STUDIES ON THE STRUCTURE-ACTIVITY RELATIONSHIP OF THIEPIN AND OXEPIN DERIVATIVES TO ANTI-INFLAMMATORY ACTIVITIES. I

10,11-DIHYDRODIBENZO[b,f]THIEPINCARBOXYLIC ACID DERIVATIVES.

Yoshio Suzuki*, Tohru Yamanaka, Yoshihiro Tanaka, Kiyosato Niu, Masakastu Mizushima, Sigeo Ikeda, and Yasuo Fujimoto
Research Institute, Nippon Chemiphar Co., Ltd. Hikokawato, Misato 341, Japan
Shigeru Yamabe
Research Institute, Kobe College, Okadayama, Nishinomiya 662, Japan

Abstract — A series of dibenzo[b,f]thiepincarboxylic acid derivatives has been synthesized and it's anti-inflammatory activity was examined by the method of carrageenan edema.

As it was known that dibenzo[b,f]thiepin derivatives had the neurotropic and psychotropic activities[1-3], we intended to study the other pharmacological activity such as anti-inflammatory activities. In our study, the deivatives of dibenzo[b,f]thiepin and dibenzo[b,f]oxepin, having carboxylic group, acetic acid, and propionic acid moiety attached to the aromatic ring were synthesized and examined of their anti-inflammatory response.

In this report, the synthetic and pharmacological results of dibenzo[b,f]thiepin carboxylic acid derivatives were described.

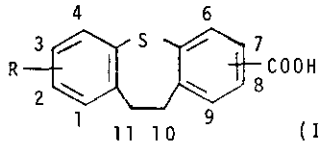
Various debenzo[b,f]thiepincarboxylic acid derivatives (I-a-o) were synthesized by the methods shown in Scheme 1 or 2 and the products were listed in Table I.

Thiepinones (III), prepared by cyclization of diphenyl thioether derivatives (II)[4] with polyphosphoric acid (PPA) at the 100-150°C, were converted to the carboxylic acid (I) by the method A or B shown in Scheme 1.

In the method A, thiepinones (III) were converted to the corresponding cyano compounds (IV) by the reaction with CuCN[5].

The compounds (IV) were treated with hydrazine hydrate, then with NaOH[6] to afford the corresponding carboxylic acid derivatives (I-a-p).

Table I Physical properties of dibenzo[b.f]thiepin derivatives



(I)

