TABLE II

N,N′-POLYMETHYLENEBISACRYLAMIDES

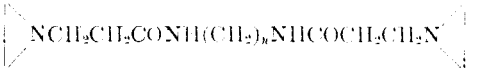
$H_2C{=}CHCONH(CH_2)_nNHCOCH{=}CH_2$

Compd	n	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
7	6[a]	MeOH	145–146	51	64.2	8.99	12.5	64.1	8.93	12.3
8	8[b]	MeOH		53						
9	10	EtOH	118–122	71	68.5	10.1	9.99	68.1	9.98	10.2
10	12	MeOH	118–122	20	70.1	10.5	9.08	70.1	10.6	9.23

[a] G. Kranzlein and M. Corell [German Patent 743,466 (1952)] report mp 138–140°; British Patent 875,378 (1961) [*Chem. Abstr.* **57**, 12006*f* (1962)] reports mp 143–144°. [b] Reference 2.

TABLE III

N,N′-BIS(AZIRIDINYLACETYL)-α,ω-POLYMETHYLENEDIAMINES



$NCH_2CH_2CONH(CH_2)_nNHCOCH_2CH_2N$

Compd	n	Crystn solvent	Mp, °C	Yield, %	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
11	6[a]		114–122	67						
	6[b]	EtOH–Et_2O	202–206		42.0	7.73	12.2	42.0	7.52	12.0
12	8		80–90	80						
	8[c]	EtOH	*Ca.* 165		44.7	7.92	11.6	44.6	7.92	11.7
13	10		74–90	62						
	10[b]	EtOH	180–194		47.0	8.22	10.9	47.2	8.26	11.0
14	12		85 dec	62						
	12[b]	EtOH	158–161		48.9	8.53	10.4	48.7	8.53	10.6

[a] T. Oshima, C. Saito, and T. Okagami, Japanese Patent 29,844 (1964); *Chem. Abstr.*, **62**, 11782*b* (1965). No data are given in this patent. [b] Bis HCl salts of the derived, bis-mustards (see Experimental Section).

acrylamides (n = 1–6) as antitumor agents has been claimed by several laboratories,[6] and the results of the antitumor screening of a large number of aziridine compounds have been tabulated.[7] The results obtained for some of the compounds reported in this paper are given in Table I along with data for "HN_2" obtained in a similar test system. Compound **12** (n = 8) demonstrated interesting activity in this screen, its favorable therapeutic index being coupled with a low degree of bone marrow depression.

Experimental Section

The following are general procedures for the preparation of compounds reported in Tables II and III.

N,N′-Decamethylenebisacrylamide (9).—Acrylyl chloride (11.8 ml, 13.5 g, 0.15 mole), dissolved in 150 ml of benzene, and K_2CO_3 (27.6 g, 0.20 mole) were stirred at 0° under N_2. To this solution was added 6.5 g (0.039 mole) of 1,10-decamethylenediamine dissolved in 250 ml of benzene. After addition was complete (0.5 hr), the reaction was stirred at 0° for 2 hr. Water was then added and the resulting precipitate collected by filtration. The residue was then triturated with 0.1 *N* HCl and 0.1 *N* NaOH, washed with water, filtered again, and dried *in vacuo*. This gave 8.2 g (70.7%) of white, solid acrylamide. Crystallization from methanol at −80° gave an analytical sample, mp 118–122°. Heating of these compounds led to polymerization: λ_{max}^{Nujol} 5.98 and 6.04 (C=O), 6.17 (C=C), 3.08 μ (NH).

N,N′-Decamethylenebis(β-aziridinylpropionamide) (13).—A mixture of 2.00 g (0.00712 mole) of bisacrylamide **9**, 50 ml of methanol, and 3.66 ml (3.05 g, 0.0712 mole) of aziridine was stirred at room temperature for 8 days under N_2. All of the acrylamide did not dissolve at first, but after 4 days the solution was clear. The solvent was removed *in vacuo* and the residue was dried at 1 mm for 12 hr to yield 1.04 g (61.5%) of white, spongy solid: λ_{max}^{Nujol} 6.1 (C=O), 3.04 μ (NH). An analytical sample, mp 194°, of the bis-mustard hydrochloride was prepared by reaction with gaseous HCl in ethanol.

