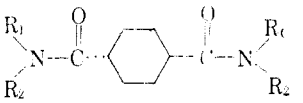
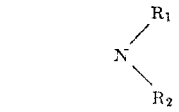
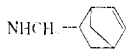
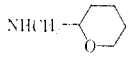
TABLE IV

N,N'-POLYSUBSTITUTED DERIVATIVES OF *trans*-CYCLOHEXANE-1,4-DICARBOXAMIDE[a]



No.		M.p., °C.	Recrystn. solvent	Formula	% C Calcd.	% C Found	% H Calcd.	% H Found
1		302–307	*b,c*	$C_{24}H_{34}N_2O_2$[d]	75.35	75.37	8.96	9.08
2		240–245	*b,e*	$C_{20}H_{34}N_2O_4$	65.54	65.40	9.35	9.31
3	$NHC(CH_3)_3$	>310	*b,e*	$C_{16}H_{30}N_2O_2$	68.05	68.29	10.71	10.73
4	$NHC(CH_3)_2CH_2C(CH_3)_3$	231–233	*b,e*	$C_{24}H_{46}N_2O_2$	73.05	73.35	11.75	11.81
5	NHC_6H_{11}[f]	>360	*g*	$C_{20}H_{34}N_2O_2$[h]	71.81	71.45	10.25	9.99
6	NHC_7H_{13}[i]	>360	*g*	$C_{22}H_{38}N_2O_2$[j]	...	...	...	...
7	C_4H_8N[k]	253–255	*l*	$C_{16}H_{26}N_2O_2$[m]	69.03	69.23	9.41	9.48
8	$C_5H_{10}N$[n]	188–189	*e*	$C_{18}H_{30}N_2O_2$[o]	70.55	70.70	9.87	9.82
9	$C_6H_{12}N$[p]	183–184	*e*	$C_{20}H_{34}N_2O_2$	71.81	71.48	10.25	9.83
10	$C_9H_{10}N$[q]	244–245	*l*	$C_{26}H_{30}N_2O_2$[r]	77.58	77.24	7.51	7.53
11	NHC_9H_9[s]	>310	*c*	$C_{26}H_{30}N_2O_2$[t]	77.58	77.62	7.51	7.52
12	NHC_9H_9[u]	>310	*v*	$C_{26}H_{30}N_2O_2$	77.58	77.37	7.51	7.63

[a] These compounds were prepared by method D (see Experimental). [b] Water. [c] Ethanol. [d] Calcd.: N, 7.32. Found: N, 7.49. [e] Methanol. [f] C_6H_{11} ≡ cyclohexyl. [g] Dimethylformamide. [h] Calcd.: N, 8.38. Found: N, 8.32. [i] C_7H_{13} ≡ cycloheptyl. [j] Calcd.: N, 7.73. Found: N, 8.15. [k] C_4H_8N ≡ pyrrolidino. [l] Chloroform. [m] Calcd.: N, 10.07. Found: N, 9.96. [n] $C_5H_{10}N$ ≡ piperidino. [o] Calcd.: N, 9.14. Found: N, 9.35. [p] $C_6H_{12}N$ ≡ hexamethyleneimino. [q] $C_9H_{10}N$ ≡ 1,2,3,4-tetrahydroisoquinolino. [r] Calcd.: N, 6.96. Found: N, 6.77. [s] C_9H_9 ≡ 1-indanyl. [t] Calcd.: N, 6.96. Found: N, 7.04. [u] C_9H_9 ≡ 2-indanyl. [v] Analytical sample sublimed at 280° (0.01 mm.).

rated *in vacuo* to yield a solid residue (20 g.). Crystallization from methanol yielded pure material.

In some cases the diamides were insoluble in benzene and these were isolated by evaporating the reaction mixture to dryness and removing amine hydrochloride by trituration with water. All the required amines were commercially available except 2-indanylamine which was prepared as described by Levin, *et al.*[10]

Acknowledgment.—The author wishes to thank Mr. G. Sawdyk, Mrs. H. Warwick, and Mr. L. Hawkins for expert technical assistance.

