tallized slowly; m.p. 40–50°. An additional 75 ml. of ether eluted another fraction, 0.17 g., m.p. 65–70°. This fraction was shown to be identical to compound XV by infrared analysis and a mixture melting point determination.

The low-melting fraction was purified by subliming it three times at 80° (0.2 mm.). The pure material (XVI) melts at 73–74°.

Spectra. Ultraviolet, λ_{max} 284 (4.1), λ_{min} 246 (2.9); λ_{max} 334 (3.7), λ_{min} 312 (3.5). N.m.r., −2.40, −1.37 d. (a.p.). +0.90; s (m.g.). +2.88; s. (m.g.) +0.53; q. +3.45; t. (*e.g.*). Infrared ($CHCl_3$) 1735, 1680 cm.$^{-1}$.

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85. Found: C, 55.16; H, 5.50; N, 5.61.

2-Methyl-3-methoxythieno[3,2-*b*]pyrrole (XVIII).—2-Carbethoxy-3-methoxythieno[3,2-*b*]pyrrole (0.132 g.) was put into 10 ml. of dry ether. Fifty mg. of lithium aluminum hydride was cautiously added while the contents of the flask were swirled. The swirling was continued until all of XIII had dissolved. The flask was loosely stoppered and left in the refrigerator overnight. The solution was then diluted with 50 ml. of dry ether before the excess lithium aluminum hydride was decomposed by the cautious addition of a few drops of water. The solution was then filtered and evaporated under vacuum to give 0.093 g. of clear, colorless oil, which crystallized completely after several minutes; m.p. 54–60°. This material was recrystallized from *n*-pentane and sublimed at 60° (0.2 mm.); m.p. 64°.

Spectra. Ultraviolet, λ_{max} 256 (4.3). N.m.r., −1.80, −1.45; t. (a.p.) +1.07; s. (m.g.) +2.45; s. (m.g.). Infrared, (CCl_4) 3480 cm.$^{-1}$.

Anal. Calcd. for C_8H_9NOS: C, 57.46; H, 5.43; N, 8.38. Found: C, 57.21; H, 5.28; N, 8.43.

2-Methyl-2*H*,3*H*-thieno[3,2-*b*]pyrrol-3-one (XVIII).—Six tenths of a gram of lithium aluminum hydride was added cautiously to a solution of 0.193 g. of V in 10 ml. of dry ether. The stoppered reaction mixture was allowed to stand overnight in the refrigerator. The excess lithium aluminum hydride was destroyed by the cautious addition of a few drops of water. Fifty ml. of dry ether was added to facilitate filtration. After the mixture was filtered, the filtrate was concentrated under vacuum to an oil (0.119 g.). When the oil was extracted with 30 ml. of boiling cyclohexane, part of it dissolved and a resinous, brown material was left undissolved. The cyclohexane solution was concentrated under vacuum to a red oil, which was then distilled at 100° (0.2 mm.). Crystals appeared in the distillate. These were sublimed at 100° (0.2 mm.) to give a white sublimate, m.p. 119–120°. The yield of analytically pure material was 0.025 g. or 18% of the theoretical amount.

Spectra. Ultraviolet, λ_{max} 278 (4.1), λ_{min} 237 (2.8); λ_{max} 331 (3.8), λ_{min} 305 (3.5). Infrared, ($CHCl_3$) 3180, 1637 cm.$^{-1}$.

Anal. Calcd. for C_7H_7NOS: C, 54.88; H, 4.61; N, 9.14. Found: C, 55.11; H, 4.41; N, 9.14.

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CAIRO UNIVERSITY]

On the Reactivity of the Exocyclic Double Bond in 5-Arylidene-3-aryl-2,4-thiazolidinediones; Their Reaction with Diazoalkanes, *p*-Thiocresol and Piperidine

BY AHMED MUSTAFA, WAFIA ASKER AND MOHAMED EZZ EL-DIN SOBHY

RECEIVED AUGUST 20, 1959

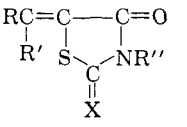
A series of 5-α-aralkylidene-3-aryl-2,4-thiazolidinediones (IV and V) has been prepared by the action of ethereal diazoalkanes on 5-arylidene-3-aryl-2,4-thiazolidinediones (III). Treatment of the appropriate 5-substituted-3-aryl-2,4-thiazolidinedione with *p*-thiocresol in the presence of piperidine give the thiol adducts VI. Under mild conditions piperidine adds to the exocyclic double bond in VIII to give a simple adduct VIII.

