[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

The Amaroids of Quassia. I. Quassin, Isoquassin and Neoquassin

BY ROGER ADAMS* AND WILSON M. WHALEY

The bitter principles, or amaroids, of quassia wood (*Quassia amara*) and Jamaica quassia wood (*Aeschrion excelsa*) have been subjected to numerous investigations since their isolation in 1835 by Winckler,[1] but they defied even accurate description prior to the recent work of E. P. Clark.[2,3,4,5] The early work yielded no information of value and is adequately discussed in Clark's first paper. Clark reported two amaroids, quassin and neoquassin, from the wood of *Quassia amara*,[2,3] and a third amaroid, picrasmin, from the wood of *Aeschrion excelsa* (formerly known as (*Picrasma excelsa*).[4,5] His analyses showed the three amaroids to be isomers having the molecular formula $C_{22}H_{30}O_6$; furthermore, all three yielded a fourth isomer, isoquassin, if treated with chromic acid. The four isomers were characterized by analyses, melting points, specific rotations and indices of refraction. All of them possessed two methoxyl groups and neoquassin was presumed to have a tertiary hydroxyl group. The various other reactions performed upon his isomers by Clark gave no clue to their structure.

Experiments, description of which follows, have served to clarify the relationship of quassin, neoquassin and isoquassin (identical with picrasmin) to each other. Neoquassin is an alcohol ($C_{22}H_{30}O_6$) and isoquassin the corresponding ketone ($C_{22}H_{28}O_6$), not isomeric as reported by Clark. Quassin is merely a molecular complex consisting of isoquassin and neoquassin.

The *Aeschrion excelsa* extracted in this Laboratory yielded a crude quassin[6] of melting point 197–206° rather than the nearly pure picrasmin (m. p. 218°) reported by Clark.[4] Microscopic examination of crystals obtained by evaporation of a solution of the crude material in 50% acetone revealed the presence of three distinct entities. By visual comparison with samples of Clark's amaroids,[7] the crystalline components of the crude mixture were identified as quassin, neoquassin and picrasmin.

Attempted separation of the three amaroids by fractional crystallization was only partially successful, but they were separated by adsorption upon alumina, their positions upon the adsorption column being determined by observation under ultraviolet light. Isolation and purification of the chromatographic fractions actually yielded only two amaroids in pure condition as indicated in Table I. Picrasmin (isoquassin) and neoquassin were identified by comparison with Clark's samples according to crystalline shapes, melting points of mixtures and infrared spectra. A compound corresponding exactly to Clark's quassin was not isolated.

TABLE I

CHROMATOGRAPHIC SEPARATION OF THE AMAROIDS

Fraction[a]	Weight, mg.	M. p., °C.	Appearance (from 50% acetone)	Final m. p., °C.
1	82	195–205	Amorphous	.....
2	299	218–227	Neoquassin	229–231[b]
3	235	195–217	Mixed crystals	205–220[c]
4	187	217–221	Isoquassin	222–225[d]
5	71	211–218	Mixed crystals	211–216[d]
6	4	211–217	Mixed crystals	.....
7	3	200–213	Isoquassin	.....
8	4	*ca.* 180	Amorphous	.....

[a] Fractions 1–5 were obtained by cutting the column, no. 1 being the top segment; fractions 6–8 were obtained as percolate. [b] Recrystallized three times from dilute methanol. [c] Recrystallized twice from dilute methanol. [d] Recrystallized once from dilute methanol.

Conversion of the mixed amaroids into isoquassin by treatment with sodium dichromate in acetic acid proceeded in excellent yield, affording a product identical in every respect with a sample of Clark's isoquassin. However, it was also identical with picrasmin obtained from the mixed amaroids by chromatography, and with Clark's picrasmin. The two compounds had the same melting point (unchanged after admixture), crystalline shape, specific rotation, infrared spectrum (Fig. 1) and X-ray diffraction pattern (Fig. 3). It is clear that isoquassin is not a synthetic isomer but is the naturally-occurring picrasmin to which the other amaroids are converted by chromic acid treatment.

