a, $R_1 = C_2H_5$; $R_2 = H$
b, $R_1 = H$; $R_2 = C_2H_5$

nitrobenzoate mp 101–103°), which on hydrolysis (**9a**) followed by methylation gave **9b** (41% from **8b**), mp 71–72.5°. Treatment of **9b** with ethylmagnesium bromide gave **10** (68%), which underwent the Wolff–Kishner reduction giving crude **11a** (65%), bp 85–90° (5 mm). This crude material was found to be contaminated with ca. 25% of the cis isomer **7c** from glpc[10] of the corresponding olefinic nitrile **11c**. Basic treatment of a pure sample of **11c**, bp 118–121° (32 mm), obtained by preparative glpc, gave a 6:5 equilibrium mixture of **7e** and **11c**, and this fact proves the trans configuration of the latter. Reduction (LiAlH₄) of pure **11c** gave the trans amine **2b**, bp 101–104° (30 mm); picrate mp 158–159.5°. From the preparative viewpoint, the crude material of **11a** was used for transformation into crude **2b** (ca. 75% purity, 58% over-all yield), bp 95–98° (24 mm), by tosylation (**11b**) and subsequent Gabriel amination.

Compounds **2a** and **b** were oxidized with lead tetra-acetate[5] giving the bridged aziridines **3a,b** (**3a**: picrate mp 152–154°, flavianate mp 173–176°; **3b**: picrate mp 142–144°, flavianate mp 167–169°), which without purification were cleaved with β-indolylacetic anhydride to give **4a,b**. On alkaline hydrolysis, the last compounds were led to the crystalline **12a,b** (33 and 20% over-all yield from **2a,b**, respectively) (**12a**: mp 206–208°; **12b**: mp 193–196°), which on oxidation by the Oppenauer method or, better, with dimethyl sulfoxide and acetic anhydride[13] were converted into the keto lactams **13a,b**. Cyclization of **13a** and **13b** without rearrangement was effected by refluxing (5–10 min) the benzene solution in the presence of 1.3–1.5 molar equiv of p-toluenesulfonic acid to give the lactam tosylates **14a,b** (**14a**: amorphous; **14b**: mp 175–178°) which were converted[4] into the methoxy lactams **15a,b** (30 and 34% over-all yield from **12a,b**, respectively) (**15a**: mp 283–285°; **15b**: mp 275–278°) Reduction of **15a**

(13) J. D. Albright and L. Goldman, J. Am. Chem. Soc., 89, 2416 (1967).

and **15b** with LiAlH₄ gave carbinolamines which without purification were dehydrated with alumina to the enamines **16a** (40%) and **16b** (32%) (**16a**: mp 185–187°, λ_{max}^{EtOH} 235 (ε 25,200), 285 mμ (ε 14,100); **16b**: mp 178–182°, λ_{max}^{EtOH} 234.5 (ε 21,100), 244 (shoulder), 285 mμ (ε 12,500). Catalytic hydrogenation of **16a,b** gave methoxyibogamine (**17a**; 55%) and methoxyepiibogamine (**17b**; 67%) (**17a**: mp 152–154°; **17b**: mp 144–147°), which were reduced[14] smoothly to dl-ibogamine (**1a**) and dl-epiibogamine (**1b**) (**1a**: mp 127–128°; **1b**: mp 196.5–197.5°). The samples of **1a** and **1b** were proven to be identical with authentic samples of dl-ibogamine and dl-epiibogamine (mixture melting point, infrared spectra, and tlc).[15] The present synthesis is parallel to our previous skeleton synthesis,[4] confirming the correctness of the latter synthesis and of the synthesis reported by Huffman and his coworkers.[16] dl-Ibogamine (**1a**) was directly obtained together with the unstable enamine **16a** (R = H instead of OCH₃) by diisobutyl-aluminum hydride reduction of the lactam tosylate **14a**. Conversion of this enamine into **1a** is currently being studied.

(14) Cf. G. Büchi and R. E. Manning, ibid., 88, 2532 (1966).

(15) The authors wish to express their sincere thanks to Professor G. Büchi for his courtesy in providing an authentic sample of dl-ibogamine and performing the identification of dl-epiibogamine.

(16) J. W. Huffman, C. B. S. Rao, and T. Kamiya, J. Am. Chem. Soc., 87, 2288 (1965); J. Org. Chem., 32, 697 (1967).

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A New Convenient Reagent for Peptide Syntheses

Sir:

The preparation and biological activity of the pseudo-base N-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline

Table I. Peptide Syntheses with EEDQ (I)

Starting acid and amine	Peptide	Reaction solvent[a]	Reaction time, hr	Yield, %
Benzoic + aniline	Benzanilide	B	12[b]	85
L-Bz-Leu + Gly-OEt	L-Bz-Leu-Gly-OEt	THF; B or B–EtOH (4:1)	6–7	95
Bz-Gly + Gly-OEt	Bz-Gly-Gly-OEt	B–EtOH (1:1)	2	99
Bz-Gly + aniline	Bz-Gly-anilide	B	2	90
CBZ-L-Ala + L-Ala-OEt	CBZ-L-Ala-L-Ala-OEt	B–EtOH (1:1)	1	98
CBZ-D-Ala + Gly-OEt	CBZ-D-Ala-Gly-OEt	B	3	90
CBZ-L-Ala + Gly-OEt	CBZ-L-Ala-Gly-OEt	B	3	90
p-Nitrobenzoic + DL-Ser-OEt	p-Nitro-Bz-Ser-OEt	B–EtOH (4:1)	3	60[c]
Cinnamic + imidazole	Cinnamoylimidazole	B	12[b]	60[c]

[a] B = benzene; THF = tetrahydrofuran.   [b] A shorter reaction time was not tried.   [c] Optimum conditions were not determined.