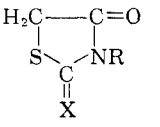
Recently, it has been reported that 5-(1-methylalkylidene)-2,4-thiazolidinedione (Ia) shows antimicrobial activity comparable to that of the most potent of the corresponding rhodanine derivatives (Ib).[1]

The fungicidal action of several organic sulfur compounds may be attributed to the presence of N–C–S linkage in Ia or Ib; or characteristic of thiazole compounds which possess considerable activity.[2]

We now have investigated the preparation of the hitherto unknown 5-α-aralkylidene-3-aryl-2,4-thiazolidinediones[3] (see Table II).

The condensation of the methylene group in 2,4-thiazolidinedione (IIa) and its N-substituted derivatives IIc with aromatic aldehydes, simple aliphatic ketones and cyclic ketones has been tried by different authors under different experimental conditions.[4]





Ia, R = CH_3; R′ = alkyl; R″ = H; X = O
b, R = CH_3; R′ = alkyl; R″ = H; X = S
c, R = H; R′ = R″ = C_6H_5; X = S
d, R = H; R′ = $C_6H_4OCH_3$-*p*; R″ = C_6H_5; X = S
e, R = H; =R′ = C_6H_3:O_2CH_2(3,4); R″ = C_6H_5; X = S
f, R = R′ = CH_3; R″ = C_6H_5; X = O
g, R = H; R′ = C_6H_5; R″ = $C_6H_4CH_3$-*p*; X = S

IIa, R = H; X = O
b, R = H; X = S
c, R = C_6H_5; X = O
d, R = C_6H_5; X = S
e, R = $C_6H_4CH_3$-*p*; X = O

Recently, Brown and co-workers[1] have shown that methyl isopropyl ketone, diethyl ketone, acetophenone and *m*-nitroacetophenone failed to

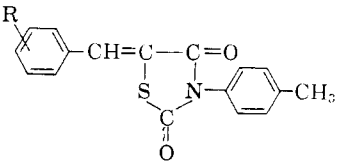
(1) *Cf.* F. C. Brown, C. K. Bradsher and S. W. Chilton, *J. Org. Chem.*, **21**, 1269 (1956); *cf.* also the pharmacological and toxicological studies on 5-benzylidene-rhodanine (S. A. Tawab, A. Mustafa and A. F. A. Shalaby, *Nature*, **183**, 607 (1959)).

(2) M. K. Rout, B. Padhi and N. K. Das, *ibid.*, **173**, 516 (1954).

(3) In view of the marked interest in many derivatives of thiazolidone which proved to be useful as anesthetics (A. R. Surrey, THIS JOURNAL, **71**, 3354 (1949), anticonvulsants (H. D. Troutman and L. M. Long, *ibid.*, **70**, 3436 (1948)) and amebacidal agents (A. R. Surrey and R. A. Cutler, *ibid.*, **76**, 578 (1954)), the presence of the thiazolidine moiety in penicillin, the fungitoxic or bacteriotoxic activity shown by many derivatives of rhodanines (H. K. Pujari and M. K. Rout, *J. Sci. Indust. Res.*, **14B**, 398 (1955); F. C. Brown and C. K. Bradsher, *Nature*, **168**, 171 (1951); F. C. Brown, C. K. Bradsher, E. C. Morgan, M. Tetenbaum and P. Wilder, THIS JOURNAL, **78**, 384 (1956)), the pharmacological results will be published elsewhere.

(4) For the different experimental conditions *cf.* (a) E. R. H. Jones, F. A. Robinson and M. N. Strachan, *J. Chem. Soc.*, 91 (1946); C. P. Lo, E. Y. Shropshire and W. J. Croxall, THIS JOURNAL, **75**, 4845 (1953), in the case of aromatic aldehydes; (b) D. Libermann, J. Himbert and L. Hengl, *Bull. soc. chim.*, **4**, 1120 (1948), in the case of cyclohexanone; (c) W. J. Croxall, C. P. Lo and E. Y. Shropshire, THIS JOURNAL, **75**, 5419 (1953), in the case of aliphatic ketones; (d) C. C. J. Culvenor, W. Davies, J. A. Maclaren, P. F. Nelson and W. E. Savige, *J. Chem. Soc.*, 2573 (1949), for the indirect preparation of 5-alkylidene-2,4-thiazolidinediones by desulfurization of 5-alkylidene rhodanines.

