tionation 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
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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
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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.

TABLE I

QUINOXALINIUM SALTS

Salt of quinoxaline with	Reaction time, days	Yield, %	M. p., °C.	Formula	Analyses, %	Calcd.	Found	Calcd.	Found	Calcd.	Found
Dimethyl sulfate	73[a]	17	144–145[d]	$C_{10}H_{12}N_2O_4S$	N,	10.93	10.86				
Diethyl sulfate	73[a]	11	171[e]	$C_{12}H_{16}N_2O_4S$	N,	9.85	9.75				
β-Phenylethyl iodide	148[c]	7	146–148[d]	$C_{16}H_{14}IN_2$	N,	7.74	8.11	C, 53.06	53.16	H, 4.15	4.37
Phenacyl bromide	29[a]	28	177[d]	$C_{16}H_{13}BrN_2O$				C, 58.35	58.06	H, 3.95	4.21
p-Chlorophenacyl bromide	37[b]	27	202.5[f]	$C_{16}H_{12}BrClN_2O$	N,	7.70	7.69				
p-Bromophenacyl bromide	10[b]	27	206[f]	$C_{16}H_{12}Br_2N_2O$	N,	6.86	6.84				
m-Nitrophenacyl bromide	28[b]	72	181[i]	$C_{16}H_{12}BrN_3O_3$	N,	11.23	11.08				
p-Methoxyphenacyl bromide	10[b]	25	182.5[f]	$C_{17}H_{15}BrN_2O_2$				C, 56.82	56.17	H, 4.18	4.34
β-Naphthacyl bromide	12[a]	73	182[j]	$C_{20}H_{15}BrN_2O \cdot H_2O$				C, 60.45	60.67	H, 4.28	3.96
Salts of 6-methylquinoxaline with											
Methyl iodide	4[c]	88	174–175[e]	$C_{10}H_{11}IN_2$				C, 41.97	41.80	H, 3.88	3.93
p-Methylphenacyl bromide	5[c]	69	192–193[e]	$C_{18}H_{17}BrN_2O$	Br^-,	22.37	22.15				
p-Fluorophenacyl bromide	7[b]	54	211[g]	$C_{17}H_{14}BrFN_2O$	Br^-,	22.13	22.10				
p-Chlorophenacyl bromide	24[a]	29	226–227[g]	$C_{17}H_{14}BrClN_2O$	Br^-,	21.27	20.95				
p-Bromophenacyl bromide	20[a]	32	226[g]	$C_{17}H_{14}Br_2N_2O$	Br^-,	18.89	18.84				
p-Methoxyphenacyl bromide	11[b]	89	198[h]	$C_{18}H_{17}BrN_2O_2$				C, 57.93	57.87	H, 4.59	4.01
Salts of 6-chloroquinoxaline with											
Methyl iodide	45[c]	94	190[e]	$C_9H_8ClIN_2$				C, 34.92	35.06	H, 2.61	2.69
Ethyl iodide	162[c]	17	171[f]	$C_{10}H_{10}ClIN_2$	I^-,	39.61	39.54				

[a] In chloroform. [b] In nitrobenzene. [c] Without solvent. [d] After recrystallization from ethanol. [e] After recrystallization from methanol. [f] After recrystallization from ethanol–isopropyl ether mixture. [g] After recrystallization from methanol–isopropyl ether mixture. [h] After recrystallization from methanol–isopropyl alcohol mixture. [i] After washing with ethanol–isopropyl ether mixture. [j] After washing with chloroform.

or brown solid products which were insoluble in ordinary solvents, did not melt below 300°, and contained more than the theoretical amount of carbon calculated for the corresponding simple quaternary salts. While quinoxaline seemed to react more readily than 2,3-dimethylquinoxaline with alkyl halides great care was necessary to obtain the desired products and the yields were not always high. For best results it was necessary to select the proper solvent and conditions for each reaction. As a rule a temperature below 50° was chosen. Chloroform was used as a solvent in the reaction with alkyl sulfates. An excess of alkyl halide was the only solvent found necessary for reactions of the simple alkyl halides. Some of the aryl halomethyl ketone reactions were carried out in chloroform, others took place more readily and gave better yields in nitrobenzene, and in a few cases no solvent was used. The time allowed for reaction also varied, but was frequently several weeks. The quaternary salts were purified by recrystallization from methanol or ethanol or a mixture of one of these alcohols with isopropyl ether. In a few cases the product was only washed with a suitable solvent because decomposition was found to occur during the attempted recrystallizations. Heating was avoided although permissible in some instances.

