Intramolecular Acylation of 3-Oxo-2-Piperidinepropionic Acid Derivatives. Synthesis of Hexahydro-2-oxopyrano[3,2-*b*]pyridines (1)

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Received September 11, 1981

The intramolecular acylation of some δ-keto acids derived from 3-oxo-2-piperidinepropionic acid are described. Bicyclic enol lactones coming from an *O*-acylation reaction are obtained in all cases. The regioselectivity of these processes is discussed in terms of the acylating agent and the δ-keto acid structure. The procedure establishes a convenient synthesis of hexahydro-2-oxopyrano[3,2-*b*]pyridines.

J. Heterocyclic Chem., **19**, 489 (1982).

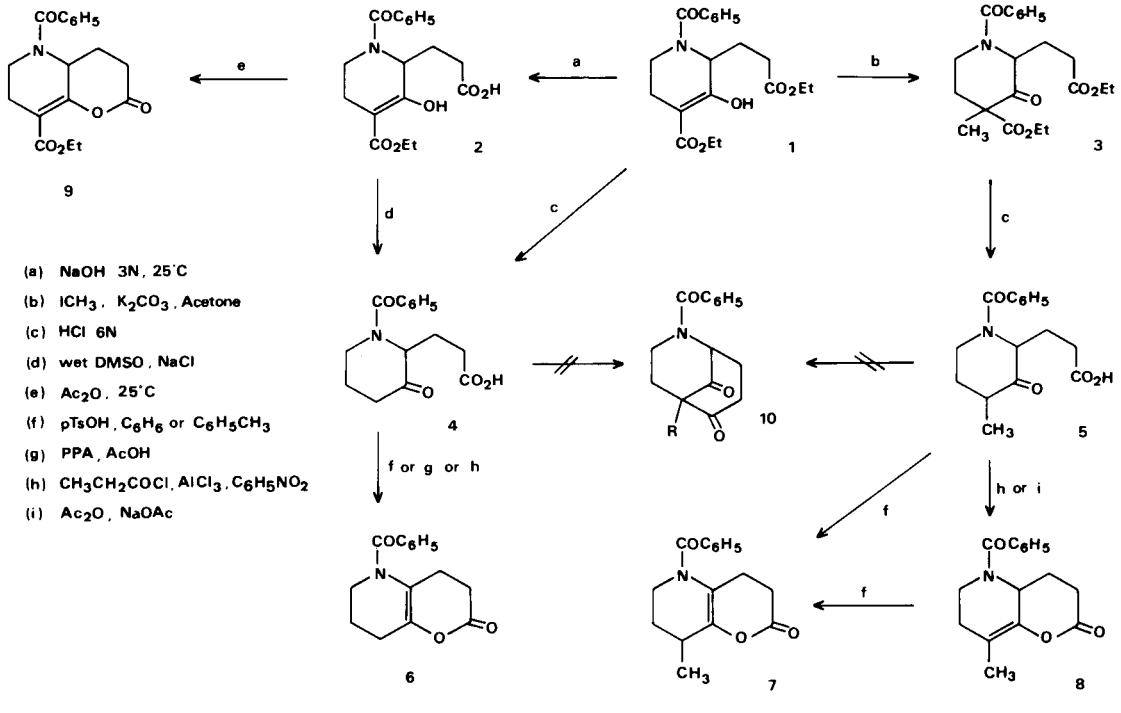
In connection with our previous work (2,3) about the reactivity of ethyl 1-benzoyl-4-ethoxycarbonyl-3-oxo-2-piperidinepropionate (**1**), in the context of the synthesis of functionalized 2-azabicyclo[3.3.1]nonane systems (4), we wish to report the intramolecular acylations of δ-keto acids **2**, **4**, and **5**, prepared from piperidine **1**.

The reactivity of keto acids in front of the acid-catalyzed intramolecular acylation has not been systematized, a different regiospecificity (*O- vs C*-acylation) being observed depending on the compound structure and the reaction conditions. Thus, *C*-acylations leading to β-diketones (5-10) have been described, as well as *O*-acylations providing enol lactones (11-15).

