of compounds, in the plaque inhibition test.[4] The activity of these compounds previously synthesized,[5-10] against other viruses in the plaque inhibition test, has been reported. The present results are summarized in Table I.

While it is not possible to draw any conclusion about structure–activity relationships for these compounds, at least one can note that different series of compounds showed some activity in the test, within its limitation.

Compounds active against rhinoviruses have been found in three series, thiosemicarbazones, biguanides, and *s*-triazines, which showed activity against other viruses.

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The Synthesis of 3,5-Diisopropyl-3′-iodo-DL-thyronine

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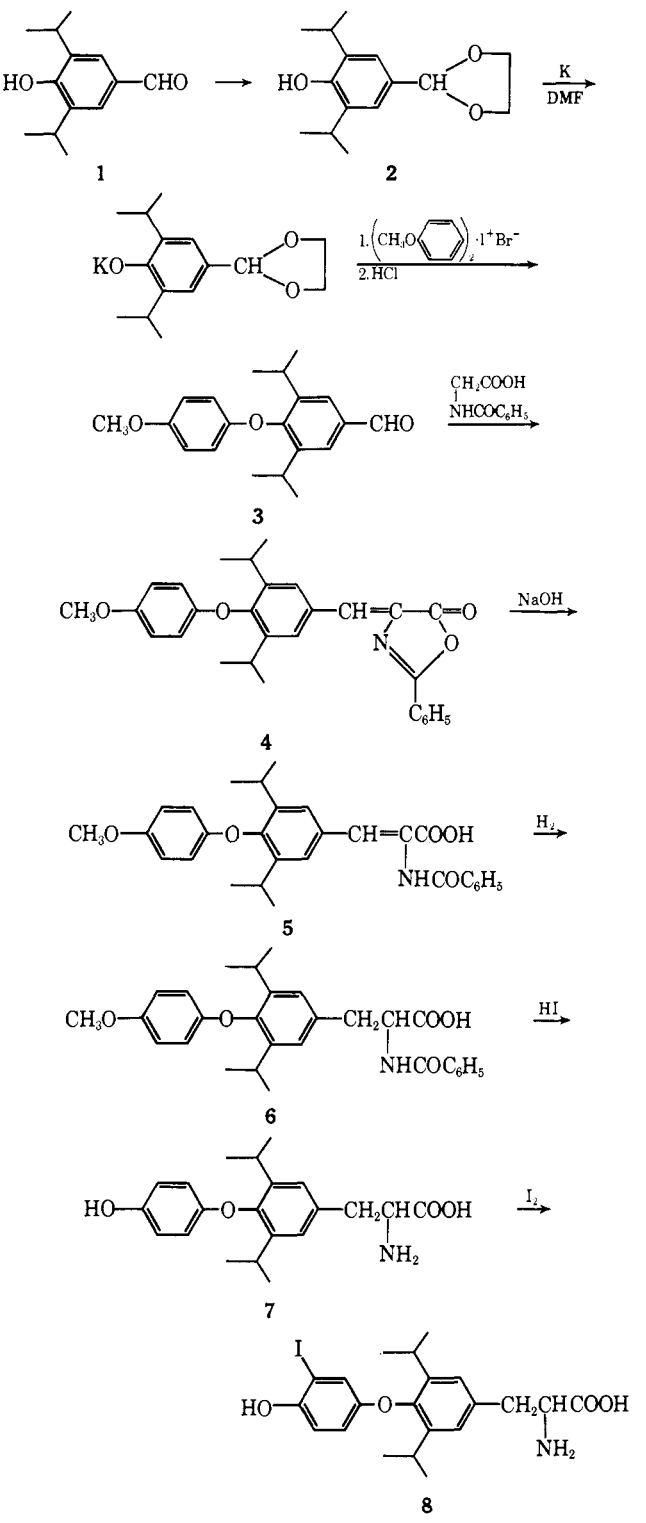
It has been shown that the high biological activity of 3,5,3′-triiodothyronine (T_3) is surpassed by its analog, 3,5-diiodo-3′-isopropylthyronine.[1-5] Thus, it has been established that the 3′-iodine atom in T_3 is not essential for its biological activity. In contrast, none of the analogs of T_3 synthesized so far with no iodine or other halogen atoms in the nonphenolic ring (3 and 5 positions) were biologically active. In view of the fact that a replacement of the 3′-iodine atom in T_3 with an isopropyl group, which has nearly the same molecular size as an iodine atom, results in a considerable increase in biological activity, it is of interest to determine whether a similar replacement of the 3- and 5-iodine atoms also enhances the biological activity of T_3 or abolishes it as in the case of other analogs of T_3 which have no halogen atom in the nonphenolic ring. Previous attempts to synthesize 3,5-diisopropyl analogs of T_3 failed.[6] In the present paper we report the synthesis of 3,5-diisopropyl-3′-iodo-DL-thyronine as summarized in Scheme I.

