

TABLE I  
 ACYL DERIVATIVES OF CYCLOHEXANEDIONE (I)

Expt. Time <sup>b</sup>	Color <sup>c</sup>	M.p., °C. <sup>d</sup>	Analyses, %		Expt.	R <sub>1</sub> <sup>a</sup>	Time <sup>b</sup>	Color <sup>c</sup>	M.p., °C. <sup>d</sup>	Formula	Analyses, %			
			Carbon Found	Hydro- gene Found							Carbon Calcd.	Hydrogen Calcd.	Carbon Found	Hydrogen Found
1	10	Y	116	60.76	11	COCH <sub>3</sub>	10	Y	145	C <sub>22</sub> H <sub>24</sub> O <sub>9</sub>	61.10	61.38	5.59	5.72
	10	Y	148	61.48										
2	10	RP	115	5.72	12	COCH <sub>2</sub> CH <sub>3</sub>	22	RP	115	C <sub>22</sub> H <sub>24</sub> O <sub>9</sub>	48.44	48.95	4.45	4.89
	48	Y	116											
3	16	Y	116	5.52	14	COCH <sub>2</sub> CH <sub>2</sub> Cl	21	Y	150	C <sub>22</sub> H <sub>24</sub> O <sub>9</sub> Cl	59.52	59.74	5.59	5.96
	12	RP	115											
4	10	Y	148	60.95	16 <sup>f</sup>	COCH=CHC <sub>6</sub> H <sub>5</sub>	24	Y	140	C <sub>22</sub> H <sub>24</sub> O <sub>8</sub>	57.23	56.74	4.97	4.92
	10	Y	129	62.30										
6	10	Y	129	62.30	18 <sup>g</sup>	SO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> NHCOCH <sub>3</sub>	6	Y	175	C <sub>27</sub> H <sub>29</sub> O <sub>11</sub> SN	56.33	56.66	5.07	5.46
	10	RP	102	62.31										
7	48	Y	163	5.93	8	48	Y	163	163	C <sub>22</sub> H <sub>24</sub> O <sub>9</sub>	57.44	57.62	5.24	5.47
	16	RP	102											
8	10	Y	129	5.93	10	10	Y	129	129	C <sub>22</sub> H <sub>24</sub> O <sub>9</sub>	57.44	57.62	5.24	5.47
	10	Y	129											

<sup>a</sup> Acyl substituent. <sup>b</sup> Reaction time in hours. Expts. 3, 4, 8 and 9 were run at room temperature, the others at approximately 100°. <sup>c</sup> Color in ferric chloride test: Y = yellow, RP = reddish purple. <sup>d</sup> Mixed melting points indicated that, in general, the compounds with the same melting point and empirical formula are identical: 116 in expts. 1, 3 and 4; 148 in 1 and 5; 129 in 6 and 10; 145 in 2 and 11; 115 in 2 and 4; 102 in 7 and 9; 115 in 7 and 12; and 163 in 8 and 12. <sup>e</sup> Calcd. for C<sub>22</sub>H<sub>24</sub>O<sub>9</sub>: C, 61.10; H, 5.59. Calcd. for C<sub>22</sub>H<sub>24</sub>O<sub>9</sub>: C, 61.87; H, 5.87. <sup>f</sup> 5-(*p*-Methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 was used instead of I. <sup>g</sup> The *m*-methoxy derivative of I was used.

A portion of the substance melting at 145° (obtained in expt. 2) was dissolved in sodium carbonate solution. It was allowed to stand at room temperature 24 hours, refluxed for 12 hours, acidified and further refluxed for seven hours. Upon cooling, a precipitate formed which was filtered and recrystallized from boiling distilled water. The product, dried over phosphorus pentoxide in a vacuum desiccator, was found to be identical with 5-(*p*-hydroxyphenyl)-cyclohexanedione-1,3.<sup>2</sup> The O-acyl at position 1 (or 3) was hydrolyzed.

