SYNTHESIS OF 2-PHENYL-2,3,4,5-TETRAHYDRO-1-BENZOXEPIN-5-ONES

Toshio Tatsuoka* , Kayoko Imao, Kenji Suzuki, Makoto Shibata, and Fumio Satoh
Suntory Institute for Biomedical Research, Suntory Ltd.
1-1-1 Wakayamadai, Shimamoto-Cho, Mishima-Gun, Osaka 618, Japan

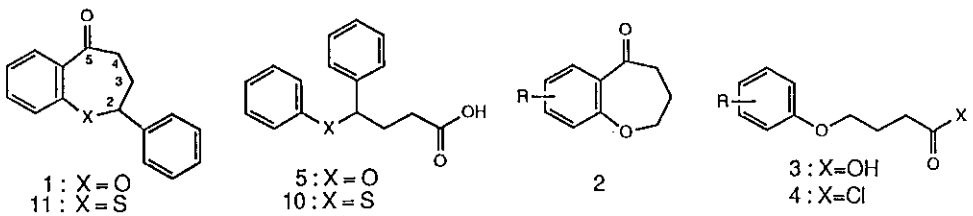
Seiji Miyano and Kunihiro Sumoto
Faculty of Pharmaceutical Sciences, Fukuoka University
8-19-1 Nanakuma, Johnan-Ku, Fukuoka 814, Japan

Abstract-A series of 2-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-ones were synthesized by 2 steps from flavones through 3,4-benzo-5-oxo-2-oxa-bicyclo[4.1.0]heptanes.

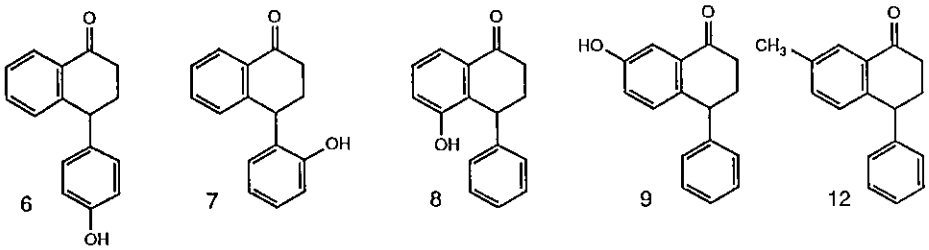
As part of an effort to offer useful frameworks for the purpose of synthesis of pharmacologically active compounds, we have prepared a series of 2-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-ones(1) by two steps through cyclopropanations of flavones followed by Pereyre's reductive cleavage of the bicyclic ring systems.

A large number of benzoxepin derivatives have been synthesized to investigate their physicochemical properties and their pharmacological activities.[1] The key intermediates for the syntheses of those compounds are 2,3,4,5-tetrahydro-1-benzoxepin-5-ones(2). However, there have been no reports concerning on the synthesis of 2-phenyl-substituted benzoxepin derivatives so far.

We report here a synthesis of 2-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-ones, which should be the key intermediates towards to prepare a new category of benzoxepin derivatives. Non-phenyl substituted 2,3,4,5-tetrahydro-1-benzoxepin-5-ones have been synthesized either by dehydrative ring formation of 4-phenoxybutyric acid(3) in polyphosphoric acid[2] (PPA) or by Friedel-Crafts reaction of 4-phenoxybutyryl chloride(4) with stannic chloride.[3]



We tried, at first, the dehydrative ring formation of 4-phenoxy-4-phenylbutyric acid(5) with PPA. None of the formation of (1) could be detected, however, we obtained only a complex mixture of α-tetralone derivatives,(6),(7),(8) and (9), whose structures were ascertained from their spectroscopic data.[4]

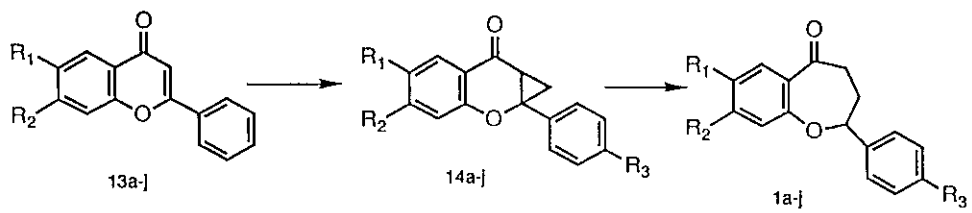


A similar type of reaction was reported for an approach to sunthesize 2-phenyl-2,3,4,5-tetrahydro-1-benzothiepin-5-one(11) by Protiva et al.[5] They obtained sulfur free product(12) in the reaction of 4-phenyl-4-phenylthiobutyric acid(10) with PPA in toluene, where a cleavage of the labile benzyl-sulfur bond followed by an attack of the produced carbocation to the para position of toluene and subsequent cyclization of the transiently formed acid was occurred.

These observations suggested us that either neutral or basic reaction condition was feasible for the purpose. Then we tried to synthesize (1) by cyclopropanation of flavones and subsequent Pereyre's reductive cleavage of the intermediate oxabicyclo[4.1.0]heptanes.