(10) N. Levin, B. E. Graham, and H. G. Kolloff, *J. Org. Chem.*, **9**, 380 (1944).

Synthesis of 3,5,3′,5′-Halogen-Substituted Thyropropionic Acids[1]

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In the course of an investigation of the reaction of 4-hydroxy-3,5-diiodophenylpyruvic acid with analogs of 3,5-diiodotyrosine in the presence of oxygen to form analogs of thyroxine,[3] it became necessary to synthesize various 3,5,3′,5′-tetrahalogenothyropropionic acids (see Table I). The synthesis of these compounds has been carried out according to the standard method using di-*p*-anisyliodonium bromide,[4] followed by halogenation of 3,5-dihalogenothyropropionic acids obtained.

(1) This work was supported by U. S. Public Health Service Grant AM 07955 from the National Institute of Arthritis and Metabolic Diseases.

(2) Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan.

(3) A. Nishinaga and T. Matsuura, *J. Org. Chem.*, **29**, 1812 (1964).

Experimental[5]

Methyl 3-(4-Hydroxy-3,5-dihalogenophenyl)propionates.—These esters were prepared by Fischer's esterification of the corresponding acids[3,6,7]; diiodo ester, m.p. 74–75°; dibromo ester, m.p. 54–55°; dichloro ester, m.p. 70–72°.

General Procedure for the Preparation of 3,5-Dihalogenothyropropionic Acids (I, X_1 = H; X_2 = Halogen).—A slight modification of the procedure of Ziegler and Maar[4] was used for the preparation of these acids. A mixture of di-*p*-anisyliodonium bromide[4] (8 mmoles), methyl 3-(4-hydroxy-3,5-dihalogenophenyl)propionate (4 mmoles), triethylamine (4 mmoles), and copper powder (8 mg.-atoms) in 4 ml. of methanol was stirred at room temperature for several hours, then allowed to stand overnight. The copper powder was removed by filtration and washed with methanol. The filtrate and washing were combined and evaporated under reduced pressure. The residue was taken up in 50 ml. of benzene and the benzene solution was washed with 1 *N* HCl, water, 1 *N* NaOH, water, and 5% aqueous acetic acid, then evaporated. The residue was subjected to steam distillation until no more *p*-iodoanisol distilled. The water was then decanted and the residue was refluxed for 2 hr. in a mixture of 8 ml. of acetic acid and 8 ml. of concentrated HBr. In the preparation of I (X_1 = H; X_2 = I), hydriodic acid (*d* 1.7) was used in place of HBr. The reaction mixture was concentrated under reduced pressure and diluted with water to yield crystals of I.

Bromination of I (X_1 = Br or I).—The bromination was carried out in an acetic acid solution with an excess of bromine. After standing at room temperature for a few days, the reaction mixture was worked up as usual.

Iodination of I (X_1 = H; X_2 = Cl or Br).—The iodination was carried out in an aqueous methylamine solution according to the procedure of Kharasch, *et al.*[8]

(4) H. Ziegler and C. Maar, *ibid.*, **27**, 3335 (1962); see also G. Hillmann, *Z. Naturforsch.*, **11b**, 419 (1956); P. E. Bevilacqua, J. T. Plati, and W. Wenner, U. S. Patent 2,895,927 (July 21, 1959).

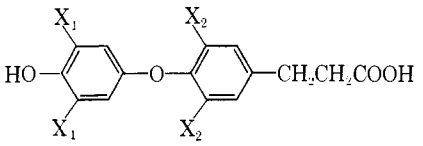
(5) Melting points were determined in capillary tubes. The microanalyses were made by Mr. J. Goda and his associates, of this faculty.