A sample of quassin with a sharp melting point has not been achieved and the melting point tends to rise upon repeated recrystallization. Purification is not easy, the crystals becoming yellow if allowed to remain long in their mother liquor. The specific rotation of quassin was reported[3] as +40°, or almost midway between the values for isoquassin (+33°) and neoquassin (+46.6°). It has been noticed, also, that quassin melts at the same temperature (205–208°) as a mixture of neoquassin and isoquassin, and its melting point is not depressed by admixture with neoquassin or isoquassin. These observations led to a suspicion that the elusive quassin might be merely a mixture of the other two amaroids.

* Harvard University Ph.D. 1912.

(1) Winckler, *Repert. pharm.*, [2] **4**, 85 (1835).

(2) Clark, THIS JOURNAL, **59**, 927 (1937).

(3) Clark, *ibid.*, **59**, 2511 (1937).

(4) Clark, *ibid.*, **60**, 1146 (1938).

(5) Clark, *ibid.*, **64**, 2883 (1942).

(6) Dr. Bywater of S. B. Penick and Company kindly supplied us with the amaroids adsorbed upon charcoal by a method devised by Clark.[2]

(7) Dr. R. C. Roark of the Bureau of Entomology and Plant Quarantine, United States Department of Agriculture, generously donated small samples of the late Dr. E. P. Clark's amaroids.

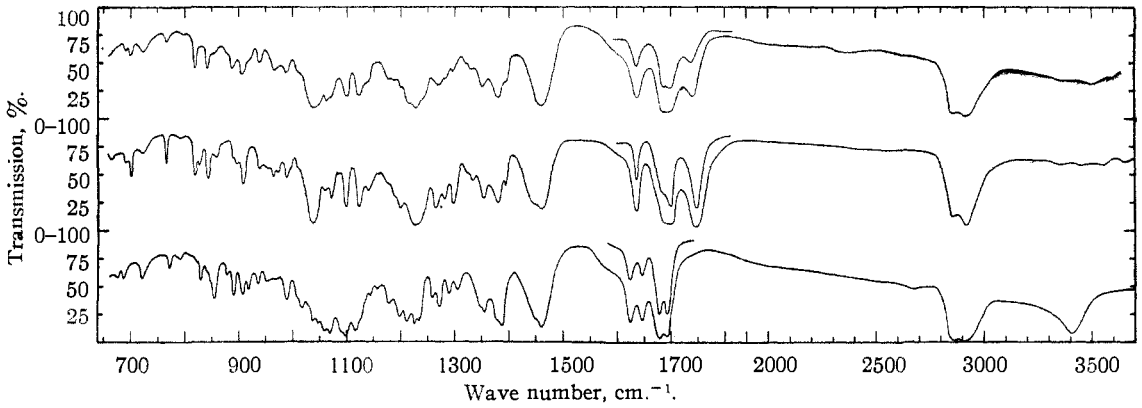


Fig. 1.—Infrared absorption in Nujol mulls; upper curve, quassin; middle curve, isoquassin; lower curve, neoquassin.

A pulverized mixture of isoquassin and neoquassin in equal parts does not have an infrared spectrum like that of quassin, as indicated in Fig. 2 by enlarged portions of the spectra. The X-ray diffraction pattern of the physical mixture (Fig. 3) is also different from that of quassin.

Co-crystallization of isoquassin and neoquassin (1:1) from dilute methanol yielded a substance having the crystalline shape, infrared spectrum (Fig. 2) and X-ray diffraction pattern (Fig. 3) possessed by quassin obtained from natural sources. The X-ray diffraction pattern of quassin is identical with that of isoquassin, indicating that neoquassin crystallizes upon the crystal lattice of isoquassin during their co-crystallization. It may be concluded that although quassin is a separate entity, it is a molecular complex consisting of isoquassin and neoquassin in approximately equal parts.