5-(*p*-Acetoxyphenyl)-2-acetylcyclohexanedione-1,3, m.p. 117°, prepared from 5-(*p*-hydroxyphenyl)-cyclohexanedione-1,3<sup>2</sup> by the method<sup>6</sup> of expt. 5, was refluxed for five hours with sodium carbonate solution. The mixture was acidified and refluxed again for one hour. After cooling, the mixture was extracted with 20 ml. of each of the following solvents: benzene, ethyl acetate and ether. The combined solvents were evaporated; water followed by a little ethanol was added to the viscous residue. The crystals formed were recrystallized from ethanol, m.p. 179°. The analysis indicates that the product retained one acetyl group.

*Anal.* Calcd. for C<sub>14</sub>H<sub>14</sub>O<sub>4</sub>: C, 68.28; H, 5.77. Found: C, 68.08; H, 6.04.

The compound melting at 115° (obtained in expts. 2 and 4 and assumed to be an O-acetyl derivative) was converted into the isomer melting at 148° (obtained in 1 and 5 and assumed to be a C-acetyl derivative) by the action of acetic anhydride and pyridine for ten hours on the water-bath. Similarly, the compound melting at 102° (obtained in expts. 7 and 9 and assumed to be O-propionyl) was converted into the isomer melting at 129° (obtained in expt. 10 and assumed to be a C-propionyl derivative) by the use of propionic anhydride and pyridine.

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### 5-(*p*-Hydroxyphenyl)-4,6-dicarboxy-2-( $\beta$ -diethylaminopropanol)-cyclohexanedione-1,3 and Derivative<sup>1</sup>

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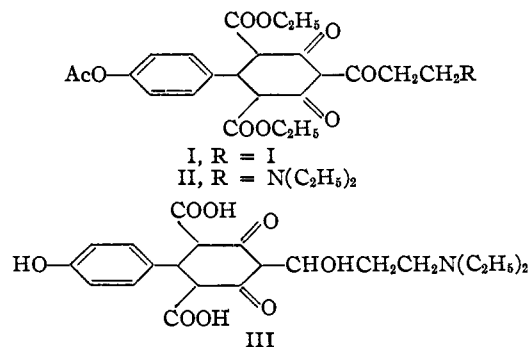
In the search for antimalarials, a great many substituted diethylaminoalkanols have been pre-

(1) Based on a paper submitted to THIS JOURNAL, Dec. 17, 1951.

pared.<sup>2-6</sup> The object of the present work was the preparation of dialkylaminoalkanol derivatives of cyclic 1,3-diones, and we describe below the synthesis of 5-(*p*-hydroxyphenyl)-4,6-dicarboxy-2-( $\beta$ -diethylaminopropanol)-cyclohexanedione-1,3 and a derivative.

Compound I, prepared by acylation of 5-(*p*-acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 with  $\beta$ -chloropropionyl chloride followed by treatment with potassium iodide, was transformed into II by the action of diethylamine. On reduction by the Meerwein-Ponndorf-Verley method, II yielded the expected secondary alcohol III and a further substance C<sub>21</sub>H<sub>25</sub>O<sub>7</sub>N, assumed to be a lactone.

Physiological properties of these compounds will be examined and reported later.



### Experimental

5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxy-2-( $\beta$ -chloropropionyl)-cyclohexanedione-1,3.—To a solution of 230 mg. of sodium in methanol, 3.90 g. (0.01 mole) of 5-(*p*-acetoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3<sup>7</sup> was added and the mixture refluxed for one hour. The methanol was distilled and the residue dried under vacuum. To the dry material absolute ether and one ml. of freshly distilled  $\beta$ -chloropropionyl chloride was added and the mixture was

- (2) H. King and T. S. Work, *J. Chem. Soc.*, 1307 (1940).
- (3) E. L. May and E. Mosettig, *J. Org. Chem.*, **11**, 1, 105, 296, 429, 631 (1946).
- (4) R. C. Elderfield and co-workers, *ibid.*, **11**, 123, 143, 247 (1946).
- (5) T. L. Jacobs and co-workers, *ibid.*, **11**, 21, 150, 215 (1946).
- (6) R. E. Lutz and co-workers, *ibid.*, **12**, 617 (1947).
- (7) P. E. Papadakis, THIS JOURNAL, **67**, 1799 (1945).

refluxed on a water-bath for 21 hours. The ether was removed and the residue treated with water, filtered, dried and washed with ether twice. The ether-insoluble portion, m.p. 149°, is soluble in alcohol and gives a yellow color with ferric chloride; yield 95%.

