[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

Mold Metabolites. VI. The Synthesis of Tropolone

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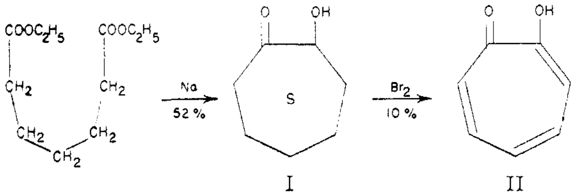
This paper reports the fifth independent synthesis of tropolone (1,2-cycloheptatrienolone). Diethyl pimelate was submitted to an acyloin condensation to give 1,2-cycloheptanolone which when treated with two and one-half moles of bromine produced tropolone. Analogous treatment of 1,2-cyclopentanolone gave 3-bromo-1,2-cyclopentadione, and attempts to convert this substance to 1,2-cyclopentadienolone failed.

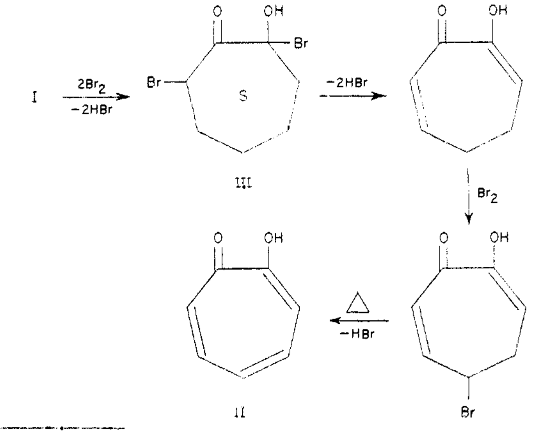
Since the suggestions of M. J. S. Dewar[2] that the behavior of the mold metabolites stipitatic, puberulic and puberulonic acids could best be explained on the basis of a tropolone type of structure,[3] four groups of investigators have reported the synthesis of tropolone by three independent methods.[4,5] We wish to report a two step synthesis of this interesting ring structure by a route which on further development[6] might prove useful in the synthesis of other tropolone-like molecules.

Compound I was prepared from diethyl pimelate[7] utilizing high-speed stirring and high-dilution techniques as applied to the acyloin reaction.[8] Ordinary conditions for this reaction found so successful for the larger rings[9] gave poor yields of cycle, an observation also made by Sheehan[7] in applying the reaction to the synthesis of the five- and six-membered acyloins. Interestingly enough this reaction as applied to the synthesis of cycles represents an inversion of the usual rule that five-, six- and seven-membered rings are the easiest to close.



Attempts to oxidize 2-hydroxycycloheptanone (I) to 1,2-cycloheptadione with chromic anhydride in acetic acid[10] gave pimelic acid while the use of yellow mercuric oxide or dry silver oxide gave back starting material. The reaction of I with copper oxide powder (250°) gave acidic oils from which no pure compounds could be isolated. Treatment of the ketol with the usual dehydrogenating agents (sulfur or palladium-on-charcoal) also failed to produce tropolone.

However, treatment of I with two and one-half moles of bromine in glacial acetic acid produced a solution which after removal of the solvent and sublimation of the residue gave a yellow solid which appeared to be a hydrogen bromide adduct of tropolone,[11] since heating of the compound in boiling cyclohexane produced hydrogen bromide and tropolone. Although this adduct was too unstable for characterization, careful sublimation afforded colorless needles melting at 168–171° with softening at 165°.



That the oxidation of acyloin I with bromine to tropolone does not appear to go through 1,2-cycloheptadione as an intermediate is shown by the fact that the first mole of bromine was decolorized instantly by I to give a colorless solution (solutions of the diketone are yellow), and further, that a bromohydrotropolone was the initial product of the reac-

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[1] Requests for reprints should be addressed to this author. Paper V, THIS JOURNAL, **73**, 1001 (1951).

[2] M. J. S. Dewar, *Nature*, **155**, 50, 141, 479 (1945). In connection with the production of 5-hydroxyisophthalic acid from stipitatic acid through the agency of strong alkali, it is of historical interest that although Dewar was led to the correct structure of stipitatic acid by looking upon the reaction as a benzil-benzilic acid rearrangement, the aromatization reaction can be envisioned equally well as a retrograde Claisen followed by an Aldol condensation reaction. Thus if stipitatic acid enolizes to a 1,3-diketone which hydrolyzes to 2,6-diketo-4-carboxy-4-heptenoic acid, this substance in the presence of base would undoubtedly give 5-hydroxyisophthalic acid.