(6) J. H. Barnes, E. T. Borrows, J. Elks, B. A. Hems, and A. G. Long, *J. Chem. Soc.*, 2824 (1950).

(7) T. Matsuura and H. J. Calnmann, *J. Am. Chem. Soc.*, **82**, 2055 (1960).

(8) N. Kharasch, S. B. Kalfayan, and J. D. Arterberry, *J. Org. Chem.*, **21**, 925 (1956).

TABLE I



I

I			Yield,	Found, %		Calcd., %			Recrystn.
X_1	X_2	M.p., °C.	%	C	H	C	H	Formula	solvents
H	I	247–248[a]	78					$C_{15}H_{12}I_2O_4$	H_2O–EtOH
H	Br	200–202	64	43.19	2.89	43.30	2.91	$C_{15}H_{12}Br_2O_4$	H_2O–EtOH
H	Cl	200–201	41	55.14	3.63	55.06	3.70	$C_{15}H_{12}Cl_2O_4$	EtOAc–C_6H_6
Br	I	207–209	94[b]	28.09	1.74	26.97	1.51	$C_{15}H_{10}Br_2I_2O_4$	C_6H_6
I	Br	179–181	100[b]	26.81	1.58	26.97	1.51	$C_{15}H_{10}Br_2I_2O_4$	C_6H_6
Br	Br	183–184	56[b]	31.89	2.02	31.39	1.76	$C_{15}H_{10}Br_4O_4$	C_6H_6
I	Cl	188–189	69[b]	31.55	1.90	31.11	1.74	$C_{15}H_{10}Cl_2I_2O_4$	C_6H_6

[a] Lit.[8] m.p. 250°. [b] Crude yield.

Synthesis of 2,2-Diphenyl-5-cyanocyclopentanone

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The structural relationships of substituted 2,2-diphenylcyclopentanones to the methadone class of analgetics have been discussed.[2-4] A previous report[5] mentions several unsuccessful attempts to synthesize 2,2-diphenyl-5-cyanocyclopentanone. This keto nitrile has now been prepared from methyl 2,2-diphenyladipate.

Experimental[6]

Methyl 2,2-diphenyladipate was synthesized as reported[5] except 5-chloro-2,2-diphenylpentanenitrile was converted to the corresponding dinitrile in 99% yield in 3 hr. by using dimethyl sulfoxide as solvent.[7]

5-Carbomethoxy-5,5-diphenylpentanoic Acid.—A solution of 73.4 g. (0.225 mole) of methyl 2,2-diphenyladipate in 200 ml. of methanol was heated under reflux with vigorous stirring. After dropwise addition of 117.5 ml. of 2 *N* NaOH (0.235 mole) over 1 hr., the solution was refluxed for an additional 2 hr. The methanol was removed by distillation and the remaining solution was diluted with 500 ml. of water. Acidification with concentrated HCl gave a yellow oil which soon solidified. The crude product, 67.8 g. (96.6%), melted at 103–108°. A sample recrystallized from methanol had m.p. 107–110° (lit.[8] 105–106°). The method of Salmon-Legagneur and Neveu[8] gave inseparable mixtures.[5]

Methyl 5-Carbamoyl-2,2-diphenylpentanoate.—A mixture of 37 g. (0.222 mole) of thionyl chloride and 63 g. (0.202 mole) of the above acid ester stood overnight, was heated at 80° for 1 hr., and the excess thionyl chloride was removed under reduced pressure. The acid chloride was dissolved in 100 ml. of dry dioxane then dropped into 1000 ml. of concentrated NH_4OH at 0° over 1 hr. After warming to room temperature, filtration gave 64.6 g. (99%) of crude product melting at 88–100°. Recrystallization of a sample from methanol–water raised the m.p. to 98–100°.

Anal. Calcd. for $C_{19}H_{17}NO$: C, 82.87; H, 6.22; N, 5.09. Found: C, 82.70; H, 6.51; N, 5.03.

