[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Elimination Studies Involving 2-Bromotropinone and 6-Hydroxytropinone: A Selective Route to the Troponoid Ring System

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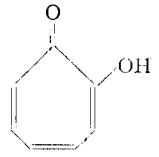
6-Hydroxytropinone methiodide and 2-bromotropinone methiodide are converted under mildly basic conditions to tropone.

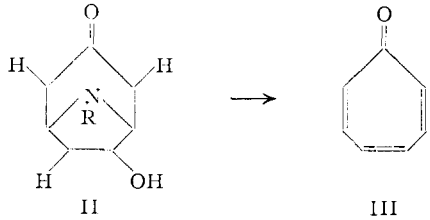
Since the tropolone (I) ring system has turned up in a number of natural products—including some of considerable complexity—it becomes of interest to



I

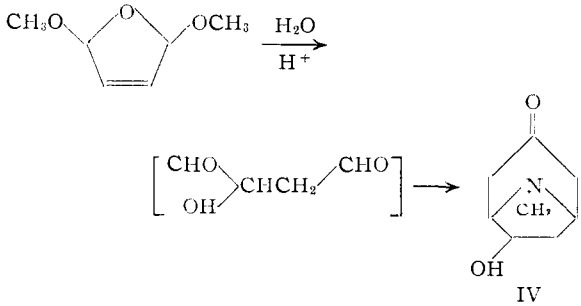
develop selective reactions which, proceeding under as mild conditions as possible, afford the tropolone or tropone (III) ring structures in good yield. The present study was undertaken with the purpose of discovering such a route.

It was considered that the collapse of a 6-hydroxytropinone (II)—brought about by the elimination of water and amine in a basic medium—should lead directly to the tropone ring



II III

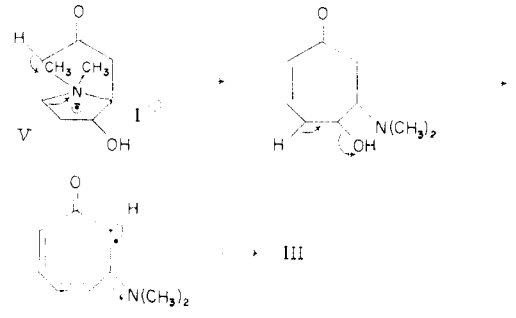
and this view was strengthened by the observation of Büchi, Meinwald and co-workers[1] that tropinone methiodide is converted under varying conditions to a mixture of cycloheptadienones. Accordingly a study of the route utilizing 6-hydroxytropinone (IV) as the starting material was initiated. Of the methods available[2-4] for the preparation of IV and



IV

related compounds—all variants of the Robinson tropinone[5] synthesis—that reported by Clauson-Kaas[4] is the most efficient, starting with 2,5-dimethoxy-2,5-dihydrofuran, methylamine and acetone dicarboxylic acid, and proceeding in an acid medium as an essentially single stage preparation. The procedure was further simplified by regenerating the free base IV from the picrate (in which form the product is isolated from the reaction mixture) through the use of Dowex 2 in the basic phase. On addition of excess methyl iodide to the crude tropinone, the methiodide V, a crystalline compound with no characteristic melting point, was obtained in high yield. In order to convert the methiodide to tropone, an elimination was carried out at 100° in dilute aqueous sodium bicarbonate, and the course of the reaction was followed spectrophotometrically in the ultraviolet. After 1.5 hours the decomposition appeared to be complete. Because of the disparity between the extinction coefficients of the several authentic tropone maxima[6] and those of the crude product obtained in solution at this stage, it was evident that some material other than tropone had formed. This material was not isolated but could be eliminated by the isolation of tropone as the picrate and regeneration from the salt through the aid of the ion exchange resin IR 45. The spectral behavior of the product obtained in this way was identical with that of authentic tropone, the yield being 82%. The picrate, recrystallized from chloroform, melted at 98–101° and was identical with the picrate of tropone obtained by another route.[7]

It is clear that tropone must be generated by a multi-stage elimination of the salt V, and it appeared that more information about the nature of the intermediate(s) could be gained through ultraviolet spectral studies. However, we could detect no relatively long-lived intermediate in that there was observed throughout the course of the reaction *only* the peaks characteristic of the starting material and the final product. Although the question of intermediates is left unsettled, it seems likely



(1) C. Büchi, N. C. Yang, S. L. Emerman and J. Meinwald, *Chemistry & Industry*, **40**, 1063 (1953).

