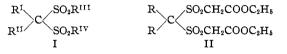
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

## Dialkyl bis-(Carbethoxymethanesulfonyl)-methanes

BY R. L. Shriner, J. M. Cross and Elmer H. Dobratz

One class of compounds which are useful for their hypnotic and sedative action is that of the dialkyl bis-(alkylsulfonyl) methanes represented by the type formula I. To this class belong such



well-known compounds as sulfonal, trional and tetronal. These compounds are rather toxic and cannot be used in certain cases of impairment of cardiac or renal function. They also have a very limited solubility in water, tetronal, the most active hypnotic, being only very slightly soluble. Many different alkyl groups have been inserted<sup>1</sup> in an effort to improve the pharmacological action. The effect of introducing other functional groups into the alkyl residues has been studied in a few cases for R<sup>I</sup> and R<sup>II</sup> but not at all for R<sup>III</sup> and R<sup>IV</sup>. This modification of structure has been made in the present investigation in which the synthesis of a series of dialkyl bis-(carbethoxymethanesulfonyl)-methanes of formula II is described.

The detoxifying action of a carboxyl or ester group is well known and it was hoped that its presence would eliminate some of the toxic effects. The compounds of formula II should also be more soluble in the alkaline body fluids since they contain two active methylene groups which are capable of forming salts.<sup>2</sup>

These compounds were synthesized by condensing ketones with mercaptoacetic acid in the presence of hydrogen chloride.

The thioketals (III) were then esterified by treatment with absolute alcohol and hydrogen chloride in the presence of anhydrous magnesium sulfate which was used to absorb the water formed,

(1) See Fränkel, "Die Arzneimittel Synthese," Verlag von Julius Springer, Berlin, 1927, pp. 526-530. thus preventing excessive hydrolysis of the thioketals. In order to isolate these esters (IV) it was necessary to dissolve the reaction mixture in absolute ether and, after the magnesium sulfate was filtered off, to wash this solution rapidly with ice water and dilute alkali. This removal of the acid was necessary to prevent hydrolysis of the thioacetal linkage in IV. The esters were then obtained in good yields by distilling off the ether and removing the last traces of ether by gentle heating *in vacuo*.

Only the dimethyl thioketal could be distilled in vacuo without decomposition. The diethyl, di-n-propyl and di-n-butyl derivatives were found to split out ethyl mercaptoacetate (V) during distillation with the formation of the corresponding carbethoxymethylmercaptoalkenes (VI), according to the general reaction

The oxidation of the thioketal (IV) to the disulfone (II) proved rather difficult owing to the sensitivity of the compounds to both acids and alkalies. Oxidations by hydrogen peroxide, chromic oxide, and neutral or alkaline permanganate were not successful. The disulfones were finally obtained in yields of 30-40% by adding a carbon tetrachloride solution of the thioketal (IV) to a 10% sulfuric acid solution into which powdered potassium permanganate was sifted so that an excess of permanganate was always present. Al-

though the acid caused some hydrolysis of the thioketal, part of the latter was oxidized to the disulfone. The disulfones corresponding to formula II were prepared in which the alkyl groups were varied from methyl to n-butyl. Their analyses and physical properties and the intermediates are given in the experimental

part. These sulfones were all soluble in sodium hydroxide solution but insoluble in sodium bicarbonate solution. They were soluble to a limited extent in 2% sodium carbonate solution.

Through the courtesy of the Lilly Research Laboratories the pharmacological action of these

<sup>(2)</sup> Ashley and Shriner, THIS JOURNAL, 54, 4410 (1932).

compounds was studied. It was found that they were comparatively non-toxic as compared to sulfones of type I, which indicates the detoxifying effect caused by the introduction of the carbethoxy group. However, regardless of the mode of administration, oral, intravenous or intraperitoneal injection, none of these disulfones caused hypnosis in the experimental animals. Evidently the presence of the salt forming methylene groups caused too great a shift in the oil-water distribution ratio which is necessary for hypnotic action.

## Experimental

Mercaptoacetic Acid.—In order to prepare the thioketals in good yields it was necessary to have the pure anhydrous acid. Eastman Kodak Co. technical mercaptoacetic acid (thioglycolic acid) was mixed with an equal volume of toluene and the mixture subjected to distillation. After the water and toluene had distilled the residual oil was distilled under reduced pressure. The fraction boiling 87–90° at 4 mm. was collected and used.

Dialkyl bis-(Carboxymethylmercapto)-methanes (III).— A mixture of 50 g. of the anhydrous mercaptoacetic acid and 50 g. of each of the anhydrous ketones was saturated with dry hydrogen chloride. The flask was stoppered and chilled in an ice-salt mixture until crystallization was complete. The crystals were filtered, washed with petroleum ether, then with cold water and dried in a vacuum desiccator. Table I summarizes their properties.

