

The Photochemical Synthesis of Novel Heterocyclic Compounds from *s*-Triazolo[4,3-*b*]pyridazine (II) (1)

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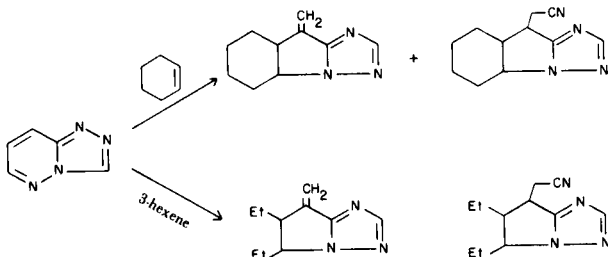
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s-Triazolo[4,3-*b*]pyridazine (I) photochemically reacted with dihydropyran; 2,3-dihydro-*p*-dioxin; 2,5-dihydrofuran; 2,5-dimethoxy-2,5-dihydrofuran; and 1,3-dioxep-5-ene to give a new series of substituted pyrrolo[1,2-*b*]-*s*-triazoles (II-IX). In most reactions, two or more products were formed. The following compounds have been prepared from I: 9-methylene-4a,5,6,7,8a,9-hexahydropyrano[2',3':4,5]pyrrolo[1,2-*b*]-*s*-triazole (IIa), the corresponding 9-cyanomethyl product (III), and 9-methylene-4a,7,8,8a-tetrahydro-6*H*,9*H*-pyrano[3',2':4,5]pyrrolo[1,2-*b*]-*s*-triazole (IIb) from dihydropyran; 9-methylene-4a,6,7,8a-tetrahydro-9*H*-*p*-dioxino[2',3':4,5]pyrrolo[1,2-*b*]-*s*-triazole (IV) from 2,3-dihydro-*p*-dioxin; 8-methylene-4a,5,7a,8-tetrahydro-7*H*-furo[3',4':4,5]pyrrolo[1,2-*b*]-*s*-triazole (V) and the corresponding 8-cyanomethyl product (VI) from 2,5-dihydrofuran; 8-cyanomethyl-5,7-dimethoxy-4a,5,7a,8-tetrahydro-7*H*-furo[3',4':4,5]pyrrolo[1,2-*b*]-*s*-triazole (VII) from 2,5-dimethoxy-2,5-dihydrofuran; and 10-methylene-4a,5,9a,10-tetrahydro-9*H*-[1,3]dioxepino[5',6':4,5]pyrrolo[1,2-*b*]-*s*-triazole (VIII) and the corresponding 10-cyanomethyl product (IX) from 1,3-dioxep-5-ene. The addition of several other compounds (1,2,3,6-tetrahydropyridine, 1-acetylimidazole, 3-sulfolene, 2,3-dihydro-*p*-dithiin, and vinylene carbonate) was attempted, but no reactions were observed.

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We have previously reported the unusual [3+2] photocycloaddition of a number of cyclic and open chain alkenes to *s*-triazolo[4,3-*b*]pyridazine (I) (3-6). The products of those reactions resulted from the addition of the alkene to the 1 and 8 positions of I with a concurrent opening of the pyridazine ring.



This reaction has been extended to include a number of ethylenic heterocycles. The following compounds have been prepared from I: 9-methylene-4a,5,6,7,8a,9-hexahydropyrano[2',3':4,5]pyrrolo[1,2-*b*]-*s*-triazole (IIa), the corresponding 9-cyanomethyl product (III), and 9-methylene-4a,7,8,8a-tetrahydro-6*H*,9*H*-pyrano[3',2':4,5]pyrrolo[1,2-*b*]-*s*-triazole (IIb) from dihydropyran; 9-

methylene-4a,6,7,8a-tetrahydro-9*H*-*p*-dioxino[2',3':4,5]pyrrolo[1,2-*b*]-*s*-triazole (IV) from 2,3-dihydro-*p*-dioxin; 8-methylene-4a,5,7a,8-tetrahydro-7*H*-furo[3',4':4,5]pyrrolo[1,2-*b*]-*s*-triazole (V) and the corresponding 8-cyanomethyl product (VI) from 2,5-dihydrofuran; 8-cyanomethyl-5,7-dimethoxy-4a,5,7a,8-tetrahydro-7*H*-furo[3',4':4,5]pyrrolo[1,2-*b*]-*s*-triazole (VII) from 2,5-dimethoxy-2,5-dihydrofuran; and 10-methylene-4a,5,9a,10-tetrahydro-9*H*-[1,3]dioxepino[5',6':4,5]pyrrolo[1,2-*b*]-*s*-triazole (VIII) and the corresponding 10-cyanomethyl product (IX) from 1,3-dioxep-5-ene.

Results and Discussion.