Donnelly et al.[6] reported the synthesis of 3,4-benzo-5-oxo-2-oxabicyco[4.1.0]heptane(14a) by the reaction of flavone(13a) with dimethyloxosulphonium methylide in DMSO. Application of this cyclopropanation reaction to the appropriate flavones (13b-j)[7] afforded the corresponding oxabicyclo[4.1.0]heptanes(14b-j) in yields of 20 ~ 65%.(Table I) The yields of the cyclopropanation were dependent on their substituents on the benzene ring. Compounds substituted by electron donating group such as methoxy gave the products in much higher yield than those substituted by electron withdrawing groups such as trifluoromethyl or ester.

To transform the oxabicyclo[4.1.0]heptanes to the oxepines, Pereyre's reaction,[8] a reductive cleavage of cyclopropyl ketone in neutral condition, was adopted. Solutions of (14a-j) in toluene were heated with one equivalent of tri-n-butyltin hydride in the presence of azobisisobutyronitrile at 90 ~ 100 ℃ for 1 h gave exclusively (1a-j).(TableII)



a : R_1=R_2=R_3=H f : R_1=R_2=H, R_3=Cl

b : R_2=Cl, R_1=R_3=H g : R_1=R_2=H, R_3=OCH_3

c : R_1=OCH_3, R_2=R_3=H h : R_1=R_2=H, R_3=CH_3

d : R_2=OCH_3, R_1=R_3=H I : R_1=R_2=H, R_3=CF_3

e : R_1=R_2=OCH_3, R_3=H j : R_1=R_2=H, R_3=CO_2CH_3

Scheme 1

These ketones are the first examples of 2-phenyl substituted benzoxepins and they should be useful intermediates for the introduction of various kinds of functional groups. For instance,introductions of amine groups at 4-position of (1) can afford compounds having both phenylethyl and phenylpropyl amine moieties, whereas introductions of amine groups at 5-position of (1) can offer compounds possessing both benzyl and phenylbutyl amine moieties concurrently. Those compounds might have new aspects of pharmacological activities derived from having the duplicate phenyl alkyl amine moieties in one molecule. Chemical reactions of (1a-j) and pharmacological activities of those reaction products will be published elsewhere.

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4.

	ir ν_{OH}	ir ν_{C-O}	Nmr (δ in $CDCl_3$) H-2	H-3	H-1	O-H	arom
6	3330	1670	2.25, 2.43	2.56-2.88	4.24	5.45	6.81, 6.96, 7.00, 7.34, 7.44, 8.10
7	3330	1670	2.32-2.55	2.57-2.81	4.69	5.78	6.77-6.86, 7.13, 7.18-7.41, 7.43, 8.11
8 and 9 (mixture)	3330	1680	2.06 ———	2 .75	4.12, 4.65	5.46	6.96-7.45, 8.01-8.10

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Table I

	yield	mp (℃)	ir($\nu_{C=O}$)	Nmr(δ in $CDCl_3$) H-7α	H-7β	H-6
a.	51 %	59 - 60	1670	1.73	2.05	2.54
b.	35 %	102 -103.5	1670	1.73	2.07	2.52
c.	45 %	78 - 81	1660	1.72	2.04	2.53
d.	52 %	115 -116.5	1650	1.67	1.99	2.46
e.	45 %	oil	1660	1.66	2.01	2.47
f.	31 %	61 - 63	1675	1.75	2.02	2.51
g.	30 %	117 - 120	1675	1.69	2.02	2.48
h.	40 %	98 - 100	1680	1.71	2.02	2.38
i.	49 %	oil	1680	1.83	2.07	2.58
j.	46 %	97.5- 98.0	1680	1.82	2.10	2.58

Table II

	yield	mp (℃)	HiMS		ir($\nu_{C=O}$)	Nmr(δ in $CDCl_3$) H-3	H-4α	H-4β	H-2	H-6
a.	85 %	oil	Calcd	238.0993	1690	2.43	2.82	3.16	5.08	7.82
			Obsd	238.1038						
b.	77 %	63-65	Calcd	272.0602	1680	2.46	2.85	3.14	5.08	7.78
			Obsd	272.0554						
c.	62 %	oil	Calcd	268.1098	1675	2.41	2.82	3.13	5.08	
			Obsd	268.1076						
d.	77 %	105-107	Calcd	268.1098	1680	2.35	2.77	3.12	5.07	7.80
			Obsd	268.1103						
e.	68 %	oil	Calcd	298.1203	1660	2.43	2.81	3.13	5.07	
			Obsd	298.1177						
f.	49 %	82-85	Calcd	272.0602	1680	2.39	2.83	3.13	5.05	7.82
			Obsd	272.0562						
g.	95 %	46.5-48.0	Calcd	268.1097	1675	2.43	2.83	3.15	5.04	7.82
			Obsd	268.1091						
h.	69 %	78-80	Calcd	252.1148	1680	2.44	2.81	3.15	5.05	7.82
			Obsd	252.1124						
i.	60 %	59-63	Calcd	306.0867	1680	2.44	2.83	3.16	5.13	7.84
			Obsd	306.0894						
j.	18 %	77.5-80.0	Calcd	296.1047	1680	2.47	2.82	3.16	5.13	7.84
			Obsd	296.1032						

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