stirred at room temperature until a clear solution had been obtained. The solution was stirred for 2 hours and then 400 g. (4 moles) of concd. hydrochloric acid was added slowly to the stirred mixture. After the latter had been stirred for 30 minutes, it was heated on a steam-bath for 3 hours. The mixture was extracted thoroughly with ether, the extract washed with concd. sodium bicarbonate solution, the ether removed and the residue treated with concd. sodium bisulfite solution. The latter converted the lower ketones into their bisulfite addition products but did not affect the cycloöctanone. The mixture was triturated thoroughly with ether to extract the cycloöctanone, filtered, the ether layer separated and the aqueous layer extracted with ether. The combined ethereal solutions were washed with concd. sodium bicarbonate solution and dried over anhydrous magnesium sulfate. Upon distillation, 92.0 g. of product, b.p. 115–120° (65 mm.), m.p. 26–29°, was obtained. This material was shaken for several hours with a saturated sodium bisulfite solution, the mixture filtered and the solid material washed with sufficient ether to dissolve all of the ketone in the filtrate. From the ether solution there was obtained 13.0 g. of ketone, b.p. 115–118° (64 mm.), m.p. 23° and 72.5 g. (61%) of ketone, b.p. 118–120° (64 mm.),[12] m.p. 38–39°.[10]

(B).—1-(Aminomethyl)-cycloheptanol (124.0 g.) dissolved in 400 cc. of 10% hydrochloric acid was stirred, cooled to 0–5° and maintained at this temperature while 69.0 g. of sodium nitrite, dissolved in 300 cc. of water, was added dropwise. During a period of 2 hours, the mixture was stirred and allowed to warm to room temperature. The mixture was heated on a steam-bath for 1 hour, cooled, the oily layer was separated and the aqueous layer extracted with ether. The combined oil and extract were dried and distilled, b.p. 85–87° (17 mm.), m.p. 32–34°, yield 67.1 g. (26.4% based on cycloheptanone).

Five grams of 1-(hydroxymethyl)-cycloheptanol was isolated from the high boiling fraction; b.p. 142–147° (22 mm.), m.p. 50–51° after recrystallization from heptane.[13]

(12) E. P. Kohler, M. Tishler, H. Potter and H. T. Thompson (THIS JOURNAL, **61**, 1057 (1939)), obtained the pure ketone by hydrolysis of the semicarbazone, b.p. 115–115.5° (60 mm.), m.p. 43.8°.

(13) O. Wallach, *Ann.*, **345**, 148 (1906), found b.p. 135–140° (16 mm.), m.p. 50–51°.

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3-Trichloromethanesulfenyloxazolidine- and Thiazolidine-2,4-diones

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RECEIVED MARCH 14, 1953

Because of the appearance of 3-trichloromethane sulfenyloxazolidine- and thiazolidine-2,4-diones in the recent literature,[1] we wish to report our independent work on compounds of this and related types.

Our method of preparation was essentially the same as that of Kittleson,[1] namely, the reaction of trichloromethanesulfenyl chloride (perchloromethylmercaptan) with the sodium or potassium salts of the appropriate oxazolidine- or thiazolidine-2,4-diones. By this method, we have prepared four 3-trichloromethanesulfenyl-5-alkyl- and/or 5,5-dialkyloxazolidine-2,4-diones (Table I); three 3-trichloromethanesulfenyl-5-alkyl- and/or 5,5-dialkylthiazolidine-2,4-diones (Table I) and twelve 3-trichloromethanesulfenyl-5-alkylidene- and/or 5-aralkylidenethiazolidine-2,4-diones (Table II).

