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Studies on Heterocyclic Compounds. VII.[1] Syntheses of Oudenone and Its Related Compounds. (2)

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In hope of antihypertensive activity, 2-(2-tetrahydrothienyl)-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (3) was synthesized by the routes of either (A) on heating a mixture of dimedone (7) and 2-chlorotetrahydrothiophene or (B) by the coupling of 7 with 2,3-dihydrothiophene (9) in the presence of acid. Several related compounds were also prepared.

Keywords——α-substituted β-hydroxy-α,β-unsaturated cyclic ketone; β-chloro-α,β-unsaturated cyclic ketone; β-amino-α,β-unsaturated cyclic ketone; 2-chlorotetrahydrothiophene; 2,3-dihydrothiophene

In the preceding paper[1] we reported that oudenone (**1**), a tyrosine hydroxylase inhibitor and its analogues were prepared in one-step reaction on heating 1,3-cyclopentanediones with 2,2-diethoxytetrahydrofurans. Ozawa, *et al.*[3] have found that among these compounds, 5,5-dimethyl-2-(4,5-dihydro-2(3*H*)-thienylidene)-1,3-cyclohexanedione (**2**) shows marked antihypertensive effect, which prompted us to prepare 2-(2-tetrahydrothienyl)-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**3**), a dihydro derivative of **2**, in hope of improving its pharmacological properties. This paper describes the synthesis of **3** and its related compounds.

Since our initial attempts to obtain **3** by direct reduction of **2** were unsuccessful under a variety of conditions such as (i) catalytic reduction with hydrogen over Pd-C, PtO_2, Ru-C or Raney-Ni, and (ii) hydrogenation using $LiAlH_4$, $NaBH_4$ or Na-Hg, efforts were then directed to the preparation of **3** or its analogues by the C-C bond formation from β-diketones and heterocycles. It was found that substitution by the 2-tetrahydrothienyl group at the

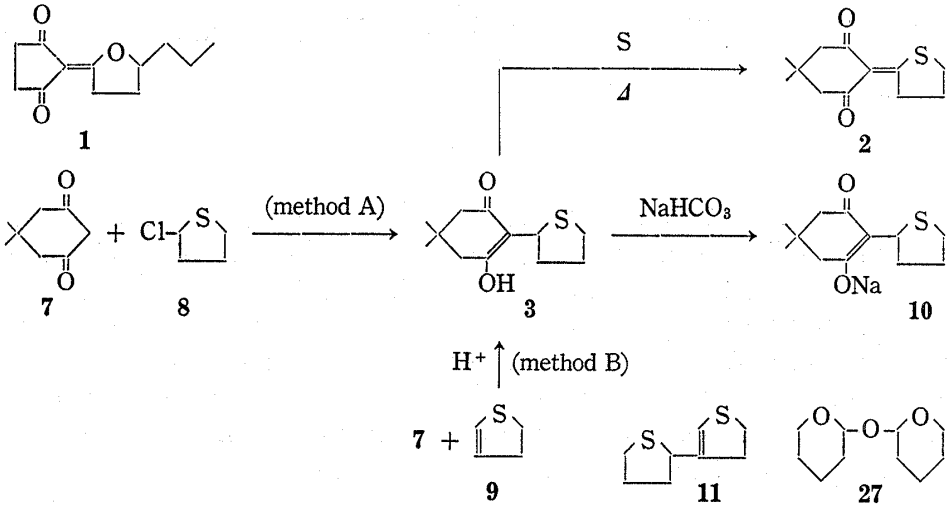

Chart 1

1) Part VI, Part (1): T. Tsujikawa, Y. Nakagawa, K. Tsukamura, and K. Masuda, *Chem. Pharm. Bull.* (Tokyo), **25**, 2775 (1977).
2) Location: *Jusohonmachi, Yodogawa-ku, Osaka.*
3) S. Hashimoto and H. Ozawa, Abstracts of Papers, 25th Kita Area Regional Meeting of Japanese Pharmacological Society, Sapporo, Hokkaido, October, 1974, p. 10.

active methylene of cyclic β-diketones was readily achieved on heating a mixture of cyclic β-diketones and 2-halogenotetrahydrothiophene (method A). For example, dimedone (**7**) was treated with 2-chlorotetrahydrothiophene (**8**)[4] in refluxing benzene to give **3** with violent evolution of hydrogen chloride in a good yield. This reaction was accompanied by the formation of a small amount of dihydrothiophene dimer (**11**)[5] as a by-product.

Although it has been reported by many investigators that considerable amounts of O-alkylated compounds were formed as by-products[6] in the base-catalyzed alkylation of active methylene of β-diketones, no O-substituted compound was isolated in the present reactions. The structure of **3** was assigned to have the mono-enol form on the basis of the nuclear magnetic resonance (NMR) spectrum which showed OH signal at δ 10.0 which disappeared on addition of D_2O.

