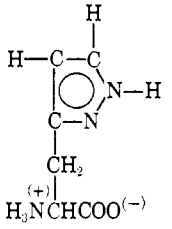
Table I. Biological Activity of [5-Valine]-angiotensin II Analogs

Analog	Rat pressor, %: Pithed	Rat pressor, %: Nephrectomized	Guinea pig myotropic, %
H-Asn-Arg-Val-Tyr-Val-His-Pro-Phe-OH ([Asn^1-Val^5]-angiotensin II)	100	100	100
H-Asn-Arg-Val-Tyr-Val-Phe-Pro-Phe-OH ([Asn^1-Val^5-Phe^6]angiotensin II)		1	
H-Asn-Arg-Val-Tyr-Val-Lys-Pro-Phe-OH ([Asn^1-Val^5-Lys^6]-angiotensin II)		0.1	
H-Asp-Arg-Val-Tyr-Val-Pyr(3)ala-Pro-Phe-OH ([Val^5-Pyr(3)Ala^6]-angiotensin II)	78.9 ± 1.33	56.6 ± 2.6	52.0 ± 0.98



β-(pyrazolyl-3)-alanine

We find that [Val^5-Pyr(3)Ala^6]-angiotensin II exhibits surprisingly high pressor and myotropic activities (Table I).

The pressor activity of the pyrazole analog was assayed in two rat preparations against [Asn^1-Val^5]-angiotensin II (angiotensinamide Ciba). In the pithed preparation the entire central nervous system was destroyed and the animal was maintained on artificial respiration. With this preparation the shape of the pressor response was almost identical with that of the reference compound. With bilaterally nephrectomized rats anesthetized with pentobarbital and pretreated with "pentolinium tartrate" the shapes of the pressor response curves were identical, but the dose–response curve did not parallel that obtained with the reference standard. The value recorded in Table I is an average of the per cent response at four dose levels. Myotropic activity was assayed on the isolated ileum of the guinea pig, and here again the dose–response curve of the analog was shifted to the right. Detailed accounts of the biological properties of [Val^5-Pyr(3)Ala^6]-angiotensin II, including its ability to elicit aldosterone release, will be presented elsewhere.

For the synthesis of [Val^5-Pyr(3)Ala^6]-angiotensin II, the azide of benzyloxycarbonylaspartylarginylvalyltyrosine was coupled with *t*-butyl valyl-β-(pyrazolyl-3)-alanylprolylphenylalaninate (*Anal.* Found for hemihydrate: C, 62.2; H, 7.5; N, 14.7; O, 15.6; $[\alpha]^{26}D$ −52.81° (*c* 1.352, water); single chlorine- and ninhydrin-positive spot with R_f^{I} 0.76; R_f^{III} 0.69; amino acid ratios in acid hydrolysate $Val_{1.01}Pyr(3)Ala_{0.97}Pro_{1.01}Phe_{1.02}$) to give *t*-butyl benzyloxycarbonylaspartylarginylvalyltyrosylvalyl-β-(pyrazolyl-3)-alanylprolylphenylalaninate which was partially deblocked by exposure to TFA. The ensuing crude benzyloxycarbonyl octapeptide was purified by chromatography on the ion exchanger AG-1 X2. Hydrogenolysis of the homogeneous benzyloxycarbonyl octapeptide afforded [Val^5-Pyr(3)Ala^6]-angiotensin II ($[\alpha]^{27}D$ −47.5° (*c* 0.29, 20% aqueous dioxane); amino acid ratios in AP-M digest $Asp_{1.04}Arg_{1.04}Val_{1.95}Tyr_{1.04}Pyr(3)Ala_{0.99}Pro_{0.99}Phe_{0.94}$; single ninhydrin-, Sakaguchi-, and chlorine-positive spot with R_f^{I} 0.49; R_f^{III} 0.55; peptide content 93% based on amino acid analysis).

(7) K. Hofmann and H. Bohn, *J. Am. Chem. Soc.*, **88**, 5914 (1966).