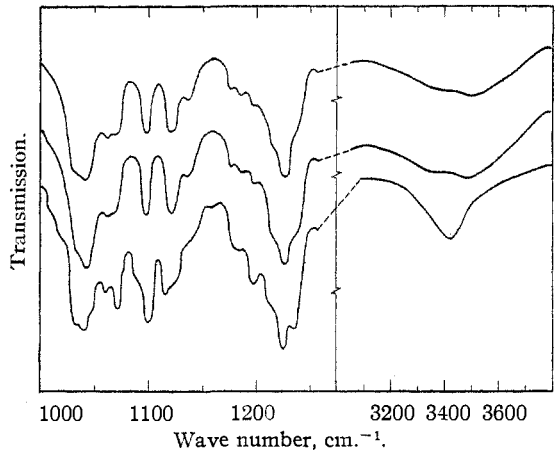


Fig. 2.—Infrared absorption in Nujol mulls; upper curve, isoquassin + neoquassin (1:1), co-crystallized; middle curve, Clark's quassin; lower curve, isoquassin + neoquassin (1:1), mechanical mixture.

It remains that the two primary amaroids of quassia are isoquassin and neoquassin. They were believed by Clark[3] to be isomers, but the "isomerization" by action of chromic acid upon neoquassin is accompanied by reduction of the chromic acid. The transformation cannot be effected by acetic acid, mineral acids or iodine. It can be effected by the Oppenauer reaction using aluminum isopropoxide, cyclohexanone and toluene. Neoquassin must therefore be oxidized in the formation of isoquassin, and infrared spectra of the two compounds suggest the nature of the oxidation. In Table II are listed spectral bands which can be interpreted in terms of molecular structure with the aid of other chemical knowledge. Neoquassin has a hydroxyl group not possessed by isoquassin, whereas isoquassin has a carbonyl group not possessed by neoquassin. As would be expected, quassin exhibits partial absorption at both frequencies.

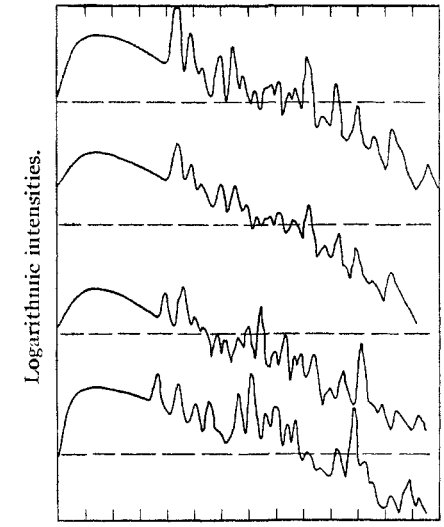


Fig. 3.—X-Ray diffraction patterns, coördinates are plotted in arbitrary units: top curve, quassin or isoquassin; second curve, isoquassin + neoquassin (1:1), co-crystallized; third curve, isoquassin + neoquassin (1:1), mechanical mixture; bottom curve, neoquassin.

Isoquassin and neoquassin possess nearly identical ultraviolet spectra ($\lambda_{max.}$ 254–257 mμ, log

TABLE II

FUNCTIONAL GROUPS INDICATED BY INFRARED SPECTRA

Frequency, cm.$^{-1}$	Probable functional group	Quassin	Neo-quassin	Iso-quassin
ca. 3400	Bonded hydroxyl	*Partial*	Strong	*Absent*
1745	Carbonyl (cyclopentanone or ester)	*Partial*	*Absent*	Strong
1700	Carbonyl (conj. ketone or ester)	Strong	Strong	Strong
1685	Carbonyl (conj. ketone)	Strong	Strong	Partial
ca. 1640	Double bond (unconj.)	Strong	Strong	Strong
1225	$-\overset{\|\|}{C}-O-$	Strong	Strong	Strong
1040	$-\overset{\|}{C}-O-$	Strong	Partial	Strong

ϵ 4.05–4.09), suggesting that there is no shift of double bonds in the formation of isoquassin and that the newly formed carbonyl group is not part of the conjugated system. The two amaroids may then have the same fundamental structure, neoquassin being an alcohol and isoquassin the corresponding ketone.

Functional groups present in isoquassin (*cf.* Table II) probably are: a cyclopentanone, a conjugated lactone, a conjugated ketone, and two methoxyl groups. Negative Zimmermann[8] and Legal[9] tests indicate with fair certainty that there are no methylene groups *alpha* to the carbonyl groups, and that the conjugated lactone is so substituted it cannot isomerize to a β,γ-unsaturated lactone.

