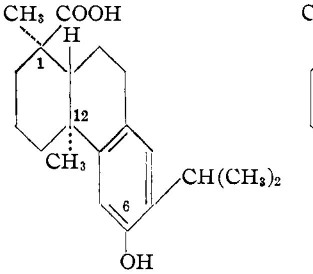
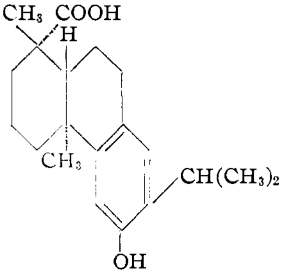
7-isopropylpodocarpic acid (II) only in the configuration of the methyl and carboxyl groups at C_1.



I



II

Since 6-hydroxydehydroabietinol (–COOH of I replaced by $-CH_2OH$) possesses a relatively high order of estrogenic activity,[2] it was of interest to prepare the isomeric 7-isopropylpodocarpinol (–COOH of II replaced by $-CH_2OH$) and to test its biological activity.[3]

Podocarpic acid, obtained from rimu resin, was converted by the previously described[4] sequence of reactions to methyl O-methyl-7-isopropylpodocarpate which was reduced to O-methyl-7-isopropylpodocarpinol (III) in 93% crude yield[5] by means of lithium aluminum hydride.[6] III was demethylated in 40% yield to the free phenol by treatment with potassium hydroxide in diethylene glycol at 210–220° for four hours.[7]

7-Isopropylpodocarpinol was assayed for estrogenic activity by the Laboratory of Industrial Hygiene, Inc.[8] Of a group of ten rats receiving 1.5 micrograms of sample per animal 30% showed positive response; under similar conditions 1.1 micrograms of estrone produced a 50% positive response. When the dosage level of the sample was raised to 2.8 micrograms per rat, 40% of ten animals showed positive response, compared again with 50% response to 1.1 micrograms of estrone.

Experimental

O-Methyl-7-isopropylpodocarpinol.—A solution of 4.7 g. of lithium aluminum hydride in 200 ml. of dry ether was prepared in a one-liter three-necked flask equipped with a reflux condenser, mercury-sealed stirrer and dropping funnel. All outlets were protected by drying tubes containing anhydrous calcium chloride and Ascarite. Then a solution of 10 g. of methyl O-methyl-7-isopropylpodocarpate[4] in 75 ml. of dry ether was added dropwise with stirring. The mixture was stirred for three days at room temperature. Cracked ice was added followed by 250 ml. of dilute sulfuric acid. The layers were separated, the aqueous layer extracted once with ether, the ether solutions combined, washed with water and dried over anhydrous sodium sulfate. The ether solution was distilled to dryness and the residue crystallized from ethanol. The yield, in two crops, was 8.5 g. (93%). A sample after one recrystallization from ethanol melted at 83–85°.

Anal. Calcd. for $C_{21}H_{32}O_2$: C, 79.69; H, 10.19. Found: C, 79.57; H, 10.30.[9]

7-Isopropylpodocarpinol.—A mixture of 5.4 g. of O-methyl-7-isopropylpodocarpinol, 18.9 g. of potassium hydroxide and 135 ml. of diethylene glycol was heated under a reflux condenser for four hours at 210–220° (internal temperature) with stirring. The mixture was cooled, diluted with one liter of water and acidified with dilute sulfuric acid. The precipitated solid was removed by filtration. The filtrate was extracted with four 100-ml. portions of ether; the previously removed solid was dissolved in the ether. The ether solution was washed with three 25-ml. portions of 5% sodium hydroxide,[10] then with water and dried over anhydrous sodium sulfate. The solution was distilled to dryness. The residue upon crystallization from ethanol–hexane gave, in several crops, 1.6 g. of product and 1.1 g. of recovered starting material (40% yield based upon net material entering reaction). Recrystallized from ethanol–hexane, the phenol–alcohol melted at 185.4–186.4°.

Anal. Calcd. for $C_{20}H_{30}O_2$: C, 79.43; H, 10.00. Found: C, 79.31; H, 9.80[9].

---

[2] Fieser and Campbell, This Journal, **61**, 2530 (1939); Fieser and Fieser, "Natural Products Related to Phenanthrene," 3rd ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 69.

[3] Brandt and Ross, *Nature*, **161**, 892 (1948), report that podocarpinol is estrogenic.

