[Contribution from the Department of Chemistry of the University of Rochester]

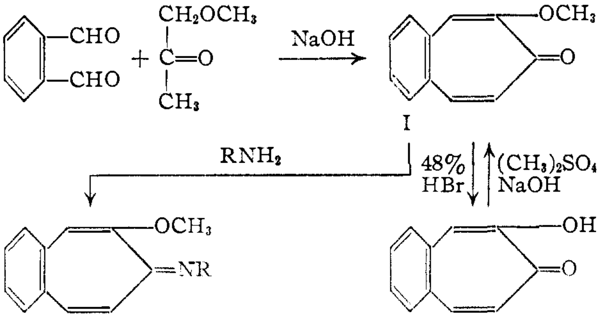
The Properties of 4,5-Benztropolone and Related Compounds, as Compared to Those of Colchicine and Other Tropolones[1,2]

By D. S. Tarbell and J. C. Bill

Phthalaldehyde has been found to condense with methoxyacetone in good yield to form 4,5-benztropolone methyl ether. The ether is readily split by strong acid to form 4,5-benztropolone, which is much more readily prepared by this procedure than by the previous process. Benztropolone and its methyl ether do not give the characteristic aromatization reactions shown by colchicine, colchiceine and the monocyclic tropolones, and benztropolone is a weaker acid than colchiceine or tropolone. An explanation is offered for this difference in behavior. 3-Nitro-4,5-benztropolone is, however, rapidly isomerized by aqueous alkali to 1-nitro-2-naphthoic acid. 4,5-Benztropolone is rapidly attacked by electrophilic reagents; it forms a dibromo substitution product, nitrates readily to form the 3-nitro derivative, and couples to form a 3-*p*-nitrophenylazo compound. Some reduction products of the oxime of benztropolone are described.

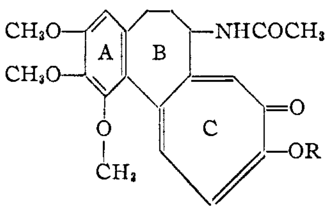
In a previous report[3] the synthesis of 4,5-benztropolone, accompanied by the formation of phthiocol[4] was described. The synthesis was carried out by the condensation of phthalaldehyde[5] and hydroxyacetone. The present paper reports a greatly improved procedure for the preparation of 4,5-benztropolone and its methyl ether, so that it has been possible to compare the chemical properties of the 4,5-benztropolone series with those of colchicine and the monocyclic tropolones.

We have found that the condensation of phthalaldehyde with methoxyacetone in dilute aqueous alkali gives a good yield of 4,5-benztropolone methyl ether (I), unaccompanied by phthiocol formation. The methyl ether (I) can be hydrolyzed to the hydroxy compound II by refluxing with 40% hydrobromic acid, and II can be obtained readily by this process in an over-all yield of nearly 50% from phthalaldehyde. This procedure is greatly simplified by the fact that methoxyacetone is now readily available by oxidation of the corresponding alcohol.[6] The product II obtained from the methoxyacetone process was shown to be identical with the product from the hydroxyacetone condensation; furthermore, II could be converted to the methyl ether (I) by treatment with methyl sulfate and alkali.

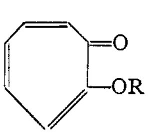


III, R = OH
IV, R = $2,4\text{-}(O_2N)_2C_6H_3NH$

A study of the properties of the benztropolone (II) and its methyl ether I shows that they are different in important respects from those of colchicine[7] (V), cholchiceine (VI) and tropolone itself[8] (VIII). Thus, 4,5-benztropolone methyl ether readily forms carbonyl derivatives, such as the oxime III and the dinitrophenylhydrazone IV, but colchicine[9] and tropolone methyl ether[8] do not. Furthermore, the ether I is only partially hydrolyzed to the hydroxy compound II by refluxing with 6 *N* hydrochloric acid for several hours, whereas cholchicine[9] and the tropolone methyl ether[8] (VII) are hydrolyzed rapidly by dilute aqueous acid.

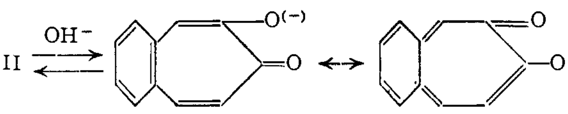


V, R = CH_3
VI, R = H



VII, R = CH_3
VIII, R = H

The resistance of the methyl ether I to acid hydrolysis is similar to that of an ordinary phenol ether, and it is found that the acid dissociation constant for II is similar to that for phenol, being 1×10^{-10}. Colchiceine (VI) is found to have K_a of 1.8×10^{-7}, and the value reported for tropolone[8a] is 2×10^{-7}, both tropolones thus being considerably stronger than benztropolone. The reason for this is apparent by considering the resonance stabilization of the anion IX derived from benzotropolone; one of these contributing forms (IXb) requires that the benzenoid ring should be in the high energy ortho-quinonoid form, and hence is not important in stabilizing the anion and increasing the acidity. The anions derived from



IXa IXb

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[1] Aided by a grant from the National Institutes of Health.

