Anal. Calcd. for $C_{20}H_{26}OS$: C, 76.38; H, 8.33; S, 10.20. Found: C, 76.55; H, 8.38; S, 10.35.

3-Cyclopentylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIc) had m.p. 102–103°; $[\alpha]_D$ +131° ($CHCl_3$); λ_{max}^{EtOH} 260–261 mμ (ε 8900); ν_{max}^{Nujol} 1733, 1590, 1556, 1496 (shoulder) 1258, 1046, 809, and 770 cm.$^{-1}$.

Anal. Calcd. for $C_{23}H_{30}OS$: C, 77.91; H, 8.53; S, 9.04. Found: C, 78.20; H, 8.48; S, 9.22.

3-Benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17β-ol (IId). A.—A solution of 500 mg. of 5β,10β-oxido-19-norandrostan-17β-ol-3-one (Ib) in a mixture of 10 ml. of acetone and 4 ml. of benzyl mercaptan was treated with 2 drops of concentrated hydrochloric acid and refluxed for 1 hr. The mixture was then cooled and the product was isolated as described for IIa. The crude product (410 mg.), recrystallized from methanol and dried under vacuum at 80° for 5 hr., afforded 360 mg. of benzyl sulfide IId: m.p. 107–108°; $[\alpha]_D$ +58° ($CHCl_3$); λ_{max}^{EtOH} 258 mμ (ε 8300); ν_{max}^{Nujol} 3540, 1588, 1556, 1496 (shoulder) 1038, 1005, 806, 768, 714, and 690 cm.$^{-1}$.

Anal. Calcd. for $C_{25}H_{30}OS$: C, 79.31; H, 7.99; S, 8.47. Found: C, 79.18; H, 8.03; S, 8.58.

B.—Sodium borohydride (50 mg.) in 2 ml. of water was added to a solution of 250 mg. of 3-thioestrone benzyl ether (IIa) in 10 ml. of tetrahydrofuran and the whole was stirred at room temperature for 8 hr. Water was added and the mixture was extracted with ether. After washing the collected extracts with water, evaporation of the solvent yielded 45 mg. of IId, m.p. 96–98°, which after crystallization from methanol and careful drying showed m.p. 107–108°, $[\alpha]_D$ +58° ($CHCl_3$), λ_{max}^{EtOH} and ν_{max}^{Nujol} as reported above.

$\Delta^{1,3,5(10)}$-Estratrien-17-one (III).—Raney nickel W2 (2 ml.) was added to a solution of 250 mg. of 3-thioestrone benzyl ether (IIa) in 10 ml. of absolute ethyl alcohol and the mixture was heated under reflux for 8 hr. After cooling, the catalyst was removed by filtration and washed with ethyl alcohol; afterwards the solution was evaporated to give 148 mg. of a product, m.p. 135–137°. Two recrystallizations from methanol yielded $\Delta^{1,3,5(10)}$-estratrien-17-one (III): m.p. 139–140°; $[\alpha]_D$ +166° (dioxane)[12]; λ_{max}^{EtOH} 214 mμ (ε 8200), 267 (470), and 274 (490); ν_{max}^{Nujol} 1735, 1601, 1574, 1494, 1050, 815, 750, and 741 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{22}O$: C, 84.99; H, 8.72. Found: C, 85.25; H, 8.72.