[4] Sherwood and Short, *J. Chem. Soc.*, 1006 (1938); Campbell and Todd, This Journal, **62**, 1292 (1940).

[5] Zeiss, *et al.*, This Journal, **70**, 1981 (1948), similarly reduced the des-isopropyl ester to the corresponding alcohol in 93% yield.

[6] Metal Hydrides, Inc., Beverly, Mass.

[7] Optimum conditions for this step were not determined.

[8] Laboratory of Industrial Hygiene, Inc., 76 Madison Ave., New York 16, N. Y.

[9] Schwarzkopf Microanalytical Laboratory, Middle Village, L. I., N. Y.

[10] The phenolic group in 7-isopropylpodocarpinol is highly hindered. The product is practically insoluble in aqueous alkali, but the caustic wash removes some colored material which interferes with the crystallization.

The New York Quinine and Chemical Works, Inc.
Brooklyn, N. Y.
S. B. Penick and Co.
New York, N. Y.

Received March 15, 1950

The Interaction of Aluminum Bromide and Sodium Iodide

By J. L. Daniel and N. W. Gregory

The properties of fused mixtures of aluminum halides and other metallic halides have been studied extensively, particularly by Plotnikov[1,2] and others[3,4] in Russia. Considerable evidence for the existence of addition compounds has been observed. In mixtures of alkali metal halides and aluminum halides, electrochemical studies provide results which indicate the presence of negative ions containing aluminum. The ion AlX_4^- has been postulated frequently. Al_2X_6 can be sublimed away from addition compounds in systems of this type at high temperatures.

The electrical properties of mixtures of sodium chloride and aluminum bromide have been explained by Mezhenii[4] in terms of ionization into Na^+ and $AlBr_3Cl^-$. Evidence for the existence of a corresponding type of mixed halide ion has also been found in the system $AlBr_3$–NaI–C_2H_5Br.[2]

---

[1] V. A. Plotnikov and U. I. Shvartsman, *J. Phys. Chem.* (*U. S. S. R.*), **12**, 120 (1938).

[2] V. A. Plotnikov and V. N. Dumarevska, *Zapiski Inst. Khim., Akad. Nauk., U. R. S. S.*, **7**, 383 (1940).

[3] E. L. Starokadomskaya, *J. Gen. Chem.* (*U. S. S. R.*), **9**, 840 (1939).

[4] Y. F. Mezhenii, *Zapiski Inst. Khim., Adad. Nauk., U. R. S. S.*, **7**, 373 (1940).

We were interested in examining the nature of the volatile product which can be sublimed away from fused mixtures in which mixed halide ions are expected, in view of the possibility that a mixed halide of aluminum might result. Plotnikov and Shvartsman[1] have made freezing point studies of several systems which present such a possibility: $AlBr_3$–$HgCl_2$, $AlBr_3$–$SbCl_3$, $AlBr_3$–KCl, $AlBr_3$–AgCl, $AlCl_3$–KBr, and $AlCl_3$–AgBr. They have interpreted their results in terms of a simple binary mixture. Maxima in the freezing point curves were observed in each of the systems named above and were taken as evidence for the formation of 1:1 addition compounds (some show incongruent melting points). Upon heating 1:1 mixtures of the first two types, exchange of halogen atoms was observed. This was not the case in the other systems.

We chose to study the $AlBr_3$–NaI system because the relatively greater difference in the vapor pressures of $AlBr_3$ and AlI_3 make these substances easier to separate than the bromide and chloride. A freezing point study of mixtures of $AlBr_3$ and NaI has been made in an attempt to obtain evidence concerning the existence of addition compounds (possibly $Na^+AlBr_3I^-$). The results are given in Table I and are shown graphically by the smoothed curve in Fig. 1. A 1:1 addition compound with an incongruent melting point would seem to be indicated by the break in the curve at 177°. However, in view of the exchange reaction discussed below, it is not possible to interpret the diagram in such a manner as to establish the nature of the compound from freezing point data alone. The break in the curve occurs at a composition corresponding to an initial composition of 51 mole per cent. $AlBr_3$. As the amount of NaI is increased beyond this, the freezing point of the mixture rises very rapidly. For this reason the last three points in Table I could not be shown conveniently on the diagram. Mixtures in which the initial composition corresponds to the range between 87 and 98 mole per cent. $AlBr_3$ form a liquid phase which consists of two immiscible layers. These liquids freeze at 96° and are completely miscible above 200°.

