Preparation of Indoles from 4*H*-3,1-Benzothiazines by Extrusion of Sulfur

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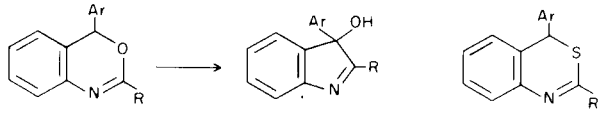
Prolonged heating of a series of α′-hydroxy-α′-aryl-*o*-toluidines in the presence of base and carbon disulfide afforded the corresponding 4*H*-3,1-benzothiazine-2-thiones. Treatment of the thiolalkyl ethers of these compounds with strong bases led to ring contraction to the corresponding 2-thioalkyl indole with concommitant extrusion of sulfur. The scope of the reaction was examined.

We have shown earlier that treatment of benzoxazines such as **1** with potassium amide in liquid ammonia leads in good yield to the ring contracted indolol **2** (1). It was thus considered of some interest to ascertain whether the analogous thiol could be obtained by contraction of a sulfur heterocycle such as **3**.



1 2 3

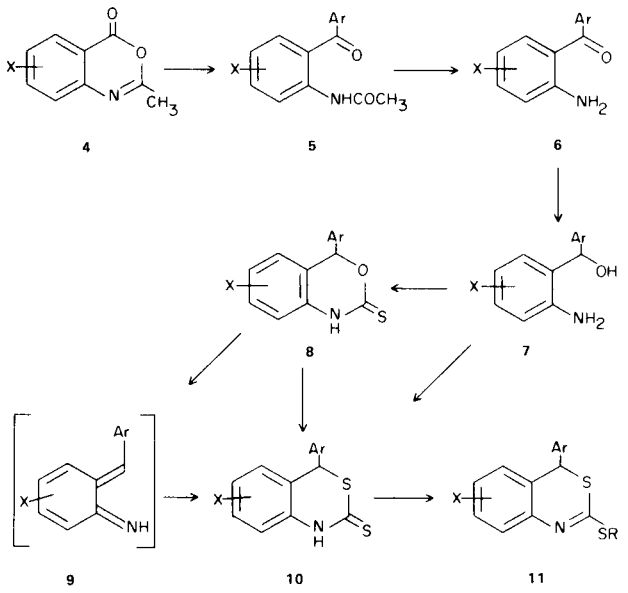
We chose 2-thioalkyl-4*H*-3,1-benzothiazines (**3**, R = S alkyl) as the substrates not only for their relative accessibility but also because the 2-position of these compounds should readily add the anion to be generated at 4.

Starting Materials.

The requisite ring system has been prepared by reaction of *o*-aminobenzyl alcohol with carbon disulfide (2). We thus chose as our initial goal a series of benzhydrols. Reaction of the appropriate benzoxazinone **4** with an aryl Grignard reagent gave upon workup the acetamide **5** (Table I); hydrolysis of this product with strong acid gave the free amine **6** (Table II). Reduction of these benzophenones as well as some of those prepared earlier (1) led cleanly to the corresponding alcohols **7** (Table III). In contrast to the earlier report, the present aminoalcohols fail to react with carbon disulfide. Treatment at reflux with carbon disulfide in the presence of sodium hydroxide, however, led to mixtures of the desired benzothiazine **10** and the corresponding benzoxazine **8**; these initially were separated chromatographically. Further investigation showed that reaction at room temperature, albeit extremely slow, favors formation of the oxygen heterocycle. Treatment of that benzoxazine under the reaction conditions - at reflux - led to conversion to the benzothiazine. These findings suggest the possible intermediacy of a reactive intermediate such as **9**.

In effect prolonged heating of the reaction mixture leads to a product sufficiently rich in **10** to allow its isolation by direct crystallization (Table IV).

The requisite intermediates **11** for the rearrangement reaction were obtained by alkylation of the benzothiazinethiones by means of a series of alkyl halides in the presence of potassium carbonate (Table V).



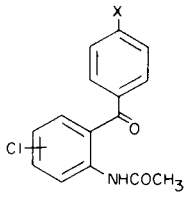
4 5 6 8 7 9 10 11

Rearrangement Reaction.

