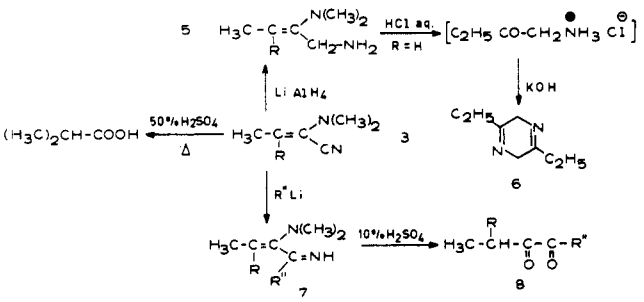
Table I. Preparation of α-Diketones from α-Cyanoenamines

α-Cyanoenamine	R″Li[a]	Solvent	α-Diketones	Yields (%)[b]
3a	CH_3Li	Ether	$(H_3C)_2CHCOCOCH_3$	75[c]
3a	C_6H_5Li	Ether	$(H_3C)_2CHCOCOC_6H_5$	90
3b	C_6H_5Li	Ether	$C_2H_5(C_6H_5)CHCOCOC_6H_5$	90
3d	C_6H_5Li	Ether	$C_2H_5COCOC_6H_5$	90
3d	C_4H_9Li	Hexane	$C_2H_5COCOC_4H_9$	90

[a] The addition of the organolithium compound was performed at 0°. [b] Yields were determined by GLPC or NMR on the crude material. [c] Yields are lower due to the competing formation of a carbanion at the γ position. This latter reaction appears to be dependent on the nature of the organolithium reagent (alkyl)Li > C_6H_5Li) and the solvent (ether > hexane).

Scheme II



rect precursors of **3d,e**, the amide chlorides **4d,e**, were treated successively with zinc cyanide in refluxing chloroform and triethylamine at room temperature, the α-cyanoenamines **3d** (bp 90° (50 Torr), $\nu_{C\equiv N}$ 2220 cm^{-1}) and **3e** ($\nu_{C\equiv N}$ 2220 cm^{-1}) were obtained in 73 and 75% (crude) yields, respectively. This one-pot sequence[2] (path b) constitutes a general method of synthesis of α-cyanoenamines. It certainly competes favorably with the few presently available methods which now exist for their preparation.[3]

The α-cyanoenamines **3a–e** gave elemental analysis and spectral (mass, ir, NMR) data in agreement with their structures.[4] They are quite resistant to aqueous acids as shown by the hydrolysis of **3a** which required 2 hr of reflux in 50% H_2SO_4 to give quantitatively isobutyric acid (Scheme II). On the other hand, the nitrile group of **3** can be easily reduced with $LiAlH_4$ to the unsymmetrical diamines, **5**, which are potential sources of α-amino ketones or dihydropyrazines (Scheme II). Thus **3a** gave **5a** (R = CH_3) in 70% yields on treatment with $LiAlH_4$ in refluxing ether followed by hydrolysis with aqueous KOH whereas **3d** gave **5b** (R = H) which was immediately converted to the dihydropyrazine (**6**) on treatment with aqueous HCl at room temperature followed by neutralization with KOH.

We have also examined the reaction of α-cyanoenamines with organolithium reagents (Scheme II, Table I). These reactions occurred smoothly to yield products resulting exclusively from 1,2-additions. The adducts, **7**, were characterized by their spectral data and hydrolyzed in 10% H_2SO_4 to the α-diketones **8**.

The overall sequence 2 → 3 → 7 provides a simple, general, and versatile process (overall yields 55–80%) for the stepwise construction of the carbon skeleton of α-diketones starting from carboxylic amides. It usefully complements an earlier synthetic route[5] which started from aldehydes or enol ethers and should have a larger scope than the other classical methods for the synthesis of α-diketones.[6]

The present results already demonstrate the synthetic potential of the readily available α-cyanoenamines. A very interesting extension of this work would result from the observation that **3a** reacts with nonnucleophilic strong bases to give a carbanionic center at the γ-carbon thus allowing in principle for carbon chain lengthening at this position. This new development of α-cyanoenamine chemistry will be reported later.

