TABLE II
TOLANES

Substance	M. p., °C. (corr.)	Solvent	Formula	Molecular weight Calcd.	Found	Method
p,p'-Diethyltolane	71.5–72.5	Methanol	$C_{18}H_{18}$	234	226	Rast
p,p'-Di-*n*-propyltolane	69.5–70.5	Methanol	$C_{20}H_{22}$			
p,p'-Di-*n*-butyltolane	41–42	Methanol	$C_{22}H_{26}$	290	270	Freezing benzene
3,3',4,4'-Tetramethyltolane	143–144	Acetic acid	$C_{18}H_{18}$			
p,p'-Diphenyltolane	243–244	Benzene	$C_{26}H_{18}$	330	347	Boiling benzene

With the low melting tolanes the crude products were oils and were extracted with ether. The ethereal solutions were dried with calcium chloride and the ether evaporated. The residues crystallized upon standing several hours in a vacuum desiccator.

Tolane and *p,p'*-diphenyltolane were prepared by the action of potassium amide on the corresponding dichloroethanes. The yields of crude product were 85 and 91%, respectively. A sample of the *p,p'*-diphenyltolane was oxidized with ozone by the method used by Harries[7] for other acetylene derivatives. The acid obtained was shown to be *p*-phenylbenzoic acid by its melting point and by a mixed melting point with known *p*-phenylbenzoic acid.

In Table II are given the physical properties of the tolanes not previously recorded.

Absorption Spectra.—In studying the absorption spectra a Hilger quartz spectrograph and a Hilger sector photometer were used. A tungsten steel spark was the source of light. The reference line from which the wave lengths were determined was that of iron at 4957 Å. units.

In Table III are given the positions of the absorption bands of tolane and substituted tolanes. Chloroethenes show non-selective absorption in the region between 200–280 millimicrons.

(7) Harries, *Ber.*, **40**, 4905 (1907).

TABLE III
POSITIONS OF ABSORPTION BANDS OF TOLANE AND SUBSTITUTED TOLANES (WAVE LENGTHS IN mμ)

	Wave length	Wave length
Tolane	298	279
Dimethyltolane	304	284
Diethyltolane	305	287
Di-*n*-propyltolane	305	288
Di-*n*-butyltolane	306	287
Tetramethyltolane	306	286
Dimethoxytolane	314	294

Summary

The action of potassium amide in liquid ammonia on 1,1-diaryl-2-chloroethenes causes the removal of hydrogen chloride and the rearrangement of the molecules to form tolane or substituted tolanes. With dichloroethanes two molecules of hydrogen chloride are removed and a similar rearrangement occurs.

The ultraviolet absorption spectra of the chloroethenes and the tolanes were determined. The chloroethenes show non-selective absorption in the region between 200–280 millimicrons. Tolane and substituted tolanes show characteristic absorption bands.

IOWA CITY, IOWA RECEIVED JULY 24, 1933

[CONTRIBUTION FROM FIXED NITROGEN DIVISION OF THE BUREAU OF CHEMISTRY AND SOILS, U. S. DEPARTMENT OF AGRICULTURE]

Action of Alkali and Ammonia on 2,4-Dialkoxypyrimidines

BY GUIDO E. HILBERT AND EUGENE F. JANSEN

There is a fundamental analogy[1] between acid chlorides, imido chlorides and 2,4-dichloropyrimidines;[2] esters, imido ethers and 2,4-dialkoxypyrimidines; and acid amides, amidines and 2,4-diaminopyrimidines as is evident by the similarity, not only of their structures, but also of their properties and chemical reactions. The essential difference between the structure of an imido derivative and a pyrimidine is in the mode of combination of the common grouping —C(R)=N—; in the former it is acyclic and in the latter it is an integral portion of the ring. In the case of 2,4-dialkoxypyrimidines apparently only two types of reactions, both of which have their analogs in the ester series, have been recorded; one involves hydrolysis with acids[3] and the other

(1) Wheeler and Bristol. *Am. Chem. J.*, **33**, 448 (1905), call attention to the relationship between imido chlorides and chloropyrimidines. Bergstrom and McAllister, THIS JOURNAL. **52**, 2845 (1930) [see also Bergstrom. *ibid.*. **53**, 3027 and 4065 (1931)], suggest that nitrogen ring compounds containing the grouping —CH=N— are cyclic ammono aldehyde acetals and that the corresponding α-chloro and α-methyl derivatives are similar to acid chlorides and ketones, respectively; the logical extension of this suggests that the α-alkoxy derivatives are analogous to esters.