TABLE I



No.	R	Color	M. p.,[a] °C.	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	H	Colorless	201	87	Yell.-green	$C_{17}H_{13}NO_2S$	69.15	69.18	4.41	4.45	4.74	4.71	10.85	10.80
2	4-OCH_3	Yellow	197	84	Yell.-green	$C_{18}H_{15}NO_3S$	66.46	66.37	4.61	4.65	4.31	4.33	9.84	9.86
3	2-OCH_3	Pale yell.	162	82	Orange	$C_{18}H_{15}NO_3S$	66.46	66.41	4.61	4.60	4.31	4.34	9.84	9.81
4	2-OC_2H_5	Yellow	170	83	Orange	$C_{19}H_{17}NO_3S$	67.26	67.23	5.01	5.07	4.13	4.16	9.44	9.41
5	3,4-O_2CH_2	Yellow	218	77	Red	$C_{18}H_{13}NO_4S$	63.72	63.66	3.83	3.87	4.13	4.17	9.44	9.46
6	2-Cl	Colorless	181	79	Yell.-green	$C_{17}H_{12}NSO_2Cl$[b]	61.91	61.94	3.64	3.59	4.25	4.19	9.71	9.74
7	4-CH_3	Colorless	179	86	Yell.-green	$C_{18}H_{15}NO_2S$	69.90	69.87	4.85	4.87	4.53	4.60	10.35	10.31

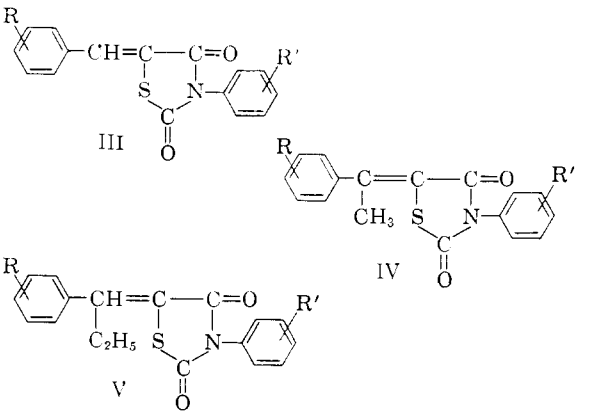
[a] All melting points are uncorrected. [b] Calcd.: Cl, 10.77. Found: Cl, 10.72.

condense with IIa. We would like to report that we have been unable to effect the condensation of acetophenone with IIc under the experimental conditions described either by Brown and co-workers[1] or by Libermann and co-workers.[4b]

An attempted reaction of IIc with acetophenone in alcoholic solution in the presence of ammonia and ammonium chloride[1] resulted in the opening of the hetero-ring with the formation of phenylurea. Similar results have also been observed when an alcoholic solution of IIc was refluxed with ammonia and ammonium chloride. This is in contrast to the stability of the hetero-ring in IIa[1] and in IIb[5] under similar conditions and is in analogy to our finding that the hetero-ring in IId is readily ruptured by the action of the same reagent, yielding phenylthiourea. Refluxing a benzene solution of of each of Ic-e with benzylamine resulted in the formation of benzylphenylthiourea.[6]

Substitution of the imino hydrogen atom in the hetero-ring with an aryl group has also been reported to effect the ready opening of the hetero-ring in IId. Thus, when IIb was allowed to react with phenylhydrazine, the corresponding 2-phenylhydrazone derivative[7] was obtained. On the other hand, treatment of IId with the same reagent effects the opening of the hetero-ring with the formation of diphenylsemicarbazide.[8]

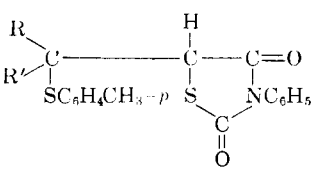
It seems possible that 5-(α-aralkylidene)-3-aryl-2,4-thiazolidinediones (IV and V, see Table II), recorded in this investigation, could be obtained by treatment of the readily accessible 5-arylidene-3-aryl-2,4-thiazolidinediones (III, see Table I) with ethereal diazoalkanes solutions.[9] This is indeed the case. Thus, when chloroform solutions of III (*cf.* Table I) are treated with ethereal diazomethane solution, IV (see Table II) are obtained, respectively. The corresponding pyrazoline derivatives have not been isolated. Similarly, when ethereal diazoethane was used for diazomethane in the case of III (R = R′ = H) and III (R = 2-Cl, R′ = H), V (*cf.* Table II) are obtained.



In view of the well-established mechanism for the addition of diazoalkanes to analogous α,β unsaturated compounds (α,β-unsaturated ketones and α,β-unsaturated esters[9]) structures IV and V are assigned for the reaction products. Compounds (IV and V, Table II) are obviously analogous. The structure of IV (R = R′ = H), which was taken as an example of these compounds, was inferred from the fact that it gives the correct analytical values. Treatment of its acetone solution with potassium permanganate effects the formation of acetophenone. Its infrared absorption spectra was found to be consistent with the proposed structure; it has a strong band at 5.95 μ attributed to a conjugated carbonyl group supported by the ultraviolet absorption data.

The fact that IV (R = R′ = H) undergoes addition reaction with *p*-thiocresol (see below) may be taken in favor of the presence of a conjugated exocyclic double bond in the 5-position of the heterocyclic ring having a carbonyl function.