3-Mercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (3-Thioestrone) (IIe).—To 120 ml. of anhydrous liquid ammonia contained in a flask cooled in a Dry Ice–acetone bath, sufficient metallic sodium was added so that the blue color finally persisted for at least 10 min. (about 200 mg.). The air was displaced by nitrogen and a solution of 600 mg. of 3-benzylmercapto-$\Delta^{1,3,5(10)}$-estratrien-17-one (IIa) in a mixture of 20 ml. of anhydrous ether and 10 ml. of anhydrous dioxane (both solvents were freed of peroxides) was rapidly added. The blue color disappeared and was regenerated by the addition of a small amount of sodium. The mixture was then stirred for 10 min. and the reaction was terminated with ammonium chloride. The cooling bath was removed and the ammonia was allowed to evaporate. After dilution with ice-cold water and acidification with diluted hydrochloric acid the mixture was extracted with peroxide-free ether. The ether extract was washed with 3% sodium bicarbonate solution and then with water until neutral, dried with anhydrous magnesium sulfate, and concentrated under vacuum. The crude product, 360 mg., m.p. 200–202°, was purified by dissolution in 0.5 *N* sodium hydroxide and reprecipitation with diluted hydrochloric acid. Crystallization from acetone gave IIe (needles), m.p. 205–207°; $[\alpha]_D$ +164° (dioxane); λ_{max}^{EtOH} 213 mμ (ε 23,200), 242 (10,300), and 285 (1070); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 16,000); ν_{max}^{Nujol} 2520 (very weak), 1732, 1591, 1556, 1493, 1253, 1116, 1047, 1002, 807, and 769 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{22}OS$: C, 75.48; H, 7.74; S, 11.20. Found: C, 75.51; H, 7.73; S, 11.36.

3-Thioestradiol (IIf). A.—Benzyl sulfide (IIa, 600 mg.) was treated with sodium in liquid ammonia as reported for the preparation of IIe, except that the reaction time was extended to 1 hr. The reduction gave 340 mg. of 3-thioestradiol (IIf), m.p. 97–99°, which, after purification as reported for IIe (taking care of using solvents freed of peroxides), recrystallization from hexane, and drying at 80° under vacuum for 10 hr., showed m.p. 106–107.5°[13]; $[\alpha]_D$ +78° (dioxane); λ_{max}^{EtOH} 214 mμ (ε 22,000), 242 (9800), and 286 (980); $\lambda_{max}^{0.1\ N\ NaOH}$ 265 mμ (ε 16,600); ν_{max}^{Nujol} 3550, 2520, 1592, 1556, 1496, 1244, 1065, 1049, 1005, 809, and 770 cm.$^{-1}$.

Anal. Calcd. for $C_{18}H_{24}OS$: C, 74.95; H, 8.39; S, 11.12. Found: C, 75.06; H, 8.27; S, 10.98.

B.—Benzyl sulfide IId, reduced as above, yielded IIf identical with the product prepared according to A.

C.—3-Thioestrone (IIe, 250 mg.) was reduced with 50 mg. of sodium borohydride in aqueous tetrahydrofuran for 8 hr. at room temperature. Isolation and purification of the product with the aforementioned care afforded 200 mg. of IIf, m.p. 106–107.5°, $[\alpha]_D$ +78.5° (dioxane), identical with the product prepared according to A and B.

17β-Hydroxy-$\Delta^{1,3,5(10)}$-estratrien-3-yl Disulfide.—A solution of 50 mg. of 3-thioestradiol (IIf) in ethanol (2 ml.) was treated with a solution of 100 mg. of $FeCl_3 \cdot 6H_2O$ in ethanol (1 ml.) and allowed to stand at room temperature for 2 hr. Dilution with water gave a crude product, which was recrystallized from methanol to give 40 mg. of the disulfide: m.p. 194–196°[2]; $[\alpha]_D$ +96° (dioxane); λ_{max}^{EtOH} 235–240 mμ (ε 22,000); ν_{max}^{Nujol} 3410, 1590, 1500 (shoulder), 1245, 1132, 1068, 1050, 1005, 876, 808, and 769 cm.$^{-1}$.

Anal. Calcd. for $C_{36}H_{46}O_2S_2$: C, 75.21; H, 8.07; S, 11.16. Found: C, 74.97; H, 8.18; S, 11.08.

Reduction of the product with sodium in liquid ammonia in the conventional manner gave 3-thioestradiol.

(12) For III, lit.[7] m.p. 135–136°, $[\alpha]_D$ +400°(?) (dioxane).

(13) Hecker[2] reported for IIf partially different data: m.p. 98–100°; λ_{max} 241 mμ (ε 9350), 273.5 (1330), and (295) (750); $\lambda_{max}^{0.1\ N\ NaOH}$ 267 mμ (ε 16,000); ν_{max}^{KBr} 3356 and 2551 cm.$^{-1}$.

