[Chem. Pharm. Bull. 31(4)1235—1242(1983)]

1,6-Dihydro-3(2*H*)-pyridinones. VI.[1] Introduction of an Amidocarbonylmethyl Chain at C-4 of the 1,6-Dihydro-3(2*H*)-pyridinone Nucleus *via* Photochemical [2+2] Cycloaddition Reaction[2]

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(Received October 6, 1982)

Photochemical reaction of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**1**) with vinyl acetate resulted in predominant formation of head-to-tail adducts with small amounts of head-to-head adducts. The head-to-tail adduct derivatives (**22** and **30**) were transformed into lactones (**24** and **34**), which were further derived to the 4-*N*,*N*-dimethylcarbamoylmethyl-1,6-dihydro-3(2*H*)-pyridinones (**2a** and **2b**, respectively).

Keywords——dihydropyridinone; photochemical [2+2] cycloaddition; vinyl acetate; Baeyer–Villiger oxidation; dimethyl amine; α,β-unsaturated ketone

Photochemical [2+2] cycloaddition reactions of α,β-unsaturated carbonyl compounds with olefins have been widely investigated in connection with organic synthesis.[3] In these reactions, electron-rich olefins were predominantly used rather than electron-deficient olefins to ensure high regioselectivity of cycloadduct formation. Although numerous reports concerning the photochemical [2+2] cycloaddition of cycloalkenones with olefins have appeared, only a few examples utilizing azacyclic compounds as an enone moiety have so far been described.[4]

In the course of our continuing studies on general alkaloid syntheses starting from *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**1**) as a common synthon,[1] our synthetic efforts are now directed toward the Corynanthe alkaloids, which possess a 3,4-dialkylsubstituted piperidine moiety in their structures. One of the promising synthetic strategies for the Corynanthe alkaloids consists in the elaboration of a 1,6-dihydro-3(2*H*)-pyridinone bearing a requisite functionalized two-carbon chain at the C-4 position, such as compound **2**. Our planning for the preparation of **2** is outlined in Chart 1. Photocycloaddition of **1** with an electron-rich olefin (**3**) is expected to afford the head-to-tail (HT) adduct (**4**) exclusively, and by several steps **4** may be derived into the lactone (**5**), which is then treated with an appropriate nucleophile, *e.g.* an amine or an alcohol, to give the desired product (**2**) *via* an intermediate (**6**).

In this paper we describe the photochemical [2+2] cycloaddition reaction of *N*-substituted 1,6-dihydro-3(2*H*)-pyridinones (**1**) with vinyl acetate, a representative electron-rich olefin, and we also report the successful preparation of 4-substituted 1,6-dihydro-3(2*H*)-pyridinone derivatives (**2a**, R=CO_2Et, Nu=NMe_2; **2b**, R=Cbz, Nu=NMe_2) starting from **1**.

First, the photocycloaddition of *N*-methanesulfonyl-1,6-dihydro-3(2*H*)-pyridinone (**1a**)[5] with vinyl acetate (**7**) was examined. A solution of **1a** and an excess of **7** in acetonitrile in the presence of acetone as a photosensitizer was irradiated using a high-pressure mercury lamp with a Pyrex filter under ice cooling for 4 h to afford the cycloadduct (**8**) as a regio- and stereoisomeric mixture in 85% yield. Without separation of each component, the adduct (**8**) was treated with ethylene glycol in a usual way and then hydrolyzed with a base to give three products, which were easily separated by column chromatography. The most non-polar product was the acetal (**10**; 9.8% yield from **1a**), which was probably derived from the head-to-head (HH) adduct (**11**) cotaminating **8**.[6] The structure of **10** was confirmed by its alternative preparation from the known aldehyde (**12**).[7] The second and third products were the regioisomeric alcohols **13** (7.3% yield) and **14** (50% yield), respectively. Oxidation of the latter (**14**) with the Jones reagent[8] or pyridinium chlorochromate (PCC)[9] afforded a single ketone

(**15**), which gave the diketone (**16**) on acidic hydrolysis. The infrared (IR) spectrum of **16** showed two carbonyl bands at 1775 and 1720 cm^{-1} due to the four- and six-membered ketone functions, respectively, indicating a non-conjugated character of the diketone system. On the other hand, the minor alcohol (**13**) was oxidized with the Jones reagent to give the alternative ketone (**17**). As both regioisomeric ketones, **15** and **17**, were found to be completely recovered upon treatment with base, the ring junction is shown to be *cis*. Thus, the photochemical [2+2] cycloaddition of **1a** with **7** under the aforementioned conditions was proved to result in predominant formation of the HT adduct with a small amount of the unexpected HH adduct.[10] The results of the photocycloaddition of **1a** with **7** under other conditions are summarized in Table I, which shows that the ratio of HT and HH adducts in this reaction is little affected by the nature of the solvents and the presence or absence of the sensitizer (acetone).