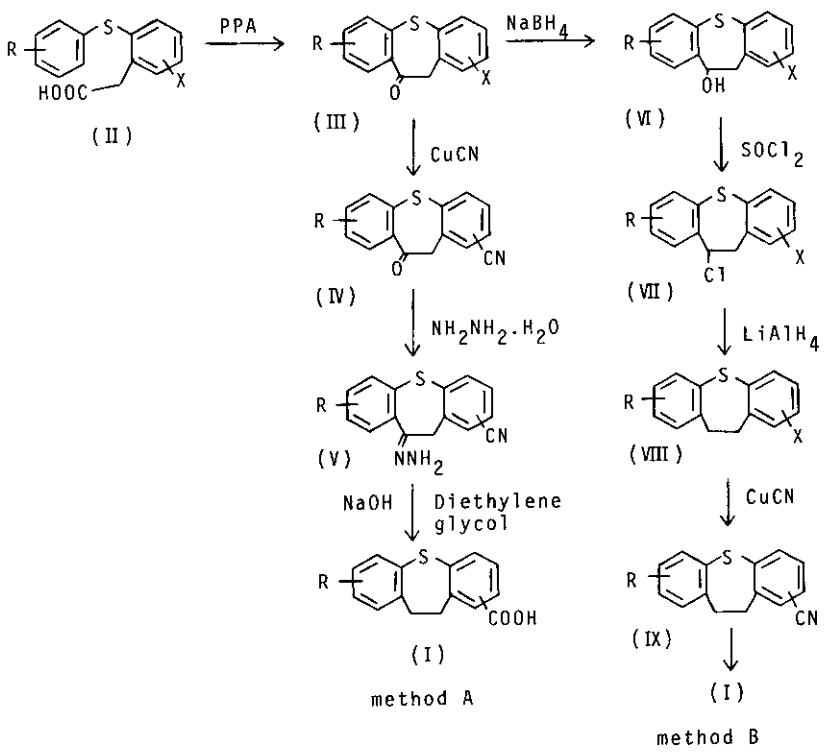
Compd. No.	Method	Starting materials(III) R	X	Products R	-COOH	Mp,°C(Recrystn.solvent)
I-a	A	H	9-Cl	H	9-COOH	187-188(Benzene)
I-b	A	3-H	9-Cl	3-F	9-COOH	209-211(MeOH)
I-c	A	3-F	9-Cl	3-DEG[a)]	9-COOH	125-128(EtOH-H_2O)
I-d	A	3-F	9-Cl	3-OH	9-COOH	219-221(EtOH-H_2O)
I-e	A	3-F	8-Br	3-F	8-COOH	208-210(MeOH)
I-f	A	3-F	8-Br	3-DEG[a)]	8-COOH	119-120(EtOH-H_2O)
I-g	A	4-F	9-Cl	4-DEG[a)]	9-COOH	128-130(AcOEt)
I-h	A	4-F	9-Cl	4-OH	9-COOH	171-173(MeOH-H_2O)
I-i	A	2-F	9-Cl	2-DEG[a)]	9-COOH	114-116(EtOH-petro.ether)
I-j	A	2-OMe	9-Cl	2-OMe	9-COOH	185-186(Benzene-n-hexane)
I-k	A	2-OEt	9-Cl	2-OEt	9-COOH	192-193(EtOH)
I-l	B	2-F	9-Cl	2-F	9-COOH	200-202(Benzene)
I-m	B	2-CF_3	9-Cl	2-CF_3	9-COOH	179-180(Benzene-n-hexane)
I-n	(Sheme 2)			2-HEH[b)]	9-COOH	167-169(Benzene)
I-o	(Sheme 2)			2-AEH[c)]	9-COOH	220-223(EtOH-ether)

a): $HOCH_2CH_2OCH_2CH_2O$- b): $HOCH_2CH_2O$- c): $HCl.NH_2CH_2CH_2O$-

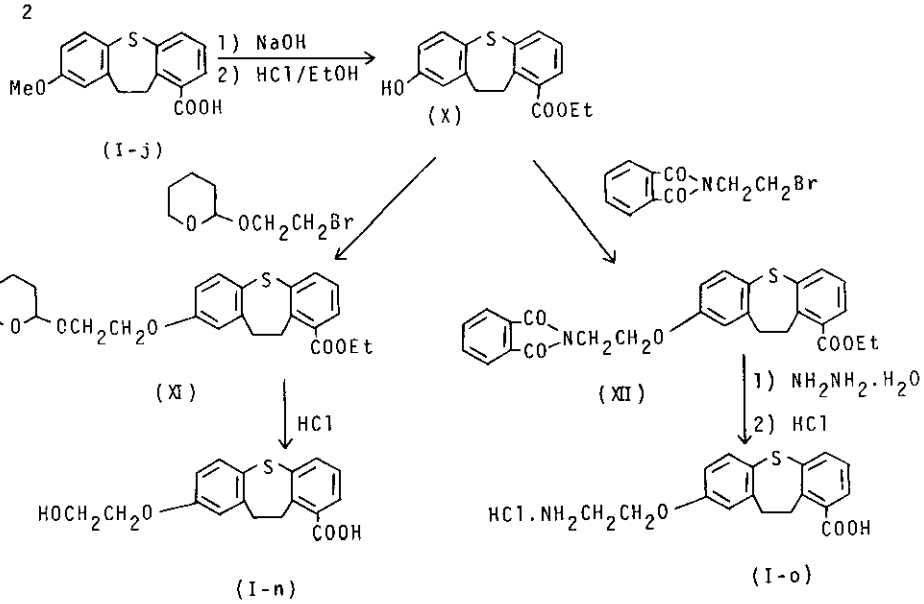
Table II Antiinflammatory Activity(carrageenan induced edema)

