# Carbamate Ester Latentiation of Physiologically Active Amines

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Carbamate ester latentiation of phenethylamine, *dl*- and *d*-amphetamine, *l*-ephedrine, and *dl*-*p*-hydroxyamphetamine is described, particularly in regard to the central activity of these drugs. By increasing lipophilicity of the amine and protecting it against enzymatic deactivation, carbamoylation facilitates transport into the brain. The lack of a carbamate-specific enzyme in mammals requires that a potency toward biological hydrolysis be intrinsic in the drug in order for amine release to occur in a useful period of time. Eight different alcoholic leaving groups were incorporated into the carbamate esters and studied for their ability to facilitate such hydrolysis. Functional groups in the alcoholic moiety which can act on the carbamate ester linkage by electron withdrawal and neighboring group participation appear to facilitate amine release. The most active carbamate esters in this series have a biphasic spectrum of activity characterized by mild sedation initially followed by moderate stimulation. Anorexigenic activity of the carbamates occurs with considerably less central stimulation than with amphetamine, and a degree of selectivity in modifying such drug action is apparent. Preliminary studies with the *o*-nitrophenyl and *o*-carbomethoxyphenyl carbamate esters of α-[$^{14}$C]amphetamine demonstrate that these carbamates rapidly enter the mouse brain where they are readily hydrolyzed.[1]

Since Ehrlich's original observation about restricted penetration of drugs into the brain[2] the blood–brain barrier has come to be recognized as a complex biochemical phenomenon with no single hypothesis explaining all of the events.[3–6] Nevertheless, in the case of amines, transport seems to depend primarily on two aspects of metabolism, lipophilicity and biotransformation. For compounds which ionize, the rate of transport appears to be proportional to the concentration of undissociated molecules in the blood and its degree of lipid solubility. Since carbamoylated amines do not ionize, they are more soluble in organic and lipoidal systems. This lipophilicity theory is one that has been broadly useful in correlating the action of centrally active drugs.[7,8] In the case of amines, however, an enzymatic barrier must be considered in addition to the lipoid barrier. Metabolizing enzymes present in the brain may deactivate amines before they reach their proper site of activity. For example, presence of monoamine oxidase (MAO) in brain capillaries destroys dopamine and other phenethylamines before their entry into the brain.[9] By protecting the amine from deactivation by MAO, carbamoylation facilitates its transport.

Success with carbamate ester latentiation of amines requires that the drug be hydrolyzed to a carbamic acid and alcohol moiety after penetration into the brain. At physiological pH values carbamic acids are unstable and decompose to the parent amine and $CO_2$.[10] The release of $CO_2$ is physiologically comparable to the decarboxylation of indogenous amino acids to form their amine analogs, such as the decarboxylation of 5-hydroxytryptophan in brain tissue to form the biogenic amine, serotonin.

$$RNHCOOR' + H_2O \longrightarrow R'OH + RNHCOOH \longrightarrow RNH_2 + CO_2$$

The alcoholic leaving group can act like a "carrier" and contains a potential for variation whereby amine drug transport and release characteristics can be modified for specific uses. Several ethyl carbamate latentiated drugs, such as normeperidine[11] and chlorphentermine,[12] have been reported and the low toxicity of EtOH favors its use as a leaving group. However, the use of simple alcohols as leaving groups in the carbamate esters has not often met with success, probably because the esters are relatively stable to biological hydrolysis. In this regard, there does not appear to be a carbamate ester specific hydrolytic enzyme in mammals, although one has been found in soil organisms.[13] Cholinesterase will hydrolyze carbamates and become reversibly inhibited during the process.[14] The hydrolysis proceeds *via* carbamoylation of the enzyme with release of the alcohol moiety, followed by decarbamoylation with release of amine. Since both rates are relatively slow, cholinesterase cannot be counted upon to split carbamate esters. Although chymotrypsin can undergo carbamoylation,[15] this reaction does not generally occur with carbamate esters.