The results which are presented in this communication demonstrate conclusively that the pressor and myotropic activities of angiotensin do not depend on the characteristic acid–base properties of the imidazole ring. In conjunction with the experiments of Paiva and Paiva[4] and Schröder,[5,6] they indicate further that the stereo structure of the five-membered heterocyclic ring of histidine and not its charge is of crucial significance for high-level angiotensin activity.

To date, we have explored the effect on biological activity of imidazole–pyrazole replacements with three peptides, *i.e.*, S-peptide,[8] [Gln^5]-β-corticotropin$_{1-20}$ amide,[1] and [Val^5]-angiotensin II. The results demonstrate different roles for histidine residues in biologically active peptides. The acid–base character of imidazole appears to be of key significance in those situations where this ring system plays a direct role in a catalytic event. This fact was demonstrated unequivocally for histidine-12 in pancreatic ribonuclease S′ by the observation[8] that [Pyr(3)Ala^{12}]-S-peptide$_{1-14}$ competes with S-peptide for S-protein to form an inactive S-protein-[Pyr(3)Ala^{12}]-S-peptide$_{1-14}$ complex. The role of histidine in the corticotropins and angiotensin is different. In these molecules the stereochemistry of the five-membered heterocyclic ring and very likely its aromatic character appear to contribute to the binding between peptide and receptor. The results to date indicate that the charge difference between imidazole and pyrazole does not influence significantly the forces which are responsible for this binding.

Acknowledgment. The skillful technical assistance of Miss Judy Montibeller and Miss Jean Yevick is gratefully acknowledged.

(8) F. M. Finn and K. Hofmann, *ibid.*, **89**, 5298 (1967).
(9) Protein Research Laboratory.
(10) Department of Pharmacology.
(11) Department of Medicine.

Klaus Hofmann,[9] Rudolf Andreatta[9]
Joseph P. Buckley,[10] William E. Hageman[10]
Alvin P. Shapiro[11]
University of Pittsburgh Schools of Medicine and Pharmacy
Pittsburgh, Pennsylvania
Received January 19, 1968

Norbornadien-7-oneiron Tricarbonyl

Sir:

Recent interest in the elusive norbornadien-7-one system (**1**)[1] prompts us to record the successful synthesis

(1) S. Yankelevich and B. Fuchs, *Tetrahedron Letters*, 4945 (1967), and references cited therein.

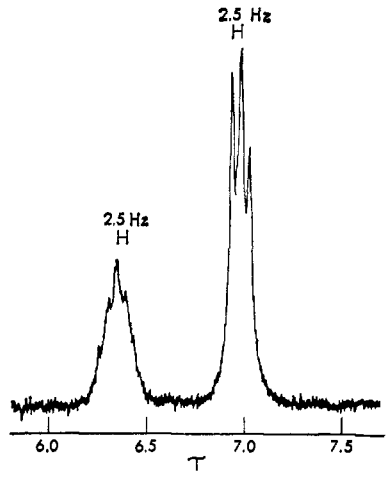
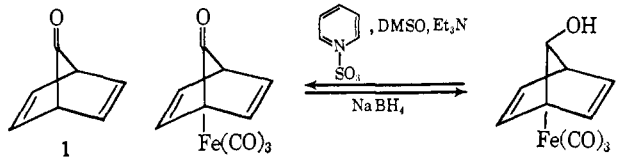


Figure 1. The nuclear magnetic resonance spectrum of norbornadien-7-oneiron tricarbonyl (**2**); sweep width 250 cps; chemical shifts are expressed in τ relative to internal tetramethylsilane.

and characterization of norbornadien-7-oneiron tricarbonyl (**2**), the simplest, stabilized derivative of **1**. Oxidation of norbornadien-7-oliron tricarbonyl (**3**)[2]



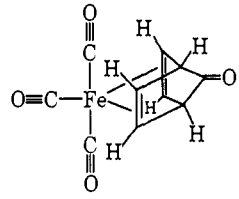
1 2 3

with the pyridine–sulfur trioxide complex in dimethyl sulfoxide containing triethylamine[3] gives **2** in 45% yield.[4] Reduction of the ketone **2** with sodium borohydride regenerates the alcohol **3**.

