CHEMISTRY LETTERS, pp. 1361-1364, 1982.

PHOTOCHEMICAL SYNTHESIS OF 1H-PYRANO[3,4-c]PYRIDIN-8[7H]-ONE AND RELATED COMPOUNDS[1)]

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3-Unsubstituted 4-acetoxy- or 4-methoxy-2-pyridones react photochemically with diethyl acetal of acrolein in acetone. Base treatment of the resultant head-to-tail adducts led to 1,2-dihydrocyclobuta[c]pyridin-3(4H)-ones having the acetal function at the 1-position. Refluxing of these cyclobutenes in aq. acetic acid resulted in the formation of the title compounds, whose framework is common in the alkaloids contained in Gentiana species and also in the non-tryptamine units in some indole and related alkaloids.

The 1H-pyrano[3,4-c]pyridine nucleus is found in a series of alkaloids isolated from various Gentiana species[2)] and also constitutes a common terpenoid unit of some indole and related alkaloids (e.g., ajmalicine,[3)] camptothecin,[4)] etc.). We now report a short-step photochemical synthesis of 1H-pyrano[3,4-c]pyridin-8[7H]-one and its derivatives from readily available 4-acetoxy- or -alkoxy-2-pyridones.

Our plan for the synthesis of the title compounds is shown in Chart 1. In the first step, 4-acetoxy-2-pyridone or its equivalent (abbreviated as 4-OR-pyridin-2-one: A) is converted to the corresponding 2+2 adduct (B) by photochemical cycloaddition of the former to α,β-unsaturated ketone or aldehyde. In the second step, the adduct (B) is transformed to 1,2-dihydrocyclobuta[c]pyridin-3(4H)-one (C) by elimination of ROH by treatment with base. In the final step, thermolysis of the cyclobutene (C) would afford the desired product (D) via the 6π electrocyclization of the Z-form of the 2-pyridone-3,4-quinodimethane (F).

In this paper, we describe how our initial plan is realized after minor modifications. According to the plan, 4-acetoxy-6-methyl-2-pyridone[5)] (I) was irradiated[6)] in acetone in the presence of methyl vinyl ketone. However, appreciable

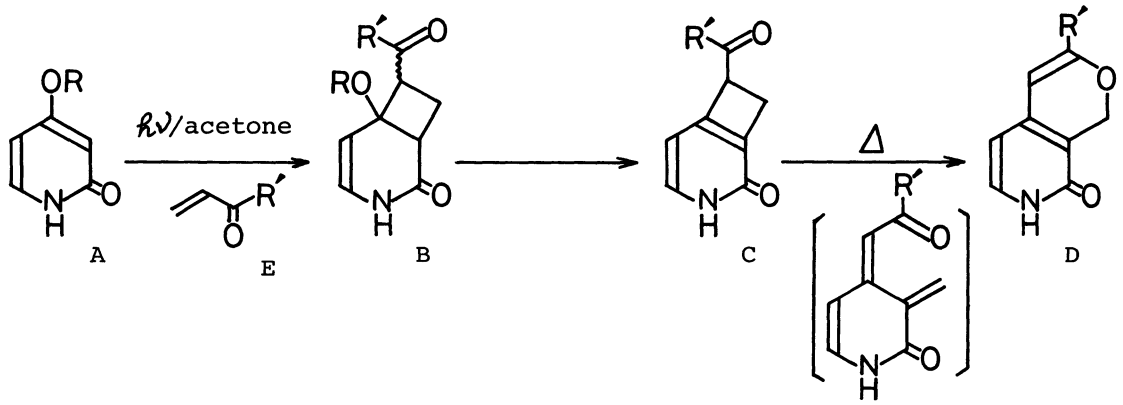


Chart 1

polymerization of the enone prevented even the isolation of the addition products. We abandoned this approach without further examination of the irradiation conditions. We know already that this and the related 2-pyridones give 2-azabicyclo-[4.2.0]oct-4-en-3-one derivatives (G) in considerable amounts, if an electron-deficient olefin is used as the counterpart of the photocycloaddition reactions.[7,8] Since electron-rich olefins are known to give the B-type adduct as the major product,[7] we next irradiated the pyridone (I) in the presence of 3-buten-2-ol. In this case, the desired adduct[9] (II) was obtained almost exclusively. By column chromatography over silica gel, the adduct (II) eliminated acetic acid spontaneously to give the cyclobutene[10] (III; a diastereomeric mixture) in 61% overall yield from I. By oxidation with chromic anhydride in acetic acid, the cyclobutene (III) was converted to the corresponding ketone: 1-acetyl-5-methyl-1,2-dihydrocyclobuta[c]pyridin-3(4H)-one [IV; mp 174-176°C; δ ($CDCl_3$): 2.20 s (3H), 2.33 s (3H), 3.23 bs (2H), 4.08 t (1H, J=3.5 Hz), 5.98 s (1H), ν_{max}^{KBr} cm^{-1}: 1704, 1660; λ_{max}^{MeOH} nm: 232, 300]. Heating of the acetylcyclobutene (IV) in xylene at reflux (2 hr) then afforded 3,6-dimethyl-1H-pyrano[3,4-c]pyridin-8[7H]-one [V; mp 211-214°C; δ ($CDCl_3$): 1.89 s (3H), 2.23 s (3H), 5.01 s (2H), 5.23 s (1H), 5.61 s (1H); ν_{max}^{KBr} cm^{-1}: 1672, 1614; λ_{max}^{MeOH} nm: 235, 298, 309, 330 sh] in 28% yield.

