peroxide (DBP), *etc.*, were useful for this purpose and the reaction condition was able to be controlled to neutral, acidic or basic conditions by the kinds of employed peroxides. The reaction proceeded as Chart 1 and the results of the experiments were listed in Table I. The study on the mechanism of the reaction is in progress.

Experimental

The General Procedure for the Preparation of α-Halo Carbonyl Compounds——To a solution of a carbonyl compound (1 mole) in ether or tetrahydrofuran, a powdered metal halide (1 mole) or a solution or a suspension of a metal halide (1 mole) in ether or tetrahydrofuran was added at room temperature, and then a peroxide (1 mole) was added to the mixture with stirring at or below room temperature. The stirring was continued for two or three hours; the reaction was followed by the thin-layer chromatography. After the reaction was complete, a diluted $NaHCO_3$ (aq.) solution was added to the reaction mixture and the product was extracted with ether. The extracted solution was washed with water, and then dried over anhydrous magnesium sulfate. The solvent was concentrated under reduced pressure and the residual oil was purified by column chromatography on silica gel using chloroform as the eluting solvent. The reaction conditions and the yields of the products are listed in the Table I. These products obtained were identified with the standard samples.

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Antianoxic Effect of Meclofenoxate related to Its Disposition

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Effect of meclofenoxate against subacute anoxia in mice was tested in view of the fact that dimethylaminoethanol derived in the brain was sequentially metabolized from free alcohol to phospholipid. Some other agents were also tested to examine the test system used and to clarify the nature of meclofenoxate effect. Chlordiazepoxide, hexobarbital and meclofenoxate (either 20 min or 4 hr after intravenous administration) produced tolerance against anoxia, whereas methamphetamine exerted the opposite effect. An equimolar mixture of dimethylaminoethanol and *p*-chlorophenoxyacetic acid, the constituents of meclofenoxate, was ineffective in this system. Chlordiazepoxide enhanced the effect of methamphetamine, whereas hexobarbital and meclofenoxate (20 min after administration) diminished the methamphetamine effect. The results were discussed in relation to the disposition of meclofenoxate in central nervous systems.

Meclofenoxate (β-dimethylaminoethyl *p*-chlorophenoxyacetate hydrochloride) has a lot of central activities.[2] It was demonstrated[3] that the drug penetrated into brain immediately after intravenous administration, and was hydrolyzed into *p*-chlorophenoxyacetic acid and dimethylaminoethanol. The acid was eliminated from brain within several hours after administration. To the contrary, the alcohol moiety was metabolized as follows: free dimethylaminoethanol (whose brain level was maximum 5 min after administration) was phosphorylated to yield phosphoryldimethylaminoethanol (whose brain level was maximum at 20 min), which was in turn converted to phosphatidyldimethylaminoethanol (maximum at 4 hr).

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1) Location: *33–94, Enoki-cho, Suita, Osaka.*

2) *a*) J. Nickel, U. Breyer, B. Claver, and G. Quadbeck, *Arzneimittel. Forsch.*, **13**, 881 (1963); G. Quadbeck, B. Claver, and G. Minet, *ibid.*, **14**, 563 (1964); *b*) J. Thuillier, P. Rumpf, and G. Thuillier, *Compt. Rend. Soc. Biol.*, **153**, 1941 (1959); J. Kugler, A. Doenicke, and E. Hartel, *Arzneimittel. Forsch.*, 23, 82 (1973).

3) *a*) H. Miyazaki, A. Kagemoto, U. Ishi-i, Y. Minaki, and K. Nakamura, *Chem. Pharm. Bull.* (Tokyo), **19**, 1681 (1971); *b*) H. Miyazaki, K. Nambu, Y. Minaki, M. Hashimoto, and K. Nakamura, *ibid.*, **24**, 763 (1976).

The purpose of the present study is to examine the effect of meclofenoxate in accordance with the sequential metabolism of dimethylaminoethanol in the brain. Since protective effect of the drug against anoxia was assumed by its pharmacological properties reported hitherto,[2a] a simple experimental system was adopted to examine tolerance of whole animal against anoxia. The effect of meclofenoxate observed was quite suggestive in relation to its disposition and metabolism described in the separate papers.[3]

Experimental

Male dd mice weighing 30—45 g were used. A pair of mice with the same age, weighing within 1 g difference, was maintained in a closed glass chamber, a glass jar with a lid of about 550 ml. One mouse was pretreated with the test drug, and another with the vehicle or suitable control agent as a control animal, as indicated in the footnote of Table I. The survival time of each animal, the time interval between the closure of the chamber and the cessation of respiration, was measured. The examination was repeated as indicated in Table I. Differences of the survival time between drug-treated and control mice were statistically analyzed as paired samples.[4]

