

# The Preparation of Benzobicyclic

## [2.2.1] Azoxy Compounds

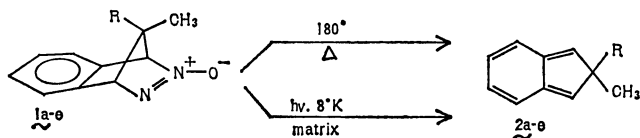
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### ABSTRACT

Benzobicyclic azoxy compounds, used as thermal and photochemical precursors of isoindenes, are synthesized from 2, 2-dialkylindane-1, 3-diones via a four-step sequence in which the key step is a sequential hydrolysis-oxidation procedure in which the use of a vibro-mixer is absolutely essential.

Sir:

Benzobicyclic azoxy compounds of the type **1**, where R=methyl, ethyl, cyclopropylcarbonyl, isopropyl and benzyl, were required as thermal and/or photochemical precursors of the interesting series of isoindenes **2**.<sup>1)2)3)</sup> The thermal stability of these azoxy compounds made



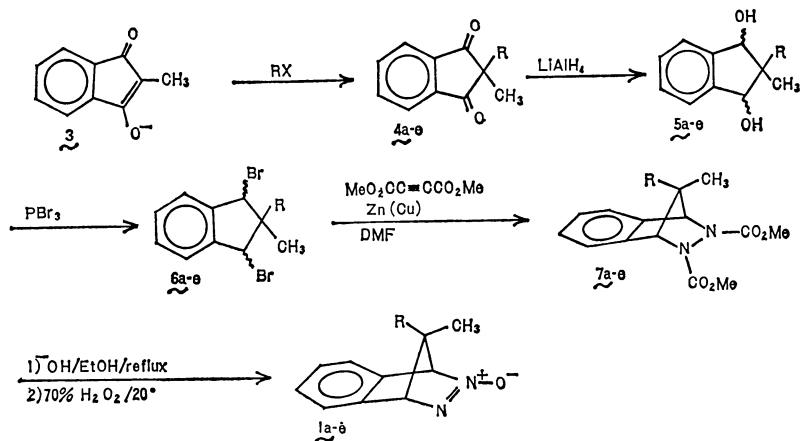
them much more desirable precursors than the analogous azo compounds which should lose  $N_2$  below room temperature.<sup>4)</sup>

Snyder had previously prepared numerous cyclic, cis-azoxy compounds by a combination hydrolysis-oxidation procedure.<sup>5)</sup> Unfortunately

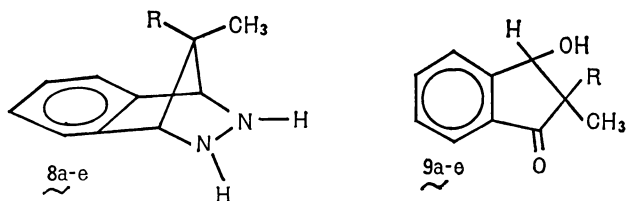
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his method was not effective for the synthesis of the benzannelated series which we required. Our procedure is outlined below:



Two features of our procedure proved to be absolutely essential for successful synthesis of the benzannelated azoxy compounds. First the vibro-mixer was found to be indispensable, particularly in the oxidation step where solubility of the organic species in the medium becomes a real problem. Secondly, the oxidation procedure must, in all cases, be carried out as a separate step and at a temperature not to exceed room temperature. The oxidation of the presumed hydrazine intermediate, **8**, is quite exothermic; hence the addition of  $H_2O_2$  must be very slow.



The major side products of these oxidative procedures were the keto alcohols **9** which are probably formed via decomposition of

intermediate azocompounds to isoindenes. Generally comparable amounts of 1 & 9 are formed and separation is effected by column chromatography.

Azo compounds have traditionally been utilized as precursors to hydrocarbon species, and where the product is not a particularly stable entity loss of nitrogen provides facile entry into some interesting systems. Two very common examples of such extrusion reactions are the formation of carbenes from diazirines and of trimethylene diradicals from 1-pyrazolines.<sup>7)</sup> On the other hand, where stable products are to be formed and where the extrusion of N<sub>2</sub> is an allowed [2+4] retrocycloaddition, nitrogen loss is too facile a process for azo compounds to be considered as reasonable precursors.<sup>4)</sup>

It has been noted by Snyder that azoxy compounds are much more thermally stable than their azo counterparts and that they seem to require about 200° greater temperature to extrude N<sub>2</sub>O than was required by the analogous azo compounds to extrude N<sub>2</sub>.<sup>9)</sup> In line with this prediction, we have found that the azoxy compounds 1 require a temperature of about 180° to extrude N<sub>2</sub>O to form the orthoquinoidal hydrocarbon species, the isoindenes. The syntheses presented here comprise the only presently known method of preparing these interesting azoxy compounds which until very recently<sup>2) 3) 10) - 12)</sup> also were the only precursors which allowed isolation of isoindene species.