(2) The numbering of the pyrimidine cycle is the same as that used by *Chemical Abstracts*.

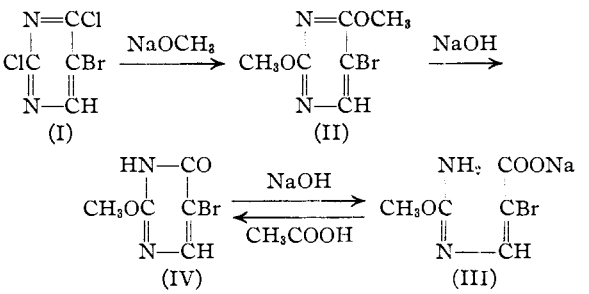
(3) Gabriel and Colman. *Ber.*, **36**, 3379 (1903).

interaction with alkyl halides.[4] On the basis of their similarity with esters one would also expect hydrolysis of the alkoxy group with alkali and ammoniation with ammonia. This view is supported by a few results recorded in the literature[5] for analogous nitrogen ring compounds, as well as by the following observations in the pyrimidine series.

In the interaction between sodium methylate and 2,4-dichloro-5-bromopyrimidine (I) the formation of 2,4-dimethoxy-5-bromopyrimidine (II) was anticipated since the halogen atoms in the α position to nitrogen are extremely reactive in contrast to the one in the 5 position. Actually the reaction yielded a mixture of the low melting (63–64°) dialkoxypyrimidine (II) and a considerably higher melting (248°) product which possessed properties differing widely from those of (II) and which was shown to be the sodium salt of α-bromo-β-methylisoureidoacrylic acid (III). In view of the disparity in their vapor pressures the former was readily separated by sublimation. The conditions of the experiment influenced markedly the proportions of the products formed in the reaction. Thus the higher melting constituent was mainly formed when an excess of alkali was present; and accordingly its formation was also favored when there was a delay in the isolation of the products or when the solvent was removed at elevated temperatures. On the other hand, the production of (II) was facilitated by a reversal of the above conditions although efforts directed toward obtaining it exclusively were without success. These results suggested that 2,4-dimethoxy-5-bromopyrimidine was an intermediate in the formation of the sodium salt (III). This has been confirmed by the subsequent hydrolysis of (II) with sodium hydroxide.

In addition to the analytical data which included a Zeisel determination showing the presence of one methoxy group, the following evidence was obtained in favor of the product (III) being sodium α-bromo-β-methylisoureidoacrylate. In aqueous solution it was relatively stable to carbonic acid. Upon treatment with strong hydrochloric acid (III) was cyclicized with the concomitant hydrolysis of the methoxy group to form 5-bromouracil. However, a weak acid, such as acetic, converted the salt into 4-keto-3,4-dihydro-2-methoxy-5-bromopyrimidine (IV); the methoxy group in this lactam was shown to be in the (2) position, since the compound gave the same type of Wheeler–Johnson color test as isocytosine.[6] A further argument in favor of the structure postulated for (III) is the similar behavior of analogous unsaturated β-ureidoacrylic acids having the proper geometrical configuration. These are stable only in the form of their salts, as on acidification the liberated acids immediately undergo cyclization.

The reaction of alkali on 2,4-dichloro-5-bromopyrimidine therefore proceeded according to the scheme



The lactam (IV) was probably an intermediate in the formation of the sodium salt (III) from (II) but the conditions of the experiment precluded any possibility of its isolation. In this connection it is interesting to note the remarkable ease with which (IV) was ruptured; a solution of sodium bicarbonate was sufficiently alkaline to bring about this change. A few other cases of ring rupture of pyrimidine lactams with the formation of ureidoacrylic acid derivatives have been recorded;[7] these, however, usually required strong alkali.

