H-Ser-Tyr-Ser-Met-Glu-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-NH_2
I

H-Ser-Tyr-Ser-Abut-Gln-His-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-NH_2
II

H-Ser-Tyr-Ser-Met-Gln-Pyr(3)ala-Phe-Arg-Trp-Gly-Lys-Pro-Val-Gly-Lys-Lys-Arg-Arg-Pro-Val-NH_2
III

IU/mg. As concerns steroidogenic potency in the hypophysectomized or dexamethasone-blocked rat[13] peptide III exhibited approximately 60% the biological activity of corticotropin A_1 on a weight basis. Rat assays in which the steroidogenic potency of III was compared to the third International Standard gave a potency of more than 50 IU/mg. Accurate evaluation of potency was difficult because of nonparallelism in the log-dose response slopes of standard and peptide. A detailed account of the biological properties of the pyrazole analog will be published elsewhere.

In addition to its adrenocorticotropic activity peptide III exhibits *in vitro* melanocyte expanding activity (8.4×10^7 U/g).[14] This value is approximately 80% that recorded for peptide I, *i.e.*, 1.1×10^8 U/g.[4] On the basis of photolysis experiments, Dedman, *et al.*,[15] suggested that histidine may not be essential for function of ACTH. The present findings prove conclusively that the characteristic acid–base properties of the imidazole portion of histidine are not essential for both the adrenocorticotropic and melanocyte expanding properties of the β-corticotropin molecule.

For the synthesis of III, phenylalanylarginyltryptophylglycine[16] was acylated with *p*-nitrophenyl N^{α},N^{pyr}-dibenzyloxycarbonyl-β-(pyrazolyl-3)-alaninate [mp 156–157°; $[\alpha]^{24}D$ −17.0° (*c* 3.99, DMF). *Anal.* Found: C, 61.8; H, 4.4; N, 10.2] to give N^{α},N^{pyr}-dibenzyloxycarbonyl-β-(pyrazolyl-3)-alanylphenylalanylarginyltryptophylglycine which was converted by hydrogenolysis into β-(pyrazolyl-3)-alanylphenylalanylarginyltryptophylglycine [dihydrate $[\alpha]^{24}D$ −7.2° (*c* 1.90, 50% acetic acid); R_f^{I} 0.29; R_f^{III} 0.51; amino acid ratios in AP-M digest, $Pyr(3)ala_{0.91}Phe_{1.06}Arg_{0.99}Trp_{1.00}Gly_{1.05}$. *Anal.* Found: C, 55.0; H, 6.7; N, 20.6; O, 17.1].

The above pentapeptide was coupled with the azide of N-*t*-butoxycarbonylseryltyrosylserylmethionylglutamine [hydrazide hydrate mp 199–202°. *Anal.* Found: C, 48.5; H, 6.7; N, 15.1; O, 25.6] to give N-*t*-butoxycarbonylseryltyrosylserylmethionylglutaminyl-β-(pyrazolyl-3)-alanylphenylalanylarginyltryptophylglycine [monohydrate mp 200–203°; $[\alpha]^{27}D$ −15.4° (*c* 0.52, DMF); amino acid ratios in acid hydrolysate, $Ser_{1.88}Tyr_{0.92}Met_{0.95}Glu_{1.07}Pyr(3)ala_{1.02}Phe_{1.03}Arg_{1.16}Gly_{0.99}$; R_f^{I} 0.40; R_f^{III} 0.68, single Ehrlich- and chlorine-positive spot. *Anal.* Found: C, 54.6; H, 6.7; N, 17.1; O, 20.2].

The tosylate salt of this protected decapeptide was then coupled with the tosylate salt of N^{ϵ}-*t*-butoxycarbonyllysylprolylvalylglycyl-N^{ϵ}-*t*-butoxycarbonyllysyl-N^{ϵ}-*t*-butoxycarbonyllysylarginylarginylprolylvaline amide[7] using DCC as the condensing reagent. The ensuing protected eicosapeptide amide was isolated by chromatography on Sephadex G 25 [acetate, hydrate $[\alpha]^{27}D$ −50.4° (*c* 0.93, 10% acetic acid); R_f^{I} 0.46; R_f^{III} 0.65; amino acid ratios in acid hydrolysate, $Ser_{2.09}Tyr_{0.91}Met_{1.07}Glu_{1.00}Pyr(3)ala_{1.00}Phe_{1.01}Arg_{2.94}Gly_{2.02}Lys_{2.96}Pro_{2.00}Val_{2.05}$]. This material was deblocked by exposure to 90% TFA, trifluoroacetate ions were exchanged for acetate ions on Amberlite IRA-400, and the product was purified by chromatography on CMC.[17] Prior to assay the peptide was incubated with 2% aqueous thioglycolic acid[18] to reduce contaminating sulfoxide [acetate hydrate $[\alpha]^{27}D$ −62.1° (*c* 1.02, 10% acetic acid); R_f^{III} 0.52, single chlorine, ninhydrin; and Ehrlich-positive spot; single band on disc electrophoresis at pH 4.3; amino acid ratios in acid hydrolysate, $Ser_{2.16}Tyr_{0.91}Met_{0.98}Glu_{1.02}Pyr(3)ala_{0.92}Phe_{0.95}Arg_{2.95}Gly_{2.04}Lys_{3.00}Pro_{1.98}Val_{2.12}$; amino acid ratios in AP-M digest, $Ser_{1.99}Tyr_{0.92}Met_{1.03}Gln_{1.10}Pyr(3)ala_{0.82}Phe_{0.92}Arg_{2.87}Trp_{0.92}Gly_{2.17}Lys_{3.08}Pro_{2.14}Val_{2.16}$; peptide content 84% based on amino acid analysis].

