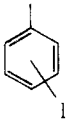
TABLE I

GLYCOL IODOBENZOATES

$COO(CH_2)_mOOC(CH_2)_nCH_3$



I

No.	Iodine position	m	n	Bp (mm) or mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % I	Found, % C	Found, % H	Found, % I	$n^{25}D$
1	*p*	2	0	36.4–37.2	$C_9H_9IO_4$	39.54	3.32	37.99	39.34	3.38	38.29	
2	*o*	2	0	129–133 (0.005)	$C_9H_9IO_4$	39.54	3.32	37.99	39.75	3.09	37.83	1.5651
3	*p*	2	1	113 (0.02)	$C_{12}H_{13}IO_4$	41.40	3.76	36.46	41.10	3.97	36.64	1.5594
4	*p*	2	3	120 (0.009)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.98	4.65	33.98	1.5470
5	*p*	2	4	154 (0.05)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	46.37	4.67	32.88	1.5414
6	*p*	2	5	143 (0.04)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.61	5.26	31.60	1.5368
7	*p*	3	0	44.0–45.0	$C_{10}H_{11}IO_4$	41.40	3.76	36.46	41.65	3.98	36.76	
8	*p*	3	1	131 (0.02)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	43.42	4.36	35.52	1.5542
9	*p*	3	2	126 (0.007)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.92	4.84	34.63	1.5479
10	*p*	3	2[a]	154 (0.05)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.82	4.71	34.17	1.5450
11	*p*	3	3	129 (0.008)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	45.93	4.78	32.83	1.5420
12	*p*	3[b]	3	135 (0.009)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	46.21	4.78	32.04	1.4530
13	*p*	3	4	154 (0.05)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.43	5.21	31.73	1.5380
14	*p*	3	c	30.0–31.8	$C_{13}H_{15}IO_5$	41.28	4.00	33.56	41.43	4.13	33.37	
15	*p*	4	0	123 (0.02)	$C_{13}H_{15}IO_4$	43.11	4.17	35.04	42.93	4.37	35.68	1.5548
16	*p*	4	1	138 (0.04)	$C_{14}H_{17}IO_4$	44.69	4.56	33.74	44.51	4.38	34.39	1.5480
17	*p*	4	2	151 (0.04)	$C_{15}H_{19}IO_4$	46.17	4.91	32.52	45.89	4.97	32.69	1.5427
18	*p*	4	3	157 (0.009)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.52	5.33	31.57	1.5394
19	*p*	4	3[d]	142 (0.02)	$C_{16}H_{21}IO_4$	47.53	5.24	31.40	47.77	5.04	31.52	1.5362

[a] $(CH_2)_nCH_3$ = isopropyl. [b] $(CH_2)_m$ = $-CH_2CH(CH_3)-$. [c] $(CH_2)_nCH_3$ = $-CH_2OCH_3$. [d] $(CH_2)_nCH_3$ = isobutyl.

Method B. 2-Acetoxyethyl *o*-Iodobenzoate (2).—To a stirred solution of 61.0 g (0.228 mole) *o*-iodobenzoyl chloride in 350 ml of dry pyridine at 60° was added 23.9 g (0.228 mole) of 2-hydroxyethyl acetate during 5 min. The mixture was stirred on a steam bath for 5 hr. After transferring to a beaker and cooling in a salt–ice bath, 880 ml of cold 6 *N* H_2SO_4 was added dropwise. After decanting the top layer, the black aqueous phase was extracted with ether. The combined organic phase was washed successively with cold H_2O, cold 5% K_2CO_3, and saturated NaCl and dried (Drierite). Acidification of the basic washes gave 24.8 g of *o*-iodobenzoic acid. After charcoaling and removal of solvent there remained a red oil which was distilled to give 28.8 g (38%) of **2**. Taking into account recovered *o*-iodobenzoic acid the yield of **2** was 67%. An aliquot was fractionally distilled to furnish an analytical sample.

