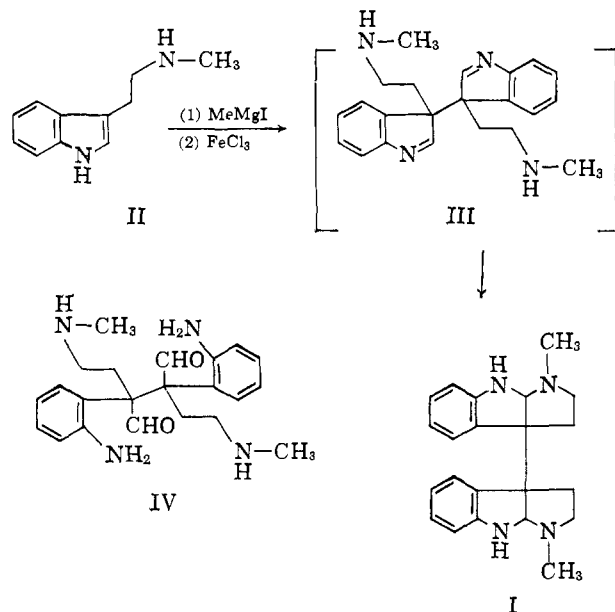to report a dramatically simple synthesis of *dl*-chimonanthine.

In view of the difference in acidity between the secondary amino and indolic hydrogens, it was assumed that addition of one equivalent of methylmagnesium iodide to the dibasic dipterin would form the ionic[4] "magnesylindole" derivative. N-methyltryptamine, prepared[5] in high yield from tryptamine,[6] was added in ether solution to an equivalent amount of methylmagnesium iodide under anhydrous conditions. Treatment of the mixture with ethereal ferric chloride, then aqueous ammonium chloride, and isolation by ether extraction gave as major product (20% yield) *dl*-chimonanthine, m.p. 183–185° from ether or benzene. Comparison of the mass spectrum,[7] showing the very characteristic symmetrical scission, with the published data,[8] gave complete correspondence of cracking pattern and abundance. The ultraviolet (λ_{max} 248, 305 mμ) and infrared (CHCl$_3$) spectra were also superimposable on those of natural *l*-chimonanthine.[9] Investigation of a crude sample[10] of the latter afforded a small amount of optically inactive material, m.p. 201–203°, which displayed small but significant differences in its n.m.r. spectrum, while retaining the other properties[11] of *l*-chimonanthine. We consider this new alkaloid to be *meso*-chimonanthine, and comparison of this with one of our synthetic fractions, m.p. 201–202°, reveals that these are identical.

A previous route[12,13] to this series of alkaloids involving coupling at the oxindole level would seem to be a less relevant biosynthetic model than the extremely direct *indole* dimerization. The present demonstration of the reaction affirms the possibility of such a mecha-

(4) M. G. Reinecke, H. W. Johnson, and J. F. Sebastian, *Tetrahedron Letters*, 1183 (1963).

(5) This preparation was devised by Dr. A. C. Day, University of Oxford, England.

(6) We are grateful to Dr. A. Brossi, of Hoffmann–LaRoche, Nutley, New Jersey, for a lavish gift of this material.

(7) Thanks are due to Dr. H. Budzikiewicz, Stanford University, for his kind determination of this spectrum.

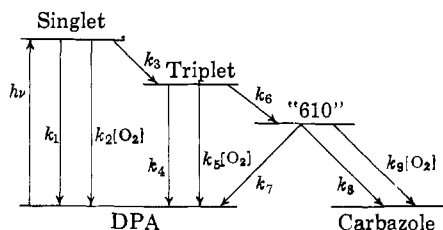(8) E. Clayton, R. I. Reed, and J. M. Wilson, *Tetrahedron*, **18**, 1495 (1962).

(9) We thank Dr. G. F. Smith, Manchester University, England, for a very generous gift of *l*-chimonanthine.

(10) Dr. G. F. Smith also has this sample under study.

(11) H. F. Hodson, B. Robinson, and G. F. Smith, *Proc. Chem. Soc.*, 465 (1961).

(12) J. B. Hendrickson, R. Rees, R. Goschke, *ibid.*, 383 (1962).

(13) J. B. Hendrickson, R. Goschke, and R. Rees, to be published. We thank Dr. Hendrickson for a copy of his manuscript before publication, and a sample of synthetic chimonanthine for comparison.

nism *in vivo* providing an exact analogy for incorporation experiments.

The resolution of our synthetic materials, and further aspects of this convenient route to the "parent" member of the series (and, by interconversion, the other structural isomers) are under investigation.

