up as previously described. The crude product was distilled over $LiAlH_4$ to give 0.92 g of pure (SE 301, 160 °C) (*S*)-**1**: 78%; $[\alpha]^{25}_D$ +19.70°.

Methyl 4-(1-Methylpropyl)benzoate (10). A solution of 15.0 g (60.4 mmol) of (*R*)-**3**, α^{25}_D (l = 1) -18.98°, 9.4 g (63.4 mmol) of ethyl orthoformate, and 2 mL of dry HCl-saturated ethanol was stirred at room temperature (16 days) and then concentrated under vacuum (18 mm).[14] The residue was distilled to give 18.0 g of a two-product (A and B) mixture in the ratio 1:10 (SE 301, 190 °C). These products were identified as the stereoisomers of ethyl 4-ethoxy-4-[4-(1-methylpropyl)phenyl]-3-butenoate (**9**) by their mass spectra [m/e (relative intensity)]: A, 133 (100), 161 (95), 217 (65), 55 (54), 57 (35), 290 (30, M^+), 159 (25), 131 (19), 189 (18), 115 (16), 233 (16), 91 (15), 162 (14); B, 161 (100), 133 (58), 217 (40), 55 (28), 57 (17) 290 (16, M^+), 162 (14).

Such a mixture was dissolved in 200 mL of dry CH_2Cl_2, ozonized at 0 °C for 8 h, and concentrated under reduced pressure (18 mm). The residue oil, dissolved in 230 mL of 95% ethanol, was treated with 138 mL of 10% NaOH solution and 92 mL of 35% H_2O_2 and then refluxed (12 h). After the usual procedure a complex mixture of organic acids was recovered, esterified with diazomethane, and purified by preparative GLC (3-m column, CW20M; 150 °C) to give chemically pure (SE 301, 160 °C) (*R*)-**10**, $[\alpha]^{25}_D$ -19.02° (*c* 2.732, ethanol).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.85; H, 8.42.

4-(1-Methylpropyl)benzoic Acid (11). A sample of 1.7 g (8.84 mmol) of (*R*)-**10**, $[\alpha]^{25}_D$ -19.02° (*c* 2.732, ethanol), dissolved in 50 mL of 95% ethanol and 50 mL of 20% NaOH aqueous solution was stirred at reflux (8 h). The cooled mixture was acidified (10% H_2SO_4) and the organic product extracted in ether and dried (Na_2SO_4). The solvent was removed to yield 1.5 g of (*R*)-**11**: 98%; mp 89 °C; $[\alpha]^{25}_D$ -20.30° (*c* 1.867, methanol) [lit.[5b] mp 89-90 °C; $[\alpha]^{25}_{D,max}$ 31.3° (methanol)]; NMR (CCl_4) δ 12.56 (s, 1 H), 8.00-6.80 (2 d, 4 H), 2.80-2.38 (m, 1 H), 1.80-1.40 (m, 2 H), 1.36-1.06 (d, 3 H), 1.00-0.62 (t, 3 H).

2-Methylbutan-1-ol (12). A sample of 7.0 g (32.0 mmol) of (*R*)-**5**, $[\alpha]^{25}_D$ -12.60° (*c* 1.774, benzene), was dissolved in 80 mL of glacial acetic acid and ozonized at room temperature (30 h). The solvent was removed at reduced pressure (18 mm), and the residue oil was reduced with an ethereal suspension of 12.0 g (0.316 mol) of $LiAlH_4$. The hydrolysis was carried out as usual, and the organic products were extracted in continuum. From the recovered mixture, by preparative GLC purification a sample of pure (*R*)-**12**, $[\alpha]^{25}_D$ +3.93° (*c* 3.738, *n*-heptane), was recovered [lit.[15] $[\alpha]^{25}_{D,max}$ 6.66° (*c* 3.020, *n*-heptane)].

