

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF TEXAS]

3,7-Dicarbethoxy-5-hydroxytropolone. A Convenient Synthesis of Pimelic Acid<sup>1</sup>

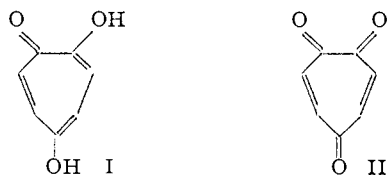
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With a view toward the synthesis of a derivative of tropoquinone, 3,7-dicarbethoxy-5,5-ethylenedioxy-1,2-cycloheptanedione was prepared by a Dieckmann ring closure using diethyl oxalate and diethyl  $\gamma,\gamma$ -ethylenedioxy-pimelate. The reaction of this substance with bromine resulted in the immediate consumption of 1 mole of bromine and formation of 3,7-dicarbethoxy-5-hydroxytropolone, thus obviating the possibility of direct formation of the quinoid compound. Work on the model substance, 3,7-dicarbethoxytropolone, afforded a very convenient synthesis of pimelic acid by a three-step procedure from furfural or by a two-step process from succinic anhydride.

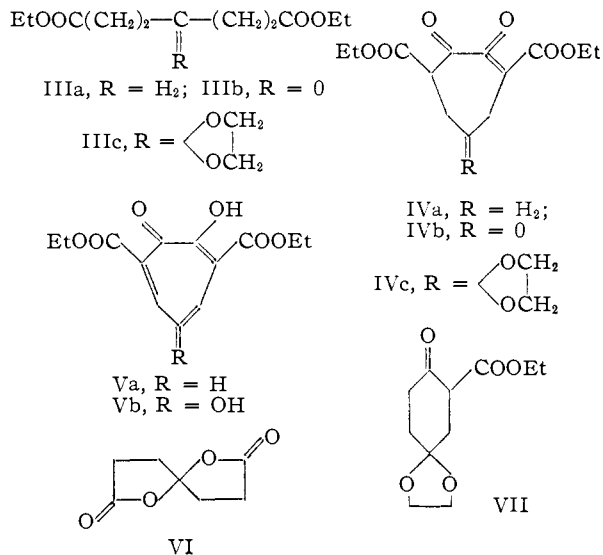
Several methods have been developed for the preparation of substituted tropolones<sup>2</sup> and other "aromatic" 7-membered ring compounds (*i.e.*, azulenes), but most suffer the disadvantage of not being entirely general. Those methods devised for the synthesis of tropolone derivatives which appear to be most capable of extension to a variety of substances are (a) the acyloin reaction using pimelic ester<sup>3</sup> and derivatives of pimelic ester<sup>4</sup> and (b) the Dieckmann ring closure involving the use of ethyl oxalate and pimelic ester.<sup>5,6</sup> The latter should also be capable of extension to substituted pimelic esters. The most severe limitation of either method is that the nature of the substituent is restricted to those stable to sodium metal (a) sodium alkoxides (b). Both methods, on the other hand, have the advantage that the positions of substituents in the tropolone would be unequivocal.

The work reported herein is concerned with the extension of the method using the Dieckmann closure and the initial objective was the synthesis of a derivative of 5-hydroxytropolone (I). We had hoped eventually to obtain "tropoquinone" (II) which is interesting on theoretical grounds. Since this work was initiated, the synthesis of I from tropolone has been reported as well as some unsuccessful oxidation experiments designed to convert it to tropoquinone.<sup>7</sup>



Before submitting valuable intermediates to the ring-closure, it was deemed wise to repeat the work of Cook, Loudon and Steel<sup>6</sup> with pimelic ester itself (sequence IIIa  $\rightarrow$  V). Further, a quantity of the product obtained thereby was needed for another problem.