The Aldol Condensation of Methylene Bis(ethyl sulfone). A Novel Synthesis of Benzofurans

MARVIN L. OFTEDAHL, JOSEPH W. BAKER, AND MARTIN W. DIETRICH

Research Department, Organic Chemicals Division, Monsanto Company, St. Louis, Missouri 63177

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Although a few 1,1-bisalkylsulfonyl-1-alkenes (**2**) are known,[1,2] a Knoevenagel condensation[3] between a methylenebis(alkyl sulfone) and an aldehyde which proceeds directly to 1,1-bisalkylsulfonyl-1-alkenes has not been described. The β-hydroxy sulfones (**1**), the

$$\underset{\mathbf{1}}{RCH(OH)CH(SO_2Et)_2} \qquad \underset{\mathbf{2}}{RCH{=}C(SO_2Et)_2}$$

expected intermediates by this procedure, are known to undergo the retro-aldol reaction common to such substances.[1,4] However, it was anticipated that the efficient removal of water from the reaction and the use of a catalyst of the type recommended by Cope[3] would suppress this side reaction. Accordingly, when an equimolar mixture of aldehyde and methylenebis(ethyl sulfone) (**3**) was heated in refluxing toluene in the presence of a trace of piperidine acetate, the desired 1,1-bis(ethylsulfonyl)-2-substituted ethylenes were obtained in moderate yield (Table I).

When salicylaldehydes were employed in the reaction sequence, a slight excess of the equimolar quan-

(1) D. L. MacDonald and H. O. L. Fischer, *J. Am. Chem. Soc.*, **74**, 2087 (1952).

(2) L. C. Rinzema, J. Stoffelsma, and J. F. Arens, *Rec. trav. chim.*, **78**, 354 (1959); A. L. Barney, U. S. Patent 2,641,594 (June 9, 1953).

(3) E. Knoevenagel, *Ber.*, **29**, 172 (1896); **31**, 730 (1898); A. C. Cope, *J. Am. Chem. Soc.*, **59**, 2327 (1937).

(4) E. Rothstein, *J. Chem. Soc.*, 684 (1934); H. J. Backer, *et al.*, *Rec. trav. chim.*, **70**, 365 (1951); L. Hough and T. J. Taylor, *J. Chem. Soc.*, 970 (1956).

TABLE I

1,1-BIS(ETHYLSULFONYL)-2-X-ETHYLENES

R—CH=C($SO_2CH_2CH_3$)$_2$

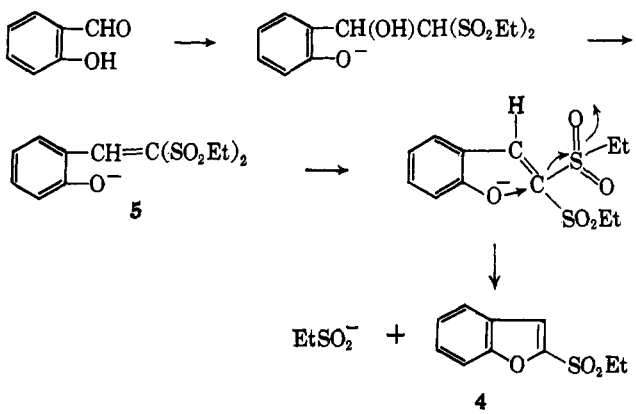
R	M.p., °C.	Yield, %[a]	Formula	Calcd., % C	H	S	X	Found, % C	H	S	X
Phenyl[b]	96–97	29	$C_{12}H_{16}O_4S_2$	50.0	5.59			49.8	5.63		
3,4-Dichlorophenyl	121–122	16.5	$C_{12}H_{14}Cl_2O_4S_2$	40.3	3.95		19.8[c]	40.5	4.16		19.6[c]
4-Nitrophenyl	180–181	48	$C_{12}H_{15}NO_6S_2$	43.2	4.54	19.2	4.20[d]	43.3	4.65	18.9	4.00[d]
n-Heptyl	180–187 (0.3)[e]	38	$C_{13}H_{26}O_4S_2$	50.3	8.44	20.7		50.4	8.60	20.9	