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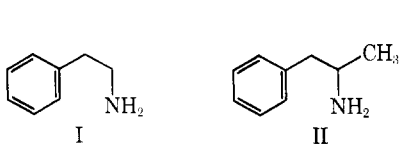
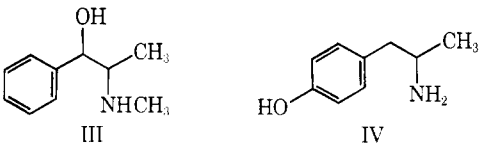
TABLE I
CARBAMATE ESTERS



I II



III IV

| Compound No. | Amine | Alkyl moiety | Purification solvent | Mp, °C | $[\alpha]^{21}D$, deg ($CHCl_3$, c 1) | Formula[a] |
|---|---|---|---|---|---|---|
| 1 | I | o-$MeO_2CC_6H_4$ | $CCl_4$–hexane | 96–98 | | $C_{17}H_{17}NO_4$ |
| 2 | dl-II | Ph | Hexane | 66–67 | | $C_{16}H_{17}NO_2$ |
| 3 | dl-II | o-$MeO_2CC_6H_4$ | i-$Pr_2O$–hexane | 71–77[b] | | $C_{18}H_{19}NO_4$ |
| 4 | dl-II | p-$MeOC_6H_4$ | $CHCl_3$–hexane | 87–88 | | $C_{17}H_{19}NO_3$ |
| 5 | dl-II | o-$OCHC_6H_4$ | $CHCl_3$–hexane | 79–81 | | $C_{17}H_{17}NO_3$ |
| 6 | dl-II | o-$O_2NC_6H_4$ | i-$Pr_2O$ | 86–90 | | $C_{16}H_{16}N_2O_4$ |
| 7 | dl-II | α-$EtO_2CC_2H_4$ | Hexane | Oil[c] | | $C_{13}H_{21}NO_4$ |
| 8 | d-II | Ph | Hexane | 64–65 | −24 | $C_{16}H_{17}NO_2$ |
| 9 | d-II | o-$MeO_2CC_6H_4$ | i-$Pr_2O$–hexane | 87–88 | −20 | $C_{18}H_{19}NO_4$ |
| 10 | d-II | o-$O_2NC_6H_4$ | i-$Pr_2O$ | 92.5–94 | −41 | $C_{16}H_{16}N_2O_4$ |
| 11 | d-II | m-$O_2NC_6H_4$ | $C_6H_6$–i-$Pr_2O$ | 123–123.5 | −11 | $C_{16}H_{16}N_2O_3$ |
| 12 | dl-II | p-$O_2NC_6H_4$ | $C_6H_6$–i-$Pr_2O$ | 124–124.5 | −29 | $C_{16}H_{16}N_2O_4$ |
| 13 | l-III | Ph | Pet ether | 72–74 | −13 | $C_{17}H_{19}NO_3$ |
| 14 | l-III | o-$MeO_2CC_6H_4$ | $CHCl_3$–hexane | 95–96 | −39 | $C_{19}H_{21}NO_5$ |
| 15 | l-III | p-$MeOC_6H_4$ | $CHCl_3$–hexane | Oil | −29 | $C_{18}H_{21}NO_4$[g] |
| 16 | l-III | o-$OCHC_6H_4$ | $CHCl_3$–hexane | Oil | −24 | $C_{18}H_{19}NO_4$[d] |
| 17 | l-III | o-$O_2NC_6H_4$ | $CHCl_3$–hexane | Oil | −21 | $C_{17}H_{18}N_2O_5$[e] |
| 18 | l-III | α-$EtO_2CC_6H_4$ | Hexane | Oil | −27 | $C_{16}H_{23}NO_5$ |
| 19 | dl-IV | Ph | $C_6H_6$ | 115–116[f] | | $C_{36}H_{44}N_2O_8$ |
| 20 | dl-IV | o-$OCHC_6H_4$ | $C_6H_6$–hexane | 114–116 | | $C_{17}H_{17}NO_4$ |

[a] All compounds were analyzed for C, H, N. [b] After several crystallizations the product was chromatographically pure on tlc. [c] Compounds 7 and 15–18 were purified by pptg and evacuating the oil. They were chromatographically pure on tlc. [d] C: calcd, 69.00; found, 68.21. [e] Calcd: C, 61.81; H, 5.49; N, 8.48. [f] Bispiperazine salt complex [J. D. Benigni and A. J. Verbiscar, *J. Med. Chem.*, **6**, 607 (1963)]. [g] C: calcd, 68.55; found, 67.42.

In searching for leaving alkyl groups that would provide some control of hydrolytic stability in a physiological environment, consideration was given to structural features which influence chemical hydrolysis.[16] The carbamate esters were readily prepared by standard methods[17] from the amine and an appropriate ester of chloroformic acid.[18] Most of the carbamates were crystalline although several of the *l*-ephedrine carbamates were resistant to crystallization and were obtained as oils. Four different physiologically active amines were carbamoylated including phenethylamine, *dl*- and *d*-amphetamine, *l*-ephedrine, and *dl*-*p*-hydroxyamphetamine (Table I). The pharmacology of these amines is relatively well known while the release of the amine could be easily confirmed by its known pharmacological action.

