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Studies on Heterocyclic Compounds. VI.[1] Syntheses of Oudenone and Its Related Compounds. (1)

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Oudenone, a tyrosine hydroxylase inhibitor, and related analogues were obtained upon heating a mixture of 1,3-cyclopentanediones and 2,2-diethoxytetrahydrofurans.

Keywords——oudenone; β-diketone derivatives; heterocyclic orthoester derivatives; cyclic iminoethers; cyclic iminothioethers

Recently Umezawa, *et al.*[3] discovered oudenone (I) in the culture filtrate of the strain which was most closely related to *Oudemansiella radicata*. As I showed the inhibition of tyrosine hydroxylase and antihypertensive activity on spontaneously hypertensive rats,[3,4] it is expected that I might become an effective agent for the treatment of hypertension. Unique structure and pharmacological properties of oudenone prompted us to synthesize it and its analogues.

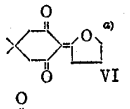
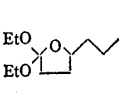
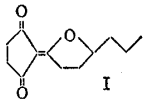
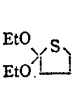
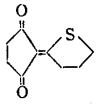
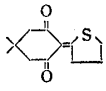
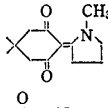
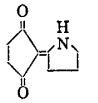
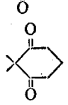
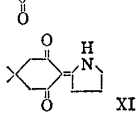
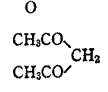
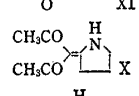
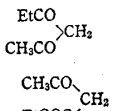
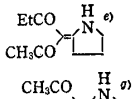
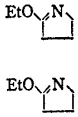
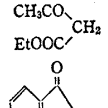
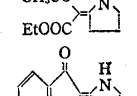
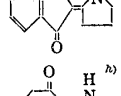
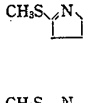
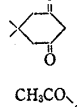
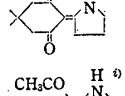
The present paper describes useful one-step synthesis of these compounds. In the synthesis of I and its analogues, the formation of carbon-carbon double bonds between β-diketones and heterocycles was achieved by the condensation reaction of β-diketones with heterocyclic orthoester derivatives or cyclic iminoethers upon heating. These reactions are particularly useful for a simple one-step synthesis of I and its analogues containing nitrogen or sulfur in place of oxygen atom of the tetrahydrofuran ring.

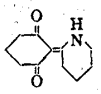
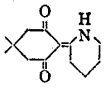
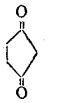
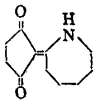
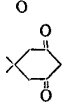
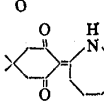
Actually, I was obtained upon heating a mixture of 1,3-cyclopentanedione (II)[5] and an excess of 2,2-diethoxy-5-propyltetrahydrofuran (III) at 95—100° in low yield and identified by comparing its physicochemical properties with those of an authentic sample prepared by the method of Ohno, *et al.*[6] The reaction of 2,2-diethoxytetrahydrofuran (IV)[7] with dimedone (V) gave 5,5-dimethyl-2-[4,5-dihydro-2(3H)-furylidene]-1,3-cyclohexanedione (VI) in 5% yield and 3-ethoxy-5,5-dimethyl-2-cyclohexen-1-one (VII) in 50% yield. Furthermore, similar condensations were carried out using cyclic iminothioethers. Heating of a mixture of 2-methylthio-1-pyrroline (VIII),[8] acetylacetone (IX) and V at 95° easily afforded 3-(2-pyrrolidinylidene)-2,4-pentanedione (X) and 5,5-dimethyl-2-(2-pyrrolidinylidene)-1,3-cyclohexanedione (XI), respectively. These compounds were completely identical with authentic samples prepared from 2-ethoxy-1-pyrroline (XII).[9]

The reaction conditions and the results are summarized in Table I.