Incidental to this work, the preparations of 5-alkylidenethiazolidine-2,4-diones were investigated. Condensation of aromatic and related aldehydes such as furfural and cinnamaldehyde, with thiazolidine-2,4-dione in acetic acid containing sodium acetate, in general, gave 5-aralkylidene-2,4-diones in good yields.[2] However, when this method was applied to certain aliphatic aldehydes, the desired 5-alkylidene derivatives were obtained in much lower yields (see Experimental section). Attempts to condense aliphatic ketones with thiazolidine-2,4-dione have been unsuccessful. Since Brown, Bradsher, McCallum and Potter[3] have reported the successful condensation of ketones with rhodanine to give 5-alkylidenerhodanines and we have found that rhodanine can be transformed into thiazolidine-2,4-dione by the treatment of chloroacetic acid,[4] three of the 5-alkylidene- (namely, isopropylidene-, *s*-butylidene- and cyclohexylidene-) rhodanines reported by Brown and co-workers were thus converted to the corresponding 5-alkylidenethiazolidine-2,4-diones. The product thus obtained apparently contained some unchanged rhodanines as evidenced by their melting points and sulfur analyses. The separation of the two materials by recrystallization was found to be difficult. However, the crude products were satisfactory for subsequent reaction with trichloromethanesulfenyl chloride.

Experimental[9]

Materials.—The sodium salts of the oxazolidine-2,4-diones were prepared according to the method of Stoughton.[10] They were not isolated but used directly in the reaction with trichloromethanesulfenyl chloride (see below).

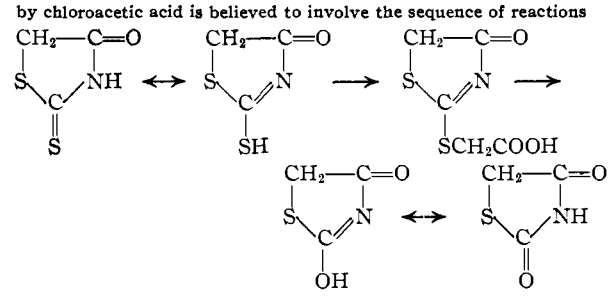
Thiazolidine-2,4-dione,[11] 5-methyl-[12] and 5,5-dimethyl-[13] thiazolidine-2,4-diones were prepared by known methods.

(1) (a) R. S. Healey, A. R. Kittleson and P. V. Smith, U. S. Patent, 2,553,775 (1951). (b) A. R. Kittleson, *Science*, **115**, 84 (1952).

(2) (a) F. Kucera, *Monatsh.*, **35**, 137 (1914); (b) D. Libermann, J. Hienberl and L. Hengl, *Bull. soc. chim., France*, 1120 (1948); (c) C. P. Lo, E. Y. Shropshire and W. J. Croxall, THIS JOURNAL, **75**, 4845 (1953).

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

(4) Many examples of "desulfurization" of heterocyclic compounds containing mercapto group by means of chloroacetic acid are known in the literature. For example, this method has been successfully applied to thiohydantoins,[5] thiouracils,[6] thiopyrimidines[7] and mercaptoquinolines.[8] The transformation of rhodanine to thiazolidine-2,4-dione by chloroacetic acid is believed to involve the sequence of reactions



(5) (a) T. B. Johnson, G. M. Pfau and W. W. Hodge, THIS JOURNAL, **34**, 1041 (1912); (b) T. B. Johnson and S. E. Hadley, *ibid.*, **37**, 171 (1915); (c) T. B. Johnson and R. Wrenshall, *ibid.*, **37**, 2133 (1915); (d) T. B. Johnson, A. J. Hill and E. B. Kelsey, *ibid.*, **42**, 1711 (1920).

(6) (a) H. L. Wheeler and L. M. Liddle, *Am. Chem. J.*, **40**, 547 (1908); (b) T. B. Johnson and E. H. Hemingway, THIS JOURNAL, **37**, 398 (1915).

(7) (a) T. B. Johnson and A. W. Joyce, *ibid.*, **38**, 1385 (1916); (b) A. R. Todd, *J. Chem. Soc.*, 357 (1946); (c) D. J. Brown, *J. Soc. Chem. Ind.* (London), **69**, 353 (1950).

(8) R. V. Jones and H. R. Henze, THIS JOURNAL, **46**, 1669 (1942).

(9) All melting points are uncorrected.

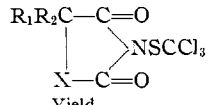
(10) R. W. Stoughton, THIS JOURNAL, **63**, 2376 (1941).