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Free-Radical Substitution on Adamantane

Sir:

Bridgehead radicals of less strained polycyclic compounds are said to be "normal"[1] for decarbonylation of RCO· (R is adamantyl-1 or bicyclo[2.2.2]oct-1-yl)[2] or photochlorination[3] and autoxidation[3] of adamantane. However, Stock concluded that the bridgehead (bicyclo-[2.2.2]-oct-1-yl) radical was unusually unstable from the observation that it readily abstracted chlorine from carbon tetrachloride or even from trichlorobromomethane in the presence of bromine.[4] Therefore, more work

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Table I. Yield and Selectivity (Ratio of Reactivity of 1-H to 2-H) of Halogenation of Adamantane

Run	Reagent[e]	Solvent	Yield,[a] % of 1-Br	2-Br	1-Cl	2-Cl	Total 1 products	Total 2 products	Selectivity (1:2) to *X*-Hal	*Y*-Hal	Selectivity (Br:Cl) at 1 position	at 2 position
1	NBS + DTBP[b]	C_6H_5Cl	27	17			27	17	4.8			
2	NBS + DTBP[c]	C_6H_5Cl	15	8			15	8				
3	NBS + AIBN	C_6H_6	Small amount	Small amount								
4	$Br_2 + h\nu$	CCl_4	15	12	8	<0.5	23	12.4	3.8	Large	1.88	
5	NCS + AIBN	C_6H_6			11	9	11	9	3.7			
6	DTBP	CCl_4			43	6	43	6		21.5		
7	AIBN	CCl_4			4	<0.8	4	0.8		Large		
8	BPO	CCl_4			22	3.3	22	3.3		20.0		
9	DTBP	$BrCCl_3$	31.4	37.1	17.6		49.0	37.1			1.78	
10	NBS + DTBP[d]	CCl_4[b]	5.0	20.9	42.8	11.8	47.8	32.7			0.12	1.77
11	DTBP	$CHCl_3$			10	1.5	10	1.5		20.0		

[a] Based on adamantane used. In most cases, unreacted adamantane was recovered and material balance was almost complete. [b] AdH 7.5 mmoles, NBS 7.5 mmoles, and DTBP 7.5 mmoles at 130° for 48 hr. [c] AdH 7.35 mmoles, NBS 3.7 mmoles, and DTBP 2.5 mmoles at 130° for 24 hr. [d] AdH 7.5 mmoles, NBS 7.5 mmoles, and DTBP 7.5 mmoles in CCl_4 825 mmoles. [e] NBS, N-bromosuccinimide; DTBP, di-*t*-butyl peroxide; AIBN, azobisisobutyronitrile; NCS, N-chlorosuccinimide; BPO, benzoyl peroxide.

is necessary to give a reasonable explanation of these contradictory observations.

Since the adamantyl-1 radical cannot be planar because of its cage structure, it is of interest to investigate adamantyl-1 in more detail in order to clarify a problem of the nature of pyramidal free radical at bridgehead position. In this communication, we present the results of free-radical substitution on adamantane, especially focusing upon a comparison of the reactivities of the 1 and 2 positions since the latter should be able to give the normal secondary free radical (probably sp^2 hybridization). Product compositions of chlorination and bromination in several reagent–solvent systems are shown in Table I.

Adamantyl-1 bromide and chloride were identical with the authentic samples.[5] Hydrolysis of mixed bromides or chlorides gave adamantanol-1 and -2 where the former was identical with the authentic alcohol[6] and the latter was converted to adamantanone[6] with CrO_3–pyridine (isolation *via* a $NaHSO_3$ adduct).