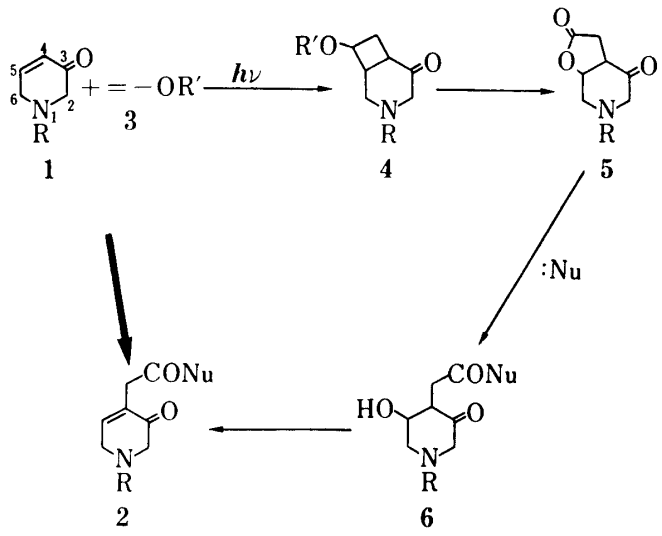

Chart 1

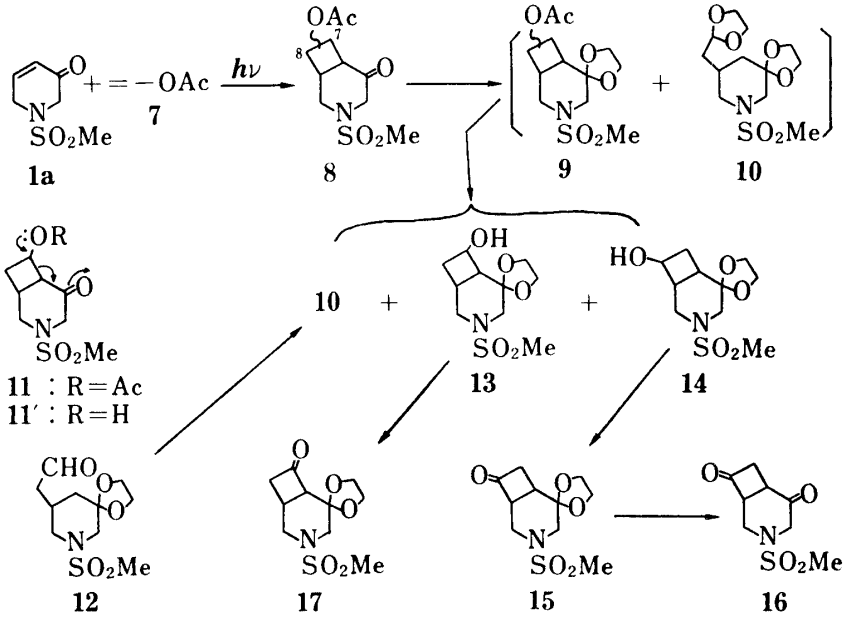

Chart 2

TABLE I. Photochemical [2+2] Cycloaddition of **1a** with **7**

Solvent	Condition Sens.	Time (h)	Products (%) 10	13	14	Ratio of HT / HH
MeCN	Acetone	4	9.8	7.3	50	75 / 25
CH_2Cl_2	Acetone	2.5	1.9	7.3	46	83 / 17
Acetone	Acetone	2.5	2.7	12	49	77 / 23
MeCN	——	4.5	3.8	15	44	70 / 30

Second, we focussed on elaboration of the 1,6-dihydro-3(2*H*)-pyridinone bearing a two-carbon chain at the C-4 position. The Baeyer–Villiger oxidation of the HT adduct derivative (**15**) with *m*-chloroperbenzoic acid (MCPBA) in boiling dichloromethane provided a 90% yield of the desired lactone (**18**); the proton nuclear magnetic resonance (^{1}H-NMR) spectrum exhibited a multiplet at 4.5—4.6 ppm due to the C_6-proton. In order to cleave the C(O)–O bond in **18**, dimethylamine was utilized as a nucleophile. Treatment of **18** with aqueous dimethylamine solution in boiling methanol afforded the amido alcohol (**19**) in 92% yield. The structure of **19** was determined by the following spectral evidence. The mass spectrum (MS) showed a parent peak at *m/e* 322, the IR spectrum showed hydroxy and amido carbonyl bands at 3400 and 1630 cm^{-1}, respectively, and the ^{1}H-NMR spectrum exhibited two singlets at 2.83 and 2.89 ppm due to the two *N*-methyl protons. Acidic hydrolysis of **19**, however, gave none of the desired ketone (**20**); the lactone (**18**) was the only isolable product. The lactone (**18**) seems to be formed *via* hydrolysis of the amido group prior to that of the ethylene ketal.

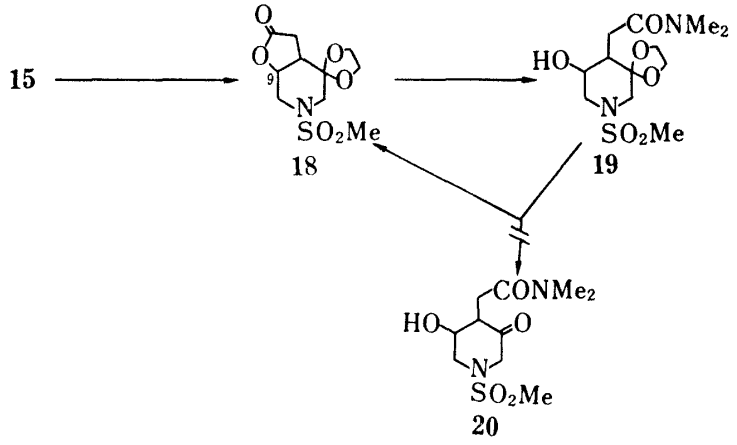

Chart 3

On the other hand, the photochemical [2+2] cycloaddition reaction of ethyl 1,6-dihydro-3(2*H*)-oxopyridine-1-carboxylate (**1b**)[5,11] with vinyl acetate (**7**) was followed by ketalization with methyl orthoformate[12] and subsequent basic hydrolysis to provide the HT adduct derivative (**22**) in 50% yield from the allylic alcohol (**21**),[13] the precursor of **1b**. Oxidation of **22** with PCC in the presence of sodium acetate afforded the ketone (**23**; 62% yield), which was reacted with MCPBA in dichloromethane to give the lactone (**24**). Exposure of **24** to dimethylamine in aqueous methanol resulted in the exclusive formation of the amide (**25**) in 61% yield from the ketone (**23**). Chemoselective hydrolysis of the dimethyl ketal in **25** was easily achieved by heating of **25** with 2% hydrochloric acid in acetone for 1 h to give the keto alcohol (**26**) in 68% yield along with the dehydrated product (**2a**; 12% yield). Longer reaction time (2.5 h) resulted in the exclusive formation of the dihydropyridinone (**2a**; 70% yield). The keto alcohol (**26**) could be dehydrated to **2a** by heating with *p*-toluenesulfonic acid in benzene. The structure of **2a** was easily determined from the ^{1}H-NMR spectrum, which exhibited two *N*-methyl singlets at 2.92 and 3.05 ppm and one olefinic proton signal at 6.85 ppm. Reduction of **2a** with sodium borohydride in methanol afforded the allylic alcohol (**27**), while catalytic hydrogenation of **2a** over 5% palladium on carbon gave the saturated ketone (**28**).

