periodate (75 ml.) and the volume was adjusted to 500 ml. by addition of water. Periodate consumption and formic acid production determined as before were: periodate consumption: 82% (21 hr.), 91% (41 hr.), 96% (64 hr.), 97% (112 hr.), 99% (7 days), 103% (16 days), 104% (22 days, constant for further 4 days); formic acid production: 67% (21 hr.), 83% (41 hr.), 89.5% (64 hr.), 96% (88 hr.), 100% (112 hr., constant for further 10 days). The theoretical values were calculated on the basis of 13 glucose residues per average repeating unit which consume 14 moles of periodate and liberate 1 mole of formic acid.

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ST. PAUL, MINN.

[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE AND RENSSELAER POLYTECHNIC INSTITUTE]

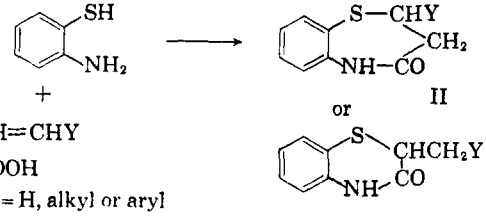
A New Synthesis of Some 2-Substituted-3,4-dihydro-3-oxo-1,4,2-benzothiazine Derivatives

BY FRED. K. KIRCHNER[1] AND E. JOHN ALEXANDER[2]

RECEIVED JULY 29, 1958

It has been found that β-benzoylacrylic acids, maleamic acids, maleanilic acids and maleic acid monophenylhydrazides condense with 2-aminobenzenethiol to form six- rather than seven-membered heterocyclic rings in a manner analogous to maleic acid.

Mills and Whitworth[3] reported that 2-aminobenzenethiol reacted with simple α,β-unsaturated acids (Ia) to produce 4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepines (II). However, treatment of 2-aminobenzenethiol with maleic acid resulted in the formation of 3,4-dihydro-3-oxo-1,4,2-benzothiazine-2-acetic acid (IIIa).[3]



Ia, Y = H, alkyl or aryl
Ib, Y = COAr
Ic, Y = CONRR′
Id, Y = CONRAr
Ie, Y = CONHNHAr

IIIa, Y = COOH
IIIb, Y = COAr
IIIc, Y = $CONHC_6H_5$

The present investigation was undertaken to determine the structure of the products formed when 2-aminobenzenethiol reacted with more complex α,β-unsaturated acids, *e.g.*, β-benzoylacrylic acids (Ib),[4-6] maleamic acids (Ic),[7] maleanilic acids (Id)[8] and maleic acid monophenylhydrazides (Ie).[9]

We have found, that when 2-aminobenzenethiol reacted with a β-benzoylacrylic acid (Ib), 3,4-dihydro-3-oxo-2-phenacyl-1,4,2-benzothiazine derivatives (IIIb, Table I) could be isolated in good yield. With the exception of compounds 7, 9, 10, 12 and 13, all of the compounds in Table I were prepared by a general technique (see Experimental part).

The 2-(4′-aminophenacyl) derivative (no. 7), which was prepared from the acetamido compound (no. 8), was acylated with butyric (no. 9) and hexanoic anhydride (no. 10). Compounds 12 and 13 were prepared by the reduction of the adducts formed from 4-chloro-2-nitrobenzenethiol[10] and the corresponding β-benzoylacrylic acid derivative.

The oxime was the only ketone derivative of 3,4-dihydro-3-oxo-2-phenacyl-1,4,2-benzothiazine that could be prepared. This was converted by a Beckmann rearrangement to 3,4-dihydro-3-oxo-1,4,2-benzothiazine-2-acetanilide (IIIc, no. 42) which was also formed directly from the acid IIIa and by the condensation of maleanilic acid (no. 25) and 2-aminobenzenethiol. This fact, coupled with the observations that the phenacyl derivative (no. 1) could be prepared alternatively from α-chloro-β-benzoylpropionic acid[11] and that compound 1 failed to acetylate when boiled with acetic anhydride,[12] substantiated the inference that 3,4-dihydro-3-oxo-2-phenacyl-1,4,2-benzothiazines were formed from the condensation of β-benzoylacrylic acids and 2-aminobenzenethiol.

When maleamic acids[7] (Ic, Table II), maleanilic acids[8] (Id, Table II), or maleic acid monophenylhydrazides[9] (Ie, Table IV) were treated with 2-aminobenzenethiol the condensation products[13] were easily isolated. This synthesis was also carried out by mixing an amine, aniline or phenylhydrazine derivative with maleic anhydride in pyridine and then adding 2-aminobenzenethiol. The fact that the condensation products were amides (Table III), anilides (Table III) and phenylhydrazides (Table

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(2) This paper is based on a thesis submitted by E. John Alexander to the Graduate School of Rensselaer Polytechnic Institute in partial fulfillment of the requirements for the degree of Doctor of Philosophy, May, 1956.

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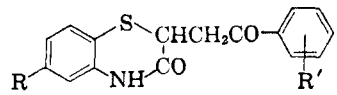
(12) Mills and Whitworth have shown (ref. 3) that 4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepines readily acetylated in the 5-position under these conditions.

(13) The nature of by-products produced during these condensations is still undergoing investigation, the results of which will be reported at a later date.

