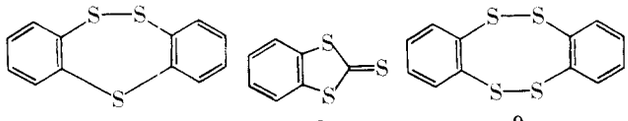
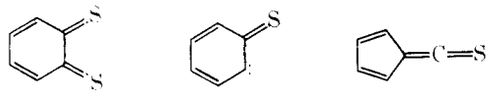
to effect such reductions using a variety of reagents (e.g., dithionite, silanes, thiols, phosphines, and phosphites) were unsuccessful, affording only ill-defined products.

The mass spectrum of sulfoxide **5** shows no molecular ion (*m/e* 396), but the appearance of a strong M − 16 peak (*m/e* 380) led us to investigate the pyrolysis of **5**. When **5** was heated to 300 °C under 0.01-mm pressure, three distinct zones of sublimate (A, B, and C) were collected. Chromatography of the yellow zone A on silica afforded colorless needles of trisulfide **7** (10%) [mp 149–153 °C;[5] *m/e* 248 (M^+, 17%), 216 (M − 32, 100%) and 184 (M − 64, 87%)]; a minor constituent of zone A (5%) was benzo-1,3-dithiole-2-thione (**8**), mp 165–167 °C, identical with an authentic sample. Silica chromatography of the orange zone B gave the known tetrasulfide **9** (14%) [mp 215–230 °C (lit.[6] mp 215–230 °C); *m/e* 280 (M^+, 100%)]. Products **7**, **8**, and **9** may all be considered to be derived from dithio-*o*-benzoquinone (**10**), which corresponds to the base peak (*m/e* 140) in the mass spectrum of **5**, and from the partially desulfurized intermediates **11** and **12** which can form from **10**.



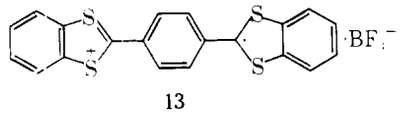
7 8 9



10 11 12

The red zone C consisted of almost pure quinodimethane **4** (38%). Recrystallization without decomposition could be achieved only from a large volume of carbon disulfide under argon, giving small crimson plates: mp 280 °C dec; *m/e* 380 (100%); IR (KBr) 3003 (w), 1527 (m), 1443 (s), 1427 (m), 1307 (m), 1285 (m), 1121 (m), 966 (m), 793 (s), 735 (s) cm^{-1}; visible λ_{max} (CS_2) (log ϵ) 478 (4.81), 503 nm (4.96). Anal. Calcd for $C_{20}H_{12}S_4$: C, 63.12; H, 3.18; S, 33.70. Found: C, 63.38; H, 2.90; S, 33.59. Proof that **4** has the unrearranged skeleton of **5** was easily obtained by treating **4** with HBF_4 in acetic anhydride, followed by crystallization from acetonitrile–HBF_4 (air present) to give an almost quantitative yield of fluoborate **6**.

Attempts to obtain a pure crystalline TCNQ complex of **4** have not yet succeeded, due to a combination of the great insolubility of **4** in organic solvents and by its ready decomposition in dilute solution in all solvents except carbon disulfide. Differential pulse polarography measurements of **6** in acetonitrile showed two reductions at $\epsilon_{1/2}{}^1 = 0.330$ and $\epsilon_{1/2}{}^2 = +0.057$ V, corresponding to the monothiolium radical cation **13** and the neutral compound **4**. As evidenced by the irre-



13

versibility for polarographic reduction, both **13** and **4** appear highly unstable with respect to **6**. Corresponding polarographic oxidation measurements of **4** were severely hampered by the presence of oxygen even though common precautionary procedures were followed. A single, irreversible oxidation was observed for **3** at approximately −0.142 V.