Furthermore, the benzyl urethane analogue (**2b**) was also obtained according tothe above procedure for preparation of **2a**. Benzyl 1,6-dihydro-3(2*H*)-oxopyridine-1-carboxylate (**1c**)[1] was photochemically treated with **7** to yield the adduct (**29**), which was reacted with methyl orthoformate and subsequently hydrolyzed with the base to afford the HT adduct derivative

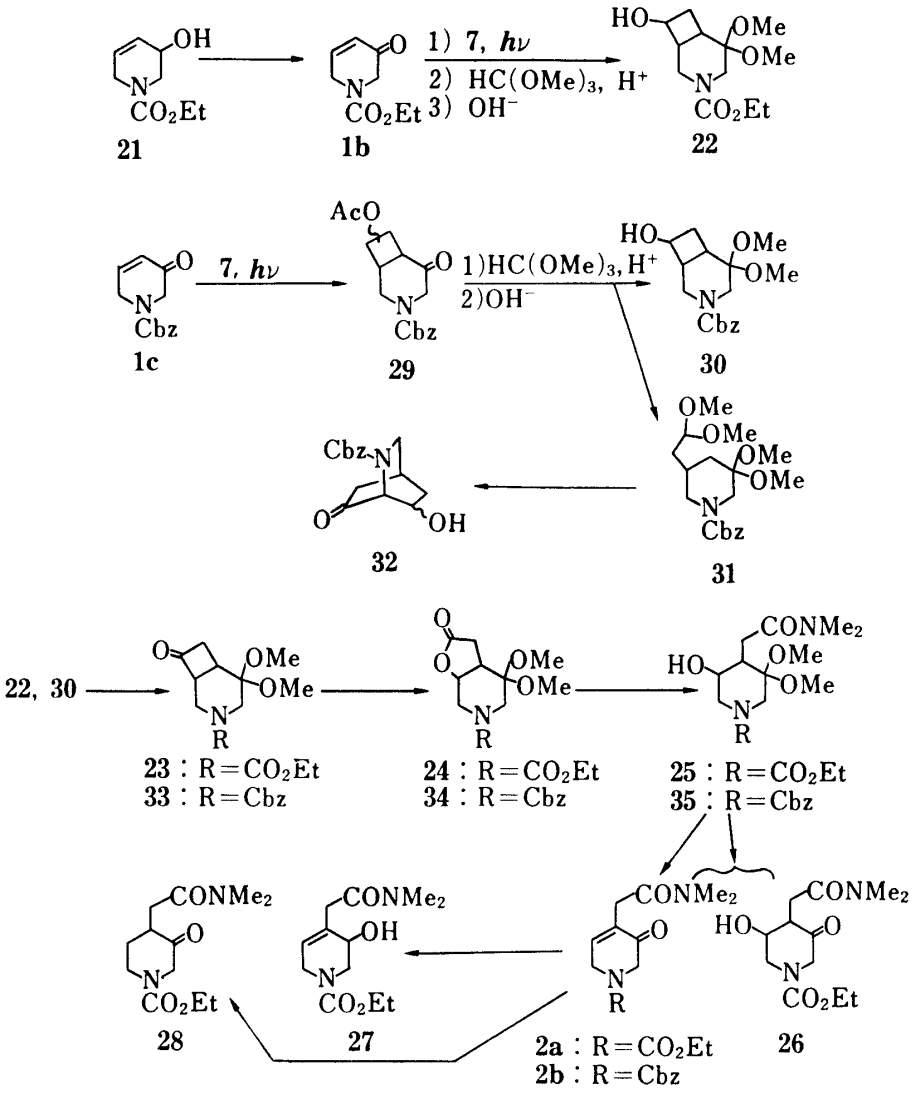

Chart 4

(**30**) and the acetal (**31**) in 45 and 16% yields, respectively. On acidic hydrolysis, the latter (**31**) was derived into the known 2-azabicyclo[2.2.2]octan-6-one derivative (**32**).[14] The former (**30**) was transformed to **2b** *via* the ketone (**33**), the lactone (**34**), and the amide (**35**).

Thus, the *N*,*N*-dimethylcarbamoylmethyl group was introduced as a functionalized two-carbon chain at the C-4 position of the 1,6-dihydro-3(2*H*)-pyridinones (**1b** and **1c**) to give **2a** and **2b**, respectively. Compounds **2a**, **2b**, **27**, and **28** represent possible intermediates for syntheses of some indole alkaloids, *e.g.* the Corynanthe alkaloids.

Experimental

All melting points are uncorrected. IR spectra were measured with a JASCO A-102 spectrometer. MS were taken with a Hitachi M-80 mass spectrometer (direct inlet, at 75 eV). ^{1}H-NMR spectra were recorded with a JEOL PMX-60 or FX-100 spectrometer in $CDCl_3$ using tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, and br=broad. Photoreactions were performed using a 100-W high-pressure mercury lamp (Riko Kagaku Co.) with a Pyrex filter. All organic extracts were dried over anhydrous Na_2SO_4 and the solvents were removed in a rotary evaporator under reduced pressure. Column chromatography was carried out with Silica gel 60 (70—230 mesh, Merck) and alumina 90 (70—230 mesh, Merck).

