[CONTRIBUTION FROM HICKRILL CHEMICAL RESEARCH LABORATORY]

The Synthesis of α-Phenyltropolone from Tropolone

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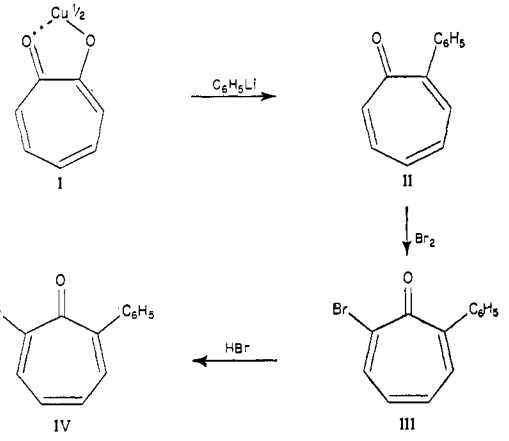
The synthesis of α-phenyltropolone has been effected from tropolone by a new method proceeding *via* 2-phenyltropolone and 7-bromo-2-phenyltropone.

In the synthesis of α-substituted tropolones, the method of Doering and Knox[2] fails, that of Nozoe and Cook is applicable[3] and that of Leonard, *et al.*,[4] affords certain α,α′-disubstituted derivatives. Very recently Nozoe, Mukai and Minegishi[5a] have communicated the synthesis of α-phenyltropolone by a new method differing only in detail from that reported here.

In this paper, three reactions, that of tropolone (or a derivative) with a lithium derivative to give a 2-substituted tropone,[5b,6] that of tropone with bromine to give 2,7-dibromotropone[7] and that of bromotropone with acid to form tropolone,[6,8] are combined into a synthesis of α-phenyltropolone (IV).

2-Phenyltropone (II)[5b,6] may be prepared conveniently from phenyllithium and copper tropolone (I), a form in which tropolone is easily isolated and stored. The bromination of II proceeds through an oily intermediate (Nozoe, *et al.*,[5a] report a crystalline perbromide) the ultraviolet absorption spectrum of which is quite similar to that of phenyltropilidene.[2] When heated alone or in a solvent or better with a small amount of pyridine, this intermediate loses hydrogen bromide to give 7-bromo-2-phenyltropone (III). The ultraviolet absorption spectrum (Fig. 1) of this compound is similar to that of phenyltropone[6] but has been shifted slightly to longer wave lengths. There are also close similarities between the infrared spectra[6] (Fig. 2). The rearrangement of III on treatment with alkali to *o*-phenylbenzoic acid coupled with the reasonable assumption that the adjacency of the oxygen atom and the phenyl group in II is not disturbed during the bromination points uniquely to the assigned structure.



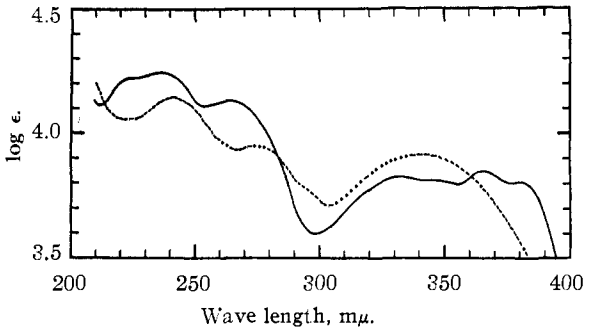


Fig. 1.—Ultraviolet absorption spectra (Beckman model DU with photomultiplier tube) of 7-bromo-2-phenyltropone (III, dotted line) and α-phenyltropolone (IV, solid line) in isoöctane.

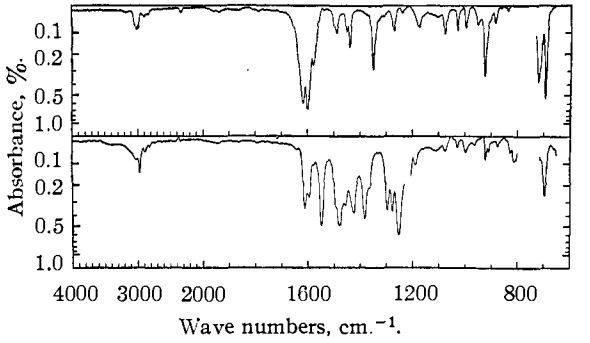


Fig. 2.—Infrared absorption spectra (Perkin-Elmer model 21, sodium chloride prism) of 7-bromo-2-phenyltropone (III, 0.300 *M* in carbon tetrachloride, 0.104, mm. cell, upper curve) and α-phenyltropolone (IV, 0.200 *M* in chloroform, 0.104 mm. cell, lower curve).