TABLE I

3,4-DIHYDRO-3-OXO-2-PHENACYL-1,4,2-BENZOTHIAZINE DERIVATIVES



No.	R	R′	Yield,[a] %	M.p.,[b] °C.	Recrystn. solvent[f]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	H	H	80	173–175	T	$C_{16}H_{13}NO_2S$	4.94	4.94	11.32	10.95
2	H	4-CH_3	78	205–206	AA–W	$C_{17}H_{15}NO_2S$	4.71	4.78	10.78	11.20
3	H	4-iso-C_3H_7	39	157–160	M–W	$C_{19}H_{19}NO_2S$	4.30	4.35	9.85	9.80
4	H	4-*n*-C_4H_9	60	131–132	A	$C_{20}H_{21}NO_2S$	4.13	4.20	9.44	9.08
5	H	4-*n*-C_8H_{17}	83	117–119	A	$C_{24}H_{29}NO_2S$	3.54	3.57	8.11	7.99
6	H	4-*n*-$C_{12}H_{25}$	85	118–120	A	$C_{28}H_{37}NO_2S$	3.10	3.14	7.10	6.79
7	H	4-H_2N	46	194–196	Al–W	$C_{16}H_{14}N_2O_2S$	9.39	9.53	10.74	11.15
8	H	4-CH_3CONH	64	236–238	Ac[d]	$C_{18}H_{16}N_2O_3S$	8.23	8.33	9.42	9.54
9	H	4-$CH_3(CH_2)_2CONH$	83	218–220	Ac–W	$C_{20}H_{20}N_2O_3S$	7.61	7.51	8.70	8.86
10	H	4-$CH_3(CH_2)_4CONH$	82	175–185	Ac–Al–C	$C_{22}H_{24}N_2O_3S$	7.07	7.31	8.08	8.12
11	H	4-F	62	171–173	T	$C_{16}H_{12}FNO_2S$	4.65	4.57	10.64	11.07
12	Cl	H	28	215–219	T	$C_{16}H_{12}ClNO_2S$	4.41	4.31	10.09	10.22
13	Cl	4-F	54	243–245	AA–W	$C_{16}H_{11}ClFNO_2S$	4.17	3.97	9.55	9.37
14	H	4-Cl	77	193–195	D–W	$C_{16}H_{12}ClNO_2S$	11.16[e]	10.85	10.09	10.29
15	H	3,4-diCl	56	192–194	D–W	$C_{16}H_{11}Cl_2NO_2S$	3.98	4.14	20.13[e]	20.05
16	H	2,4-diCl	70	186–190	T	$C_{16}H_{11}Cl_2NO_2S$	3.98	3.90	20.13[e]	20.25
17	H	2,4-diHO	39	253[c]	Ac–W	$C_{16}H_{13}NO_4S$	4.44	4.37	10.17	10.14
18	H	4-CH_3O	71	194–196	D	$C_{17}H_{15}NO_3S$	4.47	4.55	10.23	10.01
19	H	4-CH_3S	73	191–195	X	$C_{17}H_{15}NO_2S_2$	4.25	4.16	19.46	19.89
20	H	3-O_2N	57	191–194	D–W	$C_{16}H_{12}N_2O_4S$	4.26[g]	4.26	9.76	9.64

[a] All yields are based on the analytically pure sample. [b] All melting points are corrected. [c] Melts with decomposition. [d] As a suspension. [e] Chlorine analysis. [f] A = abs. ethanol; AA = acetic acid; Ac = acetone; Al = 95% ethanol; C = Skellysolve C; D = dioxane; M = methanol; T = toluene; W = water; and X = xylene. [g] The nitrogen in the nitro group was determined by reduction with titanium dichloride.

TABLE II

MALEAMIC AND MALEANILIC ACIDS CHCONRR′ ‖ CHCOOH

No.	R	R′	Yield,[a] %	M.p.,[b] °C.	Recrystn. solvent[m]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Neut. equiv.[j] Calcd.	Neut. equiv.[j] Found
21	H	H[c,l]	..	.....	....	$C_4H_5NO_3$	..	..	....	....
22	C_2H_5	C_2H_5[d]	..	.....	....	$C_8H_{13}NO_3$	..	..	....	....
23	H	$CH_3(CH_2)_7$	96	80–82	B–C	$C_{12}H_{21}NO_3$	6.16	6.05	[e]	....
24	H	C_6H_{11}	60	150–153	Ch–E	$C_{10}H_{15}NO_3$	7.10	6.93	[e]	....
25	H	C_6H_5[f,l]	..	.....	....	$C_{10}H_9NO_3$	..	..	....	....
26	CH_3	C_6H_5	78	88–92	E[n]	$C_{11}H_{11}NO_3$	6.83	6.77	205	212
27	H	4-FC_6H_4	95	204–206	A[n]	$C_{10}H_8FNO_3$	6.70	6.58	209	213
28	H	2-ClC_6H_4[g]	..	.....	....	$C_{10}H_8ClNO_3$	..	..	....	....
29	H	3-ClC_6H_4[g]	..	.....	....	$C_{10}H_8ClNO_3$	..	..	....	....
30	H	4-ClC_6H_4[g]	..	.....	....	$C_{10}H_8ClNO_3$	..	..	....	....
31	H	2,3-$Cl_2C_6H_3$	54	138–139	M–B	$C_{10}H_7Cl_2NO_3$	5.39	5.34	260	262
32	H	3,4-$Cl_2C_6H_3$	81	211–212	M–A	$C_{10}H_7Cl_2NO_3$	5.39	5.28	27.26[k]	27.38
33	H	2,4-$Cl_2C_6H_3$	95	175–177	Ch–M	$C_{10}H_7Cl_2NO_3$	5.39	5.39	27.26[k]	27.48
34	H	2,5-$Cl_2C_6H_3$	92	144–146	Ch[n]	$C_{10}H_7Cl_2NO_3$	5.39	5.32	27.26[k]	27.05
35	H	3-Cl-4-$CH_3C_6H_3$	100	196–197[i]	E[n]	$C_{11}H_{10}ClNO_3$	5.84	5.83	14.79[k]	14.74
36	H	4-BrC_6H_4	75	197–199	E[n]	$C_{10}H_8BrNO_3$	5.19	5.23	270	271
37	H	4-$C_2H_5OC_6H_4$[h]	..	.....	....	$C_{12}H_{13}NO_4$	..	..	....	....
38	H	4-$CH_3SC_6H_4$	98	175–178	E[n]	$C_{11}H_{11}NO_3S$	5.90	5.80	237	231
39	H	4-$C_2H_5OCOC_6H_4$	50	191–192[i]	E[n]	$C_{13}H_{13}NO_5$	5.32	5.36	263	263