Reaction with *p*-Thiocresol.—We now have found that conjugate addition takes place when III (R = R′ = H), IV (R = R′ = H) and If are



VI

a, R = C_6H_5; R′ = H
b, R = C_6H_5; R′ = CH_3
c, R = R′ = CH_3

(5) F. C. Brown, C. K. Bradsher, S. G. McCallum and H. Potter, *J. Org. Chem.*, **15**, 174 (1950).

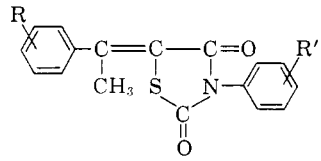
(6) This experiment was carried out with S. A. Khattab.

(7) E. Maneli and L. Zorzi (*Il farmaco (Pavia)*), *Ed., Sci.*, **9**, 691 (1954); *C. A.*, **49**, 6229 (1955).

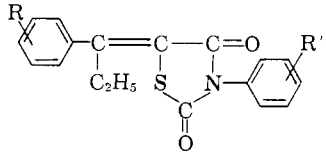
(8) C. Granacher, *Helv. Chim. Acta*, **3**, 152 (1920).

(9) For the formation of the α-methyl substituted product by the action of diazomethane on ethylene, *cf.* "Newer Methods of Preparative Organic Chemistry," Interscience Publishers, Inc., New York, N. Y., 1948, pp. 553–554.

TABLE II



No.	R	R′	M.p.,[a] °C.	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	H	H	133[1]	73	Yell.-green	$C_{17}H_{13}NO_2S$	69.15	68.89	4.41	4.23	4.74	4.61	10.85	10.71
2	4-CH_3	H	141[1]	71	Yell.-green	$C_{18}H_{15}NO_2S$	69.90	69.68	4.85	4.71	4.55	4.35	10.35	10.28
3	4-OCH_3	H	144[2]	62	Yell.-orange	$C_{18}H_{15}NO_3S$	66.46	66.25	4.61	4.51	4.31	4.22	9.85	9.58
4	2-OCH_3	H	152[1]	70	Orange	$C_{18}H_{15}NO_3S$	66.46	66.15	4.61	4.55	4.31	4.29	9.85	9.71
5	2-OC_2H_5	H	115[1]	69	Orange	$C_{19}H_{17}NO_3S$	67.26	67.11	5.01	4.98	4.13	3.91	9.44	9.31
6	2-Cl	H	153[1]	61	Colorless	$C_{17}H_{12}NO_2SCl$[b]	61.91	61.88	3.61	3.57	4.25	4.17	9.71	9.66
7	3,4-O_2CH_2	H	142[2]	66	Orange-red	$C_{18}H_{13}NO_4S$	63.72	63.61	3.84	3.58	4.13	4.07	9.44	9.35
6	4-$N(CH_3)_2$	H	177[3]	60	No color	$C_{19}H_{18}N_2O_2S$	67.45	67.29	5.32	5.30	8.28	8.01	9.47	9.32
9	H	4-CH_3	165[1]	72	Yell.-green	$C_{18}H_{15}NO_2S$	69.90	69.85	4.85	4.72	4.53	4.44	10.35	10.29
10	4-OCH_3	4-CH_3	210[1]	63	Yell.-orange	$C_{19}H_{17}NO_3S$	67.26	67.18	5.01	4.87	4.13	4.01	9.44	9.32
11	2-OCH_3	4-CH_3	161[1]	70	Orange	$C_{19}H_{17}NO_3S$	67.26	67.20	5.01	4.92	4.13	4.10	9.44	9.27
12	2-OC_2H_5	4-CH_3	137[1]	71	Orange	$C_{20}H_{19}NO_3S$	67.99	67.78	5.38	5.26	3.97	3.89	9.06	8.92
13	3,4-O_2CH_2	4-CH_3	172[2]	67	Orange-red	$C_{19}H_{15}NO_4S$	64.59	64.38	4.25	4.18	3.96	3.78	9.06	8.88

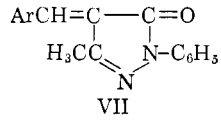


14	H	H	162[1]	62	Yell-green	$C_{18}H_{15}NO_2S$	69.90	69.72	4.85	4.78	4.53	4.34	10.35	10.22
15	2-Cl	H	142[1]	59	No color	$C_{18}H_{14}NO_2SCl$[c]	62.88	62.78	4.07	3.98	4.07	3.89	9.31	9.18

[a] Melting points are uncorrected: [1] colorless crystals, [2] pale-yellow crystals, [3] yellow crystals. [b] Calcd.: Cl, 10.77. Found: Cl, 10.73. [c] Calcd.: Cl, 10.34. Found: Cl, 10.30.

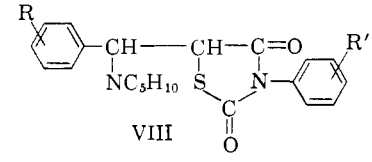
heated independently together with *p*-thiocresol in the presence of a trace of piperidine, to give the the thiol-adducts VIa-c, respectively.

