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Derivatives of the Thiazolo[2,3-a]isoquinolinium System

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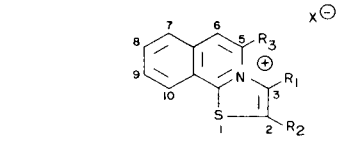
The ketosulfides (IV) formed by the reaction of α-bromoketones with 2α-thiohomophthalimide (II) have been cyclized to form hydrogen-bonded, dimeric hemiperchlorates (V). Alternative products from the cyclization, 2-[2'-(carboxymethyl)phenyl]thiazoles (VII), may be cyclized with acetic anhydride to *O*-betaines (VI). The same betaines are obtained from the hemiperchlorates (V) by deprotonation. The ketosulfide hydrobromides (XIII) from α-bromoketones and 1-thio-3,4-dihydroisocarbostyril (XII) give 5,6-dihydrothiazolo[2,3-a]isoquinolinium salts (XV) on cyclization.

A previous paper (1a) has described the synthesis of bridge-head nitrogen systems by reacting thiols with α-bromoketones and cyclizing the carbonyl functions of the resulting β-ketosulfides into an



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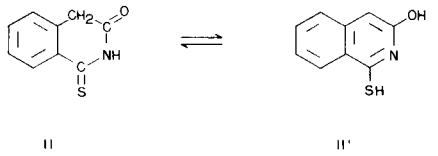

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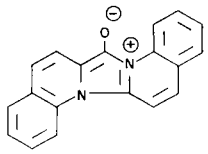

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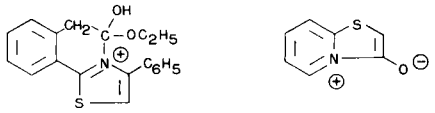


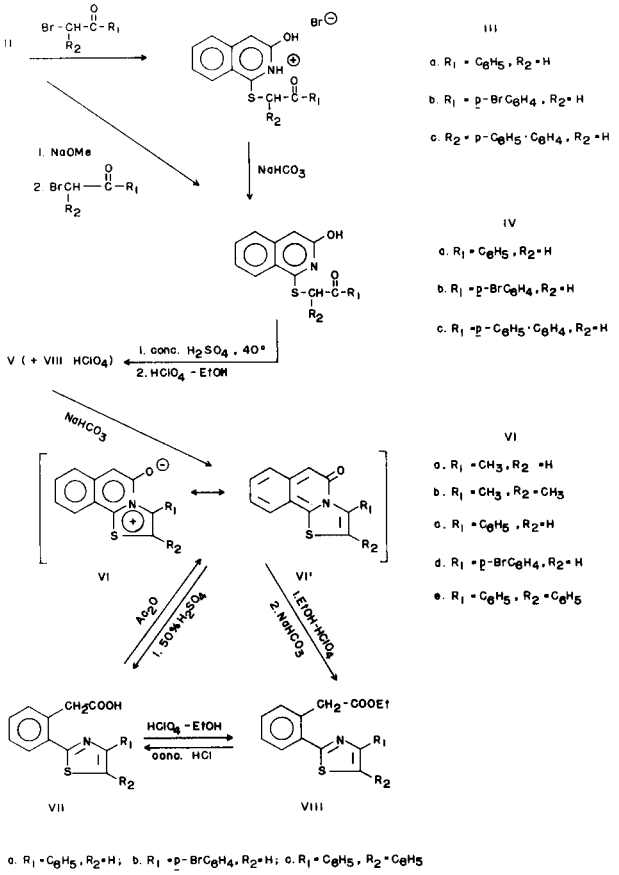
X XI

adjacent nitrogen. In particular (1b), 1-mercaptoisoquinoline provides a series of thiazolo[2,3-a]isoquinolinium salts (I, R_3 = H). Since 2α-thiohomophthalimide (II) may be considered to be a tautomer of 1-mercapto-3-hydroxyisoquinoline (II'), and is readily available (2), a convenient route to thiazoloisoquinolinium salts having a 5-hydroxyl substituent (I, R_3 = OH) was suggested. Although the synthesis was realized, the reactions of the intermediates and products were more complex than anticipated (Scheme I).