[2] Presented in part at the 118th meeting of the American Chemical Society, Chicago, Ill., September 7, 1950.

[3] D. S. Tarbell, G. P. Scott and A. D. Kemp, This Journal, **72**, 279 (1950).

[4] R. J. Anderson and M. S. Newman, *J. Biol. Chem.*, **103**, 405 (1933).

[5] *Cf.* J. Thiele and J. Schneider, *Ann.*, **369**, 287 (1908); J. Thiele and E. Weitz, *ibid.*, **377**, 1 (1910).

[6] R. P. Mariella and J. L. Leech, This Journal, **71**, 3558 (1949).

[7] The position of the substituents in ring C of colchicine is that proposed by W. E. Doering and L. H. Knox (ref. 8a), and is supported by X-ray analysis (M. V. King and R. Pepinsky, paper presented at the 119th Meeting of the American Chemical Society, Boston, Mass., April 4, 1951).

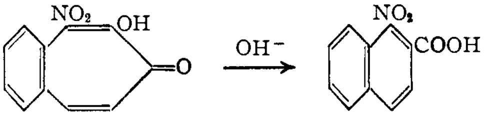
[8] (a) W. E. Doering and L. H. Knox, This Journal, **73**, 828 (1951); (b) J. W. Cook, A. R. Gibb, R. A. Raphael and A. R. Somerville, *J. Chem. Soc.*, 503 (1951); (c) R. D. Haworth and J. D. Hobson, *ibid.*, 561 (1951); (d) T. Nozoe, *Proc. Jap. Acad.*, **26**, 30 (1950), and accompanying papers.

[9] A. Windaus, *Ann.*, **439**, 59 (1924).

colchiceine and the monocyclic tropolones have two equivalent contributing forms, and hence the anion is stabilized relative to the parent compound.

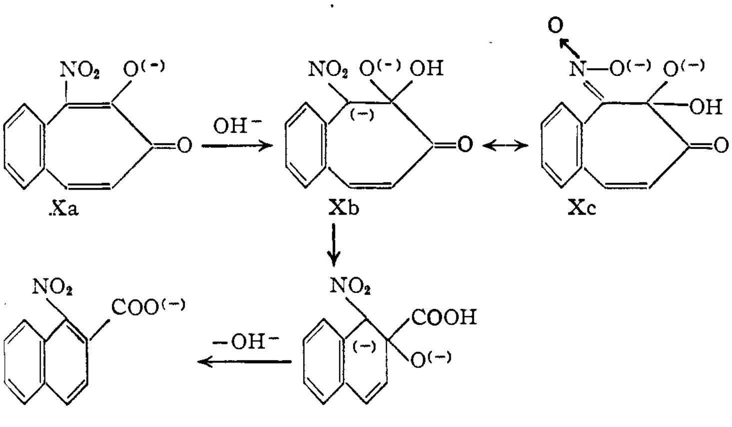
The tropolone ring in colchicine[10] and in tropolone methyl ether[8a] is very rapidly converted by sodium methoxide to an aromatic ring containing a carbomethoxyl group; benztropolone methyl ether, however, is completely unaffected by long refluxing with sodium methoxide. Benzotropolone itself does not yield any iodonaphthol upon treatment with sodium hypoiodite, although colchiceine[9] and tropolone[8a] are aromatized to iodophenols under these conditions.

The only reaction of a 4,5-benztropolone derivative leading to aromatization of the seven-membered ring, which we have so far discovered, involves the 3-nitrobenztropolone X (see below); this compound is isomerized by 10% aqueous alkali in two hours at room temperature to 1-nitro-2-naphthoic acid (XI). The structure of the isomerization product was demonstrated by comparison with an authentic sample of XI[11a]; both samples gave identical infrared and ultraviolet spectra, as well as no depression of the decomposition point on mixed melting point, and yielded the same amino compound, 1-amino-2-naphthoic acid,[11a] on reduction.[11b]



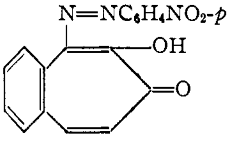
X XI

The mechanism of this interesting rearrangement is doubtless similar to that suggested for the conversion of tropolone to benzoic acid by treatment with alkali at 220°.[8a] The anion of X is rapidly attacked by hydroxide ion to form the doubly-charged ion Xb: this process is favored in this case, compared to tropolone itself, because of the stabilization of the negative charge by the nitro group through forms such as Xc.[12]

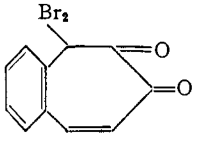


It is apparent from the foregoing that the 4,5-benztropolone nucleus represents a stable structure, and that it possesses many of the properties of a phenol. In agreement with this idea, the compound readily undergoes typical electrophilic substitution reactions.