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Deamination of 1-Methylcytosine by the Carcinogen *N*-Acetoxy-4-acetamidostilbene: Implications for Hydrocarbon Carcinogenesis[1]

Summary: Reaction of the carcinogen *N*-acetoxy-4-acetamidostilbene with 1-methylcytosine in water and acetone results in a uracil derivative, apparently 1-(4-acetamidophenyl)-1-[3-(1-methyluracilyl)]-2-hydroxy-2-phenylethane.

Sir: Upon solvolysis in water and acetone, the potent local carcinogen *N*-acetoxy-4-acetamidostilbene (*N,O*-diacetyl-*N*-(4-stilbenyl)hydroxylamine, **1**) yields α,β-dihydroxy-4-acetamidobibenzyl, while in aqueous methanol dimethoxyacetamidobibenzyl and hydroxymethoxyacetamidobibenzyl are formed.[2] Comparable products were expected in the reactions of this compound with nucleosides. In the case of 1-methylcytosine and cytidine, it appears that initial alkylation of N-3 in the pyrimidine ring is followed by neighboring group attack on the adjacent exocyclic amino group (N^4) to yield a uracil derivative (Scheme I). This appears to be the first demonstration of alteration of the CNO content of a nucleic acid base by an alkylating agent, and presents the possibility of induction of base pair transitions in DNA.

1-Methylcytosine (1 g) in water (50 mL) was treated with 1 N H_2SO_4 to reduce the pH to 7.3. **1** (300 mg) in 33 mL of acetone was added and the mixture incubated at 37 °C overnight. Acetone was evaporated under reduced pressure, the remaining mixture was extracted with four 50-mL portions of ethyl acetate, and the combined extracts were dried over sodium sulfate and evaporated. The residue was taken up in a minimal amount of 95% ethanol and applied to a dry column of silica gel (1 × 15 cm). Dihydroxyacetamidobibenzyl was eluted with CH_2Cl_2, and then adduct and some unreacted 1-methylcytosine were eluted with methanol. The residue from the methanol eluate was then applied to a 20 × 20 cm silica thin-layer plate, which was developed four times with ethyl acetate. Some residual dihydroxyacetamidobibenzyl ran close to the front, and the next major band was eluted with large volumes of methanol and evaporated and the isolated solid (31 mg) redissolved in methanol and precipitated with ether. After centrifugation and washing with ether, the product (**2**) was homogeneous on silica gel TLC: mp 252–253 °C (corr); UV absorption max at 253 nm (95% ethanol, log ϵ 4.16). Anal. Calcd for $C_{21}H_{21}N_3O_4 \cdot CH_3OH$: C, 64.23; H, 6.08; N, 10.21. Found: C, 64.30; H, 5.62; N, 10.23. Acetylation with