## EXPERIMENTAL

Boiling points and melting points were uncorrected, the latter taken on a Thomas-Hoover capillary melting point apparatus. Infrared spectral data were obtained from either a Perkin-Elmer Model 137 or a Beckman Model IR-10 spectrophotometer, and all absorption bands are listed in cm<sup>-1</sup>. Nuclear magnetic resonance spectra were obtained from a Varian model A-60A spectrometer, unless specified as the XL-100 model, utilizing TMS as an internal standard. Mass

spectral data were determined using an AEI MS-30 high resolution mass spectrometer, which was connected to a DS-30 data system. Elemental analyses were performed by Atlantic Microlab, Inc. (Atlanta, Georgia).

All reagents which are not referenced were commercially available. *Sodium enolate of 2-methylindane-1, 3-dione*, (**3**),<sup>13</sup> was prepared according to the procedure of Wislicenus & Kotzle. A crude, dark red solid product was obtained and used without purification. *2,2-Dimethylindane-1,3-dione*, (**4a**),<sup>13</sup> was also prepared by the procedure of Wislicenus & Kotzle. The overall yield based upon the ethyl propionate used was 79%. **4a** was a white solid, mp 107-108°.

*2-methyl-2-ethylindane-1, 3-dione* (**4b**), Into a 3 l., 3-necked flask was placed a soln. of 174g (<0.95 moles) impure **3** in 1600 ml EtOH. To this solution was added, over a 1 hr. period, 250g (1.60 moles) ethyl iodide. After gently refluxing for 48 hours, the unreacted ethyl iodide and most of the EtOH was removed by rotary evaporator. The dark red residue was added to a mixture of 250 ml H<sub>2</sub>O and 250 ml ether and was extracted with ether four times. After washing with satd. aq. Na<sub>2</sub>CO<sub>3</sub> solution several times, the combined ether extract became orange. Drying with Na<sub>2</sub>SO<sub>4</sub> and evaporation of the ether gave a dark, red-brown oil which upon distn. (73-78°/0.1mm) resulted in a red crystalline solid. Recrystallization from hexane yielded 33.4g (20.4%) of a white product: mp 46-47.5° Nmr (CDCl<sub>3</sub>): δ 0.74 (t,3H), 1.26 (s,3H), 1.87 (q,2H), 7.70-8.14 (m,4H); ir (KBr): 2925 (m), 1745 (s), 1715 (s), 1603 (m), 1458 (m), 1385 (m), 1375 (m), 1335 (m), 1270 (s), 797 (m) and 730(s)cm<sup>-1</sup>.

Similarly, the *2-methyl-2-cyclopropylcarbonylindane-1, 3-dione*, **4c**, (b. p. 106-110°/0.4mm) was prepared in 22% yield, and the *2-methyl-2-benzylindane-1, 3-dione*, **4e**, (mp 78-79°) was prepared in 34% yield.

*2-methylindane-1, 3-dione* (**10**). 180g of crude **3** was dissolved in 1l H<sub>2</sub>O in 2l Erlenmeyer flask. Extraction four times with ether removed various impurities and then the enolate was acidified with 6N HCl