[3] (a) Dewar further suggested (ref. 1) that colchicine also contained the tropolone ring system, and subsequently R. D. Haworth, *et al.* [*J. Chem. Soc.*, 1631 (1950)) found purpurogallin to contain the same ring. (b) H. Erdtman and J. Gripenberg, *Nature*, **161**, 719 (1948), have also shown the thujaplicins to be isopropyltropolones.

[4] (a) T. Nozoe, S. Seto, Y. Kitahava, M. Kunori and Y. Nakayama, *Proc. Japan Acad.*, **26**, [7] 38 (1950). (See T. Nozoe, S. Seto, S. Ebine and S. Ito, THIS JOURNAL, **73**, 1895 (1951), for a summary of the contributions of these authors to the general tropolone problem.) (b) W. E. Doering and L. H. Knox, *ibid.*, **72**, 2305 (1950); (c) J. W. Cook, A. R. Gibb, R. A. Raphael and A. R. Somerville, *Chem. and Ind.*, 427 (1950); (d) R. D. Haworth and J. D. Hobson, *ibid.*, 441 (1950).

[5] J. W. Cook and A. R. Somerville [*Nature*, **163**, 410 (1949)] previously reported the synthesis of 3,4-benztropolone and D. S. Tarbell, G. P. Scott and A. D. Kemp [THIS JOURNAL, **72**, 379 (1950)] 4,5-benztropolone.

[6] The authors abandoned the development of this method of synthesis when the work of Cook, *et al.*,[4c] appeared.

[7] The procedure used represents a modification of that employed by A. C. Cope and E. C. Herrick to close a four-membered ring, THIS JOURNAL, **72**, 983 (1950) [see also J. C. Sheehan, R. C. O'Neil and M. H. White, *ibid.*, **72**, 3376 (1950)].

[8] The previously reported syntheses of this molecule by entirely different routes [A. Kotz, K. Blenderman, R. Rosenbusch and E. Sirringhaus, *Ann.*, **400**, 68 (1913), and E. E. Venus-Danilova and V. F. Kazimirova, *J. Gen. Chem.*, (U. S. S. R.), **7**, 2639 (1937)] probably led to cyclohexanecarboxylic acid rather than to I.

[9] M. Stoll and I. Hulstkamp, *Helv. Chim. Acta*, **30**, 1815, 1822 (1947); V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *ibid.*, **30**, 1741 (1947).

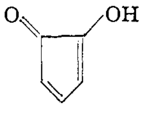
[10] V. Prelog, L. Frenkiel, M. Kobelt and P. Barman, *ibid.*, **30**, 1741 (1947).

[11] W. E. Doering and L. H. Knox, THIS JOURNAL, **73**, 828 (1951), report the preparation of a colorless tropolone hydrochloride which softened at 114–115°, partially melted at 125–127° and evolved a gas at 131–132°.

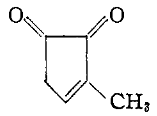
tion rather than the bromotropolone isolated by Cook[4c] by treatment of the diketone with bromine. Several paths for the reaction can be envisioned, one formulation involving III as an intermediate. The use of larger amounts of bromine in the reaction led to complex mixtures of bromine-containing products and tars.

The properties of the tropolone obtained in this investigation correspond with those reported by Cook, *et al.*,[4c] and differ only slightly from those reported by Doering, *et al.*[4b] Figure 1 reports the ultraviolet absorption spectrum of tropolone.

The preparation of the five membered analog of tropolone, 2-hydroxycyclopentadienone (pentolone or IV) is of interest since it bears a relationship to cyclobutadiene which is similar in some respects to that which tropolone bears to benzene. The facts that cyclobutadiene has never been prepared and that it has been predicted on theoretical grounds to be capable of existing only as a diradical[12] would suggest that pentolone (IV) would be considerably less stable than tropolone and probably would not possess the aromatic properties of that substance.



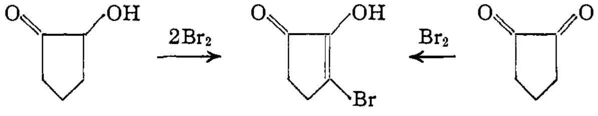
IV



V

Apparently compounds containing the nucleus of IV exist mainly in the diketonic form in contradistinction to the cyclopentanediones which exist mainly in the enolic form.[13] For example, 3,4-diphenylcyclopent-3-ene-1,2-dione[14] is reported to be insoluble in dilute base, to add two moles of Grignard reagent, and to give a negative ferric chloride test whereas 3-methylcyclopent-3-ene-1,2-dione (V)[15] is reported as a yellow solid that reacts with *o*-phenylenediamine to form a quinoxaline, that reacts with ferric chloride, and which on heating changes to a "liquid enolic form."