## TABLE I

$R_2C(-SCH_2COOH)_2$
----------------------

R	M. p., °C. (corr.)	Vield, %	Molecular formula	S Analy Calcd.	rses, % Found
CH3	134 - 135	82	$C_7H_{12}O_4S_2$	28.57	28.57
$C_2H_5$	125 - 126	96	$C_9H_{16}O_4S_2$	25.39	25.11
$n-C_3H_7$	133 - 134	92	$C_{11}H_{20}O_4S_2$	22.85	22.56
$n-C_4H_9$	86-87	94	$C_{13}H_{24}O_4S_2$	20.80	21.01

Dialkyl bis-(Carbethoxymethylmercapto)-methanes(IV). -Fifty grams of each of the above acids was dissolved in 600 ml. of absolute ethanol in a two-liter, three-necked flask fitted with a mercury-sealed stirrer and protected by a calcium chloride tube. The flask was immersed in an ice-bath and 75 g. of anhydrous magnesium sulfate was added. Dry hydrogen chloride was passed over the vigorously stirred suspension for six hours. Six hundred milliliters of absolute ether was then added. The magnesium sulfate was removed by filtration and washed with a small amount of absolute ether. The combined filtrate and washings were poured into ice-cold, dilute sodium hydroxide and shaken thoroughly. The ether layer was separated and washed again with ice-cold sodium hydroxide and twice with ice water. An emulsion formed upon washing with ice water. It was broken by adding a few grams of sodium sulfate and shaking thoroughly. After drying over sodium sulfate the ether was distilled and the last traces removed by gentle heating (not over  $60^{\circ}$ ) in vacuo. The properties of these esters are summarized in Table II.

Upon distillation *in vacuo* the diethyl, di-*n*-propyl and di*n*-butyl-*bis*-(carbethoxymethylmercapto)-methanes were found to decompose. After distillation from a Claisen flask the combined fractions obtained from each compound were separated by distillation through a column packed with glass helices.<sup>3</sup>

The lowest boiling fraction from the three compounds was found to boil at 25° at 1.8 mm. and possessed  $d^{20}_{20}$ 1.0980;  $n^{20}$ D 1.4578. The *M*D calculated for ethyl mercaptoacetate was 30.02 and the found value, 29.85. The solid derivatives of this ester mentioned in the literature are the chloromercuri derivatives which Wislicenus<sup>4</sup> mentioned as melting somewhere under 100°, and a nickel complex<sup>6</sup> which melted at 101°. The ethyl chloromercurimercaptoacetate was prepared by adding an alcoholic solution of the ester to an excess of mercuric chloride dissolved in alcohol. The white amorphous reaction HSCH<sub>2</sub>COOC<sub>2</sub>H<sub>5</sub> + HgCl<sub>2</sub> —>

#### $ClHgSCH_2COOC_2H_5 + HCl$

product was removed by filtration and recrystallized from alcohol. Fine, colorless needles melting sharply at 105° were obtained.

Anal. Calcd. for C<sub>4</sub>H<sub>7</sub>O<sub>2</sub>SHgC1: S, 9.01; Hg, 56.49. Found: S, 9.12; Hg, 56.59.

For comparison purposes, mercaptoacetic acid was esterified and the properties of the synthetic ethyl ester found to check those recorded above. The chloromercuri derivative was also made and found to melt at  $105^{\circ}$  and its melting point was not depressed by addition of the above sample.

The second fraction obtained corresponded to the carbethoxymethylmercaptoalkenes (VI). Their properties and analyses are as follows:

**3-Carbethoxymethylmercaptopentene-2.**—B. p. 78.5° at 2 mm.,  $d^{20}_{20}$  1.0127,  $n^{20}_{D}$  1.4797; *M*<sub>D</sub> calcd. 52.82; found, *M*<sub>D</sub> 52.73.

Anal. Calcd. for  $C_0H_{16}O_2S$ : S, 17.02. Found: S, 17.16.

**4-Carbethoxymethylmercaptoheptene-3.**—B. p. 90° at 1.8 mm.,  $d^{20}_{20}$  0.9838;  $n^{20}$ D 1.4749; *M*D calcd. 62.06; found, *M*D 61.87.

Anal. Calcd. for  $C_{11}H_{20}O_2S$ : S, 14.81. Found: S, 15.00.

**5-Carbethoxymethylmercaptononene-4.**---B. p. 108° at 1.8 mm.;  $d^{29}_{20}$  0.9588;  $n^{29}$ D 1.4750; *M*D calcd. 72.29; found, *M*D 72.11.

Anal. Calcd. for  $C_{13}H_{24}O_2S$ : S, 13.13. Found: S, 13.16.

Dialkyl bis-(Carbethoxymethanesulfonyl)-methanes(II). —A solution of 4 g. of each of the above esters in 35 cc. of carbon tetrachloride was added over a period of an hour to 300 cc. of 10% sulfuric acid solution to which was added powdered potassium permanganate at such a rate that the solution was always purple. From 10 to 17 g. of permanganate was required. The mixture was stirred for an additional hour and then sodium bisulfite added until the solution was clear. The carbon tetrachloride layer was

<sup>(3)</sup> Whitmore and Lux, THIS JOURNAL, 54, 3448 (1932).