In the same way, **8**, 2-chlorotetrahydrothiapyran (**12**),[4] 2-chlorotetrahydrofuran (**13**)[7] and 2-chlorotetrahydropyran (**14**)[7] were allowed to react with a variety of β-diketones such as **7**, 1,3-cyclohexanedione (**15**), 5-methyl-1,3-cyclohexanedione (**16**), and 5-phenyl-1,3-cyclohexanedione (**17**) to yield the corresponding 2-substituted β-diketones as summarized in Table I. However, the similar reactions with 1,3-cyclopentanedione, 4-cyclopentene-1,3-dione, or an acyclic β-diketone such as acetylacetone or benzoylacetone failed to afford the expected substitution products, instead giving rise to **11** or 2-(2-tetrahydropyranyloxy)tetrahydropyran (**27**)[8] when **8** or **14** was used as the reactant. The compound (**11**) was also obtained in a good yield when **8** was refluxed in benzene for 2 hr.

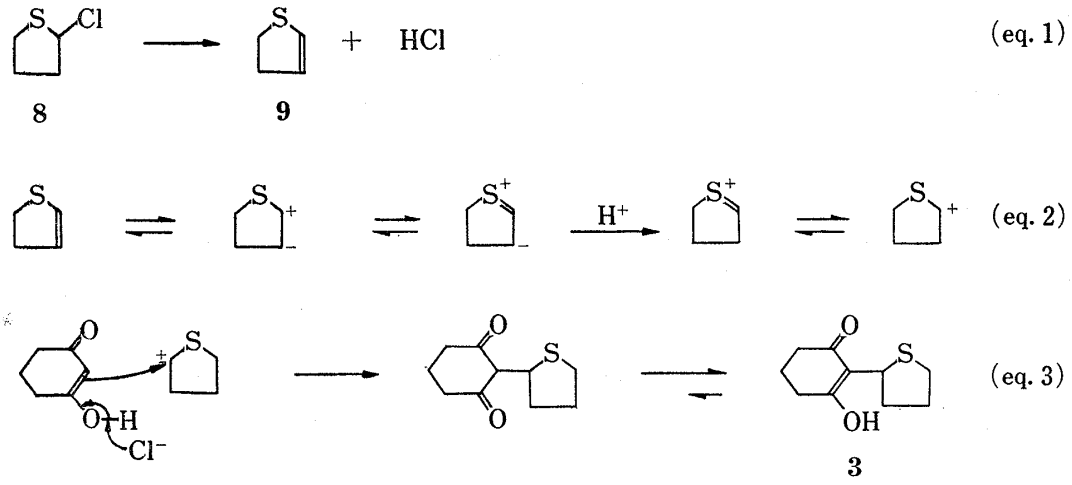

Chart 2

From these results, a mechanism for the formation of **3** can be postulated as shown in Chart 2, in which 2,3-dihydrothiophene (**9**) and the liberated hydrogen chloride play important roles. The reason for failure of the reactions with acyclic β-diketones lies in the following speculation, the equilibrium of these β-diketones shifts to the enol form in the solvent employed, and the enolic form is stabilized by the intramolecular hydrogen bonding, thus preventing the condensation in eq. 3. Failed condensation reaction of 1,3-cyclopentanedione would be ascribed to a poor solubility of this material in the medium used. It appears reasonable to presume that the by-product (**11**) in the reaction of **7** with **8** was formed *via* **9** in conformity

4) D.L. Tuleen and R.H. Benett, *J. Heterocyclic Chem.*, **6**, 115 (1969).
5) J.M. Cox and L.N. Owen, *J. Chem. Soc.* (*C*), **1967**, 1130.
6) H. Stetter, "Newer Methods of Preparative Organic Chemistry," Vol. 2, ed. W. Foerst (translated by F.K. Kirchner), Academic Press, New York and London, 1963, p. 51.
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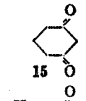
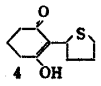
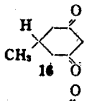
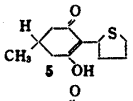
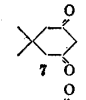
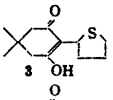
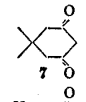
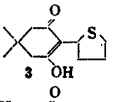
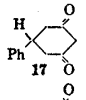
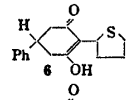
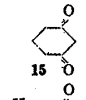
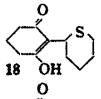
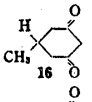
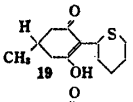
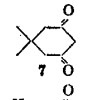
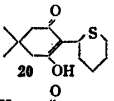
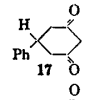
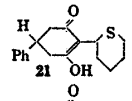
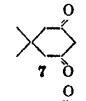
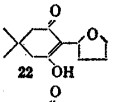
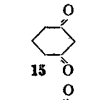
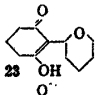
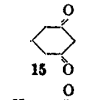
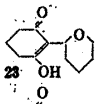
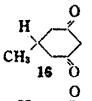
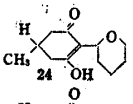
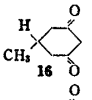
TABLE I. 3-Hydroxy-2-substituted-2-cyclohexen-1-one Derivatives