Registry No. (*R,S*)-**1**, 73494-13-0; (*S*)-(+)-**1**, 65419-63-8; (*S*)-(+)-**2**, 5787-28-0; (*S*)-(+)-**3**, 73434-44-3; (*R*)-(-)-**3**, 73434-45-4; (*S*)-(+)-**4**, 73434-46-5; (*R*)-(-)-**4**, 73434-47-6; (±)-**5**, 73434-48-7; (±)-**5** methyl ester, 73453-16-4; (±)-**5** positional isomer methyl ester, 73434-60-3; (*S*)-(+)-**5**, 73494-14-1; (*R*)-(-)-**5**, 73494-15-2; (*S*)-(+)-**6**, 73434-49-8; (*R*)-(-)-**6**, 73434-50-1; (*S*)-(+)-**7**, 73434-51-2; (*S*)-(+)-**8**, 73434-52-3; (*R*)-**9** (*E* isomer), 73434-53-4; (*R*)-**9** (*Z* isomer), 73434-54-5; (*R*)-(-)-**10**, 73434-55-6; (*R*)-(-)-**11**, 73434-56-7; (*R*)-(+)-**12**, 14898-79-4; 3-(carbomethoxy)propionyl chloride, 1490-25-1; (*S*)-(+)-**5** methyl ester, 73434-57-8; naphthalene, 91-20-3; bis(1-methylpropyl)naphthalene, 73434-58-9; methyl 4-phenylbutanoate, 2046-17-5; methyl bis(1-methylpropyl)-4-phenylbutanoate, 73434-59-0.

New Perspectives on the Semmler-Wolff Aromatization Reaction[1]

Mustafa I. El-Sheikh and James M. Cook*

Department of Chemistry, University of Wisconsin—Milwaukee, Milwaukee, Wisconsin 53201

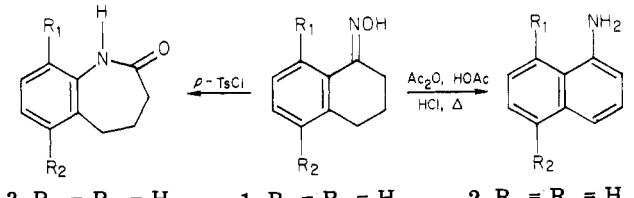
Received February 27, 1980

The conversion of 4-methyl-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-hydroxyquinoline (**13a**) to 4-methyl-5-acetamido-2-quinolone (**10**) was carried out in 53% yield under Semmler–Wolff conditions. In the pyridone **13a** the oxime must assume the anti to pyridone configuration; consequently, this transformation provides evidence that the syn to phenyl configuration is not a necessary requirement for the Semmler–Wolff aromatization reaction.

The conversion of cyclohexenone oximes to anilines was first investigated by Semmler.[2] Several years later Wolff conducted a more detailed investigation of this phenomenon[3] while Schroeter expanded the scope of the rearrangement by conversion of tetralone-1-oximes to α-naphthyl amines.[4] In addition, it was determined that these oximes could be made to undergo the Beckmann rearrangement rather than aromatization; for example, tetralone-1-oxime (**1**) gave the aromatic amine **2** (see Scheme I) when treated with Beckmann's mixture; however, the lactam **3** was formed on heating **1** with *p*-toluenesulfonyl chloride (see Scheme I).

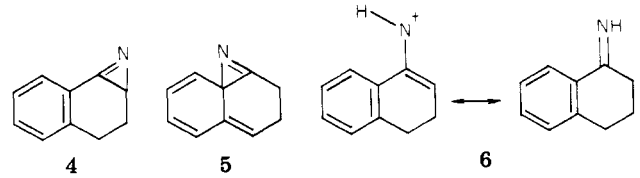
The mechanism of this transformation has been studied principally by five groups,[5a-e] and their work has been reviewed.[6] Although many species have been proposed[6]

Scheme I



3, $R_1 = R_2 = H$ **1**, $R_1 = R_2 = H$ **2**, $R_1 = R_2 = H$
8, $R_1 = R_2 = CH_3$ **7**, $R_1 = R_2 = CH_3$ **9**, $R_1 = R_2 = CH_3$

Scheme II



4 **5** **6**

as the key intermediate for this reaction, those that have received the most attention are represented by structures

(1) This is contribution no. 1572 to the Army Research Program on Malaria (Contract No. DAMD17-78-C-8003).

(2) Semmler, W. *Ber. Dtsch. Chem. Ges.* **1892**, *25*, 3352.

(3) Wolff, L. *Justus Liebigs Ann. Chem.* **1902**, *322*, 351.