It appeared that some development work would be required involving the use of large quantities of



the rather costly diethyl pimelate. Consequently, an improved synthesis of this substance was sought. It was found that although  $\gamma$ -ketopimelic acid is reported to be stable under the conditions of the Wolff-Kishner reduction,<sup>8</sup> it is reduced very efficiently by the Huang-Minlon modification<sup>9</sup> using diethylene glycol or ethylene glycol as the solvent. While the yield was satisfactory (88%) by this method, the slight ether solubility of either glycol hampered the isolation procedure, which required continuous extraction with ether. The problem was resolved by substituting the glycol with triethanolamine, thus facilitating the work-up and affording virtually quantitative yields. As was expected, diethyl  $\gamma$ -ketopimelate (IIIb) reduced, directly, equally well and since this substance may be considered readily available from either furylacrylic acid<sup>10</sup> or its ester, the reduction of it completes a three-step synthesis of pimelic acid from furfural in 86% over-all yield. The route from furfural *via* ethyl furylacrylate is also three steps in length and gives only an 80% yield but is more economical in that the use of malonic acid is avoided. Alternatively, the dilactone VI, which is reported to be formed in over 70% yield by the pyrolysis of succinic anhydride,<sup>11</sup> may also be reduced directly by the above procedure in essentially

(1) The authors are indebted to Research Corporation for the financial support of this work.

(2) P. L. Pauson, *Chem. Revs.*, **55**, 9 (1955).

(3) J. D. Knight and D. J. Cram, *THIS JOURNAL*, **73**, 4136 (1951).

(4) P. D. Gardner and G. R. Haynes, unpublished data.

(5) S. N. Naumovand and A. N. Perminova, *Acta Univ. Asiae Mediae*, 1937, No. 28; *Brit. Abstr.*, A, II, 48 (1940).

(6) J. W. Cook, J. D. Loudon and D. K. V. Steel, *J. Chem. Soc.*, 530 (1954).

(7) T. Nozoe, S. Seto, S. Ito, M. Sato and T. Katono, *Science Repts. Tohoku Univ.*, **37**, 191 (1953).

(8) G. Komppa, *Ann. Acad. Sci. Fennicae*, **A51**, No. 3 (1938); *C.A.* **34**, 2335 (1940).

(9) Huang-Minlon, *THIS JOURNAL*, **68**, 2487 (1946).

(10) F. G. Singleton, U. S. Patent 2,436,532; *C.A.* **42**, 5048 (1948).

(11) H. Hopff and H. Griesshaber, U. S. Patent 2,302,321; *C.A.*, **37**, 2020 (1943).

the same yield. This constitutes a 67%, two-step process.

Our preparation of IIIb by the novel ring-opening of furylacrylic acid<sup>10</sup> was invariably accompanied by small amounts of the half-ester, although this presented no problem in the reduction step. In one run, the dilactone VI occurred as a contaminant. It is interesting that the ring-opening reaction occurred readily with ethyl furylacrylate but failed completely in the case of diethyl furfurylidemalonate.

The condensation of diethyl pimelate with diethyl oxalate proceeded as described.<sup>6</sup> In addition to 3,7-dicarbethoxy-1,2-cycloheptanedione (IVa), there was obtained the rearrangement product, 1-carboxy-1-hydroxy-2,6-dicarbethoxycyclohexane, previously isolated from the "aromatization" reaction with IVa.<sup>6</sup> The "aromatization" step using bromine in acetic acid, although not efficient, was reproducible.

The choice of this method in the present work required the dioxolane derivative of diethyl  $\gamma$ -ketopimelate (IIIc), prepared in the usual manner from IIIb. Early in the work, difficulty was experienced in obtaining pure material, and the Dieckmann closure was found to be severely dependent upon the use of pure IIIc. To ensure that the structure assignment was correct, IIIc was cyclized in the absence of oxalate to give the expected substituted cyclohexanedione derivative VII, the identity of which was established by analytical data and infrared spectra.