Biological Methods and Results.—The compounds listed in Tables II and III were evaluated as inhibitors of reproduction in our colony of houseflies (*Musca domestica* L.). The method was that previously reported.[7]

Ehrlich Ascites.—The tumor was maintained routinely by weekly intraperitoneal injection of male Swiss mice (Simonsen Lab) with 1×10^6 tumor cells, in a volume of 0.2 ml of saline. For screening studies, the mice received 1×10^6 tumor cells intraperitoneally. Twenty-four hours later the mice were randomly distributed into control and experimental groups. There were ten mice per experimental group and between 30 and 40 control mice per experiment. The compounds were dissolved in H_2O or suspended by sonification in water with Tween 80, 2 drops/10 ml, and injected intraperitoneally once daily for six injections. All animals were sacrificed 24 hr after the last injection and the volume of ascites was measured. In some instances, the total packed-cell volume (TPCV) was determined. The TPCV is determined as the product of ascitocrit (per cent packed cells) and the total ascitic tumor volume (see Table I).

Where indicated and possible, the therapeutic index (TI) was determined. The TI is the ratio of the dose which kills 10% of the mice (LD_{10}) to the dose which inhibits TV 90% (ED_{90}).

In addition, sternal bone marrow samples were taken in some instances to determine degree of depression of marrow elements.

Acknowledgment.—This work was supported by U. S. Public Health Service Grant GM 11491. We wish to thank V. Tovar for assistance with the fly screening studies. The Ehrlich ascites data was obtained under the supervision of Dr. J. Scholler of these laboratories.

(6) (a) T. Oshima, C. Saito, and T. Okagami, Japanese Patent 29,844 (1964); *Chem. Abstr.*, **62**, 11782 (1965); (b) A. S. Toxopeus, S. D. Willson, A. W. Vogel, and A. Sloboda, *Nature*, **191**, 611 (1961); British Patent 905,186 (1962).

(7) T. H. Goodridge, W. T. Huntress, and R. P. Bratzel, *Cancer Chemotherapy Rept.*, **26**, 341 (1963).

3-Halogenated Thyronines

PAUL BLOCK, JR.

Department of Chemistry, University of Toledo, Toledo, Ohio

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The discovery of the thyroxine-antagonistic properties of 3,3′-diiodothyronine and 3,3′,5′-triiodothyronine[1] has led to a study in this laboratory of methods

(1) S. B. Barker, C. S. Pittman, J. A. Pittman, Jr., and S. R. Hill, Jr., *Ann. N. Y. Acad. Sci.*, **86**, 545 (1960).

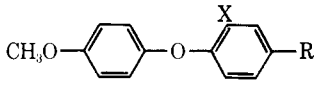
for the synthesis of 3-halogenated thyronines, particularly the unknown 3-chlorothyronine, the chlorinated derivates of which would be of pharmacological interest if they were to lead to an iodine-free thyroxine antagonist.

Of the methods available for the synthesis of 3-iodothyronine,[2] that of Roche and collaborators,[2d] wherein the diphenyl ether linkage of the thyronine analog is formed by a condensation in aqueous solution, was considered to have the potential of producing reasonable quantities of 3-halogenated thyronines with the minimum possibility of contamination by 3,5-dihalogenated products. Indeed, by this method 3-iodothyronine could readily be synthesized using, in the present instance, hippuric rather than aceturic acid in the Erlenmeyer azlactone synthesis.[3]

However, synthesis of the desired chlorothyronine was not achieved in this manner. Treatment of the diazotized amine with the strongly acid solutions of cuprous chloride usually employed in the Sandmeyer reaction caused considerable dechlorination. And, in contrast to the analogous iodine compound, the solubility characteristics of the chloro compound did not differ sufficiently from those of the unchlorinated compound to permit purification by crystallization as a matter of practical synthesis.

The lability of the iodine atom in 3-iodothyronine has been studied in depth by Jorgensen and Reid.[4] It now appears that the chlorine atom in monochlorothyronine is unstable under the conditions of the Sandmeyer reaction which readily permit synthesis of the dichloro derivative.[5]

The reaction was not investigated further since it was found possible to adapt the iodonium salt reaction, successfully used in the case of 3,5-dihalogenated thyronines,[6] to the synthesis of 3-chloro- as well as 3-iodothyronine. Optically active compounds could be expected by this route. Although no reaction took place under conditions which led to good yields of dihalogenated derivatives, in methanol either at boiling temperature[6b,d] or at room temperature,[6c] good yields of monohalogenated thyronines were obtained in dimethylformamide at slightly elevated temperature, although these conditions gave unsubstituted thyronine only in poor yield.