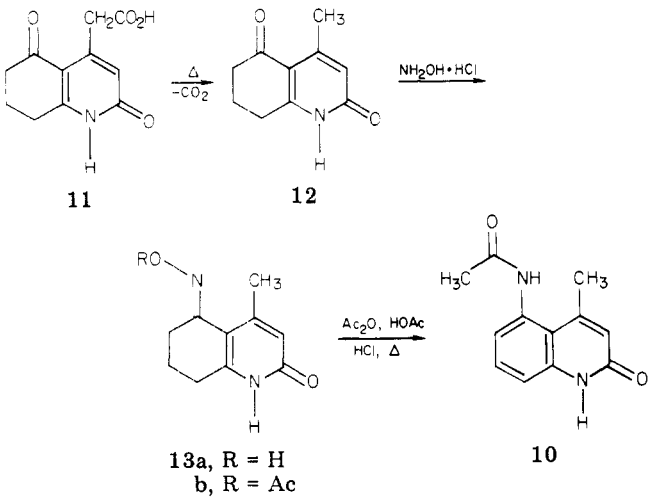
(4) Schroeter, G.; Gluschke, A.; Götzky, S.; Huang, J.; Irmisch, G.; Laves, E.; Schrader, O.; Stier, G. *Ber. Dtsch. Chem. Ges.* **1930**, *63*, 1308.

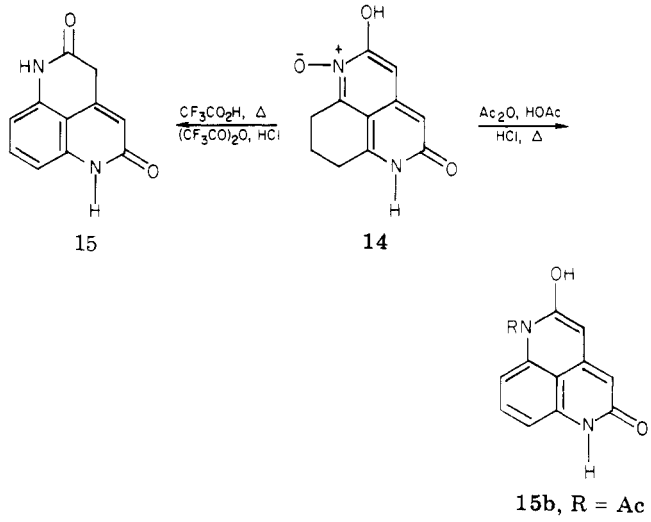
(5) (a) Bhatt, M. V. *Experienta* **1957**, *13*, 70. (b) Vorozhtsov, N. N.; Koptyug, V. A. *J. Gen. Chem. USSR (Engl. Transl.)* **1958**, *28*, 1697. (c) Bauer, L.; Hewitson, R. E. *J. Org. Chem.* **1962**, *27*, 3982. (d) Balling, P. J. Ph.D. Thesis, Seton Hall University, 1966. (e) Watnick, C. M. Ph.D. Thesis, Seton Hall University, 1970.

(6) Conley, T.; Ghosh, S. "Mechanisms of Molecular Migrations"; Thyagarajan, B. S., Ed.; Wiley-Interscience: New York, 1971; Vol. 4, pp 251-305 and references cited therein.

0022-3263/80/1945-2585$01.00/0

Scheme III





4, 5, and 6 depicted in Scheme II. The controversy as to whether the aromatization proceeds from the syn (oxime) to phenyl or anti to phenyl configuration continues today.[5a-e]

One of the strongest arguments, previously, in favor of the reaction proceeding from the syn to phenyl stereochemistry was the fact that 5,8-dimethyltetralone-1-oxime **7** did not aromatize when heated either in the Beckmann mixture or with *p*-toluenesulfonyl chloride but gave instead the Beckmann product **8** (see Scheme I). Although the possibility of syn to anti (oxime) isomerization has been employed[6] to explain earlier results, data obtained recently in our laboratory indicated that the syn to phenyl configuration was not necessary for aromatization.

During studies directed toward the preparation of potential antimalarial agents,[7] the synthesis of 4-methyl-5-acetamidocarbostyril (**10**) was required. Previously, cyclohexane-1,3-dione had been readily converted to the pyridoacetic acid derivative **11**,[8] and this material was then decarboxylated (thermally) to provide an excellent yield of the 4-methylcarbostyril **12**. The oxime **13a** was prepared in greater than 90% yield from **12** by standard methods, and the crystalline solid **13a** was then heated for 1 h in a mixture of acetic anhydride, acetic acid, and anhydrous hydrogen chloride. The white solid obtained[7] was found to be the oxime *O*-acetate **13b**; however, prolonged heating of **13a** or **13b** under analogous conditions gave 4-methyl-5-acetamidocarbostyril (**10**) in 53% yield (see Scheme III). The structure of **10** was deduced from chemical ionization mass spectroscopy ($M^+ + 1$, *m/e* 217) and NMR spectroscopy (see Experimental Section for assignments). The absence of the methylene protons of **13** and the characteristic aromatic coupling pattern observed in the spectrum of the product served to confirm the structure as **10**.