Treatment of the benzothiazine **11** (Ar = C_6H_5, R = CH_3, X = 6-Cl) with an equivalent of potassium amide in liquid ammonia gave a 1:1 mixture of starting material and a new product. Increasing the base to two equivalents

TABLE I

2-Acetamidobenzophenones

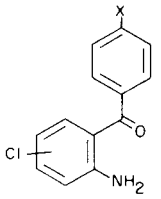


Cl	X	Chromat. Solv. (a)	Rxtal. Solv.	M.p. °C	Yield %	Formula	Analyses Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
5	CH_3		EtOAc:C_6H_{12}	157.5-160	29	$C_{16}H_{14}ClNO_2$	66.78	4.90	12.32	66.87	5.00	12.30
5	OCH_3	10	Me_2CO:SSB (b)	146.5-148.5	33	$C_{16}H_{14}ClNO_3$	63.26	4.65	11.67	63.32	4.50	11.80
5	Cl	7.5	CH_2Cl_2:C_6H_{12}	178.5-180	26	$C_{15}H_{11}Cl_2NO_2$	58.46	3.60	23.01	58.57	3.82	22.45
5	F	10	C_6H_{12}	132 -133.5	18	$C_{15}H_{11}ClFNO_2$	61.76	3.80	12.16	61.83	4.17	12.38
4	H	10	PE (c)	70.5- 75	17	$C_{15}H_{12}ClNO_2$	65.82	4.42	12.95	65.88	4.70	13.06

(a) Percentage acetone in acetone:Skellysolve B mixture. (b) Skellysolve B (12). (c) Petroleum ether.

TABLE II

2-Aminobenzophenones

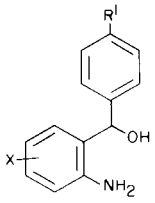


Cl	X	Rxtal. Solv.	M.p. °C	Yield %	Formula	Analyses Calcd. C	Calcd. H	Calcd. Cl	Found C	Found H	Found Cl
5	CH_3	Et_2O:SSB (a)	105.5-108	73	$C_{14}H_{12}ClNO$	68.43	4.92	14.43	68.86	4.92	14.47
5	OCH_3	Et_2O:SSB	97.5-100.5	86	$C_{14}H_{12}ClNO_2$	64.25	4.62	13.55	64.21	4.64	13.47
5	Cl	Et_2O:SSB	114.5-116.5	78	$C_{13}H_9Cl_2NO$	58.67	3.41	26.68	59.07	3.26	24.46
5	F	Et_2O:SSB	105.5-107	86	$C_{13}H_9ClFNO$	62.53	3.63	14.20	62.84	3.86	14.20
4	H	PE (b)	80 - 82	71	$C_{13}H_{10}ClNO$	67.39	4.35	15.31	67.67	4.47	15.73

(a) Skellysolve B. (b) Petroleum Ether.

TABLE III

α′-Hydroxy-α′-aryl-*o*-toluidines



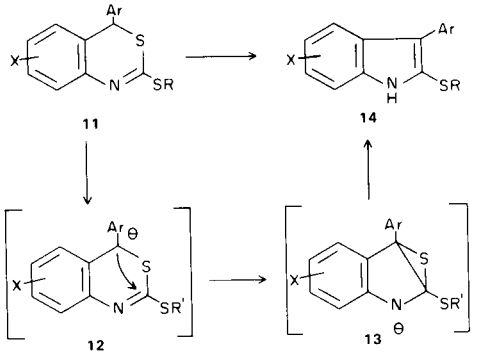
X	R^1	M.p. °C	Rxtal. Solv.	%	Formula	Analyses Calcd. C	H	Cl	Found C	H	Cl
H	OCH_3	59 - 60.5	Et_2O:PE (a)	62	$C_{14}H_{15}NO_2$	73.34	6.59	----	73.38	6.96	----
H	F	72.5- 74	Et_2O:SSB (b)	79	$C_{13}H_{12}FNO$	71.87	5.57	----	72.21	5.61	----
H	CH_3	95 - 96	Et_2O:SSB	76	$C_{14}H_{15}NO$	78.84	7.09	----	79.28	6.90	----
H	Cl	97 - 98.5	Et_2O:SSB	98	$C_{13}H_{12}ClNO$	66.81	5.18	----	66.78	5.09	----
4-Cl	CH_3	114.5-116.5	CH_2Cl_2:C_6H_{12}	98	$C_{14}H_{14}ClNO$	67.88	5.70	14.31	68.22	5.80	14.28
4-Cl	OCH_3	106 -111.5	Et_2O:SSB	87	$C_{14}H_{14}ClNO_2$	63.76	5.35	13.45	63.74	5.13	13.41
4-Cl	Cl	123.5-125	C_6H_6	94	$C_{13}H_{11}Cl_2NO$	58.23	4.14	26.45	58.19	4.07	26.57
4-Cl	F	121.5-123	C_6H_6	83	$C_{13}H_{11}ClFNO$	62.03	4.41	14.09	62.22	4.33	14.30
5-Cl	H	89.5- 92	Et_2O:SSB	89	$C_{13}H_{12}ClNO$	66.81	5.18	15.17	66.49	6.12	14.97