I, X = NO_2; R = CHO
II, X = NO_2; R = CH=C($NHCOC_6H_5$)COOH
III, X = NO_2; R = CH=C($NHCOC_6H_5$)$COOC_2H_5$
IV, X = NH_2; R = CH=C($NHCOC_6H_5$)COOH
V, X = I; R = CH=C($NHCOC_6H_5$)COOH
VI, X = I; R = CH=C($NHCOC_6H_5$)$COOC_2H_5$
VII, X = Cl; R = CH=C($NHCOC_6H_5$)COOH

Physiological Activity.—Testing of the trichlorothyronine was carried out by J. A. Pittman of the University of Alabama Medical Center. Unlike 3,3′,5′-triiodo-*dl*-thyronine, the trichlorinated thyronine showed no thyroxine antagonism when assayed by suppression of basal metabolic rate in thyroidectomized rats maintained on thyroxine. In addition, it did not elevate the thyroidal radioiodine uptake in normal rats, nor did it show any thyrominetic activity by lowering the radioiodine uptake or elevating the basal metabolic rate.

Experimental Section

3-Nitro-4-(4-methoxyphenoxy)benzaldehyde (I).—4-Chloro-3-nitrobenzaldehyde[7] (100 g, 0.54 mole), 100 g (0.81 mole) of *p*-methoxyphenol, 5.35 g of sodium bisulfite, 41.5 g (0.3 mole) of K_2CO_3, and 1100 ml of water were boiled under reflux with stirring for 1.5 hr. The reaction mixture was poured into 8 l. of water and refrigerated overnight. The supernatant was decanted and the solid crystallized from 500 ml of 95% ethanol to give 111.5 g (76%) of I, mp 65–66°.[8]

3-Nitro-4-(4-methoxyphenoxy)-α-benzoylaminocinnamic Acid (II).—The aldehyde I (21.8 g, 0.08 mole) was dissolved in 26 ml of warm acetic anhydride. To the cooled solution was added 14.5 g of hippuric acid and 8 g of $KHCO_3$.[9] The suspension was warmed until effervescence began (*ca.* 60°). The heat source was removed. Effervescence proceeded spontaneously until the reaction mixture solidified and the temperature rose to about 95°. After the temperature had fallen, 50 ml of water was added, and the yellow crystals of the oxazolone were filtered, washed with water and cold ethanol, and dried. The crude oxazolone was boiled for 5 min in 1.2 l. of 33% ethanol containing 24 g of NaOH. The cooled solution was neutralized with 5 *N* HCl, and the filtered precipitate crystallized from 400 ml of AcOH; yield 26 g (75%), mp 222–223°.

Anal. Calcd for $C_{23}H_{18}N_2O_7$: C, 63.6; H, 4.2; N, 6.45. Found: C, 63.8; H, 4.2; N, 6.4.

Ethyl 3-Nitro-4-(4-methoxyphenoxy)-α-benzoylaminocinnamate (III).—The crude, dried material from the interaction of 21.8 g of the aldehyde I and hippuric acid was suspended in 500 ml of commercial absolute ethanol, 3 g of Na_2CO_3 was added, and the suspension was boiled under reflux for 0.25 hr longer than the time required for dissolution of the solid, with only excess Na_2CO_3 remaining. The solution was filtered hot, treated with water to precipitation at the boiling point, and cooled, and the light yellow ester separated; yield 26.5 g (75%), mp 128–129°.

Anal. Calcd for $C_{25}H_{22}N_2O_7$: C, 64.9; H, 4.8; N, 6.1. Found: C, 64.9; H, 4.9; N, 5.9.

