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Photochemical Rearrangement of 8- methyl Spiro [2.5] oct-7-en-4-one to 4-methyl Spiro [2.5] oct-4-en-6-one

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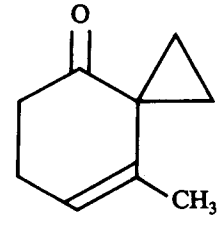
Abstract

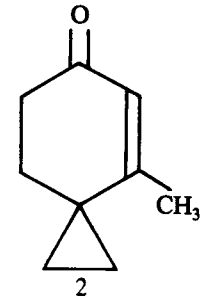
Irradiation of 8-methyl spiro [2.5] oct-7-en-4-one through its singlet excited state resulted in the formation of 4-methyl spiro [2.5] oct-4-en -6-one. We have used the cyclopropyl moiety in the molecule as a probe to study the operating mechanism in the photochemistry of β, γ-unsaturated compounds. The results showed that this photoisomerization probably occurs through a concerted process.

A variety of photochemical reactions have been observed for both the singlet and triplet excited states of β, γ-unsaturated ketones. The most common reaction which happens through the singlet excited state is a [1, 3] acyl shift, and that of the triplet is a [1,2] acyl shift or oxa-di-π-methane rearrangement[2]. Both concerted processes and stepwise mechanism involving either intimate radical pairs[4] or biradicals[5] have been suggested for these reactions. We thought that photolysis of the title compound (compound 1) would be mechanistically interesting. We were led to study this particular compound in order to determine what happens to cyclopropyl moiety during the course of reaction following excitation. If the reaction goes concerted, the cyclopropyl part should remain unchanged. Otherwise,and in a stepwise transformation, we expect to observe a skeletal change in the compound. This would arise from the formation of a cyclopropyl biradical intermediate following α-cleavage and the subsequent opening of an unstable cyclopropyl radical to a more stable allyl radical[6].

Compound 1 was prepared according to the procedure described by Newman and his co-workers[7]. A solution of 0.015 M of 1 in benzene was irradiated under nitrogen atmosphere for six hours in a pyrex tube using a Hanovia medium pressure mercury lamp with a quartz filter. After removal of the solvent, the volatiles were distilled at 150°C and 10 mmHg (total yield, 85%). Thin layer chromatography showed it to be mainly a mixture of starting material and a new compound. Gas chromatography separation of this mixture using 5% Apiozol L on chromosorb P as adsorbant gave compound 1 and the photochemical product in a ratio of approximately 1:1. Based on the spectral data, 4-methyl spiro [2.5] oct-4-en-6-one (2) was assigned as the structure of the photoproduct as indicated below[8].



1

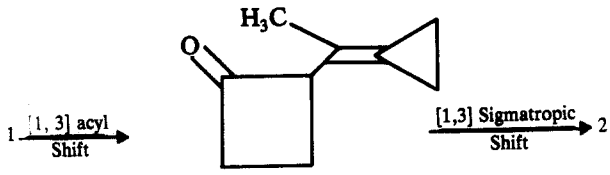


2

IR spectrum showed a strong absorption band at 1690 cm^{-1} characteristic of the six membered ring α, β-unsaturated Ketones.[9] H-NMR (δ, $CDCl_3$) showed peaks at 5.5. - 5.7 (m, 1H), 2.2 - 2.35 (m,2H), 1.35 - 1.5 (d.j = 2Hz, 3H, allylic coupling), 1.1 -1.3 (m, 2H), 1.0. - 1.2 (t,j = 4Hz, 2H), and 0.5- 0.7 (t,j = 4Hz, 2H).

Comparison of the NMR spectrum of compound 2 with **1** shows that four methylene protons in **1** appear together at 2.3 - 2.35 ppm, while these two sets are separated by approximately 1.1 ppm in 2. Because of their proximity to carbonyl group, the two adjacent protons show up at 2.2 - 2. 35 ppm while the other two appear at normal location, ie, 1.1 - 1.3 ppm[10].