The condensation of IIIc with ethyl oxalate proceeded normally and reproducibly when caution was exercised in the isolation technique. Thus, crystalline 3,7-dicarbethoxy-5,5-ethylenedioxy-1,2-cycloheptanedione (IVc) was obtained in 21% yield. It was anticipated that this substance would lead to the corresponding dicarbethoxy tropoquinone. This conjecture was based on the fact that only two positions are susceptible to facile bromination, and it was hoped that a moderately stable dibromide, still possessing the dioxolane ring, would be formed. Subsequent elimination of two moles of hydrogen bromide and hydrolysis should then afford the quinoid compound. As expected, the bromination was very rapid but, unexpectedly, only one mole of bromine was required. Even at 0° bromination and dehydrobromination with concurrent hydrolysis of the dioxolane ring occurred in a matter of minutes to yield 3,7-dicarbethoxy-5-hydroxytropolone (Vb) (84%). This behavior is reminiscent of diethyl succinylsuccinate, which reacts equally readily under virtually the same conditions to give 2,5-dicarbethoxyhydroquinone.<sup>12</sup>

Acid hydrolysis of IVc cleaved the dioxolane ring with resultant formation of the trione IVb, but further hydrolysis (of the carbethoxy functions) could not be induced.

### Experimental<sup>13</sup>

**Furylacrylic Acid.**—The following modification of the procedure by Dutt<sup>14</sup> is the most satisfactory one found.

(12) F. Herrmann, *Ann.*, **211**, 327 (1882).

(13) Melting points are corrected.

(14) S. Dutt, *J. Indian Chem. Soc.*, **1**, 297 (1925).

A solution was prepared consisting of 135 g. (1.40 moles) of furfural (freshly distilled), 152 g. (1.46 moles) of malonic acid, 250 ml. of pyridine and 3 ml. of piperidine. It was heated on a steam-bath, protected from atmospheric moisture, for 2.5 hr. and then refluxed, first gently (30 min.) and more vigorously (15 min.) and finally poured into a mixture prepared from 400 g. of sulfuric acid and 2 kg. of ice. The product was collected by suction filtration and washed well with cold water. The damp cake was then recrystallized by dissolving it as quickly as possible in 600 ml. of hot methanol and adding 900 ml. of hot water followed by cooling to 0° for 24 hr. There was obtained 166 g. (86%) of solid, m.p. 140–141° (lit.<sup>14</sup> 140°).

**Diethyl  $\gamma$ -Ketopimelate (IIIb).**—This substance was prepared by the published procedure<sup>10</sup> with only slightly different results. Thus, from 382 g. (2.77 moles) of furylacrylic acid, there was obtained 476 g. (75%) of diethyl  $\gamma$ -ketopimelate, b.p. 180–190° (26 mm.), 55.1 g. of a mixture, b.p. 190–220°, and 45.5 g. of material boiling over the range 220–235° (26 mm.). The last fraction solidified on standing and was recrystallized from ethyl acetate-petroleum ether (50–60°) to give 33.0 g. (5.9%) of ethyl hydrogen  $\gamma$ -ketopimelate, m.p. 67–69°. The sample for analysis was obtained by further crystallization from the same solvents, m.p. 71–72°.

*Anal.* Calcd. for C<sub>9</sub>H<sub>14</sub>O<sub>5</sub>: C, 53.46; H, 6.98; neut. equiv., 202.2. Found: C, 53.76; H, 7.12; neut. equiv., 202.4.

Fractionation is, of course, unnecessary if the material is to be converted to pimelic acid.

**The 2,4-dinitrophenylhydrazones,** prepared in ethanol (10 min. at reflux), was that of the diethyl ester, m.p. 82–83° after several crystallizations from ethanol.

*Anal.* Calcd. for C<sub>17</sub>H<sub>20</sub>O<sub>8</sub>N<sub>4</sub>: C, 49.75; H, 5.40; N, 13.7. Found: C, 49.90; H, 5.22; N, 13.9.

Essentially the same results were obtained when the ring-opening was conducted in methanol, although the yield of dimethyl ester was somewhat lower (60%), m.p. 51–52° (lit.<sup>15</sup> 54°). Methyl hydrogen  $\gamma$ -ketopimelate, obtained in 10% yield, melting at 62–63°, depressed when mixed with VI (m.p. 63–64°). The sample for analysis was purified as was the ethyl ester above.