Exp. No.	Starting materials A	Starting materials B	Reaction: Catalyst	Method	Solvent	Temp. (°C)	Time (hr)	Structure compd. No.	Yield (%)	Recrystd. from	Product: Appearance	mp (°C) (bp °C/mmHg)	Formula	Analysis (%) Calcd. (Found) C	H	N
1	 15	 8	—	A	Benzene	Reflux	2.5	 4	25.4	*a*)	Colorless powder	122—125	$C_{10}H_{14}O_2S$	60.58 (60.27)	7.12 (7.21)	16.17 (16.36)
2	 16	 8	—	A	Benzene	Reflux	2.0	 5	33.4	Benzene +hexane	Colorless prism	111—113	$C_{10}H_{16}O_2S$	62.23 (62.28)	7.60 (7.79)	15.10 (15.24)
3	 7	 8	—	A	Benzene	Reflux	2.0	 3	44.7	*a*)	Colorless powder	97—99	$C_{12}H_{18}O_2S$	63.68 (63.23)	8.01 (7.88)	14.17 (14.37)
4	 7		*p*-TsOH	B	Benzene	Reflux	1.5	 3	53.1	*a*)	Colorless powder	97—98[b]				
5	 17	 8	—	A	Benzene	Reflux	3.0	 6	41.1	*c*)	Colorless powder	141—142	$C_{16}H_{18}O_2S$	70.04 (69.30)	6.61 (6.45)	11.68 (11.46)
6	 15	 12	—	A	Benzene	Reflux	2.0	 18	30.2	*d*)	Colorless powder	125—128	$C_{13}H_{18}O_2S$	62.23 (61.91)	7.60 (7.70)	15.10 (15.54)
7	 16	 12	—	A	Benzene	Reflux	2.0	 19	15.1	Benzene +hexane	Colorless prism	172—175	$C_{12}H_{18}O_2S$	63.68 (63.89)	8.01 (8.10)	14.17 (13.62)
8	 7	 12	—	A	Benzene	Reflux	2.0	 20	31.0	EtOH	Colorless prism	158—160	$C_{13}H_{20}O_2S$	64.96 (65.00)	8.39 (8.47)	13.34 (13.32)
9	 17	 12	—	A	Benzene	Reflux	2.0	 21	23.8	*d*)	Colorless powder	190—192	$C_{17}H_{20}O_2S$	70.80 (70.66)	6.99 (7.12)	11.12 (11.09)
10	 7	 13	—	A	Benzene +CH_2Cl_2	Reflux	2.0	 22	5.3	*e*)	yellow oil	(105—110/ 5—6)	$C_{13}H_{18}O_3$	68.86 (68.06)	8.63 (8.80)	
11	 15	 14	—	A	Benzene +CH_2Cl_2	Reflux	3.0	 23	17.1	*f*)	Colorless oil	(116—117/ 2.5)	$C_{11}H_{16}O_3$	67.32 (67.15)	8.22 (8.54)	
12	 15		conc. H_2SO_4	B	Benzene	Reflux	1.5	 23	31.7	*a*)	Colorless oil	*g*)				
13	 16	 14	—	A	Benzene +CH_2Cl_2	Reflux	2.5	 24	18.0	*d*)	Colorless powder	57—60	$C_{12}H_{18}O_3$	68.86 (68.84)	8.63 (8.59)	
14	 16		*p*-TsOH	B	Benzene	Reflux	1.5	24	48.7	*a*)	Colorless powder	60—61[h]				
15	7	14	—	A	Benzene +CH_2Cl_2	Reflux	2.5	25	29.1	*d*)	Colorless powder	56—60	$C_{13}H_{20}O_3$	69.61 (69.61)	8.99 (8.88)	
16	7		conc. H_2SO_4	B	Benzene	Reflux	1.5	25	40.2	*a*)	Colorless powder	56—58[i]				
17	17	14	—	A	Benzene +CH_2Cl_2	Reflux	2.0	26	42.0	*f*)	Colorless powder	105—107	$C_{17}H_{20}O_3$	74.97 (74.72)	7.40 (7.53)	
18	17		*p*-TsOH	B	Benzene	Reflux	2.5	26	42.9	*a*)	Colorless powder	106—107[j]				

a) Purified by a silica gel column (Merck No. 60) using $CHCl_3$-benzene (1:1) as eluent.
b) This compound was identified with 3 obtained from Exp. No. 3 in terms of infrared (IR) spectrum and thin-layer chromatography (TLC) behavior.
c) Purified by a silica gel column (Merck No. 60) using $CHCl_3$-benzene (5:1) as eluent.
d) Purified by a silica gel column (Merck No. 60) using $CHCl_3$ as eluent.
e) Purified by a silica gel column (Merck No. 60) using $CHCl_3$-benzene (2:3) as eluent.
f) Purified by a silica gel column (Merck No. 60) using $CHCl_3$-benzene (3:1) as eluent.
g) This compound was identified with 23 obtained from Exp. No. 11 in terms of IR spectrum and TLC behavior.
h) This compound was identified with 24 obtained from Exp. No. 13 in terms of IR spectrum and TLC behavior.
i) This compound was identified with 25 obtained from Exp. No. 15 in terms of IR and NMR spectra and TLC behavior.
j) This compound was identified with 26 obtained from Exp. No. 17 in terms of mixed mp, IR spectrum and TLC behavior.

with the phenomenon presented by Cohen and Steele.[9] The formation of **27** in the reaction of **7** with **14** might be interpreted by the intervention of 2-hydroxytetrahydropyran, which was generated from 3,4-dihydro-2*H*-pyran and water during the work-up procedure.