The orange complex, mp 93–95° (sealed, partially evacuated capillary tube), is a stable solid that can be stored at 0° for as long as 1 week. At room temperature or in solution (**2** is soluble in most organic solvents) samples of **2** slowly darken and deposit an insoluble red solid, which appears to be iron or iron oxide. In the mass spectrum, **2** exhibits peaks corresponding to the molecular ion and fragments resulting from the successive loss of one, two, three, and four carbonyls; a peak corresponding to benzene is observed also; *m/e* (relative intensity) at 10 eV: 246 (0.50), 218 (0.64), 190 (30), 162 (78), 134 (100), and 78 (36). Passing the sample through a suboven (200°) attached to the mass spectrometer results only in the molecular ion of benzene.[5] This behavior is expected for **2** and is the observed cracking pattern for many iron tricarbonyl derivatives.[6]

The infrared spectrum of **2** in carbon tetrachloride shows strong carbonyl absorptions at 2040 and 1965 cm^{-1} and is typical of symmetrical diene–$Fe(CO)_3$ complexes.[2,6] As expected, the carbonyl stretching frequency for the strained ketone is low; two absorptions occur at 1860 (w) and 1780 (s) cm^{-1} and compare well with the values of known strained systems.[7] Other significant maxima for **2** appear at 3055 (w), 3025 (vw), 1580 (w), 1400 (w), 1305 (w), 1155 (m), 1090 (m), 920 (w), 895 (w), and 840 (w) cm^{-1}.

The nuclear magnetic resonance spectrum of **2** (Figure 1)[8] in $CDCl_3$ consists of a quintet centered at τ 6.35 (J = 2.5 Hz; two protons, corresponding to the bridgehead hydrogens) and a triplet centered at τ 6.98 (J = 2.5 Hz; four protons, corresponding to the olefinic hydrogens). The simplicity of the nmr spectrum indicates a C_{2v} symmetry and is analogous to the spectrum observed for norbornadieneiron tricarbonyl.[9] This is consistent with structure **2**. The upfield chemical



2

shift of the vinyl protons results from the shielding effect of the iron and is characteristic of these complexes.[10] The signals slowly broaden with time as **2** decomposes at the temperature of the probe (*ca.* 35°).

The stability of **2** deserves comment. Yankelevich and Fuchs[1] argue that the interaction of the π cloud of the carbon–carbon double bonds with that of the carbonyl leads to a net destabilizing effect. Compensation of this interaction by bending of the C_7=O bridge cannot occur in **1** as it can in norbornen-7-one. As a result, **1** rapidly decarbonylates to the thermodynamically stable molecules of carbon monoxide and benzene. This argument suggests that if electron density can be decreased in the olefinic bonds, the unfavorable π-cloud interactions would be alleviated; this should lead to stabilization. The successful synthesis of **2** supports this contention. The reduction of electron density in the π-molecular orbital of the diene ligand by the iron moiety is an effect predicted by the "forward-backward" π bonding postulated for transition metal complexes.[11] Thus, the destabilizing π-cloud interaction is relieved. The strength of the diene–metal bonds also keeps the folded configuration for the bicyclo[2.2.1] system; decarbonylation and aromatization do not take place as readily.

Oxidation of 3.00 g of norbornadien-7-oliron tricarbonyl[2] was carried out with the pyridine–sulfur trioxide complex (prepared from 6.17 g of pyridine and 4.51 g of

(2) R. Pettit and G. F. Emerson, *Advan. Organometal. Chem.*, **1**, 1 (1964).

(3) J. R. Parikh and W. von E. Doering, *J. Am. Chem. Soc.*, **89**, 5505 (1967).

(4) This is in contrast to the oxidation of **3** using chromium trioxide; benzaldehyde results from this procedure: C. P. Lillya, private communication.

(5) Mass spectra were obtained on a Perkin-Elmer Hitachi RMU-6D mass spectrometer.

(6) See G. F. Emerson, K. Ehrlich, W. P. Giering, and P. C. Lauterbur, *J. Am. Chem. Soc.*, **88**, 3172 (1966), and references cited therein.