The result of the initial displacement reaction of thioimide (II) depends upon the bromoketone involved. When bromoacetone was refluxed with the thioimide (II) in acetone for 48 hours, a yellow salt precipitated. Its infrared spectrum demonstrated the absence of a carbonyl group, and the NMR spectrum (in trifluoroacetic acid) was consistent with that expected for 5-hydroxy-3-methylthiazolo[2,3-a]-isoquinolinium bromide (I, R_1 = CH_3, R_2 = H, R_3 = OH, X = Br): Singlet at δ 3.2 (3H), attributed to the methyl group; singlet at δ 7.5 (1H), proton adjacent to the oxygen function; multiplet at *ca.* δ 8.0 (5H), remaining aromatic protons. However, a halogen analysis showed approximately half the required percentage of bromine, and analysis of the corresponding perchlorate indicated clearly that only one anion was present for every two thiazoloisoquinolinium moieties. Alternative structures V and V' proposed for these "hemiperchlorates" are not unreasonable, since analogous structures have been suggested (3,4,5), and in one case proved by x-ray analysis (5), for similar compounds. Our inability to isolate any 5-hydroxy salts of "normal" structure (I, R_3 = OH) may be explained by the stabilization of the hemiperchlorates by extensive delocalization of positive charge over both halves of the molecule as implied in structures V and V'. The possibility of resonance interaction via the hydrogen bond is noteworthy in view of current interest in this topic (6).

Among the bromoketones studied only bromoacetone gave the cyclization product V directly when refluxed with thiohomophthalimide (II) in acetone. 3-Bromobutan-2-one and desyl bromide failed to react under these conditions, whereas phenacyl bromide and its *p*-bromo and *p*-phenyl analogs gave immediate precipitates of the ketosulfide hydrobromides (III, a-c), in high yield. These hydrobromide salts were readily converted to their free bases (IV, a-c) by sodium bicarbonate or merely by crystallization from ethanol. The same three ketosulfides were alternatively obtained directly as precipitates by adding the appropriate bromoketone to a solution of the thioimide (II) containing meth-

SCHEME I



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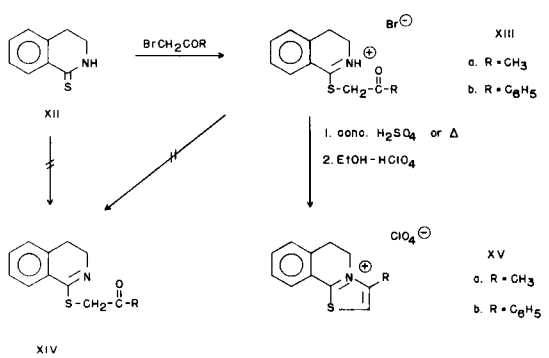

oxide ion. The ketosulfides from other bromoketones studied did not precipitate in this way, but were obtained as viscous oils on removal of the solvent. Since the oils could not be purified by crystallization or distillation, but exhibited the expected spectral characteristics, they were used directly in the next stage.

With the exception of biphenylyl derivative (IVc), which apparently underwent concomitant sulfonation, the foregoing ketosulfides were cyclized by concentrated sulfuric acid to the hydroxy salts, and isolated as their hemiperchlorates (V a-e). Temperature and reaction time were critical. After 5 minutes much of the product was the sulfate of the starting ketosulfide; and after several hours, or at temperatures greater than 60°, no hemiperchlorate (V) was obtained on work-up. A compromise of 15 minutes at 30-40° resulted in optimum (20-30%) yields of the hemiperchlorates.

Weak base instantly converted the hemiperchlorates (V) into a series of chloroform-soluble compounds (VI a-e) which may be described as betaines, although structures VI' a-e doubtless contribute substantially to the resonance hybrid. The betaines, orange to red, thermochromic, crystalline solids, are yellow in hydroxylic solvents, showing the same maxima in the U.V. and visible regions as their parent salts; but in non-hydroxylic solvents such as sodium-dried benzene, they are red with a blue fluorescence. In benzene, a bathochromic shift, with two maxima at 494 and 525 mμ replacing a single maximum at 466 mμ, was observed from VIc. Corresponding shifts were observed with VId and VIe (Table I). Besthorn's Red (IX), which has a structure (7) analogous to that of VI, shows strikingly similar spectral behavior (7a). On exposure to light, benzene solutions of VI gradually decolorized, and after several days exhibited no absorption at wavelengths longer than 204 mμ. A similar phenomenon observed with Besthorn's Red was attributed to photoautoxidation (7b). Betaines VIa and VIb, which have no phenyl substituent, are particularly unstable in solution and were unobtainable in an analytically pure condition. All the betaines, however, could be reconverted to the stable hemiperchlorates (V) by addition of perchloric acid to their ethanol solutions. Attempted methylation and benzylation of betaine VIc failed.