As might be expected, the behavior of 2,4-diethoxy-5-bromopyrimidine toward alkali was

(4) Hilbert and Johnson, THIS JOURNAL, **52**, 2001 (1930).

(5) The most comprehensive study appears to be the recent work of Lange and Sheibley, *ibid.*, **55**, 1188 (1933), on the hydrolysis of 2,4-dialkoxyquinazolines to 2-alkoxy-4-ketodihydroquinazolines with alkali; see also Baeyer and Oekonomides, *Ber.*, **15**, 2094 (1882); Asahina and Inubuse, *ibid.*, **65**, 61 (1932); Johnson and Moran, THIS JOURNAL, **37**, 2591 (1915), and Wheeler and Jamieson, *Am. Chem. J.*, **32**, 347 (1904).

(6) It is logical to expect, from a consideration of the composition of the colored precipitate [see Hantzsch, *Ber.*, **54**, 1267 (1921), and Redinger, THIS JOURNAL, **39**, 1059 (1917)] which is formed in this test, that appropriate pyrimidines having as substituents an alkoxy or substituted amino group in the (2) position would give an isocytosine color test, whereas if these substituents are in the (4) position the color test would be similar to that of cytosine. The application of the Wheeler–Johnson color test to such compounds thus affords a satisfactory means for obtaining information concerning the allocation of the groups in the ring. It should perhaps be emphasized that the purple colored precipitate formed from isocytosine is extremely sensitive to oxygen and is immediately discharged by shaking with air. Wheeler and Johnson, *J. Biol. Chem.*, **3**, 183 (1907), reported that it was discharged by an excess of barium hydroxide; this was true only because there was sufficient oxygen in the additional barium hydroxide to bring about the change.

(7) Hilbert, THIS JOURNAL, **54**, 2076 (1932).

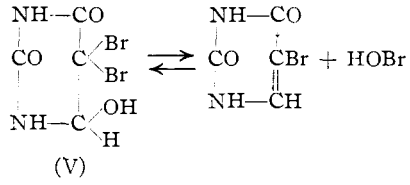
similar to that of the methoxy analog (II). The interaction of a solution of sodium hydroxide in ethyl alcohol and (I) resulted in the formation of 2,4-diethoxy-5-bromopyrimidine and the sodium salt of α-bromo-β-ethylisoureidoacrylic acid. In this particular case the latter, because of its extreme solubility in water, was difficult to purify and was not characterized as such but converted by acidification with acetic acid into 4-keto-3,4-dihydro-2-ethoxy-5-bromopyrimidine. Other 2,4-dialkoxypyrimidines would also be expected to interact with alkali, although the ease of hydrolysis and the product formed will depend largely upon the influence exerted by neighboring substituent groups.

Ammonia, in alcoholic solution, interacted with 2,4-dimethoxy-5-bromopyrimidine to form 2-methoxy-4-amino-5-bromopyrimidine. Proof of the structure of this compound was obtained by hydrolysis with hydrochloric acid. It yielded 5-bromocytosine, the crystallographic properties of which were identical with those of an authentic specimen. Although position 4 was predominantly attacked by ammonia, the reaction was not exclusively in this direction, as a small amount of a by-product was obtained which was probably the isomer 2-amino-4-methoxy-5-bromopyrimidine.

These reactions are of interest as they lend further confirmation to the idea that compounds containing the group —N=C(OR)— are chemically similar to the esters. In the pyrimidine series these reactions should prove particularly valuable as they suggest new methods of approach for the synthesis of naturally occurring pyrimidines. They also provide means for preparing previously unavailable intermediates, such as 2-keto-1,2-dihydro-4-ethoxypyrimidine, useful for the synthesis of nucleosides, as well as a method for the conversion of the synthetic alkoxy nucleosides to the amino analogs.