In an attempt to prepare IV, 2-hydroxycyclopentanone (VI)[16] was treated with two moles of bromine, and from the reaction mixture was obtained a black tar from which was sublimed the enol of 3-bromo-1,2-cyclopentadione (VII).[17] This substance was prepared by the method of Dieckman,[17] and the two samples were shown to be identical. Treatment of VIII with N-bromosuccinimide also produced VII, and treatment of VII with the same reagent gave only resinous products.



VI VII VIII

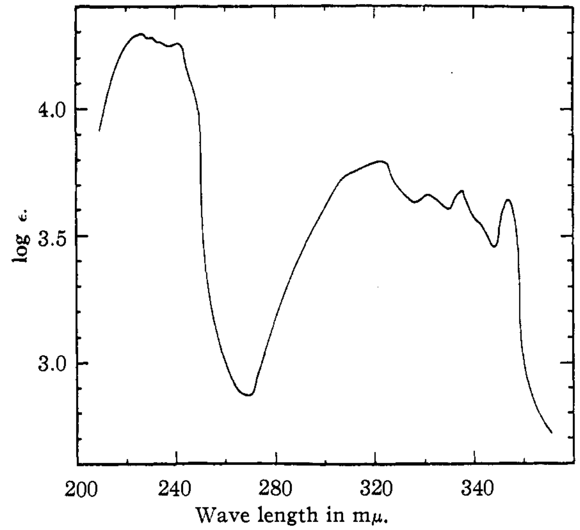


Fig. 1.—Ultraviolet absorption spectrum of tropolone in cyclohexane, Beckman spectrophotometer, model DU.

The evidence of diketonic structure in compounds containing the nucleus of IV plus the reluctance of both VI and VIII to convert into IV provides an *experimental* confirmation of a vast difference in the stability of II and IV, and makes the suggestion of Dewar[2] that IV represents a system analogous to tropolone unlikely.

Experimental Part

2-Hydroxycycloheptanone (I).—One liter of pure dry xylene (b.p. 137–139°) and 34 g. of clean sodium were placed in a 3-liter creased flask fitted with a high speed stainless steel stirrer[18] to which was attached a one-liter Hershberg dropping funnel in such a way that material added from the dropping funnel was diluted with returning solvent from a condenser. After sweeping the flask out with dry nitrogen[19] (a mercury valve was attached to the dropping funnel in order to maintain the nitrogen under a positive pressure), the solvent was heated to its boiling point, and the sodium was dispersed by stirring at 7000 r.p.m. A solution of 80 g. of diethyl pimelate[20] (b.p. 146–149° at 13 mm.) in 1000 ml. of pure xylene was added over a period of 65 hours, the mixture being constantly stirred at 7000 r.p.m. The tan-to-yellow colored mixture was stirred for an additional 30 minutes, the flask was cooled to ice temperature, and a solution of 85.5 ml. of glacial acetic acid in 100 ml. of dry ether was added with stirring over a period of 30 minutes. With the aid of a rubber dam, the sodium acetate was separated by filtering through a 14 in. buchner funnel and the resulting filter cake was stirred with two 500-ml. portions of dry ether for 30 minutes. Removal of the ether from the extracts left 200 ml. of a xylene solution which was combined with the xylene filtrate. The xylene was removed at a pressure of 14 mm. by distillation through a 56 cm. center rod column and the residue was distilled through a short-path still. Six fractions were separated. The first four were colorless and the last two were faintly yellow colored; (1) 3.35 g., b.p. 95–97° (16 mm.), $n^{25}\mathrm{D}$ 1.4764; (2) 11.93 g., b.p. 97–99° (16 mm.), $n^{25}\mathrm{D}$ 1.4746. The remaining four fractions (11.12 g.) had b.p. 97–99° (16 mm.), $n^{25}\mathrm{D}$ from 1.4735 to 1.4733. The first two fractions were contaminated with xylene. By preparing a plot of index of refraction *versus* weight per cent. of I, it was calculated that these two fractions contained 14

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[12] M. J. S. Dewar, "The Electronic Theory of Organic Chemistry," Oxford at the Clarendon Press, London, 1949, p. 11.

[13] G. Schwarzenbach and C. Wittwer, *Helv. Chim. Acta*, **30**, 663 (1947).

[14] C. F. Koelsch and T. A. Geissman, *J. Org. Chem.*, **3**, 489 (1938).

[15] E. Dane, J. Schmitt and C. Rautenstrauck, *Ann.*, **532**, 29 (1937).

[16] J. C. Sheehan, R. C. O'Neill and M. H. White, THIS JOURNAL, **72**, 3376 (1950).