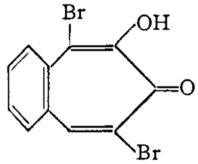
It couples readily with diazotized *p*-nitroaniline at a *p*H of 4.5 to yield the azo compound, which is presumably XI; in strongly alkaline solution, only red amorphous products result from the coupling reaction.



XI



XII



XIII

Benztropolone is readily brominated to form a dibromo compound; this compound has both bromines in the seven-membered ring because it is oxidized to phthalic acid by permanganate, and it does not have structure XI, because it gives a ferric chloride test. The most likely structure is XIII, although one of the bromines may be in the 7- rather than in the 6-position. Difficulty was encountered in obtaining a good bromine analysis on the dibromide, but good carbon and hydrogen values, as well as a good value for copper (on the copper derivative) were obtained.

4,5-Benztropolone was readily nitrated by nitric acid in glacial acetic acid; this compound is considered to be the 3-nitro compound X because the infrared spectrum shows a shift of the OH stretching frequency from that of the unsubstituted compound (3226 cm.$^{-1}$) to 3164 cm.$^{-1}$ which is due to hydrogen bonding of the hydroxyl group by the ortho-nitro group,[13] in addition to the hydrogen bonding present in the un-nitrated compound. The 3-position for the nitro group is supported by the formation of 1-nitro-2-naphthoic acid from the alkaline isomerization.

It appeared possible that 5-acetaminobenzsuberone-4 (XIV) might be a useful intermediate in the synthesis of tricyclic structures related to colchicine, and its preparation was attempted by lithium aluminum hydride reduction of the oxime III, since it has been shown[14] that enol ethers may yield ketones with this reagent. Numerous trials gave, after acetylation, a small amount of material which was probably the desired acetaminoketone XIV, since it yielded a dinitrophenylhydrazone giving a fair analysis; the reaction did not ap-

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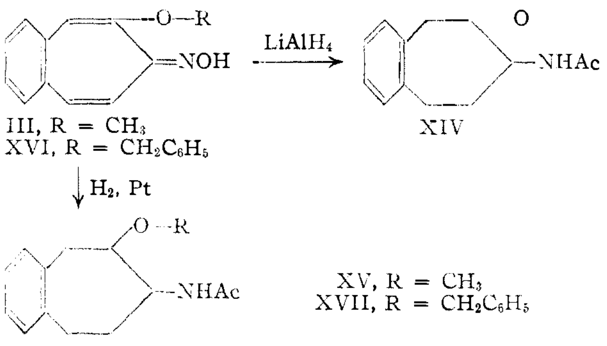
[10] F. Santavy, *Helv. Chim. Acta*, **31**, 821 (1948); H. Fernholz, *Ann.*, **568**, 63 (1950).

[11] (a) F. Mayer and T. Oppenheimer, *Ber.*, **51**, 1242 (1918); (b) 3,4-Benztropolone (J. W. Cook and A. R. Somerville, *Nature*, **163**, 410 (1949)) is converted to 1-naphthoic acid by fusion with alkali.

[12] After this work on the aromatization of nitrobenztropolone by alkali was completed, it came to our attention that Nozoe and coworkers had found that dinitro-3-isopropyltropolone was converted by recrystallization from aqueous solvents to dinitro-3-isopropylbenzoic acid; the mononitro derivative required heating with alkali at high temperatures for aromatization(T. Nozoe, *et al.*, *Proc. Jap. Acad.*, **26**, 14, 25, 38 (1950)).

[13] *Cf.* W. Gordy, *J. Chem. Phys.*, **7**, 167 (1939).

[14] P. Karrer and O. Rüttner, *Helv. Chim. Acta*, **33**, 812 (1950).



III, R = CH$_3$
XVI, R = CH$_2$C$_6$H$_5$

XIV

XV, R = CH$_3$
XVII, R = CH$_2$C$_6$H$_5$

pear practical, however. Catalytic reduction of II with platinum yielded, after acetylation, the saturated acetamino ether XV.

Benzylation of benztropolone (II) yielded the benzyl ether, analogous to I; this ether was split much more rapidly by hydrochloric acid to regenerate II than was the methyl ether I. Conversion of the benzyl ether to the oxime led to XVI, which, on treatment with hydrogen and platinum in acetic anhydride solution, was converted to the reduced acetamino ether XVII. Further studies in this series are in progress.

