TABLE II

THE CHEMORELEASE OF NOREPINEPHRINE-^{3}H FROM MOUSE HEARTS BY *dl* RING-SUBSTITUTED AMPHETAMINES

Substituent(s)	Lit. Ref	Dose, mg/kg	Norepinephrine-^{3}H in heart, % of control
3-CH_3	*a*	10	40
		1	80
		0.1	103
4-OH	*b*	10	45
		1	78
		0.1	104
3-OCH_3	*c*	10	44
		5	47
		0.5	68
		0.05	87
4-F	*d*	10	50
		5	63
		2.5	73
		0.6	81
3,4-$(OH)_2$	*e*	5	45
		2.5	58
		1.0	62
		0.1	82
NOH	*f*	10	54
		5	65
		0.5	104
NCH_3 (*d* isomer)	*b*	10	57
None	*b*	10	58
4-OCH_3	*b*	10	61
		5	77
		0.5	94
3,4-Cl_2	*g*	10	77
4-Cl	*h*	10	77
3,5-$(CH_3)_2$	*i*	10	81
3,4-O_2CH_2	*b*	10	86
2,4,6-$(CH_3)_3$	*i*	10	88
2-CH_3	*j*	10	88
3,4,5-$(OCH_3)_3$	*k*	10	89
2-OCH_3	*c*	10	90
3,4-$(CH_3)_2$	*l*	10	90
4-CH_3	*m*	10	91
3,4-$(CH_3O)_2$	*n*	10	94
3,5-$(CH_3O)_2$	*o*	10	95
3,4,5-$(CH_3)_3$	*p*	10	96
N-$CH(CH_3)_2$	*q*	10	97
2,3-$(CH_3O)_2$	*o*	10	100
2,5-$(CH_3O)_2$	*r*	10	100
2,4,6-$(CH_3O)_3$	*s*	10	100

[a] D. F. Marsh and D. A. Herring, *J. Pharmacol. Exptl. Therap.*, **100**, 298 (1950). [b] Commercially available. [c] E. R. Woodruff and T. W. Conger, *J. Am. Chem. Soc.*, **60**, 465 (1938). [d] C. M. Suter and A. W. Weston, *ibid.*, **63**, 602 (1941). [e] G. Alles, *ibid.*, **54**, 271 (1932). [f] R. T. Gilsdorf and F. F. Nord, *ibid.*, **74**, 1837 (1952). [g] M. Goldberg and S. Teitel, U. S. Patent 2,527,810 (1950); *Chem. Abstr.*, **45**, 2510*b* (1951). [h] H. B. Hass, *J. Am. Chem. Soc.*, **68**, 1009 (1946). [i] New compound. [j] M. S. Gibson, *J. Chem. Soc.*, 808 (1956). [k] P. Hey, *Quart. J. Pharm. Pharmacol.*, **20**, 129 (1947). [l] O. Schnider, U. S. Patent 2,384,700 (1945); *Chem. Abstr.*, **40**, 603 (1946). [m] H. D. Moed, J. van Djik, and H. Niewand, *Rec. Trav. Chim.*, **74**, 919 (1955). [n] C. Mannich and W. Jacobsohn, *Ber.*, **43**, 193 (1910). [o] T. R. Govindichari and M. V. Lakshimikantham, *Proc. Indian Acad. Sci.*, **46A**, 406 (1957). [p] F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **23**, 1979 (1958). [q] J. F. Kerwin, T. F. Herdegen, R. Y. Heisler, and G. E. Ullyot, *J. Am. Chem. Soc.*, **72**, 3983 (1950). [r] R. Baltzly and J. S. Buck, *ibid.*, **62**, 161 (1940). [s] F. Benington, R. D. Morin, and L. C. Clark, Jr., *J. Org. Chem.*, **19**, 11 (1954).

uents may be more important than the aminoalkyl side chain structure for norepinephrine-releasing activity.

