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(17) NASA Trainee during 1964–1967.

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A New Method for the Removal of Chloroacetyl Groups

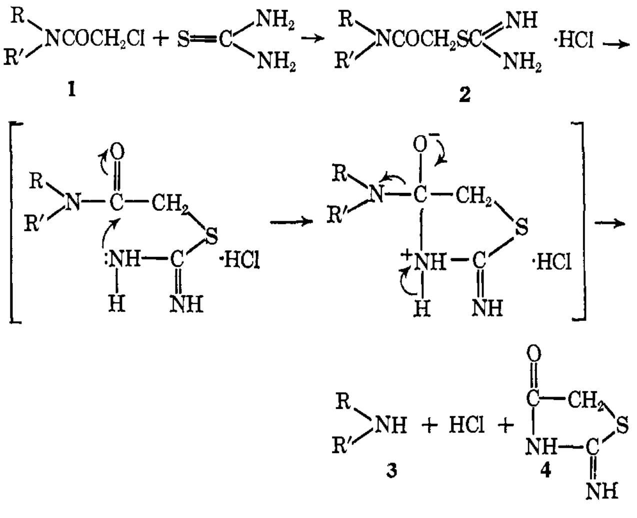
Sir:

Several methods have been known for the fission of the amide bond in chloroacetylamines. The hydrolytic fission can be effected in 10 *N* hydrochloric acid–glacial acetic acid[1] or in alcoholic hydrogen chloride.[2] Holley and Holley[3] reported an intramolecular aminolysis method which consisted in the treatment of chloroacetyl peptides with *o*-phenylenediamine in aqueous lithium hydroxide at 100°.

In this paper, we wish to report a new and milder method for the removal of chloroacetyl group from the compounds including it as a protecting group of amines.

Recently, we found that the reaction of 1-chloro-2-oximino-3-butanone or 2-bromoacetophenone oxime with thiourea led to the formation of 4-(1-oximinoethyl)- or 4-phenyl-2-aminothiazole.[4] In an extension of this reaction, it was envisaged that reacting chloroacetylamine **1** with thiourea would result in the initial formation of the S-substituted thioformamidine hydrochloride **2**, which would then undergo the intramolecular amidinolysis to liberate the corresponding amine **3** with the concomitant formation of pseudothiohydantoin **4**, as illustrated in Scheme I.

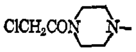
Scheme I



Thus, N-chloroacetyl-*p*-nitroaniline was treated with 1 equiv of thiourea in ethanol, giving S-(*p*-nitrophenylcarbamoylmethyl)thioformamidine hydrochloride[5] in 85% yield. When the amidine was heated in an aqueous solution for 15 min, *p*-nitroaniline was, as expected, obtained in 88% yield, together with a 71% yield of pseudothiohydantoin hydrochloride.

In analogous treatment of N-chloroacetyl-N′-formylpiperazine with thiourea, the selective removal of the chloroacetyl group was effected, and N-formylpiperazine was quantitatively liberated as the hydrochloride. The reaction was examined on a variety of chloroacetylamines, and the liberated amines were isolated in a yield between 69 and 84%, as shown in Table I.

Table I. Yields of the Reaction Products

Chloroacetylamine **1** R	R′	Products Amine **3**	Yield,[a] %	Yield of **4**,[a] %
p-$NO_2C_6H_4$–	H–	*p*-Nitroaniline	75	60
p-$CH_3OC_6H_4$–	H–	*p*-Anisidine	75	78
		Piperazine	84[b]	76
		N-Formylpiperazine	77[c]	76
$C_6H_5CH_2$ │ $C_6H_5NHCOCH$–	H–	Phenylalanylaniline	69	66
$HOOCCH_2NHCOCH_2$–	H–	Glycylglycine	75[d]	67

[a] All yields were calculated from the chloroacetylamine **1**. [b] The yield was based on conversion into the picrate. [c] The yield was based on conversion into the N′-tosyl derivative, mp 143.8–144.5°.[5] [d] The yield was of the hydrochloride monohydrate.