[17] This compound has been prepared by W. Dieckman [*Ber.*, **35**, 3201 (1902)] by the bromination of 1,2-cyclopentadione.

[18] A. Morton, *et al.*, *Ind. Eng. Chem.*, **40**, 1190 (1948).

[19] The nitrogen, which was purified by passing the gas over copper turnings maintained at 450° contained less than 0.0001% of oxygen (estimated by R. A. Crane from absorption measurements in the far ultraviolet).

[20] H. R. Snyder, L. A. Brooks and S. H. Shapiro in Blatt, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1943, p. 531.

g. of I, bringing the total yield of I to 25 g. (52.5%). In another reaction under the same conditions a 40% yield was obtained. Using fraction three as an analytical sample, the following physical properties were determined: $n^{20}\text{D}$ 1.4753, $n^{25}\text{D}$ 1.4734, $n^{55}\text{D}$ 1.4605; d^{20}_4 1.0657, d^{25}_4 1.0617, d^{55}_4 1.0360; *M*D calcd. 33.96, *M*D found 33.89.

Anal. Calcd. for $C_7H_{12}O_2$: C, 65.59; H, 9.44. Found: C, 65.66; H, 9.24.

The phenylosazone was obtained as yellow needles (dilute alcohol), m.p. 136.5–137.5°.

Anal. Calcd. for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24. Found: C, 74.18; H, 7,42.

The *p*-nitrophenylhydrazone was prepared and crystallized from aqueous alcohol as a cream colored solid, m.p. 119–120°.

Anal. Calcd. for $C_{13}H_{18}O_2N_2$: C, 71.53; H, 8.31. Found: C, 71.46; H, 8.54.

After recrystallization from alcohol, the semicarbazone was obtained as white plates, m.p. 173–173.5° with decomposition.

Anal. Calcd. for $C_8H_{15}O_2N_3$: C, 51.87; H, 8.18. Found: C, 51.74; H, 8.42.

The *p*-nitrobenzoate was prepared and crystallized from an ether-petroleum ether mixture as needles, m.p. 79–80°.

Anal. Calcd. for $C_{14}H_{15}O_5N$: C, 60.64; H, 5.45. Found: C, 60.54; H, 5.53.

Complete Removal of Diketone from Acyloin.—A column, 15 × 1.5 cm., was packed with acid-washed alumina which had first been heated to 200° and allowed to cool in a nitrogen atmosphere. Under a nitrogen atmosphere, 0.26 g. of I in petroleum ether was adsorbed on the alumina. The acyloin was eluted with benzene and the fractions tested with ferric chloride. The eluates gave no color with ferric chloride but, after standing in the air, color slowly appeared in the test solutions. In contrast, eluates through which air was bubbled for one minute gave a strong purple color with ferric chloride. The remaining material was eluted with ether to give a total of 0.18 g. of recovered acyloin.

2-Hydroxycyclopentanone (V).—This acyloin reaction was run as described above with the exception that toluene was used as the solvent instead of xylene. From 60 g. of dimethyl glutarate there was obtained 5.0 g. of 2-hydroxycyclopentanone, b.p. 58–75° (4 mm.), $n^{25}\text{D}$ 1.4692.

Reduction of I to 2-Hydroxycycloheptanol.—To a solution of 0.6 g. of lithium aluminum hydride in 75 ml. of dry ether was added 2.0 g. of I in 50 ml. of dry ether. After the addition was complete, excess lithium aluminum hydride was destroyed with 95% ethanol and the reaction mixture was filtered. The filtrate was dried over anhydrous sodium sulfate and the solvent removed to yield 1.41 g. of a white oil which deposited a very small amount of white solid[21] on cooling. The crude glycol was dried in a desiccator at one mm. and titrated with periodic acid. Calcd. for $C_7H_{12}(OH)_2$: equiv. wt., 65.1. Found: equiv. wt., 69.5.

A solution of 1.21 g. of the glycol and 3.50 g. of *p*-nitrobenzoyl chloride in 30 ml. of dry benzene and 25 ml. of dry pyridine was refluxed for four hours. Ether (100 ml.) was added and the ethereal solution was washed successively with two 50-ml. portions of 3 *N* hydrochloric acid, two 50-ml. portions of 10% sodium carbonate and water. After drying over sodium carbonate, the ether was removed and the resulting oil triturated with petroleum ether. The resulting solid was crystallized twice from benzene to yield 0.30 g. of white needles, m.p. 189–190°.

Anal. Calcd. for $C_{21}H_{20}O_8N_2$: C, 58.87; H, 4.71. Found: C, 59.12; H, 4.72.