Bromination of Uracil and Cytosine

The use of 2,4-dichloro-5-bromopyrimidine in the above work necessitated the preparation of considerable quantities of 5-bromouracil. In general, this has previously been prepared by the degradation of 5,5-dibromo-6-hydroxy-5,6-dihydrouracil (V) in absolute alcohol. A more convenient method was suggested by a consideration of the reactions involved in the formation of (V) in the bromination of uracil in aqueous solution. It has never been adequately emphasized that a solution of (V) in water (or in this case in dilute acid) is in equilibrium with 5-bromouracil and



(V)

hypobromous acid as was shown by the fact that from a warm solution iodine was liberated from an aqueous solution of potassium iodide. At room temperature the equilibrium was shifted almost entirely toward the left, and on heating and destruction of hypobromous acid the reaction toward the right was favored. For preparative purposes the removal of hypobromous acid was most conveniently accomplished by simply concentrating the reaction mixture to dryness on a steam-bath. Under these conditions the acid generated in the bromination became sufficiently concentrated to interact with hypobromous acid to form water and bromine, which was expelled. This modification has been used with repeated success in the preparation of a variety of 5-bromopyrimidines.

The bromination of cytosine[8] in aqueous solution was studied as this appeared to offer the simplest and most direct method for the preparation of 5-bromocytosine[9] which was desired for purposes of comparison. This study has incidentally also afforded information on the nature of the consecutive steps involved in the formation of 5,5-dibromo-6-hydroxy-5,6-dihydrouracil by exhaustive bromination. When an aqueous solution of cytosine was cautiously treated with bromine water in the cold, 5-bromocytosine separated, which on further bromination redissolved and was then converted to 5,5-dibromo-6-hydroxy-5,6-dihydrocytosine, from which the amino group was readily hydrolyzed by the acid generated.

We wish to express our appreciation to Mrs. M. S. Sherman and Mrs. E. K. Rist for the microanalyses recorded.

Experimental

Preparation of 5-Bromouracil.—A suspension of 10 g. of uracil in 40 cc. of water in a porcelain evaporating dish

(8) Wheeler and Johnson, *Am. Chem. J.*, **29**, 501 (1903), brominated it in acetic acid and obtained a crystalline product which was not analyzed. One would infer from its properties and its behavior toward ammonia that it was the dibromohydroxy derivative of cytosine. Bromination in aqueous solution [*J. Biol. Chem.*, **3**, 183 (1907)] yielded 5,5-dibromo-6-hydroxy-5,6-dihydrouracil.

(9) This has been prepared by an indirect route by Wheeler and Johnson, *Am. Chem. J.*, **31**, 604 (1904), and Johnson, Johns and Heyl, *Am. Chem. J.*, **36**, 168 (1906).

was treated with 10 cc. of bromine. The mixture was agitated until permanently colored and then evaporated to dryness on a steam-bath. The yellowish crystalline residue (17 g.), which did not give a violet colored precipitate with a solution of barium hydroxide, indicating the absence of 5,5-dibromo-6-hydroxy-5,6-dihydrouracil, was decolorized with bone black and recrystallized twice from hot water. It separated as colorless prisms which melted with decomposition at 312°;[10] yield 13.5 g. (75% of the theoretical). The method was applied with equal ease to much larger quantities of uracil.

2,4-Dichloro-5-bromopyrimidine.—This has been prepared by Wheeler and Bristol[11] by the action of phosphorus pentachloride and phosphorus oxychloride on 5-bromouracil. The following modification was found to be more convenient and gave a larger yield.

A suspension of 121 g. of 5-bromouracil in 350 cc. of phosphorus oxychloride was heated in an oil-bath at 125° for five days. On the fourth day the reaction mixture was brown and the 5-bromouracil was rapidly dissolving; on the last day the solution was black, homogeneous and viscous and scarcely any hydrochloric acid was evolved. The excess phosphorus oxychloride was removed under diminished pressure and the viscous residue thoroughly cooled in an ice-bath and 500 g. of ice gradually added. A dark heavy oil separated which was removed with ether; the extracts were combined, washed with a solution of sodium carbonate and dried over calcium chloride. The ether was removed and the residue distilled under diminished pressure; b. p. 145–147° (78 mm.); yield 124 g. (86% of the theoretical). 2,4-Dichloro-5-bromopyrimidine is a colorless practically odorless oil, has a very corrosive action on the skin and is also a lachrymator.