3-Amino-4-(4-methoxyphenoxy)-α-benzoylaminocinnamic Acid (IV).—The nitro compound II (21.7 g, 0.05 mole), dissolved in 200 ml of water by means of the minimum amount of NaOH solution, was hydrogenated at 2.1 kg/cm² at 20°, using 2 g of unreduced 10% $PdCl_2$–C as catalyst.[10] The absorption of hydrogen ceased within 40 min, after 3 moles had been taken up. The amine was precipitated from the filtered solution with 1:1 HCl and crystallized quickly from 100 ml of preheated ethanol; yield 17.5 g (87%), mp 183–184°. For analysis the amine was dissolved in 50% ethanol by means of a minimum quantity of concentrated HCl, treated with decolorizing carbon in the cold,

(2) (a) J. Roche, R. Michel, and W. Wolf, *Compt. Rend.*, **239**, 597 (1954); (b) *Bull. Soc. Chim. France*, 464 (1957); (c) G. L. Gemmill, J. J. Anderson, and A. Burger, *J. Am. Chem. Soc.*, **78**, 2434 (1956); (d) J. Roche, R. Michel, J. Nunez, and C. Jacquemin, *Compt. Rend.*, **245**, 77 (1957); (e) J. S. Varcoe and W. K. Warburton, *J. Chem. Soc.*, 2711 (1960).

(3) Subsequent to the work on the iodo compound, exploitation of this route was reported in the patent literature: R. I. Meltzer, U. S. Patent 2,954,399 (1960).

(4) E. C. Jorgensen and J. A. W. Reid, *J. Org. Chem.*, **29**, 3396 (1964).

(5) W. K. Warburton, *J. Chem. Soc.*, 2655 (1961).

(6) (a) G. Hillmann, *Z. Naturforsch.*, **11b**, 419 (1956); (b) U. S. Patent 2,886,592 (1957); (c) P. F. Bevilacqua, J. T. Plati, and W. Wenner, U. S. Patent 2,895,927 (1959); (d) A. Dibbo, L. Stephenson, T. Walker, and W. K. Warburton, *J. Chem. Soc.*, 2645 (1961).

(7) R. I. Meltzer, S. Farber, E. Merrill, and A. Caro, *J. Org. Chem.*, **26**, 1414 (1961).

(8) By using only one-half as much *p*-methoxyphenol as Roche and collaborators, isolation of the compound is simplified without sacrificing yield or purity: J. Roche, R. Michel, J. Nunez, and C. Jacquemin, *Compt. Rend.*, **244**, 1507 (1957).

(9) The use of $KHCO_3$ gave higher yields in this case than did NaOAc: A. Galat, *J. Am. Chem. Soc.*, **72**, 4438 (1950).

(10) R. Mozingo, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p 685. The ratio of Pd:C used was double that of procedure C, p 686. With this catalyst only the nitro group was reduced.

reprecipitated with base, and finally crystallized from its cold, dilute solution in ethanol by addition of pentane; mp 188°.

The amine was white when precipitated from its solution by base. In early runs, warming the white precipitate in ethanol caused the color to change to deep gold, with a concomitant change in the nature of the precipitate from gelatinous to sandy. In later runs this did not occur, but the final product varied in color from grayish white to tan.

Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 68.3; H, 5.0; N, 6.9. Found: C, 68.0; H, 5.2; N, 6.9.

3-Iodo-4-(4-methoxyphenoxy)-α-benzoylaminocinnamic Acid (V).—The amine IV was converted to the iodo compound by the method of Chalmers, *et al.*,[11] using one-half as much $NaNO_2$ as is required for tetrazotization. A crude yield of 75% was obtained. One crystallization from 1-propanol gave mp 210.5–211.5°, sufficiently pure for hydrolysis to 3-iodothyronine. Recrystallization raised the melting point to 213.5–214.5° (lit.[2e] 216–218°).

Ethyl 3-Iodo-4-(4-methoxyphenoxy)-α-benzoylaminocinnamate (VI).—When the ester III was reduced in ethanol with $PdCl_2$–C, no crystalline amine could be obtained. It was therefore reduced in acetic acid and diazotized as above without being isolated. The $CHCl_3$ solution was passed through an alumina column to remove dark impurities, the $CHCl_3$ was evaporated, and the residue was crystallized several times from 75% ethanol; yield 50%, mp 126–127°.

The ester could also be made from acid V by warming it in five parts of acetic anhydride until solution was effected and maintaining the reaction in a boiling water bath for 0.5 hr. The oxazolone was separated, washed, and treated as in the synthesis of the nitro ester III. Recrystallization from 75% ethanol gave 80% of the ester, mp 128–129°, identical with the ester from the diazotization by mixture melting point and infrared spectrum.