(11) J. Volhard, *J. prakt. Chem.*, [2] **9**, 9 (1874).

(12) H. L. Wheeler and B. Barnes, *Am. Chem. J.*, **24**, 78 (1900).

(13) H. Erlenmeyer and H. von Meyenburg, *Helv. Chim. Acta*, **20**, 1390 (1937).

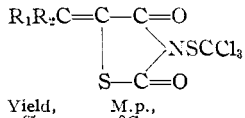
TABLE I



R_1	R_2	X	Method	Solvent[a]	Yield, %	M.p., °C.	Formula	Kjeldahl nitrogen, % Calcd.	Found
H	H	O	I	A	40	119–120	$C_4H_2Cl_3NO_3S$	5.6	5.7
CH_3	H	O	I	..	70	Oil	$C_5H_4Cl_3NO_3S$	5.3	5.3
CH_3	CH_3	O	I	B	57.5	91–93[b]	$C_6H_6Cl_3NO_3S$	5.0	5.0[c]
C_2H_5	CH_3	O	I	B	55	86–88[d]	$C_7H_8Cl_3NO_3S$	4.8	4.7[e]
H	H	S	II	C	72.5	117–118[f]	$C_4H_2Cl_3NO_2S_2$	5.3	5.1[g]
CH_3	H	S	II	..	76	Oil	$C_5H_4Cl_3NO_2S_2$	5.0	5.2
CH_3	CH_3	S	II	D	86	70–71	$C_6H_6Cl_3NO_2S_2$	4.8	4.7[h]

[a] Solvent for recrystallization: A, ethanol; B, methanol; C, acetone + petroleum ether; D, petroleum ether. [b] Kittleson (ref. 1b) reported a m.p. of 88–89°. [c] *Anal.* Calcd.: S, 11.5. Found: S, 11.6. [d] Kittleson (ref. 1b) reported a m.p. of 83–84°. [e] *Anal.* Calcd.: S, 10.9. Found: S, 10.9. [f] Hanley, Kittleson and Smith (ref. 1a) reported a m.p. of 111–116°. [g] *Anal.* Calcd.: S, 24.0. Found: S, 23.9. [h] *Anal.* Calcd.: S, 21.7. Found: S, 22.1.

TABLE II



R_1	R_2	Method	Solvent[a]	Yield, %	M.p., °C.	Formula	Nitrogen,[b] % Calcd.	Found	Sulfur, % Calcd.	Found
$(CH_3)_2CH-$	H	II	A	56	54–56	$C_8H_8Cl_3NO_2S_2$	4.4	4.4	19.9	20.2
$C_8H_{17}-$[c]	H	II	B	42	52–53.5	$C_{13}H_{18}Cl_3NO_2S_2$	3.6	3.5	16.4	16.8
OCH=CHCH=C—	H	II	C	62	149–150	$C_9H_4Cl_3NO_3S_2$	4.1	4.1	18.5	18.4
C_6H_5-	H	III	C	72	159–161	$C_{11}H_6Cl_3NO_2S_2$	4.0	3.9	18.0	18.0
2-ClC_6H_4-	H	III	D	55	141–143	$C_{11}H_5Cl_4NO_2S_2$	3.6	3.4	16.4	16.8
4-ClC_6H_4-	H	II	E	41.5	170–172	$C_{11}H_5Cl_4NO_2S_2$	3.6	3.7	16.4	16.8
3-$NO_2C_6H_4-$	H	II	E	50	148–150	$C_{11}H_5Cl_3N_2O_4S_2$	7.0	7.2[d]	16.0	15.9
4-$CH_3OC_6H_4-$	H	II	C	57	189–190	$C_{12}H_8Cl_3NO_3S_2$	3.7	3.7	16.6	16.9
3,4-$(OCH_2O)C_6H_3-$	H	II	E	65	178–179	$C_{12}H_6Cl_3NO_4S_2$	3.5	3.6	16.0	16.3
$C_6H_5CH=CH-$	H	III	C	60	173–174	$C_{13}H_8Cl_3NO_2S_2$	3.7	3.8	16.8	17.0
CH_3-	CH_3-	II	B	50	114–115	$C_7H_6Cl_3NO_2S_2$	4.6	4.9	34.8[e]	34.4[e]
$-CH_2CH_2CH_2CH_2CH_2-$		II	F	67	169–171	$C_{10}H_{10}Cl_3NO_2S_2$	4.1	4.1	18.4	18.8