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References and Notes

(1) (a) L. Ghosez, B. Haveaux, and H. G. Viehe, *Angew. Chem., Int. Ed. Engl.*, **8**, 454 (1968); (b) M. Rens and L. Ghosez, *Tetrahedron Lett.*, 3765 (1970); (c) J. Marchand-Brynaert and L. Ghosez, *J. Am. Chem. Soc.*, **94**, 2879 (1972); (d) *ibid.*, **94**, 2870 (1972); (e) J. Marchand-Brynaert and L. Ghosez, *Tetrahedron Lett.*, 377 (1974); (f) A. Sidani, J. Marchand-Brynaert, and L. Ghosez, *Angew. Chem., Int. Ed. Engl.*, **13**, 267 (1974); M. Depoortere, J. Marchand-Brynaert, and L. Ghosez, *ibid.*, **13**, 268 (1974).

(2) Typically a solution of 101 g (1 mol) of *N*-dimethylpropionamide in 400 ml of dry $CHCl_3$ saturated with HCl is treated with 80 ml of $COCl_2$. After 3 days at room temperature, the solvent is removed in vacuo and the residue is dissolved in 300 ml of $CHCl_3$. Zinc cyanide (86 g, 0.75 mol) is added cautiously at 0° and the resulting mixture is refluxed for 8 hr. The reaction mixture is further diluted with 200 ml of $CHCl_3$, then treated with 140 g of dry triethylamine and stirred for 1 hr. Addition of 200 ml of petroleum ether (bp <80°) gives two layers. After standing overnight, the upper layer is removed while the residue is washed four times with petroleum ether. The extracts are combined and, after removal of the solvents, are fractionated to give 80 g of **3d**, bp 90° (50 Torr) contaminated by ~7% starting amide.

(3) In connection with studies of vinyl monomers several α-aminoacrylonitriles have been prepared: (a) British Patent 511430, Aug 18 (1939), *Chem. Abstr.*, **34**, 5860 (1940); (b) S. C. Temin, *J. Org. Chem.*, **22**, 1714 (1957); (c) H. Plieninger, R. El-Berins, and H. Mah, *Chem. Ber.*, **104**, 3983 (1971). For the synthesis of $ArCH_2CH{=}C(CN)NR_2$ see (d) L. A. Yanovskaya, C. Shachidayatov, E. P. Prokofiev, G. M. Adrianova, and V. F. Kucherov, *Tetrahedron*, **24**, 4677 (1968). For less-general structures containing an α-cyanoenamine group, see (e) C. L. Dickinson, D. W. Wiley, and B. C. McKusick, *J. Am. Chem. Soc.*, **82**, 6132 (1960); (f) M. Atkinson and A. M. Horsington, *J. Chem. Soc. C*, 2186 (1969); (g) K. Matsumura, T. Seraie, and N. Hashimoto, *J. Chem. Soc., Chem. Commun.*, 705 (1972); (h) R. W. Begland, D. R. Hartter, F. N. Jones, D. J. Sam, W. A. Sheppard, O. W. Webster, and F. J. Weigert, *J. Org. Chem.*, **39**, 2341 (1974); (i) J. A. Deyrup and J. C. Gill, *Synthesis*, **1**, 34 (1974); (j) H. Bredereck, G. Simchem, and W. Griebenow, *Chem. Ber.*, **107**, 1545 (1974).

(4) **3b** and **3c** were obtained as a mixture of geometrical isomers. With **3d** and **3e** one geometrical isomer is predominant.

(5) T. Cuvigny and H. Normant, *C.R. Acad. Sci.*, **237**, 815 (1953); see also P. Duhamel, L. Duhamel, and V. Truxillo, *Tetrahedron Lett.*, 51 (1974).

(6) S. Coffey, "Rodd's Chemistry of Carbon Compounds", Vol I, Part D, 2nd ed, Elsevier, Amsterdam, 1965.