Compound I was irradiated with ultraviolet light in a solution of the appropriate ethylenic heterocycle in dichloromethane. After the starting material had reacted, the solvent was removed and the products were isolated on the vapor phase chromatograph (vpc). The products were subjected to analysis by ir, nmr, and high resolution mass spectrometry (ms).

The products (see Scheme I) had very distinctive nmr spectra. Compounds IIa, IIb, IV, V, and VIII (the methylene compounds) all exhibited nmr peaks at $8.03 \pm$

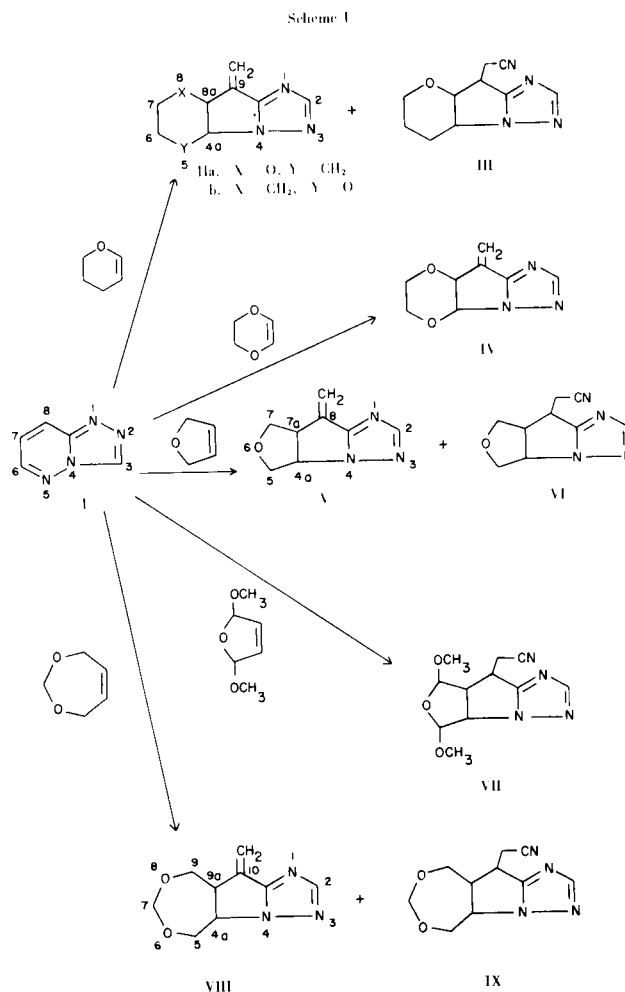
0.1 δ (H_2), 6.20 ± 0.2 and 5.50 ± 0.2 δ (methylene hydrogens), 5.9 ± 0.05 δ (H_{4a} α to ring oxygen), 5.0 ± 0.1 δ (H_{4a} β to ring oxygen), and 4.45 δ (H_{4a} removed from ring oxygen). The other hydrogen on the pyrrole ring [H_{7a} (V), H_{8a} (IIa, IIb, IV), etc.] exhibited peaks at 5.12 ± 0.03 δ (if α to ring oxygen), 4.15 ± 0.2 δ (if β to ring oxygen), and 3.15 δ (if removed from ring oxygen).

Compounds III, VI, VII, and IX (the cyanomethyl products) exhibited an ir band at 2250 ± 10 cm^{-1} indicative of the cyano group. The nmr spectra exhibited peaks at 8.03 ± 0.1 δ (H_2), 5.9 ± 0.05 δ (H_{4a} α to ring oxygen), 5.0 ± 0.1 δ (H_{4a} β to ring oxygen), 4.45 δ (H_{4a} removed from ring oxygen) and 2.92 ± 0.03 δ (CH_2CN). The other hydrogen on the pyrrole ring [H_{7a} (VI, VII), H_{8a} (III), etc.] exhibited peaks at 4.68 δ (if α to ring oxygen) and 3.59 ± 0.2 δ (if β to ring oxygen).

Product II proved to be a mixture of isomers in a ratio of 4:1. The nmr of the material isolated on the vpc exhibited an unsymmetrical doublet for the triazole hydrogen as well as two sets of methylene hydrogens. In assigning structures, it was noted that the α -shift of a CH group adjacent to an oxygen is 2δ and the β -shift negligible (7). Using the previously published values of 4.20 ± 0.2 δ (H_{4a}) and 3.0 ± 0.3 δ (H_{8a}) for the two hydrogens on the pyrrole ring as a reference (3-6), it can be shown that the major isomer is compound IIa. In compound IIa, we observe H_{4a} to have a small chemical shift and find a quartet at 4.45 δ , and for H_{8a} we find a doublet with a large shift to 5.15 δ . For compound IIb on the other hand, we find a peak with a large shift: 5.95 δ (H_{4a}) and a multiplet with a negligible shift: 3.15 δ (H_{8a}). These assignments were borne out with the synthesis of compound IV which exhibited a large chemical shift for both H_{4a} (now a doublet at 5.86 δ) and H_{8a} (a complex doublet at 5.10 δ).