Photochemical [2+2] Cycloaddition of 1-Methanesulfonyl-1,6-dihydro-3(2*H*)-pyridinone (1a) with Vinyl

Acetate (7)——a) A mixture of **1a** (790 mg), **7** (7.0 ml), acetone (2 ml), and acetonitrile (150 ml) was irradiated under ice cooling in a stream of N_2 for 4 h. The solvent was evaporated off and the residue was chromatographed on silica gel in $CHCl_3$ to afford 950 mg (85%) of a mixture of 7- and 8-acetoxy-3-methanesulfonyl-3-azabicyclo[4.2.0]octan-5-one (**8**) as a viscous colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730, 1720 (CO). ^{1}H-NMR δ: 2.02, 2.08, 2.13 (total 3H, each s, $COCH_3$), 2.85, 2.88 (total 3H, each s, SCH_3), 4.7—5.5 (1H, m, C<u>H</u>–OAc). A mixture of **8** (950 mg), ethylene glycol (2.0 ml), *p*-TsOH (trace), and C_6H_6 (50 ml) was refluxed with stirring for 3 h while water was azeotropically removed using a Dean–Stark apparatus. The reaction mixture was washed with sat. $NaHCO_3$ and brine, dried, and concentrated to leave an oily residue (930 mg), which was used for the next step without purification. Aqueous 2% NaOH solution (10 ml) was added dropwise to a stirred solution of the above product (930 mg) in EtOH (10 ml) under ice cooling over a period of 10 min. Ethanol was evaporated off and the residue was extracted with $CHCl_3$ (20 ml × 3). The extract was washed with brine, dried, and concentrated. The residue was subjected to chromatography on silica gel. The first fraction eluted with $CHCl_3$ afforded 135 mg (9.8% from **1a**) of 9-(1,3-dioxolan-2-ylmethyl)-7-methanesulfonyl-1,4-dioxa-7-azaspiro[4.5]decane (**10**) as colorless needles, mp 110.5—111.5°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 1330, 1145 (SO_2). ^{1}H-NMR δ: 2.92 (3H, s, SCH_3), 3.84—4.97 (4H, m, OCH_2CH_2O), 4.00 (4H, s, OCH_2-CH_2O), 4.91 (1H, t, J=4.5 Hz, $CH\langle^{O}_{O}$). MS *m/e*: 307 (M^+). *Anal.* Calcd for $C_{12}H_{21}NO_6S$: C, 46.90; H, 6.89; N, 4.56. Found: C, 46.81; H, 6.92; N, 4.52. The second fraction afforded 86 mg (7.3% from **1a**) of 5,5-ethylenedioxy-7-hydroxy-3-methanesulfonyl-3-azabicyclo[4.2.0]octane (**13**) as colorless needles, mp 116—117°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 3500 (OH). ^{1}H-NMR δ: 2.88 (3H, s, SCH_3), 4.0—4.1 (4H, m, OCH_2CH_2O), 4.1—4.4 (1H, m, C<u>H</u>–OH). *Anal.* Calcd for $C_{10}H_{17}NO_5S$: C, 45.62; H, 6.51; N, 5.32. Found: C, 45.47; H, 6.57; N, 5.02. The fraction eluted with $CHCl_3$–MeOH (100: 1) afforded 588 mg (50% from **1a**) of a stereoisomeric mixture of 5,5-ethylenedioxy-8-hydroxy-3-methanesulfonyl-3-azabicyclo[4.2.0]octane (**14**) as colorless needles, mp 134—136°C (from C_6H_6). IR ν_{max}^{KBr} cm^{-1}: 3350 (OH). ^{1}H-NMR δ: 2.87, 2.90 (4: 5, total 3H, each s, SCH_3), 3.85—4.10 (4H, m, OCH_2CH_2O), 4.2—4.6 (1H, m, C<u>H</u>–OH). MS *m/e* (%): 261 (0.5, M^+), 101 (100).

b) A mixture of **1a** (440 mg), **7** (5.0 ml), acetone (1.5 ml), and CH_2Cl_2 (150 ml) was irradiated under ice cooling in a stream of N_2 for 2.5 h. Evaporation of the solvent was followed by immediate ketalization and hydrolysis in the same manner as described in a) to afford 15 mg (1.9%) of **10**, 48 mg (7.3%) of **13**, and 304 mg (46%) of **14**.

c) A mixture of **1a** (418 mg), **7** (4.5 ml), and acetone (150 ml) was irradiated for 2.5 h. Work-up as described above yielded 20 mg (2.7%) of **10**, 73 mg (12%) of **13**, and 308 mg (49%) of **14**.

d) A mixture of **1a** (437 mg), **7** (4.8 ml), and acetonitrile (150 ml) was irradiated for 4.5 h. Work-up as described above yielded 29 mg (3.8%) of **10**, 101 mg (15%) of **13**, and 290 mg (44%) of **14**.

