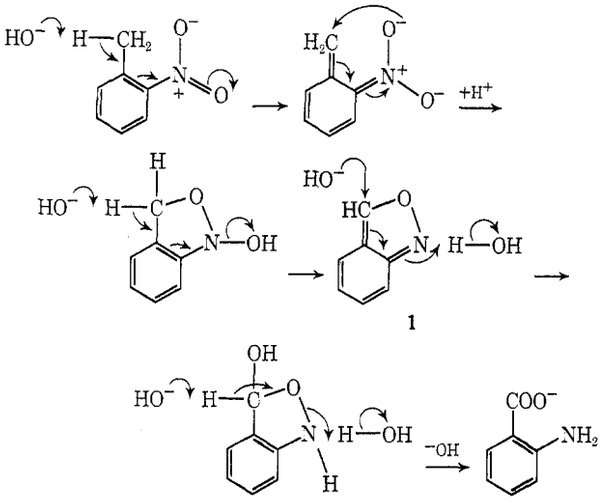
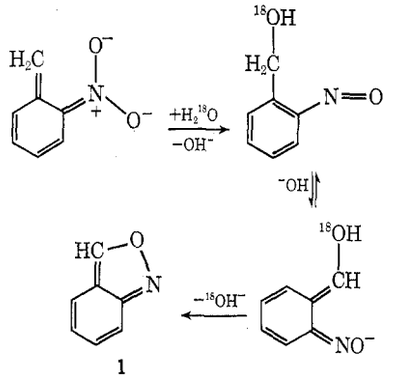
SCHEME I



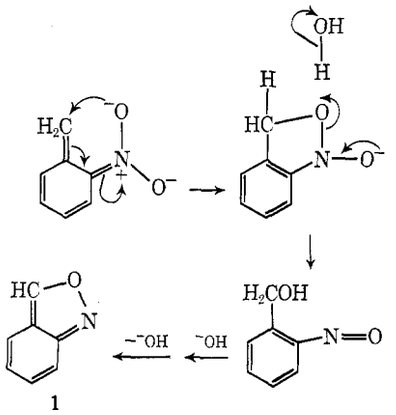
the methyl group and the hydrolysis of anthranil to anthranilic acid are well established.[5,11]

However, while anthranil is a reasonable intermediate, the present work does not comment on the detailed mechanistic pathway to this intermediate. Alternate versions of the mechanism shown, in which only one oxygen atom of the nitro group is transferred to anthranilate, would allow the involvement either of labeled[12] (Scheme II) or unlabeled (Scheme III)

SCHEME II



SCHEME III



(11) M. S. Kharasch, W. G. Brown, and J. McNab, *J. Org. Chem.*, **2**, 36 (1938).

(12) The authors gratefully acknowledge the valuable assistance of a reviewer with this section of the manuscript.

o-nitrosobenzyl alcohol. If *o*-nitrosobenzyl alcohol were an obligatory reaction intermediate and it was possible to remove it from the system as it formed, oxygen-18 analysis may enable a distinction between these latter possibilities.

Experimental Section

o-Nitrotoluene was fractionally distilled twice, the second distillation being performed under dry nitrogen, bp 94° (9.3 mm) [lit.[13] bp 94° (9.3 mm)]. 2-Methoxyethanol was redistilled three times, bp 124° (lit.[14] bp 124.4°). [^{18}O]Water (81.52 atom % ^{18}O, 0.254 atom % ^{17}O, 83.7 atom % D) was supplied by Yeda Research and Development Co., Rehovoth, Israel.

Rearrangement of *o*-Nitrotoluene in [^{18}O]Water.—*o*-Nitrotoluene (0.511 g) and potassium hydroxide (0.591 g, Baker Analyzed Reagent) were mixed with [^{18}O]water (1.071 g) and 2-methoxyethanol (3 ml). The reaction vessel was flushed rapidly with dry nitrogen, the contents were frozen, and the vessel was evacuated and sealed. The reaction was allowed to proceed for 9 hr at 100° in the dark. After the solvent was removed *in vacuo*, the residue was dissolved in water and extracted with ether. The pH was reduced to 3.4 and the extraction was repeated. This fraction was dried (Na_2SO_4), the solvent was removed, and the product was sublimed *in vacuo* to give 53 mg (10.4%) of anthranilic acid, mp 136.5–139°. Recrystallization from ether–hexane and benzene–hexane gave anthranilic acid, mp 143.8–144.2° (lit.[3] mp 145.5°). This purification procedure ensured that the product was in contact with normal water for only 30 min, under conditions unlikely to cause exchange.