The δ-keto acids **4** and **5** were prepared from the previously described (2) piperidines **1** and **3**, respectively, by treatment with 6*N*-hydrochloric acid. Alternatively, **4** was obtained by decarbethoxylation of acid **2** (2) by heating in the presence of wet dimethyl sulfoxide and sodium chloride (16). These preparations of 3-oxo-2-piperidinepropionic acid derivatives constitute an alternative route to that already developed by other authors (17). The nmr spectra of keto acids **4** and **5** show, as the most characteristic common aspects, a singlet at δ 7.35 due to the aromatic protons (18) and the chemical shift (δ ~ 5.0) of the proton on the 2-position of the piperidine ring. This value indicates that compounds **4** and **5** adopt a conformation in which the 2-carboxyethyl group is in an axial position, as it is usual in *N*-acylpiperidines (19).

Treatment of keto acid **4** with *p*-toluenesulfonic acid in refluxing benzene provided the enol lactone **6**. The same lactone was obtained on treating **4** with a mixture of polyphosphoric and glacial acetic acids as well as with

Scheme



aluminum trichloride in nitrobenzene in the presence of propionyl chloride.

The behavior of δ-keto acid **5** is different since, although with *p*-toluenesulfonic acid in refluxing toluene afforded the endocyclic enol lactone **7**, treatment of **5** either with aluminum trichloride and propionyl chloride or with acetic anhydride-sodium acetate led to the isomeric exocyclic enol lactone **8**.

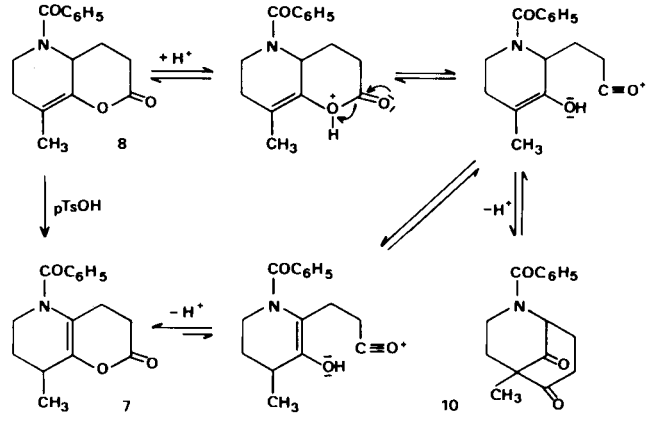
The most characteristic absorption in the ir spectrum of compounds **6** and **7** is the signal at 1770 cm^{-1} due to the enol lactone carbonyl group. In turn, in the nmr spectrum of both lactones, the four protons of the lactone ring show the same chemical shift appearing as a singlet at δ 2.6. The double bond position between the condensation positions 4a and 8a is evidenced by the absence of signals due to vinylic protons in **6** and by the existence of a doublet at δ 1.16 for the methyl group on the 8-position in **7**. Instead, in lactone **8** this methyl group resonates at δ 1.78 as a broad singlet due to the allylic coupling with the 4a methine proton (confirmed by spin-decoupling experiments). In the ir spectrum of lactone **8** absorptions at 1760 and 1705 cm^{-1} corresponding to the carbonyl and the olefinic double bonds of the enol lactone, respectively, were observed.

An enol lactone (**9**) with an exocyclic double bond was also obtained by treatment of δ-keto acid **8** with acetic anhydride at room temperature. The mild reaction conditions compared to the ones required in the lactonization of other γ- or δ-keto acids, as well as the double bond position in the resulting enol lactone, reflect the enolic character of the ketone group of **2**, being included in an enolizable β-dicarbonyl system (20). In the nmr spectrum of **9** the 4a methine proton appears as a double doublet at δ 4.95, anisotropically affected by the amide carbonyl group (19a).