The conversion of **13a** or **13b** to **10** was in direct contrast to the results obtained by Schroeter on the dimethyltetralone-1-oxime **7**. Furthermore, the *N*-oxide **14**, the synthesis of which was described earlier,[9] was converted smoothly to the aromatic 1-acetyl-1,6-diazaphenalone **15b** when treated with the Beckmann mixture. In this example, the N–O bond must assume a position anti to the aromatic pyridone ring, yet aromatization did occur quite readily. In addition, treatment of the *N*-oxide **14** under modified Semmler–Wolff conditions[10] gave better than 85% yield of the aromatic diazaphenalone **15a** while absolutely no Beckmann (ring expanded) product was isolated. Aromatization of ring A of **14** also was observed in a different study when **14** was heated in the presence of phenylphosphonic dichloride (see ref 10) which gave 2,5-dichloro-1,6-diazaphenalene[10] in better than 70% yield.

The chemistry described here clearly illustrates that the mechanism of the Semmler–Wolff rearrangement has not been firmly established, as previously reported.[4] More importantly, the experimental results presented here dispel the myth that oximes substituted with a group peri to the reaction center do not undergo the aromatization reaction. The results, in fact, support the hypothesis of Watnick[5e] (see ref 6) that aromatization may take place from the oxime anti to phenyl (pyridone) configuration.

Experimental Section

Microanalyses were performed on an F & M Scientific Corp. Model 185 carbon, hydrogen, and nitrogen analyzer. Melting points were taken on a Thomas-Hoover melting point apparatus; they are uncorrected. Nuclear magnetic resonance spectra were recorded on a Varian T-60 spectrometer and a Varian CFT-20 ^{13}C NMR spectrometer. Infrared spectra were taken on a Beckman Acculab-1 instrument, and mass spectra were recorded on Hitachi RMU-6 and AEI-MS-902 mass spectrometers.

Analytical TLC plates used were E. Merck-Brinkmann UV-active silica gel or alumina on plastic. Cyclohexane-1,3-dione, hydroxylamine hydrochloride, and dimethyl acetone-1,3-dicarboxylate were purchased from Aldrich Chemical Co.

4-Methyl-5,6,7,8-tetrahydro-5-oxo-2-hydroxyquinoline (12). The quinoline **12** was prepared by the method of Wolfe.[11] The quinolon-4-ylacetic acid **11** (4.0 g, 0.017 mol) was heated under a stream of nitrogen until the solid melted. After evolution of gas had ceased, the product sublimed as a white solid: 3.2 g (99%); IR (KBr) 3420, 2920, 1680, 1650, 1600, 1420, 1290 cm^{-1}; NMR ($CDCl_3$) δ 2.21 (q, 2 H), 2.60 (s, 3 H), 3.00 (m, 4 H), 6.32 (s, 1 H), CI mass spectrum (NH_3), *m/e* (relative intensity) 179 (4), 178 (M + 1, 100), 177 (2).

Anal. Calcd for $C_{10}H_{11}NO_2$: C, 67.79; H, 6.21; N, 7.91. Found: C, 68.45; H, 6.27; N, 7.96.

4-Methyl-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-hydroxyquinoline (13a). The 4-methyl-5-oxoquinolone **12** (8.0 g, 0.04 mol), hydroxylamine hydrochloride (4.2 g, 0.06 mol), and sodium acetate (4.0 g, 0.06 mol) were heated to reflux for 3 h in a mixture of ethanol (40 mL) and water (40 mL). After several hours, a heavy white precipitate formed which was filtered from the so-

(7) El-Sheikh, M. I.; Chang, J.-C.; Weber, R.; Cook, J. M., paper presented at the American Chemical Society Great Lakes Regional Meeting, Rockford College, Rockford, IL, June 4–6, 1979 (abstract no. 206).

(8) Oehldrich, J.; Cook, J. M. *J. Org. Chem.* **1977**, *42*, 889.

(9) El-Sheikh, M. I.; Chang, J.-C.; Cook, J. M. *Heterocycles* **1978**, *9*, 1561.

(10) Chang, J.-C.; El-Sheikh, M. I.; Cook, J. M. *Heterocycles* **1979**, *12*, 903.