Further support for the above-mentioned mechanism *via* **9** was furnished by the following experiments. The reaction of **7** with **9** in refluxing benzene in the presence of sulfuric acid or *p*-toluenesulfonic acid afforded **3** which provided an alternative route to **3** (method B). Under similar conditions of the method B, 2-(2-tetrahydropyranyl)-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**25**) was obtained in fairly good yield from **7** and 3,4-dihydro-2*H*-pyran. When the readily available material such as **9** or 3,4-dihydro-2*H*-pyran was used, the method B is recommended due to the better yields in comparison with those in the method A. The 3-hydroxy-2-substituted-2-cyclohexen-1-ones obtained by the two methods are listed in Table I.

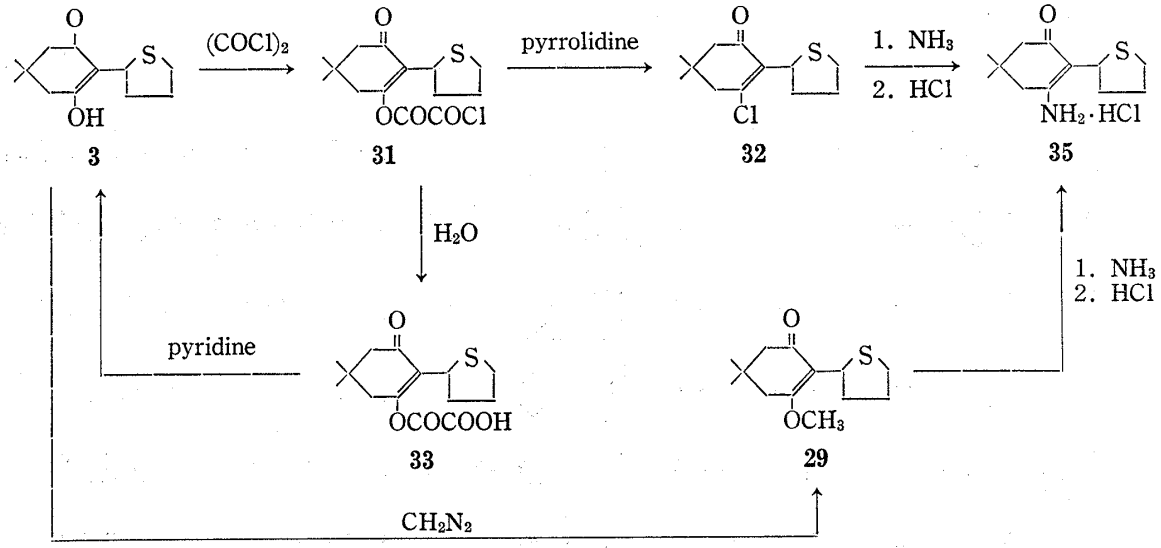


Chart 3

The compounds (**3** and **25**) were readily dissolved in an aqueous solution of sodium bicarbonate or sodium hydroxide to afford sodium salts (**10** and **28**) respectively, and **3** was readily converted to **2** on heating in the presence of sulfur. Treatment of **3** and **25** with diazomethane in ether gave the respective 3-methoxy-derivatives (**29** and **30**), which were subjected to amination with ammonia or amines to yield the 3-amino-2-cyclohexen-1-one derivatives (Table II).

A variety of chlorinating reagents such as phosphorus trichloride,[10–12] phosgene,[13] acetyl chloride,[14] thionyl chloride,[11] phosphorus oxychloride,[10,15] triphenyl phosphine-carbon tetrachloride,[16] triphenylphosphine dihalide,[17] and oxalyl chloride[18] have been generally used for preparing β-chloro-α,β-unsaturated ketone from β-diketone, of which oxalyl chloride

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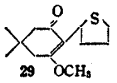
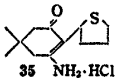
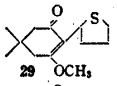
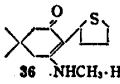
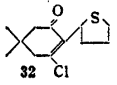
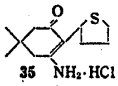
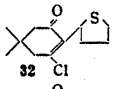
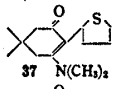
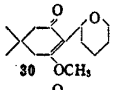
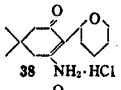
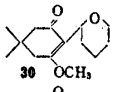
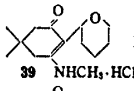
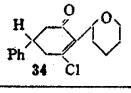
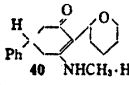
18) S.J. Rhoads and R.G. Michel, *J. Am. Chem. Soc.*, **85**, 585 (1963); R.D. Clark and C.H. Heathcock, *Synthesis*, **1974**, 47; *idem*, *J. Org. Chem.*, **41**, 636 (1976).