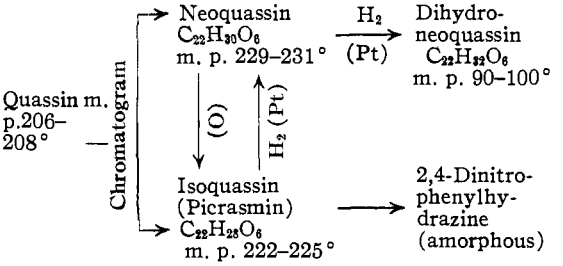
Hydrogenation of isoquassin using platinum oxide catalyst at 25° and three atmospheres pressure for eighty hours yielded a brittle, white solid, m. p. 90–100°, having the composition of a tetrahydro derivative. Its infrared spectrum indicated reduction of the cyclopentanone carbonyl to a hydroxyl group. After the first twenty-four hours of hydrogenation the product had an infrared spectrum very similar to that of quassin, and it is probable that the reduction proceeded in the order of isoquassin to neoquassin to dihydroneoquassin. However, the ultraviolet spectrum of the final product was virtually the same as that of the starting material ($\lambda_{max.}$ 254 mμ, log ϵ 3.92).

Attempts to reduce isoquassin to neoquassin by means of aluminum isopropoxide were unsuccessful. No reaction occurred in boiling isopropyl alcohol. In boiling toluene a fundamental change took place, resulting in an oily mixture of inconstant boiling point. Though neoquassin was not obtained an infrared spectrum of the oil indicated that the keto group at 1745 cm.$^{-1}$ had been reduced to a hydroxyl group.

Although isoquassin has two keto groups (one conjugated) a carbonyl derivative may be prepared only with great difficulty. Neither an oxime nor a semicarbazone could be prepared by various standard techniques tried. A 2,4-dinitrophenylhydrazone could be isolated as an amorphous powder, but samples of satisfactory melting point or analysis were not obtained. Chromatography of isoquassin 2,4-dinitrophenylhydrazone on alumina yielded several distinct zones of material, none of which could be crystallized. Thus, the derivative could not be obtained as a pure entity, but its nature was confirmed by a sharply defined infrared spectrum.

Isoquassin was recovered unchanged from a suspension in cold, aqueous sodium hydroxide after two days, but was converted to a yellow gum by hot alkali. Isoquassin slowly dissolved in cold, 28% ammonia; it was recovered in pure condition by evaporation of the solution.

The relationships discussed in this paper are shown below. They represent a considerable simplification of those suggested by Clark.



From the standpoint of structure elucidation the amaroids of quassia may be looked upon as simple derivatives of a single, easily obtained substance, isoquassin. The problem of its structure will be the subject of further investigation.

Experimental[10]

Crude Quassin.—The crude mixture of amaroids used in this work was obtained by continuous extraction from charcoal[6] with chloroform, followed by purification according to Clark.[2] Commercial "quassin" obtained from S. B. Penick and Company was also found to contain an appreciable amount of amaroids. Quassin has been obtained therefrom by preliminary extraction with petroleum ether (b. p. 40–60°) followed by extraction of a chloroformic solution with aqueous potassium hydroxide, evaporation of the chloroform and recrystallization of the gummy residue from dilute methanol after decolorization by charcoal. One sample of Penick "quassin" treated in that fashion yielded a product consisting almost entirely of neoquassin. Usually the crude quassin melted at 197–206°.

Chromatography of Crude Quassin.—A chromatographic column was packed with 40 g. of alumina (Eimer and Amend), washed with 100 ml. of pure chloroform, then treated with a solution of one gram of mixed amaroids in 10 ml. of chloroform. Development was carried out with 400 ml. of pure chloroform. The data presented in Table I illustrate that fairly good separation was effected, that neoquassin and isoquassin were isolated in a pure state, and that quassin was observed in the mixtures, particularly in fraction 5. Pure isoquassin was found to have a specific rotation of $[\alpha]^{27}D$ + 32.3°; Clark[4] reported $[\alpha]^{20}D$ +45.4° for his picrasmin.

(8) Zimmermann, *Z. physiol. Chem.*, **233**, 257 (1935).

(9) Jacobs, Hoffmann and Gustus, *J. Biol. Chem.*, **70**, 1 (1926).