The low yields experienced in the cyclization step were explained when the ethyl ester (VIIIa), characterized by its analysis, infrared and NMR spectra, was isolated from the ethanol-perchloric acid mixture used to convert the crude sulfate to its perchlorate (Vc). The colorless ester represented 36% of the yield from ketosulfide (IVa) under optimum conditions for preparing salt (Vc), and was the sole product isolated when cyclization conditions were too vigorous. That the crystallization procedure is in part responsible for cleavage of the C-N bond demonstrated by the fact that when crude sulfate was converted directly to betaine (VIc), a 50% overall yield of the latter, based on ketosulfide, was achieved. Also, successive crystallizations of the

TABLE I

Electronic Spectra (a)

α-(3-Hydroxy-1-isoquinolylthio)ketones (IV) from 2α-Thiohomophthalimide (II)

IV	R_1	R_2	λ max, mμ (log ε)
a	C_6H_5	H	230(4.56), 245sh(4.34), 284(3.88), 295(3.83), 357(3.86)
b	*p*-Br-C_6H_4	H	288(4.53), 256(4.34), 280sh(4.03), 295(3.89), 357(3.87)
c	*p*-C_6H_5-C_6H_4	H	226(4.49), 285(4.38), 295(4.38), 356(3.84)

Hemiperchlorates (V)

V	R_1	R_2	λ max, mμ (log ε)
a	CH_3	H	222(4.50), 254sh(4.22), 283(4.82), 307sh(4.05), 324(3.62), 465(4.16)
a	CH_3	H (b)	227(4.46), 268(4.71), 312sh(4.06), 322(4.13), 371(4.23), 386(4.22)
b	CH_3	CH_3	223(4.54), 256sh(4.20), 285(4.84), 312sh(3.92), 330(3.77), 464(4.20)
c	C_6H_5	H	223(4.72), 248(4.55), 280(4.76), 310sh(4.29), 466(4.17)
d	*p*-Br-C_6H_4	H	227(4.73), 250(4.68), 280(4.78), 308sh(4.32), 466(4.15)
e	C_6H_5	C_6H_5 (c)	255(4.64), 285(4.79), 315sh(4.35), 475(4.24)

Anhydro-5-hydroxythiazolo[2,3-a]isoquinolinium Hydroxides (VI)

VI	R_1	R_2	λ max, mμ (log ε)
c	C_6H_5	H	223(4.40), 248(4.23), 280(4.45), 311sh(3.96), 465(3.87)
d	*p*-Br-C_6H_4	H	226(4.36), 250(4.27), 279(4.41), 310sh(3.92), 466(3.84)
e	C_6H_5	C_6H_5 (c)	255(4.32), 285(4.48), 315sh(3.99), 475(3.94)
c	C_6H_5	H (d)	284(4.38), 315sh(3.91), 467sh(3.55), 494(3.83), 525(3.76)
d	*p*-Br-C_6H_4	H (d)	288(4.42), 316sh(4.02), 470sh(3.59), 496(3.86), 528(3.78)
e	C_6H_5	C_6H_5 (c,d)	294(4.43), 333(3.92), 476sh(3.70), 504(3.89), 534(3.84)

2-[2'-(Ethoxycarbonylmethyl)phenyl]thiazoles (VIII)

VIII	R_1	R_2	λ max, mμ (log ε)
a	C_6H_5	H	246(4.17), 254sh(4.11), 268(4.07), 310(3.76)
b	*p*-Br-C_6H_4	H	250sh(3.98), 262sh(4.09), 275(4.18), 309sh(3.70)
c	C_6H_5	C_6H_5	241(4.33), 319(4.12)

(a) Except where otherwise noted, spectra were determined in 95% ethanol. (b) The spectrum of Va in concentrated sulfuric acid closely resembles that of 3-methylthiazolo[2,3-a]isoquinolinium perchlorate (in ethanol or sulfuric acid) (1b). (c) The fact that Ve and VIe have long-wavelength maxima at 475 mμ as against *ca.* 465 mμ for all the others suggests that one phenyl ring (in position 3) is non-coplanar with the thiazoloisoquinolinium system, owing to interference from the oxygen at position 5; and the other phenyl ring (in position 2) is able to attain coplanarity. Approximately the same shift (10 mμ) is observed in benzene solution as in ethanol. (d) In sodium-dried benzene.

hemiperchlorate resulted in loss of yield. Evaporation and basification of the filtrates revealed a quantity of the ester (VIIIa) corresponding to the loss.