The infrared spectra of benztropolone II, its methyl ether I, the dibromobenztropolone XIII and the 3-nitro derivative X are given in the curves; the spectra were taken in Nujol paste, because all of the compounds were not soluble in suitable solvents. The spectrum of benztropolone determined under these conditions is somewhat different from that previously reported[3] in chloroform solution.

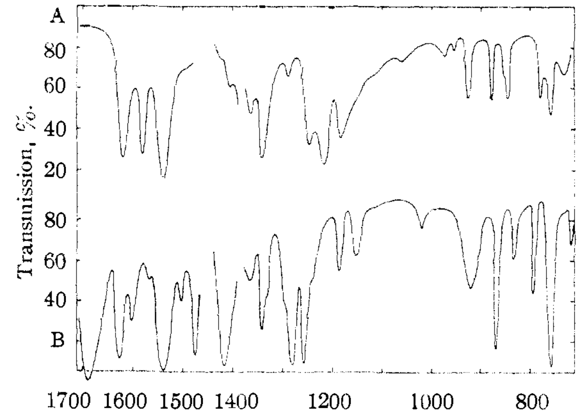


Fig. 1.—Absorption spectra: A, 3-nitro-4,5-benztropolone; B, 1-nitro-2-naphthoic acid.

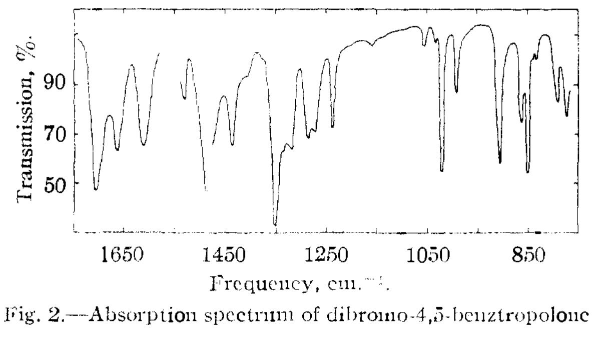


Fig. 2.—Absorption spectrum of dibromo-4,5-benztropolone.

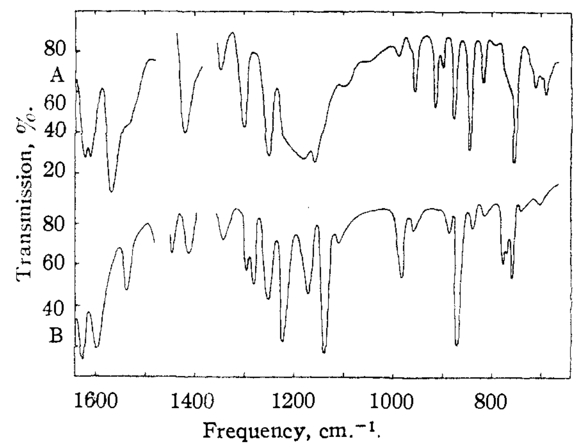


Fig. 3.—Absorption spectra: A, 4,5-benztropolone; B, 4,5-benztropolone methyl ether.

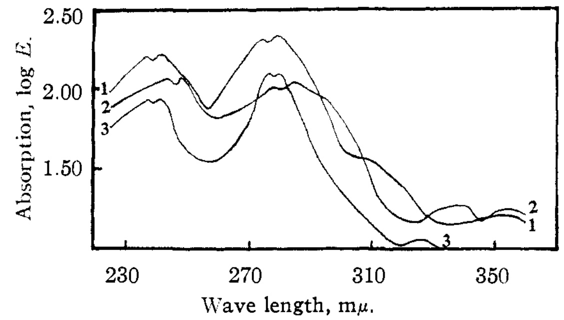


Fig. 4.—Absorption spectra: 1, 4-methyl-4,5-benztropolone; 2,3-nitro-4,5-benztropolone; 3,4,5-benztropolone.

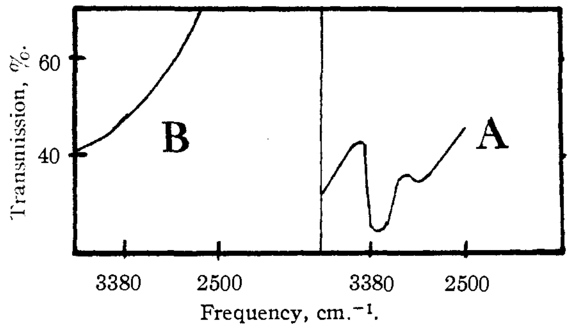


Fig. 5.—Absorption spectra: A, 4,5-benztropolone; B, 4,5-benztropolone methyl ether.