For the reagents of *X*-Hal bond with relatively small bond dissociation energy, the selectivity (reactivity ratio of positions 1:2) was around 4 and does not change much in the conditions used. The selectivity was in a good agreement with reported selectivities of radical substitution of adamantane (photochlorination in CS_2 6.3, in C_6H_6 3.5, and in CCl_4 1.9; autoxidation 5.5), demonstrating that the bridgehead position shows a normal behavior for the formation of its free radical. This finding is in agreement with Applequist's conclusion,[2] while for the reagents of *Y*-Hal bond with relatively large bond dissociation energy ($CHCl_3$ or CCl_4) apparent selectivity was increased as high as 20 or more. The discrepancy may, in part, be dependent on the nature of attacking radical and of solvent, but the effect of these on the selectivity seems not to be serious by investigating our results (see Table I). If the experimental conditions were designed to bring a halogenating reagent and a halogenated solvent into competition under comparable conditions (runs 9 and 10 in Table I), the situation became clearer and, in the case of NBS and DTBP in carbon tetrachloride, 1-adamantyl abstracted chlorine prodominantly while 2-adamantyl abstracted bromine as a major reaction. Still, the ratio of total 1 to 2 derivatives did not change much.

$$\text{adamantane} \xrightarrow{R} \begin{cases} \text{1-adamantyl} \xrightarrow{\text{X source}} \text{1-adamantyl products} \\ \text{2-adamantyl} \xrightarrow{\text{X source}} \text{2-adamantyl products} \end{cases} \quad (1)$$

In eq 1 much less discriminating halogen abstraction by adamantyl-1 from CCl_4 or $CHCl_3$ than by adamantyl-2 indicates that the bridgehead (sp^3) radical is less stable than the normal secondary radical (planar) from the usual concept of reactivity–selectivity relationship, in accord with Stock's conclusion.[4] In order to show the different selectivities of 1 and 2 radicals directly, modified Hünsdiecker reactions of 1- and 2-adamantanecarboxylic acids were carried out preliminarily by using the Br_2–CCl_4–HgO system (according to the procedure of "inverse addition").[4] The following results were obtained in good agreement with the assumed high selectivity of the adamantyl-2 radical and low selectivity of adamantyl-1 radical. From 1-adamantanecarboxylic acid, the product ratio, 1-chloroadamantane:1-bromoadamantane was 10:1 (determined by vpc) without appreciable by-product. From 2-adamantanecarboxylic acid, the product ratio 2-chloroadamantane:2-bromoadamantane was 0.11:1.

Therefore, it is concluded that the bridgehead radical (adamantyl-1) is formed "normally"[7] but it reacts "abnormally" while the bridge radical (adamantyl-2) is formed and reacts normally. A full interpretation of these observations will be made after additional experiments are carried out, but we present now a following tentative intepretation.

(5) Adamantyl-1 bromide: H. Stetter and C. Wulff, *Chem. Ber.*, **93**, 1366 (1960); and chloride: W. Hoehr, J. Strating, and H. Wynberg, *Rec. Trav. Chim.*, **85**, 1045 (1964). See also F. W. van Deunsen and P. K. Korver, *Tetrahedron Letters*, 3923 (1967), for nmr spectral analyses.

(6) Adamantanol-1: H. Stetter, M. Schwarz, and A. Hirschhorn, *Chem. Ber.*, **92**, 1629 (1959); adamantanone: R. D. Nicholas, Ph.D, Thesis, Princeton University, 1960; P. von R. Schleyer and R. D. Nicholas, *J. Am. Chem. Soc.*, **83**, 182 (1961). See H. W. Geluh and J. L. M. A. Schlatmann, *Chem. Commun.*, 426 (1967), for more convenient syntheses. The authors found that 2-chloroadamantane was only partially hydrolyzed on refluxing 1 week in aqueous tetrahydrofuran–Ag^+–Na_2CO_3.

(7) Preliminary rate measurement and product analyses of decomposition of *t*-butyladamantane 1-peroxycarboxylate indicated that the decomposition was sufficiently fast but not concerted: I. Tabushi, J. Hamuro, and R. Oda, unpublished results.

The transition state to the formation of free radical may be pyramidal. Further conversion to more stable planar form then takes place if this is not structurally inhibited. Spectroscopic evidence supports the idea that free radicals are most stable in the planar (sp^2) form.[8] In addition, Bartlett reported elegant experiments detecting an sp^3 radical of short life and the possible sequence less stable $sp^3 \rightleftarrows$ (strained) $sp^2 \rightleftarrows$ more stable sp^3 was postulated.[9,10]

In the adamantane reaction, the adamantyl-1 radical is formed more easily from adamantane than the adamantyl-2, presumably because of the usual effects which stabilize tertiary radicals more than secondary. In addition, the 1 position, which has only equatorial character, may be more sterically accessible than the 2 position, which is axial. Thus the transition state for attack at the 1 position is more favorable than for that at the 2 position. However, the adamantyl-1 radical has to stay in a pyramidal (sp^3) state and gains no more stabilization, but adamantyl-2 is capable of further stabilization by means of rehybridization to the planar (sp^2) state.[11] This explanation should be applicable to radicals at weakly strained bridgehead positions such as in bicyclo[2.2.2]octane.