Thus, our initial idea was accomplished by the route shown in Chart 2. How-

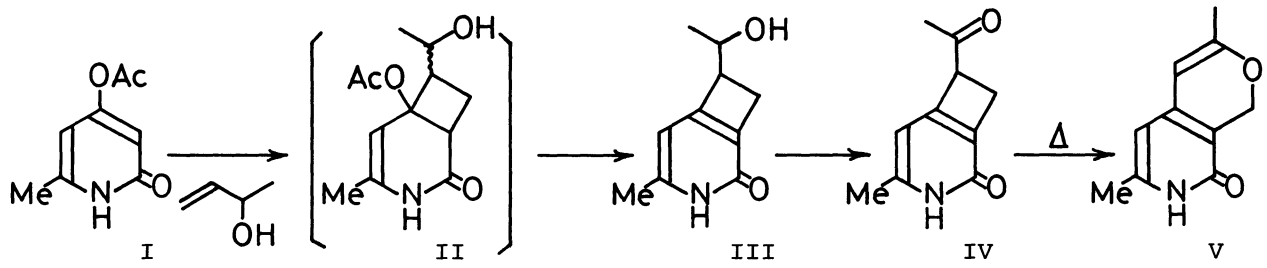
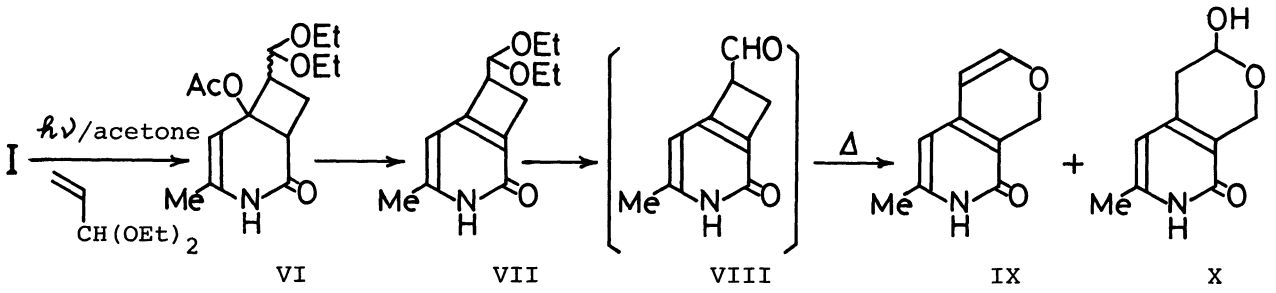


Chart 2

ever, the yield (32%) of the oxidation step is unsatisfactory. Instead of examining more suitable oxidation condition of III, the following alternative method was examined and this led to a general and satisfactory route for the preparation of the aimed compounds.

Thus, acrolein was converted to the diethyl acetal,[11] and this electron-rich olefin then added efficiently[12] to I almost regiospecifically to give the B-type adduct[13] (VI; mp 143-146°C; λ_{max}^{MeOH} nm: 250) in 82% yield. Treatment of VI with 10% aq. NaOH in methanol (4 hr at room temp.) resulted in the exclusive formation of 1-diethoxymethyl-1,2-dihydrocyclobuta-3-pyridone [VII; mp 129-131°C; λ_{max}^{MeOH} nm (log ε): 232.5 (3.87), 297.5 (3.88); ν_{max}^{KBr} cm^{-1}: 1670; $\delta(CCl_4)$: 1.18 t (6H, J=7.2 Hz), 2.30 s (3H), 2.70 dd (1H, J=13.2 and 1.2 Hz), 3.06 dd (1H, J=13.2 and 4.8 Hz), 3.1-3.9 m (5H), 4.35 d (1H, J=7.6 Hz), 5.79 s (1H), 13.10 bs (1H)] in 72% yield. Refluxing of VII in aq. acetic acid (AcOH:H_2O, 8:2 v/v) for 2 hr afforded two products (IX and X) in the respective yields of 39 and 54%. The structure of the less polar product (IX; mp 202.5-204°C) was determined as 6-methyl-1H-pyrano[3,4-c]pyridin-8[7H]-one by nmr [$\delta(CDCl_3)$: 2.25 s (3H), 4.92 s (2H), 5.27 d (1H, J=5.6 Hz), 5.54 s (1H), 6.51 d (1H, J=5.6 Hz)] and UV spectra [λ_{max}^{MeOH} nm (log ε): 235 (4.03), 297 (4.00), 308.5 (3.97), 332 (3.53)] whose absorption maxima are shifted to the longer wavelength region than that of alkylated 2-pyridone (e.g., VII). The cyclic hemiacetal structure for X was deduced from nmr [$\delta(CDCl_3$-CD_3OD, 1:1 v/v): 2.22 s (3H), 2.5-2.8 m (2H), 4.42 bd (1H, J=16.0 Hz), 4.72 bd (1H, J=16.0 Hz), 5.16 t (1H, J=4.0 Hz), 5.84 s (1H)] and UV spectra [λ_{max}^{MeOH} nm (log ε): 232.5 (3.75), 298 (3.88)]. It is obvious that X is formed by hydration of IX under these conditions.[14] The formation of IX from VII is rationally explained by assuming the initial hydrolysis of the acetal function to VIII and 6π electrocyclization of the 2-pyridone-3,4-quinodimethane (via its Z-form, cf. F in Chart 1) formed in situ from VIII by thermolysis.[15]