Method C. 4-Propionoxybutyl *p*-Iodobenzoate (16).—Dimethylformamide (300 ml) which had been dried over silica gel was heated to 110° and 43.2 g (0.159 mole) of finely powdered sodium *p*-iodobenzoate was added rapidly with stirring. In one portion 28.0 g (0.170 mole) of 4-chlorobutyl propionate[5] was added and stirring at 105–115° continued for 20 hr. The cooled mixture was poured into ice water and the aqueous layer was decanted from the oil and extracted with hexane. The combined organic extracts were washed successively with cold water, cold 5% K_2CO_3, cold 2% HCl, 10% $NaHSO_3$, water, and saturated NaCl. After drying over Drierite and treatment with decolorizing charcoal, the solvent was removed at reduced pressure to give 55.5 g of colorless oil. Distillation gave 46.6 g (78%) of **16**. An aliquot of the distillate was fractionally distilled to furnish an analytical sample.

Acknowledgment.—The authors are indebted to Dr. J. Hoppe, Mr. A. Brousseau, Mr. J. Romano, and Mr. J. Healey for the results of the biological studies and to Mr. K. Fleischer and staff for analytical services.

(5) J. B. Cloke and F. J. Pilgrim, *J. Am. Chem. Soc.*, **61**, 2667 (1939).

Some Quinolines Containing a Cyclic Hydroxamic Acid Group

D. NOBLE AND D. G. WIBBERLEY[1]

School of Pharmacy, Sunderland Technical College, Sunderland, Durham, England

Received June 14, 1966

1,2-Dihydro-1-hydroxy-2-oxoquinolines, quinolines containing a cyclic hydroxamic acid group, exhibit antibacterial activity,[2] and the nature of substituents at positions 3 and 4 of the quinoline ring appears to influence this activity.[2c] We have synthesized a series of 3-alkyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinolines by the route outlined in Scheme I.

Attempts to convert the 3-alkyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinolines into their fully aromatic counterparts have so far failed. Where aromatization was successful it was always accompanied by deoxygenation to yield a 3-alkylcarbostyril.

Experimental Section[3]

The compounds and methods are listed in Tables I and II.

Ethyl α-Alkyl-α-*o*-nitrobenzylmalonates. Method A.—*o*-Nitrobenzyl bromide (0.0525 mole) was added over 10 min at room temperature to a stirred solution of the appropriate α-alkylmalonate (0.05 mole) and sodium ethoxide (0.05 mole) in ethanol (30 ml). The mixture was stirred for 1 hr, the solvent was evaporated *in vacuo*, and the residue was triturated with

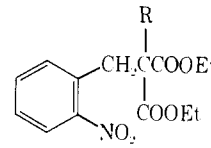
(1) Communications regarding this paper should be addressed to the Pharmacy Department, The University of Aston in Birmingham, Gosta Green, Birmingham 4, England.

(2) (a) G. T. Newbold and F. S. Spring, *J. Chem. Soc.*, 1864 (1948); (b) K. G. Cunningham, G. T. Newbold, F. S. Spring, and J. Stark, *J. Chem. Soc.*, 2091 (1949); (c) W. A. Lott and E. Shaw, *J. Am. Chem. Soc.*, **71**, 70 (1949); (d) R. T. Coutts, D. Noble, and D. G. Wibberley, *J. Pharm. Pharmacol.*, **16**, 773 (1964); (e) R. T. Coutts, W. N. Pilkethly, and D. G. Wibberley, *J. Pharm. Sci.*, **54**, 792 (1965).

(3) Microanalyses by Drs. G. Weiler and F. B. Strauss of the Microanalytical Laboratory, Oxford, England.