The three bands at approximately 1615, 1553 and 1260 cm.$^{-1}$ are believed[15,16] to be characteristic of the monocyclic tropolones and of colchicine derivatives. The benztropolone derivatives all show strong absorption in the 1615 and the 1260 cm.$^{-1}$ regions, but the 1553 bond does not seem to be a characteristic feature of the benztropolone system. It may be noted that the methyl and benzyl ethers do not show any appreciable shift of the "carbonyl" band at 1615 cm.$^{-1}$, compared to benztropolone itself.[17] This is similar to the behavior of colchicine and colchiceine.[15] The

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(15) G. P. Scott and D. S. Tarbell, THIS JOURNAL, **72**, 240 (1950).

(16) H. P. Koch, *J. Chem. Soc.*, 512 (1951); R. D. Haworth and J. D. Hobson, ref. 8c; A. Aulin-Erdtman and H. Theorell, *Acta Chem. Scand.*, **4**, 1490 (1950).

(17) It is reported [8c] that the isomeric methyl ethers of β-methyltropolone absorb at 1630 cm.$^{-1}$, while the parent compound absorbs at 1610 cm.$^{-1}$.

presence of some hydrogen bonding in benztropolone and its absence in the methyl ether are clearly shown by the curves for the OH region of the two compounds. The shift of the OH band in the nitro compound has been discussed above.

The ultraviolet spectra in alcohol for representative benztropolones are given. Benztropolone and its methyl ether show very similar curves, with double peaks at 238, 240 and 275, 278 mμ. The 3-nitro derivative shows a curve of similar type with a marked bathochromic shift. The curves differ from those of the monocyclic tropolones[8a,18] in that the latter show a broad partially resolved band in the 290–380 mμ region.

Experimental[19]

Phthalaldehyde was prepared in 41–43% yield from *o*-xylene by Thiele's method[20]; the procedure was modified by using superheated steam for the steam distillation and by extracting the product from the steam distillate with ethyl acetate in a continuous extraction for five days.

4,5-Benzotropolone Methyl Ether (I).—To a solution of 15 g. of phthalaldehyde and 10 g. of methoxyacetone[6] in 1.5 l. of water was added dropwise with stirring 40 cc. of a 2.5% aqueous sodium hydroxide solution. The stirring was continued for 24 hours, and the mixture was then acidified, saturated with sodium chloride and extracted with chloroform. After drying the solution and removing the solvent *in vacuo*, a red gum remained which, in some runs, crystallized on standing and scratching. If it did not crystallize, it was dissolved in benzene and chromatographed on alumina; the product was eluted with benzene–chloroform and recrystallized three times from butyl ether. This yielded 7–10 g. (34–50%) of a yellow solid, m.p. 86–88°, which was raised to 89–90° by repeated recrystallization from butyl ether.

The methyl ether I was also prepared by treating a solution of 300 mg. of 4,5-benztropolone in 20 cc. of 6 *N* potassium hydroxide with 3.37 g. of methyl sulfate. A vigorous reaction started after five minutes, and the solution was refluxed for one-half hour; the cooled mixture was then extracted with three portions of benzene, which were dried and evaporated to dryness. The residue consisted of 85 mg. of solid, which, after crystallization from butyl ether, yielded 70 mg. of benztropolone methyl ether, m.p. 89.5–90°, shown to be identical by mixed m.p. with the material prepared by condensation as above. From the original basic solution, 150 mg. of unchanged benztropolone was recovered by acidification and chloroform extraction.

Anal. (of the methyl ether, I). Calcd. for $C_{12}H_{10}O_2$: C, 77.40; H, 5.41. Found: C, 77.10; H, 5.35.

The dinitrophenylhydrazone (IV) was prepared in the usual way, and after recrystallization from ethyl acetate, chloroform and benzene, melted with decomposition at 268–269°.

Anal. Calcd. for $C_{18}H_{14}N_4O_5$: C, 59.01; H, 3.85; N, 15.30. Found: C, 59.12; H, 4.10; N, 15.20.

The oxime (III) was prepared from the crystalline methyl ether or, more conveniently, by the following procedure. The red gum, described above, of non-crystalline benztropolone methyl ether (2 g.) was dissolved in a mixture of 7 cc. of dry pyridine and 7 cc. of absolute ethanol, and treated with an equal weight of hydroxylamine hydrochloride. The solution was then refluxed for two hours, and the solvents were removed in an air stream. The oily solid remaining was recrystallized twice from ethanol, and 1.8 g. (85%, assuming the benztropolone methyl ether was pure) of yellow crystals, m.p. 199–200°, was obtained.

Anal. Calcd. for $C_{12}H_{11}O_2N$: C, 71.62; H, 5.51. Found: C, 71.58; H, 5.50.