Anthranilic acid was decarboxylated by heating *in vacuo* at 200–220° for 30–45 min and the carbon dioxide was purified by distillation from −80 to −196°. Isotopic ratios were measured in a Nier-type mass spectrometer.[15] The mass spectrum of anthranilic acid was determined on an AEI MS902 spectrometer at 70 eV using the direct insertion probe.

Registry No.—*o*-Nitrotoluene, 88-72-2; anthranilic acid, 118-92-3.

(13) J. Timmermans, "Physico-Chemical Constants of Pure Organic Compounds," Elsevier, New York, N. Y., 1950, p 594.

(14) J. A. Riddick and E. E. Toops, Jr., "Organic Solvents, Physical Properties and Methods of Purification," 2nd ed, Interscience, New York, N. Y., 1955, p 249.

(15) (a) A. O. Nier, *Rev. Sci. Instrum.*, **18**, 398 (1947); (b) A. O. Nier, *Phys. Rev.*, **77**, 789 (1950).

A New Synthesis of Benzocyclobutene and Bicyclo[4.2.0]octa-1(6),3-diene

PHILLIP RADLICK*[1] AND LAUREN R. BROWN

Department of Chemistry, University of California, Riverside, California 92502

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There are several methods available for the synthesis of benzocyclobutene[2] (**1**). We required large quantities of **1** and were not satisfied with presently published methods such as the improved pyrolysis of 1,3-dihydroisothionaphthene 2,2-dioxide (**2**).[3] We were not satisfied with this route as it involved the use of rather noxious compounds as synthetic intermediates and special apparatus for the final thermal decomposition. We also had a need for large amounts of bicyclo[4.2.0]octa-1(6),3-diene (**3**). We therefore have de-

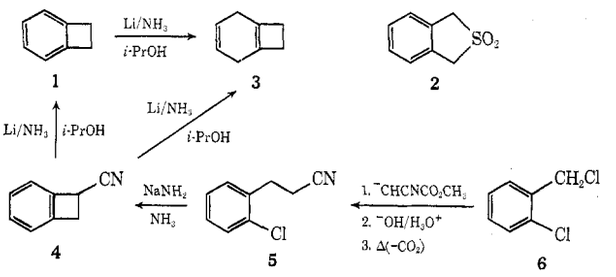
(1) Fellow of the Alfred P. Sloan Foundation.

(2) I. Klundt, *Chem. Rev.*, **70**, 471 (1970).

(3) J. Oliver and P. Ongley, *Chem. Ind. (London)*, 1024 (1965).

veloped a simple new synthetic route to both **1** and **3** which is of acceptable yield and amenable to large-scale production.

1 is prepared in 83% yield from 1-cyanobenzocyclobutene[4] (**4**) *via* reduction with Li in liquid ammonia. This is a useful example of the unusual reductive cleavage of a benzylic nitrile.[5] The nitrile **4** is readily prepared by the method of Bunnett and Skorcz as outlined above from *o*-chlorobenzyl chloride. We routinely effect the **6** → **5** → **4** conversion in 48% overall yield starting with as much as 1 kg of **6**.



While **3** is a known compound[6] it was prepared *via* an involved route. The Birch reduction of **1** has never been reported and we find that it proceeds to give **3** in excellent yield (98%). In fact, one can proceed directly from **4** to **3** without isolating **1** simply by adding the appropriate additional amounts of Li and isopropyl alcohol.

There are several dihydrobenzocyclobutene double bond isomers that could have resulted as products from the Birch reduction of **1**. In fact, the unusual chemical nature of carbocyclic four-membered rings does not permit one to predict the product with any great certainty. It is interesting that this reaction proceeds so easily and cleanly to give the double bond arrangement as in **3**. This new synthesis of benzocyclobutene and its subsequent Birch reduction to **3** may provide a ready access to some potentially new and interesting compounds.