(2) J. C. Sheehan and B. M. Bloom, THIS JOURNAL, **74**, 3825 (1952).

(3) A. Stoll, B. Becker and E. Jucker, *Helv. Chim. Acta*, **35**, 1263 (1952).

(4) P. Nedenskov and N. Clauson-Kaas *Acta Chem. Scand.*, **8**, 1295 (1954).

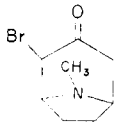
(5) R. Robinson, *J. Chem. Soc.*, 111, 762 (1917).

(6) (a) H. J. Dauben, Jr., and H. J. Ringold, THIS JOURNAL, **73**, 876 (1951); (b) W. v. E. Doering and F. L. Detert, *ibid.*, **73**, 877 (1951).

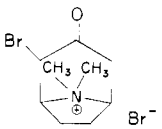
(7) E. E. van Tamelen and G. T. Hildahl, *ibid.*, **75**, 5451 (1953).

that each elimination, being of the β-type, occurs readily. The exemplary route outlined below is thus consistent with the observed facility of the over-all change.

Recently Nickon[8] described the preparation and proof of structure of 2(β)-bromotropinone (VI), a base so constituted that, again



VI

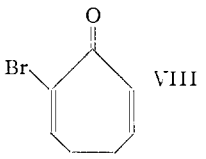


VII

elimination reactions might be expected to yield tropone. In pursuance of this notion, the free base, VI, obtained essentially as described by Nickon,[9] was converted, although in poor yield, to the crystalline methobromide (VII) required for the elimination studies.

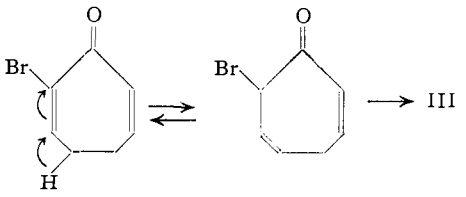
Subjection of the salt VII to the elimination conditions worked out in the hydroxytropinone series, resulted in only a few per cent. spectral yield of tropone, even after many hours of heating. Since the conditions were such as to effect conversion of bicarbonate to carbonate, the latter base was substituted in the projected elimination reaction; yields rose to about 20%. A slightly higher yield of tropone was obtained by using dilute sodium hydroxide, although there was evidence of decomposition in this case. Finally it was found that the combination sodium bicarbonate–trimethylamine at 83° gave as high a spectral yield as 60% of tropone.

Consideration of the probable mechanism involved in the bromotropinone case reveals that the necessary eliminations cannot follow as naturally as those in the hydroxytropinone case. For example, regardless of whether the elimination sequence is initiated at C-2 or C-4, it appears that the intermediate VIII would result after loss of



VIII

dimethylamine. Aromatization can ensue only after *at least* one prototropic shift; such a change is of course not integral in the hydroxytropinone



III

sequence. It is possible that this added requirement may necessitate the more drastic conditions needed experimentally.

(8) A. Nickon, THIS JOURNAL, **77**, 4094 (1955).

(9) Attempted repetition of the sulfuric acid-catalyzed rearrangement of tropinone perbromide to 2-bromotropinone hydrobromide (m.p. 192° dec.) led in our hands to a product (m.p. 212–214° dec.), which, on the basis of its analysis and that of the derived free base, appeared to be a *dibromo*tropinone hydrobromide.

Acknowledgment.—The authors are grateful to Merck and Co. for a gift of tropinone.

Experimental

6-Hydroxytropinone (IV).—The picrate of 6-hydroxytropinone,[4] after recrystallization from ethanol, melted at 197–199° with decomposition (reported[4] 199–200° with decomposition). In order to obtain the free base, the picrate was dissolved in methanol, and small portions of Dowex 2 in the hydroxyl phase were added with shaking to the methanolic solution until it became colorless. The resin was removed by filtration, and the filtrate yielded, after evaporation to dryness on the steam-bath, colorless crystals of 6-hydroxytropinone. After sublimation, the base melted at 119–121° (reported[4] m.p. 121–122°).

6-Hydroxytropinone Methiodide (V).—The crude 6-hydroxytropinone (0.5 g.) obtained directly from the ion-exchange resin treatment, was dissolved in 5.0 ml. of absolute ethanol, and to the solution was added in the cold 1 g. of methyl iodide. After a day in the refrigerator, the reaction mixture had deposited colorless crystals of the salt. After isolation by filtration and crystallization from ethanol–ether, the yield of product amounted to 84% of the theoretical (assuming the starting material was of 100% purity) and gave the correct analysis for a monomethiodide. The substance did not exhibit a characteristic melting point, but decomposed gradually at high temperatures.

