

FACILE  $\alpha, \beta'$ -ANNELATION OF 1,6-DIHYDRO-3(2H)-PYRIDINONES WITH  
1,3-DICARBONYL COMPOUNDS. A NEW SYNTHETIC METHOD FOR 2-AZA-  
BICYCLO[2.2.2]OCTAN-6-ONES

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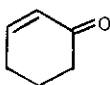
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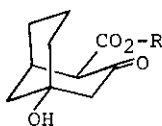
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*Abstract* — On treatment of N-substituted 1,6-dihydro-3(2H)-pyridinones with 1,3-dicarbonyl compounds proceeded a facile  $\alpha, \beta'$ -annulation to give the 2-azabicyclo[2.2.2]octan-6-ones under a basic condition, while the reaction with dimethyl acetonedicarboxylate afforded a 3-azabicyclo[3.3.1]nonanone.

2-Cyclohexenone (1) is well known to afford the bicyclo[3.3.1]nonan-3-ones (2) by the base-catalyzed reaction with ethyl acetoacetate.<sup>1</sup> As an application of this method to azacyclic enones, we have investigated the reaction of N-substituted 1,6-dihydro-3(2H)-pyridinones with several 1,3-dicarbonyl compounds and now wish to report the exclusive abnormal cyclization to the 2-azabicyclo[2.2.2]octan-6-one system (3) through an  $\alpha, \beta'$ -annulation reaction.<sup>2</sup>

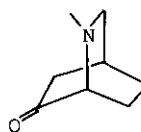


1



R=Et, H

2



3

Treatment of ethyl 1,6-dihydro-3(2H)-pyridinone-1-carboxylate<sup>3</sup> (4) with one equivalent of ethyl acetoacetate (5a) in ethanol containing 0.2 equivalent of sodium ethoxide at room temperature afforded diethyl 7-hydroxy-7-methyl-2-azabicyclo-

[2.2.2]octan-6-one-2,8-dicarboxylate ( $\xi_a$ ) in 70% yield as a sole product *via* the Michael adduct ( $\zeta_a$ ), which could be obtained by the reaction in the presence of a catalytic amount of the base. The adduct ( $\zeta_a$ ) [ $\delta$  2.24(3H, s), positive  $\text{FeCl}_3$  test] cyclized easily to afford  $\xi_a$  in good yield by passing through alumina or on further treatment with sodium ethoxide in ethanol. The planar structure of  $\xi_a$  was established from the spectral evidences. The IR spectrum showed a carbonyl band at  $1735\text{ cm}^{-1}$  characteristic of this ring system<sup>4</sup> and the PMR spectrum exhibited the  $\text{C}_7$ -methyl singlet at 1.56 ppm.<sup>5</sup> N-Methanesulfonyl-1,6-dihydro-3(2H)-pyridinone<sup>6</sup> ( $\eta$ ) also gave the corresponding isoquinuclidinone ( $\vartheta_a$ ) [ $\nu$  3475(OH), 1735(CO), 1340, 1160( $\text{SO}_2$ ),  $\delta$  1.30(3H, t,  $J=7$ ), 1.67(3H, s), 2.71(3H, s), 4.20(2H, q,  $J=7$ )] by the reaction with ethyl acetoacetate under the same condition in 78% yield. The results of the reaction using other 1,3-dicarbonyl compounds ( $\xi_b$ - $\xi_e$ ) are summarized in Table I.