Treatment of III with aqueous hydrogen bromide in acetic acid results in the acid-catalyzed replacement of bromide by hydroxyl and the formation of α-phenyltropolone (IV). The ultraviolet absorption spectrum of IV (Fig. 1) differs noticeably from those of β- and γ-phenyltropolone[2] although the position of the last intense absorption (382 mμ) is common to all three. As is general in tropolones, the absorption spectrum of IV in isoöctane shows more detail than that in methanol, which is reported by Nozoe, *et al.*[5a] The infrared spectrum of IV (Fig. 2) is similar in many respects to those of the β- and γ-isomers.[2]

(1) Department of Chemistry, Yale University, New Haven, Conn.

(2) W. von E. Doering and L. H. Knox, THIS JOURNAL, **75**, 297 (1953).

(3) See ref. 2 for complete references; also T. Nozoe, T. Mukai, M. Kunori, T. Muroi and K. Matsui, *Science Repts. Tohoku Univ., First Ser.*, **35**, 242 (1952).

(4) N. J. Leonard, G. C. Robinson and J. W. Berry, Abstracts of Papers, American Chemical Society, Atlantic City, N. J., Sept. 14, 1952, p. 10M.

(5) T. Nozoe, T. Mukai and J. Minegishi, *Proc. Japan Acad.*, (a) **28**, 287 (1952); (b) **27**, 419 (1951).

(6) W. von E. Doering and C. F. Hiskey, THIS JOURNAL, **74**, 5688 (1952).

(7) W. von E. Doering and F. L. Detert, unpublished work.

(8) W. von E. Doering and L. H. Knox, THIS JOURNAL, **74**, 5683 (1952).

The preparation of 2-(*o*-methoxyphenyl)-tropone is reported here because work with this compound has been stopped.

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Experimental[9]

2-Phenyltropone (II) **from Copper Tropolone** (I).—An ethereal solution of phenyllithium from 3.78 g. of bromobenzene and 0.666 g. of finely divided lithium was transferred under nitrogen to another flask leaving unreacted lithium behind. I (0.300 g.) was then added slowly. The mildly exothermic reaction was terminated after 20 min. by adding ether and then dilute sulfuric acid until the aqueous phase was acidic. The ether layer was separated, washed with water and then with 5% aqueous sodium hydroxide and finally concentrated to a residue, sublimation of which yielded 0.320 g. (89%) of yellow needles, m.p. 70–75°. One recrystallization from isoöctane yielded II as long yellow needles, m.p. 83–84°; reported m.p. 83.5–84°[5b] and 83–84°.[6]

α-(*o*-Methoxyphenyl)-tropone.—An ethereal solution of *o*-methoxyphenyllithium, prepared from 2.48 g. of *o*-bromoanisole and 0.370 g. of finely divided lithium, was transferred to another flask under nitrogen leaving behind unreacted lithium and treated with 0.085 g. of copper tropolone at room temperature. After 30 min., the reaction mixture was diluted with ether, washed with dilute sulfuric acid, and dried over anhydrous magnesium sulfate. Removal of the ether left an oily residue which was evaporatively distilled at 64° and 0.5 mm. until all of the anisole was removed. Sublimation of the resulting solid residue at 110° and 0.5 mm. yielded a yellow material recrystallization of which from isohexane afforded 0.075 g. (63%) of pale yellow crystals, m.p. 93.5–94.5°.

Anal. Calcd. for $C_{14}H_{12}O_2$: C, 79.2; H, 5.7. Found: C, 79.2; H, 5.7.

7-Bromo-2-phenyltropone (III).—To a stirred solution of 0.310 g. of II in 50 ml. of dry carbon tetrachloride containing 0.300 g. of anhydrous sodium carbonate, 0.091 ml. (1 equiv.) of bromine in 3.2 ml. of carbon tetrachloride was added over a period of 2 hr., after which stirring was continued for 17 hr. The clear solution remaining after centrifuging all solid material was then treated with 0.272 g. of dry pyridine and refluxed for 1 hr. The pyridine hydrobromide was centrifuged, and the organic layer was washed successively with dilute sulfuric acid, water and 5% sodium bicarbonate, and concentrated. Sublimation of the residue yielded, first a colorless crystalline solid which was removed, and then at 110° and 0.5 mm. a yellow oil which afforded 0.155 g. (35%) of yellow crystals, m.p. 68–73°, on triturating with isohexane. Recrystallization from isohexane gave about 0.12 g. of fluffy yellow needles of III, m.p. 80–81°. Further crystallization afforded an analytical sample, m.p. 83.5–84.0°; reported[5a] m.p. 82–83°.

