The copper-catalyzed conditions reported here work successfully with enones, enals, acetylenic carbonyl compounds, and acid chlorides, but aldehydes, alkyl acrylates, epoxides, and allyl acetates were found to be unreactive under such conditions. The 1,4-addition reaction could be performed in the presence of an aldehyde, no trace of ternary coupling products being detected. In the absence of Me_3SiCl, the conjugate addition is much slower than the acylation reaction; thus, a competitive experiment between benzoyl chloride and cyclohexenone gave only the γ-keto ester. The reactivity spectrum shown above is considerably different from the usual copper reagents.[7]

Even with the limited number of cases examined here, it seems already clear that the copper-catalyzed reactions of the zinc homoenolate will prove synthetically valuable.

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Novel Adducts from the Modification of Nucleic Acid Bases by Malondialdehyde[1]

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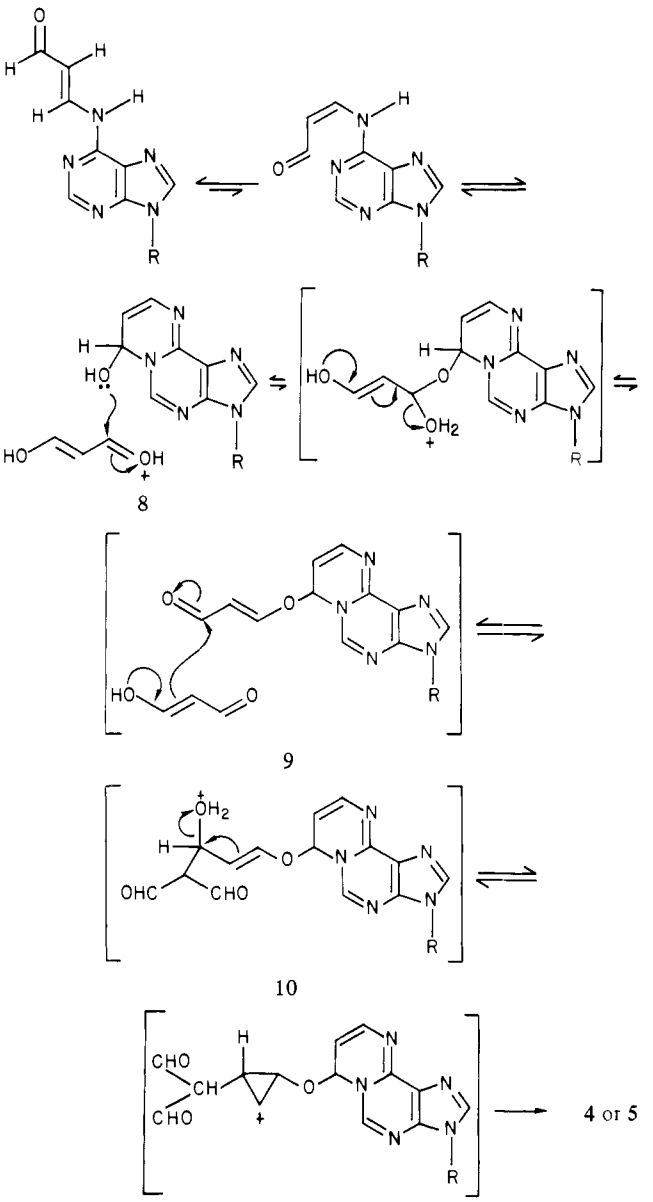
The ubiquitous natural compound, malondialdehyde (MDA) (**1**), is produced in animal tissues as an end product of unsaturated lipid peroxidation and as a side product of prostaglandin and thromboxane biosynthesis.[2] It is readily formed in the γ-irradiation of carbohydrates.[3] The reported toxicity and degenerative chemistry of MDA[4-8] may be a result of its ability to covalently bond and to cross-link a variety of biological macromolecules. Thus, the presence of MDA in foods and in living tissues in which the lipid component has undergone oxidation may be of considerable physiological importance. Malondialdehyde is reactive toward nucleic acids resulting in the loss of their template activity.[9,10] We have shown previously that MDA reacts relatively rapidly (as evidenced from kinetic data) at the α-amino group of amino acids to form both 1:1 and 1:2 adducts.[11] This communication reports on the isolation and structural elucidation of novel and unusual adducts from the reaction of MDA with adenine and cytosine.[12]