(a) Petroleum ether. (b) Skellysolve B.

resulted in complete conversion of the starting material. The crude reaction mixture on chromatography afforded a good yield of the new product as well as a 75% yield of elemental sulfur (identified by its mass spectrum). Both elemental analysis and mass spectrum of the product indicated the same empirical formula as starting material minus an atom of sulfur. The nmr spectrum of the product showed the benzyllic proton of the starting material to have disappeared; instead there were seen the characteristic NH proton of an indole (1H at 8.1 δ) a complex aromatic multiplet (8H) and the S-CH_3 protons as a sharp singlet at 2.25 δ (3H). Alkylation of the product with methyl iodide by means of sodium hydride resulted in an *N*-methyl derivative. These data in conjunction with the uv spectrum (λ max 290, 14,600), lead us to formulate the product as the 2-thiomethylindole **14** (Ar = C_6H_5, X = 5Cl, R = CH_3).

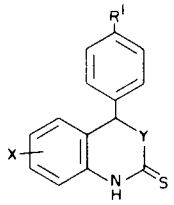
Preparation of the parent compound (**14**, Ar = C_6H_5, X = H, R = CH_3) by independent routes has been reported previously by T. Wieland *et al.* (3). These workers obtained the indole by reaction of 3-phenylindole with methylsulfenyl chloride and alternately by methylation of 2-mercapto-3-phenylindole.

In the present work, rearrangement of the appropriate benzothiazine (**11**, Ar = C_6H_5, X = H, R = CH_3), afforded a product whose uv spectrum and m.p. are in good agreement with those reported earlier.



Formation of that product can be rationalized by some scheme such as that above. Reaction is initiated by formation of a carbanion at the benzyllic position **12**. As in the case of the benzoxazines, this adds internally to the thioether, to give in this case an episulfide **13**. Though episulfides do decompose thermally, the conditions required to do this are usually more rigorous than those