Anal. Calcd. for $C_{13}H_9BrO$: C, 59.8; H, 3.4; Br, 30.7. Found: C, 60.0; H, 3.6; Br, 30.5.

Alkaline Rearrangement of III.—III (20 mg.) was dissolved in 2 ml. of freshly prepared 10% alcoholic potassium hydroxide and refluxed for 6 hr. The cooled, pale yellow solution was acidified and extracted with chloroform. Several extractions of the chloroform solution with 5% sodium bicarbonate were combined, acidified and extracted with chloroform. Removal of the solvent yielded 4.6 mg. (30%) of *o*-phenylbenzoic acid, which on recrystallization gave 4.0 mg. of the acid, m.p. 111–112°, m.p. 111–112° on admixture with an authentic sample of m.p. 111–112°. The infrared absorption spectra of the two samples were identical.

α-Phenyltropolone (IV).—A solution of 0.038 g. of III in 3 ml. of glacial acetic acid, 3 ml. of 48% hydrobromic acid and 4 ml. of water (1.75 *M* in hydrobromic acid) was heated in a sealed tube at 160° for 6 hr. The reaction mixture was extracted with chloroform until test portions of the extracts no longer gave a green coloration with a 1% alcoholic ferric chloride solution. The combined chloroform extracts were shaken vigorously with an equal volume of saturated aqueous cupric acetate for about 5 min. and separated. The aqueous layer was extracted several times with warm chloroform until a negative ferric chloride test was obtained. Removal of the chloroform from these extracts gave 0.026 g. (77%) of the green copper salt of IV, m.p. 299–300° (dec.).

When 22.5 mg. of the copper salt dissolved in about 10 ml. of warm chloroform was treated with hydrogen sulfide, a precipitate of copper sulfide formed quickly. Mixing with Super-Cel and filtration through a Super-Cel mat gave a clear, almost colorless solution. Distillation of the solvent yielded 18 mg. (93%) of yellow crystalline material. Recrystallization from isohexane afforded 14 mg. of yellow needles of α-phenyltropolone, m.p. 116–116.5°.

Anal. Calcd. for $C_{13}H_{10}O_2$: C, 78.8; H, 5.1. Found: C, 79.0; H, 5.1.

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(9) All melting points are corrected.

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Synthesis of Carnosine and Related Peptides by the Phthaloyl Method[1]

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Condensation of phthaloyl-β-alanyl chloride with L-histidine in the presence of triethylamine at low temperature has yielded phthaloyl-β-alanylhistidine. After detachment of the phthaloyl group with hydrazine, carnosine was isolated. Several related peptides have also been prepared by the present method.

The phthaloyl synthesis of peptides, reported almost simultaneously by King and Kidd,[2] and by Sheehan and Frank,[3] appears especially useful for the synthesis of those peptides whose N-terminal amino acids are either glycine or β-alanine, for in such cases there is no question of racemization during the preparation of the phthaloylamino acid.[4]

The condensation of phthaloyl-β-alanyl chloride (I) with L-histidine by the method of Sheehan and Frank[3] succeeded, but the product, phthaloyl-β-alanyl-L-histidine (phthaloylcarnosine) (II), was not isolable, for it could not be crystallized from water or alcohol when magnesium chloride, formed from the magnesium oxide added at the start of the

(1) This investigation was supported in part by a grant from the National Science Foundation.

(2) F. E. King and D. A. A. Kidd, *Nature*, **162**, 776 (1948); *J. Chem. Soc.*, 3315 (1949).

(3) J. C. Sheehan and V. Frank, THIS JOURNAL, **71**, 1856 (1949).

(4) In unpublished research the author has shown that phthaloylhistidine is prepared in good yield only when histidine and phthalic anhydride are fused above 200° (oil-bath temperature), which is higher than the usual temperature (170°) for preparing phthaloylamino acids. The phthaloylhistidine isolated was completely racemized. Recently, Sheehan, Chapman and Roth, THIS JOURNAL, **74**, 3822 (1952), have shown that racemization of phenylalanine and of leucine may be avoided by fusion at 150°, but it would seem that these amino acids are special cases.