Notes

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Metabolism of Drugs. XII.* The Effect of β-Diethylaminoethyl Diphenylpropylacetate Hydrochloride (SKF 525-A) on the Metabolism of Ethylhexabital.

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It has been reported[1~4] that β-diethylaminoethyl diphenylpropylacetate hydrochloride (SKF 525-A) prolonged the action of a wide variety of drugs including some barbiturates by lowering the rate of their metabolic transformation. As previously described, ethylhexabital (EHB) was metabolized chiefly to 3-keto-EHB,[5,6] but methylhexabital (MHB), despite its similarity in chemical structure to EHB, was biotransformed to various compounds such as 3-hydroxy-MHB, 3-keto-MHB, nor-MHB derivatives, and so on.[7] Cooper, *et al.*[2] studied the effect of SKF 525-A on MHB metabolism only based on the disappearing rate of MHB, but it is unknown which pathway is inhibited by SKF 525-A. For clarifying this different detoxication mechanism between these two barbiturates, the effect of SKF 525-A on the metabolism of EHB was first studied.

The evidence described below indicates that SKF 525-A slows the rate of conversion of EHB to 3-keto-EHB and prolongs the duration of EHB hypnosis. A study on the effect of SKF 525-A on the MHB metabolism is in contemplation.

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Experimental

1. Effect of SKF 525-A on the Duration of EHB Hypnosis—The duration of EHB hypnosis was compared in rats, mice, and rabbits of both sexes with and without administration of SKF 525-A. In the control experiments each animal received only 80 mg./kg. of EHB intraperitoneally. In the SKF experiments the animals were pretreated with SKF 525-A intraperitoneally 40 mins. prior to the administration of EHB. Each animal served as its own control. The results presented in Table I show that SKF 525-A prolonged the duration of EHB hypnosis in all animal species.

Table I. Effect of SKF 525-A on the Duration of EHB Hypnosis

Species	Sex	Dose of SKF 525-A (mg./kg.) 0	5	10	20
		Duration (min.)			
Rat	♂	55		92	165
	♀	159		476	
Mouse	♂	139	320		
	♀	145	324		
Rabbit	♂	147	155		213
	♀	121		192	

* Part XI. E. Takabatake : This Bulletin, **5**, 266(1957).

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3) J. H. Mirsky, N. J. Giarman : *Ibid.*, **114**, 240(1955).
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5) H. Tsukamoto, E. Takabatake, H. Yoshimura : This Bulletin, **2**, 201(1954).
6) H. Tsukamoto, H. Yoshimura, S. Toki : *Ibid.*, **3**, 239(1955).
7) *Idem.* : *Ibid.*, **4**, 364, 368, 371(1956).

2. Effect of SKF 525-A on the Blood Concentration of EHB—The blood concentration of EHB was determined in rabbits receiving 80 mg./kg. of EHB with and without pretreatment with SKF 525-A. The results presented in Table II show that SKF 525-A retarded the lowering of blood concentration of EHB.

TABLE II. Effect of SKF 525-A on the Blood Concentration of EHB

Time after admin. of EHB (hr.)	Dose of SKF 525-A (mg./kg.)		
	0	5	10
	Blood concn. of EHB (mg./L.)		
1	62.5	80.4	96.5
2	32.5	42.9	74.5
3		12.5	21.2

3. Effect of SKF 525-A on the *in vitro* Metabolism of EHB by Liver Slices—The animals were intraperitoneally injected with 20 mg./kg. of SKF 525-A. Forty mins. later, these animals were sacrificed and their liver slices were incubated with EHB. At the same time the liver slices of untreated animals were incubated with and without the addition of SKF 525-A. The quantity of 3-keto-EHB formed *in vitro* was determined. It is evident from the results shown in Table III that SKF 525-A added *in vivo* or *in vitro* inhibited the biotransformation of EHB to 3-keto-EHB.

TABLE III. Effect of SKF 525-A on the *in vitro* Metabolism of EHB in Liver Slices

Species	Sex	SKF 525-A added *in vitro**			SKF 525-A pretreated animal
		0 M	2.5×10^{-5} M	5.0×10^{-5} M	
		3-keto-EHB formed (γ.)			
Rat	♂	242	120	70	112
	♀	145	111	103	92
Mouse	♂	152	98	72	128
	♀	140	70	51	68
Rabbit	♂	159	133	83	104
	♀	143	111	99	80

* 500 mg. of liver slices was incubated with 500 γ of EHB in 10 cc. of Krebs-Ringer phosphate buffer (pH 7.4)-0.2% glucose at 38° for 3 hrs.

Summary

It was shown that β-diethylaminoethyl diphenylpropylacetate hydrochloride (SKF 525-A) slowed the rate of biotransformation of ethylhexabital to 3-keto-ethylhexabital and prolonged the duration of hypnosis produced by ethylhexabital.

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