Structure VI is assigned for the reaction products.[10] The fact that the thiol adducts, upon heating above their melting points for a few minutes, regenerate the original components[11] favors the proposed structure. Moreover, the ease of removal of the addend indicates that the substance is the result of simple addition and no unexpected reaction has occurred. The addition of *p*-thiocresol to the conjugation created by attachment of an exocyclic double bond to a heterocyclic ring having a carbonyl function has been reported in the case of 1-phenyl-3-methyl-4-arylidene-5-pyrazolones[12] (VII).



VII

Reaction with Piperidine.—Ruhemann[13] has reported that treatment of IIc with piperidine in boiling alcoholic solution effects the opening of the hetero-ring[14] with the formation of phenylpiperidylurea. We now have found that similar reaction, with the formation of phenylpiperidylurea, could be brought about by refluxing III (R = R′ = H) with excess of piperidine for 24 hours; however, when its benzene solution is treated with piperidine, addition reaction to the double bond of the lateral chain takes place with the formation of the adduct VIII (R = R′ = H). Similarly, under the same experimental conditions, the adducts VIII (*cf.* Table III) are obtained. In no case we have been able to record the formation of isomeric racemates which should exist in such adducts.[15] The adducts VIII (*cf.* Table III) are colorless products, decompose above their melting points yielding the corresponding 3-phenyl-5-arylidene-2,4-thiazolidinedione. The activity of the vinyl group in III toward secondary amines[12] may be compared with that in VII.



VIII

Experimental

5-Arylidene-3-p-tolyl-2,4-thiazolidinediones.—3-*p*-Tolyl-2,4-thiazolidinedione (IIe) was obtained in 98% yield after the procedure described for the preparation of IIc.[16] Condensation of IIe with the appropriate aldehyde was also carried after the procedure described for the preparation of III (R = R′ = H),[17] yielding the arylidene derivatives listed in Table I. They are readily crystallized from glacial acetic acid and from benzene.

5-Isopropylidene-3-phenyl-2,4-thiazolidinedione (If).—A procedure, similar to that described for the preparation of 5-isopropylidene-2,4-thiazolidinedione,[1] was used. A mix-

(10) For the mechanism of the addition of the thiols to α,β-unsaturated compounds *cf.* A. Mustafa and M. M. Sallam, THIS JOURNAL, **81**, 1980 (1959).

(11) *Cf.* A. Mustafa, *J. Chem. Soc.*, 1370 (1951).

(12) *Cf.* A. Mustafa, W. Asker, A. F. A. Shalaby, S. A. Khattab and Z. E. Selim, THIS JOURNAL, **81**, 6007 (1959).

(13) S. Ruhrmann, *J. Chem. Soc.*, **95**, 117 (1909).

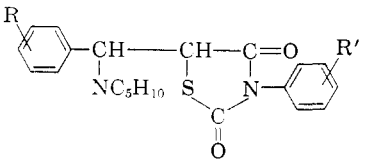
(14) *Cf.* the ready opening of the heterocyclic ring in 3-phenylrhodanine (IId) with piperidine to yield phenylpiperidylthiourea (B. Holmberg, *J. prakt. Chem.*, **84**, 634 (1911)).

(15) Similar conjugate additions have usually yielded only one diasterioisomer; see, however, P. L. Southwick and J. E. Anderson, THIS JOURNAL, **79**, 6222 (1957).

(16) K. S. Markley and E. E. Reid, *ibid.*, **52**, 2137 (1930).

(17) K. S. Markley and E. E. Reid, *ibid.*, **52**, 2981 (1930).

TABLE III



No.	R	R′	M.p.[a], °C.	Yield, %	Color with H_2SO_4	Formula	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Sulfur, % Calcd.	Sulfur, % Found
1	H	H	164	82	No color	$C_{21}H_{22}N_2O_2S$	68.85	68.82	6.01	6.04	7.65	7.63	8.74	8.69
2	4-CH_3	H	148	79	Yell.-green	$C_{22}H_{24}N_2O_2S$	69.47	69.44	6.31	6.30	6.37	7.35	8.42	8.43
3	2-Cl	H	176	73	No color	$C_{21}H_{21}N_2O_2SCl$[c]	62.92	62.90	5.24	5.27	6.99	6.97	7.99	7.97
4	3,4-O_2CH_2	H	184	74	Orange	$C_{22}H_{22}N_2O_4S$	64.39	64.39	5.36	5.35	6.83	6.85	7.80	7.78
5	H	4-CH_3	176	81	No color	$C_{20}H_{24}N_2O_2S$	69.47	69.46	6.31	6.34	7.37	7.36	8.42	8.44
6	2-OCH_3	4-CH_3	149	66	Orange	$C_{28}H_{26}N_2O_3S$	67.32	67.35	6.34	6.31	6.83	6.85	7.80	7.82
7	3-CH_3[b]	H	158[b]	76	Yell.-green	$C_{22}H_{24}N_2O_2S$	69.47	69.48	6.31	6.30	7.37	7.37	8.42	8.42
8	3-NO_2	H	155	69	No color	$C_{21}H_{21}N_3O_4S$	61.31	61.30	5.11	5.14	10.22	10.25	7.78	7.76
9	2-Cl	4-CH_3	151	67	No color	$C_{22}H_{23}N_2O_2SCl$[d]	63.69	63.65	5.55	5.56	6.75	6.73	7.72	7.71
10	4-CH_3	4-CH_3	157	70	Yellow	$C_{23}H_{26}N_2O_2S$	70.05	70.02	6.60	6.62	7.11	7.13	8.12	8.09