Anal. Calcd. for $C_9H_{16}NO_2I$: C, 36.38; H, 5.43. Found: C, 36.81; H, 5.46.

Tropone (III).—A solution of 75 mg. (0.25 mmole) of hydroxytropinone methiodide and 21 mg. (0.25 mmole) of sodium bicarbonate in 50 ml. of water was heated on a steam-bath; periodically, aliquots were removed and the ultraviolet absorptions determined. During the first 1.5 hour period, the absorption peak of the starting material at 225 mμ gradually increased to about 33,400 and the characteristic tropone peaks at 228, 231, 239 and 312 mμ began to appear. If the reaction was run at room temperature, the starting peak at 225 mμ diminished slowly but did not shift, and the peak at 312 mμ gradually began to appear. After heating beyond 1.5 hours, no further spectral changes were observed, and it was assumed that reaction was complete. Therefore, a solution of 0.5 g. of picric acid in water was added to the reaction mixture, and the tropone picrate and excess picric acid were extracted with several portions of chloroform (total volume about 250 ml.). The chloroform extract was evaporated down on a steam-bath to a volume of about 25 ml., after which the remaining solvent was blown off at room temperature with a stream of air. The residue remaining was dissolved in a minimum (about 25 ml.) of 50% ethanol and applied to an ion-exchange column (IR 45). The liberated tropone was eluted with 100 ml. of 50% ethanol. Ultraviolet analysis showed the presence of 0.205 mmole (82%) of tropone. The spectrum, both with regard to position of maxima as well as extinction coefficient values, was identical with that recorded[6a] for tropone.

In a larger run, tropone picrate was isolated and purified by adding a limited amount of picric acid to the reaction product resulting after a 2–3 hour heating period and isolating as described above. Since picric acid is less soluble than tropone picrate, the concentrated chloroform solution was allowed to evaporate slowly, first depositing crystals of picric acid. On further evaporation, large cubic crystals of the salt were obtained, which were separated manually—with the aid of a magnifying glass—from some picric acid still remaining. The melting point observed was 98–101°; the recorded melting points are 99–100° and 100–101°.[6a-b,7]

2(β)-Bromotropinone Methobromide (VII).—Five grams of 2(β)-bromotropinone was dissolved in 75 ml. of methanol and the solution placed in a polyethylene bottle. Ten grams of methyl bromide was then passed in by heating a 16% xylene solution on the steam-bath; the xylene solution was held in a side-arm flask which was connected to the bottle with a delivery tube.[10] After 48 hours, ether was added to complete precipitation of the quaternary salt.

(10) For smooth operation, it is convenient, before running in the methyl bromide, to dissolve about 50 mg. of the bromotropinone methobromide in the methanol and then add ether (about 75 ml.) to induce crystallization.

The crude product (1.3 g.), on recrystallization from ethanol–water, yielded 520 mg. as the first crop and about half again as much from the mother liquors. The total yield of such material (m.p. 264–266° dec.), which was of reasonable purity, amounted to 10–14%.

Anal. Calcd. for $C_9H_{15}Br_2NO$: C, 34.50; H, 4.78. Found: C, 34.67; H, 4.81.

Elimination Studies with 2(β)-Bromotropinone Methobromide.—When the salt was treated with sodium bicarbonate at 85° for 56 hours, a 7% spectral yield of tropone formed. The reaction conditions were the same as those used for hydroxytropinone methiodide, except that the concentration of reactants was approximately five times as great.

When sodium carbonate was substituted for sodium bicarbonate, the yield rose to about 20%. This optimum yield was obtained after about 14 hours.

In the sodium hydroxide-induced eliminations, a 34.3-mg. sample of the quaternary salt was dissolved in 10 ml. of water, and 0.66 ml. of 0.033 *N* base was added. After 5 minutes on a boiling water-bath, the spectral yield was 22–25%; longer periods of heating caused a diminution in the yield.

The best results were obtained through the use of sodium bicarbonate and trimethylamine as a pair of reagent bases. Thirty-one milligrams of the quaternary salt, dissolved in 0.5 ml. of water, was mixed with 120 mg. of bicarbonate and 2.5 ml. of a 50% solution of trimethylamine in water. After being heated for 4 hours at 83°, the reaction mixture, on the basis of spectral analysis, contained about a 60% yield of tropone. Further investigation of this technique showed that higher concentration of reactants, omission of the bicarbonate, or a large excess of bicarbonate led to decreased yields. Isolation of tropone as the picrate proceeded along lines described earlier in this account.