5,5-Ethylenedioxy-3-methanesulfonyl-3-azabicyclo[4.2.0]octan-8-one (15)——a) The Jones reagent (8 N; 0.06 ml) was added dropwise to a stirred solution of the alcohol (**14**; 48 mg) in purified acetone (2 ml) under ice cooling over a period of 10 min and the mixture was further stirred at room temperature for 30 min. After decomposition of an excess reagent with MeOH, the mixture was diluted with water and extracted with $CHCl_3$ (10 ml × 3). The extract was washed with brine, dried, and concentrated. The residue was chromatographed on silica gel in $CHCl_3$ to afford 36.5 mg (76%) of the ketone (**15**) as colorless needles, mp 126—127°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 1775 (CO). ^{1}H-NMR δ: 2.83 (3H, s, SCH_3), 4.00 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{10}H_{15}NO_5S$: C, 45.97; H, 5.79; N, 5.36. Found: C, 45.75; H, 5.73; N, 5.15.

b) A mixture of the alcohol **14** (87 mg), PCC (134 mg), NaOAc (55 mg), and CH_2Cl_2 (10 ml) was stirred at room temperature for 1.5 h. The reaction mixture was diluted with ether, the resulting mixture was passed through a short column packed with Florisil, and the column was thoroughly washed with ether. The combined eluates were concentrated and the residue was chromatographed on silica gel in $CHCl_3$ to afford 50 mg (58%) of the ketone (**15**).

3-Methanesulfonyl-3-azabicyclo[4.2.0]octane-5,8-dione (16)——A solution of the keto ketal **15** (198 mg) in tetrahydrofuran (THF) (10 ml) containing 10% HCl (3 ml) was refluxed for 8 h. The organic solvent was evaporated off and the residue was extracted with $CHCl_3$ (20 ml × 3). The extract was washed with brine, dried, and concentrated and the residue was recrystallized from AcOEt to afford 85 mg (51%) of the diketone (**16**) as colorless needles, mp 172—174°C. IR ν_{max}^{KBr} cm^{-1}: 1775, 1720 (CO). *Anal.* Calcd for $C_8H_{11}NO_4S$: C, 44.21; H, 5.11; N, 6.45. Found: C, 44.12; H, 5.12; N, 6.30.

Preparation of the Acetal (10) from 7-Methanesulfonyl-9-(2-oxoethyl)-1,4-dioxa-7-azaspiro[4.5]decane (12)——A mixture of the known aldehyde **12** (50 mg),[7] ethylene glycol (0.2 ml), *p*-TsOH (trace), and C_6H_6 (20 ml) was refluxed with stirring using a Dean–Stark apparatus. After 2 h of refluxing, work-up as usual afforded a residue. This was chromatographed on alumina in $CHCl_3$ to afford 40 mg (69%) of the acetal (**10**), which was found to be identical with the product (**10**) obtained *via* the photochemical cycloaddition described above by means of TLC and IR comparisons.

5,5-Ethylenedioxy-3-methanesulfonyl-3-azabicyclo[4.2.0]octan-7-one (17)——The Jones reagent (8 N; 0.36 ml) was added dropwise to a stirred solution of the alcohol **13** (240 mg) in purified acetone (10 ml) under ice cooling over a period of 15 min, and the mixture was further stirred at room temperature for 30 min. Work-up as usual and chromatography of the residue on silica gel in $CHCl_3$ afforded 190 mg (79%) of the

ketone (**17**) as colorless needles, mp 91—92°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 1760 (CO). ^{1}H-NMR δ: 2.86 (3H, s, SCH_3), 3.98 (4H, s, OCH_2CH_2O). *Anal.* Calcd for $C_{10}H_{15}NO_5S$: C, 45.97; H, 5.79; N, 5.36. Found: C, 45.95; H, 5.81; N, 5.22.

***rel*-(9*S*,10*R*)-9-Hydroxy-7-methanesulfonyl-1,4-dioxa-7-azaspiro[4.5]decane-10-acetic Acid γ-Lactone (18)**——A mixture of the ketone **15** (98 mg), MCPBA (180 mg), and CH_2Cl_2 (5 ml) was refluxed for 16 h. The reaction mixture was diluted with $CHCl_3$ (70 ml) and washed with a 1: 1 mixture of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ and then with brine. The dried extract was concentrated and the residue was recrystallized from C_6H_6–hexane to afford 94 mg (90%) of the lactone (**18**) as colorless needles, mp 192—194°C. IR ν_{max}^{KBr} cm^{-1}: 1775 (CO). ^{1}H-NMR δ: 3.02 (3H, s, SCH_3), 4.0—4.1 (4H, m, OCH_2CH_2O), 4.5—4.6 (1H, m, C_9–H). *Anal.* Calcd for $C_{10}H_{15}NO_6S$: C, 43.32; H, 5.45; N, 5.05. Found: C, 43.22; H, 5.50; N, 4.84. MS *m/e*: 277 (M^+).

***rel*-(9*S*,10*R*)-9-Hydroxy-7-methanesulfonyl-*N*,*N*-dimethyl-1,4-dioxa-7-azaspiro[4.5]decane-10-acetamide (19)**——Aqueous Me_2NH solution (40%; 5 ml) was added to a solution of the lactone **18** (72 mg) in EtOH (15 ml) and the mixture was refluxed with stirring for 30 min. Ethanol was evaporated off and the residue was extracted with $CHCl_3$ (10 ml × 3). The extract was washed with brine, dried, and concentrated to afford 77 mg (92%) of the amide (**19**) as colorless needles, mp 152—154°C (from C_6H_6-hexane). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1630 (NCO). ^{1}H-NMR δ (65°C): 2.83 (3H, s, NCH_3), 2.89 (3H, s, NCH_3), 2.96 (3H, s, SCH_3), 3.9—4.1 (4H, m, OCH_2CH_2O). MS *m/e* (%): 322 (0.14, M^+), 304 (1.5), 243 (53), 225 (100).

Acidic Hydrolysis of 19——A mixture of **19** (22 mg), 2% HCl (0.5 ml), and THF (1 ml) was refluxed for 6 h. The solvent was evaporated off and the residue was extracted with $CHCl_3$ (5 ml × 2). The dried extract was concentrated to leave 21 mg of the solid, which was proved to be identical with the lactone **18** by means of TLC and IR (KBr) comparisons.