An interesting property of the ester (VIIIa) is its facile hydrolysis to acid (VIIa); esterification of VIIa is equally easy. Tentatively, this facility may be attributed to intramolecular catalysis involving the thiazole nitrogen, via an intermediate such as X. Catalysis of ester hydrolysis by heterocycles such as imidazole is well known (8). Esters (VIIIb) and (VIIIc) and acids (VIIb) and (VIIc) were isolated and interconverted in the same way. The acids (VII) were also obtained, in near quantitative yield, by treatment of betaines (VI) or hemiperchlorates (V) with 50% sulfuric acid.

Duffin and Kendall (9) have prepared the betaine (XI) by heating (2-pyridylthio)acetic acid with acetic

TABLE II

Experimental Data

α-(3-Hydroxy-1-isoquinolylthio)ketone Hydrobromides (III)

						C		H		N	
III	R_1	R_2	Yield, %	M.P., °C (a)	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
a	C_6H_5	H	88	185-186	$C_{17}H_{14}BrNO_2S$	54.26	54.07	3.75	3.73	3.72	4.00
b	p-Br-C_6H_4	H	93	196-197	$C_{17}H_{13}BrNO_2S$	44.86	45.14	2.88	2.88	3.08	3.02
c	p-C_6H_5-C_6H_4	H	95	206-206.5	$C_{23}H_{18}BrNO_2S$	61.07	61.26	4.01	4.03	3.10	2.75

(a) All are pale yellow microneedles, and melt with gas evolution and decomposition.

α-(3-Hydroxy-1-isoquinolylthio)ketones (IV)

						C		H		N	
IV	R_1	R_2	Yield, % (a)	M.P., °C	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
a	C_6H_5	H	88	142-143 (b, c)	$C_{17}H_{13}NO_2S$	69.13	69.16	4.44	4.57	4.74	4.45
b	p-BrC_6H_4	H	90	186-188 (d)	$C_{17}H_{12}BrNO_2S$	54.56	54.66	3.23	3.27	3.74	3.75
c	p-C_6H_5-C_6H_4	H	93	177-178 (d)	$C_{23}H_{17}NO_2S$	74.37	74.23	4.61	4.58	3.77	3.84

(a) Directly from thioimide II; Yields from hydrobromides III were quantitative. (b) NMR spectrum in deuterochloroform: Singlet, δ 4.55 (2H), methylene group; singlet, δ 6.60 (1H), hydrogen adjacent to OH; multiplet, *ca.* δ 7.5 (10H), remaining aromatic hydrogens and phenolic proton. The methylene signal at δ 4.55 was removed by shaking the solution with deuterium oxide. That no base was required suggests that the exchange is autocatalytic, perhaps due to the ring nitrogen. (c) Pale yellow needles from benzene. (d) Pale yellow plates from benzene.

Hemiperchlorates V, by Cyclization of Ketosulfides IV

						C		H		N	
V	R_1	R_2	Yield, %	M.P., °C (a)	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
a	CH_3	H	38 (b)	246-247	$C_{24}H_{19}ClN_2O_6S_2$	54.29	54.12	3.61	3.65	5.28	5.12
b	CH_3	CH_3	38 (b, c)	257-258	$C_{26}H_{23}ClN_2O_6S_2$	55.86	55.53	4.15	4.20	5.01	4.88
c	C_6H_5	H	20	231-232	$C_{34}H_{23}ClN_2O_6S_2$	62.33	62.10	3.54	3.58	4.28	4.13
d	p-Br-C_6H_4	H	32	218-219	$C_{34}H_{21}Br_2ClN_2O_6S_2$	50.23	50.30	2.60	2.67	3.45	3.69
e	C_6H_5	C_6H_5	37 (b)	246-247	$C_{46}H_{31}ClN_2O_6S_2$	68.43	68.30	3.87	3.97	3.47	3.32

(a) All are yellow microneedles which melt with decomposition. (b) Prepared from crude ketosulfide; yield is based on thioimide II. (c) NMR spectrum in trifluoroacetic acid: Singlet, δ 2.71 (3H), methyl group; singlet, δ 3.07 (3H), methyl group; singlet, δ 7.37 (1H), hydrogen adjacent to oxygen function; multiplet, *ca.* δ 8.0 (4H), remaining aromatic hydrogens.