The Oxidation of 2-Hydroxycycloheptanone to Tropolone.—To 3.87 g. of I in 100 ml. of boiling glacial acetic acid was added 0.076 mole of bromine in glacial acetic acid over a period of 30 minutes. The dark-colored mixture was allowed to reflux for 36 hours at which time the acetic acid was removed by distillation at 25 mm. The dark tar-like residue was transferred to a sublimation apparatus and heated to 100° at 25 mm. pressure. A total of 0.95 g. of a yellow colored solid was collected during a period of 36 hours. Treatment of this sublimate (0.40 g.) in boiling cyclohexane resulted in the liberation of hydrogen bromide and the solution of most of the solid. After the insoluble material was separated, the cycohexane was removed by distillation and the residue sublimed to yield 0.15 g. of crude tropolone. Recrystallization of the crude tropolone from cyclohexane afforded analytically pure tropolone, m.p. 49–50°, green ferric chloride test. This substance forms a yellow anion with dilute sodium hydroxide and turns litmus paper red.

Anal. Calcd. for $C_7H_6O_2$: C, 68.85; H, 4.95. Found: C, 68.60; H, 5.14.

The Reaction of 2-Hydroxycyclopentanone (V) with Bromine.—To 2.45 g. (0.025 mole) of VI in 75 ml. of boiling carbon tetrachloride was added 0.052 mole of bromine in carbon tetrachloride over a period of 20 minutes. The dark-colored solution was allowed to reflux overnight at which time the carbon tetrachloride was removed by distillation. The residue was heated at 110° (14 mm.) for a period of 24 hours. A total of 0.566 g. (13%) of white crystals was obtained, m.p. 145–150°. Crystallization from carbon tetrachloride gave an analytical sample, m.p. 152–153.5°, weak violet color with ferric chloride.

Anal. Calcd. for $C_5H_5O_2Br$: C, 33.92; H, 2.85. Found: C, 34.01; H, 2.96.

Preparation of 3-Bromo-1,2-cyclopentadione (VII).—To 23 g. of 1,2-cyclopentadione[22] (VIII) in 150 ml. of carbon tetrachloride was added 0.235 mole of bromine over a period of 15 minutes. On gentle warming, evolution of hydrobromic acid occurred, and after two hours, the evolution of acid was nearly complete. The solvent was removed under an aspirator and the black-colored mixture of oil and solid was extracted with ether. After filtration and drying of the ethereal extract, the ether was removed to yield 13 g. of tan-colored crystals. After sublimation at 100° (13 mm.) followed by crystallization from carbon tetrachloride, 9 g. of white crystals were obtained, 152.5–154°. Mixed melting point with the product obtained from bromination of 2-hydroxycyclopentanone was 152–154°. In contrast to the "intense color" obtained by the former workers[17,22] with ferric chloride, only a weak violet color with ferric chloride was observed in this investigation.

Reaction of N-Bromosuccinimide with 1,2-Cyclopentadione (VIII).—Treatment of 5 g. of VIII in carbon tetrachloride with 9.2 g. of N-bromosuccinimide (m.p. 178–181° dec.) in 200 ml. of boiling carbon tetrachloride yielded, after filtering and concentration of the solvent, 2.12 g. of light-tan colored crystals. Sublimation of the material followed by crystallization afforded 50 mg. of VII, m.p. 151–153°. Mixed melting point with an authentic sample of VII gave 152–153°.

Reaction of N-Bromosuccinimide with 3-Bromo-1,2-cyclopentadione (VII).—To a solution of 9 g. of VII in hot carbon tetrachloride (300 ml.) was added 2.1 g. of N-bromosuccinimide (m.p. 178–181° dec.) and the mixture was allowed to reflux for two hours. The succinimide was filtered and the solvent removed from the filtrate. The residue, 9 g. of a black oil, would not sublime at 100° and 14 mm. pressure. The residue was then dissolved in 2 *N* sodium hydroxide and heated at 100° for 10 minutes after which the solution was acidified and saturated with ammonium sulfate. The saturated solution was transferred to a liquid–liquid continuous extractor and extracted with ether. Removal of the ether from the dark-colored ethereal extract yielded 4.0 g. of a black resinous material which gave a faintly green color with ferric chloride. Heating of this material at 100° and 14 mm. pressure yielded no crystalline material. The reaction was not investigated further.

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[21] H. G. Derx [*Rec. trav. chim.*, **41**, 312 (1922)] reports m.p. 46° or the *cis*-glycol, and m.p. 65° for the *trans*-.

[22] G. Hesse and E. Bucking, *Ann.*, **563**, 31 (1949).