The acetate of the oxime was prepared by dissolving 1 g. of the oxime in 250 cc. of ether. Acetic anhydride (0.6 g.) was then added and the solution was refluxed for 18 hours, was then extracted with alkali, and the ether removed, leaving 1.2 g. of a yellow solid. This was recrystallized from alcohol, giving 1 g. (85%) of a yellow crystalline solid, m.p. 129.5–131°. The material was recrystallized three more times from alcohol and dried for 24 hours in a drying pistol to ensure the removal of any traces of alcohol, m.p. 131–132°.

Anal. Calcd. for $C_{14}H_{13}O_3N$: C, 69.12; H, 5.39. Found: C, 69.35; H, 5.58.

The hydrobromide of benztropolone methyl ether was obtained as a yellow solid by dissolving the methyl ether in constant-boiling hydrobromic acid and allowing to stand; it was recrystallized by cooling an ether–alcohol solution to −25°. It was somewhat soluble in water, gave no ferric chloride test, and regenerated the parent compound when treated with base.

Anal. Calcd. for $C_{12}H_{11}O_2Br$: neut. equiv., 267.1. Found: neut. equiv., 269.

4,5-Benztropolone (II).—Benztropolone methyl ether (I, 1.2 g.) was refluxed for six hours with 100 cc. of 40% hydrobromic acid. The mixture was then cooled, diluted with 300 cc. of water, and extracted with chloroform. The extract was washed with 5% potassium hydroxide, and the resulting bright yellow alkaline solution was acidified; the acid solution was extracted with chloroform, the extract dried, the solvent removed, and the solid residue was recrystallized from ethanol. The product (1.07 g., 97%) melted at 158–160°, and gave no depression on mixture with a sample of benztropolone prepared from phthalaldehyde and hydroxyacetone.[3] The benztropolone methyl ether was unaffected by refluxing five hours with 5% hydrochloric acid, and only a few per cent. of hydrolysis was obtained after 20 hours. The use of 48% hydrobromic acid gave poorer yields than 40% acid.

Acid Dissociation Constants.—These were determined by titration of benztropolone and colchiceine with standard alkali using a Beckman *p*H meter. The *p*H at half neutralization was taken as pK_a; the low solubility of colchiceine in water required the use of a small amount of acetone in the aqueous solution or of a relatively large volume of water. The known pK_a values for phenol and for acetic acid were checked under the conditions used for benztropolone and colchiceine, respectively.

The Action of Reagents on Benztropolones. A. Potassium Hypoiodite and Benztropolone (II).—Benztropolone (300 mg.) was dissolved as well as possible in 100 cc. of ice-cold 1% sodium hydroxide, and to this a solution of iodine (2%) and potassium iodide (10%) was added dropwise from a buret until about 35 cc. had been added; the excess of iodine, which was shown to be present by a starch–iodide paper test on an acidified portion, was destroyed with sodium bisulfite and the solution made acid with dilute hydrochloric acid. The solution was extracted with chloroform, the solvent dried and removed, and from the oily residue was isolated 175 mg. of starting material. No other crystalline product could be obtained.

B. Sodium Methoxide and Benztropolone Methyl Ether.—The ether I (300 mg.) in 12 cc. of refluxing methanol was treated with a solution of 500 mg. of sodium in 30 cc. of methanol. The mixture was refluxed for two days, acidified, and the methanol removed. Water (25 cc.) was added, the mixture was extracted with chloroform, the extract was washed with bicarbonate and the latter acidified. No precipitate appeared. The chloroform solution was evaporated to dryness and the residue (300 mg.) recrystallized from butyl ether; the product (290 mg.) was shown to be the starting material by a mixed m.p.

3-Nitro-4,5-benztropolone (X).—Benztropolone (300 mg.) in 50 cc. of glacial acetic acid was treated with 2.5 cc. of concentrated nitric acid. After standing for 15 minutes, the mixture was poured into 200 cc. of water. The brownish-yellow solid (200 mg., 52%), which separated after standing overnight, melted, after three recrystallizations from dilute alcohol, at 210–212°. The compound, which is yellow, is soluble in aqueous sodium bicarbonate, and gives a faint green color with ferric chloride, which changes to a brown precipitate.

Anal. Calcd. for $C_{11}H_7NO_4$: C, 60.83; H, 3.25; N, 6.45. Found: C, 60.78; H, 3.63; N, 6.48.

Alkaline Isomerization of Nitrobenztropolone to 1-Nitro-2-naphthoic Acid.—3-Nitro-4,5-benztropolone (100

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[18] A. Aulin-Erdtman, *Acta Chem. Scand.*, **4**, 103 (1950).

[19] Analyses by Micro-Tech Laboratories and Miss Claire King. All melting points are corrected.