Anhydro-5-hydroxythiazolo[2,3-a]isoquinolinium Hydroxides (VI) (a)

						C		H		N	
VI	R_1	R_2	Yield, % (b)	M.P., °C	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found
c	C_6H_5	H	51 (c)	213-213.5 (d)	$C_{17}H_{11}NOS$	73.62	73.76	4.00	4.17	5.05	5.02
d	p-Br-C_6H_4	H	55	244-244.5 (d)	$C_{17}H_{10}BrNOS$	57.31	57.21	2.83	2.82	3.93	4.14
e	C_6H_5	C_6H_5	43	226-226.5 (e)	$C_{23}H_{15}NOS$	78.16	78.37	4.28	4.46	3.96	3.82

(a) Betaines (VIa) and (VIb) decomposed in solution and did not give satisfactory analyses. (b) Directly from ketosulfides (IV); yields from hemiperchlorates (V) were almost quantitative. (c) NMR spectrum in deuterochloroform: Singlet, δ 6.24 (1H), hydrogen adjacent to oxygen function; multiplet, δ 6.8-7.7 (10H), remaining aromatic hydrogens. (d) Orange needles from benzene-ligroin. (e) Scarlet needles from benzene.

TABLE II (Continued)

2-[2'-(Carboxymethyl)phenyl]thiazoles (VII)

VII	R_1	R_2	Yield, %	M.P., °C	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	C_6H_5	H	96 (a) 93 (b)	144-145 (c)	$C_{17}H_{13}NO_2S$	69.17	69.13	4.53	4.44	4.73	4.74
b	*p*-Br-C_6H_4	H	98 95	178-179 (d)	$C_{17}H_{12}BrNO_2S$	54.56	54.59	3.23	3.25	3.74	3.83
c	C_6H_5	C_6H_5	97 95	174-175 (d)	$C_{23}H_{17}NO_2S$	74.37	74.58	4.61	4.68	3.77	3.79

(a) By hydrolysis of esters VIII. (b) By cleavage of betaines (VI). (c) Needles (benzene). (d) Prisms (benzene).

2-[2'-(Ethoxycarbonylmethyl)phenyl]thiazoles (VIII)

VIII	R_1	R_2	Yield, %	M.P., °C	Formula	C Calcd.	C Found	H Calcd.	H Found	N Calcd.	N Found
a	C_6H_5	H	36 (a) 63 (b)	93-94 (c, d)	$C_{19}H_{17}NO_2S$	70.56	70.42	5.30	5.36	4.33	4.73 (e)
b	*p*-Br-C_6H_4	H	54 67	144-145 (f)	$C_{19}H_{16}BrNO_2S$	56.72	56.48	4.01	3.97	3.48	3.56
c	C_6H_5	C_6H_5	28 --	84-86 (f)	$C_{25}H_{21}NO_2S$	75.16	74.51	5.30	5.23	3.51	3.62

(a) As by-product under conditions for optimum yields of V. (b) Under more vigorous conditions: see experimental section. Yields of VIII by esterification of acids VII were quantitative. (c) NMR spectrum in deuterochloroform: Triplet, δ 1.08 (3H), quartet, δ 4.03 (2H), characteristic of an ethyl ester; singlet, δ 4.19 (2H), methylene group; multiplet, δ 7-8 (10H), aromatic hydrogens. The signal for the methylene group was not removed by shaking the solution with deuterium oxide. (d) Plates from ligroin. (e) S, Calcd. 9.92; Found 9.98. (f) Needles from ligroin.

anhydride. Analogously, acids (VII) smoothly cyclized to betaines (VI) when heated with this reagent. It is noteworthy that ketosulfides IV (which are isomers of VII) are unaffected by boiling acetic anhydride; and since concentrated sulfuric acid will cyclize the ketosulfides but not the acids, clearly a different mechanism must operate in each case. It has been suggested, though not generally accepted, that cyclization of a carboxyl group into nitrogen proceeds through a mixed anhydride (9). Acid catalyzed cyclization of a carbonyl group into nitrogen probably involves a concerted mechanism (1a).

In a parallel experiment, 1-thio-3,4-dihydroisocarbostyril (XII) (10) was used as the substrate in order to obtain dihydrothiazolo[2,3-a]isoquinolinium salts (XV) as outlined in Scheme II. Reaction of the thiolactam (XII) with bromoketones in acetone occurred almost instantaneously to give the hydrobromides (XIII), which cyclized cleanly in sulfuric acid to give the dihydrothiazoloisoquinolinium salts (XV). There was no appreciable side-reaction in this case. Ketosulfides (XIV) are apparently unstable and attempts to prepare them by basifying the hydrobromides (XIII) or by adding the bromoketones to a solution of thiolactam (XII) containing methoxide ion produced oils which rapidly decomposed on standing. Although cyclization with sulfuric acid was superior, the hydrobromides (XIII) could also be converted to the corresponding cyclic bromides (identified by their U.V. spectra and conversion to perchlorates XV) merely by heating at their melting points. This observation has obvious implications with regard to the mechanism of the cyclization of carbonyl groups into nitrogen, lending support to the concerted mechanism mentioned above.