1) Part V: T. Tsujikawa and M. Tatsuta, *Chem. Pharm. Bull.* (Tokyo), accepted.
2) Location: *a) Jusohonmachi, Yodogawa-ku, Osaka; b) Gofuku, Toyama.*
3) H. Umezawa, T. Takeuchi, H. Iinuma, K. Suzuki, M. Ito, M. Matsuzaki, T. Nagatsu, and O. Tanabe, *J. Antibiotics*, **23**, 514 (1970).
4) I. Nagatsu, T. Nagatsu, K. Mizutani, H. Umezawa, M. Matsuzaki, and T. Takeuchi, *Nature*, **230**, 381 (1971).
5) F. Merènyi and M. Nilsson, *Acta Chem. Scand.*, **18**, 1368 (1964).
6) M. Ohno, M. Okamoto, K. Kawabe, H. Umezawa, T. Takeuchi, H. Iinuma, and S. Takahashi, *J. Am. Chem. Soc.*, **93**, 1285 (1971).
7) H. Meerwein, P. Borner, O. Fuchs, H.J. Sasse, H. Schrodt and J. Spille, *Chem. Ber.*, **89**, 2060 (1956).
8) J. Tafel and P. Lawaczecki, *Ber.*, **40**, 2840 (1907).
9) A. Pilotti, A. Penterhall, K. Torssell, and C.G. Lindblad, *Acta Chem. Scand.*, **23**, 818 (1969).

TABLE I. Syntheses of Oudenone (I) and Related Compounds

Exp. No.	Starting materials A	Starting materials B	Reaction Solvent	Reaction Temp. (°C)	Reaction Time (hr)	Product (compd. No.)	Yield	Recryst. from	Appearance	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
1			PrOH	Reflux	2	 VI	5	Hexane	Colorless pillar	123—125	$C_{12}H_{10}O_3$	69.21 (69.32)	7.74 (7.96)	
2			—	95—100	6	 I	7.8	Hexane	Colorless plates	82— 83	$C_{12}H_{16}O_3$	69.21 (68.97)	7.74 (7.83)	
3			EtOH	150—160	5		32.3	b)	Yellow powber	167—168	$C_9H_{10}O_2S$	59.32 (59.38)	5.53 (5.71)	
4			EtOH	160	5		11.5	EtOH	Pale yellow needles	163—164	$C_{10}H_{12}O_2S$ c)	61.20 (60.97)	6.16 (5.80)	
5			EtOH	Reflux	6.5		73	b)	Pale yellow needles	146—148	$C_{12}H_{10}O_2S$ d)	64.25 (64.31)	7.19 (7.16)	
6			—	100	1		14	CCl_4	Colorless powder	153—155	$C_{13}H_{13}NO_2$	70.56 (70.27)	8.65 (8.70)	6.33 (6.33)
7			EtOH	Reflux	1		43	b)	Colorless needles	207—208	$C_9H_{11}NO_2$	65.44 (64.99)	6.71 (6.75)	8.48 (8.50)
8			EtOH	Reflux	1	 XI	61	Acetone	Colorless prisms	180—181	$C_{12}H_{17}NO_2$	69.54 (69.54)	8.27 (8.51)	6.76 (6.75)
9			—	100—110	4.5	 X	13	Ligroin	Colorless needles	96— 97	$C_9H_{13}NO_3$	64.65 (64.75)	7.84 (8.06)	8.38 (8.34)
10			—	110—120	3.5	 e)	18		Oil f)		$C_{10}H_{15}NO_2$	66.27 (66.25)	8.34 (8.35)	7.73 (7.76)
11			—	110—120	4	 g)	16.5	Petroleum ether	Colorless needles	98—100	$C_{10}H_{13}NO_3$	60.90 (60.85)	7.67 (7.64)	7.10 (7.10)
12			EtOH	Reflux	5		20.5	EtOH	Pale yellw plates	242—243	$C_{13}H_{11}NO_2$	73.23 (73.29)	5.20 (5.09)	6.57 (6.35)
13			—	95	5 (min.)	 h)	67.7	Acetone	Colorless prisms	180—182	—	— —	— —	— —
14			—	95	4.5	i)	8.2	Ligroin	Colorless needles	92— 94	$C_9H_{13}NO_2$	64.65 (64.87)	7.84 (7.82)	
15			EtOH	Reflux	2		76	EtOH	Colorless needles	150—154	$C_{12}H_{17}NO_2$	69.54 (69.70)	8.27 (8.38)	6.75 (6.73)
16			EtOH	100	6		13.8	Ligroin	Pale yellow needles	92— 94	$C_{13}H_{19}NO_2$	70.56 (70.28)	8.65 (8.71)	6.33 (6.19)
17			EtOH	Reflux	4		48	EtOH	Colorless needles	125—126	$C_{15}H_{23}NO_2$	72.25 (72.13)	9.30 (9.28)	5.62 (5.63)
18			EtOH	Reflux	2		50	EtOH	Colorless needles	145—147	$C_{10}H_{13}NO_2$	67.02 (66.78)	7.31 (7.35)	7.82 (7.82)