Photocycloaddition of Ethyl 1,6-Dihydro-3(2*H*)-oxopyridine-1-carboxylate (1b) with Vinyl Acetate (7)——According to the previously reported procedure[5] the allylic alcohol **21** (960 mg) was oxidized with the Jones reagent. Compound **7** (8 ml) was added to the $CHCl_3$ extract (100 ml) of the reaction mixture, and the whole solution was irradiated under ice cooling in a stream of N_2 for 4 h. The solvent was evaporated off and the residue was chromatographed on silica gel in $CHCl_3$ to afford 1.48 g of the crude cycloadduct, which was used for the next step without further purification. A mixture of 1.48 g of the crude cycloadduct, methyl orthoformate (5 ml), *p*-TsOH (trace), and abs. MeOH (20 ml) was refluxed for 12 h. The mixture was cooled, and a solution of NaOH (0.40 g) in water (10 ml) was added. The whole was stirred at room temperature for 2 h, neutralized with AcOH and concentrated. The residue was extracted with $CHCl_3$ (30 ml × 3) and the extract was washed with sat. $NaHCO_3$ and brine. The dried extract was concentrated to leave an oily residue, which was subjected to column chromatography on silica gel. The fraction eluted with $CHCl_3$–MeOH (50: 1) afforded 775 mg (50% from **21**) of the acetal (**22**) as a colorless oil (diastereoisomeric mixture). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1680 (NCOO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.10, 3.12, 3.17, 3.20 (total 6H, each s, OCH_3 × 2), 4.06, 4.08 (2H, each q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 259 (1.8, M^+), 184 (78), 170 (75), 143 (91), 140 (100). High resolution MS. Calcd for $C_{12}H_{21}NO_5$: 259.1418. Found: 259.1414.

Ethyl 5,5-Dimethoxy-8-oxo-3-azabicyclo[4.2.0]octane-3-carboxylate (23)——A mixture of the alcohol **22** (740 mg), PCC (1.23 g), NaOAc (470 mg), and CH_2Cl_2 (15 ml) was stirred at room temperature for 20 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 465 mg (62%) of the ketone (**23**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.20 (6H, s, OCH_3 × 2), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 257 (36, M^+), 226 (37), 116 (100). High resolution MS. Calcd for $C_{12}H_{19}NO_5$: 257.1262. Found: 257.1268.

***rel*-(4*R*,5*S*)-1-Ethoxycarbonyl-5-hydroxy-3,3-dimethoxypiperidine-4-acetic Acid γ-Lactone (24)**——A mixture of the ketone **23** (583 mg), MCPBA (993 mg), and CH_2Cl_2 (15 ml) was allowed to stand at room temperature for 4 d. The reaction mixture was diluted with $CHCl_3$ (30 ml) and then washed with a 1: 1 mixture of sat. $NaHCO_3$ and sat. $Na_2S_2O_3$ and with brine. The dried organic solution was concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (100: 1) to afford 231 mg (37%) of the lactone (**24**) as colorless needles, mp 88—90°C (from C_6H_6–hexane). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780 (CO), 1680 (NCOO). ^{1}H-NMR δ: 1.26 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 3.20 (6H, s, OCH_3 × 2), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 4.4—4.8 (1H, m, C_5–H). MS *m/e* (%): 273 (100; M^+), 182 (32). High resolution MS. Calcd for $C_{12}H_{19}NO_6$: 273.1210. Found: 273.1210. *Anal.* Calcd for $C_{12}H_{19}NO_6$: C, 52.74; H, 7.01; N, 5.13. Found: C, 52.56; H, 6.93; N, 5.35.

***rel*-(4*R*,5*S*)-1-Ethoxycarbonyl-5-hydroxy-3,3-dimethoxy-*N*,*N*-dimethylpiperidine-4-acetamide (25)**——The ketone **23** (863 mg) was oxidized with MCPBA (1.45 g) according to the aforementioned procedure to give 1.07 g of crude **24**, which was used for the next step without purification. Aqueous Me_2NH solution (40%; 8 ml) was added to a solution of the above lactone in abs. MeOH (30 ml) and the mixture was refluxed with stirring for 50 min. The organic solvent was evaporated off and the residue was extracted with $CHCl_3$ (10 ml × 3). The extract was washed with brine, dried, and concentrated. The oily residue was chromatographed on silica gel in $CHCl_3$ to afford 660 mg (61% from **23**) of the amide (**25**) as colorless needles, mp 137—138°C (from C_6H_6–hexane). IR ν_{max}^{KBr} cm^{-1}: 3400 (OH), 1685 (NCOO), 1630 (NCO). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.95 (3H, s, NCH_3), 3.05 (3H, s, NCH_3), 3.18 (3H, s, OCH_3), 3.20 (3H, s, OCH_3), 4.10 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). *Anal.* Calcd for $C_{14}H_{26}N_2O_6$: C, 52.81; H, 8.23; N, 8.80. Found: C, 52.97; H, 8.12; N, 8.77.

Acidic Hydrolysis of the Acetal (25)——a) A mixture of the acetal **25** (75 mg), 2% HCl (0.8 ml), and acetone (4 ml) was refluxed for 1 h. The organic solvent was evaporated off and the residue was extracted with $CHCl_3$ (10 ml×3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$. The first fraction afforded 7 mg (12%) of 1-ethoxycarbonyl-*N*,*N*-dimethyl-1,6-dihydro-3(2*H*)-oxopyridine-4-acetamide (**2a**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690—1680 (CO, NCOO), 1630 (NCO, C=C). ^{1}H-NMR δ: 1.26 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.92 (3H, s, NCH_3), 3.05 (3H, s, NCH_3), 3.27 (2H, s, C_4–CH_2), 4.12 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 6.85 (1H, br t, J=3.5 Hz, C_5–H). MS *m/e* (%): 254 (3.4, M^+), 209 (10), 153 (100), 125 (7.9). High resolution MS. Calcd for $C_{12}H_{18}N_2O_4$: 254.1264. Found: 254.1259. The second fraction afforded 44 mg (68%) of 1-ethoxycarbonyl-5-hydroxy-*N*,*N*-dimethyl-3-oxopiperidine-4-acetamide (**26**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1720 (CO), 1680 (NCOO), 1630 (NCO). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.93 (3H, s, NCH_3), 3.07 (3H, s, NCH_3), 4.13 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 272 (15, M^+), 254 (100), 156 (59), 139 (39). High resolution MS. Calcd for $C_{12}H_{20}N_2O_5$: 272.1371. Found: 272.1378.