Sodium Salt of α-Bromo-β-methylisoureidoacrylic Acid.—In one experiment 60 g. of 2,4-dichloro-5-bromopyrimidine was dissolved in 50 cc. of absolute methyl alcohol and treated with a solution of 21 g. of sodium in 300 cc. of methyl alcohol. There was a vigorous instantaneous reaction and sodium chloride precipitated. The reaction mixture was cautiously refluxed for two hours and the salt removed by filtration and thoroughly washed with hot methyl alcohol. The excess alcohol was removed by distillation on a steam-bath and the residual oil on standing solidified to a crystalline mass. After trituration with 150 cc. of water, the solid was filtered and dried; yield 58 g. Later work indicated that this was probably a mixture of the sodium salt of α-bromo-β-methylisoureidoacrylic acid and 2,4-dimethoxy-5-bromopyrimidine. The former was obtained pure by recrystallizing from alcohol; it separated as colorless crystals melting with decomposition at about 250°; yield 25 g. By this procedure the 2,4-dimethoxy-5-bromopyrimidine, unless recovered from the alcohol, was lost.

In another experiment the conditions were considerably milder and the alkoxypyrimidine was recovered from the sodium salt by sublimation. A solution of 6 g. of 2,4-dichloro-5-bromopyrimidine in 10 cc. of absolute methyl alcohol was treated with 2.2 g. of sodium in 30 cc. of methyl alcohol. After standing for a short time the salt was removed and the filtrate, after the addition of a small amount of water, was allowed to stand overnight in an ice chest. The alcohol was removed under diminished pressure at room temperature and the solid residue triturated with a small amount of water and dried. It was heated at 130° at 1 mm. pressure in a modification of Kempf's[12] vacuum sublimation apparatus (see Fig. 1). 2,4-Dimethoxy-5-bromopyrimidine sublimed into flask B; yield 1.5 g. The residue in A was triturated with a small amount of water and recrystallized from methyl alcohol, from which it separated in a columnar, somewhat prismatic form; m. p. 248° (decomp., the exact temperature depending on the rate of heating). The crystals were apparently birefringent and exhibited parallel extinction.

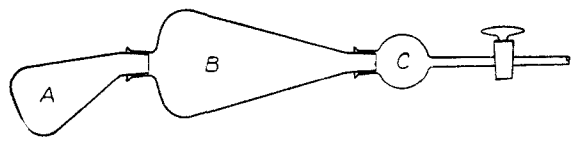


Fig. 1.—This was designed for the sublimation of relatively large quantities of material for which the apparatus of Kempf was inadequate. Flask A had a capacity of 150 cc. and B of 600 cc. A was heated in a hot gas oven against which the shoulder of B fitted snugly. This has been used repeatedly with success for the separation of solids when there was an appreciable difference in their vapor pressures.

The low index of refraction was 1.53 and the high index about 1.74. Sodium α-bromo-β-methylisoureidoacrylate was very soluble in hot water and moderately soluble in hot alcohol. All attempts to convert the sodium salt into the free acid were without success because of immediate ring closure under acidic conditions. On digesting with hot concentrated hydrochloric acid it gave 5-bromouracil. It responded to the Wheeler–Johnson color test, giving in this case a clear blue color which, upon shaking with air, immediately disappeared. The same colored precipitate was obtained when the bromine was removed by either aspirating in the cold or by boiling.

Anal. Calcd. for $C_5H_6O_3N_2BrNa$: C, 24.49; H, 2.47; N, 11.44; Na, 9.30; OCH_3, 12.66. Found: C, 25.12; H, 2.85; N, 11.42; Na, 8.98; OCH_3, 12.25.

4-Keto-3,4-dihydro-2-methoxy-5-bromopyrimidine.—A solution of 0.45 g. of the sodium salt of α-bromo-β-methylisoureidoacrylic acid in 10 cc. of water was acidified with 5 drops of acetic acid. Colorless needles immediately separated which were filtered and dried; yield, 0.32 g. It was recrystallized twice from hot water and melted with decomposition at 190°. It was insoluble in cold water, soluble in the hot, and slightly soluble in hot alcohol. It gave the same type of Wheeler–Johnson color test as that described above for the isourea derivative.