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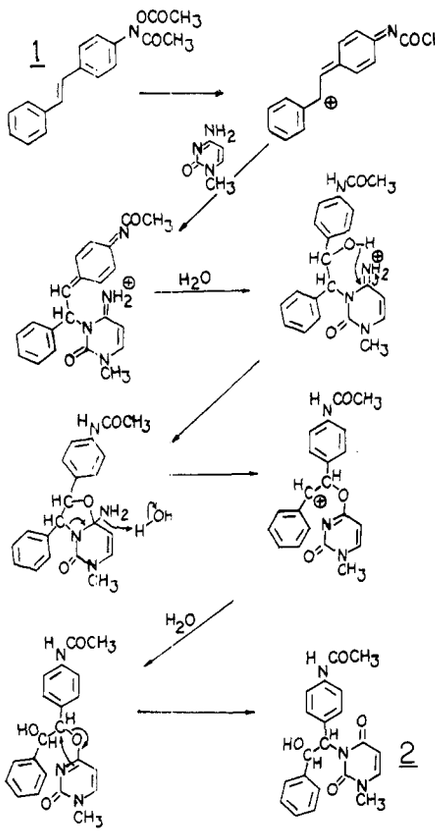
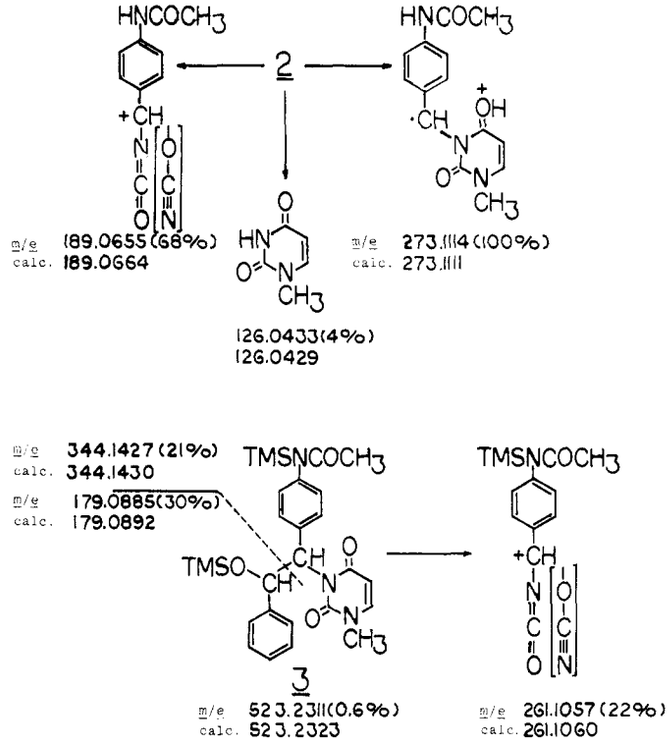
Scheme I



Scheme II



acetic anhydride and pyridine at room temperature gave a product of mp 258–260 °C (ethyl acetate/petroleum ether), with strong IR absorption at 1750, 1708, 1690, 1652, and 1230 cm^{-1}. A 270-MHz NMR spectrum in dimethyl-d_6 sulfoxide (70 °C) revealed only three CH_3 groups in the acetate at 1.86, 1.97, and 3.29 ppm (Me_2SO-d_6 reference at 2.49 ppm). Doublets corresponding to single protons were found at 5.69, 6.40, 6.98, and 7.63 ppm. In methanol, the doublets at 5.69 and 6.40 ppm appeared to have been replaced by a broad singlet at 4.65 ppm, while the remaining downfield peaks were all located between 7.08 and 7.69 ppm. 6-H of the pyrimidine ring thus seems to be little shifted from its position in cytidine or uridine,[3] while 5-H, normally found near 5.8 ppm, is now buried among the aromatic protons of the bibenzyl group.

Identification of the base in **2** as uracil was made by rigorous establishment of molecular weight and elemental composition by mass spectrometry[4] of **2** and its bis(trimethylsilyl) derivative **3**, using field desorption (**2**, M^+ 379, MNa^+ 402), field ionization (**3**, M^+ 523), and electron impact (**3**, M^+ 523) methods. Further data showing uracil and placement of substituents on the ethylene carbons were provided by exact mass measurements on fragment ions from **2**[5] and **3** (Scheme II). In particular, the two major fragments (masses 344 and 179) of the Me_3Si derivative of **2** (shown as structure **3** in Scheme II) can only be obtained by attachment of methyluracil to the "toluidine" carbon and of –OH to the benzyl carbon. The alternative substitution would yield different fragments which were not found.

The mass spectra do not permit unambiguous assignment of the position of attachment at the pyrimidine ring, as shown by the structurally plausible alternate forms of *m/e* 261 and 189 (Scheme II). The apparent change in chemical shift (NMR) of 5-H in the pyrimidine from near 6 ppm to greater than 7 ppm suggests an alteration of O^4 rather than at N-3. On the other hand, both 5-H and 6-H were found to be shifted in O^4-ethyluridine,[6] the latter to 8.32 ppm. Thus, the NMR data cannot be meaningfully compared with earlier results.