These results suggest that the rearrangement has occured by two consecutive concerted symmetry allowed [1,3] acyl shift and [1,3] sigmatropic migration processes as shown below:



The second [1,3] sigmatropic shift would have probably occured as a result of the existing strain in the molecule due to the presence of disubstituted methylenecyclopropane moiety. Photochemical fragmentation of methylenecyclopropane derivatives have been reported before[11]. It seems likely to believe that, in this case, its occurence was slower in competition with the [1,3] sigmatropic shift.

Therefore, we conclude that the [1,3] acyl shift was done in a concerted process although the stepwise intimate radical pair mechanism can not be ruled out.[12]

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The Synthesis of 1,3-bis (2-Aminoethoxymethyl) Uracil as a Novel Dealkylating Agent

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Abstract

The synthesis of the title compound is described. This compound was found to be able to dealkylate the N-7-methyl-guanosine at room temperature.

Introduction

Blistering agents used in *World War I* included sulfur mustard (H), which caused about 25% of the casualties in the American Expeditionary Force. A new distilled mustard (HD) and two kinds of nitrogen mustards (HN-1 and HN-3) are available for military use [1] [2].

Alkylating agents form covalent derivatives with DNA. Sulfur and nitrogen-mustards are bifunctional alkylating agents and therefore react with N-7 guanine residues to form cross-links between adjacent segments of DNA. The covalent modification of DNA prevents both replication and transcription. This could account for the pronounced toxicity of mustards.

Mustard gas, bis (ß-chloroethyl) sulfide, was found to be of some value in the localized lesions of skin cancer. However, the high toxicity, the low solubility in water and its vesicant properties prevented its clinical application. Nitrogen analogues of mustard gas have been found to be easier to handle because the hydrochloride or other salts which were stable solids with a high water-solubility could be formed.

It was discovered that nitrogen mustard, mechlorethamine, was an effective antineoplastic agent, since then, a larger number of related compounds and other alkylating agents have been synthesized and evaluated. The antineoplastic as well as the carcinogenicity of the nitrogen mustards has generally been considered to be a function of their property of cyclizing in water to the highly reactive ethyleneimonium ions which react with compounds containing replaceable hydrogens, such as the free amino groups and other groups of proteins, of nucleic acids and others. Although, the reaction of mustards with proteins and other nucleophilic groups in the body produces side effects which can even cause death, the worse side effect of mustards; i.e., cancer, is caused by their reaction with the nucleic acid bases of the genes.