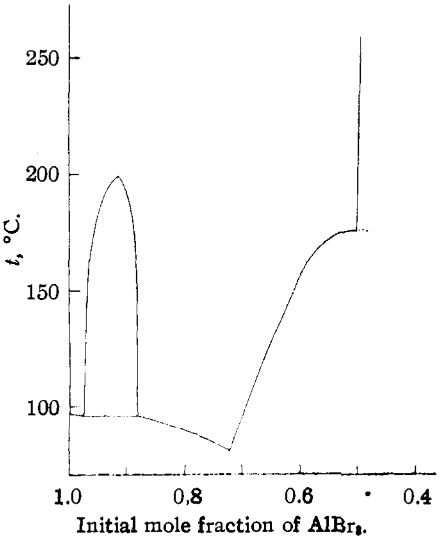


Fig. 1.—Freezing point diagram for mixtures of $AlBr_3$ and NaI.

TABLE I

FREEZING POINTS OF MIXTURES OF $AlBr_3$ AND NaI

[a]Initial mole % $AlBr_3$	Freezing point, °C.	Complete miscibility	[a]Initial mole % $AlBr_3$	Freezing point, °C.
100.0	97		74.4	86
99.5	97		72.0	84
96.9	96	148	69.9	100
93.8	96	180	66.3	120
93.5	95	198	61.9	140
89.9	95	191	58.9	164
88.9	93	179	57.4	170
83.6	92		52.2	175
82.6	93		50.0	190
82.0	88		49.0	400
80.0	87		45.8	440
75.0	83		41.5	520

[a] Composition represents mole fraction of mixtures based on initial amounts of $AlBr_3$ and NaI used.

A 1:1 mole mixture of $AlBr_3$ and NaI was fused under an inert atmosphere and cooled. When this mixture was heated under a reduced pressure, the material which sublimed away contained aluminum, bromine and iodine. The relative amounts of bromine and iodine in the sublimate were found to vary with the temperature of sublimation. At 45°, appreciable vaporization of aluminum halide did not occur ($p < 10^{-5}$ mm.; $AlBr_3$ will sublime quite readily under these conditions). At 80°, approximately 10% of a 10 g. sample sublimed away in a period of ten hours. After the first few hours the rate of vaporization appeared to be negligible. The ratio of bromine to iodine in the sublimate was found to be 25:1. When the residue was heated to higher temperatures, additional sublimation occurred. Sublimation was permitted to occur in several steps, maintaining constant temperature in each case until the rate of vaporization was practically zero. As the temperature was increased, the Br:I ratio in the sublimate became smaller. At 400°, the ratio 4:1 was observed. Sodium was not detected in the sublimate.

In view of the greater volatility of $AlBr_3$, these results are consistent with that which one might expect if the solution were composed of a non-ideal mixture of $AlBr_3$ and AlI_3 with the corresponding sodium halides. It is apparent that exchange of halogen between $AlBr_3$ and NaI does occur upon heating the mixtures. If these mixtures contain an appreciable fraction of $AlBr_3I^-$ ions, thermal decomposition does not lead to formation of mixed halide molecules of aluminum. At least if such are formed, they must undergo disproportionation during the sublimation process, as fractional sublimation of the volatile products leads only to separation into $AlBr_3$ and AlI_3.

We have also observed exchange of halogen in the system $AlBr_3$–KCl. These substances appear to form a complex which is more difficult to decompose thermally. Upon heating an equimolar mixture of $AlBr_3$ and KCl at 400°, a volatile product was obtained in which the Br:Cl ratio was found to be 5:3. Potassium was not present in the sublimate. Fractionation of this material resulted in separation into $AlBr_3$ and $AlCl_3$ with no evidence observed to indicate the presence of aluminum chlorobromides. Plotnikov and Shvartsman[1] report that exchange does not occur when the complex is heated to 250°. Appreciable vaporization does not occur below 400°.