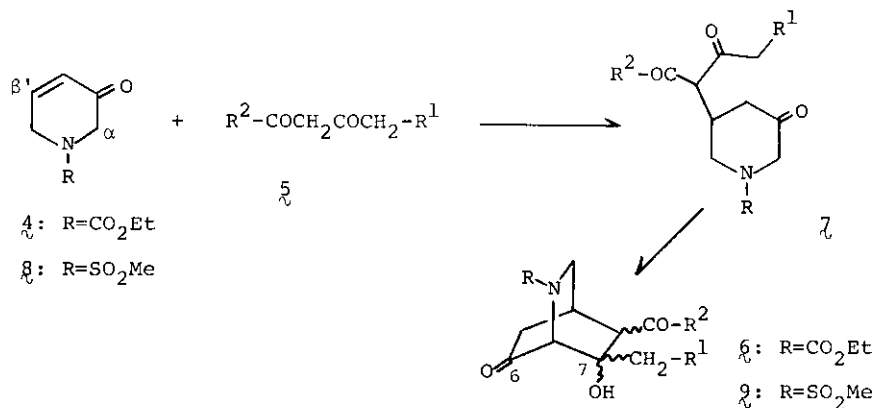


Table I. Reaction of Dihydropyridinones ( $\text{4}$  and  $\text{8}$ ) with 1,3-Dicarbonyl Compounds ( $\text{5}$ )<sup>a</sup>

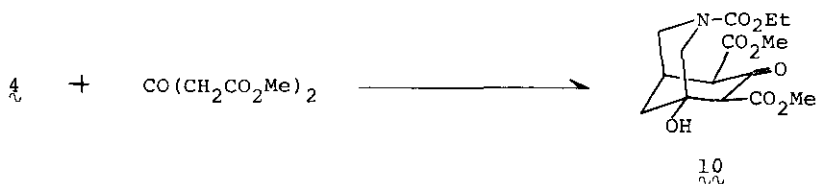
Substrate	1,3-Dicarbonyl Compd.	Yield(%) of Product	Chemical Shift of $\text{C}_7$ -Substituent( $\delta$ )
$\text{4}$	$\xi_a: \text{R}^1=\text{H}, \text{R}^2=\text{OEt}$	$\xi_a: 70$	1.56(s)
$\text{8}$	$\xi_a$	$\vartheta_a: 78$	1.67(s)
$\text{4}$	$\xi_b: \text{R}^1=\text{Me}, \text{R}^2=\text{OEt}$	$\xi_b: 60$	1.00(t), 1.76(q)
$\text{8}$	$\xi_b$	$\vartheta_b: 52$	1.00(t), 2.01(q)
$\text{4}$	$\xi_c: \text{R}^1=\text{H}, \text{R}^2=\text{OMe}$	$\xi_c: 73$	1.55(s)
$\text{4}$	$\xi_d: \text{R}^1=\text{H}, \text{R}^2=\text{Me}$	$\xi_d: 62$	1.68(s)
$\text{4}$	$\xi_e: \text{R}^1=\text{H}, \text{R}^2=\text{NHC}_6\text{H}_5$	$\xi_e: 52$	1.42(s)

<sup>a</sup> Reaction with  $\text{5}$  (1 equiv.) in the presence of  $\text{NaOEt}$  (0.2 equiv.) in  $\text{EtOH}$  at room temperature for 4 hr.

The difference between 2-cyclohexenone ( $1$ ) and the azacyclic enone ( $4$  or  $8$ ) in behavior toward ethyl acetoacetate would be attributed to the high acidity of  $\alpha$ -H in  $4$  or  $8$  in comparison with that of  $1$ . The higher acidity is due to an inductive effect of the electron-withdrawing substituent attached at the nitrogen atom.

Although there are lots of reports<sup>7</sup> concerning syntheses of 2-azabicyclo[2.2.2]octanones, the present method seems to be noteworthy from the viewpoint of facility in operation and functionality in products, and would serve as a novel synthetic method for 2-azabicyclo[2.2.2]octan-6-one moiety.