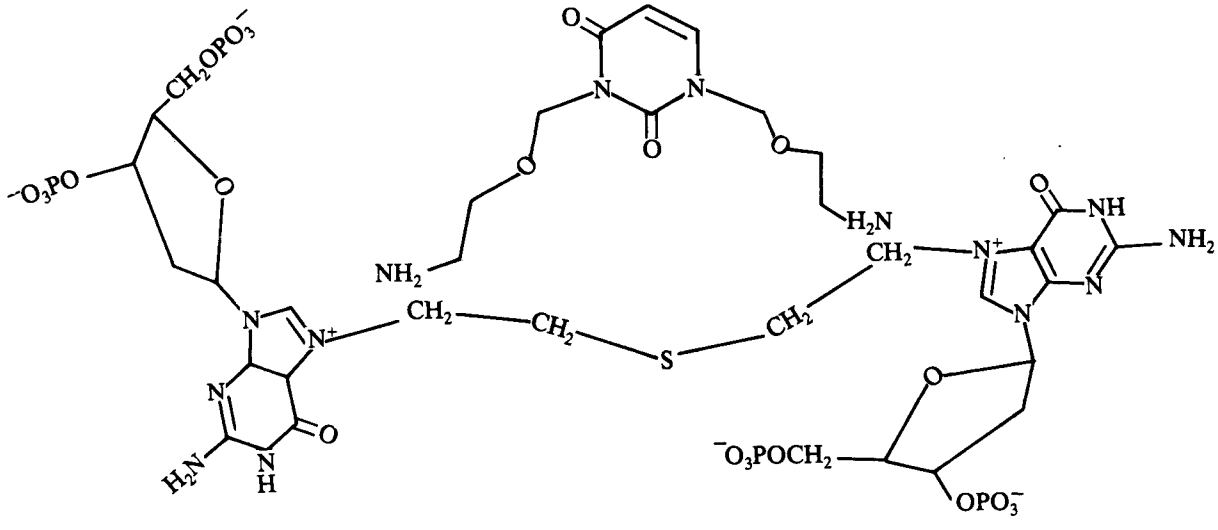


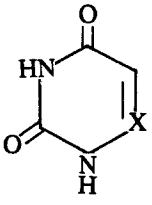
Fig 1

In this paper we wish to describe the synthesis of compound **3j**, which is able to dealkylate the N-7 alkyl derivative of guanosine. On the other hand, model studies with CPK-atomic models indicate that the distance between the CH_2-functions in diguanin-7-yl derivatives joined by the-CH_2 $CH_2SCH_2CH_2$-bridge is such that they might simultaneously undergo nucleophilic attack by the NH_2 functions of compound **3j** (Fig.1). This could possibly result in preparing an excellent antidote for treatment of mustard gas poisoned persons.

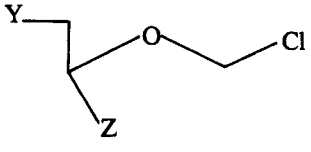
Results and Discussion. Compounds **3a-b**, **3e-h**, **3k-l**, **4a-b** and **4d** were prepared (Scheme 1 & 2) by condensing the persilylated base **1a-b** with the corresponding chloromethyl ethers **2a-d** [3]. t-n-Butylammonium iodide (Bu_4NI) was used as catalyst in the coupling reaction.

The treatment of **3b** with Na SH in refluxing MeOH did not afford **3c** but instead gave **3d** in high yield (reaction with acetyl chloride/NEt_3 resulted in recovery of **3d**). Similarly **4b** in the presence of Na SH afforded **4c**. At this point, it was decided to prepare **3j**. Compound **3h** served as the starting material. Thus, the bromo-derivative **3h** was reacted with NaN_3 in DMF to afford, after 24 h, the azido compound **3i** quantitatively. Reduction of the azide functions with NaSH/MeOH gave the desired amino compound **3j** in about 30% yield. Compound **3j** was found to be able to dealkylate the N-7-methylguanosine to guanosine in quantitative yield.

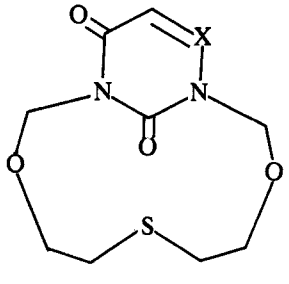
Removal of the benzoyl group from **3k-l** and **4d** to give the respective unprotected acyclonucleoside analogues **3m-n** and **4e** proceeded smoothly (MeOH/NH_3 [3]) in high yields. The properties of the prepared compounds are collected in Table 1.



1a X = C
b X = N

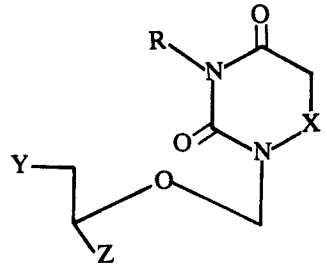


2a Y = Cl, Z = H
b Y = F, Z = H
c Y = Br, Z = H
d Y = OBz, Z = CH_2 Cl



3d X = C
4c X = N

Scheme 1



3a X = C, R = Z = H, Y = Cl
b X = C, R = $CH_2O(CH_2)_2$ Cl, Y = Cl, Z = H
c X = C, R = $CH_2O(CH_2)_2$ SH, Y = SH, Z = H
e X = C, R = Z = H, Y = F
f X = C, R = $CH_2O(CH_2)_2$ F, Y = F, Z = H
g X = C, R = Z = H, Y = Br
h X = C, R = $CH_2O(CH_2)_2$ Br, Y = Br, Z = H
i X = C, R = $CH_2O(CH_2)_2N_3$, Y = N_3, Z = H
j X = C, R = $CH_2O(CH_2)_2NH_2$, Y = NH_2, Z = H
k X = C, R = H, Y = OBZ, Z = CH_2Cl
l X = C, R = $CH_2OCH(CH_2OBZ)$ CH_2Cl, Y = OBZ, Z = CH_2Cl
m X = C, R = H, Y = OH, Z = CH_2Cl
n X = C, R = $CH_2OCH(CH_2OH)CH_2Cl$, Y = OH, Z = CH_2Cl