Conversion of the aldehyde **1** to the diphenyl ether **3** was a key step in the course of the synthesis. The aldehyde **1** did not react with dianisyliodononium bromide under various conditions. This was the reason why the acetal **2** of the aldehyde was used in this step. The etherification was carried out according to a modification of the procedure of Ziegler and Maar,[7] using drastic conditions. The diphenyl ether **3** was obtained in fair yield only at elevated temperatures. Its structure was confirmed through its nmr spectrum. Condensation of **3** with hippuric acid gave the azlactone **4**. Alkaline hydrolysis of the azlactone

SCHEME I



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led to an amido acid **5** whose structure was confirmed through its nmr spectrum. Catalytic hydrogenation of **5** gave the saturated amido acid **6**. Hydrolysis with hydroiodic acid converted **6** to 3,5-diisopropylthyronine (**7**) which showed color reactions with ninhydrin (amino acid) and with MBTH[8] (phenol). The structure of **7** was confirmed through its nmr spectrum. Iodination of **7** in alkaline medium easily led to **8** in excellent yield.

3,5-Diisopropyl-3′-iodo-DL-thyronine (**8**) was tested for antigoitrogenic activity by Professor Kenkichi Tomita, Faculty of Pharmaceutical Science, Kyoto University, but it showed practically no activity.

Experimental Section

Where analyses are indicated only by symbols of the elements analytical results obtained for those elements were within ±0.4% of the theoretical values.

3,5-Diisopropyl-4-hydroxybenzaldehyde (**1**) was prepared according to the method of Nikiforov, *et al.*;[9] mp 106–108°, lit.[9] 119–120°; nmr ($CDCl_3$), δ 9.87 (s, 1, CHO), 7.60 (s, 2, aromatic protons), 6.90 (s, 1, OH), 3.30 (septet, 2, J = 6 Hz, $2CH(CH_3)_2$), 1.30 (d, 12, J = 6 Hz, $2CH(CH_3)_2$).

Ethylene Acetal of 3,5-Diisopropyl-4-hydroxybenzaldehyde (**2**).—A solution of 10 g (0.048 mole) of aldehyde **1**, 20 ml (0.35 mole) of ethylene glycol, and 5 g of NH_4Cl in 250 ml of dry C_6H_6 was saturated with dry HCl gas. The mixture was refluxed and H_2O generated in the course of the reaction was removed by azeotropic distillation. After 30 hr no more H_2O was formed. The reaction mixture, after neutralization with 15 g of Na_2CO_3, was evaporated *in vacuo* to dryness. The residue was taken up with ether and water. The ether layer was washed (H_2O), dried, and evaporated to give a crystalline residue. Recrystallization from cyclohexane gave 10.6 g (88%) of **2** as colorless prisms, mp 132–134°. This substance shows no carbonyl band in its ir spectrum.

3,5-Diisopropyl-4-(4-methoxyphenoxy)benzaldehyde (**3**).—To a solution of 10 g (0.04 mole) of **2** in 150 ml of DMF, dried over BaO, was added 1.56 g (0.04 g-atom) of K. To the green solution was added 21.1 g (0.05 mole) of dianisyliodonium bromide[7] and 1 g of active powder.[10] The mixture was heated on an oil bath of 150–180° for 6 hr with stirring and under exclusion of moisture. The reaction mixture was cooled to room temperature, then taken up with ether and water. The ether layer was washed (dilute NaOH, H_2O) and evaporated. The residue was dissolved in 150 ml of EtOH containing *ca.* 4 ml of concentrated HCl, then heated for 30 min. The reaction mixture was evaporated *in vacuo* to dryness and the residue was taken up with ether and water. The ether layer was washed (H_2O), dried, and evaporated *in vacuo* to dryness. The residue (11.1 g) was chromatographed on a column of 200 g of silica gel (Mallinckrodt 100 mesh). Elution with C_6H_6 gave 2.05 g (16.5%) of **3**, which was recrystallized from benzene-isooctane to give colorless needles: mp 87–88°; ir (Nujol), 1700 cm^{-1} (C=O); nmr ($CDCl_3$), δ 1.16 (d, 12, J = 6.1 Hz, $2CH(CH_3)_2$), 3.11 (septet, 2, J = 6.1 Hz, $2CH(CH_3)_2$), 3.77 (s, 3, OCH_3), 6.68 (d (incompletely resolved), 4, *para*-disubstituted C_6H_4), 7.66 (s, 2, aromatic protons adjacent to formyl group), and 9.89 (s, 1, CHO). *Anal.* ($C_{29}H_{34}O_3$).

