

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

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

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Abstract—A series of dibenzo[b,f]thiepinicarboxylic acid derivatives has been synthesized and its 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 activities¹⁻³⁾, we intended to study the other pharmacological activity such as anti-inflammatory activities. In our study, the derivatives 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.

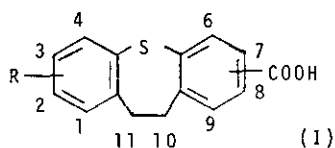
In this report, the synthetic and pharmacological results of dibenzo[b,f]thiepin carboxylic acid derivatives were described.

Various dibenzo[b,f]thiepinicarboxylic 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 CuCN⁵⁾.

The compounds (IV) were treated with hydrazine hydrate, then with NaOH⁶⁾ to afford the corresponding carboxylic acid derivatives (I-a-p).

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



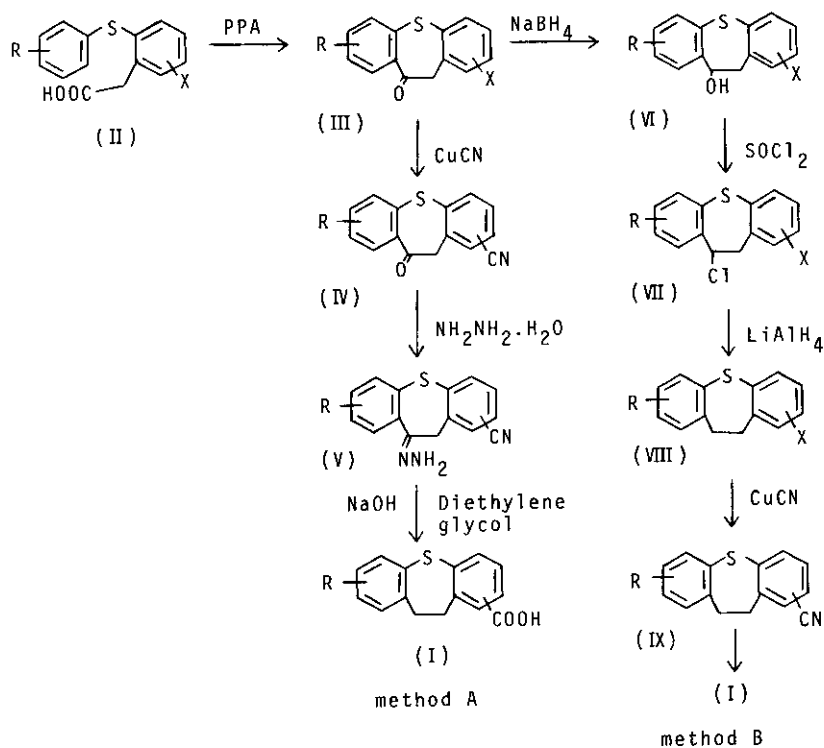
Compd. No.	Method	Starting materials(III)		Products		Mp, °C(Recrystn.solvent)
		R	X	R	-COOH	
I-a	A	H	9-Cl	H	9-COOH	187-188 (Benzene)
I-b	A	3-H	9-Cl	3-F	9-COOH	209-211 (MeOH)
I-c	A	3-F	9-Cl	3-DEG ^{a)}	9-COOH	125-128 (EtOH-H ₂ O)
I-d	A	3-F	9-Cl	3-OH	9-COOH	219-221 (EtOH-H ₂ O)
I-e	A	3-F	8-Br	3-F	8-COOH	208-210 (MeOH)
I-f	A	3-F	8-Br	3-DEG ^{a)}	8-COOH	119-120 (EtOH-H ₂ O)
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 ₂ O)
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	(Scheme 2)			2-HEH ^{b)}	9-COOH	167-169 (Benzene)
I-o	(Scheme 2)			2-AEH ^{c)}	9-COOH	220-223 (EtOH-ether)

a): HOCH₂CH₂OCH₂CH₂O-b): HOCH₂CH₂O-c): HCl.NH₂CH₂CH₂O-

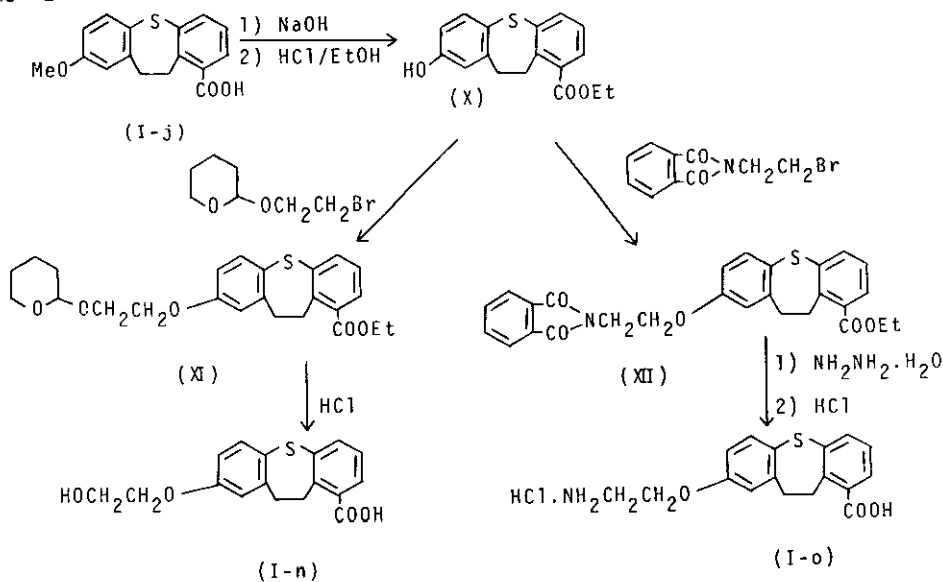
Table II Antiinflammatory Activity(carrageenan induced edema)

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

Scheme 1



Scheme 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 (VIII) with $\text{CuCN}^{5)}$ 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 -(0-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 (X) 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 Winter⁷⁾.

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

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