VI VII VIII IX X

Chart 3

Generality of the synthetic method shown in Chart 3 is provided from the syntheses of 1H-pyrano[3,4-c]pyridin-8[7H]-one[16] (XII, mp 209-211°C) from 4-methoxy-2-pyridone (XI) and its f-benzo-fused analog[17] (XIV, mp 204-205°C) from 4-methoxy-2-quinolone (XIII).

References

1) Part XII of "Cycloadditions in Syntheses". Part XI: C. Kaneko and N. Shimomura, Tetrahedron Lett., 23, 2571 (1982).
2) R. Livingstone, "Rodd's Chemistry of Carbon Compounds (2nd edition)" ed by S. Coffey, Vol. IV, Part H, Elsevier, Amsterdam (1978), p 354.
3) "Natural Product Chemistry", ed by K. Nakanishi et al., Vol. 2, Kodansha, Tokyo (1975), p 365.
4) Ibid., p 358 and references cited therein.
5) C. Wang, J. Heterocyclic Chem., 7, 389 (1970).
6) Irradiation was performed at $\geq$300 nm (Toshiba 400W high-pressure mercury lamp, Pyrex filter) under argon atmosphere.
7) H. Fujii, K. Shiba, and C. Kaneko, J. Chem. Soc., Chem. Comm., 537 (1980).
8) We noticed that the presence of substituent at the 6-position of 2-pyridones (e.g., I) prevented somewhat the formation of G-type adduct, thus increased the amount of the desired adduct (B). For example, upon cycloaddition to acrylonitrile, while 4-methoxy-2-pyridone afforded the B:G ratio of ca. 2:3, its 6-methyl derivative (I) afforded the adducts in ca. 5:1 ratio.
9) Monitoring of the irradiation reaction by UV spectroscopy showed that absorption maxima of I were replaced by the maximum at 247 nm. The final spectrum resembled that of VI very closely.
10) Satisfactory spectral and analytical data were obtained for all new compounds.
11) H. O. L. Fisher and E. Baer, Helv. Chim. Acta, 18, 516 (1935).
12) Photoaddition of I and the related 2-pyridones to electron-rich olefins proceeds much faster than that to electron-deficient olefins. See ref. 7.
13) VI: λ_{max}^{MeOH} nm (log ε): 250 (3.71); ν_{max}^{KBr} cm^{-1}: 1735, 1664; δ(CCl_4): 1.13 and 1.19 each t (6H, J=6.8 Hz), 1.85 bs (3H), 1.89 s (3H), 1.5-2.7 m (3H), 3.0-3.8 m (5H), 4.56 d (1H, J=5.6 Hz), 4.71 bs (1H), 9.29 bs (1H).
14) Refluxing of IX in aq. acetic acid under the same condition as above resulted in the concomitant formation of IX and X in ca. 1:2 ratio.
15) Essentially the same conversions as that from IV to V (or from VIII to IX) have been reported in the corresponding benzocyclobutene series: a) R. Hug, H. -J. Hansen, and H. Schmidt, Helv. Chim. Acta, 55, 10 (1972); b) B. J. Arnold, P. G. Sammes, and T. W. Wallace, J. Chem. Soc. Perkin I, 415 (1974); c) W. Oppolzer, Heterocycles, 14, 1615 (1980); d) T. Kametani, Y. Enomoto, K. Takahashi, and K. Fukumoto, J. Chem. Soc. Perkin I, 2836 (1979).
16) The corresponding cyclic hemiacetal (mp 252-253°C) was also obtained in the final step.
17) The corresponding cyclic hemiacetal (mp 233-234°C) was also obtained in the final step.

(Received June 5, 1982)