[a] All yields are based on the analytical by pure sample. [b] All melting points are corrected. [c] M. Frankel, Y. Liwschitz and Y. Amiel, THIS JOURNAL, **75**, 330 (1953). [d] M. L. Stein and G. Giacomello, *Ricerca sci.*, **22**, 1007 (1952); *C. A.*, **47**, 6872d (1953). [e] Calcd.: C, 63.40; H, 9.31. Found: C, 63.42; H, 9.27. [f] D. Pressman, J. H. Bryden and L. Pauling, THIS JOURNAL, **70**, 1352 (1948). [g] W. Herz, *ibid.*, **67**, 1854 (1945). [h] G. LaParola, *Gazz. chim. ital.*, **64**, 919 (1934). [i] Melts with decomposition. [j] Neutralization equivalent. [k] Chlorine analysis. [l] Sample generously supplied by the Cyanamid Co. [m] A = abs. ethanol; B = benzene; C = Skellysolve C; Ch = chloroform; E = ether; and M = methanol. [n] As a suspension. [o] Calcd.: C, 60.89; H, 7.67. Found: C, 61.10; H, 7.57.

V) of 3,4-dihydro-3-oxo-1,4,2-benzothiazine-2-acetic acid (IIIa) was proved when it was found that identical compounds could be prepared from IIIa by anhydride procedures.[14,15]

Since the structural proof of the compounds we have prepared has been based mainly on 3,4-dihydro-3-oxo-1,4,2-benzothiazine-2-acetic acid (IIIa), the structural characterization of this compound

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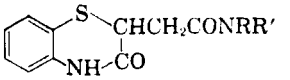
TABLE III

AMIDES AND ANILIDES OF 3,4-DIHYDRO-3-OXO-1,4,2-BENZOTHIAZINE-2-ACETIC ACID

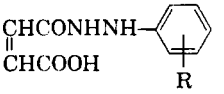


No.	R	R'	Yield,[a] %	M.p.,[b] °C.	Recrystn. solvent[i]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
40	H	H	30[d]	223–225	A	$C_{10}H_{10}N_2O_2S$	12.61	12.38	14.42	14.62
41	C_2H_5	C_2H_5	35[d]	156–158	M	$C_{14}H_{18}N_2O_2S$	10.07	10.11	11.52	11.33
42	H	C_6H_5	37,[d] 62[f]	265–270	P-W	$C_{16}H_{14}N_2O_2S$	9.39	9.39	10.75	10.48
43	CH_3	C_6H_5	40[d]	172–173	A-B-C	$C_{17}H_{16}N_2O_2S$	8.97	8.86	10.26	10.20
44	H	$CH_3(CH_2)_7$	26[d]	188–191	M	$C_{18}H_{26}N_2O_2S$	8.38	8.18	9.58	9.51
45	H	C_6H_{11}	8[e]	250–252	M-D	$C_{16}H_{20}N_2O_2S$	9.20	9.17	10.53	10.33
46	H	4-FC_6H_4	25[d]	267–270	P-B-C	$C_{16}H_{13}FN_2O_2S$	8.86	8.75	10.13	10.47
47	H	2-ClC_6H_4	13.5[e]	232–237	P-A-W	$C_{16}H_{13}ClN_2O_2S$	8.42	8.31	9.63	9.80
48	H	3-ClC_6H_4	24[e]	229–230	A	$C_{16}H_{13}ClN_2O_2S$	8.42	8.46	9.63	9.43
49	H	4-ClC_6H_4	36,[d] 12[e]	276–282	P	$C_{16}H_{13}ClN_2O_2S$	8.42	8.60	9.63	9.57
50	H	2,3-$Cl_2C_6H_3$	45[d]	270–272	P-W	$C_{16}H_{12}Cl_2N_2O_2S$	7.63	7.56	19.31[h]	19.44
51	H	3,4-$Cl_2C_6H_3$	34[d]	242–244	P-W	$C_{16}H_{12}Cl_2N_2O_2S$	7.63	7.59	19.31[h]	19.56
52	H	2,4-$Cl_2C_6H_3$	23[e]	241–242	P-B-C	$C_{16}H_{12}Cl_2N_2O_2S$	7.63	7.50	19.31[h]	19.75
53	H	2,5-$Cl_2C_6H_3$	41.5[d]	261–165	P-B-C	$C_{16}H_{12}Cl_2N_2O_2S$	7.63	7.55		...
54	H	3-Cl-4-$CH_2C_6H_3$	40[d]	240–242	P-W	$C_{17}H_{15}ClN_2O_2S$	8.08	8.00	10.22[h]	10.19
55	H	4-BrC_6H_4	42[d]	284[k]	P-W	$C_{16}H_{13}BrN_2O_2S$	7.43	7.50	8.50	8.31
56	H	4-$C_2H_5OC_6H_4$	23,[c] 29[f]	267–269	P-B	$C_{18}H_{18}N_2O_3S$	8.18	8.12	9.36	9.65
57	H	4-$CH_3SC_6H_4$	42[d]	263–265	M[m]	$C_{17}H_{16}N_2O_2S_2$	8.13	8.01	18.62	19.00
58	H	4-$C_2H_5OCOC_6H_4$	22[e]	205–206	M	$C_{19}H_{18}N_2O_4S$	7.56	7.42	[j]	...
59	H	4-$H_2NNHCOC_6H_4$	55[g]	261–263	P[m]	$C_{17}H_{16}N_4O_3S$	15.72	15.50	8.99	8.77
60	H	4-$C_2H_5SC_6H_4$	58[f]	235–237	P-W	$C_{18}H_{18}N_2O_2S_2$	7.82	7.88	17.89	17.90
61	H	4-$CH_3SO_2C_6H_4$	52[f]	234–236	P-W	$C_{17}H_{16}N_2O_4S_2$	7.44	7.40	17.03	16.99
62	H	4-$NH_2SO_2C_6H_4$	69[f]	280–283	P-W	$C_{16}H_{15}N_3O_4S_2$	11.13	10.98	16.99	17.22