(I, EEDQ) was recently disclosed.[1] An investigation of the chemical behavior of this compound showed that it can readily induce the formation of peptide linkages. The new reagent allows the coupling in high yield of acylamino acids with amino acid esters in a single operation and without racemization. The coupling reaction was carried out at 30–35° in benzene, ethanol, or tetrahydrofuran (THF). In order to detect the possible occurrence of racemization, the supersensitive Young test,[2-4] involving the synthesis of Bz-Leu-Gly-OEt, was applied.

A typical procedure was as follows. To a solution of 0.003 mole of Bz-Leu and 0.003 mole of Gly-OEt in 25 ml of THF was added 0.0032 mole of I and the mixture was stirred at room temperature for 6–7 hr. After evaporation, the residue was crystallized from ethyl acetate-petroleum ether (bp 30–60°) to give Bz-Leu-Gly-OEt (95% yield), mp 157–158°, $[\alpha]^{25}$D $-33.5 \pm 0.5°$ (c 3, EtOH); washing the crude material with warm absolute ether followed by evaporation of the ether and fractional crystallization of the residue from EtOH–H_2O gave no detectable quantity of racemic peptide.[4] Similar results were obtained using benzene or benzene–EtOH mixtures. Additional examples of peptide bond syntheses using I as the coupling agent are assembled in Table I.

Experimental evidence was obtained that the mechanism of carboxyl group activation by I involves the transient formation of a mixed carbonic anhydride intermediate. Whereas I fails to react with amines under conditions of ready peptide synthesis, its 2-ethoxy substituent is readily displaced by alcohols and thiols in the presence of an acid catalyst.[1] However, with carboxylic acids such as benzoic and cinnamic acids, the expected product of exchange II cannot be isolated (even at low temperatures) presumably because of rapid breakdown by way of a six-membered transition state (II, arrows) to quinoline and the mixed carbonic anhydride III. In fact, the mixed anhydrides of benzoic and cinnamic acids could be readily detected and characterized (ir, nmr, mass spectrometry) when the reaction was carried out in the absence of amines. The selective activation by I of carboxyl functions in the presence of other nucleophiles and the absence of racemization in the product peptide may offer special advantages over other well-known coupling reagents.[5] The use of I as a substitute in the classical mixed carbonic anhydride method[3-5] is indicated because the slow formation and rapid consumption of intermediate III precludes its accumulation and thus minimizes the possibility of side reactions (such as racemization). The reaction of I with various enzymes will be reported separately.
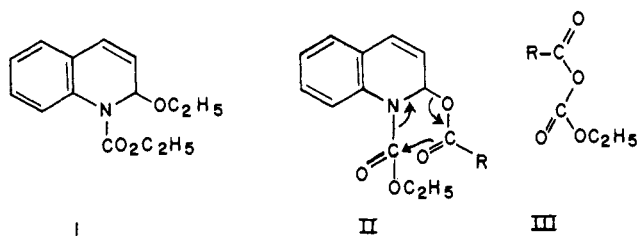
Acknowledgment. The authors are indebted to the National Research Council of Canada for the financial support of this work.

(5) M. Bodanszky and M. A. Ondetti, "Peptide Synthesis," Interscience Publishers, Inc., New York, N. Y., 1966.

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Electron Spin Resonance Study of the Electrolysis of Trifluoronitrosomethane and Trifluoronitromethane. Bis(trifluoromethyl) Semidiazoxide

Sir:

Various perfluoro nitroxides have been studied by electron spin resonance.[1] We report here the electron spin resonance of bis(trifluoromethyl) semidiazoxide[2]

$$\underset{CF_3N-NCF_3}{\overset{O\cdot \quad O^-}{| \qquad |}}$$

I   II   III

(1) B. Belleau, R. Martel, G. Lacasse, M. Ménard, N. L. Weinberg, and Y. G. Perron, *J. Am. Chem. Soc.*, **90**, 823 (1968).
(2) M. W. Williams and G. T. Young, *J. Chem. Soc.*, 881 (1963).
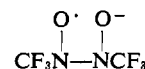(3) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *J. Am. Chem. Soc.*, **89**, 5012 (1967).
(4) G. W. Anderson, J. E. Zimmerman, and F. M. Callahan, *ibid.*, **88**, 1338 (1966).

(1) W. D. Blackley and R. R. Reinhard, *J. Am. Chem. Soc.*, **87**, 802 (1965); W. D. Blackley, *ibid.*, **88**, 480 (1966); E. T. Strom and A. L. Bluhm, *Chem. Commun.*, 115 (1966).