TABLE I

α-ALKYL-α-o-NITROBENZYLMALONATES

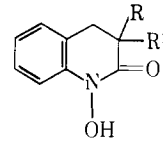


R	Yield, %[a] Method A	Method B	Bp, °C (mm)	Formula	Calcd, % C	H	N	Found, % C	H	N
Ethyl	60.1	...	158 (0.7)	$C_{16}H_{21}NO_6$	59.44	6.50	4.33	59.58	6.65	4.70
n-Propyl	53.1	...	164 (0.9)	$C_{17}H_{23}NO_6$	60.53	6.82	4.16	60.33	6.77	4.42
Isopropyl	4.0	43.3	174 (2.0)	$C_{17}H_{23}NO_6$	60.53	6.82	4.16	60.45	6.88	4.24
n-Butyl	67.2	...	188 (1.6)	$C_{18}H_{25}NO_6$	61.54	7.12	3.99	61.77	7.19	4.45
Isobutyl	...	50.2	180 (1.75)	$C_{18}H_{25}NO_6$	61.54	7.12	3.99	61.39	6.98	4.12
sec-Butyl	3.9	37.2	196 (4.5)	$C_{18}H_{25}NO_6$	61.54	7.12	3.99	61.43	6.78	4.48

[a] After one distillation.

TABLE II

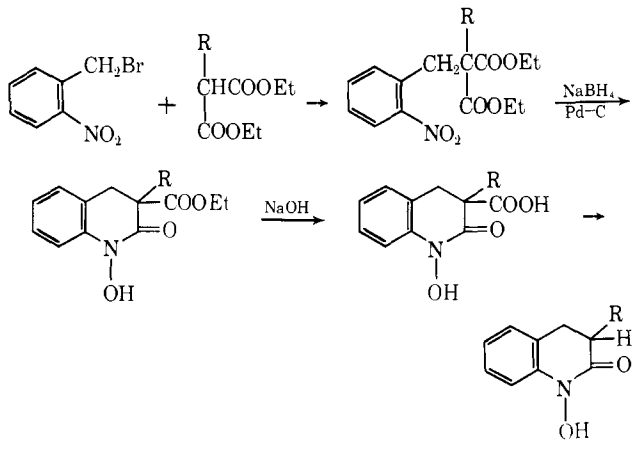
1,2,3,4-TETRAHYDRO-1-HYDROXY-2-OXOQUINOLINES



R	R¹	Method	Yield, %	Bp (mm) or mp, °C	Formula	Calcd, % C	H	N	Found, % C	H	N
Ethyl	$CO_2C_2H_5$	C	53.6	178 (1.8)[a]	$C_{14}H_{17}NO_4$	63.88	6.46	5.32	63.93	6.56	4.95
n-Propyl	$CO_2C_2H_5$	C	72.5	62–63	$C_{15}H_{19}NO_4$	64.99	6.86	5.05	64.77	6.81	4.83
Isopropyl	$CO_2C_2H_5$	C	76.8	108–109	$C_{15}H_{19}NO_4$	64.99	6.86	5.05	64.67	6.60	5.22
n-Butyl	$CO_2C_2H_5$	C	79.8	184 (2.2)	$C_{16}H_{21}NO_4$	65.98	7.22	4.81	66.41	7.37	5.05
Isobutyl	$CO_2C_2H_5$	C	71.7	168 (1.5)	$C_{16}H_{21}NO_4$	65.98	7.22	4.81	66.16	7.40	4.71
sec-Butyl	$CO_2C_2H_5$	C	72.5	82–83	$C_{16}H_{21}NO_4$	65.98	7.22	4.81	65.80	6.95	4.64
Ethyl	CO_2H	D	76.0	140 dec	$C_{12}H_{13}NO_4$	61.27	5.53	5.96	60.99	5.73	5.60
n-Propyl	CO_2H	D	73.2	127 dec	$C_{13}H_{15}NO_4$	62.65	6.02	5.62	62.61	6.16	5.71
Isopropyl	CO_2H	D	85.4	103–106	$C_{13}H_{15}NO_4 \cdot H_2O$[c]	58.43	6.37	5.24	58.34	6.02	4.92
				131 dec[b]	$C_{13}H_{15}NO_4 \cdot 0.5H_2O$[d]	60.47	6.20	5.43	60.19	6.06	5.49
n-Butyl	CO_2H	D	72.1	97–99	$C_{14}H_{17}NO_4$	63.88	6.46	5.32	64.12	6.59	5.51
Isobutyl	CO_2H	D	85.4	111 dec[b]	$C_{14}H_{17}NO_4 \cdot H_2O$	59.78	6.76	4.98	60.70	6.88	5.27
sec-Butyl	CO_2H	D	88.4	120 dec[b]	$C_{14}H_{17}NO_4 \cdot H_2O$	59.78	6.76	4.98	59.90	6.55	5.35
Ethyl	H	E	49.9	134 (1.0)	$C_{11}H_{13}NO_2$	69.12	6.81	7.33	69.23	6.68	7.36
n-Propyl	H	E	32.1	145 (0.8)	$C_{12}H_{15}NO_2$	70.25	7.32	6.83	70.29	7.32	6.83
Isopropyl	H	E	33.3	118–119[b]	$C_{12}H_{15}NO_2$	70.25	7.32	6.83	70.00	7.33	6.92
n-Butyl	H	E	30.8	155 (1.2)	$C_{13}H_{17}NO_2$	71.24	7.76	6.39	71.51	7.72	6.29
Isobutyl	H	E	31.6	83–84	$C_{13}H_{17}NO_2$	71.24	7.76	6.39	70.96	7.85	6.71