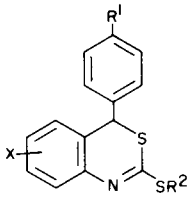
TABLE IV

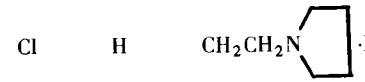


X	Y	R^1	M.p. °C	Rxtal. Solv.	Formula	Yield %	Ratio O/S	Analyses Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
H	S	H	187 -188	MeOH	$C_{14}H_{11}NS_2$	10	3.5	65.33	4.31	----	65.58	4.34	----
H	O	H	179 -181 (a)	MeOH	$C_{14}H_{11}NOS$	35		69.68	4.60	----	70.06	5.07	----
6-Cl	S	H	161 -163	MeOH	$C_{14}H_{10}ClNS_2$	26	1	57.67	3.45	21.98	57.51	3.37	22.28
6-Cl	O	H	190 -192	MeOH	$C_{14}H_{10}ClNOS$	25		60.97	3.66	11.63	60.55	3.75	11.64
H	S	OCH_3	159 -164 (a)	MeOH	$C_{15}H_{13}NOS_2$	65		----	---	----	----	---	----
H	S	F	151 -153.5	MeOH	$C_{14}H_{10}FNS_2$	37	0.5	61.06	3.66	23.29	61.32	2.88	21.28
H	O	F	177 -183 (a)	MeOH	$C_{14}H_{10}FNOS$	19		64.84	3.89	12.37	65.38	3.77	11.95
H	S	CH_3	162 -164	MeOH	$C_{15}H_{13}NS_2$	34	0.26	66.38	4.83	23.63	64.46	4.89	24.12
H	O	CH_3	178 -183 (a)	MeOH	$C_{15}H_{13}NOS$	9		70.56	5.13	12.56	70.35	5.34	12.23
H	S	Cl	167 -168.5	Me_2CO:SSB	$C_{14}H_{10}ClNS_2$	38	1	57.62	3.45	21.98	57.76	3.41	21.83
H	O	Cl	182.5-186 (a)	MeOH	$C_{14}H_{10}ClNOS$	36		60.97	3.66	11.63	60.97	3.75	11.50
6-Cl	S	CH_3	172.5-176	EtOAc:C_6H_{12}	$C_{15}H_{12}ClNS_2$	47		58.90	3.96	20.97	59.31	3.67	19.27
6-Cl	S	OCH_3	186 -189.5	MeOH	$C_{15}H_{12}ClNOS_2$	53		55.97	3.76	19.93	56.42	3.74	18.55
6-Cl	S	Cl	200 -202	EtOAc:C_6H_{12}	$C_{14}H_9Cl_2NS_2$	62		51.54	2.78	19.66	51.77	2.95	19.25
6-Cl	S	F	188 -190	EtOAc:C_6H_{12}	$C_{14}H_9ClFNS_2$	70		54.27	2.93	20.70	54.61	3.12	20.42
7-Cl	S	H	172 -174.5	(b)	$C_{14}H_{10}ClNS_2$	53		57.62	3.45	21.98	57.76	3.39	22.01

(a) Melting with decomposition. (b) Product chromatographed on silica gel with benzene; no recrystallization.

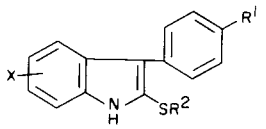
TABLE V

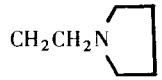


X	R^1	R^2	M.p. °C	Rxtal. Solv.	Formula	Yield %	Analyses Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
H	H	CH_3	107 -109	SSB (a)	$C_{15}H_{13}NS_2$	56	66.38	4.83	23.63	66.63	4.92	23.26
Cl	H	CH_3	112 -115	SSB	$C_{15}H_{12}ClNS_2$	87	58.90	3.96	20.97	59.00	3.82	20.72
6-Cl	H	CH_2CO_2Et	94 - 96	SSB	$C_{18}H_{16}ClNO_2S_2$	76	57.25	4.27	16.98	57.00	4.32	16.90
6-Cl	H	$C(CH_3)_2CO_2Et$ (b)	-------	---	$C_{20}H_{20}ClNO_2S_2$	88	----	---	----	----	---	----
Cl	H	 ·HCl	172 -173.5	CH_2Cl_2:E (c)	$C_{20}H_{22}Cl_2N_2S_2$	83	56.46	5.21	15.07	57.11	5.20	14.88
H	OCH_3	CH_3	98.5-101	Et_2O:SSB	$C_{16}H_{15}NOS_2$	72	63.75	5.02	21.28	63.84	5.02	21.45
H	F	CH_3	123 -124.5	SSB	$C_{15}H_{12}FNS_2$	91	62.25	4.18	22.16	62.50	4.51	21.69
H	CH_3	CH_3 (b)	-------	---	$C_{16}H_{15}NS_2$	98	----	---	----	----	---	----
H	Cl	CH_3	120 -122.5	Et_2O:SSB	$C_{15}H_{12}ClNS_2$	95	58.90	3.96	----	58.79	4.06	----
6-Cl	CH_3	CH_3	78 - 80	P.E.	$C_{16}H_{14}ClNS_2$	70	60.07	4.41	20.05	60.05	4.63	19.81
6-Cl	OCH_3	CH_3	112 -115.5	SSB	$C_{16}H_{14}ClNOS_2$	79	57.21	4.20	19.09	57.46	4.63	18.93
6-Cl	Cl	CH_3	103 -105	SSB	$C_{15}H_{11}Cl_2NS_2$	85	52.94	3.26	18.85	53.05	3.19	19.19
6-Cl	F	CH_3	112 -113	SSB	$C_{15}H_{11}ClFNS_2$	88	55.63	3.42	19.80	55.75	3.55	19.27
7-Cl	H	CH_3	130 -133	C_6H_{12}	$C_{15}H_{12}ClNS_2$	97	58.90	3.96	20.97	59.09	4.52	20.73

(a) Skellysolve B. (b) Compound not crystalline; purified by chromatography only. (c) Ethylacetate.