Compd. No.	Maximum inhibition(%)	Time after dosing(hr)	Compd. No.	Maximum inhibition(%)	Time after dosing(hr)
I-a	9.6	2	I-i	50.3	5
I-b	37.7	4	I-j	37.7	3
I-c	31.7	2	I-k	27.7	3
I-d	25.5	4	I-l	19.9	4
I-e	41.0	4	I-m	40.6	2
I-f	23.2	6	I-n	35.4	2
I-g	23.9	4	I-o	46.4	3

Sheme 1



Sheme 2



When 9-cyano-3-fluorodibenzo[b,f]thiepin-11-one hydrazone (V) was heated with NaOH in diethylene glycol at 190-200°C for 2 hours, the mixture of three products, 3-fluoro-10,11-dihydrodibenzo[b,f]thiepin-9-carboxylic acid (I-b, 11%), 3-diethylene glycoxy-10,11-dihydrodibenzo[b,f]thiepin-9-carboxylic acid (I-c, 12%) and 10,11-dihydro-3-hydroxydibenzo[b,f]thiepin-9-carboxylic acid (I-d, 5%) were obtained simultaneously (each product was isolated by column chromatography from the mixture).

The compounds I-l and I-m, which could be not obtained by the method A, were synthesized through the another method B.

The thiepinons (III) were reduced with $NaBH_4$ to afford hydroxythiepin derivatives (VI), which were converted to the chlorothiepin derivatives (VII).

Reduction of the compounds (VII) with $LiAlH_4$ gave the dihydrothiepin derivatives(VIII). Treatment of (VII) with CuCN[5] yielded the cyano compounds (IX), which were converted to the carboxylic acid derivatives by hydrolysis.

In view of the experimental result that compound I-i has strong pharmacological activity, compounds I-n and I-o were synthesized by the another methods as shown in Scheme 2, respectively.

Hydrolysis of the compound I-j with NaOH afforded the 2-hydroxy compound, which was converted to the compound (X).

The compound (X) on heating with β-(O-tetrahydropyranyl)hydroxyethyl bromide and NaH in Hexamethylphosphoramide (HMPA) at 130°C for 19 hours gave the compound (XI), which was converted by hydrolysis to 10,11-dihydro-2-(β-hydroxyethyl)dibenzo[b,f]thiepin-9-carboxylic acid (I-n).

Similarly, the compound (XII) was obtained by the reaction of the compound (XI) with β-(N-phthalyl)aminoethyl bromide.

On refluxing with hydrazine hydrate in EtOH followed by hydrolysis, the compound (XII) gave 2-(β-aminoethyl)hydroxy-10,11-dihydrodibenzo[b,f]thiepin-9-carboxylic acid (I-o).

The compounds prepared in this study were tested for their anti-inflammatory activity on carrageenan induced edema in male Wistar rats according to the method of Winter[7].

The compounds were administered orally as suspension in 0.2%CMC to the animals in dose of 100 mg/kg.

Among the compounds tested, the activity of I-i was the strongest of all.

In the series of 2-substituted-10,11-dihydrodibenzo[b,f]thiepin-9-carboxylic acid derivatives, the anti-inflammatory activity increased as the molecular weight of the substituents increased except in the case of methoxy group.
In the case of 3 or 4-substituted derivatives, the anti-inflammatory activity was increased in the following order ; $F > CF_3 > DEG > OH$.

References and note

1). K.Plez, I. Ernest, E. Adlerova, J. Metysova and M. Protiva, Coll. Czech. Chem. Comm., 1968, 33, 1852.

2). K. Plez, I. Jirkosky, E. Adlerova, J. Metysova and M. Protiva, Coll. Czech. Chem. Comm., 1968, 33, 1895.

3). M. Protiva, Z. Sedivy and J. Metysova, Coll. Czech. Chem. Comm., 1975, 40, 2667.

4). Compounds (II) was orepeared according to the method of K. Plez[1] using substituted thiophenol and dihalogenated benzaldehyde or benzoic acid as the starting materials.

5). M. S. Newman and H. Boden, J. Org. Chem., 1961, 26, 2525.

6). H. H. Szmant, Angew. Chem. Int. Ed., 1968, 7, 120.

7). C. A. Winter, E. A. Risley and G. W. Nuss, Proc. Soc. Exp. Biol. Med., 1962, 111, 544.

Received, 14th November, 1980