has been reported to be particularly superior for the chlorination of six-membered cyclic β-diketone. It was found, however, that when **3** was treated with an excess of oxalyl chloride, the chlorooxalate ester (**31**) was obtained with evolution of hydrogen chloride instead of direct chlorination. Subsequently, **31** was treated with a base to yield 3-chloro-2-(2-tetrahydrothienyl)-5,5-dimethyl-2-cyclohexen-1-one (**32**) in a 30% yield. Since **32** was fairly unstable, it was converted to 3-amino-2-(2-tetrahydrothienyl)-5,5-dimethyl-2-cyclohexen-1-one hydrochloride (**35**) by ammonolysis without purification. The compound (**35**) was identical with the sample prepared by ammonolysis of **29**. This reaction was also applicable to **26** to afford the corresponding 3-chloroenone (**34**), which was subjected to the reaction with methylamine giving 2-(2-tetrahydropyranyl)-3-methylamino-5-phenyl-2-cyclohexen-1-one (**40**).

Treatment of **31** with ice-water readily afforded the half ester (33) of oxalic acid, while treatment with a base effected hydrolysis to **3**.

These results are summarized in Table II together with results of the similar reactions of related compounds.

TABLE II. 3-Amino-2-cyclohexen-1-one Derivatives

Exp. No.	Starting materials: A compd. No.	Starting materials: B	Reaction: Method	Reaction: Solvent	Reaction: Temp. (°C)	Reaction: Time (hr)	Reaction: Structure compd. No.	Reaction: Yield (%)	Reaction: Recrystd. from	Product: Appearance	Product: mp (°C)	Product: Formula	Analysis (%) Calcd. (Found): C	H	N
1	 **29** OCH_3	NH_3-MeOH	C	MeOH	80	6	 **35** $NH_2 \cdot HCl$	54.0	EtOH +CH_3CN	Colorless powder	175—178 (dec.)	$C_{12}H_{19}NOS \cdot HCl$[a]	55.05 (55.46)	7.70 (7.56)	5.35 (5.54)
2	 **29** OCH_3	40% CH_3NH_2	C	MeOH +H_2O	60	7	 **36** $NHCH_3 \cdot HCl$	87.1	EtOH +AcOEt	Colorless powder	180—182 (dec.)	$C_{13}H_{21}NOS \cdot HCl$[b]	56.61 (57.11)	8.04 (8.02)	5.08 (5.00)
3	 **32** Cl	NH_3-MeOH	D	MeOH	100	10	 **35** $NH_2 \cdot HCl$	41.0	EtOH +CH_3CN	Colorless powder	174—175 (dec.)	c)			
4	 **32** Cl	$(CH_3)_2NH$	D	MeOH +H_2O	r.t.	12	 **37** $N(CH_3)_2$	38.7	$CHCl_3$ +hexane	Colorless prisms	124—125	$C_{14}H_{23}NOS$[d]	66.36 (66.24)	9.15 (9.05)	5.53 (5.51)
5	 **30** OCH_3	NH_3-MeOH	C	MeOH	80	10	 **38** $NH_2 \cdot HCl$	16.2	CH_3CN +AcOEt	Colorless powder	120—122 (dec.)	$C_{13}H_{21}NO_2 \cdot HCl$	60.11 (59.98)	8.15 (8.28)	5.39 (5.71)
6	 **30** OCH_3	40% CH_3NH_2	C	MeOH +H_2O	r.t.	12	 **39** $NHCH_3 \cdot HCl$	15.4	EtOH +AcOEt	Colorless needless	163—165 (dec.)	$C_{14}H_{23}NO_2 \cdot HCl$	61.41 (60.94)	8.84 (8.75)	5.16 (5.08)
7	 **34** Cl	40% CH_3NH_2	D	MeOH +H_2O	r.t.	12	 **40** $NHCH_3 \cdot HCl$	39.6	EtOH +AcOEt	Colorless prisms	173—174 (dec.)	$C_{18}H_{25}NO_2 \cdot HCl$	67.17 (66.87)	7.52 (7.88)	4.35 (4.37)

a) Calcd.: S, 12.25. Found: S, 12.26. b) Calcd.: S, 11.62. Found: S, 11.57.
c) This compd. showed no depression of mixed melting point with 35 obtained by Exp. No. 1 and had IR spectrum identical to that of 35.
d) Calcd.: S, 12.65. Found: S, 12.47. Ph=phenyl.

Experimental[19]

Materials——2-Chlorotetrahydrothiophene (**8**),[4] 2-chlorotetrahydrothiapyran (**12**),[4] 2-chlorotetrahydrofuran (**13**),[7] and 2-chlorotetrahydropyran (**14**)[7] were prepared according to the literatures and used as solution of crude products without purification.