Methyl 5-Cyano-2,2-diphenylpentanoate.—Dehydration of the above amide ester with phosphorus oxychloride[9] gave the cyano ester in 79% yield. It had b.p. 220–225° (6 mm.) and m.p. 65–66.5° after recrystallization from methanol.

Anal. Calcd. for $C_{19}H_{19}NO_2$: C, 77.82; H, 6.48; N, 4.78. Found: C, 77.67; H, 6.81; N, 4.83.

2,2-Diphenyl-5-cyanocyclopentanone.—To a stirred, refluxing solution of 0.0793 mole of potassium *t*-butoxide in 150 ml. of dry *t*-butyl alcohol was added a solution of 21.7 g. (0.0741 mole) of methyl 2,2-diphenyl-5-cyanopentanoate in 350 ml. of *t*-butyl alcohol over 2.5 hr. After completion of the addition, the solution was refluxed for 8 hr. About two-thirds of the solvent was removed under reduced pressure and a white solid formed. After cooling, a solution of 5 ml. of acetic acid in 200 ml. of water was added, and the solid redissolved. Concentration of the resulting solution to about half its volume gave white crystals which were filtered. The product, 17.6 g. (91.2%), melted at 97–101°. After several recrystallizations from methanol, the m.p. was 103.5–106°.

Anal. Calcd. for $C_{18}H_{15}NO$: C, 82.76; H, 5.75; N, 5.36. Found: C, 82.61; H, 6.01; N, 5.28.

The infrared spectrum (CCl_4 solution) had absorption peaks at 4.42 (CN) and 5.64 μ (CO).

Hydrolysis with 80% sulfuric acid for 1 hr. then dilution to 40% and refluxing for 6 hr. gave 2,2-diphenylcyclopentanone, m.p. 86–88°. A mixture melting point of this material with an authentic sample[3] was not depressed.

(1) Taken from the Senior Honors thesis of S. A. I., Moravian College, 1964.

(2) P. N. Craig and I. H. Witt, *J. Am. Chem. Soc.*, **72**, 4925 (1950).

(3) N. R. Easton and S. J. Nelson, *ibid.*, **75**, 640 (1953).

(4) N. R. Easton, H. E. Reiff, G. Svarnas, and V. B. Fish, *ibid.*, **74**, 260 (1952).

(5) S. S. Kulp, V. B. Fish, and N. R. Easton, *J. Med. Chem.*, **6**, 516 (1963).

(6) Melting points are corrected and were determined in a Mel-Temp apparatus.

(7) L. Friedman and H. Shechter, *J. Org. Chem.*, **25**, 879 (1960).

(8) F. Salmon-Legagneur and C. Neveu, *Bull. soc. chim. France*, [5] **23**, 929 (1956).

(9) A. R. Surrey, "Organic Syntheses," Coll. Vol. III, John Wiley and Sons, Inc., New York, N. Y., 1955, p. 535.

Some 2,3-Disubstituted Quinazolones[1]

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In a series of 2,3-disubstituted quinazolones[2] possessing hypnotic activity,[3] 2-methyl-3-(*o*-tolyl)-4-quinazolone was found to be a potent anticonvulsant, superior to sodium phenobarbital against pentylenetetrazole seizures.[4] Furthermore, Darwin,

(1) The authors wish to express their thanks to the State Medical Research Council (U.P.) for a research grant and to the Indian Council of Medical Research for financial assistance to R. K.

(2) I. K. Kacker and S. H. Zaheer, *J. Indian Chem. Soc.*, **28**, 344 (1951).

(3) M. L. Gujral, R. P. Kohli, and P. N. Saxena, *J. Assoc. Physicians India*, **2**, 29 (1955).

(4) M. L. Gujral, P. N. Saxena, and R. P. Kohli, *Indian J. Med. Res.*, **45**, 207 (1957).