Samples of the compounds listed in Table I have been submitted to the National Cancer Institute for screening tests. Others are being prepared.

Experimental

The chemicals used were obtained as follows: methyl iodide, ethyl iodide and phenylethyl iodide from Edcan Laboratories, phenacyl bromide, *o*-phenylenediamine, *p*-methyl-*o*-phenylenediamine, β-naphthyl methyl ketone, chlorobenzene, bromobenzene, *p*-dichlorobenzene and anisole from Eastman Kodak Company, and glyoxal sodium bisulfite from Carbide and Carbon Chemicals Corporation. Quinoxaline, 6-methylquinoxaline and 6-chloroquinoxaline was prepared by the method of Cavagnol and Wiselogle.[8] The aryl halomethyl ketones were prepared in the conventional way by bromination of the corresponding aryl methyl ketones or by Friedel–Crafts reaction of bromoacetyl bromide with the proper hydrocarbon. Methods of preparation of the quaternary salts are illustrated by the following examples.

Method I.—A solution of 3.61 g. (0.025 mole) of 6-methylquinoxaline in 17.7 g. (0.125 mole) of methyl iodide was allowed to stand four days. The red crystals which precipitated weighed 6.3 g. and melted with decomposition at 174–175°. This melting point remained unchanged after recrystallization from a mixture of methanol and isopropyl ether. *Anal.* Calcd. for $C_{10}H_{11}IN_2$: C, 41.97; H, 3.88. Found: C, 41.80; H, 3.93.

Method II.—A solution of 19.9 g. (0.1 mole) of phenacyl bromide and 13 g. (0.1 mole) of quinoxaline in 50 ml. of chloroform was allowed to stand for four weeks. The yellow crystals which formed were removed by suction filtration and washed with several small portions of chloroform. After recrystallizing twice from absolute ethanol 1.6 g. of product, m. p. 177°, was obtained. *Anal.* Calcd. for $C_{16}H_{13}BrN_2O$: C, 58.35; H, 3.95. Found: C, 58.06; H, 4.21.

Method III.—A mixture of 8.52 g. (0.04 mole) of *p*-methylphenacyl bromide and 5.75 g. (0.04 mole) of 6-methylquinoxaline was warmed to 40° for one hour, then kept five days at room temperature. The hard greenish-yellow reaction mixture was then dissolved in boiling methanol and an equal volume of isopropyl ether was added to the hot solution. Upon cooling, 9.8 g. of crude product was obtained, m. p. 192–193° after repeated recrystallization. *Anal.* Calcd. for $C_{18}H_{17}BrN_2O$: Br^-, 22.37. Found: Br^-, 22.15.

The decomposition temperatures of the salts listed in the accompanying table were determined in a Thiele tube by heating rapidly to a temperature about five degrees below the expected melting point, then raising the temperature gradually. While the decomposition temperature was relatively sharp in most instances it is well known that such decomposition temperatures are somewhat variable. The yields recorded do not necessarily represent the highest yield attainable, since for the purposes of this project it

(8) Cavagnol and Wiselogle, THIS JOURNAL, 69, 796 (1947).

was more important to obtain pure products than high yields. The bromide salts, which were greenish yellow in color, formed pink solutions with water, in which they were slightly to moderately soluble. The alkyl sulfates were brown and the iodides ranged from orange-red to brown.

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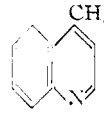
CHEMICAL LABORATORIES OF
CARSON-NEWMAN COLLEGE
JEFFERSON CITY, TENN. RECEIVED FEBRUARY 20, 1950

Claisen and Aldol Condensations of α-Picoline and Quinaldine with Ethyl Oxalate by Alkali Amides[1]

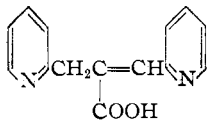
BY CHARLES R. HAUSER AND WILBERT J. HUMPHLETT[2]

It was shown recently in this Laboratory that lepidine may be acylated with ethyl oxalate by means of potassium amide to form in good yield the corresponding Claisen condensation product (I).[3] However, under similar conditions, α-picoline with this ester gave a substance which apparently was not the corresponding Claisen condensation product.