TABLE III

COMPARISON OF NOREPINEPHRINE RELEASE BY β-PHENETHYLAMINES AND THE CORRESPONDING AMPHETAMINES

Substituent(s)	Norepinephrine-^{3}H in heart, % of control: β-Phenethylamines	Norepinephrine-^{3}H in heart, % of control: Amphetamines
4-OH	50	45
3,4-$(OH)_2$	50	45
N-CH_3	80	57
None	65	58
4-OCH_3	102	61
4-Cl	101	77
2-CH_3	103	88
3,4,5-$(OCH_3)_3$	99	89
4-CH_3	94	91
2,3-$(OCH_3)_2$	87	100
2,5-$(OCH_3)_2$	98	100

Experimental Section

Materials.—All of the compounds were obtained in the *dl* form and were isolated and purified as their hydrochloride salts. The two substituted amphetamines not previously reported (2,4,6-trimethyl and 3,5-dimethyl) gave satisfactory analytical values for C, H, and N. *dl*-Norepinephrine-7-^{3}H was obtained from the New England Nuclear Corp. (specific activity, 5 mcuries/μmole).

Assay of Norepinephrine Release.—The assay procedure reported by Daly, *et al.*,[2] was used with slight modification. A 0.2-ml solution (isotonic NaCl (0.9%) containing 50 mg of heparin/l.) of 5 μcuries of norepinephrine-7-^{3}H was used for the tail vein injection of the mice (male Swiss white, random bred, 18–20 g). Drugs were administered subcutaneously after 1 hr, and the mice were sacrificed after 3 hr by neck fracture. The hearts (five mice/assay) were removed and treated as described.[2] After centrifugation, 0.5 ml of the supernatant solution was added to 10 ml of a modified Brays phosphor solution,[4] and the radioactivity was determined by liquid scintillation counting. Two sets of controls were run for each drug assay, which was also done in duplicate. Assays using tyramine at 5 mg/kg were included routinely as a standard to check on the experimental techniques. Injected norepinephrine-7-^{3}H retained by the heart tissue after drug treatment was calculated as per cent of the control value based on the average counts per minute for each set of samples.

(4) C. D. Kochakian and J. Hill, *Biochemistry*, **5**, 1696 (1966).

Some Compounds Active as Antirhinovirus in the Plaque Inhibition Test

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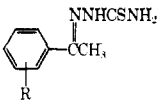
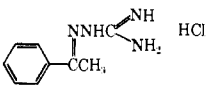
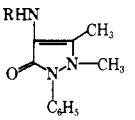
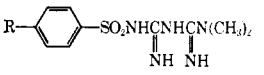
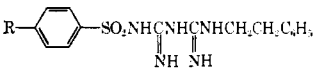
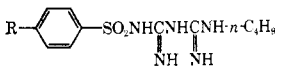
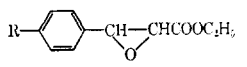
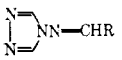
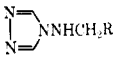
Few data concerning compounds active against rhinovirus have appeared in the literature.[1,2] In a previous paper we reported the antirhinovirus activity of some *p*-alkoxybenzensulfonylbiguanides,[3] and we now wish to report data concerning the activity against rhinoviruses 1059 and HGP shown by a different series

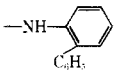
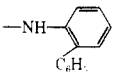
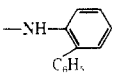
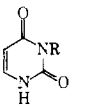
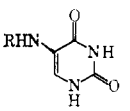
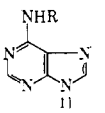
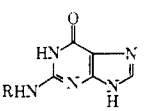
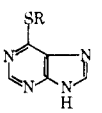
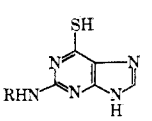
(1) K. Takagi, Y. Kurokawa, and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **14**, 658 (1966).

(2) M. Ridi, G. Franchi, and S. Mangiavacchi, *Farmaco., Ed. Sci.*, **23**, 16 (1968).

(3) C. Runti, A. Colautti, and F. Rubessa, *ibid.*, in press.

TABLE 1: ACTIVITY AGAINST RHINOVIRUS 1059[a] IN THE PLAQUE INHIBITION TEST

R	R′	Cytotoxicity[c]	Antiviral act.[c]
Thiosemicarbazones and Guanyl Hydrazones of Acetophenone Derivatives[3]			
			
3,4-$(OCH_3)_2$		2	1
2,4-$(OCH_3)_2$		2	1
3,4,5-$(OCH_3)_3$		2	1
p-$OC_{10}H_{21}$		1	1
			
3,4,5-$(OCH_3)_3$		1[b]	1[b]
3,4-O_2CH_2		2[b]	1[b]
Acyl Derivatives of 4-Aminoantipyrine[5]			
			