[a] Solvent for recrystallization: A, ethanol; B, methanol; C, acetone + methanol; D, chloroform + acetone; E, chloroform; F, carbon tetrachloride + petroleum ether. [b] Kjeldahl method. [c] $(CH_3)_3CCH_2CH(CH_3)CH_2-$. [d] By A.O.A.C. salicylic acid + sodium thiosulfate method. [e] Chlorine, %.

The 5-aralkylidenethiazolidine-2,4-diones were prepared in good yields by the condensation of thiazolidine-2,4-dione with aromatic aldehydes in acetic acid containing sodium acetate.[2] By applying this method to isobutyraldehyde and 3,5,5-trimethylhexaldehyde, two new compounds were prepared.

5-Isobutylidenethiazolidine-2,4-dione, m.p. 69–71°, yield 19%. *Anal.* Calcd. for $C_7H_9NO_2S$: N, 8.2. Found: N, 7.8.

5-(3,5,5-Trimethylhexylidene)-thiazolidine-2,4-dione, m.p. 69–72°, yield 16.2%. *Anal.* Calcd. for $C_{12}H_{19}NO_2S$: N, 5.8. Found: N, 5.7.

Conversion of Rhodanine to Thiazolidine-2,4-dione.—A mixture of rhodanine (27 g.), chloroacetic acid (30 g.) and water (100 ml.) was heated under reflux for 18 hr. The solid which separated upon cooling was collected and washed with water. The air-dried product weighed 11.5 g. (49%) and melted at 121–123°. A mixture of this and an authentic sample of thiazolidine-2,4-dione showed no depression of melting point.

The following three 5-alkylidenethiazolidine-2,4-diones were similarly prepared from the corresponding 5-alkylidenerhodanines.[14]

5-Isopropylidenethiazolidine-2,4-dione, m.p. 160–162°,[15] yield 77%.

5-*s*-Butylidenethiazolidine-2,4-dione, m.p. 141–145°, yield 38%. *Anal.* Calcd. for $C_7H_9NO_2S$: N, 8.2. Found: N, 8.2.

5-Cyclohexylidenethiazolidine-2,4-dione, m.p. 139–142°,[16] yield 69%.

3-Trichloromethanesulfenyloxazolidine-2-4-dione. Method I.—A mixture of *n*-butyl glycolate (72 g.), urea (32 g.), sodium methoxide (29 g.) and anhydrous ethanol (250 ml.) was stirred and heated under reflux on a steam-bath for two hours while a slow current of air was drawn through the mixture. The ethanol was removed by distillation under diminished pressure. Water (200 ml.) was added to the residue and the mixture again concentrated under reduced pressure to ensure the complete removal of the ethanol. To the cooled solution of the sodium salt of oxazolidine-2,4-dione was slowly added a solution of trichloromethanesulfonyl chloride (100 g.) in petroleum ether (100 ml.) and the mixture stirred at room temperature for three hours. The white solid was collected, washed with petroleum ether and air-dried. The product weighed 53 g. and melted at 117–118°. Recrystallization from ethanol raised the m.p. to 119–120°.

3-Trichloromethanesulfenyl-5,5-dimethylthiazolidine-2,4-dione. Method II.—To a cooled and stirred solution containing 5,5-dimethylthiazolidine-2,4-dione (24.6 g.), sodium hydroxide (6.8 g.) and water (100 ml.) was slowly added a solution of trichloromethanesulfenyl chloride (31.4 g.) in carbon tetrachloride (70 ml.). After the addition was completed, the mixture was stirred at room temperature for several hours. The organic layer was separated and the

(14) By using ammonium hydroxide alone as the condensing agent in the reaction of ketones and rhodanine,[3] we were able to obtain 5-isopropylidenerhodanine in 80% and 5-*s*-butylidenerhodanine in 74% yield.