[a] Melting points are uncorrected. [b] The new arylidene derivative III (R = 3-CH_3, R′ = H) is now obtained in 98% yield after the procedure described for the preparation of IIc (*cf.* ref. 16) as colorless crystals from acetic acid, m.p. 157° (yellowish-green with H_2SO_4). Calcd. for $C_{17}H_{13}NO_2S$: C, 69.15; H, 4.41; N, 4.74; S, 10.84. Found: C, 69.17; H, 4.43; N, 4.70; S, 10.86. [c] Calcd.: Cl, 8.86. Found: Cl, 8.82. [d] Calcd.: Cl, 8.56. Found: Cl, 8.51.

ture of 20 g. of IIc an 30 ml. of acetone in 200 ml. of dry benzene containing 0.5 ml. of glacial acetic acid and 1 ml. of piperidine was refluxed for 36 hours. The benzene was removed by evaporation and the solid, so obtained, was washed thoroughly with cold ethyl alcohol. It was crystallized from hot ethyl alcohol or from benzene–light petroleum mixture as colorless crystals, m.p. 122°, yield *ca.* 80%.

Anal. Calcd. for $C_{12}H_{11}NO_2S$: C, 61.80; H, 4.72; N, 6.01; S, 13.73. Found: C, 61.77; H, 4.73; N, 5.89; S, 13.67.

5-Cyclohexylidene-3-phenyl-2,4-thiazolidinedione was prepared after the procedure described for the preparation of 5-cyclohexylidene-2,4-thiazolidinedione.[5] A mixture of 5.8 g. of IIc and 2.5 g. of sodium acetate was refluxed for 3 hours. The cooled reaction mixture was poured into water and the solid that separated was filtered off, washed thoroughly with water, dried and crystallized from benzene as colorless crystals, m.p. 112°, yield *ca.* 35%.

Anal. Calcd. for: $C_{15}H_{15}NO_2S$: C, 65.93; H, 5.49; N, 5.13; S, 11.72. Found: C, 65.87; H, 5.31; N, 5.05; S, 11.57.

Action of Ethereal Diazoalkanes Solutions on 5-Arylidene-3-aryl-2,4-thiazolidenediones (III). General Procedure.—A chloroform solution of one gram of each of III was treated with ethereal diazomethane solution[18] (prepared from 5 g. of nitrosomethylurea). The reaction mixture was kept at 0° for few days and then was treated with a fresh amount of ethereal diazomethane solution. It was worked up by evaporating the solution to dryness and the oily residue, so obtained, was dissolved in boiling ethyl alcohol; the crystals, that separated on cooling, were filtered off and washed with cold ethyl alcohol. The reaction products IV were recrystallized from hot ethyl alcohol (*cf.* Table II).

Compounds V are similarly obtained by allowing 1 g. of each of III (R = R′ = H) and III (R = 2-Cl, R′ = H) to react with ethereal diazoethane solution (prepared from 6 g. of nitrosoethylurea). They are readily crystallized from ethyl alcohol (*cf.* Table II).

The 5-α-aralkylidene derivatives listed in Table II are easily soluble in hot benzene, ether and chloroform, but are sparingly soluble in cold ethyl alcohol and light petroleum (b.p. 30–50°).

Action of Potassium Permanganate on 5-α-Methylbenzylidene-3-phenyl-2,4-thiazolidenedione (IV, R = R′ = H).—A solution of 0.5 g. of IV (R = R′ = H) in 30 ml. of acetone was treated portionwise with 40 ml. of 5% aqueous potassium permanganate solution. The reaction mixture was then refluxed for 2 hours, cooled and poured into ice-cold water. It was extracted with ether, dried and evaporated. A solution of the oily residue in 40 ml. of absolute ethyl alcohol was treated with a concentrated solution of 2,4-dinitrophenylhydrazine containing few drops of hydrochloric acid. The crystals, so obtained, were collected and were identified as acetophenone 2,4-dinitrophenylhydrazone (m.p. and mixed m.p.).