EXPERIMENTAL

Elemental analyses were by Janssen Pharmaceutica, Beerse, Belgium. Melting points, taken with a Thomas-Hoover apparatus, are corrected. U.V. and visible spectra were determined using 1 cm. matched quartz cells in a Cary Model 14 spectrophotometer, and IR spectra were determined as Nujol mulls with a Perkin-Elmer Model 137 Infracord spectrometer. NMR spectra were obtained with a Varian A-60 instrument, using tetramethylsilane as an internal standard.

Reaction of 2α-Thiohomophthalimide (II) with Bromoacetone.

2α-Thiohomophthalimide (II) (1.77 g., 0.01 mole) (2) and redistilled bromoacetone (1.5 g. slight excess) were refluxed for 48 hours in reagent acetone (130 ml.). The resulting yellow solid was filtered from the dark supernatant, washed with acetone and crystallized from methanol-ethyl acetate to give 1.5 g. (51%) of the hemibromide (Va, Br in place of ClO_4) as yellow needles, m.p. 252-254° (dec.), ν max 1640 cm^{-1}.

Anal. Calcd. for $C_{12}H_{10}BrNOS$: Br, 26.98, and for $C_{24}H_{19}BrN_2O_2S_2$: Br, 15.63. Found: Br, 15.99.

As the hemibromide was unstable in warm water, it was best converted to the hemiperchlorate (Va) (Table II) by adding perchloric acid (70%) to its ethanol solution, and cooling in ice. A mixed melting point with Va prepared as described below was undepressed.

When either 3-bromobutan-2-one or desyl bromide was refluxed with II in acetone for 48 hours some decomposition occurred, but most of the starting material could be recovered. Refluxing for longer periods resulted in extensive decomposition.

(3-Hydroxy-1-isoquinolylthio)acetophenone Hydrobromide (IIIa).

When II (1.77 g., 0.01 mole) was refluxed with phenacyl bromide (2.00 g., slight excess) in acetone (130 ml.), yellow needles of IIIa appeared almost immediately. After 1 hour further refluxing, they were collected and the filtrate concentrated to yield more product, making 3.29 g. in all (88%). Hydrobromides IIIb and IIIc were pre-

pared similarly from *p*-bromo- and *p*-phenylphenacyl bromides (Table II). In each case the material obtained was analytically pure; recrystallization from ethanol-ether caused some decomposition to the free base IV. The hydrobromides were insoluble in ethanol, ν max 1650-1675 cm^{-1} (C=O hydrogen bonded to N).

The hydrobromides (III) were converted by sodium bicarbonate solution (10%) to the ketosulfides (IV) which were extracted with chloroform. The chloroform layer was dried and evaporated to leave a quantitative yield of IV. Particularly in the case of IVb and IVc, this conversion could also be achieved simply by refluxing IIIb and IIIc in ethanol and cooling, ν max 1680 and 1575-1620 cm^{-1}.

(3-Hydroxy-1-isoquinolylthio)acetophenone (IVa).
Direct Method.

Phenacyl bromide (4.5 g.) was added in portions to a stirred solution of II (4.0 g.) in sodium methoxide (120 ml.) prepared from 0.52 g. of sodium, at 30°. A yellow precipitate of ketosulfide (IVa) which appeared at once was collected after 1 hour, washed with cold methanol and crystallized from benzene-ligroin, yield 5.9 g. (88%). Ketosulfides (IVb) and (IVc) were obtained in the same way (Table II) using *p*-bromo and *p*-phenyl phenacyl bromides. Bromoacetone, bromobutanone and desyl bromide failed to give precipitates of the corresponding ketosulfides, so that the procedure was modified as follows: after 1 hour the methanol was removed *in vacuo*. Addition of chloroform to the residual dark oil left undissolved a quantitative yield of sodium bromide. The chloroform layer was washed with water, dried and evaporated to leave a dark, viscous oil, which decomposed on attempted distillation, adhered firmly to an alumina column, and could not be crystallized. However, the oils showed C=O stretching absorptions in the IR and UV spectra characteristic of the ketosulfides (IV) (with, significantly, an extra absorption at 440 mμ indicating that some premature cyclization had occurred). They were used without purification in the next stage.

Anhydro-5-hydroxythiazolo[2,3-a]isoquinolinium Hydroxide Hemiperchlorates (V).