*Anal.* Calcd. for C<sub>8</sub>H<sub>12</sub>O<sub>5</sub>: C, 51.06; H, 6.43; neut. equiv., 188.2. Found: C, 50.86; H, 6.40; neut. equiv., 188.6.

**The dinitrophenylhydrazones,** prepared in ethanol, was that of the dimethyl ester, m.p. 67–68° after several crystallizations from methanol.

*Anal.* Calcd. for C<sub>15</sub>H<sub>18</sub>O<sub>8</sub>N<sub>4</sub>: C, 47.12; H, 4.75. Found: C, 47.19; H, 4.79.

$\gamma$ -Ketopimelic acid dilactone (2,2'-spirotetrahydropyran-5-one) (VI) was inexplicably obtained in about 10% yield from one run, m.p. and mixed m.p.<sup>10</sup> 63–64°.

An attempted ethanolysis of ethyl furfurylidemalonate<sup>16</sup> under the same conditions as used above gave only recovered starting material and non-distillable resin. Ethyl furylacrylate<sup>17</sup> gave the same yield of IIIb as did the acid.

**Pimelic Acid.**—A suspension was prepared consisting of 53.8 g. (0.234 mole) of diethyl  $\gamma$ -ketopimelate, 230 ml. of 95% triethanolamine, 60 g. (0.91 mole) of 85% potassium hydroxide and 37 ml. (0.65 mole) of 85% hydrazine hydrate. On warming, it became homogeneous and was refluxed for 2.5 hr., after which time the condenser water was drained. The temperature was raised to 195°, the flow of water through the condenser resumed and reflux continued for an additional 2 hr. The cool mixture was acidified with 450 ml. of hydrochloric acid (sp. gr. 1.18) and submitted to continuous ether extraction for 16 hr. The presence of solid salts offered no problem, as these re-

(15) M. V. Likhoshesterov, E. F. Zeberg and I. V. Karitskaya, *J. Gen. Chem.*, **20**, 635 (1950); *C.A.*, **44**, 7823 (1950).

(16) The reported preparation of this substance<sup>17</sup> was unsatisfactory in our hands. An alternate synthesis, described for ethyl benzylidenemalonate,<sup>18</sup> proved to be more convenient. Thus, from 100 g. of diethyl malonate, 63 g. of furfural, 200 ml. of benzene and 3 ml. of piperidine, there was obtained, after 4.5 hr. of reflux, an 89% yield of diethyl furfurylidemalonate, b.p. 136–144° (1.0 mm.).

(17) H. Hinz, G. Meyer and G. Schücking, *Ber.*, **76B**, 676 (1943).

(18) C. F. H. Allen and F. W. Spangler, *Org. Syntheses*, **25**, 42 (1945).

mained suspended entirely in the aqueous phase. The evaporation of ether left a solid residue which, after one crystallization from concentrated hydrochloric acid (several crops), melted at 103.5–105° (yield 37.2 g., 99.5%). A mixture m.p. with authentic pimelic acid was not depressed. The use of  $\gamma$ -ketopimelic acid in this procedure gave the same yield and the dilactone VI was reduced in 94% yield. When the heating time at the higher temperature (195°) was increased to 6 hr.,<sup>9</sup> the yield was 96.2%. Ethylene glycol or diethylene glycol complicated the procedure in that these solvents were partially extracted into the ether phase in the continuous extraction. This problem was partially solved by distillation of the bulk of the glycol at an oil-pump before the acidification step. This was only partially satisfactory due to the danger of charring, even though an oil-bath was used. In this respect, diethylene glycol was superior to ethylene glycol. Despite these manipulative problems, an 88% yield was obtained using the former and 70% from the latter.

**3,7-Dicarbethoxytropolone (Va).**—This sequence of reactions was found to be as reported<sup>6</sup> and will not be described. The only point of difference was in the formation of 3,7-dicarbethoxy-1,2-cycloheptanedione (IVa) ( $\lambda_{\max}$  302  $m\mu$ ,  $\log \epsilon$  3.95 in alcohol) in which a 3% yield of 1-carboxy-1-hydroxy-2,6-dicarbethoxycyclohexane was obtained, m.p. 132° (lit.<sup>6</sup> 128–130°).