In all cases yields are based on the analytically pure sample [b] All melting points are corrected. [c] Prepared by method A (see Experimental part). [d] Prepared by method B (see Experimental part). [e] Prepared by method C (see Experimental part). [f] Prepared by method D (see Experimental part). [g] Preparative procedure given in Experimental part. [h] Chlorine analysis. [i] Calcd.: C, 52.32; H, 3.29. Found: C, 52.50; H, 3.07. [j] Calcd.: C, 61.60; H, 4.90. Found: C, 61.84; H, 4.90. [k] Melts with decomposition. [l] A = abs. ethanol; B = benzene; C = Skellysolve C; D = dioxane; M = methanol; P = pyridine; and W = water. [m] As a suspension.

TABLE IV

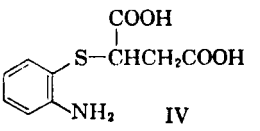
MALEIC ACID MONOPHENYLHYDRAZIDES



No.	R	Yield,[a] %	M.p.,[b] °C.	Recrystn. solvent[i]	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Halogen, % Calcd.	Halogen, % Found
63	H[c]	..	.....	...	$C_{10}H_{10}N_2O_3$	...	...	....	....
64	4-F	42[d]	155–156	A-B	$C_{10}H_9FN_2O_3$	12.50	12.79	224[j]	220
65	4-Cl	55[e]	162–165	M-B	$C_{10}H_9ClN_2O_3$	11.64	11.51	14.73	14.54
66	2,3-diCl	79[h]	189–190	M-B	$C_{10}H_8Cl_2N_2O_3$	10.18	9.91	25.78	25.72
67	3,4-diCl	75[h]	175–177	M-B	$C_{10}H_8Cl_2N_2O_3$	10.18	10.07	25.78	25.59
68	2,4-diCl	54[f]	166–167[k]	M-B	$C_{10}H_8Cl_2N_2O_3$	10.18	10.47	25.78	25.65
69	2,5-diCl	80[h]	153–156[k]	A-B	$C_{10}H_8Cl_2N_2O_3$	10.18	10.57	25.78	25.91
70	2,4,6-triCl	65[h]	159–161	M	$C_{10}H_7Cl_3N_2O_3$	9.05	9.10	34.36	34.12
71	4-Br	65[g]	165[k]	E[i]	$C_{10}H_9BrN_2O_3$	9.83	9.94	28.03	27.50
72	2,4,6-triBr	82[h]	169–171	M	$C_{10}H_7Br_3N_2O_3$	6.32	6.28	54.12	54.03

[a] All yields are based on the analytically pure sample. [b] All melting points are corrected. [c] Reference 9. [d] Yield is based on 4-fluoroaniline. [e] Yield is based on 4-chloroaniline hydrochloride. [f] Yield is based on 2,4-dichloroaniline. [g] Yield is based on 4-bromophenylhydrazine hydrochloride. [h] Yield is based on corresponding pure phenylhydrazine. [i] As a suspension. [j] Neutralization equivalent. [k] Melts with decomposition. [l] A = abs. ethanol; B = benzene; M = methanol; and E = ether.

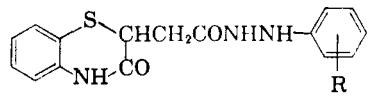
was essential. Mills and Whitworth[3] concluded from the fact that IIIa was formed by the reaction of either chlorosuccinic acid or maleic acid and 2-aminobenzenethiol that this compound contained a six-membered heterocyclic ring. Chemical evidence points to this structure, but the structural proof is inconclusive since both of these acids can react with 2-aminobenzenethiol to give the same intermediate (IV) from which either a six- or a seven-membered heterocyclic ring might form.