(10) A calibrated apparatus was used to determine melting points

Anal. (neoquassin) Calcd. for $C_{22}H_{30}O_6$ (390.46): C, 67.67; H, 7.75. Found: C, 67.63; H, 7.98.

Anal. (isoquassin) Calcd. for $C_{22}H_{28}O_6$ (388.44): C, 68.00; H, 7.27. Found: C, 67.60; H, 7.52.

Rotation. 0.1144 g. of isoquassin made up to 10 ml. with chloroform gave α_D + 0.37°; *l*, 1; $[\alpha]^{27}D$ + 32.3°.

Preparation of Isoquassin.—A solution of 2 g. of crude quassin in 10 ml. of hot, glacial acetic acid was treated with 8 ml. of a 10% solution of sodium dichromate in acetic acid and allowed to stand two days at room temperature. After adding two volumes of water the green solution was evaporated *in vacuo* nearly to dryness, water was added again, and the mixture was heated to boiling. The cooled mixture yielded 1.582 g. (79%) of nearly white needles which melted at 220–223° after recrystallization from dilute methanol.

This preparation is an adaptation[11] of Clark's procedure,[2] which afforded 40–50% yields. The mixed amaroids could not be converted to isoquassin by acetic acid, lead tetraacetate in acetic acid, sulfuric acid in acetic acid, nitric acid in acetic acid, iodine in acetic acid, sirupy phosphoric acid, Tollens reagent, or calcium hydroxide solution.

Oppenauer Oxidation.—A solution of 100 mg. of quassin (m. p. 192–200°) in 25 ml. of dry toluene and 1.5 ml. of pure cyclohexanone was refluxed briefly and a few ml. distilled to ensure dryness. After addition of 150 mg. of redistilled aluminum isopropoxide the clear solution was refluxed for two hours. The solution was evaporated to dryness *in vacuo*; chloroform and 10% hydrochloric acid were added to dissolve the residue and then were separated. The chloroformic extract was washed with water, dried over magnesium sulfate and evaporated. A fragrant yellow oil was obtained. Addition of ether and petroleum ether caused the precipitation of a white solid which was recrystallized from dilute methanol. The white crystals weighed 51 mg. and melted at 218–220°; they had an infrared spectrum identical with that of isoquassin. A mixture with pure isoquassin melted at 218–221°.

Anal. Calcd. for $C_{22}H_{28}O_6$ (388.44): C, 68.00; H, 7.27; OCH_3 (2), 15.98. Found: C, 67.84, 67.72, 67.81; H, 7.52, 7.46, 7.36; OCH_3, 15.94.

Rotation. 0.5210 g. of isoquassin made up to 10 ml. with chloroform gave α_D + 1.72°; *l*, 1; $[\alpha]^{25}D$ + 33.0°. Clark[2] reported $[\alpha]^{20}D$ + 35.1°.

Dihydroneoquassin.—A solution of 200 mg. of isoquassin in 30 ml. of absolute ethanol was treated with 20 mg. of platinum oxide and hydrogenated at three atmospheres pressure and room temperature for twenty-four hours. Removal of catalyst and solvent afforded an ether-soluble oil which was stripped *in vacuo* to yield 178 mg. of a brittle, white solid. Its infrared spectrum resembled that of quassin. Further reduction for thirty hours resulted in change in spectrum of the product. Subsequent reduction up to eighty hours led to no further modification. There was obtained 155 mg. of brittle, white solid, m. p. 90–100°.

Anal. Calcd. for $C_{22}H_{32}O_6$ (392.48); C, 67.32; H, 8.22. Found: C, 66.90, 67.19; H, 8.05, 8.04.

The product was partially decomposed by distillation at 0.03–0.04 mm. (bath 200–240°).

Meerwein-Ponndorf-Verley Reduction.—Isoquassin was recovered unchanged after being refluxed for four hours with aluminum isopropoxide and isopropyl alcohol.

A solution of 200 mg. of isoquassin and 1 g. of redistilled aluminum isopropoxide in 25 ml. of dry toluene was refluxed for nineteen hours. Most of the toluene was removed by distillation; the first few ml. of distillate contained acetone, as indicated by reaction with 2,4-dinitrophenylhydrazine. Chloroform and 10% hydrochloric acid were added to dissolve the residue. The organic layer was washed with water, dried over magnesium sulfate and evaporated. A light yellow oil was obtained; it was distilled and two small fractions were collected. The first was a fragrant, white oil boiling below 150° at 0.1 mm.