General Procedures for 3-Hydroxy-2-substituted-2-cyclohexen-1-ones (Table I)——Method A_1: Dimedone (**7**) (2.5 g) was added to 8% solution (70 ml) of **8** in benzene and the mixture was refluxed with stirring for 2 hr and allowed to stand overnight at room temperature (r.t.). The resulting solution was washed with H_2O,

19) All melting points and boiling points were uncorrected. The IR spectra were taken with a Hitachi Model 215 spectrophotometer and all NMR spectra were measured on a Varian A-60 spectrometer using tetramethylsilane as the internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, m=multiplet. Unless otherwise stated, column chromatography was performed using silica gel (Merck, 0.063—0.20 mm), and the extracts were dried over anhydrous $MgSO_4$ or Na_2SO_4.

and treated with 5% NaOH (3×20 ml). The resulting aqueous layer was separated,[20] washed with ether and adjusted to pH 4 with 6 N HCl keeping the temperature below 10°. A pale yellow precipitate was collected and chromatographed on silica gel column (15 g). The column was eluted with $CHCl_3$ to afford 2-(2-tetrahydrothienyl)-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**3**). To a suspension of **3** (1.3 g) in H_2O (5 ml) was added 1 N NaOH (5.57 ml) and the mixture was stirred for 1 hr. Insoluble materials were filtered off and the filtrate was lyophilized to afford Na salt of **3** as colorless powder (1.2 g, 90.8%), mp 190—195° (dec.). *Anal.* Calcd. for $C_{12}H_{17}NaO_2S \cdot 1/2H_2O$: C, 56.01; H, 7.05; S, 12.46. Found: C, 55.97; H, 7.00; S, 12.41.

Method A_2: A mixture of **7** (19.8 g), 50% solution (66.0 g) of **14** in CH_2Cl_2 and benzene (400 ml) was refluxed with stirring for 2.5 hr and allowed to cool to r.t. The resulting solution was washed with H_2O, treated with 5% NaOH (3×30 ml)[21] and the separated aqueous layer was washed with ether and adjusted to pH 4 with conc. HCl while keeping the temperature below 10°. After salting out with NaCl, the mixture was extracted with ether (3×30 ml). The combined extracts were washed with saturated aqueous NaCl and dried. Removal of the solvent by evaporation gave an oil (26 g), which was distilled under reduced pressure. The distillate (bp 110—112°/2—3 mmHg) was collected and chromatographed on silica gel column (100 g). The column was eluted with $CHCl_3$ to afford 2-(2-tetrahydropyranyl)-3-hydroxy-5,5-dimethyl-2-cyclohexen-1-one (**25**). To a suspension of **25** (4.5 g) in H_2O (50 ml) was added 1 N NaOH (20 ml) and the mixture was stirred for 2 hr. A trace of insoluble material was filtered off and the filtrate was lyophilized to give Na salt of **25** as colorless powder (4.7 g, 98.0%), mp 185—190° (dec.). *Anal.* Calcd. for $C_{13}H_{19}NaO_3 \cdot H_2O$: C, 59.08; H, 8.01. Found: C, 58.96; H, 8.09.

Method B_1: A mixture of **7** (0.7 g), dihydrothiophene (2,3-dihydrothiophene (**9**) and 2,5-dihydrothiophene (1:1)[22] (1.4 g) and *p*-toluenesulfonic acid (70 mg) in benzene (15 ml) was refluxed with stirring for 1.5 hr. The resulting solution was washed with H_2O, treated with 10% NaOH (2×7 ml)[23] and the separated aqueous layer was washed with ether and adjusted to pH 2 with 6 N HCl. A pale yellow precipitate was collected and chromatographed on silica gel column (5 g). The column was eluted with $CHCl_3$–benzene (1:1) to afford 0.8 g (53.1%) of **3**. This compound was identified with an authentic specimen obtained from method A_1 by IR spectrum and TLC behavior.

Method B_2: To a mixture of **7** (5.6 g) and 3,4-dihydro-2*H*-pyran (6.7 g) in benzene (168 ml) was added dropwise conc. H_2SO_4 (1.5 g) at r.t., and the resulting solution was refluxed with stirring for 1.5 hr and allowed to cool to r.t. After a tarry substance which was adhered to the glass surface was removed by decantation, the supernatant solution was washed with H_2O and treated with 10% NaOH (2×40 ml). The aqueous layer was separated, washed with ether and adjusted to pH 2 with 6 N HCl. The resulting pale yellow precipitate was collected and chromatographed on silica gel column (20 g). The column was eluted with $CHCl_3$–benzene (1:1) to afford 3.6 g (40.2%) of **25**. This compound was identified with an authentic specimen from method A_2 by IR and NMR spectra and TLC behavior.

5,5-Dimethyl-2-(4,5-dihydro-2(3*H*)-thienylidene)-1,3-cyclohexanedione (2) from 3——A mixture of **3** (1.1 g) and sulfur (160 mg) was heated at 210—220° (bath temp.) for 40 min with stirring and allowed to cool to r.t. The resulting mixture was dissolved in benzene (100 ml), washed with 5% NaOH and saturated aqueous NaCl and dried. Removal of the solvent gave an oil (0.9 g), which was chromatographed on silica gel column (22 g) and eluted with $CHCl_3$–benzene (1:1) to afford 0.5 g (45.4%) of **2** as pale yellow prisms, mp 146—147°. This compound was identified with an authentic specimen[1] by mixed mp, IR and NMR spectra and TLC behavior.