UNIVERSITY OF BRITISH COLUMBIA A. I. SCOTT
VANCOUVER 8, BRITISH COLUMBIA FRANK McCAPRA
CANADA E. S. HALL

Reaction Pathways in the Photochemical Conversion of Diphenylamines to Carbazoles

Sir:

Quantum yield and flash-photolytic studies have been made of the effects of oxygen and temperature on the photoconversion of diphenylamines to carbazoles, using diphenylamine itself (DPA) and the N-methyl and N-phenyl (TPA) derivatives. These experiments confirm our suggestion[1] that a transient species absorbing at 610 mμ (probably a closed-ring, polar structure) is an intermediate in the reaction and establish the existence of two concurrent pathways for the conversion. One pathway requires oxygen as reagent, while the other appears to involve a unimolecular step with very low or zero activation energy. This work also resolves an apparent contradiction between our aerobic oxidation studies,[1] done mainly on N-meDPA, and the recent work of Bowen and Eland[2] on DPA, in which it is stated that oxygen inhibits the reaction.

In hexane at room temperature, in the presence of oxygen, the quantum yield of carbazole production (φ), as f(O$_2$) concentration, passes through a maximum whose location depends on the particular amine. For DPA, $\varphi_{max} \approx 0.08$ at $[O_2]_{max} \approx 2 \times 10^{-5}\ M$, while for N-meDPA, $\varphi_{max} = 0.30$ at $[O_2]_{max} = 6 \times 10^{-4}\ M$. In air-saturated hexane ($[O_2] = 3 \times 10^{-3}\ M$), φ (DPA) is less than 0.02, but φ (N-meDPA) is much less oxygen-sensitive. In order to reduce φ (N-meDPA) to 0.02, oxygen pressures in excess of 3 atm. are required. The residual φ-values, in exhaustively degassed solution, are about 0.05 for DPA and less than 0.01 for N-meDPA. The maximum is thus much more pronounced for the methyl derivative, while oxygen inhibition is more apparent for DPA.[2]

Flash experiments, under favorable conditions of yield and lifetime (TPA in degassed glycerol, at −60°) show that 610 is formed from the amine triplet. Moreover, in TPA solutions containing oxygen, the disappearance of 610 and formation of carbazole take place at the same rate. The maximum in the φ *vs.* [O$_2$] curve can thus be understood as a combined effect of oxygen quenching of the triplet (yield-limiting at high [O$_2$]) and oxygen-dependent conversion of 610 to carbazole (yield-limiting at low [O$_2$]).

In degassed solution, down to −70°, 610 decays back to the parent amine by a first-order process, with $E_A = 10$ kcal. Below −70°, 610 decay becomes independent of temperature and irreversible. Steady ultraviolet irradiation of N-meDPA in degassed hexane at −76° produces N-me carbazole with $\varphi \approx 0.2$. The temperature-independent 610 decay appears to correspond to this carbazole-forming reaction.

All these observations are consistent with the reaction scheme shown at the top of the next page. Using this mechanism, with values of k_4, k_6/k_5, k_7, k_8, and k_9 measured directly in flash experiments, and taking k_2 and k_5 to be diffusion-controlled, the φ *vs.*

(1) K. H. Grellmann, G. M. Sherman, and H. Linschitz, *J. Am. Chem. Soc.*, **85**, 1881 (1963).

(2) E. J. Bowen and J. H. D. Eland, *Proc. Chem. Soc.*, 202 (1963).

Singlet

k_3 Triplet

k_6 "610"

$h\nu$ k_1 $k_2[O_2]$ k_4 $k_5[O_2]$ k_7 k_8 $k_9[O_2]$

DPA Carbazole

$[O_2]$ curve was calculated for N-meDPA. Good agreement with the experimental curve was obtained with one parameter, $k_3/(k_1 + k_3)$, adjusted for best fit (0.37).

The maximum in φ occurring in degassed solutions as the temperature is lowered (observed both in our work and by Bowen and Eland[2]) is a result of different temperature dependence of 610 yield and k_7. At room temperature, although 610 yield is high, the reversible decay (k_7) is fast, and φ is low. As the temperature is lowered, a relatively strong decrease in k_7 occurs $(E_A = 10$ kcal.). The temperature-independent process (k_8) can then predominate and φ rises. At still lower temperatures the 610 yield drops also, and causes the final decrease in φ.

The nature of the process k_8 (0.28 sec.$^{-1}$ for N-meDPA), responsible for carbazole formation in degassed solutions at low temperatures, is of the greatest interest. We suggest that k_8 corresponds to a decomposition of 610 by a "tunneling" process, of the type discussed by Robinson[3] in connection with the problem of radiationless transitions in complex molecules. In this case, the "radiationless transition" would occur along the particular vibrational coordinate leading to splitting out of hydrogen[2] from 610 and would correspond to chemical reaction instead of return to the ground state. Alternatively, k_8 may be an internal conversion process, with very low activation energy, leading to a high vibrational level of the amine ground state and *subsequent* decomposition of the resulting hot molecule.[4] In condensed phase, one would expect that vibrational deactivation would be too rapid to permit efficient thermal decomposition of such a complex molecule and the tunneling mechanism is therefore favored. One may further conjecture that the two central hydrogens of 610[1] are in the *cis* configuration.

Experiments using deuterated DPA are in progress. A detailed report of these experiments will appear shortly.