Anet and Muchowski (8) have shown that in five-membered rings which cannot deviate appreciably from planarity, the J_{cis} of the ring protons is appreciably larger than the corresponding J_{trans} . We have previously reported this phenomenon in the photocycloadduct of 3-hexene to compound I (5,6). By using various types of models, it was observed that a *trans* addition, if geometrically allowed, would be highly strained in all but 1,3-dioxep-5-ene adducts. However, since the J values for the two hydrogens on the pyrrole ring are 5.5 ± 1.0 Hz for all compounds (II-IX), we have concluded all additions were *cis*.

A mechanism for this addition has been proposed (6), in which the initial reaction is addition to the nitrogen in position 1 giving the most stable diradical intermediate. This diradical would then close at position 8 with the concurrent homolytic cleavage of the N_4-N_5 bond to form a vinyl nitrene. Vinyl nitrenes are known to form cyano



compounds (9), hence our cyanomethyl products. A hydride transfer by the ring hydrogen followed by a loss of hydrogen cyanide would form the methylene products.

EXPERIMENTAL

All ir spectra were obtained on a Hilger and Watts H1200 Infragraph. The nmr spectra were obtained on a Varian EM-390 spectrometer in deuteriochloroform. Varian model 202B and 1700 vapor phase chromatographs were used in the isolation of all products. A 6' x 1/4" copper tube packed with 5% SE-30 on 60/100 mesh Chromasorb G/AW was used except where noted. The mass spectra (ms) were obtained on a CEC-20-110C high resolution mass spectrometer.

All reactions were carried out with a Hanovia 450-W lamp in a water-cooled immersion reactor. In most cases, 200 mg. of compound I and about 2 ml. of the appropriate ethylenic heterocycle were dissolved in approximately 100 ml. of reagent dichloromethane. The irradiation was continued until no starting compound I was observed when the mixture was subjected to tlc. The solvent was then removed under vacuum and the products separated by vpc. Each reaction with its products is given below. Yields are relative percentages and were calculated from the vpc data as a function of individual peak area divided by the total peak area and expressed as a percent.

Dihydropyran Photoproducts.

The reaction with dihydropyran (Aldrich) gave two major peaks which were isolated on the vpc. Peak 1 (24% of the total) proved to be a mixture of two possible isomers in a ratio of 4:1. The major isomer, compound IIa, exhibited the following peaks in the nmr (δ): 1.40-2.30 (m, 4H, $J = 5.60$ Hz, H_{5,6}), 3.74 (t, 2H, $J = 6.0$ Hz, H₇), 4.45 (quartet, 1H, $J = 5.8$ Hz, H_{4a}), 5.15 (d, 1H, $J = 6.0$ Hz, H_{8a}), 5.58 (d, 1H, $J = 1.5$ Hz, methylene H), 6.06 (d, 1H, $J = 1.5$ Hz, methylene H), 7.99 (s, 1H, H₂); Compound IIb exhibited the following peaks, nmr (δ): 1.40-2.30 (m, 4H, H_{7,8}), 3.15 (m, 1H, H_{8a}), 3.74 (t, 2H, H₆), 5.42 (s, 1H, methylene H), 5.95 (m, 1H, H_{4a}), 6.37 (s, 1H, methylene H), 7.93 (s, 1H, H₂); molecular weight for compound IIa,b: calcd. for C₉H₁₁N₃O: 177.09021. Found: 177.09058.

Peak 2 (76%, compound III) exhibited the following spectra: ir: 2245 cm⁻¹ (C≡N); nmr (δ): 1.40-2.50 (m, 4H, $J = 5.5$ Hz, H_{5,6}), 2.88 (m, 2H, CH₂CN), 3.30-3.85 (m, 3H, H_{7,9}), 4.45 (quartet, 1H, $J = 5.0$ Hz, H_{4a}), 4.68 (dd, 1H, H_{8a}), 7.95 (s, 1H, H₂); molecular weight: calcd. for C₁₀H₁₂N₄O: 204.101105. Found: 204.100729.

2,3-Dihydro-*p*-dioxin Photoproducts.

2,3-Dihydro-*p*-dioxin was prepared by the dehydrogenation-dehydration of diethylene glycol and distilled before use in this reaction (10).