IV

TABLE V

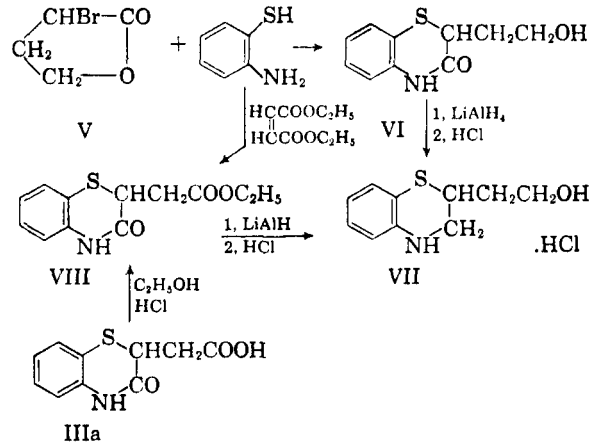
3,4-DIHYDRO-3-OXO-1,4,2-BENZOTHIAZINE-2-ACETOPHENYLHYDRAZIDES



No.	R	Yield,[a] %	M.p.,[b] °C.	Recrystn. solvent	Formula	Nitrogen, %, Calcd.	Nitrogen, %, Found	Sulfur, %, Calcd.	Sulfur, %, Found
73	H	24,[g] 16[h]	223–225	P–W	$C_{16}H_{15}N_3O_2S$	13.41	13.35	10.23	9.84
74	4-F	39[g]	225–227	P–W	$C_{16}H_{14}FN_3O_2S$	12.68	12.73	9.67	10 02
75	4-Cl	43[g]	235–237	P–W	$C_{16}H_{14}ClN_3O_2S$	10.20[d]	10.28	9.22	8.90
76	2,3-diCl	58[g]	264–266	P–W	$C_{16}H_{13}Cl_2N_3O_2S$	10.99	10.64	18.55[d]	18.42
77	3,4-diCl	46[g]	260–262[c]	P–W	$C_{16}H_{13}Cl_2N_3O_2S$	10.99	10.96	18.55[d]	18.73
78	2,4-diCl	27[g]	262–263	P–B	$C_{16}H_{13}Cl_2N_3O_2S$	10.99	11.17	18.55[d]	18.81
79	2,5-diCl	28[f]	266–267	D–W	$C_{16}H_{13}Cl_2N_3O_2S$	10.99	10.84	18.55[d]	18.76
80	2,4,6-triCl	24[f]	248–251	P–A–W	$C_{16}H_{12}Cl_3N_3O_2S$	25.53[d]	25.10	7.69	7.59
81	4-Br	42[g]	230.2[c]	P–W	$C_{16}H_{14}BrN_3O_2S$	10.71	10.76	8.17	7.98
82	2,4,6-triBr	38[g]	253–255	P–W	$C_{16}H_{12}Br_3N_3O_2S$	7.64	7.49	43.58[e]	44.15

[a] In all cases the yield is based on the analytically pure sample. [b] All melting points are corrected. [c] Melts with decomposition. [d] Chlorine analysis. Bromine analysis. [f] Prepared by method A (see Experimental part). [g] Prepared by method B (see Experimental part). [h] Prepared by Method D (see Experimental part). [i] A = ethanol; B = benzene; D = dioxane; P = pyridine; and W = water.

An unsymmetrical reagent, of such a nature that the formation of a seven-membered ring would be impossible, was needed to obtain an unambiguous proof of the structure of IIIa. The substance chosen was α-bromo-γ-butyrolactone (V)[16] whose reaction with 2-aminobenzenethiol, and subsequent reactions, are indicated in the accompanying scheme. We believe that this sequence of reactions constitutes a conclusive proof of the structure of IIIa.



To substantiate the structure of the reduction product VII, 3,4-dihydro-3-oxo-1,4,2-benzothiazine[17] was treated with lithium aluminum hydride to yield 3,4-dihydro-1,4,2-benzothiazine[18] in good yield. This base, previously prepared by another method,[19] was characterized by analysis and by its 4-phenylthiocarbamyl derivative.[19]

In view of the anthelmintic activity reported by Mackie and co-workers[20] for some 6-substituted-3,4-dihydro-3-oxo-1,4,2-benzothiazine derivatives, a number of the compounds reported in this paper have been submitted for biological screening.

(16) H. Plieninger, *Chem. Ber.*, **83**, 265 (1950).

(17) O. Unger, *Ber.*, **30**, 607 (1897).

(18) At the time of this work the authors were not aware that this reaction had been carried out; J. Cymerman-Craige, W. P. Rogers and G. P. Warwick, *Australian J. Chem.*, **8**, 252 (1955); *C. A.*, **50**, 3449a (1956).

(19) N. A. Langlet, *Bihang till K. Svenska Vet. akad. Handlingar*, **22**, afd. II, 3 (1896); Beilstein, "Handbuch der Organischen Chemie," fourth edition, Springer, Berlin, 1937, Vol. 27, p. 34.

(20) A. Mackie and J. Raeburn, *J. Chem. Soc.*, 787 (1952); A. Mackie and A. A. Cutler, *Rec. trav. chim.*, **71**, 1198 (1952).

Experimental[21]

Preparation of 3,4-Dihydro-3-oxo-2-phenacylbenzothiazine Derivatives (*Table I*).—The β-benzoylacrylic acid derivatives that were used as intermediates in the present investigation are described in the literature[4–6] with the exception of the 4-fluoro derivative. This compound was prepared in 59% yield and melted at 132–138° (uncor.) after recrystallization from benzene.

Anal. Calcd. for $C_{10}H_7FO_3$: neut. equiv., 194. Found: neut. equiv., 195.

The 3,4-dihydro-3-oxo-2-phenacyl-1,4,2-benzothiazine derivatives (IIIb) listed in Table I, with the exception of compounds 7, 9, 10, 12 and 13, were prepared from 2-aminobenzenethiol by the following general procedure: To a solution of a β-benzoylacrylic acid derivative in boiling toluene in a flask equipped with a water-separator of the Dean–Stark type was added a toluene solution of an equivalent amount of 2-aminobenzenethiol. The rate of addition was regulated by the vigor of the resulting exothermic reaction. The separation of water, which started at once, ended soon after the addition was completed. The reaction mixture was heated for an additional hour and the crystals which separated during the reaction (or upon cooling or concentrating) were collected and washed with cold toluene. Recrystallization from the appropriate solvent (see Table I) produced a pure product.