3-Methoxy-2-substituted-2-cyclohexen-1-ones——(A) To an ethereal solution of diazomethane (500 ml), which was prepared from N-nitrosomethyl urea (47 g) and 40% KOH (140 ml), was added **3** (17.7 g) over a period of 15 min and the solution was stirred for 15 hr. After addition of AcOH (5.0 g), the solution was washed with 1 N NaOH and then saturated aqueous NaCl and dried. Removal of the solvent by evaporation gave an oil (21.4 g), which was chromatographed over silica gel column (140 g) and eluted with $CHCl_3$–benzene (1:3) to afford 5.7 g (30.3%) of 2-(2-tetrahydrothienyl)-3-methoxy-5,5-dimethyl-2-cyclohexen-1-one (**29**) as

20) The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. The residue was distilled under reduced pressure to give 1.0 g of dihydrothiophene dimer (**11**) as a yellow oil (bp 113—114° (5 mmHg)) (lit.,[5] bp 89° (0.1 mmHg)). *Anal.* Calcd. for $C_8H_{12}S_2$: C, 55.76; H, 7.02; S, 37.22. Found: C, 55.48; H, 6.76; S, 36.90. MS *m/e*: 172 (M^+). The NMR spectrum was identical with that of the authentic sample.[5]

21) The organic layer was washed with H_2O, dried over Na_2SO_4 and evaporated *in vacuo*. Distillation afforded 5.5 g of 2-(2-tetrahydropyranyloxy)tetrahydropyran (**27**) as a colorless oil (bp 75—76° (5 mmHg)) lit.,[8b] bp 106—110° (12 mmHg)). *Anal.* Calcd. for $C_{10}H_{18}O_3$: C, 64.49; H, 9.74. Found: C, 64.32; H, 9.85. NMR spectrum was identical with that of the authentic sample.[8b]

22) S.F. Birch and D.T. McAllan, *J. Chem. Soc.*, **1951**, 2556.

23) The organic layer was washed with H_2O, dried, and evaporated *in vacuo* to recover 2,5-dihydrothiophene as a brown oil (0.5 g). The identity of this compound was comfirmed by comparison of NMR spectra with that of the authentic sample.[24]

24) P.K. Korver, P.J. Vander Haak, H. Steinberg, and T.H.J. DeBoor, *J. Org. Chem.*, **38**, 2967 (1973).

colorless flakes, mp 111—112°. *Anal.* Calcd. for $C_{13}H_{20}O_2S$: C, 64.96; H, 8.39; S, 13.34. Found: C, 64.93; H, 8.64; S, 12.99.

(B) To an ethereal solution of diazomethane (200 ml), which was prepared from N-nitrosomethyl urea (18.8 g) and 40% KOH (56 ml), was added **25** (7.0 g) over a period of 20 min and the solution was stirred for 15 hr. After addition of AcOH (1.5 g), the solution was washed with 1 N NaOH and then saturated aqueous NaCl, and dried. Removal of the solvent by evaporation gave an oil (7.5 g), which was chromatographed on silica gel column (15 g) and eluted with $CHCl_3$ to afford 6.9 g of 2-(2-tetrahydropyranyl)-3-methoxy-5,5-dimethyl-2-cyclohexen-1-one (**30**) as a yellow oil.

A mixture of crude **30** (5.6 g) and 5% NH_3–MeOH (132 g) was heated at 80° in a sealed tube for 10 hr. The solvent was removed by evaporation *in vacuo*. The residue was dissolved in benzene (100 ml) and the resulting solution was treated with 6 N HCl (30 ml). The aqueous layer was separated, washed with ether and adjusted to pH 7—8 with K_2CO_3 (powder). The mixture was extracted with $CHCl_3$ (3×15 ml) and dried. Removal of the solvent by evaporation gave an oil (4.9 g), which was chromatographed on silica gel column (150 g) and eluted with $CHCl_3$–MeOH (100: 1). The eluent was concentrated *in vacuo*. The residue (2.7 g) was treated with 30% HCl–EtOH (2.7 g) and evaporated *in vacuo*. The resulting crude powder was recrystallized from CH_3CN–AcOEt (1: 1) to afford 0.98 g of 3-amino-2-(2-tetrahydropyranyl)-5,5-dimethyl-2-cyclohexen-1-one hydrochloride (**38**) as colorless powder, mp 120—122° (dec.). *Anal.* Calcd. or $C_{13}H_{21}NO_2 \cdot HCl$: C, 60.11; H, 8.15; N, 5.39. Found: C, 59.98; H, 8.28; N, 5.71.

3-Chloro-2-substituted-2-cyclohexen-1-ones——(A) To oxalyl chloride (9.9 g) was added **3** (3.0 g) with stirring at r.t. over a period of 10 min and the solution was stirred or 1.5 hr and evaporated *in vacuo* at the temperature ranging from 40° to 50°. The residue was dissolved in benzene (40 ml) and to the solution was added dropwise pyrrolidine (10 g). The reaction mixture was stirred for 1 hr and allowed to stand overnight at r.t. The resulting solution of the chlorooxalate ester (**31**) was washed successively with H_2O, saturated aqueous $NaHCO_3$ and saturated aq. NaCl, and then dried. Removal of the solver t gave an oil (4.8 g), which was chromatographed on silica gel column (192 g) and eluted with $CHCl_3$–benzene (2: 1) to give 1.1 g (19.0%) of 3-chloro-2-(2-tetrahydrothienyl)-5,5-dimethyl-2-cyclohexen-1-one (**32**) as a brown oil. NMR ($CDCl_3$) δ: 1.07 (6H, s, CH_3), 1.87—2.33 (6H, m, CH_2), 2.65 (2H, s, CH_2CO), 2.90—3.27 (2H, m, CH_2S), 4.90 (1H, t, J= 7 Hz, =CHS).