Action of p-Thiocresol on III (R = R′ = H), IV (R = R′ = H) and If.—To a melted mixture of 0.5 g. of each of the above-mentioned substituted 2,4-thiazolidinediones and 0.5 g. of *p*-thiocresol one drop of piperidine was added. The reaction mixture was heated for 2 hours at 100° in the case of IV (R = R′ = H) and If, and for 3 hours at 140° in the case of III (R = R′ = H). It was cooled, treated with light petroleum, and the solid, so obtained, was crystallized from the proper solvent.

The thiol adduct VIa forms colorless crystals from a mixture of benzene and petroleum ether (b.p. 60–80°); m.p. 152°, yield *ca.* 88%.

Anal. Calcd. for $C_{23}H_{19}NO_2S_2$: C, 68.15; H, 4.69; N, 3.46; S, 15.80. Found: C, 68.19; H, 4.57; N, 3.29; S, 15.56.

The thiol adduct VIb forms colorless crystals from light petroleum; m.p. 118°, yield *ca.* 81%.

Anal. Calcd. for $C_{24}H_{21}NO_2S_2$: C, 68.74; H, 5.09; N, 3.34; S, 15.27. Found: C, 68.46; H, 4.99; N, 3.31; S, 15.15.

The thiol adduct VIc forms colorless crystals from light petroleum; m.p. 98°, yield *ca.* 83%.

Anal. Calcd. for $C_{19}H_{19}NO_2S_2$: C, 63.86; H, 5.32; N, 3.92; S, 17.93. Found: C, 63.76; H, 5.12; N, 3.91; S, 17.58.

When the thiol adducts VIa-c were heated above their melting points, at 160, 130 and 110°, respectively, the original components were regenerated (m.p. and mixed m.p. determinations). *p*-Thiocresol was identified as its lead salt (m.p. and mixed m.p.[19]).

Action of Ammonia on: (a) IIc.—To a mixture of 5 g. of IIc, 10 ml. of concentrated ammonia solution and 25 ml. of ethyl alcohol was added a solution of 10 g. of ammonium chloride in 20 ml. of water. The reaction mixture was refluxed for 3 hours, cooled and evaporated *in vacuo*. The solid residue was crystallized from hot water as colorless crystals, m.p. 148°, identified as phenylurea (m.p. and mixed m.p.).

(b) IId.—Similar treatment of IId with ammonia and ammonium chloride in alcohol yielded a solid, which upon crystallization from ethyl alcohol gave colorless crystals, m.p. 154°, identified as phenylthiourea (m.p. and mixed m.p.).

Action of Benzylamine on Ic-e.—A solution of 1 g. of each of Ic-e in 40 ml. of dry benzene was treated with 2 ml. of benzylamine. The reaction mixture was refluxed for 4 hours, cooled, evaporated. The oily residue was triturated with cold light petroleum and the solid so obtained was crystallized from ethyl alcohol as colorless crystals, m.p. 153°. It was identified as phenylbenzylthiourea (m.p. and mixed m.p.[20]).

(18) *Org. Syntheses*, **15**, 3 (1935).

(19) T. Posner, *Ber.*, **35**, 809 (1902); B. H. Nicolet, THIS JOURNAL, **53**, 3066 (1931).

(20) A. E. Dixon, *J. Chem. Soc.*, **55**, 301 (1889).

Anal. Calcd. for $C_{14}H_{14}N_2S$: N, 11.57. Found: N, 11.01.

Ring Cleavage by Piperidine.—A reaction mixture of 1 g. of III (R = R′ = H) and 25 ml. of piperidine was refluxed for 24 hours. It was cooled, poured into dilute hydrochloric acid and was then extracted with ether. The ethereal solution gave upon evaporation colorless crystals, which upon crystallization from ethyl alcohol melted at 171°; identified as phenylpiperidylurea (m.p. and mixed m.p.[17]).

Piperidinium Adducts.—A mixture of 1 g. of the appropriate 5-arylidene-3-aryl-2,4-thiazolidinedione and 1 ml. of piperidine in 30 ml. of dry benzene was kept aside for 48 hours, during which time the solid substance dissolved gradually. The benzene was evaporated slowly, and the residue was triturated with cold ethyl alcohol. The solid, so obtained, was crystallized from benzene or from hot ethyl alcohol.

The piperidinium adducts VIII (see Table III) give colorless crystals, which decompose above their melting points to give the corresponding arylidene derivative.

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The Thermodynamic Stability of Porphyrinogens

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Uroporphyrinogen rapidly isomerizes in hot acid solution to a random mixture of isomers, yet the reduced porphyrin can be recovered in high yield. An explanation for the thermodynamic stability of this macrocycle based on the chelate effect is offered.