**Pharmacological Results.**—In Table II the pharmacological effects of 8 of these carbamate esters are compared with those of *d*-amphetamine. The most active compounds in this group appeared to have a biphasic spectrum of activity, characterized by mild sedation initially, followed by moderate stimulation. By comparison with amphetamine the most active carbamate derivatives were no more than 0.1 as effective in producing central stimulation (hyperactivity) and peripheral sympathetic effects. As for anorexigenic potency, the nitrophenyl derivatives of the amphetamine carbamates compared favorably with amphetamine itself. Although less active than the $NO_2$, the formyl derivatives exhibited both stimulating and anorexigenic activity. This series of compounds possess anorexigenic activity at doses somewhat less than those required to produce moderate central stimulation. It would appear that the anorexigenic action of the carbamates occurs with considerably less central stimulation than with amphetamine.

TABLE II
PHARMACOLOGICAL EFFECTS OF THE CARBAMATE ESTERS

| Compd | Hyperactivity[a] | Initial tranquilization[b] | Anorexigenic[c] |
|---|---|---|---|
| *d*-Amphetamine | 1 | 0 | 1 |
| 5 | 0 | + | 1/5 |
| 6 | 1/10 | ++ | 1/2 |
| 10 | 1/10 | ++ | 1/2 |
| 11 | 1/15 | + | 1/3 |
| 12 | 1/15 | + | 1/3 |
| 16 | 0 | 0 | 1/15 |
| 17 | 1/30 | + | 1/3 |
| 19 | 1/100 | + | 1/4 |

[a] Hyperactivity is expressed relative to amphetamine (10 mg/kg) and as for the 1–2 hr period following administration of 25 mg/kg ip the "initial tranquilization" period referred to the first 40 min. [b] Initial tranquilization observed for 0–40 min. [c] Anorexigenic action was measured for a period of 5 days, following administration of 10 mg/kg of the drug twice daily, 12 hr apart. The results are expressed relative to a 1 mg/kg dose of amphetamine, also administered twice daily.

Gross behavioral effects in mice were observed for all of the carbamate esters. Sedative action and central stimulation appeared in various degrees depending upon the particular amine and structure of the leaving alkyl group. There was always a delayed sedative action prior to the onset of central stimulation although

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the degree of hyperactivity caused by certain drugs such as **1**, **4**, **5**, **13**, **16**, and **19** was slight. It is not known for certain whether the initial depressant action is centrally mediated and attributable to the carbamate as such.

The 5 carbamate esters of amphetamine and ephedrine with nitrophenyl leaving groups showed the highest degree of activity. A contributory factor to the higher activity of the nitrophenolic carbamates is their ease of hydrolysis in aqueous media, which is attributable to the electron-withdrawing character of the $NO_2$ substituent. It also appears that the *o*-$NO_2$ participates in this hydrolysis to some degree because of the higher overall activity of *o*-nitrophenyl *d*-amphetaminecarbamate compared with the *m*- and *p*-$NO_2$ isomers. The *o*-carbomethoxyphenyl carbamates **3**, **9**, and **14** also show somewhat higher activities as compared with the phenyl, *p*-methoxyphenyl, and lactyl carbamates. Although the *o*-carbomethoxyphenyl carbamates are not as active as the nitrophenyl carbamates, the toxicity of salicylate as a leaving group is somewhat lower.

Direct evidence that the carbamate esters were hydrolyzed after entering the brain was obtained from radiotracer studies. Two carbamate esters of *d*-amphetamine labeled with $^{14}C$ in the amine side chain $\alpha$ to the ring were found to enter the brain (Table III).

Table III

Distribution of $^{14}C$-Labeled Compounds in Mouse Brain

| Drug administered | Dose, μCi | Dose, μg | Time of sacrifice, hr | Amount in brain, μg: Carbamate | Amount in brain, μg: *d*-Amphetamine |
|---|---|---|---|---|---|
| [$^{14}C$]-*d*-Amphetamine[a] | 1.20 | 200 | 0.5 | | 12.0 |
| **21**[b] | 0.70 | 200 | 0.5 | 3.0 | 3.6 |
| | | | 1.0 | 2.0 | 4.0 |
| **22**[c] | 0.74 | 200 | 0.5 | 3.3 | 2.8 |
| | | | 1.0 | 3.8 | |

[a] Sulfate salt. [b] *o*-Carbomethoxyphenyl [$^{14}C$]-*d*-amphetaminecarbamate. [c] *o*-Nitrophenyl [$^{14}C$]-*d*-amphetaminecarbamate.