The reaction of MDA (as its sodium salt)[11] with adenosine was carried out in aqueous solution at pH 4.2[13] and 37 °C for 3 days to furnish two adducts, which were separated and purified by multiple reverse phase HPLC on Amberlite XAD-4 resin (40–50 μm) using ethanol/water as the eluting solvent. The first adduct, mp 125–127 °C, formed in about 7.0% conversion, showed UV

Scheme I



absorption at $\lambda_{max}^{H_2O}$ 326 (ϵ = 46 000), 241 (ϵ = 8500), and 222 nm (ϵ = 9900). The presence of a molecular ion at m/z 321 and fragments in the mass spectrum and the UV data suggested the formation of a nucleoside modified at the 6-position by an α,β-unsaturated aldehyde moiety. The 360-MHz high-field ^1H NMR data (including homonuclear decoupling) together with the 90.6-MHz ^{13}C NMR data in Me_2SO-d_6 provided excellent supporting evidence for the complete structure and stereochemistry as **2**. The NH resonance appeared at δ 11.36 (d, J = 11.4 Hz) and the aldehyde proton at δ 9.42 (d, J = 8.5 Hz). The two vinyl protons gave resonances at δ 6.01 (d, d, $J_{c,d}$ = 8.5, $J_{b,c}$ = 13.3 Hz, H_c) and 8.71 (d, d, $J_{b,c}$ = 13.3, $J_{a,b}$ = 11.4 Hz, H_b) indicative of a trans geometry. The adenine ring protons appeared as singlets at δ 8.71 (H_2) and 8.56 (H_8). The ribose protons gave the expected resonance pattern with the anomeric proton appearing as a doublet at δ 6.01 (J = 5.7 Hz). The ^{13}C NMR spectrum of **2** showed 13 carbons with appropriate chemical shifts. The spectral data also suggest that the enaminal moiety in **2** is coplanar with the purine ring, and the marked downfield shift of the N–H is due largely to the diamagnetic anisotropic deshielding by the purine ring. An adduct similar to **2** was isolated (20%) as the single product from the reaction of methylmalondialdehyde (MMDA) and adenosine.

The second adduct (mp 149–151 °C, 11%) exhibited UV absorbances in H_2O at 327 (ϵ = 29 700), 260 (sh, ϵ = 13 960), and

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(12) Cf.: Moschel, R. C.; Leonard, N. J. *J. Org. Chem.* **1976**, *41*, 294.
(13) Reaction occurs at a pH range of 4.0–7.0. However, the optimum conditions for reaction are at pH 4.2, slightly below the pK_a of MDA.

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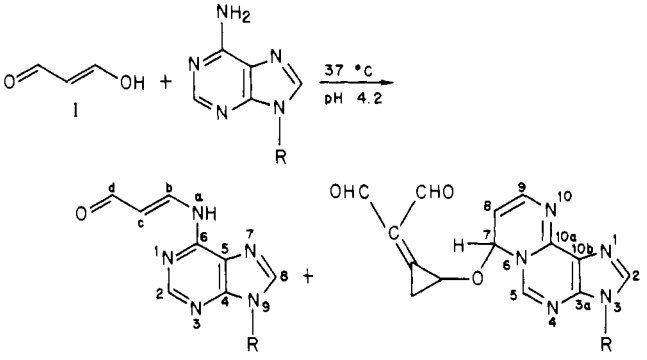
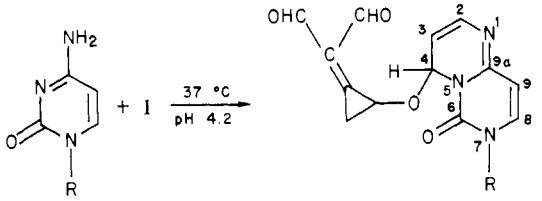


