hydrazones (III).[2] This reaction appears to proceed according to the mechamism reported in Chart 3.

The structure of the products (IIIa, b) was established spectroscopically. Thus, their IR spectra show strong bands at 1715—1710 cm^{-1} (νC=O) and 1610 cm^{-1} (νC=O).

Further evidence for the structure was obtained from their NMR spectra which show signals at δ 4.2—4.12 (q, 2H) and 1.20—1.03 (t, 3H) attributable to OCH_2CH_3 proton as well as a multiplet for the aromatic (δ 8.13—6.67) and NH (δ 8.67—7.60) protons.[2] The similarity of their electronic spectra reflect their structural identity. They show absorption maxima at 318—315 nm due to π—π^* transition in the conjugated system.

These results indicated that the type of the product separated from the reaction of α,β-unsaturated ketones with hydrazine derivatives depends mainly on the catalyst used. Thus, in the presence of a base (*i.e.* piperidine), the hydrazine derivatives will be separated in good yields (1,4-addition). However, by addition of acetic acid, the reaction mixture gave the corresponding hydrazone-carboxylate derivatives,[2] (1,2-addition).

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Effects of Vegetable Oils on the Biological Disposition of Ethchlorvynol. II. The Effects on the Brain Distribution of Ethchlorvynol in Rat

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The blood and tissue levels of unchanged ethchlorvynol (EC) were determined after intraperitoneal administration of EC suspended in 5% polyethylene glycol 400 aqueous solution (5% PEG). Pre-oral administration of 5% PEG did not show any effect on the levels of EC in blood and tissues, compared with the pre-treatment of normal saline as a control. However, pre-administered corn oil as well as peanut oil and soybean oil decreased the brain levels of EC. In order to exclude the effect of the vegetable oils, the thoracic fistula rats were used in the studies. When EC was administered orally in corn oil to the fistula rats, the brain levels of EC were fairly improved, and were higher than in the intact rats. As little as 0.06 and 0.05% ot total dose were recovered in the lymph as EC and EC-glucuronide (ECG), respectively after oral administration of EC in corn oil. While both EC and ECG were not detected in the lymph when EC was given in 5% PEG.

Keywords——ethchlorvynol; distribution; brain level; vegetable oils; corn oil; peanut oil; soybean oil; thoracic fistula rat

In the preceding paper of this series,[2] the distribution of ethchlorvynol (EC), a short acting hypnotic, to rat brain was found to be inhibited significantly by the co-administration with such vegetable oils as corn, peanut and soybean oil.

In order to confirm the inhibitory effect of the oils on the brain distribution of EC, the present studies were carried out.

Experimental

Animal——Female rats of Wistar strain weighing 200—250 g were fasted for 20—24 hr prior to use. Under ether anaesthesia, the thoracic duct of the rat was cannulated according to the method as reported

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2) Y. Nitta, T. Aimoto, T. Murata and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **26**, 1257 (1978).

by Bollman *et al.*[3] to make the thoracic fistula rat. The operated rat was held in restraining cage to collect the lymph, and was allowed free access to water.

Administration of EC——EC was suspended in 5% polyethylene glycol 400 aqueous solution (5% PEG) or dissolved in corn oil. Both solutions were prepared to contain 30 mg/ml of EC. a) Oral administration: EC was administered orally by intubation to the thoracic fistula rats (150 mg/kg). b) Intraperitoneal administration: Two hours after receiving orally each 1 ml/rat of 5% PEG, normal saline, corn oil, peanut oil and soybean oil, rat was given intraperitoneally at a dose of 75 mg/kg of EC in 5% PEG.

Determination of EC in Blood, Lymph and Tissues——At the definite times after dosing EC, rats were sacrificed by bleeding from carotid, and were immediately dissected to remove brain, lung, liver, jejunum, kidney and adipose tissue. The blood samples were hemolyzed with 10 volumes of water to assay for EC. To the lymph was added the water to assay for EC and EC-glucuronide (ECG). The tissues were homogenized, and the homogenates were used for the determination of EC. All the estimation of EC and ECG were carried out according to the GLC method as reported by the authors.[4]

Table I. Tissue Levels of Unchanged EC in Rats after Intraperitoneal Administration of 75 mg/kg of EC suspended in 5% PEG