The different regioselectivity in the above lactonization processes can be interpreted in terms of the acylating agent and the δ-keto acid structure (21). Thus, the acylation of enols in the presence of *p*-toluenesulfonic acid is a reversible process leading to the thermodynamically most stable system. Formation of enol lactones **6** and **7** when *p*-toluenesulfonic acid was used indicates therefore their greater stability with respect to the exocyclic double bond lactones and to the *C*-acylation products of 2-azabicyclo-[3.3.1]nonane pattern, **10**. Moreover, the isomeric enol lactones of constitutionally unsymmetrical ketones are equilibrated by prolonged treating with *p*-toluenesulfonic acid. In fact, our enol lactone **8** was totally converted into the endocyclic isomer **7** under these conditions.

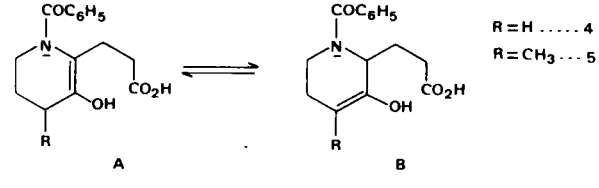
In order to explain the formation of the enol lactone **8** when acetic anhydride-sodium acetate or aluminum trichloride-propionyl chloride are used, we must consider that the products are formed in an irreversible manner

Figure 1



under these conditions and that the acid catalyzed enolization of ketones is usually found to follow the Saytzeff rule and to be an example of a reaction controlled by hyperconjugative factors (22). According to this hypothesis, an increasing number of hydrogens stabilizing the enol by hyperconjugation would increase the enolization rate. Thus, enol **5B** would be more stable than **5A**, and the irreversible acylation by the mixed anhydride generated on the side chain would lead to the enol lactone **8**. Instead, ketone **4** gives the more stable, more substituted, enol, **4A** faster than alterantive as it is usual in α-alkylcycloalkanones (22), and lactonization under irreversible conditions affords the same enol lactone **6** that under thermodynamic control conditions.

Figure 2



Formation of the *O*-acylation product **8** and not of the *C*-acylation one **10** (R = CH_3) can be attributed to the steric crowding existing at the 4 position of the piperidine ring due to the presence of a methyl group (23). In fact, only few examples of *C*-acylation processes leading to bridged non enolizable diketones from γ- or δ-keto acids in which an *O*-acylation process was possible have been described (6b, 6d,7b,10).

The above results show the difficulty in achieving intramolecular acylations upon the 4-position of 3-oxo-2-piperidinepropionic acid derivatives. Presumably, this difficulty should be lesser when the piperidine nitrogen atom is included in an amide system since piperidine acylation diminishes the stability of the 2-piperidine type enol (**A**) and favours the ring conformation that maintains the

2-carboxyethyl chain in an axial position (19), which is the required for *C*-acylation. However, even though the precedure is not applicable to the direct preparation of 2-azabicyclo[3.3.1]nonan-6,9-diones (24), it establishes the first method for the synthesis of hexahydro-2-oxopyrano-[3,2-*b*]pyridines.

EXPERIMENTAL

Nuclear magnetic resonance spectra were determined in deuteriochloroform solution with a Perkin-Elmer R-24B (60 MHz) Spectrometer using internal tetramethylsilane (δ 0) as a reference. Infrared spectra were obtained with a Perkin-Elmer 577 Spectrophotometer as potassium bromide discs (except where noted). Melting points were determined on a Büchi apparatus and are uncorrected. Brine refers to a saturated aqueous sodium chloride solution. Prior to concentration, under reduced pressure, all organic extracts were dried over anhydrous magnesium sulfate powder. Elemental analyses were performed by the Instituto de Química Bio-Orgánica, Barcelona.

Ethyl 1-benzoyl-4-ethoxycarbonyl-3-oxo-2-piperidinepropionate (**1**), 1-benzoyl-4-ethoxycarbonyl-3-oxo-2-piperidinepropionic acid (**2**), and ethyl 1-benzoyl-4-ethoxycarbonyl-4-methyl-3-oxo-2-piperidinepropionate (**3**) were prepared by previously described procedures (2).

1-Benzoyl-3-oxo-2-piperidinepropionic Acid (**4**).