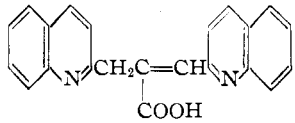
We have found that α-picoline with ethyl oxalate and either potassium amide or sodium amide forms an α,β-unsaturated pyridyl acid (II) and that quinaldine similarly gives a corresponding product (III).[4] These condensations were carried out in refluxing ether employing two molecular equivalents of the pyridyl compound and alkali amide to one of ethyl oxalate (Method B).[3] The yield of (II) was 23% and of (III), 53%.



(I)

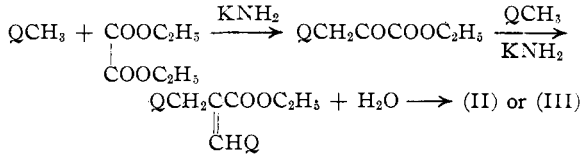


(II)



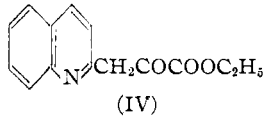
(III)

Compounds (II) and (III) evidently are formed by a Claisen condensation followed by an aldol condensation, the water thereby liberated hydrolyzing the ester group. The reactions may be represented by the following equations in which Q is α-pyridyl or α-quinolyl.



Attempts to obtain the Claisen product in these cases were unsuccessful. When the reaction with α-picoline was stopped by acidification immediately after the addition of the ethyl oxalate, no definite product could be isolated. When the reaction with quinaldine was carried out at room temperature in pentane, instead of ether, and the mixture acidified immediately after addition of the ester, the only product isolated was (III) (20%). The reason that the Claisen product from lepidine did not undergo the aldol reaction under the conditions employed, may be attributed to its relative insolubility (see experimental).

Although sodium or potassium amide converts quinaldine and ethyl oxalate to an aldol derivative of the Claisen product, it was shown by Wislicenus[5] and confirmed by us that potassium ethoxide yields apparently only the Claisen product (IV).



(IV)

The ethoxalyl derivatives of lepidine and of quinaldine, (I) and (IV), respectively, were converted to the corresponding oximes which were hydrogenated in the presence of Raney nickel. However, the products failed to give satisfactory analytical values for the corresponding amino acid esters.

Experimental[6]

2-α-Picolal-3-α′-pyridylpropionic Acid (II).—In a one-liter three-necked flask equipped through ground glass joints with a reflux condenser (drying tube), mercury-sealed stirrer and dropping funnel, was prepared 0.40 mole of potassium amide[7] (or sodium amide) in approximately 400 ml. of anhydrous liquid ammonia. To this reagent was added 37.2 g. (0.40 mole) of α-picoline (b. p. 129–130°) in an equal volume of dry ether. The reaction flask was placed on the steam-bath and 300 ml. of ether was added gradually as the ammonia was evaporated. After the suspension was stirred and refluxed for thirty minutes.

(1) Paper XLVI on Condensations; paper XLV, THIS JOURNAL, **72**, 1352 (1950).

(2) Eli Lilly Fellow, 1949–1950.

(3) Weiss and Hauser, THIS JOURNAL, **71**, 2023 (1949).

(4) α-Picoline failed to react appreciably with ethyl oxalate in the presence of diethylaminomagnesium bromide in refluxing ether for three hours, 75% of the α-picoline being recovered. Quinaldine and ethyl oxalate with sodium hydride in refluxing ethyl ether liberated only about 25% of the calculated amount of hydrogen and no definite product was isolated. Perhaps the condensation might be realized in a higher boiling solvent; see Swamer and Hauser, THIS JOURNAL, **72**, 1352 (1950).

(5) Wislicenus and Kleisinger, *Ber.*, **42**, 1140 (1909).

(6) Analyses are by Clark Microanalytical Laboratory, Urbana, Illinois.

(7) Yost and Hauser, THIS JOURNAL, **69**, 2325 (1947).