Table I. Effect of Several drugs on Survival Time under Anoxia

Experiment	Drug treated	Dose (mg/kg)	Time after administration	Difference of survival time[a] (min)	p	Number tested
A[b]	chlordiazepoxide	50	10 min	3.3±1.2	<0.05	9
	hexobarbital	67	5 min	6.6±2.0	<0.01	10
	methamphetamine	2	10 min	−4.6±1.2	<0.01	10
	meclofenoxate	120[c]	5 min	2.1±1.4	>0.10	20
			20 min	4.0±1.4	<0.01	20
			1 hr	2.4±1.4	<0.10	20
			4 hr	2.3±0.7	<0.01	20
B[d]	chlordiazepoxide	50	10 min	−2.4±0.8	<0.02	10
	hexobarbital	67	5 min	19.2±4.0	<0.01	6
	meclofenoxate	120[c]	20 min	4.8±1.8	<0.02	15
			4 hr	−0.8±0.7	>0.10	15
C[b]	meclofenoxate	12	20 min	0.4±1.3	>0.10	15
		60		1.6±0.8	<0.10	20
		180		4.5±1.2	<0.01	15
	mixture of dimethylaminoethanol and *p*-cl-phenoxyacetic acid	120[e]	20 min	0.6±1.3	>0.10	20
			4 hr	−0.8±0.9	>0.10	20

a) mean ±S.E.
b) Control animal was treated with vehicle.
c) 0.4 mmole/kg
d) Control and test animals were treated with methamphetamine 10 min before examination.
e) sum of each 0.4 mmole
All agents, except meclofenoxate and its constituents, were given intraperitoneally.

Results and Discussion

According as oxygen was consumed in the closed jar by the mice, the apparent behavior of normal control animal (treated with vehicle only) changed as follows: normal, hyperkinetic, hypokinetic, motionless with occasional convulsions seemingly without consciousness and cessation of breathing reflex occurred. The survival time of 64 normal control mice was 22.8±0.8 min. Possitive difference of the survival time, given in Table I, therefore indicates how longer the drug treatment prolonged the survival time of the animal than control. When a pair of normal mice was maintained in the chamber, the difference of the survival time

4) Y. Kondo and W. Funasaka (eds.), "Tokeitekihoho," Kyoritsu Publishing Co., Ltd., Tokyo, 1969.

between them was 0.0±1.5 min (32 tests), indicating that the two mice died simultaneously. The anoxic condition would be subacute similarly to that described by Fourneau, *et al.*[5]

Experiment A: with Normal Animals

All of the experimental results are given in Table I. Protective effect of minor tranquilizer and hypnotic against hypoxia was reported by Nakanishi, *et al.*[6] and Goldstein, *et al.*,[7] respectively. To check this in the present system was at first performed and confirmed the followings. Administration of chlordiazepoxide or hexobarbital prolonged the survival time. In contrast, psychic energizer methamphetamine shortened the survival time in mice.

The effect of meclofenoxate was examined in accordance of the sequential metabolism of dimethylaminoethanol in the brain, as described previously.[3b] Five minutes after administration, mice were slightly hyperkinetic and no significant change in survival time was observed. Twenty minutes later, mice were obviously hypokinetic and significant elongation of the survival time was observed. Then apparent hypokinesia gradually disappeared and 1 hr after dosing when phosphatidation of dimethylaminoethanol was actively occurring,[3b] slight protection against anoxia was observable. However, 4 hr after dosing, the protective effect was again significant while animal behavior apparently normal in the chamber. The protective effect of meclofenoxate against anoxia has been strongly demonstrated by many reports concerning its pharmacological properties.[2a]

Experiment B: with Methamphetamine-treated Animals

The second examinations were performed to see whether or not shortening effect of methamphetamine on survival time might be overcome by drugs effective for elongation of the survival time. Control mice were treated with methamphetamine while test animals with methamphetamine and a test drug.

Interestingly, chlordiazepoxide enhanced the effect of methamphetamine. In contrast, marked prolongation of the survival time was resulted from hexobarbital treatment: sleeping mice survived much longer than mice received methamphetamine alone. The effect of meclofenoxate was somewhat different from these agents. Twenty minutes after administration, the effect of methamphetamine was overcome and mice died later. In this respect, meclofenoxate is similar to hexobarbital although the drug is not a hypnotic. The survival time was not so long as that exerted by hexobarbital. On the other hand, 4 hr after dosing, mice died simultaneously with the control, indicating no influence on the shortening of the survival time by methamphetamine.