Pre-administered substance[a]	Tissue	EC, μg/ml or μg/g wet tissue Time after administration, min		
		5	15	30
Normal saline (control)	Blood	32.1±3.6[b]	18.3±3.2	16.4±1.7
	Liver	90.6±11.7	42.9±11.2	30.7±4.0
	Jejunum	20.2±1.3	19.9±3.9	14.6±2.1
	Lung	27.8±3.6	16.3±3.7	14.1±2.0
	Kidney	31.1±5.4	17.7±2.7	14.7±2.8
	Adipose	742±49	603±106	540±62
	Brain	21.9±3.6	18.7±2.6	13.4±2.0
5% PEG	Blood	31.6±1.1	19.6±2.7	15.4±1.2
	Liver	82.0±2.8	42.1±1.7	29.1±5.5
	Jejunum	23.9±2.9	17.5±2.0	16.1±1.2
	Lung	27.9±3.9	14.4±2.5	11.7±0.8
	Kidney	29.7±4.7	18.6±2.6	17.2±0.8
	Adipose	740±27	698±23	603±28
	Brain	18.2±0.9	16.3±3.3	12.4±1.2
Corn oil	Blood	28.4±1.6	22.8±1.6	17.8±0.6
	Liver	93.7±8.6	61.5±5.9	27.4±2.6
	Jejunum	31.6±3.9	22.2±4.6	15.3±2.3
	Lung	25.1±6.0	18.0±2.7	11.9±2.3
	Kidney	35.0±5.6	22.3±2.2	14.7±3.6
	Adipose	712±62	587±78	490±49
	Brain	6.4±0.4[c]	5.2±0.6[c]	3.7±0.6[c]
Peanut oil	Blood	26.4±0.9	21.4±1.5	19.0±2.3
	Liver	77.5±6.0	54.9±7.7	27.2±2.4
	Jejunum	26.7±3.7	22.4±1.3	15.2±2.2
	Lung	23.1±1.2	18.1±2.6	10.4±2.8
	Kidney	31.5±2.7	22.7±2.7	14.6±1.8
	Adipose	739±47	590±51	517±34
	Brain	7.6±0.2[c]	6.8±0.9[c]	4.9±0.3[c]
Soybean oil	Blood	27.9±2.6	24.2±1.4	18.3±1.5
	Liver	74.0±6.7	55.0±11.2	22.8±1.3
	Jejunum	31.0±5.4	26.6±2.2	17.4±2.0
	Lung	22.0±3.4	18.0±1.6	14.7±2.8
	Kidney	31.9±3.9	24.3±0.3	19.0±3.2
	Adipose	663±50	632±23	435±36
	Brain	6.7±1.4[c]	6.7±0.7[c]	4.9±0.4[c]

a) Orally given 1 ml/rat 2 hr before *i.p.* administration of EC.
b) Values reported are mean±SEM for 3 rats.
c) Significantly different level from control group; $p<0.05$.

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Results and Discussion

Tissue Levels of EC at Intraperitoneal Administration

In order to exclude the effects of vegetable oils used at the oral administration,[2] EC was injected intraperitoneally. The results are shown in Table I.

Five, 15 and 30 min after the intraperitoneal dosing of 75 mg/kg of EC, the blood and tissue levels of unchanged EC were determined. Orally given 1 ml of 5% PEG did not affect on the distribution of EC, compared with the treatment of 1 ml of normal saline as a control. The pre-administration of each 1 ml of corn oil, peanut oil and soybean oil, however, significantly decreased the transfer of EC into rat brain.

Tissue Levels of EC in the Thoracic Fistula Rats at Oral Administration

In order to minimize the effects of substances originated from the oils in lymphatic system on the distribution of EC to rat brain, EC was given orally to the thoracic fistula rat. The blood and tissue levels of EC after receiving the drug in 5% PEG and corn oil are shown in Table II.