[20] J. Thiele and O. Günther, *Ann.*, **347**, 106 (1906).

mg.) was dissolved in 10% sodium hydroxide (7 cc.) and allowed to stand at 21° for two hours. It was then cooled in ice and acidified with dilute hydrochloric acid. The solid (90 mg.) which separated was centrifuged and washed three times with water. It was then recrystallized twice from alcohol–water, m.p. 243–247° with decomposition. The compound was shown to be 1-nitro-2-naphthoic acid by mixed m.p., and by the identity of the infrared and ultraviolet spectra, with those of an authentic sample prepared by oxidation of 1-nitro-2-naphthylpyruvic acid.[11] Both samples were reduced by ferrous sulfate to 1-amino-2-naphthoic acid,[11] m.p. and mixed m.p. 205–206° with decomposition.

3-(*p*-Nitrophenylazo)-4,5-benztropolone (XI).—*p*-Nitroaniline (450 mg.) in 27 cc. of 4.4 *N* hydrochloric acid was diazotized, in an ice–salt-bath, by the addition of a cooled solution of sodium nitrite (300 mg.) in 20 cc. of water. Benztropolone (500 mg.) was dissolved as well as possible in a mixture consisting of 75 cc. of acetic acid, 109.5 g. of hydrated sodium acetate, and 100 cc. of water. This was cooled in an ice–salt-bath, and the solution of the diazotized amine added to it. The solution, which turned red at once, was allowed to stand three hours at room temperature and filtered. The red product was washed by suspending in 200 cc. of water and filtering again. The dried product (800 mg., m.p. 203–210°) was recrystallized from acetone until a constant decomposition point (229–232°) was reached.

Anal. Calcd. for $C_{17}H_{11}N_3O_4$: C, 63.55; H, 3.45; N, 13.08. Found: C, 63.37; H, 3.75; N, 13.28.

3,6(?)-Dibromo-4,5-benztropolone (XIII).—To a solution of 200 mg. of benztropolone in 50 cc. of glacial acetic acid, 2 cc. of bromine was added dropwise with stirring, and the stirring was continued for 30 hours. The red solution was poured into 250 cc. of water, and the excess bromine was destroyed with sodium bisulfite. The product was collected by filtration, and 350 mg. (91%) of yellow product was obtained, which, after three recrystallizations from ethanol, melted at 145–146°.

Anal. Calcd. for $C_{11}H_6O_2Br_2$: C, 40.03; H, 1.83; Br, 48.83. Found: C, 40.42; H, 1.93; Br, 45.10.

Oxidation of the dibromo compound with permanganate in acetone yielded some phthalic acid, which was identified by sublimation to form phthalic anhydride, m.p. and mixed m.p. 130–131.5°. A carbon–hydrogen analysis confirmed the fact that the material was phthalic anhydride and not bromophthalic anhydride.

The copper derivative was prepared by adding a hot saturated alcoholic solution of copper acetate to an alcoholic solution of dibromobenztropolone. The solution cooled and the green solid which was collected appeared to be mainly copper acetate. The mother liquor on concentration yielded a yellow solid, which was recrystallized five times from chloroform, and was a yellowish-green solid which did not melt below 275°.

Anal. Calcd. for $C_{22}H_{10}Br_4O_4Cu$: C, 36.62; H, 1.40; Cu, 8.96. Found: C, 36.78; H, 1.85; Cu, 8.96.

The dibromobenztropolone acetate was prepared by treating a solution of 200 mg. of dibromobenztropolone in 7 cc. of pyridine with 2.5 cc. of acetic anhydride; the mixture was allowed to stand overnight at room temperature, and was then heated for an hour on the steam-bath, was poured into 75 cc. of 6 *N* hydrochloric acid and extracted with ether. The product obtained from the ether solution was dissolved in alcohol and decolorized with charcoal. A white solid (200 mg., 89%) was obtained, which melted at 144.5–145.5°, and when mixed with dibromobenztropolone, showed a depression to 115–125°.

Anal. Calcd. for $C_{13}H_8Br_2O_3$: C, 41.97; H, 2.17; Br, 42.97. Found: C, 42.15; H, 2.32; Br, 40.35; ash, 0.97.

The acetate of the dibromide was hydrolyzed by refluxing with 6 *N* hydrochloric acid, and the product appeared from its m.p. to be the dibromobenztropolone XIII, but it did not give a proper carbon–hydrogen value for XIII.