2-Phenyl-4-[3,5-diisopropyl-4-(4-methoxyphenoxy)benzal]-5-oxazolone (**4**).—A mixture of 1.0 g (0.0032 mole) of **3**, 0.69 g (0.0038 mole) of hippuric acid, 0.316 g (0.0038 mole) of anhydrous NaOAc, and 4 ml (0.039 mole) of Ac_2O was heated at 100° for 5 hr. The reaction mixture was kept overnight at 2° to give a semisolid material which was pressed on a suction filter and washed (cold H_2O, hot H_2O), yielding 1.13 g of yellow crystals. Recrystallization from MeOH gave 0.87 g (73.5%) of yellow needles: mp 149–152°; uv, λ_{max} (95% C_2H_5OH) 360 mμ (ε 41,300), 372 (59,200), and 388 (43,600); ir (Nujol), 1795, 1770, 1655, and 1560 cm^{-1}. *Anal.* ($C_{33}H_{35}NO_5$) C, H, N.

α-Benzamido-3,5-diisopropyl-4-(4-methoxyphenoxy)cinnamic Acid (**5**).—A solution of 4.2 g (0.0092 mole) of azlactone **4** in 300 ml of EtOH and 100 ml of 2 *N* NaOH was warmed at 60° for 30 min. The reaction mixture, after cooling, was acidified with chilled dilute HCl and concentrated *in vacuo* at room temperature to yield a brown solid residue. Crystallization from C_6H_6–isooctane gave 2.5 g (57%) of acid **5** as colorless needles: mp 200–202°; uv, λ_{max} 223 mμ (ε 35,800) and 292 (24,100); ir (Nujol), 2700–2500 (COOH), 1673, and 1623 cm^{-1}; nmr ($CDCl_3$), δ 1.02 (d, 12, J = 6.1 Hz, $2CH(CH_3)_2$), 3.02 (septet, 2, J = 6.1 Hz, $2CH(CH_3)_2$), 3.72 (s, 3, OCH_3), 6.68 (incompletely resolved doublet, 4, aromatic H), 7.65 (s, 2, aromatic H), 7.20–7.90 (m, 5, aromatic H), and 10.00 (s, 1, $COOH$). *Anal.* ($C_{29}H_{33}NO_5$) C, H, N.

3,5-Diisopropyl-DL-thyronine (**7**).—A solution of 0.93 g (0.002 mole) of **6**[11] prepared by catalytic hydrogenation (Pd, MeOH, 1 mole of H_2 uptake) of **5** in 24 ml of HI (sp gr 1.7) and 40 ml of AcOH was refluxed for 5 hr under N_2. The reaction mixture was evaporated *in vacuo*, and AcOH was completely removed by repeated additions and evaporations of H_2O *in vacuo*. The residue was dissolved in dilute NaOH, and the solution was decolorized with Norit and then neutralized (pH 7.2) with dilute AcOH. Fine crystals of 3,5-diisorpopyl-DL-thyronine (0.51 g, 73%) were obtained which were collected by centrifugation, washed (H_2O), and dried. Paper chromatography (*n*-BuOH–concentrated NH_4OH–H_2O, 5:1:2) (R_f 0.71) showed a single spot: mp 227°; nmr (CD_3OD), δ 1.10 (d, 12, J = 6.1 Hz, $2CH(CH_3)_2$), 3.00 (septet, 2, J = 6.1 Hz, $2CH(CH_3)_2$), and 6.45–6.98 (two broad singlets, 6, aromatic H). A sample for elemental analysis was prepared by reprecipitation with H_2O from a solution in MeOH. *Anal.* ($C_{21}H_{27}NO_4 \cdot 0.5H_2O$) C, H, N.

3,5-Diisopropyl-3′-iodo-DL-thyronine (**8**).—To a stirred, ice-cooled solution of 71.4 mg (0.2 mmole) of 3,5-diisopropylthyronine (**7**) in 2 ml of 0.2 *N* NaOH and 2 ml of 0.1 *M* Na_2CO_3 was added dropwise 2 ml (0.2 mmole) of 0.1 *M* KI$_3$ solution. After the addition was completed, a small amount of $NaHSO_3$ solution was added and the mixture was neutralized (pH 6.5) with dilute AcOH to yield 870 mg (90%) of colorless microcrystals which were collected by centrifugation, washed (H_2O), and dried: mp 185° dec. *Anal.* ($C_{21}H_{26}O_4NI \cdot 0.5H_2O$) C, H, N.

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Synthesis and Pharmacology of Some Indanamines. Dialkylaminoethylindans

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In view of the potent hypoglycemic activity shown by hexahydroindeno[1,2-*c*]pyrroles and their possible degradation products indanamines,[2-4] a series of dialkylaminoethylindans (**1**, **2**) were prepared. Syntheses and a brief pharmacology of these compounds are reported. A few of these compounds showed slight

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