(11) Wolfe, J. F.; Trimitsis, G. B.; Morris, D. R. *J. Org. Chem.* **1969**, *34*, 3263.

lution and washed with water. The white crystalline solid was crystallized from aqueous alcohol to provide **13a** (8.0 g, 93%) as a white powder: mp 308–310 °C; IR (KBr) 3200, 1625, 1600, 1390, 1200 cm^{-1}; NMR (CF_3COOD) δ 2.23 (m, 2 H), 2.70 (s, 3 H), 3.06 (m, 4 H), 6.97 (s, 1 H); CI mass spectrum (NH_3), *m/e* (relative intensity) 193 ($M^+ + 1$, 100).

Anal. Calcd for $C_{10}H_{12}N_2O_2$: C, 62.48; H, 6.29; N, 14.57. Found: C, 62.60; H, 6.52; N, 14.38.

4-Methyl-5,6,7,8-tetrahydro-5-(hydroxyimino)-2-hydroxyquinoline-5-acetate (13b). The oxime **13a** (0.50 g, 0.003 mol) obtained from the previous experiment was dissolved in a mixture of acetic acid (4 mL) and acetic anhydride (1.5 mL). The solution was saturated with anhydrous hydrogen chloride and then heated to reflux for 1 h. The light brown solution which resulted was cooled and diluted with water, and a white solid precipitated from the mixture. The material was crystallized from alcohol to provide **13b**: 0.43 g (70%); mp 268–270 °C; IR (KBr) 3450, 1760, 1650, 1610, 1580 cm^{-1}; NMR (warm Me_2SO) δ 1.63 (q, 2 H), 2.20 (s, 3 H), 2.40 (s, 3 H), 2.60 (m, 4 H), 6.10 (s, 1 H); CI mass spectrum (NH_3), *m/e* (relative intensity) 236 (18), 235 ($M^+ + 1$, 100), 177 (15).

Anal. Calcd for $C_{12}H_{14}N_2O_3$: C, 61.54; H, 5.98; N, 11.96. Found: C, 62.29; H, 5.95; N, 12.02.

4-Methyl-5-acetamido-2-quinolone (10). The oxime (**13a**; 0.5 g, 0.003 mol) was dissolved in a mixture of acetic acid (4 mL) and acetic anhydride (1.5 mL). The solution was saturated with anhydrous hydrogen chloride gas and then held at reflux for 18 h. At the end of the reaction period, the solution had become dark whereupon it was cooled, diluted with water, and allowed to stand for several hours. The white precipitate which formed was washed with water and crystallized from alcohol to provide the quinolone **10**: 0.30 g (53%); mp 355 °C; IR (KBr) 3280, 1690, 1650, 1610, 1535 cm^{-1}; NMR (warm Me_2SO, 220 MHz) δ 2.04 (s, 3 H), 2.41 (2 s, 3 H, rotomers), 6.32 (s, 1 H), 6.93 (d, 1 H), 7.25 (d, 1 H), 7.43 (t, 1 H), 9.72 (s, 1 H); CI mass spectrum (NH_3), *m/e* (relative intensity) 218 (16), 217 ($M^+ + 1$, 100), 216 (14).

Anal. Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.50; N, 12.96. Found: C, 66.41; H, 5.28; N, 13.05.

There were two other materials (20%) present in the mother liquor of this reaction mixture. One of these compounds still contained a signal due to methylene protons; however, it was present in only minute quantities, and it was not possible to separate the compound from the starting material (**13a** or **13b**).

2,5-Dihydroxy-1,6-diazaphenalene-1-acetamide (15b). The *N*-oxide **14** (2.0 g, 0.009 mol) was dissolved in acetic acid (32 mL) and acetic anhydride (12 mL), after which the solution was saturated with hydrogen chloride gas. The mixture was heated to reflux for 18 h, cooled, and diluted with water, and the precipitate which formed upon standing was filtered from the medium. The green solid was washed with water, dissolved in acetic acid, and reprecipitated upon dilution with water. The orange-green solid obtained from this treatment was dried to provide **15b**: 1.7 g (86%); mp >350 °C; IR (KBr) 3200, 1670, 1630, 1600, 1370, 1300 cm^{-1}; NMR (warm Me_2SO, 60 MHz) δ 2.50 (s, 3 H), 6.20 (s, 1 H), 6.60–7.30 (m, 4 or 5 H), 10.57 (s, 1 H), 11.60 (s, 1 H) (on addition of D_2O, the singlets at δ 10.57 and 11.60 disappeared); NMR (CF_3COOH) δ 2.80 (s, 3 H), 7.00–8.00 (m, 5 H); CI mass spectrum (NH_3), *m/e* (relative intensity) 244 (19), 243 ($M^+ + 1$, 100), 242 (17), 201 (13).