$CO(CH_2)_6CH_3$		1	1
$CO(CH_2)_7CH_3$		1	1
$CO(CH_2)_9CH_3$		1	1
$CO(CH_2)_{11}CH_3$		0	1
$CO(CH_2)_{14}CH_3$		0	1
$CO(CH_2)_{16}CH_3$		1[b]	1[b]
1-Adamantoyl		0	1
***p*-Alkoxybenzenesulfonylbiguanides[4]**			
			
n-OC_3H_7		0	1
n-OC_4H_9		1	1
n-OC_5H_{11}		0	1
			
n-OC_3H_7		0	1
n-OC_4H_9		0	1
n-OC_5H_{11}		0	1
n-OC_6H_{13}		0	1
n-$OC_{12}H_{25}$		0	1
			
n-OC_4H_9		1	1
Propoxydes[6]			
			
OC_2H_5		1	1
1,2,4-4H-Triazole Derivatives[8]			
			
C_6H_5		1	1
p-$CH_3OC_6H_4$		1	1
o-$CH_3C_6H_4$		0	1
p-ClC_6H_4		1	1
			
p-$CH_3C_6H_4$		0	1

R	R′	Cytotoxicity[c]	Antiviral act.[c]
Acyl Derivatives of *s*-Triazines[7,10]			
			
$CO(CH_2)_4CH_3$		1	1
$CO(CH_2)_{10}CH_3$		0	1
$CO(CH_2)_{14}CH_3$		0	1
$CO(CH_2)_4CH_3$		1[b]	1[b]
$CO(CH_2)_5CH_3$		1[b]	1[b]
$CO(CH_2)_{14}CH_3$		1[b]	1[b]
$CO(CH_2)_{10}CH_3$	$N(CH_2C_6H_5)_2$	1	1
$CO(CH_2)_{16}CH_3$	$N(CH_2C_6H_5)_2$	0	1
Acyl Derivatives of Pyrimidine and Purine Bases[7,9]			
			
$CO(CH_2)_3CH_3$		0[b]	1[b]
			
$CO(CH_2)_{12}CH_3$		0	1
			
$CO(CH_2)_4CH_3$		0	1
$CO(CH_2)_5CH_3$		1	1
$CO(CH_2)_{16}CH_3$		0[b]	1[b]
			
$CO(CH_2)_3CH_3$		1	1
$CO(CH_2)_{10}CH_3$		0	1
			
$CO(CH_2)_4CH_3$		0	1
$CO(CH_2)_7CH_3$		1	1
$CO(CH_2)_{11}CH_3$		0	1
$CO(CH_2)_{12}CH_3$		0	1
			
$CO(CH_2)_4CH_3$		1[b]	1[b]
$CO(CH_2)_7CH_3$		0[b]	1[b]
$CO(CH_2)_8CH_3$		0	1
$CO(CH_2)_{12}CH_3$		0	1
$CO(CH_2)_{14}CH_3$		1	1
$CO(CH_2)_{16}CH_3$		1	1

[a] Unless otherwise mentioned (see footnote *b*). [b] Data concerning activity against rhinovirus HGP. [c] 0 = no zone, 1 = <10-mm radius zone, 2 = >10-mm radius zone. For more details concerning testing procedures see ref 4a.

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.

(4) (a) R. C. Stewart, Proceedings of an International Symposium on Methods in Drug Evaluation, Milano, 1965, p 374. (b) The biological data were obtained from Smith Kline and French Laboratories, Philadelphia, Pa., through Robert J. Ferlauto, Director of Microbiological Research, and all tests were performed under the supervision of Dr. Richard C. Stewart.

(5) C. Runti, F. Collino, and G. Pescani, *Farmaco, Ed. Sci.*, **23**, 114 (1968).

(6) C. Runti and F. Ulian, *ibid.*, **23**, 122 (1968).

(7) C. Runti and T. Sciortino, *ibid.*, **23**, 106 (1968).

(8) C. Runti, C. Nisi, and F. Rubessa, Proceedings of the 5th International Congress of Chemotherapy, Wien, 1967, Vol. IV, p 351.

(9) C. Runti and A. Colautti, ref 8, Vol. V, p 307.

(10) C. Runti and T. Sciortino, ref 8, Vol. VI, p 551.