b) A mixture of the acetal **25** (486 mg), 2% HCl (3 ml), and acetone (30 ml) was refluxed for 2.5 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 430 mg (70%) of **2a**.

Dehydration of the Alcohol (26)——A mixture of **26** (60 mg), *p*-TsOH (trace), and dry C_6H_6 (10 ml) was heated with stirring at 100°C for 30 min while C_6H_6 was slowly distilled off in order to remove water formed. The remained C_6H_6 was then evaporated off and the residue was taken up in $CHCl_3$ (20 ml). The $CHCl_3$ solution was washed with sat. $NaHCO_3$ and brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 43 mg (77%) of the dihydropyridinone (**2a**).

1-Ethoxycarbonyl-3-hydroxy-*N*,*N*-dimethyl-1,2,3,6-tetrahydropyridine-4-acetamide (27)——Under ice cooling, $NaBH_4$ (6 mg) was added all at once to a stirred solution of **2a** (43 mg) in MeOH (10 ml), and the mixture was further stirred under cooling for 20 min. After addition of 2—3 drops of AcOH, the solvent was evaporated off and the residue was taken up in $CHCl_3$ (30 ml). The $CHCl_3$ layer was washed with brine, dried, and concentrated to afford 42 mg (97%) of the alcohol (**27**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3360 (OH), 1680 (NCOO), 1620 (NCO). ^{1}H-NMR δ: 1.25 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.93 (3H, s, NCH_3), 3.03 (3H, s, NCH_3), 3.23 (2H, br s, C_4–CH_2), 4.13 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$), 5.50 (1H, m, C_5–H). MS *m/e* (%): 256 (8.3, M^+), 211 (100), 155 (95), 72 (89), 45 (82). High resolution MS. Calcd for $C_{12}H_{20}N_2O_4$: 256.1421. Found: 256.1393.

1-Ethoxycarbonyl-*N*,*N*-dimethyl-3-oxopiperidine-4-acetamide (28)——The dihydropyridinone **2a** (91 mg) was hydrogenated in MeOH (10 ml) over 5% Pd-C (50 mg) under atmospheric pressure at room temperature for 1 h. The catalyst was filtered off and the filtrate was concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–MeOH (200: 1) to afford 83 mg (87%) of the saturated ketone (**28**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1720 sh (CO), 1680 (NCOO). 1635 (NCO). ^{1}H-NMR δ: 1.23 (3H, t, J=7 Hz, $OCH_2C\underline{H}_3$), 2.90 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 4.08 (2H, q, J=7 Hz, $OC\underline{H}_2CH_3$). MS *m/e* (%): 256 (19, M^+), 211 (100), 140 (52), 87 (51), 72 (48). High resolution MS. Calcd for $C_{12}H_{20}N_2O_4$: 256.1422. Found: 256.1425.

Benzyl 7- and 8-Acetoxy-5-oxo-3-azabicyclo[4.2.0]octane-3-carboxylate (29)——A solution of **1c** (920 mg) and **7** (5.0 ml) in $CHCl_3$ (100 ml) containing acetone (3 ml) was irradiated under ice cooling in a stream of N_2 for 4 h. The solvent was evaporated off and the residue was chromatographed on silica gel in $CHCl_3$ to afford 960 mg (79%) of the colorless cycloadduct (**29**) as a regio- and stereoisomeric mixture. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1730 sh (COO), 1720—1690 (CO, NCOO). ^{1}H-NMR δ: 1.70, 1.85, 2.00, 2.05 (total 3H, each s, $COCH_3$), 5.07, 5.10 (total 2H, each s, CH_2Ar), 7.25 (5H, s, Ar–H). MS *m/e* (%): 317 (0.7, M^+), 231 (1.6), 107 (28), 91 (100). High resolution MS. Calcd for $C_{17}H_{19}NO_5$: 317.1262. Found: 317.1264.

Benzyl 8-Hydroxy-5,5-dimethoxy-3-azabicyclo[4.2.0]octane-3-carboxylate (30) and Benzyl 3,3-Dimethoxy-5-(2,2-dimethoxyethyl)piperidine-1-carboxylate (31)——A mixture of **29** (840 mg), methyl orthoformate (1.0 ml), *p*-TsOH (trace), and abs. MeOH (12 ml) was refluxed for 3.5 h. The reaction mixture was cooled and 10% NaOH aq. solution (4 ml) was added. The whole mixture was stirred under ice cooling overnight. The solvent was evaporated off and the residue was extracted with $CHCl_3$ (30 ml×3). The extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on alumina in $CHCl_3$. The first fraction afforded 190 mg (20%) of the acetal (**31**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1680 (NCOO). ^{1}H-NMR δ: 3.10, 3.18, 3.25 (total 12 H, each s, $OCH_3\times4$), 4.40 (1H, t, J=4.5 Hz, $CH\langle^{O}_{O}$), 5.10 (2H, s, CH_2Ar), 7.20 (5H, s, Ar–H). MS *m/e* (%): 365 (0.3, M^+), 189 (41), 75 (100). High resolution MS. Calcd for $C_{19}H_{27}NO_6$: 365.1836. Found: 365.1844. The second fraction afforded 481 mg (57%) of the alcohol (**30**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3400 (OH), 1680 (NCOO). ^{1}H-NMR δ: 3.05, 3.08 (total 6H, each s, $OCH_3\times2$), 5.03, 5.05 (total 2H, each s, CH_2Ar), 7.22 (5H, s, Ar–H). MS *m/e* (%): 321 (1.1, M^+), 304 (1.9), 143 (47), 91 (100). High resolution MS. Calcd for $C_{17}H_{23}NO_5$: 321.1575. Found: 321.1586.