Although it is not known whether the hydrolyzed products were formed entirely in the brain, it is reasonable to assume that the carbamates can be hydrolyzed in the brain, particularly since they can be shown to do so *in vitro*. Both the delayed onset and the greater duration of action of the carbamates support the notion that the hydrolytic product is required for their stimulating action.

The present studies suggest that latentiation of centrally active amines appears feasible *via* carbamoylation. A degree of selectivity in modifying the drug action is possible through the leaving alkyl group, which temporarily protects the amine against deactivation by MAO and increases lipophilicity. Further manipulation is possible through leaving groups containing substituents which can act on the carbamate ester linkage by electron withdrawal or by neighboring group participation to facilitate hydrolysis. The concepts developed in this study are being extended to the latentiation of biogenic and other amines.

## Experimental Section

Melting points were determined using a Thomas-Hoover melting point apparatus and are corrected. Analyses were performed by Midwest Microlab, Inc., Indianapolis, Ind. 46226. Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ± 0.4% of the theoretical values. Specific rotations were measured on a Franz Schmidt and Haensch, Berlin, S., polarimeter. Radioscanning of the tlc sheets was done with an atomic scanner, Atomic Accessories, Inc., New York, N. Y.,

**Pharmacological Measurements.**—The measurement of motor activity was carried out as described elsewhere.[19] For the results described in Table II a dose of 25 mg/kg (in propylene glycol) administered ip was employed, although similar effects were obtained in the 10–50 mg/kg dose range. Usually the animals were sedated the first 30–50 min prior to the onset of increased motor activity. During this initial period the animals also exhibited decreased skeletal muscle tonus and were generally less responsive to noxious stimuli. The increase in motor activity was observable 1–2 hr following drug administration. With **6**, **10**, and **11** some pupillary dilation and piloerection were observed during the 1–2 hr period. The anorexigenic action was measured over a period of 5 days utilizing a dose of 10 mg/kg administered ip twice daily at intervals of 12 hr. Amphetamine (1 mg/kg twice daily) was used as a reference standard. The food consumption of both the experimental and control groups was measured.

**Radiochemical Drug Study.**—The drugs in Table III were given to mice in a single injection at 10 mg/kg ip in propylene glycol. One-half and one hour later the mice were sacrificed and their brains removed and analyzed. An average of 4 animals were used to obtain each value and agreement was good. The original drug penetrating into the brain and the hydrolyzed products were separated and identified using tlc and autoradiography. The values given in Table III are for micrograms present in the whole brain. All mice were extremely hyperactive at time of sacrifice. Onset of activity was within 3–5 min with amphetamine and 8–10 min with **21** and **22**.

**Chloroformic Acid Esters. *o*-Formylphenyl Chloroformate.**—A soln of 97.6 g (0.8 mole) of salicaldehyde, 96.7 g (0.8 mole) of $PhNMe_2$, and 8.1 g (0.08 mole) of $Et_3N$ in 100 ml of solvent A (10% PhMe and 90% $C_6H_6$) was added slowly with cooling to 90 g (0.9 mole) of $COCl_2$ in 400 ml of solvent A. After stirring for 6 hr, $H_2O$ was added cautiously. The organic phase was washed with 5% HCl and $H_2O$, and dried ($CaCl_2$). The solvent was removed and the residue crystallized nicely from hexane as white needles, 97.5 g (66%), mp 80.5–81.5°. The product is unstable and slowly decomposes while standing in a closed container, apparently eliminating HCl. It can be stored for only a short time. *Anal.* ($C_8H_5ClO_3$) C, H, Cl.

The other chloroformic acid esters were prepared similarly from $COCl_2$, an alcohol, and with an organic base as a scavenger for HCl and as a catalyst. The various products, their yields and a brief description are given here: **p-methoxyphenyl chloroformate,**[20] 89% colorless oil, bp 85–88° (3 mm), ir $\lambda_{max}^{film}$ 5.58; **α-carboethoxyethyl chloroformate,**[21] 66%, colorless lachrymatory oil, bp 55–57° (4 mm), ir $\lambda_{max}^{CS_2}$ 5.58, 5.66; **o-carbomethoxyphenyl chloroformate,**[22,23] 65%, colorless oil, bp 106–108° (3 mm), ir $\lambda_{max}^{film}$ 5.58, 5.77; **p-nitrophenyl chloroformate,**[20,24] 42%, white crystals (from *i*-$Pr_2O$), mp 65–72° (reported mp 80–81°). ***m*-Nitrophenyl chloroformate**[25] and ***o*-nitrophenyl chloroformate**[26,27] were prepared by standard methods and were used immediately without isolation. **Phenyl chloroformate** was a commercial product.