Sodium chloride (820 mg, 14 mmoles), water (720 mg, 40 mmoles), and dimethyl sulfoxide (20 ml) were added to β-keto ester **2** (5.05 g, 13.5 mmoles), and the heterogeneous reaction mixture was heated at 155-160° for 3 hours. After cooling, the mixture was diluted with 0.05 *M* aqueous hydrochloric acid and extracted with chloroform. The organic layer was exhaustively washed with brine. Evaporation afforded 2.8 g (75%) of keto acid **4**, mp 138-140° (acetone); ir: 2500-3500 (acid), 1725 (ketone and acid), 1595 (benzamide); nmr: 1.8-2.8 (m, 8H, CH_2), 3.35 (m, 1H, C_6-H_{ax}), 3.95 (broad signal, 1H, C_6-H_{eq}), 4.9 (broad signal, 1H, C_2-H_{eq}), 7.35 (s, 5H, ArH), 9.85 (broad signal, 1H, COOH).

Anal. Calcd. for $C_{15}H_{17}NO_4 \cdot \frac{1}{4}H_2O$: C, 64.39; H, 6.30; N, 5.00. Found: C, 64.68; H, 6.31; N, 4.86.

Alternatively, **4** was obtained from **1** (21.4 g, 57 mmoles) by treatment with 6*N* aqueous hydrochloric acid (330 ml) at 100-110° for 2 hours. The reaction mixture was cooled, basified with potassium carbonate and extracted with ether. The aqueous layer was acidified with 1*N* hydrochloric acid and extracted with chloroform. Evaporation left a viscous oil which solidified on standing. The crude material was digested with boiling hexane (to dissolve the benzoic acid) and then dried affording 11.2 g (72%) of **4**.

1-Benzoyl-4-methyl-3-oxo-2-piperidinepropionic Acid (**5**).

A solution of δ-keto ester **3** (36.9 g, 95 mmoles) in 6*N* aqueous hydrochloric acid (570 ml) was heated at 100-110° for 2 hours. The mixture was worked up as in the above procedure to give 17.6 g (63%) of acid **5**, mp 122-124° (acetone-ether); ir: 2500-3500 (acid), 1730 (ketone and acid), 1590 (benzamide); nmr: 1.07 (d, 3H, CH_3), 1.5-2.9 (m, 7H, CH_2 and C_4-H), 3.1-4.0 (m, 2H, NCH_2), 5.0 (broad signal, 1H, C_2-H_{eq}), 7.35 (s, 5H, ArH), 9.75 (s, 1H, COOH).

Anal. Calcd. for $C_{16}H_{19}NO_4$: C, 66.43; H, 6.57; N, 4.84. Found: C, 66.65; H, 6.72; N, 4.85.

5-Benzoyl-2-oxo-3,4,5,6,7,8-hexahydro-2*H*-pyrano[3,2-*b*]pyridine (**6**). Method A.

A solution of keto acid **4** (1.05 g, 3.8 mmoles) and *p*-toluenesulfonic acid (150 mg) in 50 ml of benzene was refluxed with removal of water by a Dean-Stark trap. After 8 hours the solution was washed with brine. Evaporation gave a mixture of enol lactone **6** and acid **4**. Crystallization from acetone-ether gave 440 mg (50%) of **6**, mp 135-137°; ir (chloroform): 1770 (enol lactone), 1635 (benzamide); nmr: 1.9 (m, 2H, 7-CH_2), 2.3 (m, 2H, 8-CH_2), 2.6 (s, 4H, 3- and 4-CH_2), 3.6 (m, 2H, NCH_2), 7.45 (s, 5H, ArH).

Anal. Calcd. for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.87; N, 5.44. Found: C, 69.91; H, 5.96; N, 5.33.

Method B.

To a solution of keto acid **4** (530 mg, 1.9 mmoles) in glacial acetic acid (9 ml), polyphosphoric acid (5 g) was added. The mixture was stirred at 100° for 5 hours, poured into ice-water and extracted with benzene. The benzene solution was washed with aqueous 5% sodium bicarbonate solution. Evaporation afforded 150 mg (30%) of crude **6**.

Method C.

Propionyl chloride (290 mg, 3.1 mmoles) and freshly sublimed aluminum trichloride (1.25 g, 9.4 mmoles) were slowly added to a solution of acid **4** (850 mg, 3.1 mmoles) in nitrobenzene (12 ml). The mixture was stirred at 80° for 4 hours, cooled, poured into ice-water and extracted with methylene chloride. The combined organic extracts were exhaustively washed with brine and with aqueous 5% sodium bicarbonate solution. After removal of the solvent 325 mg (40%) of **6** were obtained.