until a pH of 2 was reached (needed approx. 250 ml of acid). A dark red oil separated during the acidification. Extraction four times with 250 ml ether, washing the combined ether extracts with satd. NaCl soln, drying with  $\text{MgSO}_4$  and evapn. of the ether led to a clear, dark red oil which may crystallize upon standing. Distillation (98–115°/0.12mm) led to an orange-red product which crystallized. Recrystallization (2 : 1, EtOH– $\text{H}_2\text{O}$ ) led to 28.8g creamy white crystals (20.6%, based on ethyl propionate) : mp 83–84.5° ; Nmr ( $\text{CDCl}_3$ ) :  $\delta$ 1.40 (d,3H), 3.07 (g,1H), 7.70–8.20 (m,4H) ; ir (neat, NaCl) : 2920 (m), 1775 (m), 1745 (s), 1720 (s) 1600 (m), 1468 (m), 1453 (m), 1370 (m), 1345 (m), 1280 (m), 1235 (m), 743 (m)  $\text{cm}^{-1}$ . 2-methyl-2-Isopropylindane-1, 3-dione, (4d). 100 ml of freshly prepared NaOEt in EtOH (0.1 mole) was added to 12.0g (0.075 mole) of 10 in 100 ml EtOH. The deep red enolate solution was added to a 800 ml pyrex pyrolysis tube along with 40g (0.235 mol) isopropyl iodide. Additional EtOH (50ml) was used to wash down the sides of the tube which was sealed under  $\text{N}_2$ . Thermolysis at 150° for 10 hr. in a tube furnace led to a clear yellow-orange solution which after opening of the tube was poured into 750 ml  $\text{H}_2\text{O}$  in a 2l separatory funnel. Three 250 ml extractions with ether were combined, washed with water and then satd aq.  $\text{Na}_2\text{CO}_3$ , dried over  $\text{MgSO}_4$  and the ether removed in vacuo to give 8.2g of a brown oil Distillation (73–84°/0.1mm) led to 6.7g (44%) of product : Nmr ( $\text{CDCl}_3$ ) :  $\delta$ 0.94 (d,6H), 1.28 (s,3H), 1.84–2.56 (m,1H), 7.72–8.12 (m,4H) ; ir (neat, NaCl) : 2930 (m), 2850 (w), 1740 (m), 1710 (s), 1600 (m), 1460 (m), 1370 (m), 1270 (s), 988 (m), 785 (m), and 730 (m)  $\text{cm}^{-1}$ .

2,2-Dimethylindane-1,3-diol (5a), was prepared by the procedure of Alder & Fremery<sup>14</sup> by reduction of 4a with  $\text{LiAlH}_4$  in 91% yield. The white solid had a mp of 145–150°.

Similarly, 2-methyl-2-ethylindane-1,3-diol (5b) (mp 68–95°), 2-methyl-2-cyclopropylcarbonylindane-1, 3-diol (5c) (yellow oil), 2-methyl-2-isopropylindane-1, 3-diol (5d) (white sticky solid), and 2-

*methyl-2-benzylindane-1,3-diol* (**5e**) (mp 43–51°), were also prepared in 80–99% yields.

1,3-Dibromo-2,2-dimethylindane (**6a**)<sup>14</sup> was prepared by the procedure of Alder & Fremery. An 84% yield of a light yellow oil was obtained, (bp 190–112°/0.5mm): Nmr (CDCl<sub>3</sub>),  $\delta$ 1.35 (m,6H), 5.14 (s,1H), 5.24 (s,1H) and 7.35 (m,4H).

Similarly, 2-methyl-2-ethyl-1,3-dibromoindane (**6b**), (bp 101–104°/0.125mm), 2-methyl-2-cyclopropylcarbiny1-1,3-dibromoindane (**6c**), 2-methyl-2-isopropyl-1,3-dibromoindane (**6d**), (bp 94–96°/0.045mm) and 2-methyl-2-benzyl-1,3-dibromoindane (**6e**), (bp 152–158°/0.10mm) were prepared in 50–95% yields.

*Dimethyl-7,7-dimethyl-5,6-diaza-2,3-benzobicyclo (2.2.1)-hept-2-ene-5,6-dicarboxylate* (**7a**),

12g of Zn-Cu couple was freshly prepared according to the method of LeGoff. The 12g of couple were then placed in a 500 ml 3-neck flask equipped with a mechanical stirrer, a reflux condenser, and a dropping funnel. In the flask were also placed 30 ml of dimethylformamide (previously dried by standing for 1 week over a 4A molecular sieves). A solution containing 10g (0.033 mol) of the dibromide, **6a**, 9.8g (0.067 mol) of dimethyl azodicarboxylate, and 30 ml of dry dimethylformamide was added dropwise over a 30 min. period to the rapidly stirred Zn-Cu couple. The reaction mixture immediately began to turn green, and it became warm. After completing the addition of the reagents, stirring was continued for about 1 hr., until the reaction mixture cooled to room temperature. The Zn-Cu couple was filtered off, using a Celite pad. Ether and water were then added to the filtrate, along with a few ml of dilute HCl, in order to dissolve the ZnBr<sub>2</sub> precipitate. The resultant mixture was separated, and the aqueous layer was extracted three times with ether. The combined extracts were washed with water, and then dried by filtration through anhydrous MgSO<sub>4</sub>. Solvent removal under vacuum resulted in 8.7g (91% yield of crude product) of a light yellow glassy solid. Sublimation

(at 100° and a pressure of <0.005mm) gave a white solid, mp 105-106°. Nmr (CDCl<sub>3</sub>): δ0.75 (s,3H), 1.23 (s,3H), 3.73 (s,6H), 4.93 (broad s,2H), 7.10-7.45 (m,4H); ir (CCl<sub>4</sub>, KBr liquid cell): 2935 (w), 1745 (s), 1700 (vs), 1435 (s), 1325 (vs); mass spectrum: exact m/e 290.1290 (M<sup>+</sup>).