4a X = N, R = $CH_2O(CH_2)_2$ F, Y = F, Z = H
b X = N, R = $CH_2O(CH_2)_2$ Cl, Y = Cl, Z = H
d X = N, R = H, Y = OBZ, Z = CH_2Cl
e X = N, R = H, Y = OH, Z = CH_2Cl

Scheme 2

Compound	MP. [°C]	R_f [AcOET/ether] (1:1)	UV. [MeOH] (nm)
3a	foam	0.61	257
b	oil	0.80	260
d	foam	0.36	260.5
e	oil	0.68	257
f	oil	0.81	260
g	100	0.33	257
h	oil	0.62	260
i	oil	0.55	260
j	foam	0.06	260
k	oil	0.56	257
l	oil	0.78	260
m	162	0.18	257
n	156	0.45	260
4a	oil	0.88	261
b	oil	0.82	261
c	foam	0.32	261
d	oil	0.50	259
e	105	0.15	259

a) ^1H - NMR. and IR. Spectra of all compounds are consistent with the proposed structures.

Table 1. Physical Properties of Acyclonucleosides[a]

Experimental Section

General Remarks: see ref. [3].

General Procedure for the Preparation of Acyclonucleosides.

All compounds, **3a-b** , **3e-h**, **3k-l**, **4a-b**, and **4d**, were prepared in high yields by an identical manner. Their ^{1}H-NMR. and IR. spectra were similar except for variations due to substituents. The following is a representative procedure.

Uracil (20 mmol) and $(NH_4)_2SO_4$ (0.5 g) were added to hexamethyldisilazane (HMDS, 70 ml). The mixture was heated at reflux under the exclusion of moisture until the solution became clear (2h). The solvent was removed at reduced pressure and the residue was dried under vacuum. The residue was dissolved in CH_2Cl_2 (100 ml) and Bu_4NI (0.10 mmol) was added. The mixture was heated below reflux temperature and chloromethyl ether **2a** (20 mmol) was added. The mixture was heated at reflux for 3 h. The solution was cooled at 25°C and diluted with H_20 (20 ml) and MeOH (50 ml). After stirring for 5 min. the solvents were removed at reduced pressure and the residue was dissolved in CH_2Cl_2 (100ml). The solution was washed with H_2O, and dried ($MgSO_4$). The solvent was removed at reduced pressure and the product obtained by chromatography over silica gel. Compounds **3a**(80%) and **3b** (15%) were obtained using CCl_4/CH_2Cl_2 (1:1). It should be noted that when chloromethyl ether **2a** was used in (60 mmol), the products ratio was reverse (**3a** (20%) and **3b** (78%)). Properties are collected in Table 1. **3a**: ^{1}H-NMR. δ 3.65 (m, 2H, CH_2Cl), 3.86 (m, 2H, CH_2O), 5.22 (s, 2H, OCH_2N), 5. 80 (d, 1H, H-C (5), J=8 Hz), 7. 31 (d, 1H, H-C(6) J=8 Hz), 10.3 (br. 1H, NH). 3b: ^{1}H-NMR. δ 3.60 (m, 4H, $2CH_2Cl$), 3.89 (m, 4H, $2CH_2O$), 5.21, 5.49 (2s, 4H,2 OCH_2N), 5.82 (d, 1H, H-C (5) J =8 Hz), 7.35 (d, 1H, H-C (6) J =8 Hz). Representative ^{1}H-NMR. Spectra of 6-azauracil derivatives. **4b**: 3. 70 (m, 4H, $2CH_2Cl$), 4.00 (m, 4H, $2CH_2O$), 5.41, 5.49 (2s, 4H, $2OCH_2N$), 7.50 (s, 1H, H-C (5)).