**Carbamate Esters.**—The carbamate esters in Table I were prepared by methods similar to the examples given below, with minor variations.

**Phenyl *l*-Ephedrinecarbamate.**—A mixture of 6.6 g (0.04 mole) of *l*-ephedrine in 40 ml of $CHCl_3$ and 2.33 g (0.022 mole) of $Na_2CO_3$ in 12 ml of $H_2O$ was cooled to 10°. A soln of 6.66 g (0.044 mole) of phenyl chloroformate in 10 ml of $CHCl_3$ was added

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(27) Y. Iwakura, Y. Ishizuka, and T. Saito, *Nippon Kagaku Zasshi*, **76**, 1108 (1955); *Chem. Abstr.*, **51**, 17,750 (1957).

over 10 min with good stirring, keeping the temp below 20°. The cooling bath was removed and stirring was continued for 1 hr, after which time the evolution of $CO_2$ stopped. The $CHCl_3$ layer was washed with 20 ml of 5% HCl, then $H_2O$ and dried ($Na_2SO_4$) and the solvent evaporated. The oily product was crystallized from $CCl_4$–hexane, decolorizing with charcoal, to give 6.7 g (59%) of small white needles, mp 68–70°. Recrystallization from pet ether (bp 60–110°) gave an analytical sample: mp 72–74°; ir $\lambda_{max}^{CHCl_3}$ 3.0 (OH), 5.87 (C=O).

**o-Carbomethoxyphenyl *l*-Ephedrinecarbamate.**—A mixture of 4.95 g (0.03 mole) of *l*-ephedrine in 50 ml of $CHCl_3$ and 1.7 g (0.016 mole) of $Na_2CO_3$ in 20 ml of $H_2O$ was cooled to 5°. A soln of 6.66 g (0.031 mole) of *o*-carbomethoxyphenyl chloroformate in 20 ml of $CHCl_3$ was added over 10 min with good stirring, keeping the temp below 15°. The cooling bath was removed and the reaction mixture was stirred for 1.5 hr. The organic layer was washed with 20 ml of 5% HCl and 20 ml of $H_2O$ and dried ($Na_2SO_4$) and the solvent evaporated. The solid product was recrystallized from $CHCl_3$–hexane, decolorizing with charcoal, to give 7.66 g (74%) of fine long white needles, mp 95–96°.

**Bis(phenyl *dl*-*p*-hydroxy-α-methylphenethylcarbamate)piperazine Salt.**—A stirred mixture of 6.96 g (0.03 mole) of *dl*-*p*-hydroxyamphetamine·HBr, 3.4 g (0.032 mole) of $Na_2CO_3$, 30 ml of $H_2O$ and 60 ml of $CHCl_3$ was cooled in an ice bath. A soln of 4.85 g (0.031 mole) of phenyl chloroformate in 20 ml of $CHCl_3$ was added over 5 min. After stirring at room temp for 2 hr, the partially soluble free phenolic amine gradually reacted and dissolved in the $CHCl_3$ giving 2 clear layers. The $CHCl_3$ layer was washed with 2 × 50 ml of 5% HCl, dried ($Na_2SO_4$), and the solvent evaporated to give 8 g of a colorless oil. This was dissolved in 150 ml of $C_6H_6$ and 4 g of piperazine was added to the warm soln, followed by 80 ml of hexane. The resulting ppt was recrystallized from $C_6H_6$ giving 4.9 g (52%) of white crystalline product, mp 115–116°, that analyzed correctly for the bis salt.

**o-Nitrophenyl *dl*-α-Methylphenethylcarbamate.**—A soln of 13.9 g (0.1 mole) of *o*-nitrophenol in 30 ml of solvent A was added to a solution of 17 g (0.17 mole) of $COCl_2$ in 150 ml of solvent A at 0° with no noticeable rise in temperature. However, an exothermic reaction occurred during the gradual addition of 10.1 g (0.1 mole) of $Et_3N$ in 30 ml of solvent A and a solid formed. After stirring out of the cooling bath for 1 hr, 100 ml of $H_2O$ was added cautiously to dissolve the pptd salt. The organic phase was washed with $H_2O$, dried ($CaCl_2$), and evapd to about 50 ml of yellow soln containing the *o*-nitrophenyl chloroformate, from which the carbamate was prepared.