Anal. Calcd. for $C_5H_5O_2N_2Br$: C, 29.27; H, 2.46; N, 13.67; OCH_3, 15.14. Found: C, 29.12; H, 2.52; N, 13.64; OCH_3, 14.82.

Hydrolysis of 4-Keto-3,4-dihydro-2-methoxy-5-bromopyrimidine with Hydrochloric Acid.—It was treated with concentrated hydrochloric acid and evaporated to dryness

(10) All temperatures were corrected.

(11) Wheeler and Bristol, *Am. Chem. J.*, **33**, 443 (1905).

(12) Kempf, *J. prakt. Chem.*, [2] **78**, 206 (1908).

on the steam-bath; this treatment was repeated twice. The 5-bromouracil was recrystallized from water; m. p. 305°.

Anal. Calcd. for $C_4H_3O_2N_2Br$: C, 25.14; H, 1.58. Found: C, 25.17; H, 1.83.

Reaction of 4-Keto-3,4-dihydro-2-methoxy-5-bromopyrimidine with Sodium Bicarbonate.—A solution of 0.25 g. of sodium bicarbonate in 10 cc. of water was brought to a boil and 0.2 g. of the lactam added. The solution was cooled and evaporated to half volume. The crystals that separated were filtered and recrystallized from water. They melted with decomposition at 248° and were shown to be the sodium salt of α-bromo-β-methylisoureidoacrylic acid.

Anal. Calcd. for $C_5H_6O_3N_2BrNa$: N, 11.44. Found: N, 11.56.

Preparation of 2,4-Dimethoxy-5-bromopyrimidine.—The same proportions as well as the same reactions and solvent were used in this experiment as those already described for the preparation of the sodium salt of α-bromo-β-methylisoureidoacrylic acid. After removal of the salt, the filtrate was immediately concentrated under diminished pressure at room temperature. The oily residue was treated with water and extracted with ether. After drying over calcium chloride, the ether was distilled and the residue sublimed under a pressure of 1 mm. at 100°. 2,4-Dimethoxy-5-bromopyrimidine sublimed in the form of prisms and melted at 63–64°; yield 80% of the theoretical. It was sparingly soluble in water and very soluble in organic solvents. The Wheeler–Johnson color test was negative. A small amount of the sodium salt of the isourea derivative was also formed under these conditions.

Anal. Calcd. for $C_6H_7O_2N_2Br$: C, 32.88; H, 3.22; N, 12.79. Found: C, 32.77; H, 3.15; N, 12.79.

In order to obtain 2,4-dimethoxy-5-bromopyrimidine in good yield, it is not only essential that it be removed as quickly as possible from the alkaline solution but that heating also be avoided at this stage.

Action of Alkali on 2,4-Dimethoxy-5-bromopyrimidine.—One gram of 2,4-dimethoxy-5-bromopyrimidine was dissolved in a solution of 60% alcohol containing 2.5 g. of sodium hydroxide. This was heated on the steam-bath until most of the solvent was removed. The oily residue was treated with boiling absolute alcohol and filtered. The sodium salt of α-bromo-β-methylisoureidoacrylic acid separated on cooling; m. p. 248° (dec.); yield 0.62 g. A similar result was obtained when the pyrimidine was hydrolyzed with a 15% solution of sodium hydroxide in absolute methyl alcohol.

Action of Ammonia on 2,4-Dimethoxy-5-bromopyrimidine.—A mixture of 2 g. of 2,4-dimethoxy-5-bromopyrimidine and 10 cc. of absolute methyl alcohol, saturated at 0° with dry ammonia, was heated in a bomb tube at 80° for ninety-six hours. The resulting clear solution was evaporated to dryness on the steam-bath. The colorless crystalline cake, which melted at 115–133°, was recrystallized twice from water. 2-Methoxy-4-amino-5-bromopyrimidine separated in small prisms, melted at 134–136°, and was quite soluble in hot water and alcohol. It did not give a Wheeler–Johnson color test when the bromine was removed by aspiration in the cold; however, when the bromine was removed by boiling, it gave an excellent isocytosine color test, implying that the amino group in the bromination product was very labile and in the hot acid medium was hydrolyzed to 2-keto-5,5-dibromo-6-hydroxy-1,2,5,6-tetrahydro-2-methoxypyrimidine.