On the contrary, the normal cyclization to 3-azabicyclo[3.3.1]nonanone was achieved by the condensation with the 1,3,5-tricarbonyl compound. Reaction of  $4$  with dimethyl acetonedicarboxylate in the presence of a catalytic amount of sodium ethoxide yielded the 3-azabicyclo[3.3.1]nonan-7-one ( $10$ ) [64%, positive  $\text{FeCl}_3$  test,  $\delta$  12.00 (1H, enol H)] without any amount of 2-azabicyclooctanones. The same ring



system is also accessible from the 2-azabicyclo[2.2.2]octanonecarboxylate ( $6a, b$  and  $9a, b$ ) *via* ring isomerization. Hydrolysis of  $6a$  with 10% hydrochloric acid in acetic acid was accompanied by decarboxylation to give the 3-azabicyclo[3.3.1]nonanone ( $11a$ ) [20%,  $\nu$  3350 (OH), 1680 (CO, NCO),  $\delta$  2.20 (2H, broad s,  $\text{C}_9$ -H)] along with the 2-azabicyclo[2.2.2]octanones,<sup>8</sup>  $12a$  [24%,  $\nu$  3400 (OH), 1735 (CO), 1675 (NCO),  $\delta$  1.35 (3H, s)] and  $13a$  [3%,  $\nu$  3400 (OH), 1738 (CO), 1675 (NCO),  $\delta$  1.25 (3H, s)]. The longer treatment of  $6a$  under the same condition effected complete ring isomerization to give  $11a$  as a sole product. Other results are summarized in Table II. Such ring isomerization would proceed through the retro-aldol and subsequent aldol reaction.

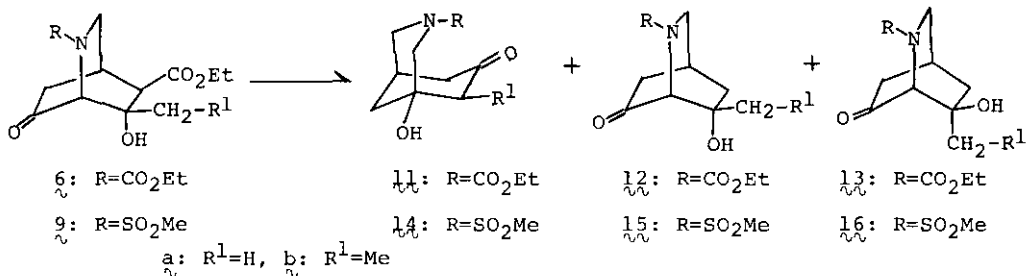


Table II. Acid Hydrolysis of 2-Azabicyclo[2.2.2]octanone-carboxylates ( $\delta_a, \delta_b$  and  $\rho_a, \rho_b$ )<sup>a</sup>

Substrate	Reaction Time(hr)	Products(%)		
$\delta_a$	3	$\delta\delta_a$ (20)	$\delta\delta_b$ (24)	$\delta\delta_c$ (3)
$\delta_b$	3	$\delta\delta_b$ (80)	-	-
$\rho_a$	3	-	$\rho\rho_a + \rho\rho_b$ (35) <sup>b</sup>	-
$\rho_b$	1	$\rho\rho_b$ (56)	-	-

<sup>a</sup> On treatment of the esters (1 mmole) with 10% HCl (4 ml) in AcOH (4 ml) under reflux. <sup>b</sup> Obtained as a diastereoisomeric mixture of  $\rho\rho_a$  and  $\rho\rho_b$  (ca. 2:1).

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5. Stereochemistry of  $\delta$  and  $\rho$  remains unsolved.
6. Prepared from 1,2,3,6-tetrahydropyridine according to the method of ref. 3.
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8. Stereochemistry of  $\rho\rho_a$  and  $\rho\rho_b$  was determined from the chemical shift of C7-Me in the PMR spectra. The chemical shift ( $\delta$  1.25) of the latter is higher than that ( $\delta$  1.35) of the former owing to a diamagnetic effect of the C<sub>6</sub>-carbonyl function. A similar argument has appeared in T. Ibuka, Y. Mori, T. Aoyama, and Y. Inubushi, Chem. Pharm. Bull., 1978, **26**, 456.

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