

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

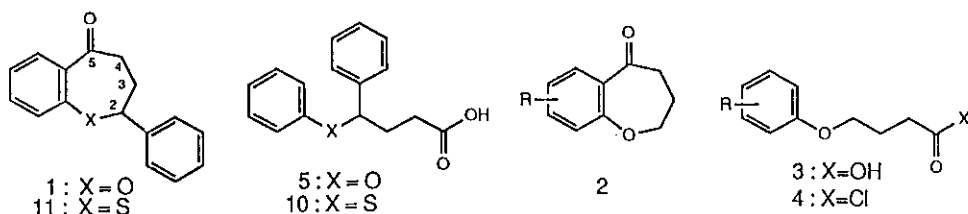
Seiji Miyano and Kunihiro Sumoto
 Faculty of Pharmaceutical Sciences, Fukuoka University
 8-19-1 Nanakuma, Johnan-Ku, Fukuoka 814, Japan

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.

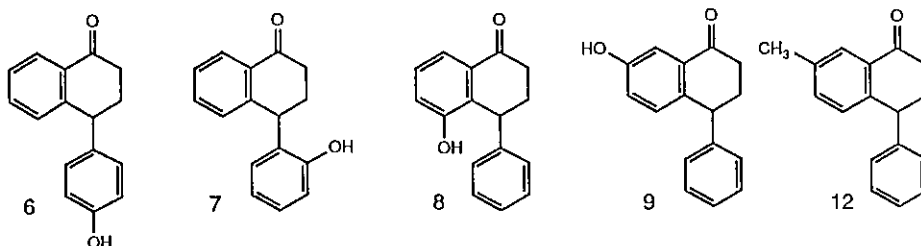
As part of an effort to offer useful frameworks for the purpose of synthesis of pharmacologically active compounds, we have prepared a series of 2-phenyl-2,3,4,5-tetrahydro-1-benzoxepin-5-ones(1) by two steps through cyclopropanations of flavones followed by Pereyre's reductive cleavage of the bicyclic 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 acid² (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

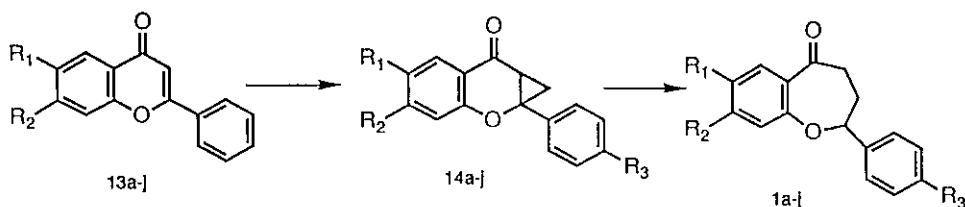


A similar type of reaction was reported for an approach to synthesize 2-phenyl-2,3,4,5-tetrahydro-1-benzothiepin-5-one(11) by Protiva et al.⁵ They obtained sulfur free product(12) in the reaction of 4-phenyl-4-phenylthiobutyric acid(10) with PPA in toluene, where a cleavage of the labile benzyl-sulfur 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-oxabicyclo[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 °C for 1 h gave exclusively (1a-j).(Table II)



- | | |
|----------------------------|-------------------------------|
| 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.

ACKNOWLEDGEMENT

The authors are grateful to Dr. Teruhisa Noguchi, Director of Suntory Institute for Biomedical Research, for his encouragement and helpful advices throughout the work.

