HETEROCYCLES. Vol. 6, No. 3. 1977

SYNTHESIS OF OUDENONE AND ITS RELATED COMPOUNDS

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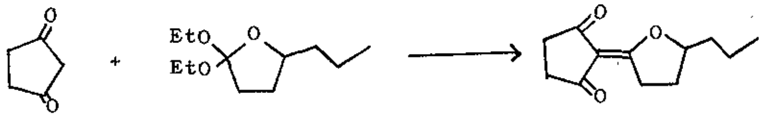
Oudenone, a tyrosine hydroxylase inhibitor, was obtained by heating 1,3-cyclopentanedione with 2,2-diethoxy-5-propyltetrahydrofuran. A similar one-step synthesis afforded several related analogues.

Umezawa, et al.[1] discovered oudenone (Ia) in the culture filtrate of a strain related to Oudemansiella radicata. As Ia showed inhibition of tyrosine hydroxylase and an antihypertensive activity in spontaneously hypertensive rats,[1,2] it was expected that the chemical modification of Ia might provide an effective agent for the treatment of the hypertension.

This communication describes useful one-step synthesis of these compounds. In the present synthesis of Ia and its analogues, formation of carbon-carbon double bonds between 1,3-diketones and heterocycles was achieved by the condensation of 1,3-diketones with heterocyclic orthoester derivatives or cyclic iminoethers. This reaction is particularly useful for the synthesis of Ia and its analogues containing nitrogen or sulfur in place of oxygen of the tetrahydrofuran ring. A typical example is shown below.

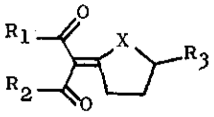
A mixture of 2,2-diethoxy-5-propyltetrahydrofuran (IVb) (12.5 g) and 1,3-cyclopentanedione (VIa)[3] (3.0 g) was heated in an oil bath at 95-100° for 6 hr and the low boiling fraction was distilled off. The resulting residue was purified by column chromatography to give Ia as colorless plates (mp 82-83°, 7.8%), *the structure of which was established* by comparison of its IR and NMR spectra ($CDCl_3$) with those of an *authentic sample* obtained by the method of Ohno, et al.[4] In this reaction, the addition of acetic anhydride and anhydrous zinc chloride, which are usually employed in the condensation of orthoesters with active methylene compounds,[5] did not affect the reaction time and the yield.



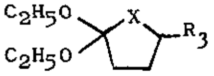
VIa IVb Ia

The reaction of 2,2-diethoxytetrahydrofuran (IVa)[6] with dimedone (VIc) gave 5,5-dimethyl-2-(4,5-dihydro-2(3H)-furylidene)-1,3-cyclohexanedione (Ib) in a yield of 5% and 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one in 50% yield. Similar condensations were carried out using cyclic iminothioethers. Thus, heating of 2-methylthio-1-pyrroline (Vb)[7] with VIc and acetylacetone (VIe) at 95° easily afforded 5,5-dimethyl-2-(2-pyrrolidinylidene)-1,3-cyclohexanedione (Ih) and 3-(2-pyrrolidinylidene)-2,4-pentanedione (Ii), respectively. These compounds showed good identity with authentic samples prepared from 2-ethoxy-1-pyrroline (Va).[8] Other compounds in Table I were prepared by similar procedures.

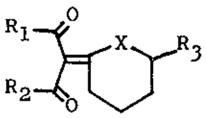
	R_1	R_2	R_3	X
Ia	$(CH_2)_2$		C_3H_7	O
b	$CH_2C(CH_3)_2CH_2$		H	O
c	$(CH_2)_2$		H	S
d	$(CH_2)_3$		H	S
e	$CH_2C(CH_3)_2CH_2$		H	S
f	$CH_2C(CH_3)_2CH_2$		H	NCH_3
g	$(CH_2)_2$		H	NH
h	$CH_2C(CH_3)_2CH_2$		H	NH
i	CH_3	CH_3	H	NH
j	CH_3	C_2H_5	H	NH
k	CH_3	OC_2H_5	H	NH
l			H	NH
m	$(CH_2)_2$		C_3H_7	NH
n	$(CH_2)_3$		C_3H_7	NH
o	$CH_2C(CH_3)_2CH_2$		C_3H_7	NH
IIa	$(CH_2)_2$		H	NH
b	$(CH_2)_3$		H	NH
c	$CH_2C(CH_3)_2CH_2$		H	NH
IIIa	$(CH_2)_2$		H	NH
b	$CH_2C(CH_3)_2CH_2$		H	NH