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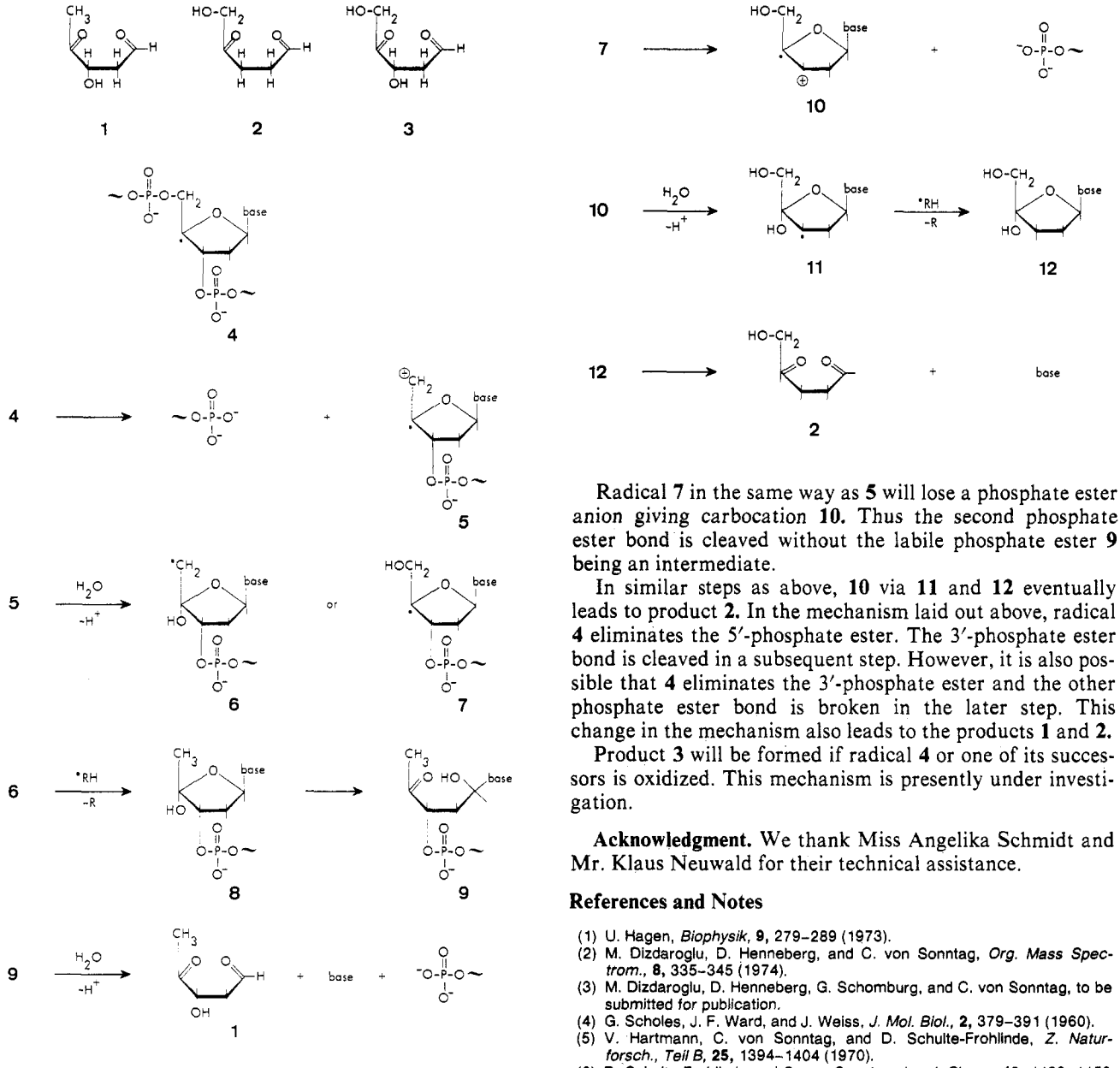
Strand Breaks and Sugar Release by γ-Irradiation of DNA in Aqueous Solution

Sir:

The lethal damage done to the living cell by ionizing radiation is thought to be partially due to DNA strand breaks.[1] The chemical steps of the radiation induced strand breaks are presently not well understood.

From deoxygenated N_2O-saturated aqueous solutions of DNA (500 mg/l.), we have isolated after γ-irradiation (dose, 3.5×10^{19} eV/g; dose rate 4.3×10^{18} eV/(g hr)) the three sugars 2,5-dideoxypentos-4-ulose (**1**), 2,3-dideoxypentos-4-ulose (**2**), and 2-deoxypentos-4-ulose (**3**). These products were obtained from herring sperm DNA as well as from calf thymus DNA (Serva).