(7) P. R. Story and S. R. Fahrenholz, *ibid.*, **86**, 1270 (1964); leading references and examples are listed in this paper.

(8) Recorded on a Varian A-60; sweep width 250 cps; values are expressed in τ relative to internal tetramethylsilane.

(9) D. R. Falkowski, D. F. Hunt, C. P. Lillya, and M. D. Rausch, *ibid.*, **89**, 6387 (1967).

(10) M. L. H. Green, L. Pratt, and G. Wilkinson, *J. Chem. Soc.*, 3753 (1959).

(11) (a) M. J. S. Dewar, *Bull. Soc. Chim. France*, **18**, C71 (1951); (b) J. Chatt and L. A. Duncanson, *J. Chem. Soc.*, 2939 (1953).

chlorosulfonic acid in 15 ml of carbon tetrachloride[12]) in 80 ml of dimethyl sulfoxide containing 34 ml of triethylamine, according to the general procedure of Parikh and Doering.[3] The crude product (1.50 g) was recrystallized from pentane at Dry Ice–acetone temperature and gave 1.35 g (45%) of norbornadien-7-one-iron tricarbonyl, mp 93.5–95.5° (sealed, partially evacuated capillary tube); resolidified material melted at 93–95° and evolved some gas. The major impurities were dimethyl sulfoxide decomposition products which gave the solid a pungent odor; several recrystallizations from pentane reduced the odor and gave orange needles. *Anal.* Calcd for $C_7H_6OFe(CO)_3$: C, 48.82; H, 2.46. Found: C, 48.89; H, 2.51. A stable orange 2,4-dinitrophenylhydrazone, mp 164° dec, was obtained.

Future communications will deal with the chemical reactivity, including photochemistry, of this novel system.

Acknowledgment. We thank Miss V. Parmakovich, Columbia University, for determining the mass spectra. We gratefully acknowledge financial support by a Petroleum Research Fund grant from the American Chemical Society and by a Frederick Gardner Cottrell grant from the Research Corporation.

(12) L. F. Fieser, "Experiments in Organic Chemistry," 3rd ed, D. C. Heath and Co., Boston, Mass., 1955, p 337.

J. M. Landesberg, J. Sieczkowski

Department of Chemistry, Adelphi University
Garden City, New York 11530

Received January 20, 1968

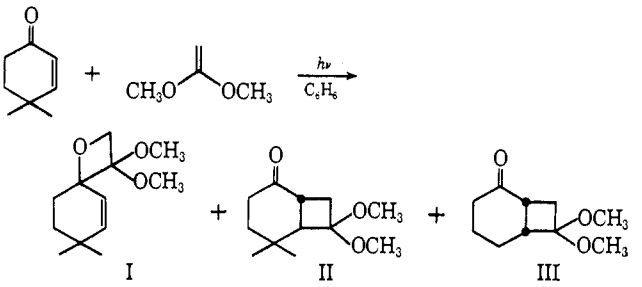
Two Triplet Mechanisms in Photochemical Addition of 2-Cyclohexenones to 1,1-Dimethoxyethylene[1]

Sir:

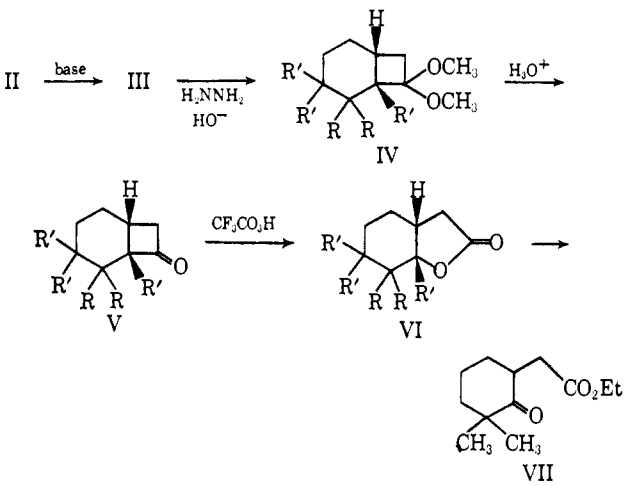
Photocycloaddition of 2-cyclohexenone[2] and 2-cyclopentenone[3] to olefins gives bicyclo[4.2.0]octan-2-ones and bicyclo[3.2.0]heptan-2-ones. In the case of cyclohexenone both *cis* and *trans* isomers of the bicyclic system are formed.[2] Cyclopentenone gives only the *cis* isomer.[3]