Acidic Hydrolysis of the Acetal (31)——A mixture of the acetal **31** (120 mg), 10% HCl (1.0 ml), and acetone (5 ml) was refluxed for 1.5 h. Work-up as usual gave an oily crude product, which was chromatographed on silica gel in $CHCl_3$–EtOH (20: 1) to afford 65 mg (72%) of benzyl 7-hydroxy-6-oxo-2-azabicyclo[2.2.2]octane-2-carboxylate (**32**). This product was proved to be identical with an authentic sample of **32**[14]

by means of TLC and IR comparisons.

Benzyl 5,5-Dimethoxy-8-oxo-3-azabicyclo[4.2.0]octane-3-carboxylate (33)——A mixture of the alcohol **30** (350 mg), PCC (0.60 g), NaOAc (0.30 g), and CH_2Cl_2 (10 ml) was stirred at room temperature for 5 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 295 mg (85%) of the ketone (**33**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1782 (CO), 1685 (NCOO). ^{1}H-NMR δ: 3.16 (3H, s, $OCH_3 \times 2$), 5.05 (2H, s, CH_2Ar), 7.31 (5H, s, Ar–H). MS *m/e* (%): 319 (1.8, M^+), 228 (23), 91 (100). High resolution MS. Calcd for $C_{17}H_{21}NO_5$: 319.1419. Found: 319.1420.

***rel*-(4*R*,5*S*)-1-Benzyloxycarbonyl-5-hydroxy-3,3-dimethoxypiperidine-4-acetic Acid γ-Lactone (34)**——A mixture of the ketone **33** (260 mg), MCPBA (450 mg), and CH_2Cl_2 (10 ml) was allowed to stand at room temperature for 15 h and then refluxed for 7 h. Work-up as usual gave an oily residue, which was chromatographed on silica gel in $CHCl_3$ to afford 166 mg (61%) of the lactone (**34**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1780 (COO), 1690 (NCOO). ^{1}H-NMR δ: 3.10 (6H, s, $OCH_3 \times 2$), 4.4—4.7 (1H, m, C_5–H), 5.00 (2H, s, CH_2Ar), 7.17 (5H, s, Ar–H). MS *m/e* (%): 335 (1.8, M^+), 303 (12), 112 (38), 91 (100). High resolution MS. Calcd for $C_{17}H_{21}NO_6$: 335.1367. Found: 335.1371.

***rel*-(4*R*,5*S*)-1-Benzyloxycarbonyl-5-hydroxy-3,3-dimethoxy-*N*,*N*-dimethylpiperidine-4-acetamide (35)**——A mixture of the lactone **34** (108 mg), aqueous Me_2NH solution (40%; 2.5 ml), and EtOH (10 ml) was refluxed with stirring for 20 min. Work-up as usual gave 120 mg (98%) of the amide (**35**) as a colorless oil. This product showed one spot on TLC (alumina, $CHCl_3$). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3380 (OH), 1685 (NCOO), 1620 (NCO). ^{1}H-NMR δ: 2.45 (2H, d, J=4.5 Hz, C_4–CH_2), 2.87 (3H, s, NCH_3), 2.99 (3H, s, NCH_3), 3.10 (6H, s, $OCH_3 \times 2$), 5.02 (2H, s, CH_2Ar), 7.15 (5H, s, Ar–H). MS *m/e* (%): 380 (0.7, M^+), 330 (100), 202 (99). High resolution MS. Calcd for $C_{19}H_{28}N_2O_6$: 380.1945. Found: 380.1939.

1-Benzyloxycarbonyl-*N*,*N*-dimethyl-1,6-dihydro-3(2*H*)-oxopyridine-4-acetamide (2b)——A mixture of the ketal **35** (0.10 g), 2% HCl (1.0 ml), and acetone (10 ml) was refluxed for 1 h. Acetone was evaporated off and the residue was extracted with $CHCl_3$ (15 ml × 2). The $CHCl_3$ extract was washed with brine, dried, and concentrated to leave an oily residue, which was chromatographed on silica gel in $CHCl_3$–EtOH (50: 1) to afford 56 mg (67%) of the dihydropyridinone (**2b**) as a colorless oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1685 (NCOO), 1640 (NCO, C=C). ^{1}H-NMR δ: 2.86 (3H, s, NCH_3), 2.98 (3H, s, NCH_3), 3.20 (2H, br s, C_4–CH_2), 4.12 (2H, s, C_2–H), 4.25 (2H, d, J=3.5 Hz, C_6–H), 5.04 (2H, s, CH_2Ar), 6.72 (1H, t, J=3.5 Hz, C_5–H), 7.16 (5H, s, Ar–H). MS *m/e* (%): 316 (0.2, M^+), 180 (87), 91 (99), 72 (100). High resolution MS. Calcd for $C_{17}H_{20}N_2O_4$: 316.1422. Found: 316.1433.

References and Notes

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11) According to the known procedure,[5,10] the allylic alcohol (**21**) was oxidized and the $CHCl_3$ extract was used in the photocycloaddition reaction without isolation of the dihydropyridinone (**1b**).
12) From the viewpoint of facility in deprotection, dimethyl ketal was utilized instead of ethylene ketal.
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