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(3) G. W. Robinson, *J. Mol. Spectry.*, **6**, 58 (1961).

(4) R. Srinavasan and J. C. Power, *J. Chem. Phys.*, **39**, 580 (1963); *J. Am. Chem. Soc.*, **85**, 1355 (1963).

DEPARTMENT OF CHEMISTRY   HENRY LINSCHITZ
BRANDEIS UNIVERSITY   KARL-HEINZ GRELLMANN
WALTHAM, MASSACHUSETTS

Solid Phase Peptide Synthesis. II. The Synthesis of Bradykinin

Sir:

Solid phase peptide synthesis was introduced recently[1,2] as a new approach to the preparation of polypeptides. This process, which was designed to speed and simplify peptide synthesis, depends on the attachment of the C-terminal amino acid residue to a solid particle, the stepwise addition of succeeding amino acids to the peptide chain, and finally the cleavage of the completed peptide from the solid support. The

(1) R. B. Merrifield, *Federation Proc.*, **21**, 412 (1962).

(2) R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149 (1963).

feasibility of the idea was demonstrated by the synthesis of a tetrapeptide, which was shown to be identical with a sample made by conventional procedures.[2] More recently, a dipeptide has also been made by a related method.[3] It was recognized at the outset that, for the method to be of real value, it would be necessary to apply it to the preparation of larger peptides, and preferably to ones with biological activity. We wish to report here the successful application of the method to the synthesis of the nonapeptide hormone, bradykinin.

The structure of bradykinin was elucidated by Elliott, *et al.*,[4] and the peptide was synthesized by Boissonnas, *et al.*,[5] and by Nicolaides and De Wald.[6] The present synthesis followed the basic concept of solid phase peptide synthesis outlined previously,[2] but differed in several important details: (1) *t*-Butyloxycarbonyl (*t*-BOC) amino acids were used in place of benzyloxycarbonyl derivatives to permit milder conditions for the deacylation, and thus to decrease the loss of peptide from the resin. With this modification it was unnecessary to nitrate the resin. (2) The coupling steps were carried out in dimethylformamide (DMF) and an excess of each *t*-BOC amino acid was used. (3) The acetylation steps were eliminated. With these modifications, the total time required for each cycle was shortened to 4 hr., and the over-all yield of peptide was improved.

For the synthesis of bradykinin, *t*-BOC-nitro-L-arginine triethylammonium salt was coupled in ethanol with 10 g. of chloromethylcopolystyrene–divinylbenzene (2%) to give the ester. All of the remaining reactions were carried out in the reaction vessel described previously.[2] First, the acyl group was removed (1 *N* HCl–acetic acid, 25°, 30 min.), and the resulting hydrochloride was neutralized by washing with triethylamine in DMF. The free base was then coupled in DMF with an excess of *t*-BOC-L-phenylalanine by the aid of dicyclohexylcarbodiimide to give *t*-BOC-L-phenylalanyl-nitro-L-arginyl resin. Excess reagents and by-products were removed from the totally insoluble and easily filterable product by thorough washing with DMF, ethanol, and acetic acid. In exactly the same way the peptide chain was lengthened one amino acid at a time until the protected nonapeptide, *t*-BOC-nitro-L-arginyl-L-prolyl-L-prolyl-glycyl-L-phenylalanyl-O-benzyl-L-seryl-L-prolyl-L-phenylalanyl-nitro-L-arginyl resin was produced. The product contained 0.150 mmole of peptide per gram of resin, yield 83% based on the C-terminal nitroarginine residue. Therefore, the average retention of the peptide on the resin during each of the 8 deprotection steps was over 97%. The coupling reactions also were nearly quantitative at each step as indicated by the amino acid analysis of a hydrolysate of the resin-bound peptide. Amino acid ratios were: arg, 2.00; pro, 2.74; phe, 2.13; gly, 1.01; ser, 1.04. The peptide was cleaved from the resin in 75% yield with HBr in trifluoroacetic acid. The amount liberated was followed by measurement of the absorption of the soluble material at 268 mμ due to nitroarginine. Catalytic hydrogenation with palladium black in methanol-acetic acid gave a quantitative yield of free nonapeptide, based on the decrease in absorption at 268 mμ and a corresponding increase in the Sakaguchi reaction for arginine. The product was purified chromatographically on IRC-50 ion-exchange resin by gradient elution

(3) R. L. Letsinger and M. J. Kornet, *ibid.*, **85**, 3045 (1963).

(4) D. F. Elliott, G. P. Lewis, and E. W. Horton, *Biochem. Biophys. Res. Commun.*, **3**, 87 (1960).

(5) (a) R. A. Boissonnas, St. Guttmann, and P.-A. Jaquenoud, *Helv. Chim. Acta*, **43**, 1349 (1960); (b) St. Guttmann, J. Pless, and R. A. Boissonnas, *ibid.*, **45**, 170 (1962).

(6) E. D. Nicolaides and H. A. De Wald, *J. Org. Chem.*, **26**, 3872 (1961).