I



IV



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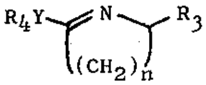

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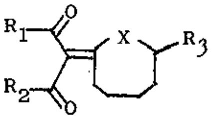

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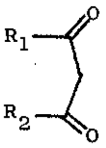


VI

	R_3	X
IVa	H	O
b	C_3H_7	O
c	H	S
d	H	NCH_3

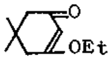
	R_3	R_4	Y	n
Va	H	C_2H_5	O	2
b	H	CH_3	S	2
c	C_3H_7	C_2H_5	O	2
d	H	C_2H_5	O	3
e	H	C_2H_5	O	4

	R_1	R_2
VIa	$(CH_2)_2$	
b	$(CH_2)_3$	
c	$CH_2C(CH_3)_2CH_2$	
d		
e	CH_3	CH_3
f	CH_3	C_2H_5
g	CH_3	OC_2H_5

Table I. Synthesis of Oudenone (Ia) and Related Compounds

Starting materials		Reaction conditions			Product[a]	Yield (%)	Mp (°C)
A	B	Solvent	Temp. (°C)	Time (hr)			
IVb	VIa	—	95-100	6	Ia	7.8	82-83
IVa	VIc	PrOH	reflux	2	Ib[b]	5	123-125
IVc	VIa	EtOH	150-160	5	Ic	32.3	167-168
IVc	VIb	EtOH	160	5	Id	11.5	163-164
IVc	VIc	EtOH	reflux	6.5	Ie	73	146-148
IVd	VIc	—	100	1	If	14	153-155
Va	VIa	EtOH	reflux	1	Ig	43	207-208
Va	VIc	EtOH	reflux	1	Ih	61	180-181
Va	VIe	—	100-110	4.5	Ii	13	96-97
Va	VIf	—	110-120	3.5	Ij[c]	18	oil[d]
Va	VIg	—	110-120	4	Ik[e]	16.5	98-100
Va	VId	EtOH	reflux	5	Il	20.5	242-243
Vb	VIc	—	95	5(min)	Ih	67.7	180-182
Vb	VIe	—	95	4.5	Ii	8.2	92-94
Vc	VIa	EtOH	reflux	2	Im	76	150-154
Vc	VIb	EtOH	100	6	In	13.8	92-94
Vc	VIc	EtOH	reflux	4	Io	48	125-126
Vd	VIa	EtOH	reflux	2	IIa	50	145-147
Vd	VIb	EtOH	140-150	2	IIb	9	103-104
Vd	VIc	—	110-120	2	IIc	44.2	163-164
Ve	VIa	—	120-130	2	IIIa	39.3	164-165
Ve	VIc	—	120-130	2	IIIb	33.6	142-143

a) All compounds gave satisfactory elemental analyses.

b) 

, bp 95-96° (2 mmHg), 50%.

c) Another possible structure ($R_1 = Et$, $R_2 = Me$) remains to be established at present.

d) Purified by a silica gel column (Merck No. 60) using benzene: acetone (9:1) as eluent.

e) Another possible structure ($R_1 = OEt$, $R_2 = Me$) remains to be established at present.

The starting materials for the above-mentioned reactions: IVa,[6] 2,2-diethoxytetrahydrothiophene (IVc),[6] 2,2-diethoxy-1-methylpyrrolidine (IVd),[6] Va,[8], Vb,[7] Vc,[9] 2-ethoxy-3,4,5,6-tetrahydropyridine (Vd),[10] 7-methoxy-3,4,5,6-tetrahydro-2H-azepine (Ve),[11] VIa,[3] and 2,4-hexanedione (VIf),[12] were all obtained by the methods described in literatures. According to the procedure of Meerwein, et al.,[6] IVb was accessible from γ-propylbutyrolactone (VII) and obtained as colorless oil [bp 78-86° (18-20 mmHg), 24.5%], and 2-ethoxy-5-propyl-1-pyrroline (Vc) was also prepared as colorless oil [bp 55-56° (0.5 mmHg), 97%] by a similar procedure.

ACKNOWLEDGEMENT The authors are grateful to Dr. S. Tatsuoka, Dr. E. Ohmura, Dr. T. Masuda and Dr. S. Yurugi for encouragement throughout this work.

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Received, 2nd December, 1976