Anal. Calcd. for $C_5H_6ON_3Br$: C, 29.41; H, 2.96; N, 20.60. Found: C, 29.42; H, 3.09; N, 20.75.

5-Bromocytosine.—A solution of 0.3 g. of 2-methoxy-4-amino-5-bromopyrimidine in 10 cc. of concentrated hydrochloric acid was evaporated to dryness on a steam-bath; this operation was repeated twice, since the methoxy group in this case is rather firmly attached. The colorless crystalline residue consisted of the hydrochloride of 5-bromocytosine. It was dissolved in water, filtered and made faintly ammoniacal. It separated as prisms and was recrystallized from 50% aqueous alcohol; decomposition at 254° was to a black solid, varying somewhat with the rate of heating. 5-Bromocytosine was soluble in water, practically insoluble in most other solvents, and gave a Wheeler–Johnson color test similar to that of cytosine. Mr. Jefferson very kindly made a crystallographic examination of the crystals. They showed parallel extinction, and had a high birefringence, and there was a good rectangular cleavage. The minimum index of refraction was 1.54 and the maximum greater than 1.74. The crystallographic data obtained on 5-bromocytosine, prepared by the bromination of cytosine, were the same as the above. The mixed decomposition point with an authentic specimen of 5-bromocytosine decomposing at 245–255° was unchanged.

Anal. Calcd. for $C_4H_4ON_3Br$: C, 25.27; H, 2.12; N, 22.12. Found: C, 25.57; H, 2.52; N, 21.95.

Preparation of 5-Bromocytosine from Cytosine.—A solution of 0.50 g. of cytosine in 10 cc. of water was treated with bromine until the yellowish crystalline product which separated appeared to redissolve upon further addition of bromine. It was filtered and recrystallized from warm (50°) slightly ammoniacal water and separated as needles; decomposition at 245–255° (dependent upon the rate of heating); yield 0.16 g.

Anal. Calcd. for $C_4H_4ON_3Br$: C, 25.27; H, 2.12; N, 22.12. Found: C, 25.50; H, 2.13; N, 22.34.

An aqueous solution of 5-bromocytosine was neutral toward litmus and decolorized bromine; it did not give a purple precipitate with barium hydroxide solution in the cold or when boiled with dilute acid, indicating the absence of the dibromohydroxy derivative. It did not respond to the Wheeler–Johnson color test when the bromine was removed in the cold; an excellent test was obtained when the bromine was removed by boiling the solution.

The original filtrate from 5-bromocytosine was cooled in the ice chest and deposited crystalline plates; yield 0.13 g.; decomposition with evolution of gas at 175–180°. It did not decolorize bromine water. The analysis agreed with that for 5,5-dibromo-6-hydroxy-5,6-dihydrocytosine hydrobromide.

Anal. Calcd. for $C_4H_6O_2N_3Br_3$: N, 11.38. Found: N, 11.59.

2,4-Diethoxy-5-bromopyrimidine.—This was prepared in a manner similar to that already described for 2,4-dimethoxy-5-bromopyrimidine. The sublimed product consisted of prisms melting at 72–74°; yield 55% of the theoretical.

Anal. Calcd. for $C_8H_{11}O_2N_2Br$: C, 38.86; H, 4.49; N, 11.34. Found: C, 39.12; H, 4.28; N, 11.17.

4-Keto-3,4-dihydro-2-ethoxy-5-bromopyrimidine.—To a solution of 16.5 g. of 2,4-dichloro-5-bromopyrimidine in 10 cc. of absolute ethyl alcohol was carefully added 5.89 g. of sodium in 50 cc. of alcohol. After the vigorous reaction had subsided, the reaction mixture was refluxed for two hours, filtered, and the alcohol removed under diminished pressure on a steam-bath. The residue was diluted with water and extracted with ether; the ether extract yielded 2.5 g. of 2,4-diethoxy-5-bromopyrimidine. On acidification of the aqueous extract with acetic acid 4-keto-3,4-dihydro-2-ethoxy-5-bromopyrimidine immediately precipitated. This was filtered and recrystallized from water; it separated as colorless needles; yield 8.4 g.; sintered at 160° and melted at 163°. It gave a Wheeler–Johnson color test similar to that of isocytosine when the bromine was removed by aspiration in the cold.