*Anal.* Calcd. for  $C_{15}H_{20}O_7$ : C, 54.16; H, 7.04; neut. equiv., 288.3. Found: C, 54.44; H, 7.04; neut. equiv., 288.0.

**Diethyl  $\gamma,\gamma$ -Ethylenedioxympimelate (IIIc).**—In a system equipped for azeotropic distillation of water, a solution was prepared comprised of 1.5 l. of benzene, 476 g. (2.07 moles) of IIIb, 134 g. (2.17 moles) of ethylene glycol and 2.0 g. of toluenesulfonic acid monohydrate. During a period of 15 hr. of reflux, 40 ml. of aqueous layer was collected (theory, 37.3). The cool reaction mixture was then treated with a solution prepared by dissolving 0.5 g. of sodium in 15 ml. of ethanol. After one minute of swirling, cold water was added and the benzene layer was washed several times with additional portions of water and then dried with sodium sulfate. Solvent was distilled at the aspirator (steam-bath) and the residue fractionally distilled through a 30  $\times$  1.6 cm., helices-packed column. There was obtained 129.7 g. (27.2%) of recovered IIIb, b.p. 124° (0.4 mm.),  $n_D^{25}$  1.4383, and 169.7 g. (30%) of the dioxolane derivative IIIc, b.p. 134° (0.3 mm.),  $n_D^{25}$  1.4463.

*Anal.* Calcd. for  $C_{15}H_{22}O_6$ : C, 56.92; H, 8.09. Found: C, 57.01; H, 8.30.

**2-Carbethoxy-4,4-ethylenedioxy-cyclohexanone (VII).**—Sodium ethoxide was prepared by treating 2.3 g. (0.10 mole) of sodium with 125 ml. of ethanol followed by distillation of excess ethanol under diminished pressure (steam-bath). To the dry base was added 27.4 g. (0.100 mole) of IIIc dissolved in 50 ml. of dry ether. After shaking vigorously, a stirring bar was introduced and the contents of the stoppered flask were stirred magnetically until the stirrer would no longer turn. After standing for 48 hr. in the dark, the mixture was cooled to 0° and acidified by the addition of a cold solution of 11 ml. of concentrated hydrochloric acid in 50 ml. of water. The two phases were quickly separated and the ethereal layer was washed successively with water, 10% aqueous sodium hydrogen carbonate and water. The dried (sodium sulfate) solution was freed of solvent by distillation and further distilled at an oil-pump. There was obtained 12.4 g. (54%) of VII, b.p. 114° (0.5 mm.),  $n_D^{25}$  1.4846.

*Anal.* Calcd. for  $C_{11}H_{16}O_5$ : C, 57.88; H, 7.07. Found: C, 57.97; H, 7.38.

Following a small intermediate fraction, 8.1 g. (30%) of recovered IIIc was collected, b.p. 127° (0.7 mm.),  $n_D^{25}$  1.4486. The infrared spectrum of this recovered material was identical in all respects with that of the starting material. The spectrum of VII possessed, in addition to absorption attributable to carbonyl stretching, a strong band at 6.0–6.2 $\mu$ , characteristic of  $\beta$ -dicarbonyl compounds capable of enolization.<sup>19</sup> Absorption in the 9–10 $\mu$  region,

probably due to the dioxolane ring, was very similar to that of the starting material.