[a] Solidified slowly on standing. [b] With preliminary shrinking. [c] Dried at room temperature under vacuum. [d] Dried at 80° under vacuum.

SCHEME I



water and acidified with acetic acid. The product was extracted into chloroform, and the extract was dried and distilled.

Method B.—A mixture of the appropriate α-alkylmalonate (0.05 mole) in dry benzene (40 ml) and sodium (0.05 mole) was heated under reflux until solution was complete. *o*-Nitrobenzyl bromide (0.0525 mole) was added over 10 min and the mixture was heated under reflux on the water bath for a further 10 min. The solvent was evaporated and the product was isolated as in method A.

Reductive Cyclization of α-Alkyl-α-*o*-nitrobenzylmalonates. Method C.[14]—A stream of nitrogen was bubbled through a vigorously stirred solution of $NaBH_4$ (0.05 mole) in 0.5 *N* NaOH (6 ml/g of *o*-nitro ester). Palladium–charcoal (10%) was shaken with a little water to form a slurry and this was carefully added to the borohydride solution. A solution of the *o*-nitro ester (0.025 mole) in dioxane (3 ml/g of *o*-nitro ester) was added over 5 min and the mixture was stirred for a further 1 hr and filtered through Celite. The filtrate was acidified with concentrated HCl to yield the cyclic hydroxamic acid either as an oil or as a solid. Oily products were extracted into chloroform and distilled, and solids were filtered, dried, and recrystallized.

[14] A similar method has been previously described[2d] but molar proportions were incorrectly stated, and the present method avoids a possible fire hazard.

Hydrolysis of the 3-Alkyl-3-ethoxycarbonyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinolines. Method D.—The ester to be hydrolyzed was heated under reflux with 5 *N* NaOH (4 ml/g) for a time dependent on the nature of the 3-alkyl group (20 min for ethyl, *n*-propyl, *n*-butyl; 15 min for isopropyl; 10 min for *sec*-butyl and isobutyl). The solution was poured into dilute HCl and ice to yield the corresponding 3-carboxylic acid.

Decarboxylation of the 3-Alkyl-1,2,3,4-tetrahydro-1-hydroxy-2-oxoquinoline-3-carboxylic Acids. Method E.—The carboxylic acid was dissolved in warm diphenyl ether (10 g/g of acid) and the temperature carefully was raised until CO_2 evolution commenced. This temperature was maintained until the decomposition was complete, and the solution was cooled and diluted with ether. The hydroxamic acid was extracted into 1 *N* NaOH and liberated by addition of acid.