Anal. Calcd for $C_{25}H_{22}INO_5$: C, 55.3; H, 4.1; I, 23.4. Found: C, 55.4; H, 4.1; I, 23.2.

3-Chloro-4-(4-methoxyphenoxy)-α-benzoylaminocinnamic Acid (VII).—The amine IV was diazotized as above as well as in aqueous solution,[3] and added to a cold solution of cuprous chloride[5,12] made from 70 g of $CuSO_4$ in 400 ml of concentrated HCl, 80 ml of water, and 400 ml of $CHCl_3$. The reaction mixture was stirred and slowly warmed to 40° and allowed to stand overnight. From the $CHCl_3$ solution on evaporation there was obtained 35 g of a product, mp 187–189° after two recrystallizations from 60% ethanol. Further crystallization from a mixture of benzene and acetonitrile raised the melting point to 193–195°. In several runs the percent of chlorine averaged only two-thirds of the theoretical 8.4%. The same free acid was obtained from the ester after anhydrous diazotization.[11]

The impure material was reduced and hydrolyzed as in the preparation of 3-iodo-*dl*-thyronine below. The mixed thyronines were chromatographed on paper, using *t*-amyl alcohol–5 *N* NH_4OH as solvent.[2e] A strong spot appeared under uv light which ran parallel with and showed the same fluorescence as thyronine, as well as a darker spot which ran ahead ($R_f \sim 0.34$). A solution of the mixture was streaked on glass plates coated with 1-mm thick layers of cellulose and developed in the same solvent system. Under uv light the two constituents were removed from the plates and eluted from the cellulose with dilute NH_4OH. The infrared spectrum of the substance with the lower R_f was identical with that of an authentic sample of *dl*-thyronine.

3-Iodo-DL-thyronine.—The substituted α-benzoylaminocinnamic acid V or its ethyl ester VI (7 g) was boiled under reflux in 45 ml of AcOH containing 3 g of red phosphorous and 1.2 ml of 57% HI. After 1.5 hr 7.5 ml of 48% HBr was added and the refluxing was continued a further 3.5 hr.[13] P was removed and the filtrate was evaporated to dryness under vacuum. The residue was taken up in 70 ml of water, extracted twice with ether, and neutralized (NH_4OH) at the boiling point. There resulted 4.5 g (83%) of crude iodothyronine, mp 235–237°. Elimination of a small amount of thyronine, as determined by paper chromatography, was best effected *via* the hydrochloride,[2e] mp 246–248°.

3-Chloro-*l*- and -*dl*-tyrosine.—*l*- and *dl*-tyrosine were chlorinated by the method of Zeynek.[14] It was preferable to use 2.5 times the amount of AcOH suggested to avoid solidification of the reaction mixture. The yield was not adversely affected.

N-Acetyl-3-chloro-*l*-tyrosine.—A stirred solution of 15 g of 3-chloro-*l*-tyrosine in 330 ml of 2 *N* NaOH was treated by the dropwise addition of 36 ml of Ac_2O during 1 hr while the reaction temperature was maintained at 5–10°. The solution was allowed to stand overnight. It was then treated with sufficient 40% NaOH to raise the pH to 11 and allowed to stand another 3 hr. Concentrated HCl was added to pH 1. During both neutralizations the temperature was maintained below 20°. After refrigeration the 15.5 g of crude product obtained was crystallized from 7.5 vol. of water to give 11.9 g (66%) of product, mp 165°, $[\alpha]^{26}D$ +62° (*c* 1, ethanol).

Anal. Calcd for $C_{11}H_{12}ClNO_4$: C, 51.3; H, 4.7. Found: C, 51.6; H, 4.7.

3-Chloro-*dl*-tyrosine was acetylated as above to give a 65% yield of a crude product, mp 173–174° after crystallization from 4 vol. of water.

Anal. Calcd for $C_{11}H_{12}ClNO_4$: C, 51.3; H, 4.7. Found: C, 51.0; H, 4.6.

N-Acetyl-3-iodo-*l*- and -*dl*-tyrosine.—Acetylation of 3-iodo-*l*-tyrosine as above gave a monohydrate, mp 102–103° after recrystallization from 7 vol. of 20% ethanol and drying (vacuum, 20°),[15] $[\alpha]^{26}D$ +54 (*c* 1.034, ethanol).