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(9) P. D. Bartlett, R. E. Pincock, J. H. Rolston, W. G. Schindel, and L. A. Singer, *J. Am. Chem. Soc.*, **87**, 2590 (1965).

(10) Similar stereochemical studies of free radicals have been reported by F. D. Greene and N. N. Lowry, *J. Org. Chem.*, **32**, 875, 882 (1967).

(11) Professor Schleyer kindly pointed out that the observed selectivity can also be explained by the difference of the second barrier (from adamantyl radical to products) without crossover of energy diagram. However, this explanation also concedes that the 1 radical is destabilized (relative to its transition state) to a greater extent than is the 2 radical. We feel this is the most important point. The extent to which the 1 radical is destabilized may bring its energy either below or above that of the 2 radical. More work is needed to decide this point.

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Radical-Anion Reactions in Hexamethylphosphoramide

Sir:

Solvent exerts a large effect upon the equilibria and kinetics of reactions involving radical ions by modifying their state of aggregation.[1] For example, the equilibrium between the free ions and ion pairs, or the structure of ion pairs, is greatly modified by the solvent.[2] We wish to report now the dramatic effects observed in radical-anion reactions performed in hexamethylphosphoramide (HMPA).

Conductance studies[3] demonstrated that 10^{-3} *M* solutions of lithium, sodium, or potassium salts of anthracene radical anions are virtually completely dissociated in HMPA at 25°. Similar results were obtained with various alkali and quaternary alkylammonium salts of tetraphenyl boride.[3] Therefore, it is plausible to assume that alkali salts of most radical ions are completely dissociated in this solvent. Conversion of ion pairs into free ions enormously affects the equilibria and rates of some radical-ion reactions. Three examples are singled out to illustrate these phenomena: disproportionation of radical ions of tetraphenylethylene, dimerization of radical ions of diphenylacetylene, and dimerization of radical ions of quinoline.

(1) Disproportionation of radical ions of tetraphenylethylene ($T\cdot^-$) into the salts of dianion (T^{2-}) and the parent hydrocarbon (T) is shifted far to the right in most ethereal solvents. At room temperature a large excess (about 1000-fold) of the hydrocarbon (T) has to be present to maintain an appreciable concentration of radical anions ($T\cdot^-$) in the THF solution.[4] In HMPA virtually *all* $T\cdot^-$ remain as radical ions, even in the absence of the parent hydrocarbon. This is evident from the following observations.

(a) A slight excess of T added to a solution of T^{2-} changes the spectrum into that attributed to $T\cdot^-$ (see ref 4 for the pertinent spectral data). Further addition of a large excess of T does not change the spectrum any more. The intensity of the esr signal demonstrates that the concentration of free spins is nearly equivalent to the initial concentration of alkali, even if only a slight excess of T was added to a solution of T^{2-}.

(b) Similar results were obtained by adding a slight excess of T to a solution of sodium naphthalene.

The enormous change in the position of equilibrium is caused by the virtually complete dissociation of $T\cdot^-,Na^+$ into free ions. The dianion is only half dissociated; *i.e.*, its bulk is present in the form of T^{2-},Na^+. The equilibrium

$$T\cdot^- + T\cdot^-,Na^+ \rightleftarrows T^{-2},Na^+ + T$$

is shifted, therefore, to the left because the concentration of $T\cdot^-,Na^+$ is vanishingly small. The equilibrium constants of reactions

$$T\cdot^-,Na^+ + T\cdot^-,Na^+ \rightleftarrows T^{2-},2Na^+ + T \quad K_1$$

$$T\cdot^- + T\cdot^-,Na^+ \rightleftarrows T^{2-},Na^+ + T \quad K_2$$

were determined previously in tetrahydrofuran[4b] at a temperature range of −20 to +20°.

It is obvious that quantitative studies of $T\cdot^-$ radical ions now become feasible. For example, the electron affinity of T in HMPA has been determined,[5] whereas such studies were impossible in tetrahydrofuran.[6] Also, electron-transfer reactions, $T\cdot^- + T \rightleftarrows T + T\cdot^-$ and $T\cdot^- + T^{2-} \rightleftarrows T^{2-} + T\cdot^-$, have been successfully studied.[6]

(2) Diphenylacetylene reacts with alkali metals, or other electron donors, yielding the respective radical

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