(15) C. C. J. Culvenor, W. Davies, J. A. Maclaren, P. F. Nelson and W. B. Savige, *J. Chem. Soc.*, 2573 (1949), prepared this compound by desulfurization of 5-isopropylidenerhodanine with lead acetate and reported a m.p. of 166°.

(16) D. Libermann, *et al.*,[2b] obtained this compound (m.p. 147°) by the direct condensation of cyclohexanone with thiazolidine-2,4-dione. This method yielded a purer product and is therefore preferred.

aqueous layer extracted with carbon tetrachloride. The combined carbon tetrachloride solution was evaporated under reduced pressure. The residue was an amber oil (43 g.) which solidified upon standing in the cold. The solid after recrystallization from petroleum ether weighed 37 g.

3-Trichloromethanesulfenyl-5-benzylidenethiazolidine-2,4-dione. Method III.—A mixture of the potassium salt of 5-benzylidenethiazolidine-2,4-dione[2c] (20 g.), trichloromethanesulfenyl chloride (15.3 g.) and carbon tetrachloride (150 ml.) was stirred for three hours. The solid was collected and recrystallized from a mixture of acetone and methanol. The 3-trichloromethanesulfenyl-5-benzylidenethiazolidine-2,4-dione thus obtained weighed 21 g.

Acknowledgment.—The authors are indebted to Mr. T. P. Callan and his staff for chemical analyses.

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Cholesterol and Companions. VII. Steroid Dibromides

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Among many reported instances of the bromination of Δ^5-stenoids, occasional reference has been made to the use of pyridine[1] or sodium acetate[2] as a buffer to neutralize traces of hydrogen bromide. Being unaware of any prior comparison, I wish to report that whereas bromination of cholesterol (150-g. lots) in ether by addition of a solution of bromine in acetic acid (Windaus[3] procedure) gave the dibromide (as the acetic acid complex) in 72–74% yield, the yield rose to 84% on addition of 0.14 equivalent of sodium acetate.

Windaus' method[3] of debromination with zinc dust in boiling acetic acid is applicable, with some limitations,[4,5] to stenyl acetate dibromides[6] and to the conversion of 5,6-dibromo-3-ketones into Δ^4-stene-3-ones,[3] but not to free sterol dibromides because of the ready acetylation of sterols in hot acetic acid.[7] Since newer methods of debromination utilizing sodium iodide,[8] ferrous chloride[9] or chromous chloride[5] did not seem well adapted to rapid, large-scale operation, the Windaus method was reinvestigated and a simple modification found that eliminates the difficulties: a suspension of the dibromide in ether containing a small amount of acetic acid is stirred at room temperature and zinc dust is added. A vigorous, exothermic reaction reminiscent of the formation of a Grignard reagent sets in and is soon complete; the yield of cholesterol from the dibromide is 93%. This material is free from cholestanol, 7-dehydrocholesterol, and lathosterol[7]; the first-crop material from methanol is free also from cerebrosterol[10] and from 25-hydroxycholesterol, a product of autoxidation that has been found present in old samples.

(1) A. Serini and W. Logemann, *Ber.*, **71**, 1362 (1938).
(2) J. Hier and K. Miescher, *Helv. Chim. Acta*, **34**, 359 (1951).
(3) A. Windaus, *Ber.*, **39**, 518 (1906).
(4) A. Butenandt and U. Westphal, *ibid.*, **67**, 2085 (1934).
(5) P. L. Julian, W. Cole, H. Magnani and E. W. Meyer, THIS JOURNAL, **67**, 1728 (1945).
(6) A. Windaus and A. Hauth, *Ber.*, **39**, 4378 (1906).
(7) L. F. Fieser, THIS JOURNAL, **75**, 4395 (1953).
(8) R. Schoenheimer, *Z. physiol. Chem.*, **192**, 86 (1930); *J. Biol. Chem.*, **110**, 461 (1935).
(9) H. Bretschneider and M. Ajtai, *Monatsh.*, **74**, 57 (1943).
(10) A. Ercoli and P. de Ruggieri, THIS JOURNAL, **75**, 3284 (1953).