Anal. Calcd for $C_{11}H_{12}INO_4 \cdot H_2O$: C, 36.0; H, 3.8; I, 34.6, 4.9. Found: C, 36.2; H, 3.8; H_2O, 4.6.

3-Iodo-*dl*-tyrosine similarly acetylated gave a 75% yield of an anhydrous acetyl derivative after crystallization from 7 vol. of 33% ethanol, mp 190–192°.

Anal. Calcd for $C_{11}H_{12}INO_4$: C, 37.8; H, 3.5. Found: C, 37.5; H, 3.6.

The 3-iodotyrosines made by direct iodination[16] were contaminated by a small amount of diiodotyrosine, estimated at 2% by paper chromatography, that could not be removed by recrystallization either of the free amino acid or its N-acetyl derivative. In the latter case, the system 1-butanol–ethanol–0.5 *N* NH_4OH[17] was satisfactory for separation of 3-iodo- from 3,5-diiodo-N-acetyltyrosines.

3-Iodotyrosines and the acetyl derivatives synthesized by the method of Harington and Pitt-Rivers[18] were chromatographically pure.

N-Acetyl-3-chloro-*l*- and -*dl*-tyrosine Ethyl Esters. A. By Chlorination of N-Acetyl-*dl*-tyrosine Ethyl Ester.—The ester (10 g) was dissolved in 100 ml of AcOH and treated at room temperature with 3 ml of SO_2Cl_2. After standing several hours the solution was evaporated to a light yellow syrup. This was dissolved in 50 ml of $CHCl_3$, and the solution was washed with 25 ml of water followed by enough 2 *N* Na_2CO_3 to maintain an excess after neutralization of acid. After washing with a further 25 ml of water and drying ($MgSO_4$), the solution was evaporated at reduced pressure using a few milliliters of added methanol to remove all of the $CHCl_3$. The residue was crystallized twice from 33% MeOH; 7.3 g (65%), mp 126–127°.

Anal. Calcd for $C_{13}H_{16}ClNO_4$: C, 54.6; H, 5.6; Cl, 12.4. Found: C, 54.2; H, 5.6; Cl, 12.2.

Similarly, N-acetyl-*l*-tyrosine ethyl ester[19] was chlorinated to N-acetyl-*l*-tyrosine ethyl ester, mp 99–100° after several recrystallizations from 17 vol. of 33% MeOH; $[\alpha]^{26}D$ +27° (*c* 1, ethanol).

Anal. Found: C, 54.6; H, 5.7.

B. By Esterification of N-Acetyl-3-chloro-*l*- and -*dl*-tyrosine.—N-Acetyl-3-chloro-*l*-tyrosine (10 g), 1 g of *p*-toluenesulfonic acid, 7 ml of ethanol, and 325 ml of $CHCl_3$ were heated under reflux with separation of the water formed. After 4 hr a further 3 ml of ethanol was added, and the refluxing continued for 4 more hr. The $CHCl_3$ solution was washed (H_2O, Na_2CO_3, H_2O), dried

(11) J. R. Chalmers, G. T. Dickson, J. Elks, and B. A. Hems, *J. Chem. Soc.*, 3431 (1949).

(12) C. S. Marvel and S. M. McElvain, "Organic Syntheses," Coll. Vol. I, John Wiley and Sons, Inc., New York, N. Y., 1956, p 170.

(13) P. Block, Jr., and G. Powell, *J. Am. Chem. Soc.*, **64**, 1073 (1942).

(14) R. Zeynek, *Z. Physiol. Chem.*, **144**, 247 (1925).

(15) Mp 159–160.5° (uncor) is referred to by W. E. Mayberry, J. E. Ball, and D. Bertoli, *J. Am. Chem. Soc.*, **86**, 5302 (1964). On the basis of the analysis presented, this is the anhydrous compound.

(16) R. Pitt-Rivers, *Chem. Ind.* (London), 21 (1956).

(17) M. F. S. El Hawary and R. H. S. Thompson, *Biochem. J.*, **53**, 311 (1953).

(18) C. R. Harington and R. Pitt-Rivers, *ibid.*, **38**, 320 (1944).