The advantages of this method are as follows. (1) The selective removal of the chloroacetyl group is possible, as illustrated in the cases of N-chloroacetyl-N′-formylpiperazine, chloroacetylphenylalanylaniline, and chloroacetylglycylglycine, since the reaction can be carried out under mild conditions, where the other usual amide bonds cannot be hydrolyzed. (2) The reaction is effected in a medium having an acidity based on thioformamidine hydrochloride and/or amine hydrochlorides during the entire reaction time, while Holley and Holley's method[3] using *o*-phenylenediamine is performed in the presence of lithium hydroxide. (3) Separation of products is not difficult, since the bulk of pseudothiohydantoin crystallizes out when the reaction mixture is cooled, while the liberated amines remain usually as the hydrochloride in aqueous solution.[6]

The following procedure is representative, but some variations should be made mainly in reaction time according to the compounds used. A suspension of chloroacetylglycylglycine (2.09 g, 0.01 mol) and thiourea (95%, 0.80 g, 0.01 mol) in ethanol (30 ml) was heated at 60–65° for 1 hr, and the resultant solution was refluxed for 40 min. The ethanol was removed by rotary evaporation, and water (14 ml) was added to the crystal-

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(1) G. Hanson, *Chem. Abstr.*, **50**, 15419*h* (1956).

(2) A. Hillman and G. Hillman, *Z. Naturforsch.*, **6b**, 340 (1951).

(3) R. W. Holley and A. D. Holley, *J. Am. Chem. Soc.*, 74, 3069 (1952).

(4) M. Masaki, M. Sugiyama, S. Tayama, and M. Ohta, *Bull. Chem. Soc. Japan*, **39**, 2745 (1966).

(5) A satisfactory elemental analytical result was obtained for this new compound.

(6) In general, the basicity of pseudothiohydantoin is weaker than that of the liberated amines. However, *p*-nitroaniline is a weaker base than pseudothiohydantoin; thus the former was liberated as the free base. See the following references for the basicity of pseudothiohydantoin: (a) E. V. Vladzimirs'ka and Yu. M. Pashkevich, *Zh. Obshch. Khim.*, **33**, 3149 (1963); (b) M.-L. Girard and C. Dreux, *Compt. Rend.*, **260**, 2225 (1965).

line residue. The mixture was refluxed for 90 sec and cooled in a refrigerator to yield pseudothiohydantoin (0.78 g, 67%) as colorless needles, mp 233–235° dec. The filtrate was concentrated to dryness by rotary evaporation to give a crystalline residue, which was extracted with hot aqueous ethanol (90%, 40 ml). The extract upon cooling afforded glycylglycine hydrochloride monohydrate as colorless needles (1.13 g), mp 137–138°. The residue from the extraction was again extracted with the alcoholic filtrate to yield additional colorless needles (0.27 g), mp 136–138°. The total yield was 1.40 g. The product was substantially pure without further purification, and it was identical in melting point and ir spectrum with an authentic sample.[7]

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The Butatrienyl Radical

Sir:

In the course of studying the series of radicals having the general formula HC_nCH_2, we have prepared the hitherto unreported butatrienyl radical (n = 3) and observed its paramagnetic resonance spectrum in an argon matrix near 4°K. The radical was produced by photolyzing a mixture of diacetylene[1] with argon containing 1% hydrogen iodide during deposition on a sapphire surface in thermal contact with liquid helium. The dewar and spectrometer system have been described previously.[2] The essential reaction is the addition of hydrogen atoms, produced by photodissociation of HI, to diacetylene.[3] Addition appears to occur predominantly at the terminal positions.