Compound 1 was also prepared from 2-aminobenzenethiol and β-benzoylacrylic acid in ether solution containing a drop of piperidine at room temperature; and by the interaction of α-chloro-β-benzoylpropionic acid[11] and 2-aminobenzenethiol in absolute ethanol when kept at room temperature under an atmosphere of nitrogen for a week.

After compound 1 was refluxed for 30 minutes with acetic anhydride it was isolated unchanged.[18]

3,4-Dihydro-3-oxo-2-phenacyl-1,4,2-benzothiazine Oxime.—A suspension of 14 g. (0.05 mole) of compound 1, 5.0 g. (0.07 mole) of hydroxylamine hydrochloride and 11.0 g. (0.08 mole) of sodium acetate trihydrate in 400 ml. of absolute ethanol was boiled gently on a steam-bath for 1 hour. At the end of this time the reaction mixture which had concentrated somewhat, was filtered from insoluble material and 100 ml. of water was added to the hot filtrate. The solid that was produced by cooling the solution was collected, washed with water and dried at 70°. The pure product (11 g., 74%) melted at 196–201°.

Anal. Calcd. for $C_{16}H_{14}N_2O_2S$: N, 9.39; S, 10.74. Found: N, 9.04; S, 10.51.

(21) Melting points are corrected unless otherwise indicated. Analytical data are given in the appropriate table.

The oxime underwent a Beckmann rearrangement when treated with benzenesulfonyl chloride according to the procedure of Roberts and Chambers,[22] and the product, which was isolated in poor yield, melted at 267–269° (uncor.) and showed no melting point depression when mixed with 3,4-dihydro-3-oxo-1,4,2-benzothiazine-2-acetanilide (IIIc, no. 42).

2-(4'-Aminophenacyl)-3,4-dihydro-3-oxo-1,4,2-benzothiazine, No. 7.—A suspension of 16.5 g. (0.05 mole) of the 2-(4-acetamidophenacyl) derivative (no. 8) in 500 ml. of absolute ethanol and 100 ml. of concentrated hydrochloric acid was refluxed on a steam-bath. After a short time a clear solution developed and then solid again began to separate. The suspension was heated for 2 hours and allowed to stand overnight. The solid was then collected, washed with ethanol and recrystallized from dilute ethanol. The pure product (6.7 g., 46%) melted at 194–196°.

The above amino compound was acylated in hot pyridine solution with butyric and hexanoic anhydride to form compounds 9 and 10, respectively.

6-Chloro-3,4-dihydro-3-oxo-2-phenacyl-1,4,2-benzothiazine, No. 12.—A suspension of 13 g. (0.068 mole) of crude 4-chloro-2-nitrobenzenethiol[10] and 12 g. (0.068 mole) of β-benzoylacrylic acid in 100 ml. of glacial acetic acid containing 1 ml. of piperidine was heated on a steam-bath for about 15 minutes. Zinc dust (30 g.) was then added in portions to the hot reaction mixture, a vigorous reaction following each addition. After an additional 15 minutes the supernatant liquid became lighter and finally a pale-green in color at which time the reduction was considered complete. Glacial acetic acid (200 ml.) was added and the hot slurry filtered by suction. When the filtrate was cooled a solid was produced which was collected and washed with water and dry ether. After it was recrystallized from toluene the pure product (6 g., 28%) melted at 215–219°.

The 2-(4'-fluorophenacyl) analog (no. 13) was prepared similarly in 54% yield, m.p. 243–245°.

Amides (Table III), Anilides (Table III) and Phenylhydrazides (Table V) of 3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-acetic Acid (IIIa).—The preparation of the amides, anilides and phenylhydrazides of IIIa was accomplished with or without the isolation of an intermediate maleamic acid (Ic),[7] maleanilic acid (Id)[8] or maleic acid monophenylhydrazide (Ie).[9] When these intermediate (Tables II and IV) were new, they were prepared separately using known procedures.[8,9]

The amides, anilides and phenylhydrazides of IIIa were prepared from 2-aminobenzenethiol by two methods. As a means of structure proof several were prepared directly from IIIa by anhydride procedures.[14,15] Typical examples of the methods used follow:

Method A. Preparation Directly from an Amine, Aniline or Phenylhydrazine Derivative; 3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-(3'-chloroacetanilide), No. 48.—To a cooled solution of 13 g. (0.1 mole) of 3-chloroaniline in 50 ml. of pyridine was added 10 g. (0.1 mole) of powdered maleic anhydride. A yellow solution formed that slowly darkened as it warmed to room temperature. After 5 minutes 12.5 g. (0.1 mole) of 2-aminobenzenethiol was added and the solution was heated on a steam-bath for 1 hour. The addition of 150 ml. of benzene caused the separation of a solid. The suspension was then boiled to eliminate the water that was formed in the reaction. After a further dilution with benzene the solid was collected, washed with benzene and recrystallized from absolute ethanol. The pure product (8 g., 25%) melted at 229–230°.

Method B. Preparation from a Maleamic Acid, Maleanilic Acid or Maleic Acid Monophenylhydrazide Derivative; 3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-aceto-(3',4'-dichlorophenyl)-hydrazide, No. 77.—A suspension of 18.5 g. (0.067 mole) of maleic acid mono-(3,4-dichlorophenyl)-hydrazide (no. 67) in 15 ml. of pyridine was treated with 8.4 g. (0.067 mole) of 2-amino-benzenethiol. A slight exothermic reaction was accompanied by the formation of a light-yellow solution. After warming a short time on a steam-bath the whole set to a solid. Dry benzene (200 ml.) was added, the solid broken up and the suspension boiled to remove the water formed in the reaction. After the suspension was cooled the solid was collected and washed with benzene. The pure product (12 g., 46%) melted at 260–262° after it was recrystallized from a pyridine–water mixture.