Kuśmierek and Singer[6] noted that O^4-methyluridine is 90% converted to uridine in 0.01 N HCl after 21 h at room temperature, and that O^4-ethyluridine is converted to cytidine after 2 days in methanolic ammonia at 37 °C. **2** shows no change in its UV spectrum between pH 12 and 2, and is stable toward both mild acid and methanolic ammonia. This chemical evidence thus speaks for alkylation of N-3, and is supported by several C=O peaks in the IR spectrum of the acetate of **2** (acetate, amide, O^2 and O^4 of uracil).

Treatment of cytidine with **1** under the same conditions, or with *trans*-4-acetamidostilbene α,β-epoxide,[7] results in a major adduct with the same UV properties as **2**. RNA was prepared with ^{14}C in cytosine, treated with **1** in acetone and water, isolated, degraded enzymatically, and the enzyme digest chromatographed on Sephadex LH-20. About one-third of the carcinogen-modified cytidine appeared at the same retention volume as the major nucleoside adduct. Details of the cytidine and RNA studies will be published in the near future, together with studies on other nucleosides and polynucleotides.

While conjectural, the mechanism in Scheme I has certain features which make it consistent with previous observations of reactions of both **1** and cytosine derivatives. A referee has suggested that the deamination could occur simply by hydrolysis of the intermediate immonium ion. This suggests, however, that any alkylation of N-3 of a 1-alkylcytosine would largely lead to a uridine product. However, this has never been observed with monofunctional alkylating agents, such as benzyl bromide or dimethyl sulfate. Thus, it seems essential that a neighboring group in the alkylating agent be involved. One could also well ask why the initial site of reaction between cytosine and nitrenium ion is proposed to be the benzyl carbon, rather than the toluidine carbon of the nitrenium ion. Reaction of **1** with methionine at pH 7.5 leads to β-methylmercapto-4-acetamidostilbene as the major product (76% of all methionine adducts),[8] while HMO calculations for the *N*-acetyl-*N*-(4-stilbenyl)nitrenium ion show that the molecular orbital coefficient for the β carbon is higher tha that for the α carbon in the two lowest unoccupied orbitals, and that

there is a higher positive charge on the β carbon.[9] These data suggest that the reactions with nucleosides should also begin at the β carbon. An alternative mechanism would have initial attack by water, with the nucleoside attacking the intermediate quinone imide methide. Further pursuit of this mechanism, however, leads to structures which appear less likely than those proposed in Scheme I.

It is clear that the mechanism shown in Scheme I, or one of the alternatives suggested above, could apply equally well to any reaction which would result in an initial adduct bearing a hydroxyl group vicinal to N-3. Such a reaction could well take place between cytidine or a nucleic acid and a hydrocarbon epoxide. Reaction of benzo[*a*]pyrene-7,8-dihydrodiol 9,10-oxide with poly(C) in vitro[10] and with cytosine in RNA in tissue explants[11] has already been demonstrated. However, it has not been established that the products are actually cytosine compounds. In light of our finding, it appears worthwhile to undertake structural studies on the putative benzpyrene–cytidine adducts.

References and Notes

(1) This is part 6 of the series "*N*-Arylnitrenium Ions in Aromatic Amine Carcinogenesis". This work was supported by Grants CA 18632 (J. D. S.) and CA 18024 (J. A. M.) from the National Cancer Institute. We thank N. C. Yang, University of Chicago, for obtaining NMR spectra.
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Meldrum's Acid in Organic Synthesis. 2. A General and Versatile Synthesis of β-Keto Esters

Summary: On acylation with various acyl chlorides Meldrum's acid, 2,2-dimethyl-1,3-dioxane-4,6-dione, gave the corresponding acyl Meldrum's acids, which readily underwent alcholysis with methanol, ethanol, *tert*-butyl alcohol, benzyl alcohol, and trichloroethanol to give various β-keto esters; the acyl Meldrum's acids can be regarded as a synthetic equivalent of mixed diketenes.