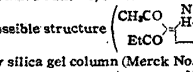
Exp. No.	Starting materials A	Starting materials B	Reaction Solvent	Reaction Temp. (°C)	Reaction Time (hr)	Product (compd. No.)	Yield	Recryst. from	Appearance	mp (°C)	Formula	Analysis (%) Calcd. (Found) C	H	N
19			EtOH	140—150	2		9	Ligroin	Yellow needles	103—104	$C_{11}H_{15}NO_2$	68.37 (68.29)	7.82 (7.98)	7.25 (7.15)
20			—	110—120	2		44.2	Ligroin	Pale pink prisms	163—164	$C_{13}H_{19}NO_2$	70.56 (69.83)	8.65 (8.69)	6.33 (6.22)
21			—	120—130	2		39.3	Ligroin	Colorless needles	164—165	$C_{11}H_{15}NO_2$	68.37 (68.25)	7.82 (7.88)	7.25 (7.21)
22			—	120—130	2		33.6	Ligroin	Pale pink prisms	142—143	$C_{14}H_{21}NO_2$	71.46 (71.69)	8.99 (9.09)	5.95 (6.15)

a)  , bp 95—96° (2 mmHg) (50%).

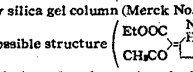
b) After the reaction was over, the reaction mixture was allowed to stand at r.t. The precipitated crystal was collected and washed with EtOH.

c) Calcd.: S, 16.34. Found: S, 16.42.

d) Calcd.: S, 14.29. Found: S, 14.23.

e) Another possible structure  remains at present.

f) Purified by silica gel column (Merck No. 60) using benzene-acetone (9:1) as eluant.

g) Another possible structure  remains at present.

h) This compd. showed no depression of mixed melting point with XI obtained by exp. No. 6, and had IR spectrum identical to that of XI.

i) This compd. showed no depression of mixed melting point with X obtained by exp. No. 9, and had IR spectrum identical to that of X.

Experimental[10]

Materials——2,2-Diethoxy-tetrahydrofuran (IV),[7] 2,2-diethoxy-tetrahydrothiophene,[7] 2,2-diethoxy-1-methyl-pyrrolidine,[7] 2-methylthio-1-pyrroline (VIII),[8] 2-ethoxy-1-pyrroline (XII),[9] 5-propyl-2-pyrrolidone (XIII),[11] 7-methoxy-3,4,5,6-tetrahydro-2H-azepine,[12] 1,3-cyclopentanedione (II)[5] and 2,4-hexanedione[13] were all prepared by the methods described in literature.

γ-Propylbutyrolactone (XIV)——To an ice-cooled solution of ethyl 4-oxoheptanoate (XV)[14] (500 g) in 80% MeOH (1740 ml) was added $NaBH_4$ (55.2 g) in small portions, and the reaction mixture was stirred at room temperature (r.t.) for 1 hr. After neutralization with 10% HCl, MeOH was evaporated *in vacuo* and the residue was extracted twice with ether (580 ml). The extract was dried (Na_2SO_4), and evaporated *in vacuo*. The residue was subjected to vacuum distillation to give XIV (294 g, 78.9%) as colorless oil (bp 104—105° (2 mmHg)), which was identified by comparing its IR and NMR spectra ($CDCl_3$) with those of the authentic sample obtained by the method of Organic Syntheses.[15]

2,2-Diethoxy-5-propyltetrahydrofuran (III)——To triethyloxonium tetrafluoroborate[16] (142 g) was added XIV (88 g), and the mixture was stirred for 3 hr and then left standing for 3 days at r.t. The solution was added dropwise to NaOEt–EtOH prepared from Na (17.5 g) and EtOH (100 ml) under ice cooling, and

10) All melting and boiling points are uncorrected. NMR spectra were taken with a Varian HA-100 spectrometer using tetramethylsilane as an internal standard.