Although, at the present stage of knowledge, the mechanisms by which the survival time was prolonged or shortened are unknown, it is certain that the effect of meclofenoxate is different from that of chlordiazepoxide and hexobarbital. Meclofenoxate effect at 20 min after dosing seems to be different from that at 4 hr. It is noteworthy that significant increases in cerebral levels of both phosphoryldimethylaminoethanol at 20 min and phosphatidyldimethylaminoethanol at 4 hr are occurring, respectively.[3b]

Experiment C: with Normal Animals

Since the effect of meclofenoxate 20 min after dosing was significant enough to overcome the shortening by methamphetamine, the effect was confirmed by some other doses: doses larger than 60 mg/kg produced resistance against anoxia under the condition, seemingly depending on the dose.

An equimolar mixture of dimethylaminoethanol and *p*-chlorophenoxyacetic acid, the constituents of meclofenoxate, was given intravenously to examine whether the protective

5) J.P. Fourneau, M. Davy, M. Clément, M. Ranson, F. Darmois and M. Lamarche, *Arzneimittel. Forsch.*, **24**, 27 (1974).
6) M. Nakanishi, H. Yasuda, and T. Tsumagari, *Life Sci.* **13**, 467 (1973).
7) A. Goldstein Jr., B.A. Wells, and A.S. Keats, *Arch. Int. Pharmacodyn.*, **161**, 138 (1966).

effect against anoxia is observed. No significant prolongation of the survival time was observed either 20 min or 4 hr after dosing. It should be pointed out that after intravenous administration of meclofenoxate, the brain levels of dimethylaminoethanol and *p*-chlorophenoxyacetic acid were more than several times higher than those after administration of the constituents.[3] Therefore, the protective effect of meclofenoxate against anoxia is closely related to its penetration into the central nervous systems due to the high permeability of the ester to blood-brain barrier.

Results obtained here strongly support the view that the penetration of meclofenoxate into brain is primarily important to exhibit its protective effect against anoxia. It may be likely that the effect is closely related to the cerebral metabolism of dimethylaminoethanol, since the effects observed 20 min and 4 hr after administration were conceivably exerted by different mechanisms. The present system adopted to test the tolerance of mice against anoxia is convenient, since it is very simple and easy to be carried out, using a commonly available laboratory glass jar with a lid by measuring the survival time of a paired mice. However, the statistical analysis is essential for the evaluation of the results.

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Hydrogenolysis of Allylic Alcohols with Mixed Hydride Reagent of Lithium Aluminum Hydride-Titanium Tetrachloride[1]

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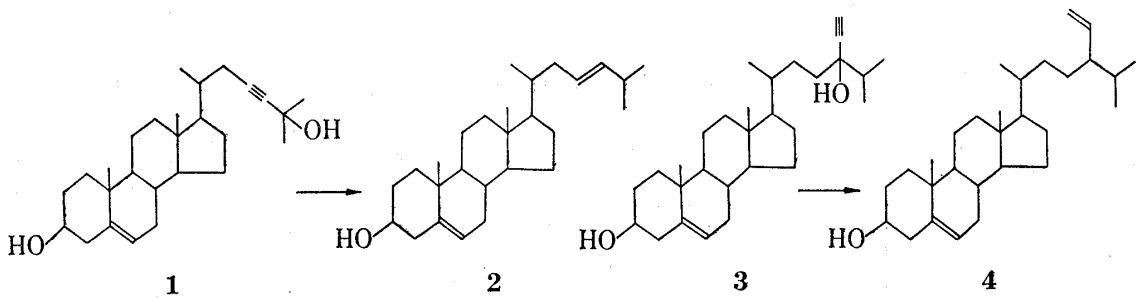
Five steroidal allylic alcohols were treated with lithium aluminum hydride–titanium tetrachloride in comparison with lithium aluminum hydride–aluminum chloride. The former reagent was found to be useful for the hydrogenolysis of allylic alcohols, especially for tertiary ones.

In the course of our synthetic studies of steroidal allenes,[3] the propargylic alcohols **1** and **3** were treated in tetrahydrofuran with an excess of a mixed hydride reagent of lithium aluminum hydride(LAH)–titanium tetrachloride($TiCl_4$) (molar ratio of 4:1). The products were not be the expected allenes, but the deoxygenated olefines **2** (78%) and **4** (50%),



1 **2** **3** **4**

Chart 1

1) This is Part 30 in the series of "Studies on Steroids." For Part 29 see ref. 3.
2) Location: *2-12-1, Ookayama, Meguro-ku, Tokyo, 152 ,Japan.*