Anal. Found: C, 75.97; H, 7.60.

The second fraction was an odorless yellow gum boiling at a bath temperature of 150–200° at 0.05 mm. Its infrared spectrum was not sharp but it showed a hydroxyl band and the keto band of isoquassin at 1745 cm.$^{-1}$ was gone.

Anal. Found: C, 69.43; H, 8.53.

A similar reduction carried out for only forty-five minutes yielded some of the same oily product and some unchanged isoquassin.

Isoquassin 2,4-Dinitrophenylhydrazone.[11]—A solution of 55 mg. of 2,4-dinitrophenylhydrazine in 20 ml. of methanol and one drop of concentrated hydrochloric acid was heated and then 100 mg. of isoquassin was dissolved in it. Heating under reflux was continued for two and a half hours. After standing four days the solution was diluted with water and the fluffy, orange precipitate collected. After drying, the product weighed 80 mg. and melted at 125–135°. It could not be crystallized, but could be precipitated from solution in isopropyl alcohol by addition of dilute sodium sulfate solution. However, this procedure yielded a product containing ash even after careful washing with water. Samples melting at 142–144° gave the following analytical values.

Anal. Calcd. for $C_{28}H_{32}O_9N$ (568.57): C, 59.14; H, 5.67; N, 9.85. Found: C, 58.49, 58.02, 61.35; H, 6.08, 5.74, 6.17; N, 9.55.

The remainder of the product was dissolved in benzene, filtered through a thin layer of charcoal and precipitated with petroleum ether. After drying *in vacuo* at 100° it melted at 170–175°, but could not be analyzed because it weighed less than a milligram.

The preparation of the 2,4-dinitrophenylhydrazone was repeated; the product was dissolved in dry benzene and adsorbed upon a column containing 35 g. of activated alumina (ALCOA). Development of the column was achieved with 1200 ml. of pure chloroform which slowly eluted four separate zones of amorphous orange material. The third fraction contained most of the product. It could not be crystallized from the ordinary solvents and was precipitated as a flocculent solid by dilution of a methanolic solution with water. It melted at approximately 150°.

Anal. Found: C, 60.99; H, 6.62.

Physical Data.—Infrared spectra were determined and interpreted by Mrs. James L. Johnson and Miss Elizabeth Petersen, using a Perkin–Elmer spectrometer. Ultraviolet spectra were determined by Mrs. John C. Brantley. Photographic X-ray diffraction patterns of the amaroids were obtained by Mr. Jacob Fuchs and Mr. Melvin H. Mueller, using a Hayes diffraction camera. The photographic patterns were converted into linear intensity curves (Fig. 3) by a recording microphotometer (Leeds and Northrup). Similar curves were obtained directly by means of a North American Philips recording X-ray diffraction apparatus. Analytical data were determined by analysis in this Laboratory and by the Clark Microanalytical Laboratory of Urbana, Illinois.

The authors wish to express their gratitude for assistance received in the collection of physical data.

Summary

It has been demonstrated that:

1. *Aeschrion excelsa* (Jamaica quassia) contains the three amaroids: quassin, isoquassin and neoquassin.

(11) First carried out by B. F. Aycock and A. E. Senear, formerly of this Laboratory.

2. Picrasmin and isoquassin are identical.
3. Quassin is a molecular complex containing isoquassin and neoquassin in approximately equal amounts.
4. Neoquassin ($C_{22}H_{30}O_6$) is a hydroxy compound and isoquassin ($C_{22}H_{28}O_6$) is the corresponding ketone.

URBANA, ILLINOIS RECEIVED JULY 25, 1949

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

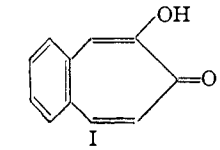
4,5-Benztropolone and Related Compounds[1]

BY D. STANLEY TARBELL,* GEORGE P. SCOTT AND ALEXANDER D. KEMP

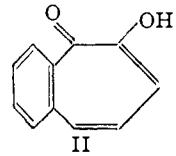
The evidence that has been presented for the occurrence of the seven-membered "tropolone" ring[2] in colchicine,[3] the thujaplicins[4] and purpurogallin[5] has made the problem of synthesizing examples of this interesting ring system an attractive one. Model tropolones have obvious value in elucidating the properties of colchicine, and possess in addition considerable intrinsic chemical interest.