(19) J. H. Barnes, R. C. Cookson, G. T. Dickson, J. Elks, and V. D. Poole, *J. Chem. Soc.*, 1463 (1953). Available commercially from Nutritional Biochemicals Corp., Cleveland, Ohio.

($MgSO_4$), and evaporated. Crystallization from 17 vol. of 33% MeOH gave the ester, mp 99–100°.

N-Acetyl-3-iodo-*dl*-tyrosine Ethyl Ester.—Esterification of N-acetyl-3-iodo-*dl*-tyrosine by the above method gave a 75% yield of the ester, mp 138.5–140.5°, from aqueous ethanol.

Anal. Calcd for $C_{13}H_{16}INO_4$: C, 41.4; H, 4.3. Found: C, 41.2; H, 4.15.

N-Acetyl-3-iodo-*l*-tyrosine ethyl ester was prepared as above but has not yet been crystallized. It was used for the preparation of 3-iodothyronine in the form of a gum.

3-Chloro-*dl*-thyronine.—Unrecrystallized di(*p*-anisyl)iodonium bromide[20] (21 g, 0.05 mole) and 7.2 g (0.046 mole) of Ag_2SO_4 were stirred 2 hr in 120 ml of water. Some decolorizing charcoal was added, the solids were removed by filtration, and the solution was treated with an aqueous solution of 3 g of NaCl. There resulted 14.5 g (83%) of the iodonium chloride, mp 202–203°, not raised by recrystallization. This salt (3.77 g, 0.01 mole), N-acetyl-3-chloro-*l*-tyrosine ethyl ester (3.43 g, 20% excess), and 0.65 g of NaOMe were added to 30 ml of redistilled DMF. The reaction was stirred while being kept at 50–55° for 14 hr. The solvent was removed under vacuum and the residue, treated as has been described, was shaken with 40 ml of benzene together with 25 ml of 3% HCl. The separated benzene layer was washed (two 15-ml portions of H_2O, two 10-ml portions of 1 *N* NaOH, three 10-ml portions of H_2O) and dried, the benzene was removed by evaporation, and the residue was treated with 25 ml of petroleum ether (bp 30–60°). The solvent was removed by decantation and the residual oil refluxed in 30 ml of AcOH and 5 ml of HBr (48%) for 3.5 hr. After evaporation under reduced pressure, the residue was taken up in 35 ml of water and extracted twice with ether. The solution was heated to remove ether and neutralized hot (NH_4OH). The yield of crude 3-chloro-*dl*-thyronine was 2.3 g (75%). For purification it was suspended in hot water, dissolved with the help of HCl, treated with charcoal, and reprecipitated (NH_4OH) after the addition of a few drops of AcOH, mp 221–223°. To remove all traces of thyronine for analysis, the hydrochloride was precipitated by adding concentrated HCl to the solution of the amino acid in 2 *N* HCl and reconverted to the free amino acid.

Anal. Calcd for $C_{15}H_{14}ClNO_4$: C, 58.5; H, 4.6; Cl, 11.5. Found: C, 58.3; H, 4.8; Cl, 11.4.

In similar fashion, by substituting 4.5 g of either iodo isomer, 3-iodothyronine results. It is purified by crystallization from 2 *N* HCl without adding concentrated acid.[2e]

3,3′-Dichloro-*dl*-thyronine.—3-Chloro-*dl*-thyronine (1.23 g, 0.004 mole) was dissolved by warming in 20 ml of AcOH. To the cooled solution was added 0.4 ml (0.67 g, 0.005 mole) of SO_2Cl_2. After 1 hr the solution was warmed to 60° then evaporated under vacuum. The residue was taken up in water and precipitated from the hot solution (NH_4OH); yield 1.1 g (80%). A product containing only a trace of trichlorothyronine was obtained by repeating the precipitation from acid solution, but for analysis the hydrochloride was precipitated as above. After neutralization of the hydrochloride in the usual manner, the dichlorothyronine melted at 226–228°.

Anal. Calcd for $C_{15}H_{13}Cl_2NO_4$: Cl, 20.7. Found: Cl, 20.4.