11) A.A. Ponomarer and V.A. Sedavkina, *Khim. Geterotsikl. Soedin.*, **1969**, 809 [*C.A.*, **72**, 100402*n* (1970)].

12) R.E. Benson and T.L. Cairns, "Organic Syntheses," Coll. Vol. IV, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 588.

13) G.T. Morgan and H.G. Reeves, *J. Chem. Soc.*, **123**, 447 (1923).

14) I.F. Bel'skii, N.I. Shuikin, V.M. Schostakovskii, and S.N. Khav'kov, *Zh. Obshch. Khim.*, **32**, 1030 (1962) [*C.A.*, **58**, 2365*b* (1963)].

15) E. Schwenk, D. Papa, H. Hankin, and H. Ginsberg, "Organic Syntheses," Coll. Vol. III, ed. by E.C. Horning, John Wiley and Sons, Inc., New York, 1955, p. 742.

According to the procedure of Organic Syntheses, XIV is usually prepared from the reduction of furylacrylic acid with Ni-Al alloy. In practice, however, this is obviously a tedious method, and because of the formation of the by-product, 3-(tetrahydrofuryl)propionic acid, this method gives XIV in yield not more than 50%, usually 33—37%. This search was made to find a more excellent method for the preparation of XIV. For this purpose, since XV is easily obtained from the reduction of ethyl 3-furyl acrylate, this procedure is recommended for the preparation of XIV in laboratories.

16) H. Meerwein, "Organic Syntheses," Vol. 46, ed. by E.J. Corey, John Wiley and Sons, Inc., New York, 1966, p. 113.

stirred at r.t. for 3 hr. The reaction mixture was evaporated and the resulting residue was treated with 5% Na_2CO_3 aq. (1800 ml) and extracted twice with ether (500 ml). The ether extract was dried (Na_2SO_4) and evaporated. The residue was purified by vacuum distillation to give III (33.6 g, 24.5%) as colorless oil, bp 78—86° (18—20 mmHg). *Anal.* Calcd. for $C_{11}H_{22}O_3$: C, 65.31; H, 10.96. Found: C, 65.40; H, 10.69.

2-Ethoxy-5-propyl-1-pyrroline (XVI)——A solution of triethyloxonium tetrafluoroborate (114 g) and XIII (63.5 g) in anhyd. CH_2Cl_2 (100 ml) was stirred at r.t. for 24 hr. To the mixture, 20% K_2CO_3 aq. (400 ml) was added with stirring and the mixture was extracted with ether, and the resulting extract was dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by vacuum distillation to give XVI (75.0 g, 97%) as colorless oil, bp 55—56° (0.9 mmHg).

2-Ethoxy-3,4,5,6-tetrahydropyridine (XVII)——According to the method of Pilotti, *et al.*[9] XVII was obtained as colorless oil, bp 64—66° (22 mmHg) (Yield: 81.5%).

Oudenone (I)——A mixture of II (3.0 g) and III (12.5 g) was heated in an oil bath at 95—100° for 6 hr and low boiling fraction was distilled off. The resulting residue was purified by column chromatography ($CHCl_3$–MeOH=10: 1) te give I as colorless plates, which was identified by comparison of its IR and NMR spectra ($CDCl_3$) with those of an authentic sample obtained by the method of Ohno, *et al.*[6] In this reaction, the additions of Ac_2O and anhyd. $ZnCl_2$, which are usually employed in the condensations of orthoesters with active methylene compounds,[17] did not affect the reaction time and yield of I.

Other compds. in Table I were also prepared from materials A and B by the similar procedures.

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Studies on the Syntheses of Heterocyclic Compounds containing Benzopyrone. I. Syntheses of Cycloalkenochromones

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Cycloalkenochromones (IV) were prepared from salicylaldehyde methoxymethyl ether and cycloalkanones *via* aldol condensation.

Keywords——cycloalkenochromones; salicylaldehyde methoxymethyl ether; cycloalkanones; Aldol condensation; CrO_3-acetone oxidation; heterocyclic compounds containing benzopyrone

Chromones have been prepared by many investigators, some of the more important synthetic methods being: condensation of phenol with ethyl acetoacetate in the presence of phosphorus pentoxide (Simonis reaction),[2] condensation of ethylacetate[3] or diethyl oxalate[4]

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