Anal. Calcd. for C<sub>23</sub>H<sub>25</sub>O<sub>9</sub>Cl: C, 57.44; H, 5.24. Found: C, 57.62; H, 5.47.

**5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxy-2-( $\beta$ -iodopropionyl)-cyclohexanedione-1,3 (I).**—The procedure was similar to the above with the exception that to the dry sodio derivative and  $\beta$ -chloropropionyl chloride in dry ether two grams of dry potassium iodide was added and the mixture refluxed as described. The product melted at 145° and gave a yellow color with ferric chloride; yield almost quantitative. This compound was prepared first by Greenfield.<sup>8</sup>

Anal. Calcd. for C<sub>23</sub>H<sub>25</sub>O<sub>9</sub>I: C, 48.44; H, 4.45. Found: C, 48.95; H, 4.89.

**5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxy-2-( $\beta$ -diethylamino-propionyl)-cyclohexanedione-1,3 (II).**—5-(*p*-Acetoxyphenyl)-4,6-dicarbethoxy-2-( $\beta$ -chloropropionyl)-cyclohexanedione-1,3 (4.8 g.) and 2.0 ml. diethylamine in dry ether were mixed, allowed to stand in ice-bath for 1 hour and then refluxed for 5 hours. The ether was removed and the residue was treated with chloroform. The undissolved part was washed with chloroform, then dissolved in a mixture of methyl alcohol and chloroform. The solution was filtered and to the cooled filtrate ether was added. A precipitate formed, m.p. 201–202°, yield 87%. The product gave a yellow color with the ferric chloride test.

Anal. Calcd. for C<sub>27</sub>H<sub>35</sub>O<sub>9</sub>N: C, 62.65; H, 6.81. Found: C, 62.37; H, 7.24.

**5-(*p*-Hydroxyphenyl)-4,6-dicarboxy-2-(3-diethylamino-1-hydroxypropyl)-cyclohexanedione-1,3 (III).**—Compound II was converted to III by the Meerwein-Ponndorf-Verley reduction. The procedure was similar to that described by Wilds.<sup>9</sup> In a 500-cc. round-bottomed flask were placed 4 g. of II (0.0076 mole), 3.5 g. of aluminum isopropoxide (0.0156 mole) and 250 ml. of dry isopropyl alcohol. A small fractionating column was attached to the flask with a water condenser set for distillation. After six hours of slow distillation, the distillate showed a negative acetone test. The remaining isopropyl alcohol was removed and the residue was dried under reduced pressure. Benzene was added to the residue to dissolve any unreacted aluminum isopropoxide. The residue was then treated with cold water and ammonium hydroxide was added to the mixture with mechanical stirring. After removal of the aluminum hydroxide, the filtrate was cooled, acidified with cold hydrochloric acid and allowed to stand in the refrigerator several hours. The precipitate which formed was collected, washed with distilled water, dried, and crystallized from alcohol. The first crop of crystals had m.p. 209° (IV).

Anal. Calcd. for C<sub>21</sub>H<sub>25</sub>O<sub>7</sub>N: C, 62.52; H, 6.23. Found: C, 62.72; H, 5.97.

Distilled water was added to the filtrate and the precipitate formed was dissolved in alcohol and reprecipitated with distilled water, collected and dried, m.p. 193° (III). It gave an orange color with ferric chloride.

Anal. Calcd. for C<sub>21</sub>H<sub>27</sub>O<sub>9</sub>N (III): C, 59.84; H, 6.46. Found: C, 60.06; H, 6.57.

(8) L. Greenfield, Creighton University M.S. Thesis, 1948.

(9) A. L. Wilds, "Organic Reactions," Editors Roger Adams, W. E. Bachmann, L. F. Fieser, J. R. Johnson, H. R. Snyder, Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1944, pp. 200–204.