A mixture of 9.02 g (0.245 mole) of *dl*-amphetamine sulfate and 5.3 g (0.05 mole) of $Na_2CO_3$ in 70 ml of $H_2O$ with 50 ml of $CHCl_3$ was cooled to 0°. The *o*-nitrophenyl chloroformate solution was added with stirring and cooling over 10 min. The cooling bath removed and the mixture was stirred for 2 hr whereupon both layers became clear yellow at pH 7–7.5. The organic phase was washed with 50 ml of $H_2O$, two 50-ml portions of 5% HCl, $H_2O$ again and then dried ($Na_2SO_4$). Most of the solvent was evaporated and upon the addn of hexane a solid formed. Recrystallization from $CCl_4$ gave 12.3 g (84%) of crude product, mp 80–86°. Further recrystn from dry *i*-$Pr_2O$ gave analytically pure product, mp 89–90°, as very light yellow needles.

**o-Carbomethoxphenyl [$^{14}$C]-*d*-α-Methylphenethylcarbamate (21).**—A mixture of 20 mg (0.055 μmole) of [$^{14}$C]-*d*-amphetamine sulfate (6.0 μCi/mg), 35 mg (0.33 μmole) of $Na_2CO_3$, 40 mg (0.2 μmole) of *o*-carbomethoxyphenyl chloroformate, 1 ml of $H_2O$, and 3 ml of $CHCl_3$ was shaken for 0.5 hr at room temperature. The mixture was dild with 10 ml of $CHCl_3$ and 4 ml of $H_2O$. The organic phase was washed with dil HCl and $H_2O$, dried ($Na_2SO_4$), and evaporated to an oil that crystallized. After trituration with pet ether the solid was recrystallized from $CCl_4$ and pet ether, eventually giving 30 mg (87%) of white needles with a specific activity of 3.5 μCi/mg. Tlc on an Eastman Kodak 6060 chromagram silica gel sheet using $C_6H_6$ developer indicated that the product was homogeneous with an $R_f$ 0.21 corresponding exactly to that of the unlabeled material. A radioscan of the strip showed a single peak corresponding to the visual spot, indicating radioactive homogeneity as well.

**o-Nitrophenyl [$^{14}$C]-*d*-α-methylphenethylcarbamate (22)** was prepd from 25 mg (0.068 μmole) of [$^{14}$C]-*d*-amphetamine sulfate (6.0 μCi/mg) by procedures similar to those in the preceding experiment and those given here for the prepn of the unlabeled product. A 30-mg yield of long, yellow-tinted needles was eventually obtained with a specific activity of 3.7 μCi/mg. Tlc on Eastman Kodak 6060 Chromagram silica gel sheet using $C_6H_6$ as the developer showed the product to be homogeneous with an $R_f$ 0.54 corresponding exactly to that of the unlabeled product. A radioscan indicated that the product was radiochemically pure and corresponded to the visual spot.

# Peripheral Inhibition of Thyroxine by Thiohydantoins Derived from Amino Acids[1a]

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A number of 3-phenyl-2-thiohydantoins with nonpolar substituents at the 5 position inhibited the peripheral effect of $T_4$ as measured by the liver GPD response. Like TU and PTU, they also increased the PBI in rats given exogenous $T_4$. These PTH derivatives of valine, leucine, norleucine, isoleucine, etc., were very weak goiterogens which had only little or no effect on thyroid weight or radioiodine uptake.

Barker, *et al.*[2a] originally showed that a given dose of $T_4$ did not restore the metabolic rate as well in rats made hypothyroid with TU as it did in surgically thyroidectomized rats. In a recent summary by de Escobar and del Rey[2b] the minimal daily $T_4$ requirement was found to be increased twofold in rats receiving TU, PTU, or MTU when a variety of biological endpoints was used (metabolic rate, liver GPD, goiter prevention, pituitary basophilia, normal plasma TSH, and suppression of thyroid $^{131}$I release). These thiouracils, in addition to preventing the biosynthesis of thyroid hormones, inhibited the peripheral action of $T_4$.[3,4]

This paper reports a study of the inhibition of the GPD response to exogenous $T_4$ by a series of 5-alkyl-3-phenyl-2-thiohydantoins derived from amino acids by the Edman reaction[5,6] in an attempt to establish the

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