A mixture of **32** (800 mg) and 15% NH_3–MeOH (13.0 g) was heated at 100° in a sealed tube for 10 hr. The solvent was evaporated *in vacuo* and the residue was dissolved in $CHCl_3$ (10 ml). The solution was washed with 10% K_2CO_3 (10 ml) and saturated aq. NaCl (10 ml), and then dried. Removal of the solvent by evaporation gave an oil (700 mg), which was chromatographed on silica gel column (7.0 g) and eluted with $CHCl_3$. The eluent was concentrated *in vacuo* and the residue was treated with 30% HCl–EtOH (10 ml) and evaporated *in vacuo*. The residue was crystallized from EtOH–CH_3CN (1: 1) to afford 350 mg of 3-amino-2-(2-tetrahydrothienyl)-5,5-dimethyl-2-cyclohexen-1-one hydrochloride (**35**) as colorless powder, mp 174—175° (dec.). This compound was identified with an authentic specimen obtained by the ammonolysis of **29**, described below, by mixed mp and NMR spectra and TLC behavior.

The crude **31** (5 g), prepared by the procedure described above, was dissolved in ether (20ml) and thoroughly shaken with ice-water (50 g) for 30 min. The ethereal extract was separated and dried. Removal of the solvent by evaporation afforded the oxalic acid half ester (**33**) as a colorless oil. NMR (CCl_4) δ: 1.07 (6H, s, CH_3), 1.66—3.30 (10H, m, CH_2), 5.15 (1H, t, CHS, J=7 Hz), 10.83 (1H, s, COOH), IR ν cm^{-1}: 1735 (COCO).

A mixture of **33** (50 mg), EtOH (10 ml) and pyridine (400 mg) was stirred at r.t. for 3 hr to give **3** quantitatively. This compound showed IR and NMR spectra identical with those of an authentic sample.

(B) To oxalyl chloride (2.8 g) was added 2-(2-tetrahydropyranyl)-2-hydroxy-5-phenyl-2-cyclohexen-1-one (**26**) (1.0 g) with stirring over a period of 10 min, while keeping the temperature below 10° by cooling. The resulting solutin was stirred at 0° for 40 min and at r.t. for 2 hr, then evaporated *in vacuo* at 40—50°. The residue was dissolved in benzene (100 ml) and to the resulting solution was added drowpise pyrrolidine (0.55 g). The reaction mixture was stirred for 3 hr and allowed to stand overnight at r.t. Removal of the solvent by evaporation gave an oil (2.0 g), which was chromatographed on silica gel (50 g) and eluted with $CHCl_3$–benzene (5: 1) to afford 150 mg (14.0%) of 3-chloro-2-(2-tetrahydropyranyl)-5-phenyl-2-cyclohexen-1-one (**34**) as colorless powder, mp 95—97°. *Anal.* Calcd. for $C_{17}H_{19}ClO_2$: C, 70.21; H, 6.50; Cl, 12.19. Found: C, 70.42; H, 6.48; Cl, 12.18.

3-Amino-2-substituted-2-cyclohexen-1-ones——The reactions in Table II were carried out in the manner similar to the method (C) and (D) described below.

Method (C): A mixture of **29** (1.7 g) and 15% NH_3–MeOH (40 g) was heated at 80° in a sealed tube for 6 hr. The resulting solution was evaporated *in vacuo* and the residue was dissolved in benzene (50 ml) and treated with 6 N HCl (3×20 ml). The aqueous layer was separated, and washed with ether and adjusted to pH 8—9 with K_2CO_3 (powder). The mixture was extracted with $CHCl_3$ (3×20 ml) and the extract was dried. The solvent was evaporated *in vacuo* and the residue was dissolved in 30% HCl–EtOH (1.5 g). Removal of the solvent by evaporation gave a powder which was recrystallized from MeOH to afford 3-amino-2-(2-tetrahydrothienyl)-5,5-dimethyl-2-cyclohexen-1-one hydrochloride (**35**).

Method (D): A mixture of **34** (0.8 g), MeOH (10 ml) and 40% $MeNH_2$ (2.5 g) was stirred at r.t. for 7 hr and allowed to stand overnight at r.t. The resulting solution was concentrated *in vacuo* and to residue was

added 10% K_2CO_3 (100 ml). The mixture was extracted with benzene (3 × 100 ml) and the extract was dried. The solvent was evaporated *in vacuo* and the residue was dissolved in 30% HCl–EtOH (1.5 g). Removal of the solvent by evaporation gave a powder which was recrystallized from EtOH–AcOEt to afford 2-(2-tetrahydropyranyl)-3-methylamino-5-phenyl-2-cyclohexen-1-one hydrochloride (**40**).

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