(22) J. D. Roberts and V. C. Chambers, THIS JOURNAL, **73**, 3176 (1951).

Method C. Mixed Anhydride Procedure[14]; 3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-(4'-chloroacetanilide), No. 49.—A solution of 22.3 g. (0.1 mole) of IIIa and 10 g. (0.1 mole) of triethylamine in 800 ml. of dry acetone was treated with an acetone solution of 13.6 g. (0.1 mole) of isobutyl chloroformate followed in the usual fashion by an acetone solution of 12.7 g. (0.1 mole) of 4-chloroaniline. After the product was isolated and recrystallized twice from a pyridine–water mixture it weighed 4 g. (12%), melted at 275–278° (uncor.) and showed no melting-point depression when mixed with a sample prepared from 4-chloromaleanilic acid (no. 30) according to method B

Method D. Anhydride Method of Brewster and Ciotti[15]; 3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-acetophenylhydrazide, No. 73.—A solution of 4.4 g. (0.02 mole) of IIIa in 15 ml. of pyridine was treated with 1.7 g. (0.1 mole) of benzenesulfonyl chloride and allowed to stand at room temperature for several minutes. Phenylhydrazine (1 g., 0.1 mole) was then added to the amber solution producing a slight exothermic reaction. After several minutes the solution was warmed briefly on a steam-bath, cooled again and diluted with 50 ml. of 5% sodium hydroxide solution containing a small amount of sodium bisulfite. The separation of the solid product was completed by further dilution with water. The brownish solid was collected, washed well with water, ethanol and ether and recrystallized from a pyridine–water mixture. The pure product (1.3 g., 42%[23]) melted at 224–225° (uncor.) and showed no melting point depression when mixed with a sample prepared by method B.

3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-(4'-carbohydrazidoacetanilide), No. 59.—To a filtered solution of 15 g. (0.04 mole) of 3,4-dihydro-3-oxo-1,4,2-benzothiazine-2-(4'-carbethoxyacetanilide) (no. 58) in 350 ml. of hot absolute ethanol was added a solution of 30 ml. of 85% hydrazine hydrate in 20 ml. absolute ethanol. After refluxing gently for 5 hours the solution was allowed to evaporate slowly while standing at room temperature. After about 1 month the pasty mass was suspended in 300 ml. of hot absolute ethanol and filtered. The filter cake was suspended in hot pyridine and again collected and washed with water, ethanol and absolute ether. The pure product (7.5 g., 55%) melted at 261–263°.

Structure Proof of 3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-acetic Acid (IIIa).—This compound was prepared by a modification of the method of Mills and Whitworth.[8] When ethanol solutions of equivalent amounts of 2-aminobenzenethiol and maleic acid were mixed an exothermic reaction took place and the crude product separated in good yield. An analytical sample, recrystallized from aqueous ethanol, melted at 196–199° (lit.[8] m.p. 195–196°).

Anal. Calcd. for $C_{10}H_9NO_3S$: N, 6.27; neut. equiv., 223. Found: N, 6.34; neut. equiv., 227.

Ethyl Ester of 3,4-Dihydro-3-oxo-1,4,2-benzothiazine-2-acetic Acid (VIII).—This compound was prepared in two ways: (a) Diethyl maleate (51 g., 0.3 mole) at 190° was treated dropwise with 37.5 g. (0.3 mole) of 2-aminobenzenethiol in an atmosphere of nitrogen. Nearly an equivalent amount of ethanol separated as the temperature slowly rose to 215°. The solid mass that formed on cooling was dissolved in a minimum amount of hot absolute ethanol. The addition of two volumes of Skellysolve C followed by cooling produced the product (64 g., 85%) which melted at 127–128°.

Anal. Calcd. for $C_{12}H_{13}NO_3S$: N, 5.57; S, 12.76. Found: N, 5.48; S, 12.51.

(b) A suspension of 4.5 g. (0.02 mole) of IIIa in 50 ml. of absolute ethanol, that had been saturated with hydrogen chloride at 0°, was warmed on a steam-bath until solution was completed. After 1 hour the solution was cooled and white needles separated. These weighed 5.0 g. (100%) and showed no melting-point depression when mixed with a sample of ester prepared from diethyl maleate and 2-aminobenzenethiol.

2-(2'-Hydroxyethyl)-3,4-dihydro-3-oxo-1,4,2-benzothiazine (VI).—When a solution of 16.5 g. (0.1 mole) of α-bromo-γ-butyrolactone[16] in 25 ml. of absolute ethanol was treated with 12.5 g. (0.1 mole) of 2-aminobenzenethiol an exothermic reaction took place. The solution was heated on a steam-bath for 15 minutes, then neutralized with sodium bicarbonate and diluted with water. The oil that separated solidi-

(23) The yield is based on the theoretical recovery of one-half of IIIa from the postulated intermediary anhydride (ref. 15).

fied after standing for several days at room temperature. The solid when recrystallized from an absolute ethanol–Skellysolve C mixture weighed 9.0 g. (43%) and melted at 105–107°.

Anal. Calcd. for $C_{10}H_{11}NO_2S$: N, 6.69; S, 15.32. Found N, 6.63; S, 15.21.