**3,7-Dicarbethoxy-5,5-ethylenedioxy-1,2-cycloheptanedione (IVc).**—Sodium ethoxide was prepared by dissolving 8.72 g. (0.379 mole) of sodium in 300 ml. of ethanol followed by the removal of excess ethanol under diminished pressure. This was suspended in 150 ml. of dry ether and treated with a solution of 28.0 g. (0.190 mole) of diethyl oxalate and 49.2 g. (0.180 mole) of IIIc. The dark red mixture, protected from moisture, was gently refluxed for 1 hr. and then heated in an oil-bath (120–125°) until ether and ethanol ceased to distill. This required about 3 hr. The resulting dark mass was cooled, dissolved in water, acidified with cold, dilute hydrochloric acid and extracted twice with ether. The ether solution was washed with saturated, aqueous sodium carbonate and then several times with water. Treatment with 8 *N* sodium hydroxide solution resulted in the precipitation of a yellow salt which was collected on a sintered glass funnel by filtration with suction. This material was readily soluble in water and acidification of the aqueous solution caused the precipitation of crude IVc. Several crystallizations from ethanol afforded 10.5 g. (20.6%) of colorless needles, m.p. 122.5–124°, unchanged by further purification attempts; ultraviolet absorption spectrum (alcohol):  $\lambda_{\max}$  295  $m\mu$ ,  $\log \epsilon$  4.08.

*Anal.* Calcd. for  $C_{15}H_{20}O_8$ : C, 54.87; H, 6.14. Found: C, 54.99; H, 6.18.

A sample of this material melted at 102–115° after several months storage. Recrystallization did not appreciably change this value.

The dipyrzolonone derivative was prepared by refluxing a solution of 0.10 g. of IVc and 0.14 g. of phenylhydrazine in 5 ml. of ethanol for 20 min. Recrystallization from ethanol gave the pure substance as a pale yellow solid, m.p. 237–250° with gradual decomposition.

*Anal.* Calcd. for  $C_{23}H_{20}O_4N_4$ : C, 66.38; H, 4.84. Found: C, 66.20; H, 4.85.

**3,7-Dicarbethoxy-1,2,5-cycloheptanetrione (Vb).**—One gram of IVc was refluxed in 10 ml. of 25% aqueous sulfuric acid for 2 hr. The cool solution was diluted with 20 ml. of water and extracted twice with chloroform. Following washing with aqueous sodium hydrogen carbonate and water, the solution was dried and distilled to remove solvent. The addition of ether induced crystallization of the residual oil which, on crystallization from ethanol, yielded 0.21 g. (24.3%) of Vb, m.p. 128–128.5°. Essentially the same results were obtained using hydrochloric acid.

*Anal.* Calcd. for  $C_{13}H_{16}O_7$ : C, 54.95; H, 5.68. Found: C, 55.43; H, 5.85.

The ultraviolet absorption spectrum (alcohol) exhibited a principal maximum at 296  $m\mu$ ,  $\log \epsilon$  4.07.

**3,7-Dicarbethoxy-5-hydroxytropolone (Vb).**—A solution of 0.56 g. (0.0035 mole) of bromine was added dropwise and with stirring to a solution of 1.00 g. (0.0035 mole) of IVc in 15 ml. of acetic acid. The temperature was maintained at 10° during the early part of the addition and was allowed to rise to 25° at the end. After addition was complete, solvent was removed by distillation under reduced pressure, leaving a yellow residue which was virtually insoluble in the ether used to transfer it from the flask. Filtration with suction and crystallization from ethanol gave 0.708 g. (83.7%) of yellow solid, m.p. 168–170° dec. The sample for analysis was prepared by further purification in the same manner.

*Anal.* Calcd. for  $C_{13}H_{14}O_7$ : C, 55.34; H, 5.00. Found: C, 55.41; H, 5.12.

The substance produced a yellow coloration in sodium hydrogen carbonate solution, a black color with alcoholic ferric chloride and gave a solid, turquoise copper salt from aqueous copper sulfate. A qualitative elemental analysis indicated it to be halogen-free. The ultraviolet absorption spectrum (95% ethanol) had the following features:  $\lambda_{\max}$  241  $m\mu$ ,  $\log \epsilon$  4.3;  $\lambda_{\min}$  293  $m\mu$ ,  $\log \epsilon$  3.0;  $\lambda_{\text{plat}}$  348–416  $m\mu$ ,  $\log \epsilon$  3.90–3.95.

(19) N. J. Leonard, H. S. Gutowsky, W. J. Middleton and E. M. Peterson, *THIS JOURNAL*, **74**, 4070 (1952).