2, R = ribosyl
3, R = Et

4, R = ribosyl
5, R = Et

237 nm (ϵ = 27 060). The EI and FAB mass spectral data and elemental analysis suggested a molecular formula of $C_{19}H_{19}N_5O_7$. The delayed-decoupled high-field ^{13}C NMR spectrum (in Me_2SO-d_6) revealed the presence in the structure of the following proton substitution pattern: 2 CH_2, 12 CH, 5 C. An unusual feature in the ^{13}C spectrum was the presence of a CH at δ 16.2 and a CH_2 at δ 24.1. This information in conjunction with other ^{13}C and ^1H NMR data led to the conclusion that a methylidene cyclopropane moiety was present within the structure. Two aldehyde carbons were seen at δ 187.9 and 187.1, with the corresponding protons appearing as singlets at δ 9.38 and 9.21. The cyclopropyl CH appeared as a broadened quartet at δ 4.03 and the geminal protons at δ 2.08 and 1.97 (J_{gem} = 13.5 Hz). The ^{13}C and ^1H NMR data were also consistent with the formation of a new six-membered ring with carbon resonances at δ 77.2, 142.9, and 162.4 and corresponding proton resonances at δ 7.72 (brs), 7.63 (brd, J = 6.8 Hz), and 9.21 (brd, J = 6.8 Hz). The purine and ribose components were intact and gave expected ^{13}C and ^1H peaks. The spectral data were completely consistent with **4**, a 3:1 adduct of MDA and adenosine.

Modified bases identical with those present in **2** and **4** were formed in the reaction of 9-ethyladenine[14] with MDA. When cytidine and 1-methylcytosine[15] were treated with MDA, adducts **6** and **7** were isolated as the sole products.



6, R = ribosyl
7, R = Me

A plausible mechanism for the formation of the intriguing 3:1 adducts is shown in Scheme I for the adenine case. The mechanism implies the intermediacy of the enaminal **2** (or **3**). Thus, cyclization of this enaminal gives a tricyclic base **8**. Reaction of **8** with another molecule of MDA followed by elimination of water results in the formation of the ether **9**. Intermediate **9** can be attacked further by a molecule of MDA to give **10**, which can undergo cyclization and 1,2-hydrogen shifts to give the observed products **4** (and **5**). Although in the formation of the 3:1 adducts two new chiral centers are introduced, the relative stereochemistry of the resulting diastereoisomeric structures is not readily discernible from the high-field NMR data.

We conclude that MDA is capable of modifying both adenine and cytosine bases at the amino group. Subsequent cyclization of these primary products followed by further reaction with MDA results in the formation of hypermodified bases with methylene cyclopropane rings. The alteration of adenine and cytosine by MDA has not been reported previously. The formation of cyclopropane rings in the degenerative chemistry of MDA is also novel. The toxic effects of MDA that involve nucleic acids could be mediated by the formation of such bicyclic and tricyclic bases or interstrand and intrastrand crosslinking involving enaminal structures.

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Supplementary Material Available: NMR (^1H and ^{13}C), UV, and mass spectral data for all adducts (6 pages). Ordering information is given on any current masthead page.

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Preparation of Thiolate-Bridged Dimolybdenum Complexes from Mo-Mo Quadruple Bonds by Both Conventional and Unconventional Reactions

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Transition-metal chemistry with thiolate ligands, SR or SAr, is an important field, with special pertinence to some biochemical problems.[1] It is not always an easy field for the preparative chemist since thiols and thiolate anions are capable of a variety of reactions with metal atoms. We wish to report here some new synthetic chemistry together with structural characterization of representative products. Our synthetic reactions are novel in several ways, but generally in that they employ oxidative addition to quadruple M-M bonds. Other examples of oxidative addition to metal-metal quadruple bonds have appeared in the literature. Compounds containing Mo-Mo,[2,3] W-W,[4] Re-Re,[5] and Mo-W[6] cores have been shown to oxidatively add acids (HCl, HBr) and/or halogens. In most cases, extensive ligand rearrangement occurs with concomitant reduction of bond order.

We have found that compounds of the general class $Mo_2X_4L_4$ react with alkyl and aryl disulfides, RSSR, to yield $Mo_2X_4(\mu\text{-}SR)_2L_4$ species. The first such product was serendipitously discovered by the reaction of $K_4Mo_2Cl_8$[7] and 3,6-dithiaoctane (dto) in methanol. Initially, it appeared as if no reaction occurred, but after several weeks large green crystals of $Mo_2Cl_4(\mu\text{-}SEt)_2(dto)_2$, **1**, formed in 12% yield. The reaction is presumably the very novel one shown in eq 1, whereby EtS and ethylene are formed from

$$[Mo_2Cl_8]^{4-} + 3EtSCH_2CH_2SEt \xrightarrow{dto} [MoCl_2(dto)]_2(\mu\text{-}SEt)_2 + C_2H_4 \quad (1)$$

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