Anal. Calcd. for $C_6H_7O_2N_2Br$: C, 32.88; H, 3.22; N, 12.78; OC_2H_5, 20.57. Found: C, 33.28; H, 3.17; N, 12.93; OC_2H_5, 20.53.

Summary

The alkoxy groups in 2,4-dialkoxypyrimidines have been found to be sensitive toward alkali and in the particular case of 2,4-dialkoxy-5-bromopyrimidine, the alkoxy group in the 4 position was hydrolyzed to give the intermediate lactam, 4-keto-3,4-dihydro-2-alkoxy-5-bromopyrimidine, which under the alkaline conditions suffered ring rupture to yield the sodium salt of α-bromo-β-alkylisourcidoacrylic acid. This salt was readily cyclicized to the lactam by acid. Ammonia was also found to interact with 2,4-dialkoxypyrimidines and with 2,4-dimethoxy-5-bromopyrimidine; replacement of the methoxy group in 4 position by an amino group was effected. These reactions suggest new methods of approach for the synthesis of naturally occurring pyrimidines.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VASSAR COLLEGE]

α,α'-Dimethyl-α-phenylsuccinic Acid

BY H. MARJORIE CRAWFORD

In some earlier work, Smith and Crawford[1] obtained by the oxidation of 2,3,5,6-tetramethyl-3-phenylcyclohexene-5-dione-1,4 an acid which they regarded as α,α'-dimethyl-α-phenylsuccinic acid. This acid was not previously known, and the present paper is the result of attempts to synthesize it.

Bone and Sprankling[2] give a review of methods for the preparation of substituted succinic acids. Two of the methods they mention were tried without success. The first method, heating the corresponding dibromide with potassium cyanide, gave only tars. In the second trial the following series of reactions was carried out

$$C_6H_5CH(OH)COOH \xrightarrow{PBr_3,\ then\ C_2H_5OH} C_6H_5CHBrCOOC_2H_5$$

$$CH_2(COOC_2H_5)_2 \xrightarrow{Na,\ then\ CH_3I} CH_3CH(COOC_2H_5)_2$$

$$CH_3C(COOC_2H_5)_2\ (Na) + C_6H_5CHBrCOOC_2H_5 \longrightarrow C_6H_5{-}CHCOOC_2H_5\ |\ CH_3{-}C(COOC_2H_5)_2$$

This triester, which was not known, was identified by analysis, molecular weight determinations, and by hydrolysis to α-methyl-α'-phenylsuccinic acid which had previously been made.[3] Attempts to introduce another methyl group by means of sodium and methyl iodide were unsuccessful.

The method which finally gave the desired acid was the reaction between α-bromopropionic ester and the sodium derivative of α-phenylpropionitrile, followed by hydrolysis.

$$C_6H_5C(CH_3)CN\ (Na) + CH_3CHBrCOOC_2H_5 \longrightarrow$$

$$C_6H_5{-}\underset{|}{\overset{CH_3}{C}}{-}CN \longrightarrow C_6H_5{-}\underset{|}{\overset{CH_3}{C}}{-}COOH$$

$$CH_3{-}CHCOOC_2H_5 \qquad CH_3{-}CHCOOH$$

The acid, as first obtained by hydrolysis, melted around 145°. The two racemic forms, when finally separated, melted at 170–172° and 159–160°. The higher melting form is identical with the acid obtained by the oxidation of 2,3,5,6-tetramethyl-3-phenylcyclohexene-5-dione-1,4.[1]

No attempt was made to resolve the two acids into optically active forms.

Experimental

Mandelic Acid.—This was prepared from benzaldehyde and sodium cyanide by the method outlined in "Organic Syntheses."[4]

(1) Smith and Crawford, THIS JOURNAL, **50**, 869 (1928).

(2) Bone and Sprankling, *J. Chem. Soc.*, **75**, 839 (1899).

(3) Zelinsky, *Ber.*, **24**, 1878 (1891).

(4) "Organic Syntheses," John Wiley and Sons, Inc., New York, Vol. VI, p. 58.