Two peaks from the reaction of 2,3-dihydro-*p*-dioxin were isolated on the vpc. Peak 1 (>90%, compound IV) exhibited the following spectra: nmr (δ): 3.80 (m, 4H, H_{6,7}), 5.10 (m, 1H, H_{8a}), 5.73 (d, 1H, $J = 2.0$ Hz, methylene H), 5.86 (d, 1H, $J = 5.1$ Hz, H_{4a}), 6.24 (d, 1H, $J = 2.0$ Hz, methylene H), 8.13 (s, 1H, H₂); molecular weight calcd. for C₈H₉N₃O₂: 179.06904. Found:

Sufficient quantity of peak 2 (>10%) was not isolated for nmr analysis, but the ir spectrum indicated the frequently observed cyanomethyl cycloaddition compound may also be present in the reaction; ir: 2240 cm⁻¹ [C≡N].

2,5-Dihydrofuran Photoproducts.

The reaction with 2,5-dihydrofuran (PCR, Inc.) gave two large peaks which were isolated on the vpc through an 8' column of 10% SE-30 on Chromasorb G/AW. Peak 1 (33%, compound V) exhibited the following spectra: nmr (δ): 3.62-4.32 (m, 5H, $J = 5.5 \pm 1$ Hz, H_{5,7,7a}), 5.00 (m, 1H, H_{4a}), 5.40 (d, 1H, methylene H), 5.96 (d, 1H, methylene H), 8.05 (s, 1H, H₂); molecular weight calcd. for C₈H₉N₃O: 163.07556. Found: 163.07431.

Peak 2 (67%, compound VI) exhibited the following spectra: ir: 2250 cm⁻¹ (C≡N); nmr (δ): 2.78-2.95 (m, 2H, CH₂CN), 3.05-4.33 (m, 6H, H_{5,7,7a,8}), 5.09 (m, 1H, H_{4a}), 8.03 (s, 1H, H₂); molecular weight calcd. for C₉H₁₀N₄O: 190.08546. Found: 190.08512.

2,5-Dimethoxy-2,5-dihydrofuran Photoproduct.

The reaction with 2,5-dimethoxy-2,5-dihydrofuran (Pfaltz and Bauer) gave only one major peak and several minor peaks. The major peak (>90%, compound VII) proved to be a variety of *cis-trans* isomers which could not be separated (5-6). This composite peak exhibited the following spectra: ir: 2250 cm⁻¹ (C≡N); nmr (δ): 2.92 (t, 2H, CH₂CN), 3.35-4.10 (m, 8H, (OCH₃)₂ H_{7a,8}), 4.85-5.45 (m, 3H, $J = 6.2$ Hz, H_{4a,5,7}), 7.95-8.07 (m, 1H, H₂); molecular weight calcd. for C₁₁H₁₃N₄O₃(M-1)⁺: 249.09876. Found: 249.09921.

Sufficient quantities of the minor peaks were not isolated for nmr analysis; however, the ir spectrum of one of these minor peaks is similar to those of other methylene products; ir:

1660 cm⁻¹ (C=CH₂).

1,3-Dioxep-5-ene Photoproducts.

The reaction with 1,3-dioxep-5-ene (Alfred Bader Library, Aldrich) gave two large peaks. Peak 1 (12%, compound VIII) exhibited the following spectra: nmr (δ): 3.97-4.90 (m, 8H, $J = 5.5 \pm 1.0$ Hz, H_{4a,5,7,9,9a}), 5.36 (d, 1H, methylene H), 6.07 (d, 1H, methylene H), 8.07 (s, 1H, H₂); molecular weight calcd. for C₉H₁₁N₃O₂: 193.0851. Found: 193.0857.

Peak 2 (88%, compound IX) exhibited the following spectra: ir: 2250 cm⁻¹ (C≡N); nmr (δ): 2.90-3.01 (m, 2H, CH₂CN), 3.20-3.48 (m, 2H, H_{9a,10}), 3.82-4.10 (m, 2H, H₉), 4.25-4.81 (m, 4H, H_{5,7}), 5.10 (d, 1H, $J = 6.2$ Hz, H_{4a}), 8.08 (s, 1H, H₂); molecular weight calcd. for C₁₀H₁₂N₄O₂: 220.0960. Found: 220.0963.

Attempts to Add 1,2,3,6-Tetrahydropyridine, 1-Acetylimidazole, 3-Sulfolene, 2,3-Dihydro-*p*-dithiin, and Vinylene Carbonate.

The starting materials were either purchased: 1,2,3,6-tetrahydropyridine (Aldrich), 1-acetylimidazole (Aldrich), 3-sulfolene (Parish), vinylene carbonate (Aldrich), or synthesized: 2,3-dihydro-*p*-dithiin (11).

These reactions were carried out under similar conditions to those which gave photoproducts. In each case the starting material (I) was detected on tlc after long periods of irradiation. Also when reaction mixtures were injected on the vpc, no peaks indicative of photoproducts were observed.

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