2-(2'-Hydroxyethyl)-3,4-dihydro-1,4,2-benzothiazine Hydrochloride (VII).—This compound was prepared in two ways: (a) A suspension of 6.5 g. (0.17 mole) of lithium aluminum hydride in 600 ml. of dry ether was stirred in a flask containing a condenser and drying tube while 25 g. (0.1 mole) of solid VIII was added in portions. After the addition the suspension was stirred and refluxed for 3 hours, the excess reductant and the complex salts decomposed with 20 ml. of ethanol, 20 ml. of water and 2 ml. of glacial acetic acid and the suspension filtered. After the filtrate was washed twice with water it was dried over anhydrous magnesium sulfate. The addition of an ethereal solution of hydrogen chloride precipitated an oil that solidified. The product (12 g., 52%) which was light-pink after it was recrystallized from an absolute ethanol–ether mixture melted at 145–148°.

Anal. Calcd. for $C_{10}H_{14}ClNOS$: N, 6.04; S, 13.83. Found: N, 6.02; S, 13.88.

(b) A slurry of 4 g. (0.02 mole) of VI in 200 ml. of dry ether was added to a suspension of 1 g. (0.026 mole) of lithium aluminum hydride and the reduction conducted the same as in method (a) (above). The precipitated pink hydrochloride salt (1.25 g., 28%) after it was recrystallized from an absolute ethanol–ether mixture showed no melting-point depression when mixed with a sample prepared by a similar reduction of VIII. These two samples also were shown to be identical by their ultraviolet and infrared absorption spectra.

3,4-Dihydro-1,4,2-benzothiazine[18,19,24,25] was prepared from 3,4-dihydro-3-oxo-1,4,2-benzothiazine[17] in nearly quantitative yield by reduction with lithium aluminum hydride in ether; m.p. 36–37° (lit.[18] m.p. 35°).

Anal. Calcd. for C_8H_9NS: N, 9.26. Found: N, 9.19.

The 4-phenylthiocarbamyl derivative melted at 128–129° (lit.[19,24] m.p. 129°).

Anal. Calcd. for $C_{15}H_{14}N_2S_2$: N, 9.78. Found: N, 9.82.

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(24) O. Hromatka, M. Vacutny, J. Augle and K. Wiltschke, *Monatsh.*, **88**, 822 (1957).

(25) C. Angelini, G. Grandolini and L. Mignini, *Ann. chim. (Rome)*, **46**, 235 (1956); *C. A.*, **51**, 396d (1957).

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[CONTRIBUTION FROM THE LABORATORY OF BIOCHEMISTRY, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

Studies on Diastereoisomeric α-Amino Acids and Corresponding α-Hydroxy Acids. X. The Preparation of β-Hydroxy-β-methylaspartic Acid

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β-Hydroxy-β-methylaspartic acid was prepared in 60% yield by allowing a mixture of pyruvic acid and copper glycinate in *N* NaOH to stand at 5° for 12–18 hours. The compound gives a bright yellow initial color with ninhydrin on paper chromatograms. Proof of the structure of the isolated compound was obtained by means of elemental analyses, reduction to β-methylaspartic acid, reaction with ninhydrin which yielded 2 moles of carbon dioxide per mole of compound, and reaction with periodate to yield ammonia. The synthetic amino acid was composed of nearly equal amounts of the two theoretically possible diastereomers as shown by the ready separation of the latter on columns of Dowex 1-acetate eluted with acetic acid.

Earlier studies on the properties of N-pyruvoylglycine revealed that the characteristic absorption in the ultraviolet of aqueous solutions of this compound, as well as its ability to form a crystalline dinitrophenylhydrazone, were irreversibly lost when the compound was exposed to *p*H levels higher than 10.[1,2] A reinvestigation of this phenomenon with the aid of paper chromatography has since revealed that when a solution of pyruvoylglycine in *N* NaOH was allowed to stand at room temperature glycine began to appear after 1 hour and gradually increased to a maximum after 6 days. At this time alanine made its appearance while glycine decreased, the ratio of glycine to alanine reaching an apparently constant value of approximately 2:1 by the 18th day of standing as determined by the intensity of the ninhydrin spots. At the same time that glycine appeared, a hitherto unrecognized ninhydrin spot also made its appearance, which was initially bright yellow in color, gradually darkening through grayish-brown to the usual amino acid purple after 24 hours. The R_f values of this new compound in several solvents were very close to those of γ-hydroxyglutamic acid under the same conditions.[3,4]

Substantially the same results were obtained with mixtures of glycine and pyruvic acid. Thus, when an equimolar mixture of glycine and pyruvic acid was allowed to stand in *N* NaOH solution at room temperature, alanine and the unknown compound began to appear within a few hours. With further standing, the concentration of alanine increased, that of glycine decreased, whilst that of the unknown compound remained apparently constant.[5]

(1) M. Errera and J. P. Greenstein, *Arch. Biochem. Biophys.*, **14**, 477 (1947); **15**, 445 (1947).

(2) S-C. J. Fu, V. E. Price and J. P. Greenstein, *ibid.*, **31**, 83 (1951).

(3) L. Benoiton and L. P. Bouthillier, *Can. J. Chem.*, **33**, 1473 (1955).

(4) L. Benoiton, M. Winitz, S. M. Birnbaum and J. P. Greenstein, THIS JOURNAL, **79**, 6192 (1957).

(5) The formation of alanine under these conditions clarifies the earlier observation on the isolation of this amino acid from the acid hydrolysate of previously alkalinized pyruvoylglycine.[2] It is evident that pyruvoylglycine is readily hydrolyzed on standing in alkali even at room temperature, the alanine formed by secondary reaction increasing with time. Hydrolysis of pyruvoylglycine, of previously alkalinized pyruvoylglycine, or of equimolar amounts of glycine and pyruvic acid in refluxing *N* NaOH for 2 hours, leads to still greater amounts of alanine. On the other hand, pyruvoylglycine exposed to alkali for only a relatively brief time and then acid-hydrolyzed, leads