3,3′,5′-Trichloro-*dl*-thyronine.—3-Chloro-*dl*-thyronine (1.23 g, 0.004 mole) was dissolved in 6 ml of AcOH by warming. To the cool solution 0.9 ml (1.5 g, 0.011 mole) of SO_2Cl_2 was added slowly with stirring. The temperature of the reaction was allowed to rise while gas was evolved and a precipitate appeared. After 1 hr the reaction was warmed to 60–70° for 0.5 hr, 6 ml of 3.3 *N* HCl was added, and the hydrochloride, after refrigeration, was filtered and dissolved in 35 ml of 20% ethanol containing a few drops of AcOH. The hot solution was filtered and reheated, and the amino acid precipitated (NH_4OH); yield 1 g (65%), mp 224–225°.

Anal. Calcd for $C_{15}H_{12}Cl_3NO_4$: Cl, 28.2. Found: Cl, 28.0.

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(20) J. T. Plati, U. S. Patent 2,839,583 (1958).

N,N′-Dimethyl-1-phenyl-1,2-propanediamine. A Hitherto Unreported Product in Ephedrine Synthesis[1]

SEYMOUR HYDEN, SANTO EMMANUELE, HENRY WETSTEIN, AND GODFREY WILBERT

Nepera Chemical Company, Harriman, New York, a Subsidiary of Warner-Lambert Pharmaceutical Company

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The usual method of preparation of racemic ephedrine is by catalytic hydrogenation of acetylbenzoyl in the presence of methylamine. In all previous reported syntheses, regardless of reaction conditions or hydrogenation catalyst used, the only basic products isolated were ephedrine and small amounts of pseudoephedrine, the *erythro* and *threo* diasteroisomers. In the conversion to the ephedrines the aminomethyl group was found to enter exclusively β to the phenyl group. This was attributed by Manske and Johnson[2] to deactivation of α-carbonyl group by the phenyl ring. Skita and Keil[3] considered the selectivity to be a function of steric control, whereby methylamine reacts with the carbonyl adjacent to the smaller group. Couturier[4] explicitly stated that no monoamine α to the phenyl or α,β-diamine is formed in this synthesis. The catalysts that have been employed in prior syntheses are PtO_2,[2,5] colloidal Pt,[3] activated Al,[6] Pt–Pd,[7] and Raney nickel.[4,8]

We now wish to report the isolation, characterization, and pharmacology of N,N′-dimethyl-1-phenyl-1,2-propanediamine (I), obtained in the ephedrine synthesis from acetylbenzoyl.

$$C_6H_5COCOCH_3 \xrightarrow[H_2]{CH_3NH_2-CH_3OH} C_6H_5CHOHCH(CH_3)NHCH_3 + C_6H_5(CHNHCH_3)_2CH_3$$

dl-ephedrine I

The initial catalyst employed was 1:1 5% Pt/C–5% Pd/C since that catalyst system has been found to be very effective for the conversion of isonitrosopropiophenone to phenylpropanolamine.[9] In almost all of the previous reported ephedrine syntheses 1–2 moles of methylamine/mole of acetylbenzoyl were employed and in the present program the first experiments utilized a ratio of 2.5:1. Catalytic hydrogenation was carried out at ambient temperature except for the initial stage which was approximately 10° higher due to the reaction exotherm. The reaction mixture was treated in the typical manner used to isolate ephedrine hydrochloride, but the melting range of the product was broad and exceeded the reported melting point of ephedrine hydrochloride. The dihydrochloride of I was isolated by virtue of its insolubility in hot 2-

(1) Presented at the 153rd National Meeting of the American Chemical Society, Miami Beach, Fla., April 9–14, 1967.

(2) R. H. F. Manske and T. B. Johnson, *J. Am. Chem. Soc.*, **51**, 580 (1929).

(3) A. Skita and F. Keil, *Ber.*, **62B**, 1142 (1929).

(4) P. Couturier, *Compt. Rend.*, **207**, 345 (1938).

(5) G. Sunagawa and K. Okuda, *J. Pharm. Soc. Japan*, **72**, 117 (1952).

(6) W. Klavehn, British Patent 336,412 (1930).

(7) K. Kawahara, K. Kato, and I. Sasabe, Japanese Patent 177,598 (1949).

(8) J. Homma and Y. Kato, Japanese Patent 290 (1951).

(9) G. Wilbert and P. Sosis, U. S. Patent 3,028,429 (1962).