<sup>(4)</sup> Wislicenus, Ann., 146, 145 (1868).

<sup>(5)</sup> Drummond and Gibson, J. Chem. Soc., 3073 (1926).

$R_2C(SCH_2COOC_2H_5)_2$									
R	В. р., °С.	Press., mm.	Vield, %	d <sup>20</sup> 20	n <sup>20</sup> D	MD Calcd.	$M_{D}$ Found	S Analy Calcd.	yses, % Found
CH8	152 - 153	1.8	69	1,1368	1.4970	72.26	72.18	22.81	22.92
$C_2H_5$	162 - 163	<b>2</b>	65	1.1140	1.4969	81.50	80.80	20.77	20.73
$n-C_3H_7$	178-179	3	89	1.0758	1.4909	90.74	90.49	19.04	19.06
n-C <sub>4</sub> H <sub>9</sub>	183 - 184	3	90	1.0269	1.4862	99.99	99.64	17.58	17.55

TABLE II R.C(SCH2COOC1H5)

separated, washed with water and sodium bicarbonate solution and dried with sodium sulfate. The carbon tetrachloride was evaporated and the residual oil chilled in an ice-bath until it solidified. The sulfones were recrystallized from a mixture of ethanol and water. They were all

# TABLE III

$R_2C(-SO_2CH_2COOC_2H_b)_2$							
R	M. p., °C. (corr.)	Yield, %	Mol. formula	S Analy Calcd.	ses, % Found		
CH3	84-85	32	$C_{11}H_{20}O_8S_2$	18.61	18.79		
$C_2H_5$	73-74	41	$C_{13}H_{24}O_8S_2$	17.20	17.08		
$n-C_{3}H_{7}$	90-91	37	$C_{15}H_{28}O_8S_2$	16.00	15.82		
$n - C_4 H_9$	74-75	42	$C_{17}H_{32}O_8S_2$	14.95	15.07		

colorless crystals. Their properties are summarized in Table III.

### Summary

A series of dialkyl *bis*-(carbethoxymethanesulfonyl)-methanes has been prepared by oxidizing dialkyl *bis*-(carbethoxymethylmercapto)-methanes. The latter were obtained by esterification of the corresponding acids which were produced by the reaction between mercaptoacetic acid and the simple ketones. These disulfones possessed no hypnotic activity.

URBANA, ILLINOIS

RECEIVED APRIL 28, 1939

[CONTRIBUTION FROM THE NOVES CHEMICAL LABORATORY OF THE UNIVERSITY OF ILLINOIS]

## Cyclization of Dienynes. VII.<sup>1</sup> Dehydrogenation of *trans*-Dodecahydrophenanthrene and a Further Study of *trans*-3,4-Dialkyloctalones

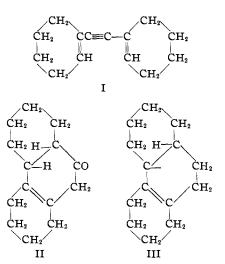
By C. S. MARVEL, RALPH MOZINGO<sup>2</sup> AND E. C. KIRKPATRICK<sup>3</sup>

In an attempt to prepare phenanthrene derivatives<sup>4</sup> it was found that the cyclization of di- $\Delta^{1}$ cyclohexenylacetylene (I) gave a ketone described as  $\Delta^{11}$ -dodecahydro-9-phenanthrone (II), which on Clemmensen reduction yielded a hydrocarbon considered to be  $\Delta^{11}$ -dodecahydrophenanthrene (III). Attempts to dehydrogenate these compounds with selenium did not give phenanthrene or a phenanthrol. The hydrocarbon (III) was converted by this treatment to a compound which appeared to be identical with the *trans-as*-octahydrophenanthrene (IV) reported by van de Kamp and Mosettig.<sup>5</sup> Moreover, reduction of the hydrocarbon (III) gave a product with physical properties which checked closely those of tetradecahydrophenanthrene obtained by the hydrogenation of phenanthrene.<sup>4</sup> These facts seemed to establish the phenanthrene

(1) For the sixth communication in this series see Pinkney and Marvel, THIS JOURNAL, 59, 2669 (1937).

(2) Röhm and Haas Special Research Assistant in Chemistry, 1937-1939.

(4) (a) Pinkney, Nesty, Wiley and Marvel, THIS JOURNAL, 58, 972 (1936);
(b) Pinkney, Nesty, Pearson and Marvel, *ibid.*, 59, 2666 (1937).



structure and pointed to the conclusion that selenium does not dehydrogenate fused *trans* ring systems.

Recently, however, Cook, Hewett and Robinson<sup>6</sup> have shown that van de Kamp and Mosettig's *trans-as*-octahydrophenanthrene contains also the *cis*-isomer (V) and the spiran (VI).

(6) Cook, Hewett and Robinson, J. Chem. Soc., 168 (1939).

<sup>(3)</sup> Solvay Company Fellow in Organic Chemistry, 1937-1938.

<sup>(5)</sup> Van de Kamp and Mosettig, ibid., 58, 1062 (1936).