The ketosulfide (IV), whether a pure solid or crude oil, was dissolved in concentrated sulfuric acid (10 ml. per g.) at 30°, causing warming to 40°. After 15 minutes the solution was added carefully to dry ether, affording a yellow solid. The solid was washed with ether, dissolved with minimum warming in ethanol and treated with 70% perchloric acid. On cooling, yellow needles of the hemiperchlorate (V) were obtained. Recrystallization from a large volume of ethanol resulted in some loss, yields varying from 20-40% (Table II). The product from cyclization of IVc did not melt below 400° and could not be purified satisfactorily. Its IR and UV spectra indicated that sulfonation had occurred along with cyclization. An attempt to cyclize IVc in hydrogen fluoride failed.

The combined ethanol and ethanol-perchloric acid filtrates from crystallization of V were concentrated, diluted with water and made basic with sodium carbonate. Extraction of the resulting white solid with chloroform gave a pink solution which, on evaporation, left a red contaminant (probably a trace of betaine VI) with charcoal, yielded the ester (VIII).

2-[2'-(Ethoxycarbonylmethyl)phenyl]thiazoles (VIII).

The ratio of ester (VIII) to hemiperchlorate (V) isolated by the above procedure increased with increasing duration of the temperature of reaction. After 24 hours at 30°, or 1 hour at 100°, *ca.* 65% yields of VIII were attained (Table II). All esters had ν max at 1740 cm^{-1} (very sharp). Their hydrobromides, obtained as oils by passing dry hydrogen bromide into their benzene solutions, reverted to the esters on attempted crystallization.

Anhydro-5-hydroxythiazolo[2,3-a]isoquinolinium Hydroxides (VI).
(a) From hemiperchlorates (V).

When shaken with sodium bicarbonate solution, the hemiperchlorate (V) was converted to a red solid which was extracted with chloroform. Removal of the chloroform from the dried extract *in vacuo* left a quantitative yield of betaine (VI).

(b) From crude sulfate.

The sulfate obtained from crystallization of the ketosulfides (IV) was directly converted to the corresponding betaine by the same procedure. By this means the overall conversion of ketosulfide to betaine was increased to *ca.* 50% (Table II).

Crystallization of VIc-VIe from benzene-ligroin raised their melting points by 3-5° with little loss of yield; but the methyl-substituted betaines VIa and VIb were unstable in solution, gave unsatisfactory analyses and had intermediate melting points. All betaines had ν max at 1660 cm^{-1} in the infrared. Solutions in benzene and chloroform are red with blue fluorescence; in ethanol yellow with no fluo-

TABLE III

α-(3,4-Dihydro-1-isoquinolylthio)ketone Hydrobromides (XIII)

					C		H		N		
XIII	R	Yield, %	M.P., °C	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	U.V. Spectrum, λ max, mμ (log ε)
a	CH_3	79	169-170 (a, b)	$C_{12}H_{14}BrNOS$	48.01	47.98	4.70	4.71	4.67	4.36	282 (4.24)
b	C_6H_5	99	191-192 (c)	$C_{17}H_{16}BrNOS$	56.36	56.12	4.45	4.50	3.87	3.84	282 (4.22)

(a) This melting point is uncertain and depends on the rate of heating; probably cyclization to XV is occurring. When sample is introduced at 165°, the melting point is 172-173° with gas evolution, and is followed by resolidification. (b) Prisms from ethanol-acetone-ether. (c) Needles from ethanol-ether.

5,6-Dihydrothiazolo[2,3-a]isoquinolinium Perchlorates (XV)

					C		H		N		
XV	R	Yield, %	M.P., °C	Formula	Calcd.	Found	Calcd.	Found	Calcd.	Found	U.V. Spectrum, λ max, mμ (log ε)
a	CH_3	62 (a) 45 (b)	185-186 (c)	$C_{12}H_{12}ClNO_4S$	47.76	47.69	4.01	4.08	4.64	4.53	320 (4.19)
b	C_6H_5	96	254-256 (c, d)	$C_{17}H_{14}ClNO_4S$	56.12	56.15	3.88	3.94	3.85	3.77	325 (4.13)

(a) By cyclizing XIII in concentrated sulfuric acid. (b) By heating XIII at its melting point. (c) Colorless microneedles. (c) NMR spectrum in trifluoroacetic acid: Triplet, δ 3.37 (2H), methylene group adjacent to phenyl ring; Triplet, δ 4.51 (2H), methylene group adjacent to thiazolium ring; multiplet, *ca.* δ 7.7 (10H), aromatic protons.

rescence. The red color of dilute solutions in sodium-dried benzene gradually faded on exposure to light, until after 48 hours the solutions were colorless. The UV spectrum then showed no maxima in the observable region (*i.e.* at $\lambda > \lambda$ max for benzene at 204 mμ). The solid betaines are thermochromic. Heating caused a deepening of the red color, and the original color was restored on cooling. Quantitative reconversion of the betaines to the corresponding hemiperchlorates (V) was achieved by adding 70% perchloric acid to their ethanol solutions and refrigerating.