Metal Complexes of 2′,3′-*O*-Isopropylidene-6-thioinosine[1a]

ALEXANDER HAMPTON[1b] AND J. C. FRATANTONI

Division of Biological Chemistry, Sloan-Kettering Institute for Cancer Research, New York 21, New York

Received May 5, 1966

Some metabolic inhibitions brought about by the antineoplastic agent 6-mercaptopurine are attributable to its anabolite, 6-thioinosinic acid.[2] Among other effects, this nucleotide enhances inhibition of adenylosuccinase by cupric ions,[3] possibly by formation of a cupric–6-thioinosinate complex. Isopropylidene-6-thioinosine forms 2:1 complexes with copper and nickel in which the metal is presumably bound to the sulfur and to N-7 of the purine moiety, in analogy to copper and nickel chelates of 8-hydroxyquinoline and a series of aza analogs of 8-hydroxyquinoline related to 6-hydroxypurine.[4]

Experimental Section

Nickel Complex of 9-(2,3-*O*-Isopropylidene-β-D-ribofuranosyl)-6-mercaptopurine.—To a solution of 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-mercaptopurine[5] (48.6 mg, 0.15 mmole) in water (10 ml) containing 0.15 ml of 1 *N* NaOH was added, at *ca.* 45°, 0.15 ml of 0.5 *M* $NiCl_2$. The yellow-green suspension was cooled, extracted with three 25-ml portions of chloroform, and the $CHCl_3$ solution was washed with water (25 ml), dried (Na_2SO_4), and evaporated to dryness. The dark solid (51 mg) was dissolved in acetone; addition of petroleum ether (bp 40–60°) gave a yellow-green precipitate which was collected by centrifugation and washed with acetone–petroleum ether (1:1).

Anal. Calcd for $C_{26}H_{30}N_8NiO_8S_2$: C, 44.27; H, 4.29; N, 15.89; Ni, 8.32. Found for material dried at 90° (0.01 mm): C, 44.38; H, 4.55; N, 16.00; Ni, 8.09.

The complex slowly decomposed without melting at 300°. In ethanol, it showed absorption maxima at 228 and 322 mμ, A_{322}/A_{228} 0.79, and a minimum at 265 mμ.

Copper complex of 9-(2,3-*O*-isopropylidene-β-D-ribofuranosyl)-6-mercaptopurine was prepared from $CuSO_4$ and the above nucleoside by the procedure used for the nickel complex. The complex was isolated by extraction with chloroform and obtained as a yellow precipitate by addition of petroleum ether to its solution in acetone.

Anal. Calcd for $C_{26}H_{34}CuN_8O_8S_2 \cdot 3CH_3COCH_3$: C, 47.53; H, 5.95; Cu, 7.19; N, 12.68. Found for material dried at 60° (0.1 mm): C, 49.34; H, 5.60; Cu, 6.70; N, 13.20.

Acknowledgment.—The authors thank Dr. George Bosworth Brown for continued encouragement.

The Interaction of Alkyl 2-Naphthyl Ketones with Isatin[1]

RONALD D. GARRETT,[2] AND HENRY R. HENZE

Department of Chemistry, The University of Texas, Austin, Texas

Received June 11, 1966

Serious pharmacological side effects noted to occur with the administration of 2-phenylcinchoninic acid[3,4] have led to intensified research in the synthesis of analogs of this compound.[5,6]

In this investigation, a homologous series of 3-alkyl-2-(2-naphthyl)cinchoninic acids, extended through the hendecyl member, has been prepared under Pfitzinger reaction conditions, which invalidates the assumption of Bau-Hoi, *et al.*,[7] that compounds of type $RCO(CH_2)_nCH_3$ in which R represents a 2-naphthyl group and *n* is an integer greater than 2 would be so sterically hindered that ring closure could not occur.

Experimental Section

C,H,N analyses were performed by Huffman Laboratories, Inc., Wheatridge, Colo. Melting points were determined by the capillary method and are corrected. The molecular weight of each cinchoninic acid was determined by the nonaqueous titration procedures as outlined by Fritz.[8]

General Procedure for 2-Naphthyl Ketone Synthesis.—All ketones in this investigation were prepared in good yield by the interaction of 2-naphthoyl chloride with the appropriate dialkylcadmium reagent.