The porphyrinogens are hexahydro porphyrins in which the four pyrrole residues are linked through methylene bridges. These macrocycles were first studied by Fischer and co-workers[1] and have recently been shown to be the intermediates on the biosynthetic pathways of both heme and chlorophyll.[2] It has now been found that porphyrinogens isomerize readily in hot acid. Fischer and Rotthaus had previously noted that the reduction of mesoporphyrin with zinc dust in hot acetic acid, followed by autoxidation, produced porphyrins having one to three carboxyl groups per molecule.[3] Reduction in the cold or in alkaline solution did not form such mixtures. This isomerization offered a unique opportunity to study the thermodynamic stability of a macrocyclic compound. Uroporphyrinogen was chosen for this study because of its solubility properties, and because of its ready formation from porphobilinogen, its biosynthetic precursor. The isomers of uroporphyrinogen (or of the porphyrin) are composed of the four possible arrangements of the four similar pyrrole residues having two different substituents in the β,β'-positions (Fig. 1).

The isomerization of uroporphyrinogen in hot acid will reach equilibrium only if several conditions are met. First, the mixture of isomers should be a completely random one, since inspection of models of the four isomeric porphyrinogens shows no detectable hindrance among the side chains. Second, the same mixture must be obtained from any isomer. And third, this mixture should be independent of time. These conditions are met, and an explanation of the observed stability of this macrocycle is discussed in the first section. Some aspects of the mechanism of this isomerization are discussed in the second section.

Experimental

Materials.—Uroporphyrin III was obtained from the copper chelate found in turacao features,[4] uroporphyrin I and coproporphyrin I from the urine of a porphyric bull,[5] and coproporphyrin III from a fraction of broth used in the preparation of diphtheria toxin. In isolating uroporphyrin III *via* the porphyrinogen, acid was avoided to eliminate any possibility of isomerization. The porphyrinogen was titrated with iodine at *p*H 7, thus avoiding the green by-product formed during autoxidation in alkaline solution.[2,4] Coproporphyrin II was obtained by quantitative decarboxylation of uroporphyrin II.[6] Opsopyrroledicarboxylic acid, uroporphyrin II and a mixture of uroporphyrin isomers were synthetic products and the generous gifts of Dr. S. F. MacDonald. The porphyrins were purified by repeated chromatography on alumina and crystallization of the methyl esters. Porphyrinogens were prepared by reducing the porphyrins with sodium amalgam, as described.[2] Formaldehyde-C^{14} was obtained from Nuclear Chicago, activity $\sim$ 1 curie/mole. Other chemicals were of reagent grade.

Methods.—Spectra were measured with a Beckman model DU spectrophotometer equipped with a photomultiplier or with a Cary model 11. Melting points are corrected and were taken on a heated microscope stage, using polarized light to observe birefringence. Formaldehyde was assayed by the chromotropic acid method[7] and stock solutions standardized by the dimedon method.[8] The free porphyrins were measured spectrophotometrically in 1 *M* hydrochloric acid, and the esters in freshly distilled chloroform. The extinction coefficients are given in Table I.

TABLE I

MOLAR EXTINCTION COEFFICIENTS OF UROPORPHYRIN

Octamethyl ester in chloroform					
λ_{max}, mμ	406	502	536	572	627
$\epsilon \times 10^{3a}$	215	15.8	9.35	6.85	4.18
λ_{min}, mμ	458	522	554	598[b]	608
$\epsilon \times 10^3$	1.9	3.3	1.4	1.4	0.85

Uroporphyrin in 1 *M* HCl			
λ_{max}, mμ	406	552	593
$\epsilon \times 10^3$	505	17.5	6.15
λ_{min}, mμ	520[b]	570[b]	584
$\epsilon \times 10^3$	2.9	6.1	3.9

[a] ϵ = (l/cm. × mole per liter) log I_0/I; slit widths $\sim$ 0.01/mm. [b] Shoulder.

(1) H. Fischer and A. Stern, "Die Chemie des Pyrrols," Leipzig, 1940, Vol. II, pt. 2, p. 420 ff.

(2) D. Mauzerall and S. Granick, *J. Biol. Chem.*, **232**, 1141 (1958).

(3) H. Fischer and A. Rotthaus, *Ann. Chem.*, **484**, 85 (1930).

(4) R. E. H. Nicholas and C. Rimington, *Biochem. J.*, **50**, 194 (1951).

(5) T. K. With, *ibid.*, **68**, 715 (1958).

(6) P. R. Edmondson and S. Schwartz, *J. Biol. Chem.*, **205**, 605 (1953).

(7) E. Bremanis, *Z. Anal. Chem.*, **130**, 44 (1949).

(8) D. Spencer and T. Henshall, *Anal. Chim. Acta*, **11**, 428 (1954).