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.

5) R.I. Levy, R.S. Lees and D.S. Fredrickson, *J. Clin. Invest.*, **45**, 63 (1966).

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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.

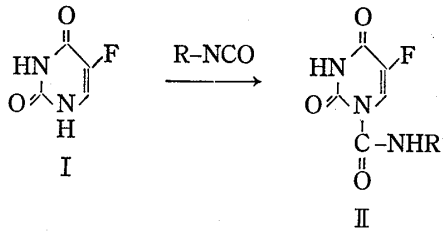
We have synthesized 7-*n*-alkylcarbamoyltheophyllines (V) during the course of our investigations in search for new antitumor agents.

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).

1) Location: *2-2-1 Oshika, Shizuoka.*

2) S. Ozaki, Y. Ike, H. Mizuno, K. Ishikawa and H. Mori, The 26th IUPAC Congress Abstracts, Session I, 1977, p. 323.

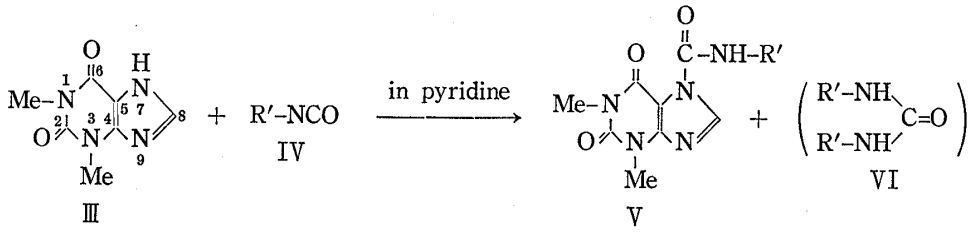
The structures of V were assigned by elemental analyses, mass (MS) spectra, the presence of the three characteristic carbonyl stretching absorption bands at around 1735, 1700 and 1645 cm^{-1} in their infrared (IR) spectra and the presence of the characteristic signals of *n*-alkyl group above δ 1.5 ppm, two N-methyl groups at about δ 3.5 ppm, C^8-proton at about δ 8.5 ppm and the broad signal of intramolecular hydrogen bonding proton between NH-proton and carbonyl group of 6-position at about δ 10.4 ppm in



I II

R: methyl, ethyl, isopropyl, phenyl, *n*-hexyl, cyclohexyl

Chart 1



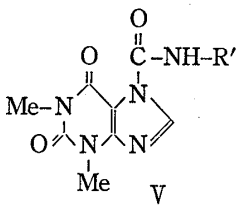
III IV V VI

R′ R′ R′

a: *n*-propyl d: *n*-heptyl g: *n*-undecyl
b: *n*-butyl e: *n*-octyl h: *n*-dodecyl
c: *n*-hexyl f: *n*-nonyl i: *n*-octadecyl

Chart 2

TABLE I. 7-*n*-Alkylcarbamoyltheophyllines (V)



V

Compd. No.	Substituent R′	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. (Found) C	H	N	MS (*m/e*) M^+
Va	*n*-C_3H_7	103—105	60.7	$C_{11}H_{15}N_5O_3$	49.80 (49.54	5.70 5.74	26.40 26.17)	265
Vb	*n*-C_4H_9	89—90	62.0	$C_{12}H_{17}N_5O_3$	51.60 (51.48	6.14 6.20	25.08 24.87)	279
Vc	*n*-C_6H_{13}	99—100	67.0	$C_{14}H_{21}N_5O_3$	54.71 (54.42	6.89 6.88	22.79 22.77)	307
Vd	*n*-C_7H_{15}	100—101	32.4	$C_{15}H_{23}N_5O_3$	56.06 (56.09	7.21 7.20	21.79 21.83)	321
Ve	*n*-C_8H_{17}	86—88	57.1	$C_{16}H_{25}N_5O_3$	57.29 (57.39	7.51 7.61	20.88 20.63)	335
Vf	*n*-C_9H_{19}	80—82	34.5	$C_{17}H_{27}N_5O_3$	58.43 (58.63	7.79 7.91	20.04 19.93)	349
Vg	*n*-$C_{11}H_{23}$	86—88	24.7	$C_{19}H_{31}N_5O_3$	60.45 (60.29	8.28 8.23	18.55 18.58)	377
Vh	*n*-$C_{12}H_{25}$	89—91	38.0	$C_{20}H_{33}N_5O_3$	61.35 (61.41	8.50 8.51	17.89 17.95)	391
Vi	*n*-$C_{18}H_{37}$	93.5—95	39.4	$C_{26}H_{45}N_5O_3$	65.65 (65.47	9.54 9.53	14.72 14.97)	475

their nuclear magnetic resonance (NMR) spectra. The presence of the signal at δ 10.4 ppm is the proof of 7-carbamoyltheophylline, not 9-carbamoyltheophylline. The VI were identified with the synthetic samples prepared by another method[3] by MS spectra, IR spectra, the mixed melting point tests and elemental analyses.

Experimental[4]

7-*n*-Alkylcarbamoyltheophyllines (Va—i)——A solution of theophylline (III) (0.5 g) and an excess amount (1.2—1.5 equivalents) of respective *n*-alkyl isocyanates (IVa—i) in pyridine (10 ml) was heated on a boiling water bath for 2 hr. After reaction was completed, pyridine was evaporated under reduced pressure. White solid residue was extracted with $CHCl_3$. $CHCl_3$-soluble part was purified through silicic acid column chromatography (solvent, $CHCl_3$). Eluated white solid through the column was extracted with acetone. Acetone soluble part was recrystallized from MeOH to give the pure colorless needles (Va—i). Acetone insoluble part of the eluated solid was crystallized from EtOH to give glossy needles (VI). The yields of VI are as follows: VId (19.8%), VIf (18.1%), VIg (28.6%), VIh (25.4%), VIi (11.2%). $CHCl_3$-insoluble part of the evaporated residue of the reaction mixture and the eluate of column chromatography (solvent, $CHCl_3$: MeOH = 4: 1) were collected together and recrystallized from EtOH to give colorless needles of III.

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3) S. Komori, Y. Kawahara, M. Otsuka and N. Ito, *Kogyo Kagaku Zasshi*, **64**, 1592 (1961).
4) Melting points are not corrected. Mass spectral measurements were run on Hitachi Model RMU-7 spectrometer. NMR spectra were recorded using tetramethylsilane as an internal standard on Hitachi Model R-24 spectrometer at 60 MHz. IR spectra were obtained by JASCO Model IRA-2 spectrometer.