4-Methoxy-5-acetamido-1,2-benzocycloheptene (XV).—The oxime III (697 mg.) in 75 cc. of pure methanol was hydrogenated at room temperature and pressure with platinum oxide catalyst. The hydrogen uptake was 350 cc. (calcd. 468 cc.). The catalyst was removed by filtration and the solvent removed *in vacuo*. The greenish basic oil which remained was heated on the steam-bath for one hour with 10 cc. of acetic anhydride. The mixture was poured into water, acidified and extracted with ether. The ether solution was washed with bicarbonate, dried, and from it was obtained a crude solid; this was recrystallized from 10% ethanol with charcoal decolorization, and 300 mg. (62%) of white solid was obtained, which melted at 184–186° after three more recrystallizations. It could also be purified by sublimation, and it gave a positive test for nitrogen.

Anal. Calcd. for $C_{14}H_{16}NO_2$: C, 73.02; H, 7.00. Calcd. for $C_{14}H_{18}NO_2$: C, 72.38; H, 7.81. Found: C, 72.14; H, 7.83.

Lithium Aluminum Hydride Reduction of Benztropolone Methyl Ether Oxime.—The oxime III (1 g.) in 300 cc. of dry ether was refluxed for 20 hours with 75 cc. of 1.4 molar lithium aluminum hydride solution, and the excess reagent was destroyed by pouring into ice and hydrochloric acid. About 20 mg. of starting material was recovered by filtration. The ether layer was worked up and found to contain very little material. The aqueous acid solution was then added slowly to a strongly basic tartrate solution, and the solution extracted five times with 100-cc. portions of chloroform. The brown oil (850 mg.) obtained from this solution was allowed to stand overnight with a mixture of 10 cc. of pyridine and 5 cc. of acetic anhydride, and was then heated on the steam-bath for an hour. The solution was poured into water, 15 cc. of concentrated hydrochloric acid was added, and the mixture was extracted with chloroform. From the chloroform solution was obtained 850 mg. of viscous oil, which gave a negative ferric chloride test, and formed a **dinitrophenylhydrazone**. This was chromatographed, and after recrystallization from ethanol and from ethyl acetate, melted at 253–254° (uncor.).

Anal. Calcd. for $C_{18}H_{18}N_5O_5$ (DNP of XIV): C, 57.57; H, 4.58; N, 17.67. Found: C, 57.78; H, 5.10; N, 17.41.

Benztropolone Benzyl Ether (I, $CH_2C_6H_5$ instead of CH_3).—4,5-Benztropolone (300 mg.) was dissolved in 50 cc. of methyl ethyl ketone, and 3 cc. of 10% potassium hydroxide was added. Benzyl chloride (2 cc.) was added, the solution was refluxed for five hours and was diluted with 300 cc. of water. The basic solution was then extracted with three 50-cc. portions of ether. The ether was dried with potassium carbonate and the solvent removed in vacuum. It was essential to remove all of the solvent. The oily residue, after crystallization from alcohol–water, yielded 210 mg. (46%), and, after three more crystallizations from alcohol, melted at 90–91°.

Anal. Calcd. for $C_{18}H_{24}O_2$: C, 82.44; H, 5.38. Found: C, 82.52; H, 5.41.

The ether (10 mg.) was heated for five minutes on the steam-bath with 2 cc. of concentrated hydrochloric acid; the reaction mixture, which gave a ferric chloride test, was diluted with water. The precipitated solid (6 mg.) was shown to be 4,5-benztropolone by m.p. (159–161°) and by mixed m.p.

The oxime XVI was prepared by refluxing 140 mg. of the crude benzyl ether in a mixture of 1 cc. each of pyridine and alcohol with 100 mg. of hydroxylamine hydrochloride, for two hours. The solvents were removed in an air stream and the remaining material (150 mg., 35%) was recrystallized three times from alcohol, giving yellow needles, m.p. 200–202° (sintering from 194°).

Anal. Calcd. for $C_{18}H_{15}NO_2$: C, 77.96; H, 5.42. Found: C, 77.85; H, 5.52.

4-Benzyloxy-5-acetamido-1,2-benzocycloheptene (XVII).—The oxime XVI (264 mg.) was reduced with hydrogen and platinum in acetic anhydride solution at room temperature and pressure. The uptake of hydrogen stopped after the consumption of 3.6 moles. The catalyst was removed, 300 cc. of water was added to the mixture, and, after standing, 104 mg. of solid was deposited. An additional 50 g. was removed from the solution by ether extraction. The product, after three crystallizations from alcohol, had a constant m.p. of 196–197°.

Anal. Calcd. for $C_{29}H_{22}NO_2$: C, 77.89; H, 7.19. Found: C, 77.58; H, 7.51.

Infrared Spectra.—We are indebted to Mr. Carl Whiteman for the tracings, which were obtained with a Perkin-Elmer Spectrometer, Model 12-A, and to Dr. G. A. Nicholls and Mr. M. Petropoulos for assistance with the curves.

ROCHESTER, N. Y. RECEIVED MAY 29, 1951