Table II. Tissue Levels of Unchanged EC in Thoracic Fistula Rats after Oral Administration of 150 mg/kg of EC suspended in 5% PEG and dissolved in Corn Oil

	Tissue	EC μg/ml or μg/g wet tissue Time after administration, hr			
		0.5	1	3	6
In 5% PEG	Blood	20.1±1.4[a]	21.6±1.8	8.1±0.7	6.7±0.4
	Liver	41.0±3.5	39.6±2.2	6.0±0.3	5.2±0.4
	Jejunum	80.9±3.3	47.1±4.0	5.6±1.8	4.5±0.4
	Lung	24.0±4.4	6.9±2.4	4.9±3.2	3.0±1.0
	Kidney	22.1±0.6	16.4±1.6	4.1±0.0	4.5±0.8
	Adipose	548±32	243±25	138±8	133±8
	Brain	18.6±1.1	8.4±0.9	8.6±0.0	3.6±0.5
In corn oil	Blood	2.2±0.4	13.9±1.6	20.2±3.2	4.4±2.1
	Liver	7.3±1.9	40.3±6.1	49.7±6.1	11.3±2.1
	Jejunum	15.0±2.4	48.6±7.5	81.8±13.6	13.3±1.8
	Lung	3.9±0.1	10.4±3.6	9.1±3.6	7.2±5.1
	Kidney	5.4±0.9	15.9±2.6	14.2±2.6	8.1±3.8
	Adipose	71±11	189±9	240±42	147±35
	Brain	3.0±0.2	6.9±0.9	6.1±1.1	1.2±0.3

a) Values reported are mean±SEM for 3 rats.

Table III. Recovery of EC and ECG in Thoracic Lymph of Rats after Oral Administration of 150 mg/kg of EC suspended in 5% PEG and dissolved in Corn Oil

		Cumulative amount (% of dose) Time after administration, hr		
		1	3	6
In 5% PEG	EC	n.d.[a]	n.d.	n.d.
	ECG	n.d.	n.d.	n.d.
In corn oil	EC	0.02±0.00[b]	0.03±0.00	0.06±0.01
	ECG	0.02±0.00	0.03±0.00	0.05±0.01

a) Not detected (<0.001 % of dose).
b) Values reported are mean±SEM for 3 rats.

When EC was given to the thoracic fistula rats together with corn oil, the brain levels of EC were shown to be still lower than those of the fistula rats given in 5% PEG. However, the brain levels of EC in the thoracic fistula rats given the drug in corn oil were higher than those in the intact rats (brain level: 3.0 μg/g at 0.5 hr, 1.4 μg/g at 1 hr, 1.2 μg/g at 3 hr) reported by the authors,[2] while blood and other tissue levels of EC were almost similar to those in the intact rats.[2]

This fact suggests that such substance as chylomicron originated from the oil ingested might prevent the brain distribution of EC to rat brain.

The lymph was collected for 6 hr after oral administration of EC. Table III shows the cumulative amount of EC and ECG.

A small part of total dose were recovered in the lymph as EC (0.06%) and ECG (0.05%), respectively after oral administration of EC in corn oil. While both EC and ECG were not detected in the lymph when EC was given orally in 5% PEG.

These results suggest that the main absorption of EC is *via* a portal system even when the drug was administered together with corn oil.

A large portion of the vegetable oils are reported to be absorbed from the digestive tract *via* lymphatic system.[5]

Thus, these findings also suggest that the vegetable oils did not interact with EC in digestive tract to make a substance which is hard to transfer into rat brain.

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Syntheses of 7-*n*-Alkylcarbamoyltheophyllines

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7-*n*-Alkylcarbamoyltheophyllines (V) were synthesized from theophylline and *n*-alkyl isocyanates.

Keywords——7-*n*-alkylcarbamoyltheophylline; carbamoyltheophylline; theophylline; N,N-dialkylurea; *n*-alkyl isocyanate; isocyanate

Ozaki *et al.*[2] reported that 1-carbamoyluracils (II) were synthesized from uracil derivative (I) and alkyl isocyanates, and that II have an antitumor activity.

We have synthesized 7-*n*-alkylcarbamoyltheophyllines (V) during the course of our investigations in search for new antitumor agents.

Reaction of theophylline (III) and an excess amount of *n*-alkyl isocyanates (IVa—i) in pyridine on a boiling water bath for 2 hours gave 7-*n*-alkylcarbamoyltheophyllines (Va—i). These compounds are new substances. In some cases the reaction gave N,N′-dialkylureas (VId, f, g, h, i) as by-products, too (Table I).

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