[a] Corrected for unchanged starting material. [b] Lit.[2] m.p. 92–93°. [c] Chlorine. [d] Nitrogen. [e] B.p., °C. (mm.).

tity of piperidine was employed as catalyst in order to neutralize the phenolic hydroxyl group in the aldehyde. Completion of this reaction resulted in the elimination of one of the ethylsulfonyl groups as ethanesulfinic acid and the formation of a 2-ethylsulfonylbenzofuran (**4**) in good yield. Application of the reaction to a variety of substituted salicylaldehydes indicated the cyclization to be general for the salicylaldehydes. The ethylsulfonylbenzofurans were characterized by means of elemental analysis and infrared and nuclear magnetic resonance spectra (Tables II and III). The n.m.r. spectra were particularly useful for structure determinations, yielding data that were readily interpreted by first-order methods.

The scission of the carbon–sulfur bond in sulfones with the resultant formation of a sulfinic acid is well known.[5–7] The formation of ethanesulfinic acid in the course of forming **4** from a salicylaldehyde and **3** was established by means of a color test for sulfinic acids[8] on the aqueous extracts of the cyclization reaction mixtures.

The 2-ethylsulfonylbenzofurans **4** probably arise *via* the reaction sequence shown. Following the initial condensation–dehydration sequence, intramolecular attack of the phenolate anion upon the carbon bearing the sulfone group results in ring closure with the concomitant elimination of ethanesulfinic acid, yielding **4**. Any pathway to **4** involving attack of phenolate or piperidine at the olefinic position β to the sulfone groups in **5** is improbable because of the geometry of **5** and the fact that the phenolate anion can supply electrons to the sulfone olefin, offsetting the strong inductive effect of the sulfone groups **5a–5b** and materially reducing the tendency of **5** to add nucleophiles.



The cyclization proceeded with equal facility and comparable yields when triethylamine was employed as the catalyst and no reaction occurred when piperidine acetate was used. The benzofuran **4** may be obtained, but in much lower yield, if less than an equimolar quantity of piperidine is employed, indicating the importance of neutralizing the phenolic hydroxyl group. Attempts to isolate the intermediate *o*-hydroxy-β-bis(ethylsulfonyl)styrene were unsuccessful.

Experimental

Melting points were determined on a Fisher-Johns melting point apparatus and are corrected. Appropriate analytical and spectroscopic data may be found in Tables I, II, and III. Methylenebis(ethyl sulfone) (**3**) was prepared by peracetic acid oxidation of methylenebis(ethyl sulfide).[9,10]

1,1-Bis(ethylsulfonyl)-2-Substituted Ethylenes (2).—A toluene solution, 0.5 *M* each in the appropriate aldehyde and **3**, was treated with a small quantity of piperidine acetate (1–3 g./mole of reactants) and heated at reflux in a flask fitted with a Dean–Stark trap. Upon completion of the reaction, as indicated by the cessation of water evolution, the reaction mixture was freed of toluene at reduced pressure. The product was purified either by distillation or by recrystallization from isopropyl alcohol.

Substituted 2-Ethylsulfonylbenzofurans (4).—A toluene solution, 0.5 *M* each in the appropriate salicylaldehyde and **3**, was treated with 1.1 times the equimolar quantity of piperidine and heated at reflux in a flask fitted with a Dean–Stark trap. Upon completion of the reaction (cessation of water evolution), the mixture was freed of solvent at reduced pressure. The oily or semisolid residue was dissolved in the minimum amount of boiling isopropyl alcohol and the resulting solution was treated with an amount of glacial acetic acid slightly in excess of the quantity of piperidine used to catalyze the condensation. The acidified mixture was decolorized with activated charcoal, and allowed to cool. The resulting crystalline product was purified by recrystallization from isopropyl alcohol.