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## A Synthesis of 1,3-Butylene Oxide

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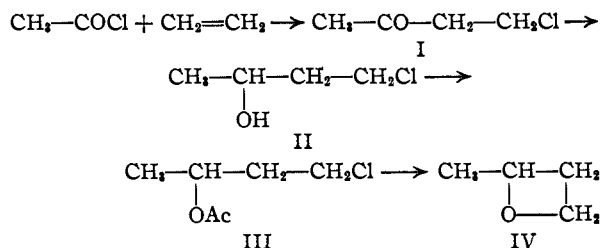
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1,3-Butylene oxide (1,3-epoxybutane) (IV) was required for synthetic purposes. The previously

(1) Syntex, S. A., Laguna Mayran 413, Mexico, D. F.

described<sup>2</sup> method of preparation of this substance proceeded only in poor yield, and was not particularly suitable for laboratory scale production. For these reasons a convenient new synthesis of IV was developed.

The first step, the condensation of ethylene with acetyl chloride to give 4-chloro-2-butanone (I), has been described previously.<sup>3</sup> The use of excess acetyl chloride and the absence of solvent were recommended, and I was obtained in 40% yield. We have found that these precautions are unnecessary, and by applying the conditions used with propionyl chloride,<sup>4</sup> I could be isolated in 61% yield. The reduction of this chloro-ketone with lithium aluminum hydride proceeded smoothly to yield the corresponding alcohol II, which was acetylated to III.



The procedure for carrying out the last step, heating to 140° with *ca.* 90% aqueous potassium hydroxide, was based on that employed with the lower homolog, 3-chloropropyl acetate.<sup>5</sup> It seems however that the secondary nature of the acetoxy group in III favors this type of reaction, for a 66% yield of the required 1,3-butylene oxide (IV) was realized as compared with the 42–44% yield of 1,3-propylene oxide obtained from the above mentioned lower homolog containing a primary acetoxy group. The over-all yield in the present process is 30%.

### Experimental<sup>6</sup>

**4-Chloro-2-butanone (I).**—Acetyl chloride (510 g., 6.50 moles) was added during 20 minutes to a mixture of aluminum chloride (910 g., 6.82 moles) and chloroform (2 l.) with stirring and ice-salt cooling. At the end of the addition the temperature had risen to *ca.* 25°, and cooling was continued until it had fallen to 0°. Ethylene was then bubbled into the stirred mixture at such a rate that all was absorbed, the internal temperature being kept between 5 and 10° by continued ice-salt cooling. Gas started escaping after *ca.* 2 hours, and after another 30 minutes the reaction mixture was poured into a mixture of 1 l. of concentrated hydrochloric acid and 5 kg. of ice. The organic layer was washed with dilute hydrochloric acid, sodium bicarbonate and water, and was then dried and slowly evaporated through a 25-cm. Vigreux column. Distillation of the residue through the same column yielded the  $\beta$ -chloro-ketone I as a mobile liquid, b.p. 47° (16 mm.),  $n_D^{20}$  1.4299 (reported<sup>3</sup> b.p. 43° (15 mm.)). The yield was 421 g. (3.95 moles), or 61%.

**4-Chloro-2-butanol (II).**—The chloro-ketone (388 g.) in dry ether (400 cc.) was added during 1 hour to a stirred solution of 50 g. of lithium aluminum hydride in 1.5 l. of ether, so as to maintain gentle reflux. After stirring for another 30 minutes, water was added dropwise to decompose excess

(2) Celanese Corp. of America, British Patent 585,245 (C. A., **41**, 4167 (1947)).

(3) *Inter al.*, J. R. Catch, D. F. Elliott, D. H. Hey and E. R. H. Jones, *J. Chem. Soc.*, 278 (1948).

(4) E. M. McMahon, J. N. Roper, W. P. Utermohlen, R. H. Hasek, R. C. Harris and J. H. Brandt, *THIS JOURNAL*, **70**, 2971 (1948); R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler and W. M. McLamore, *ibid.*, **74**, 4223 (1952).

(5) C. R. Noller, *Org. Syntheses*, **29**, 92 (1949).

(6) Boiling points are uncorrected.