The new procedure is also applicable to the debromination of 5,6-dibromocholestanone, obtainable on a large scale in 96.5% yield by oxidation of cholesterol dibromide with sodium dichromate in place of chromic acid.[11,12] The reaction with zinc dust in ether–acetic acid proceeds rapidly at 15–20° and Δ^5-cholestene-3-one of high purity is obtained in 88% yield. Debromination to the Δ^5-stenone with zinc dust and boiling ethanol[11] proceeds satisfactorily on a small scale but on a large scale gives material of inferior quality.

The three steps leading to Δ^5-cholestene-3-one seemed so satisfactory for preparative purposes that the further conversion to Δ^4-cholestene-3-one was explored. Isomerization catalyzed by a mineral acid or a base, while applicable on a micro scale,[11] gave inferior material as applied to 100-g. lots. However, oxalic acid in ethanol effected isomerization smoothly and afforded in 98% yield cholestenone corresponding in melting point (81–82°) and extinction coefficient to material purified by chromatography[13]; the over-all yield from cholesterol is 69%. Because of the high purity of the product and since all the steps from cholesterol can be completed in a few hours, this route rivals direct Oppenauer oxidation, which affords cholestenone, m.p. 77–79°, in 70–81% yield.[14]

Experimental

Cholesterol Dibromide.—One hundred and fifty grams of commercial cholesterol was dissolved in 1 l. of absolute ether by brief boiling in a 4-l. beaker, the solution was cooled to 25°, and a solution of 5 g. of anhydrous sodium acetate and 68 g. of bromine in 600 cc. of acetic acid was added. The solution turned yellow and a stiff paste of dibromide promptly resulted. The mixture was cooled to 20° and the product collected and washed with acetic acid (500 cc.) until the filtrate was colorless. A second crop of satisfactory material was obtained by adding 800 cc. of water to the combined yellow filtrate and washings, filtering the precipitate and washing it free of yellow mother liquor with acetic acid. When spread out on a paper and let dry in a hood at room temperature overnight, the material reaches a weight unchanged by drying for another day or two and appears from the infrared spectrum to be a 1:1 acetic acid complex, and percentage yields are calculated on this basis. Yields obtained in the first and second crops are: 182.4, 14.7 g.; 171.5, 25.2 g.; total yield 197.1, 196.7 g. (84%).

The infrared spectrum of the air-dried dibromide in chloroform resembles that of the 2:1 cholesterol–oxalic acid complex. In each case the band in the hydroxyl region is minor and shifted to about 3.0 μ, bands ordinarily associated with free carboxyl group and ester groups are absent, and a prominent band at 5.79–5.81 μ and a less intense band at 5.6–5.7 μ probably are characteristic of a carbonyl group in this particular type of acid–alcohol complex.

Cholesterol already purified through the dibromide afforded dibromide in only slightly higher yield (85%). In numerous earlier brominations made in exactly the same way but without addition of the small amount of sodium acetate the yield in the first crop was only 72–74% and the second crop contained much unbrominated material. Doubling of the amount of sodium acetate specified produced no change in the result.

Cholesterol from the Dibromide.—The acetic acid–moist dibromide from 150 g. of cholesterol was suspended in 1.2 l. of ether in a flask equipped with a stirrer and with provision for ice cooling when required. Fresh zinc dust (40 g.) was added in the course of 5 min. The first 5–10 g. was added without cooling; when the reaction had started, as evi-

(11) A. Butenandt and J. Schmidt-Thomé, *Ber.*, **69**, 882 (1936).
(12) H. H. Inhoffen, *ibid.*, **69**, 1134 (1936).
(13) E. R. H. Jones, P. A. Wilkinson and R. H. Kerlogue, *J. Chem. Soc.*, 392 (1942).
(14) R. V. Oppenauer, *Org. Syntheses*, **21**, 18 (1941).