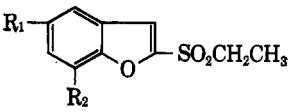
The presence of ethanesulfinic acid was indicated by trituration of a portion of the oily reaction residue (after removal of the solvent) with water. The water layer was collected and treated with a hydrochloric acid solution of ferric chloride as described by Feigl.[8] The resulting precipitate indicated the presence of sulfinic acid in the reaction mixture.

When 3,5-dichlorosalicylaldehyde was treated with **3** as described above, but with 1.1 times the equimolar quantity of triethylamine as the catalyst, 5,7-dichloro-2-ethylsulfonylbenzofuran was obtained in 65% yield. The yield of this compound

(5) G. W. Fenton and C. K. Ingold, *J. Chem. Soc.*, 705 (1930).
(6) A. W. Johnson, *Chem. Ind.* (London), 1119 (1963).
(7) S. Hünig and O. Boes, *Ann.*, **579**, 28 (1953).
(8) F. Feigl, "Spot Tests in Organic Chemistry," translated by R. E. Oesper, Elsevier Publishing Co., New York, N. Y., 1956, p. 251.
(9) H. Böhme, *Ber.*, **69B**, 1610 (1936).
(10) Although a procedure for this oxidation with hydrogen peroxide employing glacial acetic acid as the solvent has been described,[9] we found that treatment of the pure dithioacetal (b.p. 81–82° at 20 mm.) with an equivalent amount of peracetic acid without a solvent gave pure **3** (m.p. 102–103°), which crystallized from the reaction mixture in 75% yield. As with all peracid–sulfide oxidations, efficient cooling and control of the addition rate was necessary to moderate the strongly exothermic reaction.

TABLE II

2-ETHYLSULFONYLBENZOFURANS

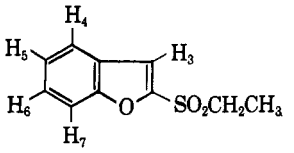


R_1	R_2	M.p., °C.	Yield, %	Formula	Calcd., % C	H	S	X	Found, % C	H	S	X
H	H	91–92	59.5	$C_{10}H_{10}O_3S$	57.1	4.79	15.2		57.2	4.87	15.0	
Cl	H	123–124	54	$C_{10}H_9ClO_3S$	49.1	3.71	13.0	14.5[a]	49.0	3.87	13.1	14.4[a]
Br	H	113–114	39	$C_{10}H_9BrO_3S$	41.5	3.14	11.1	27.6[b]	41.6	3.22	10.8	27.9[b]
NO_2	H	181–182	22	$C_{10}H_9NO_5S$	47.0	3.55	12.6	5.49[c]	47.3	3.58	13.0	5.22[c]
H	NO_2	187–188	25	$C_{10}H_9NO_5S$	47.0	3.55	12.6	5.49[c]	47.2	3.78	12.3	5.62[c]
Cl	Cl	141–142	62	$C_{10}H_8Cl_2O_3S$	43.0	2.89	11.5	25.4[a]	43.0	2.88	11.2	25.6[a]

[a] Chlorine. [b] Bromine. [c] Nitrogen.

TABLE III

N.M.R. PROPERTIES OF SUBSTITUTED 2-ETHYLSULFONYLBENZOFURANS[a]