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

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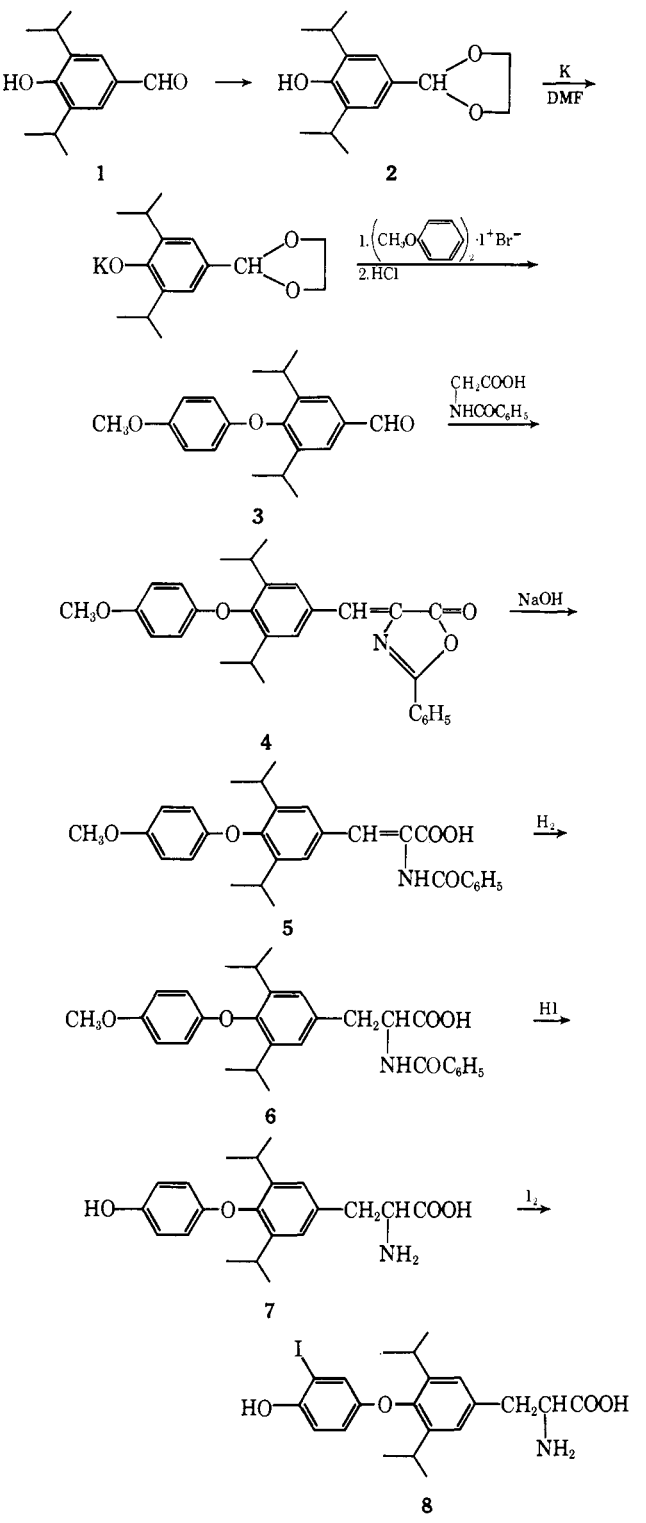
Received March 4, 1968

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



(1) B. Blank, F. R. Pfeiffer, C. M. Greenberg, and J. F. Kerwin, *J. Med. Chem.*, **6**, 554, 560 (1963).

(2) B. Blank, C. M. Greenberg, and J. F. Kerwin, *ibid.*, **7**, 53 (1964).

(3) C. M. Greenberg, B. Blank, F. R. Pfeiffer, and J. F. Pauls, *Am. J. Physiol.*, **205**, 821 (1963).

(4) S. B. Barker, M. Shimada, and M. Makiuchi, *Endocrinology*, **76**, 115 (1965).

(5) M. Wool, V. S. Fong, and H. A. Selenkow, *ibid.*, **78**, 29 (1966).

(6) B. Blank and F. R. Pfeiffer, *J. Med. Chem.*, **10**, 653 (1967).

(7) H. Ziegler and C. Maar, *J. Org. Chem.*, **27**, 3335 (1962).