Attempts to Alkylate Betaine VIc.

Betaine VIc was refluxed with excess methyl iodide in acetone for 12 hours. Evaporation of the solvent left only starting material. With benzyl bromide, a yellow salt which precipitated was identified as the hemibromide Vc (Br in place of ClO_4) by its spectra and conversion to the known hemiperchlorate.

2-[2'-(Carboxymethyl)phenyl]thiazoles (VII).

(a) By cleavage of betaines VI.

Heating with 50% sulfuric acid converted betaine VI first to the sulfate, which subsequently redissolved to give a clear, almost colorless solution. Dilution of the cooled solution with water precipitated the acid VII which was collected and dried, ν max 1710 cm^{-1}. In one experiment, a quantity of wet betaine left in an oven to dry at 140° was completely converted to VII in 30 minutes.

(b) By hydrolysis of esters VIII.

A solution of the ester in hot concentrated hydrochloric acid was cooled and diluted with water. The precipitated acid was collected, dried and crystallized from benzene.

Crystallization of the acids (VII) from hot ethanol containing a trace of mineral acid was sufficient to ensure complete conversion to the corresponding esters (VIII).

Cyclization of Acids VII to Betaines VI.

The acid (0.1 g.) was heated in acetic anhydride (5 ml.) to the boiling point, when the developing red color had reached maximum intensity. After 2 minutes the cooled solution was poured with vigorous stirring into sodium carbonate solution, yielding a red precipitate of the betaine (VI). It was extracted with chloroform, the chloroform layer washed with sodium carbonate and water, dried and distilled to leave a near-quantitative yield of VI.

Phenylethylisothiocyanate.

Material prepared by a general procedure for alkyl isothiocyanates (11) was found to contain a substantial quantity of a solid, m.p. 89-91°, identified by NMR (in deuterochloroform) (Triplet, δ 2.85 (4H); quartet, δ 3.69 (4H); broad triplet, δ 6.33 (2H), NH protons; singlet, δ 7.32 (10H), aromatic protons) and by mixed melting point with an authentic sample, as *N,N*-diphenylethylthiourea. Low yields were experienced at the next stage if this impurity was not removed by efficient fractionation. A 12 inch helix-packed column was satisfactory. Fifty grams of crude product, b.p. 104.5-108.5/2 mm. yielded 31 g. of material, b.p. 118°/2.6 mm.

1-Thio-3,4-dihydroisocarbostyril (XII).

Phenylethylisothiocyanate was cyclized by the method of Smith and Kan (10), but the yield was raised from 42 to 62% by using starting material purified as above. The thiolactam (XII) was best purified by passage of its benzene solution through a short alumina column, yellow prisms, m.p. 98-99° (Lit. 97-98°) were obtained.

α-(3,4-Dihydro-1-isoquinolylthio)ketone Hydrobromides (XIII).

These were prepared by exactly the same procedure as that given for the hydrobromides (III) above, except that the reaction was judged to be complete when the yellow color of thiodihydroisocarbostyril (XII) was discharged (Table III).

Attempted Preparation of α-(3,4-Dihydro-1-isoquinolylthio)ketones (XIV).

Treatment of the above hydrobromides with sodium bicarbonate solution yielded yellow-green oils which decomposed rapidly on standing, even when removed quickly from contact with alkali by extraction with chloroform. The procedure used to obtain ketosulfides (III) directly from II, when applied to XII, resulted in tar formation.

5,6-Dihydrothiazolo[2,3-a]isoquinolinium Perchlorates (XV).

Method (a).

Hydrobromide (XIII) dissolved in concentrated sulfuric acid with evolution of hydrogen bromide to give a red solution which became colorless overnight. The solid obtained on pouring the solution into ether was washed with ether and dissolved in ethanol. Perchloric acid was added, and the cooled solution afforded the perchlorate (XV) as colorless microneedles.

Method (b).

When the hydrobromide (XIII) was heated in an open test-tube placed in an oil bath which was maintained at a temperature 10° above its melting point, a gas was evolved and the melt resolidified. The new solid was identified by its UV spectrum and by conversion to the perchlorate as the bromide of XV. A mixed melting point with material prepared by method (a) was undepressed. Some decomposition occurred during the reaction, and in the case of XIIIb a liquid which condensed in the tube was identified by infrared spectroscopy and gas-liquid phase chromatography as acetophenone.

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