Substituent	Chemical shift[b] δ (p.p.m.)[c]	Assignment	Coupling constant, J (c.p.s.)
None	7.94 (s)	H_3	
	7.3 (m)	H_4, H_5, H_6, H_7	
	3.13 (q)	$-CH_2-$	
	1.28 (t)	$-CH_3$	
5-Chloro	8.39 (s)	H_3	
	8.05 (d, d)	H_4	$J_{46} = 1.8$
	7.65 (m)	H_6, H_7	$J_{47} = 0.8$
	3.32 (q)	$-CH_2-$	$J_{67} = 8.2$
	1.39 (t)	$-CH_3$	
5-Bromo	7.99 (s)	H_3	
	7.78 (m)	H_4	
	7.32 (m)	H_6, H_7	$J_{67} = 9.0$
	3.17 (q)	$-CH_2-$	
	1.32 (t)	$-CH_3$	
5-Nitro	8.95 (d)	H_4	$J_{46} = 2.3$
	8.54 (d, d)	H_6	$J_{67} = 9.9$
	8.49 (s)	H_3	
	7.87 (d, d)	H_7	$J_{47} = 0.8$
	3.38 (q)	$-CH_2-$	
	1.43 (t)	$-CH_3$	
7-Nitro	8.54 (s)	H_3	
	8.40 (m)	H_4, H_6	$J_{45} = J_{56} = 8.5$
	7.70 (t)	H_5	
	3.32 (q)	$-CH_2-$	
	1.42 (t)	$-CH_3$	
5,7-Dichloro	8.36 (s)	H_3	
	7.85 (d)	H_4	$J_{46} = 1.9$
	7.55 (d)	H_6	
	3.27 (q)	$-CH_2-$	
	1.38 (t)	$-CH_3$	

[a] Spectra were obtained in deuteriochloroform solution containing internal tetramethylsilane (TMS). A Varian HR-60 high resolution n.m.r. spectrometer operating at 60 Mc./sec. was employed. Spectra were calibrated by the audiofrequency side-band technique [J. T. Arnold and M. E. Packard, *J. Chem. Phys.*, **19**, 1608 (1951)] utilizing a frequency counter. [b] Referred to internal TMS. [c] s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet.

was 62% when piperidine was employed as the catalyst (Table II).

The use of 0.1 the equimolar amount of piperidine in the cyclization of 3,5-dichlorosalicylaldehyde with **3** resulted in the isolation of 5,7-dichloro-2-ethylsulfonylbenzofuran in only 11.7% yield and the recovery of 55% of unchanged **3**.

Attempts to cyclize 3,5-dichlorosalicylaldehyde employing a small amount of piperidine acetate (10 g./mole of aldehyde) resulted in no detectable reaction and 92% of **3** was recovered unchanged.

Acknowledgment.—We are indebted to Mr. D. R. Beasecker and his staff for the elemental analyses and to Mr. Alan Tharp for assistance in the infrared measurements.

The Addition of Alcohols to Dicyandiamide. A Correction of the Literature

GUY D. DIANA, ETHEL S. ZALAY, AND ROYAL A. CUTLER, JR.

Sterling-Winthrop Research Institute, Rensselaer, New York

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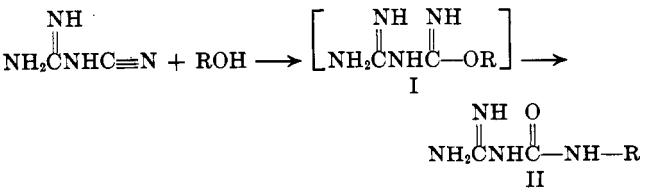
Among the methods claimed as being useful for the synthesis of 1-amidino-3-alkylureas is the one published by Dutta and Ray.[1] The procedure, as reported, involved the addition of an alcohol to dicyandiamide in the presence of copper acetate. The resulting chelate salt was treated with ammonium sulfate which precipitated the insoluble copper ammonium sulfate salt of the alleged 1-amidino-3-alkylurea. Treatment with hydrogen sulfide produced the free base. The authors suggested that a rearrangement occurred by which the 1-amidino-O-alkylurea originally formed (I) was transformed into the compounds in question (II).



We have now shown unequivocally that the compounds prepared by Dutta and Ray are, in fact, not the 1-amidino-3-alkylureas (II) but rather the O-alkylureas (I).

A search of the literature revealed a method of synthesizing 1-amidino-3-alkylureas (II)[2] which was unambiguous. This method involved the reaction

(1) R. L. Dutta and P. Ray, *J. Indian Chem. Soc.*, **36**, 499 (1959).

(2) F. H. S. Curd, D. G. Davey, and D. N. Richardson, *J. Chem. Soc.*, 1732 (1949).