TABLE VI



X	R^1	R^2	M.p. °C	Rxtal. Solv.	Formula	Yield %	Analyses Calcd. C	Calcd. H	Calcd. S	Found C	Found H	Found S
H	H	CH_3	84 - 86 (a)	SSB (b)	$C_{15}H_{13}NS$	76	75.27	5.47	----	75.07	5.63	----
H	OCH_3	CH_3	107 -110	Me_2CO:SSB	$C_{16}H_{15}NOS$	83	71.34	5.61	----	71.70	6.17	----
H	F	CH_3	82 - 85	Et_2O:P.E. (c)	$C_{15}H_{12}FNS$	88	70.00	4.70	12.46	69.64	4.67	12.78
H	CH_3	CH_3	80 - 83	Me_2CO:SSB	$C_{16}H_{15}NS$	91	75.89	5.97	12.66	75.64	6.14	13.36
H	Cl	CH_3	105 -107	Et_2O:SSB	$C_{15}H_{12}ClNS$	86	65.80	4.42	11.71	66.05	4.65	11.70
5-Cl	H	CH_3	116 -118	Et_2O:SSB	$C_{15}H_{12}ClNS$	64	65.80	4.42	----	65.84	4.41	----
5-Cl	H	$CH_2CO_2CH_3$ (d)	137 -138	Me_2CO:SSB	$C_{17}H_{14}ClNO_2S$	57	61.53	4.26	9.69	61.65	4.20	9.88
5-Cl	H	$C(CH_3)_2CO_2Et$	137 -140	SSB	$C_{20}H_{20}ClNO_2S$	22	64.24	5.39	----	64.38	5.68	----
5-Cl	H		160 -162	Me_2CO:SSB	$C_{20}H_{21}ClN_2S$	52	67.30	5.93	----	67.34	6.05	----
5-Cl	OCH_3	CH_3	80 - 81.5	Et_2O:SSB	$C_{16}H_{14}ClNOS$	69	63.25	4.64	10.56	63.67	4.96	10.10
5-Cl	CH_3	CH_3	79 - 81	SSB	$C_{16}H_{14}ClNS$	66	66.77	4.90	11.14	66.64	5.10	11.68
5-Cl	F	CH_3	128 -129	SSB	$C_{15}H_{11}ClFNS$	86	61.74	3.80	10.99	62.09	3.82	11.08
5-Cl	Cl	CH_3	77 - 79	SSB	$C_{15}H_{11}Cl_2NS$	79	58.45	3.60	10.40	58.02	3.92	10.52
6-Cl	H	CH_3	73.5- 75	SSB	$C_{15}H_{12}ClNS$	73	65.80	4.42	11.71	66.01	4.60	12.09

(a) Lit. m.p. 85-86° (3). (b) Skellysolve B. (c) Petroleum ether. (d) Prepared by special procedure; see Experimental Section.

employed in this work (4-8). The close proximity of the anionic nitrogen may in this case serve to further destabilize the episulfide. It is of note in this connection that the base catalyzed loss of sulfur from benzo[*b*]-1,4-thiazepines has been similarly ascribed to the intermediacy of an episulfide (9). In an attempt to gain some insight into the reaction, a sample was removed *one minute* after the addition to the base; workup of that aliquot showed that only product was present.

As may be seen from Table VI, this reaction is quite general. A variety of substituents can be tolerated on the attached aromatic ring, or on the exocyclic sulphur atom.

EXPERIMENTAL

2-Acetamidobenzophenones (Table I).

In a typical experiment a solution of 0.0512 mole of *p*-tolylmagnesium bromide (from 8.77 g. of *p*-bromotoluene and 1.24 g. of magnesium) in 85 ml. THF was added to an ice-cooled suspension of 10.0 g. (0.0512 mole) of the benzoxazinone over 2.75 hours. The mixture was then stirred in the cold for 1 hour and at room temperature for 1.5 hours. The solution was then again cooled in ice and 85 ml. of 2.5*N* hydrochloric acid added at a rate to keep the temperature below 4°. Following 15 minutes stirring, the organic layer was separated and washed in turn with water, 5% sodium hydroxide, water and finally brine. The solution was taken to dryness and the residue either recrystallized or chromatographed over Florisil (11).