In our investigation of the photodimerization of isophorone we were led to postulate that two excited triplets react with ground-state isophorone.[4] Earlier, Yang had considered the possibility that two triplets were involved in the photochemical addition of 9-anthraldehyde to trimethylethylene[5] and in the photochemistry of 9-nitroanthracene[5,6] and has shown that two reactive excited states are involved in the former reaction.[7] Yang has also detected phosphorescence from 1-indanone which involves two triplet states of differing lifetimes.[8] Recently, de Mayo has suggested that an upper triplet of 2-cyclopentenone is involved in its photochemical addition to cyclohexene.[9] We now wish to describe the addition of 4,4-dimethyl-2-cyclohexenone to 1,1-dimethoxyethylene and the addition of isophorone to 1,1-dimethoxyethylene. In each case two triplets are involved which lead to different products.

Irradiation of 4,4-dimethyl-2-cyclohexenone (0.2 *M*) and 1,1-dimethoxyethylene (0.1 *M*) in benzene gave an oxetane (I), a *trans* adduct (II), and a *cis* adduct (III). The structure of the oxetane is based on the empirical



formula ($C_{12}H_{20}O_3$), the nmr spectrum, the absence of carbonyl absorption in the infrared spectrum, and the loss of CH_2O on electron-impact ionization. The *trans* isomer was isomerized to the *cis* isomer by base.



a, R = CH_3; R′ = H
b, R = H; R′ = CH_3

Reduction, hydrolysis, and oxidation gave γ-lactone VIa. The γ-lactone was reduced to a diol which on oxidation and esterification gave keto ester VII identical with an authentic sample.

Irradiation of isophorone and 1,1-dimethoxyethylene in benzene gave a mixture of products from which the *cis* and *trans* adducts VIII and IX were isolated and characterized. The *trans* adduct isomerized to the *cis* adduct which was converted to lactone VIb by the same series of transformations used above. Lactone VIb was synthesized from 2,4,4-trimethyl-2-cyclohexenone by catalytic reduction, a Reformatsky reaction using ethyl

(1) Photochemical Transformations. XXV. Portions of this work were described at the 20th National Organic Chemistry Symposium of the American Chemical Society, June 18–22, 1967, Burlington, Vt., Abstracts, pp 127–139.

(2) E. J. Corey, J. D. Bass, R. LeMahieu, and R. B. Mitra, *J. Am. Chem. Soc.*, **86**, 5570 (1964).

(3) P. Eaton, *ibid.*, **84**, 2454 (1962); *Tetrahedron Letters*, 3695 (1964).

(4) O. L. Chapman, P. J. Nelson, R. W. King, D. J. Trecker, and A. A. Griswold, *Record Chem. Progr.*, **28**, 167 (1967).

(5) N. C. Yang, *Pure Appl. Chem.*, **9**, 591 (1964).

(6) O. L. Chapman, A. A. Griswold, E. Hoganson, G. Lenz, and J. W. Reasoner, *ibid.*, **9**, 585 (1964); O. L. Chapman, D. C. Heckert, J. W. Reasoner, and S. P. Thackaberry, *J. Am. Chem. Soc.*, **88**, 5550 (1966).

(7) N. C. Yang, R. Loeschen, and D. Mitchell, *ibid.*, **89**, 5465 (1967).

(8) N. C. Yang and S. Murov, *J. Chem. Phys.*, **45**, 4358 (1966).

(9) P. de Mayo, J.-P. Pete, and M. Tchir, *J. Am. Chem. Soc.*, **89**, 5712 (1967).