*Preparation of Compounds **3d** and **4c**.* Both compounds were obtained by an identical procedure in about 95% yield. Their spectroscopic data were similar except for variations due to the chemical structure. Representative procedure: Compound **3b** (1 mmol) was dissolved in MeOH. NaSH (2 mmol) was added and the mixture was refluxed for 12 h. Filteration and evaporation gave **3d** (95%). ^{1}H-NMR. ($CDCl_3$) δ 2.70 (br. t, 4H, CH_2SCH_2, J_1 =6 Hz, J_2 = 12 Hz), 3. 79 (br.t, 4H, $2CH_2O$, J_1 =6 Hz, J_2 = 11 Hz), 5.20, 5.41 (2s, 4H, $2OCH_2N$), 5.84 (d, 1H, H-C (5), J =8 Hz), 7.46 (d, 1H, H-C (6), J=8 Hz) MS: 258 (M^+, sulfur cluster). **4c** was prepared from **4b** in a similar manner; ^{1}H-NMR ($CDCl_3$) δ 2.67 (br.t, 4H, CH_2SCH_2, J_1 =6 Hz, J_2 = 12 Hz), 3.65 (br.t, 4H, $2CH_2O$, J_1 = 6 Hz), 5.28, 5.38 (2s, 4H, $2OCH_2N$), 7.44 (s, 1H, H-C (5)). MS: 260 (M^+, sulfur cluster).

*Preparation of Compounds **3i** and **3j**.* Compound **3h** (1 mmol) and NaN_3 (5 mmol) were dissolved in DMF. The mixture was stirred at 25°for 24 h. Ethyl acetate(50 ml)was added and the solution was washed with water (5× 50 ml). The organic layer was dried ($MgSO_4$) and evaporated to afford pure **3i** in quantitative yield. ^{1}H-NMR. ($CDCl_3$) δ 3.40 (br.t, 4H, $2CH_2N_3$, J_1 = 5 Hz, J_2 = 10 Hz), 3. 81 (m, 4H, 2 CH_2O), 5.22, 5.47 (2s, 4H, $2OCH_2N$), 5.82 (d, 1H, H-C (5), J =8 Hz), 7.36 (d, 1H, H-C (6), J=8 Hz). IR. (neat): 2090 (N_3), 1715, 1660 cm^{-1}. MS:310 (M^+).

Azido compound **3i** was dissolved in MeOH (1 mmol/3 ml). NaSH (5 mmol) was added and stirred. After 24 h, it was filtered and the solution was evaporated to dryness. The residue was washed with $CHCl_3$ to afford **3j** in about 30% yield. ^{1}H-NMR (DMSO-d6, D_2O) δ 2.71 (m, 4H, $2CH_2ND_2$), 3.65 (m, 4H, $2CH_2O$), 5.21, 5.33 (2s, 4H, 2 OCH_2N), 5.73 (d,1H, H-C(5), J=8 Hz), 7.71 (d, 1H, H-C (6), J = 8 Hz). IR. (neat): 3100 - 3680 (NH_2), 1720, 1670, 1050 cm^{-1}.

*Preparation of Compounds **3M-N** and **4e**.* All compounds were prepared (— 95%) by an identical manner. Their ^{1}H-NMR. and IR. spectra were similar except for variations due to substituents. Representative procedure: Compound **4d** (0.01 mol) was dissolved in MeOH (100 ml). NH_3gas was bubbled into the solution until saturation. After 35 h at 25°C, the solution was evaporated to dryness. Crystallization from ether/MeOH (9:1) gave **4e** (98%). ^{1}H-NMR (DMSO-d6) δ 3.50 - 3.95 (m,5H, CH_2OH and CH_2Cl) 4.21 (m, 1H, CHO), 5.41 (s, 2H, OCH_2N), 7.40 (s, 1H, H-C (5)), IR (NuJol): 3300 - 3600 (OH, NH), 1670, 1715, 1100 cm^{-1}.

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