2-Aminobenzophenones (Table II).

In a typical experiment a mixture of 0.027 mole of the appropriate acetamide, 37 ml. each of concentrated hydrochloric acid and water and 75 ml. of ethanol was heated at reflux overnight. The bulk of the solvent was then removed on the rotary evaporator. The residue was dissolved in methylene chloride and washed with aqueous sodium bicarbonate. The organic layer was taken to dryness to afford the crude amino-ketone.

α-Hydroxy-α′-aryl-*o*-toluidines (Table III).

In a typical experiment sodium borohydride (11.4 g., 0.32 mole) was added to a suspension of 20 g. (0.092 mole) of 2-amino-5-chlorobenzophenone in 200 ml. of ethanol. Following 3 hours stirring at room temperature the solution was poured into water. The precipitated solid was recrystallized from methylene chloride cyclohexane to afford 17.7 g. of product, m.p. 103-107°.

Mixture of Benzoxazines and Benzothiazines (Table IV).

In a typical experiment a mixture of 0.163 mole of the aminoalcohol, 24 ml. of carbon disulfide, 33.5 ml. of 45% potassium hydroxide and 23.5 ml. of water in 590 ml. of ethanol was heated at reflux for 18 hours. The bulk of the solvent was removed in vacuum. The residue was suspended in water and the suspension made strongly acidic with hydrochloric acid. The precipitated gum slowly solidified. The solid was collected on a filter, dried and chromatographed on 3 l. of silica gel. Elution with benzene afforded 16.05 g. of the thiazine, followed by 17.76 g. of the oxazine.

1,4-Dihydro-4-aryl-2*H*-1,1-benzothiazine-2-thiones (Table IV).

In a typical experiment a mixture of 0.034 mole of the aminoalcohol, 5.1 ml. of carbon disulfide, 7 ml. of 45% aqueous potassium hydroxide and 5 ml. of water in 125 ml. of ethanol was heated at reflux overnight. At the end of this time and again after another 6 hours heating, additional like portions of carbon disulfide and base were added. The mixture was again heated at reflux overnight and then concentrated in vacuum. The residue was treated with water and made strongly acidic. The precipitated solid was collected on a filter and then recrystallized.

1,4-Dihydro-4-phenyl-2*H*-3,1-benzothiazine-2-thione from 1,4-Dihydro-4-phenyl-2*H*-3,1-benzoxazine-2-thione.

A mixture of 2.36 g. (0.0098 mole) of the benzoxazine, 1.8 ml. (0.03 mole) of carbon disulfide, 2.5 ml. of 45% potassium hydroxide and 1.8 ml. of water in 45 ml. of ethanol was heated at reflux for 24 hours. The reaction mixture was worked up exactly as above. The precipitated solid was chromatographed on 200 ml. of silica gel (elution with 1:1 methylene chloride:Skellysolve B) to afford 1.15 g. (0.00447 mole) of the benzothiazine, m.p. 179-180°, m.m.p. with authentic material 179-183°.

2-Alkylthiobenzothiazines (Table V).

a. $R^2 = CH_3$

A mixture of 0.034 mole of the thiazine, 30 ml. (0.485 mole) of methyl iodide and 4.80 g. (0.0348 mole) of potassium carbonate in 250 ml. of acetone was stirred vigorously under reflux for 5 hours. The solid was removed by filtration and the filtrate taken to dryness in vacuum. The residue was then chromatographed on 1 l. of florisil (elution with 5% acetone in Skellysolve B). The crystalline fractions were then combined and recrystallized.

b. $R^2 = CH_2CO_2C_2H_5$

Proceeding as above the thiazine was alkylated by means of 1 equivalent of ethylbromoacetate and 1 equivalent of potassium carbonate. Following workup the product was eluted from Florisil with 10% acetone in Skellysolve B.