Butatrienyl is the first vinylog of vinyl radical (n = 1), which has a bent, planar structure.[3–5] Unlike vinyl, any bending of HC_nCH_2 radicals with $n > 1$ would occur at the expense of optimum π bonding, so that the ground-state structures most likely have C_{2v} symmetry. There are then n π orbitals quantized in the molecular plane and $(n + 1)$ orbitals normal to this plane, so that one always has a linear polyyne which is even-alternant in one plane and odd-alternant in the other. In a neutral radical, the odd electron would be found in the essentially nonbonding orbital of the odd-alternant system, leading one to expect a $^2B_2$ ground state for radicals with n even and a $^2B_1$ ground state when n is odd. The unpaired electron in butatrienyl accordingly should be in the molecular plane and delocalized over three carbon atoms.

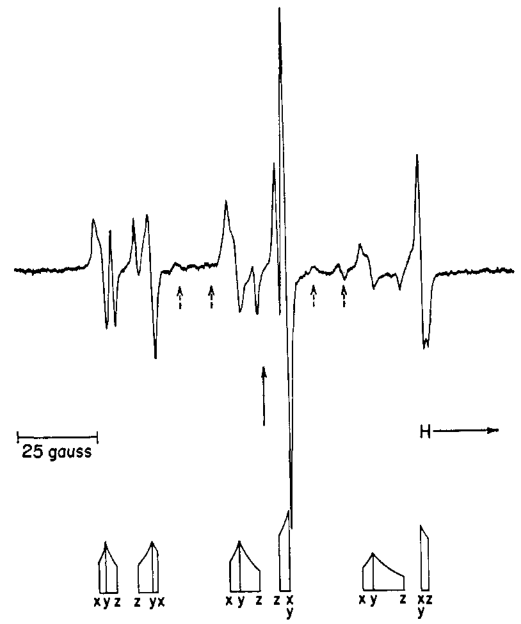


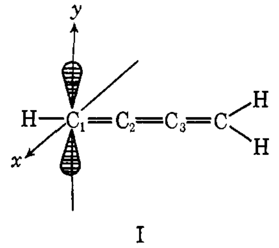
Figure 1. Esr spectrum (9436 GHz) of butatrienyl radical in argon near 4°K. A schematic analysis of the spectrum is indicated at the bottom. Weak signals indicated by broken arrows are believed due to vinylacetylenyl (see text). The solid arrow indicates the field corresponding to g = 2.0023.

The electron-spin resonance spectrum, shown in Figure 1, confirms this prediction. It shows an anisotropic pattern corresponding to a rigid system containing three protons, two of which are structurally equivalent. Its preliminary analysis yields the hyperfine splittings listed in Table I. There are weak additional lines indicated by broken arrows in Figure 1 which could result from hyperfine splittings of ~45 and ~10 G by each of two protons in a second species, most likely the vinylacetylenyl radical produced by hydrogen atom addition to an internal carbon atom of diacetylene.

Table I. Hyperfine Splittings (in Gauss at 9.3 GHz) in the Epr Spectrum of Butatrienyl Radical

	Doublet		Triplet	
	Obsd splitting	Dipolar part	Obsd splitting	Dipolar part
A_x	19	±5.3	42.3	∓1.1
A_y	15	±1.3	42.3	∓1.1
A_z	7	∓6.7	45.7	±2.3
$A_{iso} = {}^1/_3(A_x + A_y + A_z)$	±13.7		±43.4	

In the main spectrum, the principal axes can be assigned by considering the dipolar couplings in the principal valence-bond structures I and II.[6] The



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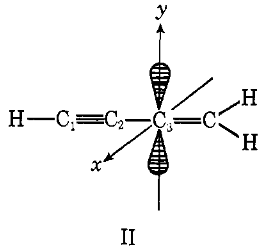

II

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[1] J. B. Armitage, E. R. H. Jones, and M. C. Whiting, *J. Chem. Soc.*, 44 (1951).

[2] P. H. Kasai, W. Weltner, Jr., and E. B. Whipple, *J. Chem. Phys.*, **42**, 1120 (1965).

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[4] P. H. Kasai and E. B. Whipple, *J. Am. Chem. Soc.*, **89**, 1033 (1967).

[5] R. W. Fessenden and R. H. Schuler, *J. Chem. Phys.*, **39**, 2147 (1963).

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