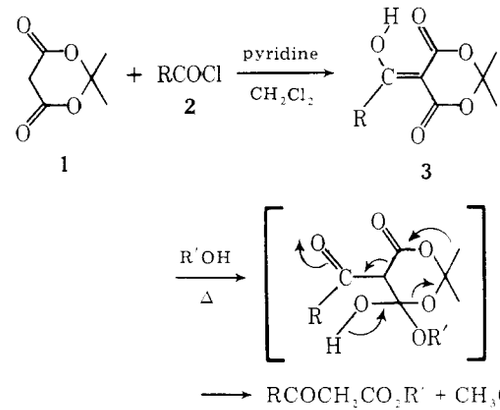
Sir: Since the first example of the Claisen condensation was discovered more than a century ago, β-keto esters have been one of the most important intermediates in organic synthesis.[1] However, it is still required to establish a general and practical method for the preparation of arbitrary β-keto esters of the type $RCOCH_2CO_2R'$.[2] Among the many methods for synthesizing β-keto esters of the type $RCOCH_2CO_2C_2H_5$, two classical syntheses via acetoacetic esters[4] and via mixed malonic esters[5] rather than some modern methods[6] are practically useful, though not always satisfactory in yield, and none is capable of modifying the ester group. We wish to report here a general and versatile method for the synthesis of β-keto esters based on the noteworthy reactivity of Meldrum's acid (**1**), 2,2-dimethyl-1,3-dioxane-4,6-dione,[7] as outlined in Scheme I.

Table I. Yields of Various β-Keto Esters (4–7)[a]

Starting chloride	Yield, % 4	5	6	7
2a	82	74	74	86
2b	79	70	77	75
2c	75	74	80	78
2d	84	80	80	82
2e	86	78	71	75
2f	90	77	73	74
2g	92	85	79	80
2h	85	82	60	74
2i	79	84	74	82
2j	81	78	78	73
2k	69	73	73	71

[a] See footnote 19.

Scheme I



4, R′ = CH_3
5, R′ = CH_2CH_3
6, R′ = $CH_2C_6H_5$
7, R′ = $C(CH_3)_3$

a, R = CH_2CH_3
b, R = $(CH_2)_2CH_3$
c, R = $(CH_2)_3CH_3$
d, R = $(CH_2)_4CH_3$
e, R = $(CH_2)_5CH_3$
f, R = $(CH_2)_6CH_3$
g, R = $(CH_2)_7CH_3$
h, R = $(CH_2)_7CH{=}CH_2$
i, R = $CH_2C_6H_5$
j, R = $(CH_2)_2CO_2CH_3$
k, R = $(CH_2)_2OCH_2CH_3$

In marked contrast with acetoacetic esters (pK_a 10.7)[8] and acyclic malonic esters (pK_a 13.7),[8] **1** readily reacts with electrophiles such as aldehydes even in the absence of a strong base[9] because of its great acidity (pK_a 4.97).[10] Therefore, acylation of **1** is also expected to occur under similar conditions. When a dichloromethane solution of **1** was treated with 1.1 equiv of propionyl chloride (**2a**) in the presence of pyridine (2 equiv) at 0 °C for 1 h and then at room temperature for 1 h under nitrogen, an acyl Meldrum's acid (**3a**) [mp 55 °C; δ (CCl_4) 1.26 (3 H, t, J = 7 Hz), 1.70 (6 H, s), 3.08 (2 H, q, J = 7 Hz), 15.0 (1 H, s)] was isolated in almost quantitative yield.[11] Similarly, **1** was acylated with various chlorides (**2b–k**) to give the corresponding acyl Meldrum's acids (**3b–k**) almost quantitatively.[12]

Although ethanolysis of **1** and its monoalkyl derivatives

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