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[CONTRIBUTION FROM THE MCPHERSON CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

The Base-catalyzed Rearrangement of 2-Nitrobenzenesulfenanilide

BY M. P. CAVA AND C. E. BLAKE[1]

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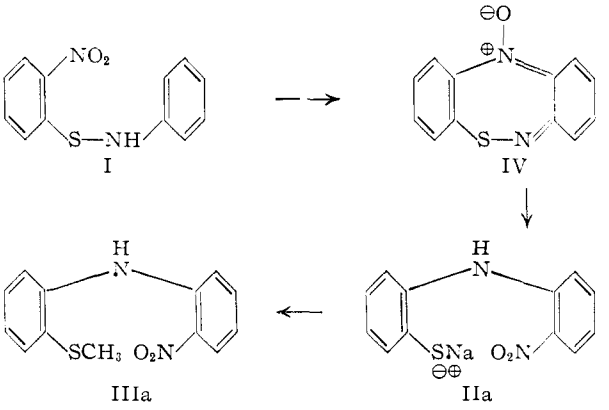
The rearrangement of 2-nitrobenzenesulfenanilide by sodium hydroxide does not yield the sodium salt of 2-mercapto-2′-nitrodiphenylamine, as previously claimed. The product actually formed is sodium azobenzene-2-sulfinate, converted by methyl iodide to 2-methylsulfonylazobenzene. Confirmation of these structures is shown by a number of transformation reactions and by an independent synthesis of 2-methylsulfonylazobenzene.

It has been reported by Moore and Johnson[2] that 2-nitrobenzenesulfenanilide (I) is transformed by boiling alcoholic sodium hydroxide into an orange sodium salt $C_{12}H_9N_2O_2SNa$ (II). Methylation of this salt with methyl iodide gave a neutral orange compound $C_{13}H_{12}N_2O_2S$, m.p. 97–98° (III). Compound III was assigned the structure 2-thiomethyl-2′-nitrodiphenylamine (IIIa), since it was identical both in elementary composition and in melting point[3] with a substance of known structure IIIa prepared by a different route by Evans and Smiles.[4] The original sodium salt II was then assumed to be the sodium salt of 2-mercapto-2′-nitrodiphenylamine (IIa).

The exact course of the alkaline rearrangement of 2-nitrobenzenesulfenanilide, not previously commented upon, seemed to us rather difficult to explain by simple and logical mechanistic steps. A possible path was one involving seven-membered heterocyclic intermediates such as IV. This hypothesis predicts that the nitro group in the methylated product IIIa is derived from the sulfenamide nitrogen of the starting material I,[5] a prediction which could be checked by using N^{15}-labeled starting material and systematically degrading the methylated rearrangement product.



As the first stage in the stepwise degradation of the thiomethyl ether IIIa, reduction of the nitro group of IIIa to a primary amino group was desired. An excellent reagent for this type of reduction is ethanolic hydrazine containing a trace of Raney nickel.[6] In a model experiment this reagent reduced *o*-nitrodiphenylamine to *o*-aminodiphenylamine in 82% yield. Reduction of the methylated rearrangement product III occurred readily to give an almost quantitative yield of a colorless reduction product V, m.p. 124–125°. Analysis of V showed it had the formula $C_{13}H_{14}O_2N_2S$, a structure in which two hydrogens had been gained but in which *no oxygens had been lost.* The reduction, therefore, could not have involved the conversion of a nitro group to a primary amino group. The reduction product V was insoluble in cold dilute hydrochloric acid, but dissolved in the acid when heated. After neutralization of the acid solution there was obtained a new compound VI, m.p. 163–164°, which was isomeric with V. Since a cold acid solution of VI reacted with sodium nitrite, followed by alkaline β-naphthol to give a red precipitate, VI was evidently a primary aromatic amine. Acetylation of VI by acetic anhydride in pyridine gave a diacetyl

(1) From the M.S. Dissertation of C. E. Blake, The Ohio State University, 1956.

(2) M. L. Moore and T. B. Johnson, THIS JOURNAL, **57**, 2235 (1935).

(3) No mixed melting point was reported.

(4) W. J. Evans and S. Smiles, *J. Chem. Soc.*, 187 (1935).

(5) For a detailed discussion of this argument, see ref. 1.

(6) D. Balcom and A. Furst, THIS JOURNAL, **75**, 4334 (1953).