c. $R^2 = C(CH_3)_2CO_2C_2H_5$

The alkylation was carried out with 1 equivalent of ethyl α-bromoisobutyrate and 1 equivalent of potassium carbonate. Chromatography in this case afforded the product as a gum as well as a small amount of starting material.

d. $R^2 = CH_2CH_2N$ ·HCl

Proceeding as above the thiazine (6.0 g.) was heated with one equivalent each of *N*-(β-chloroethyl)pyrrolidine and potassium carbonate in 250 ml. of acetone for 8 hours. The solid was collected on a filter and the filtrate taken to dryness. The residual gum was dissolved in methylene chloride and this solution washed with 100 ml. 2.5*N* hydrochloric acid. The organic layer was taken to dryness to afford the hydrochloride as a solid.

Rearrangement of 2-Alkylthiobenzoxazines (Table VI).

In a typical experiment, a solution of 7.0 g. (0.023 mole) of the benzoxazine (X = Cl, R^1 = H, $R^2 = CH_3$) in 70 ml. of THF was added to a solution of 0.046 mole of potassium amide (from 1.8 g. of potassium) in 250 ml. of redistilled liquid ammonia. Following 4 hours stirring under a Dry Ice condenser the reaction was quenched with 5 g. of ammonium chloride and blown to dryness with a stream of nitrogen. The residue was taken up in ether and water; the organic layer was washed with water and brine and taken to dryness. This last residue was chromatographed on 600 ml. of Florisil. Elution with Skellysolve B gave 0.31 g. (0.0097 mole) of sulfur. The crystalline fractions obtained on elution with 2% acetone were combined and recrystallized.

5-Chloro-1-methyl-2-(methylthio)-3-phenylindole.

To a solution of 2.73 g. (0.01 mole) of the indole in 10 ml. DMF and 40 ml. benzene there was added 0.42 g. (0.01 mole) of 56% sodium hydride in mineral oil. Following 10 minutes stirring, 1 ml. of methyl iodide was added and the mixture brought to reflux. At the end of 4 hours the mixture was allowed to cool and diluted with benzene and water. The organic layer was washed with water and brine and taken to dryness. The residual solid was recrystallized twice from Skellysolve B to give 2.28 g. (80%) of product, m.p. 101-104°.

Anal. Calcd. for $C_{16}H_{14}ClNS$: C, 66.77; H, 4.90; S, 11.14. Found: C, 66.79; H, 4.94; S, 11.12.

Methyl [(5-Chloro-3-phenylindol-2-yl)thio]acetate.

The thiazine (18.28 g., 0.0485 mole) in 190 ml. of THF was added to a solution of potassium amide prepared from 3.85 g. (0.0985 mole) of the metal in 1 l. of ammonia. Following 2 hours stirring under a Dry-Ice condenser 20 g. (0.375 mole) of ammonium chloride was added and the reaction mixture evaporated with a stream of nitrogen. The residue was taken up in ether and water; the organic layer was washed with water and brine and taken to dryness. A solution of the residue and 17 ml. of 50% aqueous sodium hydroxide in 175 ml. of methanol was heated at reflux for 2 hours. The bulk of the solvent was removed in vacuum and the mixture diluted with water. The solution was washed with ether, made strongly acidic and extracted with ether. These last extracts were taken to dryness to afford the crude acid as a gum.

An ethanol solution of the above acid was treated with diazomethane prepared from 18 g. (0.123 mole) of *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine and 40 ml. of 40% aqueous potassium hydroxide. The waxy solid which remained when this solution was taken to dryness was chromatographed on 1.8 l. of silica gel (elution with methylene chloride). The crystalline fractions were combined and recrystallized from acetone Skellysolve B to give 8.34 g. (0.0252 mole) of product, m.p. 137-139.5°.

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(10) All melting points are uncorrected and recorded as observed on a Thomas-Hoover capillary melting point apparatus. Nmr spectra were determined in deuteriochloroform of a Varian A-60-A spectrometer. The authors are indebted to the Department of Physical and Analytical Chemistry of The Upjohn Company for elemental and spectral analysis.

(11) Florisil is a synthetic magnesia silica gel absorbent manufactured by the Floridin Co., Warren, Pa.

(12) Skellysolve B is a petroleum fraction, b.p. 60-70°, sold by the Skelly Oil Co.