REFERENCES AND NOTES

- 1.a) J.M.F. Gagan, *Rodd's Chemistry of Carbon Compounds*, Vol. IV, Part K, Elsevier Scientific Pub. Comp. (1979) pp.149-157 and references therein.
- b) L.O. Randall, R.E. Bagdon, *Ann. New York Acad. Sci.*, 1959, **80**, 626.
- c) Z.P. Horovitz, J.J. Piala, J.P. High, J.C. Burke, and R.C. Leaf, *Internat. J. Neuropharmacol.*, 1966, **5**, 405.
- d) D. Muckle, I.M. Lockhart, and N.E. Webb, *J. Chem. Soc. (C)*, 1971, 2252.
- e) M. Protiva, V. Seidlova, E. Svatek, and F. Hradil, *Coll. Czech. Chem. Commun.*, 1972, **37**, 868.
- f) J.M. Khanna, B. Lal, V.K. Tandon, and N. Anand, *J. Indian Chem. Soc.*, 1974, **15B**, 264.
- g) V.K. Tandon, J.M. Khanna, and N. Anand, *Indian J. Chem.*, 1975, **13**, 1.
- h) I.I. Badilescu, *Revue Roumaine de Chimie*, 1975, **20**, 761.
- i) V.K. Tandon, J.M. Khanna, and N. Anand, *Indian J. Chem.*, 1977, **15 B**, 264.
2. O. Dann and W.D. Arndt, *Justus Liebig's Ann. Chem.*, 1954, **587**, 38.
- 3.a) G. Fontaine and P. Maitte, *C. R. Acad. Sci. (Paris)*, 1964, **258**, 4583.
- b) G. Fontaine, *Ann. Chim. (Paris)*, 1968, **3**, 179.

4.

	ir ν_{OH} $\nu_{C=O}$		H-2	Nmr (δ in CDCl ₃) 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

5. K. Sindelar, E. Svatek, B. Kakac, F. Hradil, and M. Protiva, *Coll. Czech. Chem. Commun.*, 1972, **37**, 1195.
6. P. Bennett, J.A. Donnelly, and M.J. Fox, *J. Chem. Soc., Perkin Trans. I*, 1979, 2990.

7. a) S.Wawzonek, *Heterocyclic Compounds*, Vol 2, Ed. by R.C.Elderfield, John Wiley & Sons, Inc.(1951). pp.229-276 and references therein.
 b) R.Livingstone, *Rodd's Chemistry of Carbon Compounds*, Vol.IV , Part E,Elsevier Scientific Pub. Comp, (1977), pp.51-222 and references therein.
8. J-Y.Godet and M.Pereyre,*Bull. Chim. Soc. France* , 1976, 1105.

Table I

	yield	mp (°C)	ir ($\nu_{C=O}$)	H-7 α	Nmr(δ in CDCl ₃) H-7 β	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 (°C)	HIMS	ir ($\nu_{C=O}$)	H-3	Nmr(δ in CDCl ₃) H-4 α	H-4 β	H-2	H-6
a.	85 %	oil	Calcd 238.0993 Obsd 238.1038	1690	2.43	2.82	3.16	5.08	7.82
b.	77 %	63-65	Calcd 272.0602 Obsd 272.0554	1680	2.46	2.85	3.14	5.08	7.78
c.	62 %	oil	Calcd 268.1098 Obsd 268.1076	1675	2.41	2.82	3.13	5.08	
d.	77 %	105-107	Calcd 268.1098 Obsd 268.1103	1680	2.35	2.77	3.12	5.07	7.80
e.	68 %	oil	Calcd 298.1203 Obsd 298.1177	1660	2.43	2.81	3.13	5.07	
f.	49 %	82-85	Calcd 272.0602 Obsd 272.0562	1680	2.39	2.83	3.13	5.05	7.82
g.	95 %	46.5-48.0	Calcd 268.1097 Obsd 268.1091	1675	2.43	2.83	3.15	5.04	7.82
h.	69 %	78-80	Calcd 252.1148 Obsd 252.1124	1680	2.44	2.81	3.15	5.05	7.82
i.	60 %	59-63	Calcd 306.0867 Obsd 306.0894	1680	2.44	2.83	3.16	5.13	7.84
j.	18 %	77.5-80.0	Calcd 296.1047 Obsd 296.1032	1680	2.47	2.82	3.16	5.13	7.84

Received, 28th August, 1989