The present paper reports the synthesis of 4,5-benztropolone (I) and some of its derivatives, by a method which promises to be of general application. Preparation of an isomer of I, 3,4-benztropolone, by a different method, has been reported recently by Cook.[6]

Our approach to the benztropolone was suggested by work of Thiele,[7] who showed that *o*-phthalaldehyde condensed with a carbonyl compound such as methyl ethyl ketone or acetonedicarboxylic ester to yield derivatives of benzocycloheptadienone III. In some cases, the product of the condensation was the acylhydrindone IV, which differed from the seven-ring ketone type (III) by its enolic character, and by the presence of the elements of water.



I



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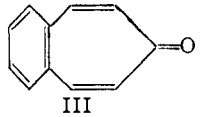

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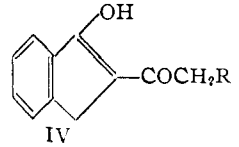
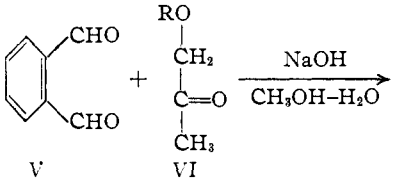
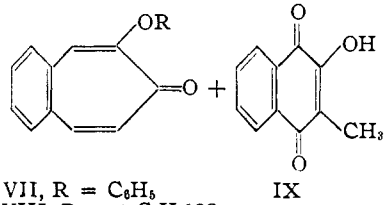


IV

We have found that Thiele's reaction can be applied to aryloxyacetones and to hydroxyacetone itself, to yield 4,5-benztropolone and its aryl ethers. The latter (VII and VIII) were obtained readily, and were assigned the benztropolone structure on the basis of analysis, absence of enolic properties and formation of carbonyl derivatives. The last fact is noteworthy, because colchicine does not form carbonyl derivatives. Furthermore, the infrared spectra of VII and VIII were quite similar to that of I, indicating analogous structures.



V VI



VII, R = C_6H_5
VIII, R = *p*-$C_6H_4NO_2$
I, R = H

IX

The condensation of phthalaldehyde with hydroxyacetone itself led to an unexpected result; two products were obtained in about equal amount, one with the composition $C_{11}H_8O_2$, corresponding to the desired benztropolone I, and the other apparently containing one more atom of oxygen, $C_{11}H_8O_3$.

The properties of the latter, such as its melting point, bright yellow color and the formation of intensely red solutions in alkali or bicarbonate, suggested that it was phthiocol (IX),[8] and this was confirmed by the melting point of the monoacetate, and by a mixed melting point of the compound and its monoacetate with known synthetic samples.[9] The absorption curves for the synthetic phthiocol and that derived from the condensation were identical. The formation of phthiocol may be plausibly explained by the following steps, although experimental evidence is not yet available to support this mechanism.

* Harvard University Ph.D. 1937.

(1) Aided by a grant from the National Institutes of Health; presented at the Atlantic City Meeting of the American Chemical Society, September 21, 1949.

(2) Dewar, *Nature*, **155**, 141, 479 (1945).

(3) (a) Arnstein, Tarbell, Scott and Huang, THIS JOURNAL, **71**, 2448 (1949); (b) Scott and Tarbell, *ibid.*, **72**, 240 (1949).

(4) Erdtman and Gripenberg, *Acta Chim. Scand.*, **2**, 625 (1948), and following papers.

(5) Haworth, Moore and Pauson, *J. Chem. Soc.*, 1045 (1948).

(6) Cook and Somerville, *Nature*, **163**, 410 (1949). We have adopted the numbering system used by these authors.

(7) Thiele and Schneider, *Ann.*, **369**, 287 (1909); Thiele and Weitz, *ibid.*, **377**, 1 (1910).

(8) Anderson and Newman, *J. Biol. Chem.*, **103**, 405 (1933).

(9) Creighton and Anderson, *ibid.*, **130**, 429 (1939).