*Anal.* Calc for C<sub>15</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>: C, 62.05; H, 6.25; N, 9.65.

Found: C, 62.14; H, 6.29; N, 9.63.

The analogous *Dimethyl 7-alkyl-7-methyl-5, 6-diaza-2, 3-benzobicyclo [2.2.1] hept-2-ene-5, 6-dicarboxylates*, **7b**, c, d and e, where alkyl = ethyl, cyclopropylcarbonyl, isopropyl and benzyl, respectively, were prepared as viscous oils or glassy solids by identical procedures in 86-92% yields.

*7, 7-Dimethyl-5, 6-diaza-2, 3-benzobicyclo [2.2.1] hepta-2, 5-diene-5-N-oxide*, **1a**.

A solution of 10.0g (0.0345 mol) of the diester (**7a**) in 100 ml of absolute EtOH was placed in a reaction vessel designed to accomodate a vibromixer, a reflux condenser, gas inlet and outlet tubes, a solid addition funnel, and a rubber septum (fitted on a side arm). After placing 10g (0.18 mol) of KOH in the solid addition funnel, the solution and the reaction vessel were flushed with argon for 1.5 hr. From this point on, a positive argon pressure and the vibromixing were maintained. The solution was heated to reflux, followed by the rapid addition of the KOH pellets. After 3.5 hr of refluxing, the hydrolysis step was completed (as indicated by TLC, using Al<sub>2</sub>O<sub>3</sub>, CHCl<sub>3</sub>, and I<sub>2</sub>) and the reaction mixture was cooled to room temperature. A fairly rapid flow of argon was passed through the vessel during the next part of the reaction sequence. Using a syringe, 50 ml of 70% H<sub>2</sub>O<sub>2</sub> were gradually added over a 15 hr period. The slow rate of addition prevented the reaction mixture from rising above room temperature, a condition which is important to the success of the reaction. For convenience, it was possible to leave the reaction overnight at room temperature, under an argon atmosphere. The

mixture was extracted with 5 portions of  $\text{CH}_2\text{Cl}_2$ . After filtering the combined extracts through  $\text{MgSO}_4$ , solvent removal under vacuum resulted in 5.3g of a yellow oil. The g. l. p. c. analysis (2.5 ft. x 0.25 in column containing 1% SE-30 on chromosorb W, silanized, operating at  $140^\circ$ ) indicated that 55% of the crude product was the desired azoxy compound.

The other 45% consisted largely of the keto alcohol side product, **9a**. The azoxy compound was separated and partially purified by column chromatography, using 300g of 80/200 mesh  $\text{Al}_2\text{O}_3$  as the absorbent, and  $\text{CH}_2\text{Cl}_2$  as the elution solvent. The  $\text{Al}_2\text{O}_3$  was coated with Dupont 906 luminescent indicator (5% w/w) which, under ultraviolet irradiation, showed the development of three bands during the elution. The relatively small first band contained nothing of interest, but the large second band consisted of 2.37g of partially pure azoxy compound. Material obtained from the third band weighed 3.25g, but glpc analysis indicated that only 20% of it was the desired product. Further purification of the azoxy fraction (from band 2) was done by triturating the solid several times in pentane. The resulting white powder weighed 1.7g (26%), mp  $71^\circ$ – $73^\circ$  (with gas evolution). Nmr ( $\text{CDCl}_3$ ):  $\delta$  0.85 (s,3H), 1.43 (s,3H), 5.04–5.17 (m,1H), 5.20–5.37 (m,1H), 7.17–7.67 (m,4H).

Anal. Calc for  $\text{C}_{11}\text{H}_{12}\text{N}_2\text{O}$ : C, 70.18, H, 6.43; N, 14.88.

Found: C, 70.10; H, 6.45; N, 14.89.

The analogous 7-alkyl-7-methyl-5, 6-diaza-2, 3-benzobicyclo [2, 2, 1] hepta-2, 5-diene-5-N-oxides, **1b**, c, d, and e, where alkyl = ethyl, cyclopropylcarbinyl, isopropyl and benzyl respectively, were prepared by essentially identical procedures in 22–29% yield. **1b** and **1c** were viscous oils while **1d** and **1e** were white crystalline solids, mps  $108$ – $110^\circ$  and  $122$ – $124^\circ$  respectively.

## References

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