5-Benzoyl-8-methyl-2-oxo-3,4,5,6,7,8-hexahydro-2*H*-pyrano[3,2-*b*]pyridine (**7**).

Acid **5** (920 mg, 3.2 mmoles) was dissolved in anhydrous toluene (70 ml) containing *p*-toluenesulfonic acid (300 mg) in a flask fitted with a Dean-Stark apparatus. The mixture was azeotropically refluxed removing water for 24 hours. The solution was washed with brine and evaporated to give 450 mg (52%) of lactone **7**, mp 122-123° (ether); ir: 1770 (enol lactone), 1630 (benzamide); nmr: 1.16 (d, 3H, CH_3), 1.5-2.5 (m, 3H, 7-CH_2 and C_8-H), 2.6 (s, 4H, 3- and 4-CH_2), 3.4-3.9 (m, 2H, NCH_2), 7.4 (s, 5H, ArH).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.84; H, 6.27; N, 5.16. Found: C, 70.74; H, 6.32; N, 5.02.

5-Benzoyl-8-methyl-2-oxo-3,4,4a,5,6,7-hexahydro-2*H*-pyrano[3,2-*b*]pyridine (**8**). Method A.

Propionyl chloride (1.48 g, 16 mmoles) and freshly sublimed aluminum trichloride (6.58 g, 49 mmoles) were slowly added to a solution of acid **5** (4.8 g, 16 mmoles) in nitrobenzene (80 ml). After stirring for 4 hours at 80° the reaction mixture was cooled and water was added. The resulting cloudy suspension was filtered through Hygflo Super-Cel. The filtrate was extracted with chloroform. The organic extract was washed with brine, dried, and evaporated in high *vacuo* in order to remove nitrobenzene giving 2.7 g (62%) of lactone **8** mp 126-127° (ether); ir: 1760 (enol lactone), 1705 (C=C), 1630 (benzamide); nmr: 1.77 (broad s, 3H, CH_3), 1.90-2.95 (m, 6H, CH_2), 3.0-3.5 (m, 1H, C_6-H_{ax}), 3.65-4.15 (m, 1H, C_6-H_{eq}), 4.8 (broad signal, 1H, C_{4a}-H), 7.35 (s, 5H, ArH).

Anal. Calcd. for $C_{16}H_{17}NO_3$: C, 70.84; H, 6.27; N, 5.16. Found: C, 70.75; H, 6.29; N, 5.07.

Method B.

A solution of keto acid **5** (400 mg, 1.38 mmoles) and anhydrous sodium acetate (100 mg) in acetic anhydride (5 ml) was refluxed for 4 hours. The reaction mixture was poured into methylene chloride. The organic solution was washed with water, saturated sodium bicarbonate solution, and water. After drying and evaporation, 187 mg (50%) of enol lactone **8** were obtained.

Method C.

Boron trifluoride-etherate (3.5 ml) was added to a solution of acid **5** (2.65 g, 9.1 mmoles) in 2 ml of acetic anhydride and 12 ml of glacial acetic acid. The mixture was stirred at room temperature for 24 hours and diluted with chloroform. The organic solution was exhaustively washed with water and evaporated. The residue was crystallized from acetone-ether to give 750 mg (34%) of enol lactone **8**.

Ethyl 5-Benzoyl-2-oxo-3,4,4a-5,6,7-hexahydro-2*H*-pyrano[3,2-*b*]pyridine-8-carboxylate (**9**).

A solution of acid **2** (1.23 g, 3.5 mmoles) in acetic anhydride (35 ml) was stirred at room temperature for 14 hours. The crystalline material which remained after removal of acetic anhydride represented a quantitative yield of the enol lactone **9**, mp 143-145° (benzene-petroleum ether); ir: 1775 (enol lactone), 1695 (enol ester), 1630 (benzamide); nmr: 1.30 (t, 3H, CH_3), 1.7-3.1 (m, 6H, CH_2), 3.25 (m, 1H, C_6-H_{ax}), 4.0-4.3 (masked, 1H, C_6-H_{eq}), 4.25 (q, 2H, OCH_2), 4.95 (m, 1H, C_{4a}-H), 7.40 (s, 5H, ArH).