Experimental Section

Preparation of Benzocyclobutene from 1-Cyanobenzocyclobutene (1).—A 3-l. three-necked flask, equipped with mechanical stirrer and gas inlet and outlet, was flame dried under a vigorous nitrogen flow. Ammonia (*ca.* 1.75 l.) was condensed and a solution of 1-cyanobenzocyclobutene (77.4 g, 0.6 mol) and isopropyl alcohol (72 g, 1.2 mol) in diethyl ether (300 ml) was added. The temperature was maintained at −40 to −45° and lithium wire (7.91 g, 1.14 mol) was added over a 30-min period. When all the lithium has reacted, ammonium chloride (64.0 g, 1.2 mol) was added while the temperature was kept below the boiling point of ammonia with a Dry Ice–acetone bath. The ammonia was evaporated overnight and water (1.5 l.) was added to the residue. The organic products were extracted with diethyl ether (4 × 300 ml), and this solution was washed successively with water (1 l.), 3 *N* hydrochloric acid (500 ml), saturated sodium bicarbonate solution (200 ml), and saturated sodium chloride solution (200 ml) and dried over magnesium sulfate. After filtration and concentration, distillation of the residue afforded benzocyclobutene (41.0 g), bp 79–83° (95 mm), 82.5% based on recovered starting material, and 1-cyanobenzocyclobutene (15.7 g), bp 75–78° (1 mm). Integration of the nmr spectrum showed the benzocyclobutene to be contaminated with bicyclo[4.2.0]octa-1(6),3-diene only to the extent of 3%: nmr (CCl_4) τ 6.88 (s, 4 H), 3.0 (A_2B_2, 4 H).

Preparation of Bicyclo[4.2.0]octa-1(6),3-diene from Benzocyclobutene (3).—A 1-l. three-necked flask was equipped with a Dry Ice condenser, mechanical stirrer, and gas inlets and outlet and was flame dried under a vigorous nitrogen flow. Ammonia (400 ml) was condensed. A solution of benzocyclobutene (13.0 g, 0.125 mol), isopropyl alcohol (15 ml), and tetrahydrofuran (50 ml, freshly distilled from lithium aluminum hydride) was added. Lithium wire (2.5 g, 0.36 mol) was added over a period of 2 hr. At this point the nmr of an aliquot showed no remaining aromatic protons. Ammonium chloride (18.7 g, 0.36 mol) was added cautiously and the ammonia was evaporated. Water (100 ml) was added to the residue and the organic product was extracted with diethyl ether (3 × 100 ml).

The ethereal solution was washed with water (2 × 100 ml) and saturated sodium chloride solution (2 × 50 ml), dried over magnesium sulfate, filtered, and concentrated. Distillation of the residue gave 12.78 g (98%) of the bicyclo[4.2.0]octa-1(6),3-diene: bp 78–79° (90 mm); nmr (CCl_4) τ 4.33 (s, 2 H), 7.50 (s, 8 H).

Acknowledgment.—This investigation was supported by a Public Health Service Research Career Development Award (GM-70,394-01) from the Institute of General Medical Sciences.

Registry No.—**1**, 694-87-1; **3**, 38325-66-5; **4**, 6809-91-2.

(4) J. Skorcz, *et al.*, *J. Med. Chem.*, **9**, 656 (1966).
(5) P. Arapakos, M. Scott, and F. Huber, Jr., *J. Amer. Chem. Soc.*, **91**, 2059 (1969).
(6) J. Garrett and G. Fonken, *Tetrahedron Lett.*, 191 (1969).

Prostaglandins. A Total Synthesis of (±)-11,15-Dideoxy-PGE$_2$ and (±)-11-Deoxy-PGE$_2$ Methyl Ester

PAUL A. GRIECO* AND JAMES J. REAP

Department of Chemistry, University of Pittsburgh, Pittsburgh, Pennsylvania 15260

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The synthesis of deoxyprostaglandins which represent potential intermediates for conversion into the naturally occurring prostaglandins *via* microbiological hydroxylation has recently been the subject of considerable synthetic effort. During the course of our work, a number of alternate 11-deoxy-PGE$_2$ syntheses have been developed.[1] We wish to report practical syntheses of (±)-11,15-dideoxyprostaglandin E$_2$ (**2**) and (±)-11-deoxyprostaglandin E$_2$ methyl ester (**1**).

The readily available cyclopentenone **7b** (*vide infra*) plus the recently reported capabilities of appropriately functionalized organocopper reagents to undergo smooth 1,4 conjugate addition to cyclopentenones[2] have allowed us to develop a short route to the deoxyprostaglandins of the E$_2$ series. Previous approaches to (±)-11-deoxy-PGE$_2$ methyl ester have constructed the C$_8$ side chain from dimethyl 2-oxoheptylphosphonate,[3] which was originally introduced by Corey.[4]

We now describe the synthetic sequence. Reduction

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(3) For a versatile synthesis of dimethyl 2-oxoalkylphosphonates see P. A. Grieco and C. S. Pogonowski, *J. Amer. Chem. Soc.*, **95**, 3071 (1973).
(4) E. J. Corey, I. Vlattas, N. H. Andersen, and K. Harding, *J. Amer. Chem. Soc.*, **90**, 3247 (1968).