General Procedure for Preparation of 5-Substituted 5-(2-Naphthyl)hydantoin.—The 300-ml Pyrex liner of a monel-metal bomb was charged with 0.01 mole of a 2-naphthyl ketone dissolved in 100 ml of dimethylformamide (DMF). To this solution was added 1.5 equiv of KCN, dissolved in the least amount of H_2O, and 4 equiv of $(NH_4)_2CO_3$. The bomb was quickly closed and placed in an oven regulated at 115° for 24 hr. The reaction mixture was then rendered alkaline by the addition of 10% aqueous NaOH and any unreacted ketone was subsequently ether extracted. Acidification of the aqueous layer with concentrated HCl caused precipitation of the hydantoin derivative.

General Procedure for Preparation of 3-Substituted 2-(2-Naphthyl)cinchoninic Acids.—A reaction solvent was prepared from 12 g of 85% KOH, 15 ml of water, and 85 ml of ethyl alcohol. To this solution, 0.05 mole of a 2-naphthyl ketone and 0.07 mole of isatin was added, and the resulting mixture was refluxed for 96 hr with rapid stirring. The ethyl alcohol was then removed by distillation and the residual dark brown solution was diluted with 50 ml of water and ether extracted to remove any unreacted ketone. Adjustment of the pH of the aqueous layer to 8.0 with concentrated HCl produced a gelatinous precipitate which was removed by suction filtration, found to be an inorganic salt, and discarded. Subsequent adjustment of the pH of the filtrate to 5.0 with concentrated HCl resulted in the formation of a thick granular tan precipitate which, after decolorization and recrystallization from ethanol, proved to be the desired cinchoninic acid. Results are summarized in Table I.

(1) (a) This work was supported by funds from the National Cancer Institute, U. S. Public Health Service (Grant CY-3190), and from the Atomic Energy Commission (Contract No. AT(30-1)-910). (b) University of Alberta Cancer Research Unit, McEachern Laboratory, Edmonton, Alberta, Canada.

(2) R. W. Brockman and E. P. Anderson, *Ann. Rev. Biochem.*, **32**, 463 (1963).

(3) W. A. Bridger and L. D. Cohen, *Biochim. Biophys. Acta*, **73**, 514 (1963).

(4) A. Albert and A. Hampton, *J. Chem. Soc.*, 505 (1954).

(5) A. Hampton, *J. Am. Chem. Soc.*, **83**, 3640 (1961).

(1) Constructed from a portion of the Ph.D. dissertation of R. D. Garrett at the University of Texas.

(2) The University of Tennessee Medical Units, Memphis, Tenn.

(3) D. G. Mandel and C. Davison, "Drill's Pharmacology in Medicine," J. R. DiPalma, Ed., 3rd ed., McGraw-Hill Book Co., Inc., New York, N. Y., 1965, p 319.

(4) "The Merck Index," 7th ed, Merck & Co., Inc., Rahway, N. J., 1960, p 263.

(5) W. Pfitzinger, *J. Prakt. Chem.*, [2] **33**, 100 (1886); **38**, 583 (1888); **56**, 283 (1897); **66**, 263 (1902).

(6) H. R. Henze and D. W. Carroll, *J. Am. Chem. Soc.*, **76**, 4582 (1954).

(7) (a) N. P. Buu-Hoi, *J. Chem. Soc.*, 795 (1946); (b) N. P. Buu-Hoi and P. Cagniant, *Bull. Soc. Chim. France*, 123 (1946); (c) N. P. Buu-Hoi and R. Royer, *J. Chem. Soc.*, 374 (1948).

(8) J. S. Fritz, "Acid-Base Titrations in Nonaqueous Solvents," G. Frederick Smith Chemical Co., Columbus, Ohio, 1952, pp 13–14.