For identification the isolated sugars were reduced with $NaBD_4$, trimethylsilylated, and analyzed by coupled GLC–MS. The interpretation of the mass spectra was done on the basis of typical fragmentation patterns of this class



of compounds.[2] Retention indices substantiated the assignments.[3] Further details will be given elsewhere.[3]

When DNA is γ-irradiated in deoxygenated N_2O saturated aqueous solution, the OH radicals and H atoms produced in the system will attack the DNA. Nearly all H atoms and the major part of the OH radicals add to the double bonds of the bases but 10–20% of the OH radicals react with the sugar moiety by abstracting hydrogen.[4] About one-fifth[5,6] of these are expected to abstract the hydrogen atom bound to C-4 of the deoxyribose moiety to form radical **4.**

For the cleavage of the phosphate ester bond two possible routes have been postulated on the basis of studies on model compounds, e.g., glycerophosphates[7,8] and ribose 5-phosphate.[9,10] **4** may eliminate a phosphate ester anion involving a carbocation **5** as an intermediate which adds water with the loss of a proton to give **6** or **7.** Alternatively[9,10] radical **4** ring-opens by adding water and undergoes β-elimination.

In a disproportionation reaction with other radicals (·RH) present, **6** forms compound **8. 8** is unstable and via **9** gives **1** together with free base and the other part of the DNA strand with a 5′-phosphate end group. The release of free base is observed in the radiation chemistry of DNA.[11,12]

Radical **7** in the same way as **5** will lose a phosphate ester anion giving carbocation **10.** Thus the second phosphate ester bond is cleaved without the labile phosphate ester **9** being an intermediate.

In similar steps as above, **10** via **11** and **12** eventually leads to product **2.** In the mechanism laid out above, radical **4** eliminates the 5′-phosphate ester. The 3′-phosphate ester bond is cleaved in a subsequent step. However, it is also possible that **4** eliminates the 3′-phosphate ester and the other phosphate ester bond is broken in the later step. This change in the mechanism also leads to the products **1** and **2.**

Product **3** will be formed if radical **4** or one of its successors is oxidized. This mechanism is presently under investigation.

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References and Notes

(1) U. Hagen, *Biophysik*, **9**, 279–289 (1973).
(2) M. Dizdaroglu, D. Henneberg, and C. von Sonntag, *Org. Mass Spectrom.*, **8**, 335–345 (1974).
(3) M. Dizdaroglu, D. Henneberg, G. Schomburg, and C. von Sonntag, to be submitted for publication.
(4) G. Scholes, J. F. Ward, and J. Weiss, *J. Mol. Biol.*, **2**, 379–391 (1960).
(5) V. Hartmann, C. von Sonntag, and D. Schulte-Frohlinde, *Z. Naturforsch., Teil B*, **25**, 1394–1404 (1970).
(6) D. Schulte-Frohlinde and C. von Sonntag, *Isr. J. Chem.*, **10**, 1139–1150 (1972).
(7) A. Samuni and P. Neta, *J. Phys. Chem.*, **77**, 2425–2429 (1973).
(8) S. Steenken, G. Behrens, and D. Schulte-Frohlinde, *Int. J. Radiat. Biol.*, **25**, 205–210 (1974).
(9) L. Stelter, C. von Sonntag, and D. Schulte-Frohlinde, *Int. J. Radiat. Biol.*, **25**, 515–519 (1974).
(10) L. Stelter, C. von Sonntag, and D. Schulte-Frohlinde, *Z. Naturforsch.*, in press.
(11) G. Hems, *Nature (London)*, **186**, 710–712 (1960).
(12) M. Ullrich, and U. Hagen, *Int. J. Radiat. Biol.*, **19**, 507–517 (1971).

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MINDO/3 Study of Some Simple Carbocations[1,2]

Sir:

It has been frequently stated that semiempirical MO methods cannot be used for ions with parameters appropriate to neutral molecules and in particular that they inevita-