha]^{25}D$ +40.7 ±1.7° (*c* 3, EtOH); ethyl carbobenzoxy-L-alanylglycinate, 65% yield, m.p. 98–99°, $[\alpha]^{25}D$ −21.7 ±0.5° (*c* 5, EtOH).[6]

Possible racemization was investigated in the reaction of carbobenzoxyglycyl-L-phenylalanine with ethyl glycinate, a sensitive case.[7] The acylimidazole was formed at −10° in dimethylformamide (a better solvent than THF at low temperatures) in order to minimize racemization, and the reaction solution was allowed to warm to room temperature after the addition of ethyl glycinate. A crude yield of 96% of tripeptide, m.p. 115.5–117°, was obtained and recrystallization from a 2% solution in absolute ethanol gave 0.5% containing some DL form, m.p. 119–133.5°, and 87% of the L form, m.p. 119.8–120.3°, $[\alpha]^{25}D$ −12.2 ±1.25° (*c* 2, ethanol). Approximately 5% of DL form was obtained when both reactions were carried out at room temperature in THF.

(1) T. Wieland and G. Schneider, *Ann.*, **580**, 159 (1953).

(2) H. A. Staab, *ibid.*, **609**, 75 (1957).

(3) We thank Mr. L. Brancone and staff for analysis, and Mr. W. Fulmor and staff for optical rotations.

(4) J. R. Vaughan, Jr., and R. L. Osato, THIS JOURNAL, **74**, 676 (1952).

(5) G. W. Anderson and A. C. McGregor, *ibid.*, **79**, 6180 (1957).

(6) M. Bergmann, *et al.*, *J. Biol. Chem.*, **109**, 325 (1935).

(7) G. W. Anderson and F. M. Callahan, THIS JOURNAL, **80**, 2902 (1958).

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STEROIDS. CIII.[1] A NEW CLASS OF POTENT CORTICAL HORMONES, 6α-FLUOROCORTICOIDS

Sir:

We wish to report the synthesis of a series of 6α-fluorocortical hormones which we have found to be powerful corticoids.

Peracid oxidation of Δ^5-pregnene-3β,17α,21-triol-20-one-17,21-diacetate (I)[2] gave the 5α,6α-epoxide (II) (m.p. 198–200°, $[\alpha]D$ −54°)[3] which underwent fission with boron trifluoride[4] to the corresponding 5α-hydroxy-6β-fluoro compound (III) (m.p. 176–178°, $[\alpha]D$ −10°). Oxidation of III gave the corresponding 3-ketofluorohydrin (IV) (m.p. 227–228°, $[\alpha]D$ ±0°) whence acid catalyzed dehydration and concomitant inversion of the fluorine atom, yielded 6α-fluoro compound "S" 17,21-diacetate (V) (m.p. 241–242°, $[\alpha]D$ +53°; λ_{max} 236 mμ, log ε 4.17). Under milder conditions the principal product was 6β-fluoro "S" diacetate (VI) (m.p. 187–189°, $[\alpha]D$ −14°; λ_{max} 233 mμ, log ε 4.05). Selenium dioxide oxidation[5a,b,c,d] of V led to the Δ^1 derivative (VII) (m.p. 247–249°, $[\alpha]D$ ±0°, λ_{max}

(1) Paper CII, J. S. Mills, H. J. Ringold and C. Djerassi, THIS JOURNAL, **80**, Oct. (1958).

(2) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *ibid.*, **78**, 820 (1956).

(3) All new compounds described had correct analytical data. Unless stated otherwise rotations were measured in chloroform and ultraviolet spectra in 96% ethanol.

(4) (a) H. B. Henbest and T. I. Wrigley, *J. Chem. Soc.*, 4765 (1957). (b) A. Bowers and H. J. Ringold, *Tetrahedron*, **3**, 14 (1958).

(5) (a) H. J. Ringold, G. Rosenkranz and F. Sondheimer, *J. Org. Chem.*, **21**, 239 (1956). (b) Ch. Meystre, H. Frey, W. Voser and A. Wettstein, *Helv. Chim. Acta*, **39**, 734 (1956). (c) S. A. Szpilfogel, T. A. P. Posthumus, M. S. De Winter and D. A. Van Dorp, *Rec. Trav. Chim.*, **75**, 475 (1956). (d) K. Florey and A. R. Restivo, *J. Org. Chem.* **22**, 406 (1957).