Experimental

Samples of known composition were prepared by mixing together weighed quantities of the pure anhydrous components. The pyrex sample tubes were evacuated and sealed, leaving the smallest volume practical. Freezing points were determined by observing the temperature at which crystals first appeared when the fused samples were cooled slowly in an aluminum block. Repeated measurements were made with a given sample, shaking to minimize any tendency to supercool. The freezing temperatures are considered to be accurate within 2°. The melts were characterized by a red coloration. It seems likely that this may have been due to the presence of a small amount of moisture with subsequent liberation of halogen on heating. However, considerable care was taken in an effort to prevent appreciable contamination of the samples by water vapor or oxygen.

DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING
UNIVERSITY OF WASHINGTON
SEATTLE 5, WASHINGTON RECEIVED JANUARY 3, 1950

Photography of Antibiotic Papergrams

BY N. A. DRAKE

There has been considerable demand in our laboratories for photographic records of antibiotic papergrams of the type described by D. H. Peterson elsewhere in THIS JOURNAL. The following simple method for making clear pictures of high contrast has been made standard with us.

The bacterial agar plates are prepared according to the procedure described by Peterson. After paper contact and incubation have been completed, the surface of the agar has a layer of milky growth with clearly defined zones of inhibition reflecting the presence of antibiotic substances in the paper chromatogram. Since the contrast between the growth and the clear agar is very low, photographs made with ordinary lighting fail to give good detail.

We have found that if plane polarized light is used to illuminate the tray, with a dead black surface beneath it and a polarizer at the camera lens crossed with the polarizer at the light source, a satisfactorily high contrast is attained. Two 200-watt lamps in reflectors, or a fluorescent strip lamp serves as a light source when fitted with a sheet of Polaroid. In order to obtain precise crossing of the polarizers, a view camera is used and the exposure is made on high contrast negative material such as Contrast Process Ortho or Kodalith. With such a low level of illumination, the exposure is necessarily a time exposure. One must, of course, use care to avoid burning the sheet Polaroid at the light source.

For identification and necessary notes, a sheet of tracing paper lettered with India ink is placed on the agar plate. A one inch square of paper is also placed on the plate before photography in order to form a size scale for measurement of the areas of zones of inhibition and distance traveled by the zones.

Metal pans coated with Black Heresite[1] can be substituted for the Pyrex trays. In this case, the necessary black background is already incorporated within the tray.

This method has also proved satisfactory in photographing agents of growth as well as inhibition.

---

(1) Heresite coating is done by Heresite and Chemical Co., Manitowoc, Wisconsin.

RESEARCH DIVISION
UPJOHN COMPANY
KALAMAZOO 99, MICH. RECEIVED JANUARY 7, 1950

Some Quaternary Ammonium Salts of Quinoxalines

BY WILLIAM K. EASLEY AND CARL T. BAHNER

The biological results obtained by Shear and associates[1] at the National Cancer Institute using quaternary salts containing a pyridine or quinoline ring have led us to prepare similar quaternary salts containing other rings. Previous reports from this Laboratory have discussed salts of thiazoles,[2] of hexamethylenetetramine,[3] and of pyrazine.[4] This paper deals with the preparation of quaternary salts of quinoxaline, 6-methylquinoxaline and 6-chloroquinoxaline with alkyl sulfates, alkyl halides, phenylethyl halides and aryl halomethyl ketones.

The difficulties encountered in the preparation of quaternary salts of 2,3-dimethylquinoxaline have been discussed by Bennett and Willis[5] and by Cook, Garner and Perry.[6] Fritts,[7] working in this Laboratory, found that 2,3-dimethylquinoxaline heated two to three hours at 100° with phenacyl bromide, *p*-methylphenacyl bromide and *m*-nitrophenacyl bromide, respectively, formed green

---

(1) Shear, *et al.*, in "Approaches to Cancer Chemotherapy," American Association for the Advancement of Science, F. R. Moulton, Editor, Washington, D. C., 1947, p. 236 ff.; Hartwell and Kornberg, THIS JOURNAL, **68**, 1131 (1946).

(2) Bahner, Pickens and Bales, *ibid.*, **70**, 1652 (1948).

(3) Bahner, Pickens and Easley, *ibid.*, **72**, 2266 (1950).

(4) Bahner and Norton, *ibid.*, **72**, 2881 (1950).

(5) Bennett and Willis, *J. Chem. Soc.*, 1960 (1928).

(6) Cook, Garner and Perry, *ibid.*, 710 (1943).

(7) Fritts, unpublished communication.