Anal. Calcd for $C_{13}H_8N_2O_2$: C, 64.46; H, 4.13; N, 11.57. Found: C, 64.43; H, 3.97; N, 11.48.

N.B. When the reaction was scaled up to the 8-g level, the yield fell off considerably, and **15b** was contaminated with other material. It was felt that some dimeric material may be the contaminant; however, numerous attempts to observe a dimer (CI mass spectroscopy) failed; moreover, the product contained no methylene protons, and therefore any dimer formation (if present) would have occurred after the Semmler–Wolff aromatization took place.

Registry No. **10**, 73636-01-8; **11**, 61062-45-1; **12**, 29707-35-5; **13a**, 73636-02-9; **13b**, 73636-03-0; **14**, 68871-44-3; **15b**, 73636-04-1.

Studies on Ketene and Its Derivatives. 100.[1] 1-(Dimethylphosphono)- and 1-(Diphenylphosphinyl)-5-oxo-4-oxaspiro[2.3]hexanes. Synthesis and Some Reactions

Tetsuzo Kato,* Nobuya Katagiri, and Renzo Sato

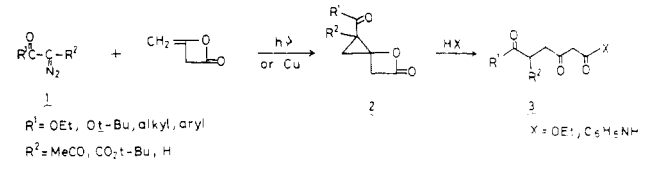
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Received January 25, 1980

Reaction of diketene with dimethyl (α-diazoalkyl)phosphonates **4–8** and (diazomethyl)diphenylphosphine oxide (**14**) under irradiation gave *E* and *Z* 1-substituted 1-(dimethylphosphono)-5-oxo-4-oxaspiro[2.3]hexanes **9a,b–13a,b** and (*E*)- and (*Z*)-1-(diphenylphosphinyl)-5-oxo-4-oxaspiro[2.3]hexanes (**15a,b**), respectively. The stereochemical assignment was made on the basis of the NMR spectral data. Methanolysis of 1-(dimethylphosphono)-5-oxo-4-oxaspiro[2.3]hexane (**9**) and 1-(dimethylphosphono)-1-phenyl-5-oxo-4-oxaspiro[2.3]hexane (**11**) gave dimethyl 4-(methoxycarbonyl)-3-oxobutylphosphonates **16** and **17**. Treatment of **9** and **11** with anilines gave dimethyl 4-(*N*-arylcarbamoyl)-3-oxobutylphosphonates **18a–d** and **19a–d**. Compounds **9** and **11** reacted with *o*-phenylenediamine and phenols to give 4-[2-(dimethylphosphono)ethyl]-1,5-benzodiazepin-2-ones **20** and **21** and 4-[2-(dimethylphosphono)ethyl]-7-hydroxycoumarin derivatives **22a,b** and **23a,b**, respectively. Compound **11** and (*E*)-1-(dimethylphosphono)-1-(*p*-methoxyphenyl)-5-oxo-4-oxaspiro[2.3]hexane (**12a**), on treatment with methyl acetoacetate in the presence of sodium hydride, underwent ring transformation to give 2-cyclopentenones **24** and **25**.

Previously, we have reported reactions of diketene with α-diazo ketones and esters **1**, in the presence of copper powder or under irradiation, to give 1-substituted 5-oxo-4-oxaspiro[2.3]hexanes **2**[2–4] (Scheme I). Compounds of type **2**, upon treatment with nucleophiles, undergo opening

Scheme I



of β-lactone and cyclopropane rings to give β-keto carboxylic acids **3**, which subsequently cyclize to heterocycles.[3,4] The reactions which form **2** are taken to involve

(1) Part 99: Kato, T.; Chiba, T.; Sasaki, T., *Yakugaku Zasshi*, **1980**, *100*, 571.
(2) Kato, T.; Katagiri, N. *Chem. Pharm. Bull.* **1973**, *21*, 729.
(3) Kato, T.; Katagiri, N.; Sato, R. *J. Chem. Soc., Perkin Trans 1* **1979**, 525.
(4) Kato, T.; Katagiri, N.; Sato, R. *Chem. Pharm. Bull.* **1979**, *27*, 1176.

0022-3263/80/1945-2587$01.00/0