Anal. Calcd. for $C_{18}H_{19}NO_5$: C, 65.65; H, 5.77; N, 4.25. Found: C, 65.40; H, 5.86; N, 4.21.

Conversion of Enol Lactone **9** Into Ester **1** and Into Acid **2**.

Enol lactone **9** (200 mg,0.61 mmole) was dissolved in anhydrous chloroform (15 ml) and treated with absolute ethanol (25 ml) containing a drop of sulfuric acid. The resulting solution was stirred overnight at room temperature, neutralized with solid sodium bicarbonate and evaporated. The residue was dissolved in chloroform and washed with water. The organic layer was dried and evaporated affording β-keto ester **1** (190 mg, 84%).

Enol lactone **9** (510 mg, 1.55 mmoles) was treated with 15 ml of 1 *M* sodium hydroxide for 1 hour at room temperature. The resulting solution was acidified with 1 *M* hydrochloric acid and extracted with ether. The organic extracts were dried and evaporated to give 470 mg (87%) of acid **2**.

Ethyl 1-Benzoyl-3-oxo-2-piperidinepropionate (**11**).

A mixture of β-keto ester **1** (12 g, 32 mmoles), sodium chloride (2 g, 35 mmoles), water (1.8 ml, 0.1 mole), and dimethyl sulfoxide (25 ml) was heated at 150-155° for 3 hours. The suspension was cooled, diluted with ether and exhaustively washed with brine. The ethereal solution was evaporated to afford 6.5 g (67%) of **11**, bp 230-240/0.5 mm (26); ir (chloroform): 1725 (ester), 1630 (benzamide); nmr: 1.20 (t, 3H, CH_3), 1.8-2.8 (m, 8H, CH_2), 3.35 (m, 1H, C_6-H_{ax}), 3.7-4.2 (masked, 1H, C_6-H_{eq}), 4.07 (q, 2H, OCH_2), 4.85 (broad signal, 1H, C_2-H_{eq}), 7.35 (s, 5H, ArH).

Anal. Calcd. for $C_{17}H_{21}NO_4$: C, 67.31; H, 6.98; N, 4.61. Found: C, 67.03; H, 7.19; N, 4.65.

Ethyl 1-Benzoyl-4-methyl-3-oxo-2-piperidinepropionate (**12**).

A mixture of β-keto ester **3** (5.10 g, 13.1 mmoles), lithium chloride (1.11 g, 26 mmoles), water (0.25 ml, 14 mmoles), and dimethyl sulfoxide (30 ml) was heated at 165° for 10 hours. Water was added and the solution was extracted with benzene. The organic layer was exhaustively washed with brine, dried and evaporated. Chromatography of the residue on silica gel (9:1 benzene-chloroform as eluent) afforded 3 g (71%) of keto ester **12**, bp 240-250/0.5 mm (26); ir (chloroform): 1720 (ketone, ester), 1625 (benzamide); nmr: 1.07 (d, 3H, C_4-CH_3), 1.20 (t, 3H, CH_3), 1.6-3.0 (m, 7H, CH_2 and C_4-H), 3.1-3.9 (m, 2H, NCH_2), 4.05 (q, 2H, OCH_2), 4.85 (broad signal, 1H, C_2-H_{eq}), 7.30 (s, 5H, ArH).

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.14; H, 7.88; N, 4.42. Found: C, 68.11; H, 7.71; N, 4.70.

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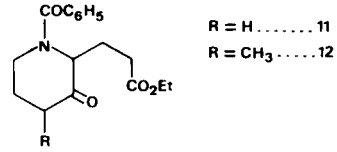
(24) Not either the base-catalyzed (sodium hydride, sodium ethoxide, potassium *t*-butoxide) intramolecular acylation of keto esters **11** and **12** afforded these kind of systems but complex reaction mixtures.

Figure 3



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