2,4-Dihydroxy-6-nitrobenzimidazole (VI).—Two millimoles (417 mg.) of 2-hydroxy-4-methoxy-6-nitrobenzimidazole (V) did not dissolve in 6 ml. of hydrobromic acid (48%) after two hours of refluxing. Solution was effected by adding 5 ml. of glacial acetic acid. The solution was refluxed for 4 hours, cooled and poured into 100 ml. of water. The precipitate of 2,4-dihydroxy-6-nitrobenzimidazole (364 mg., 93%), was collected, washed with water and dried. It crystallized from 10% ethanol solution, m.p. 338° dec.

6-Amino-2-hydroxy-4-methoxybenzimidazole (VII).—Reduction of 386 mg. (2 mmoles) of 2-hydroxy-4-methoxy-6-nitrobenzimidazole (V) in 100 ml. of ethanol was accomplished as described for II. The 6-amino-2-hydroxy-4-methoxybenzimidazole was recrystallized from a minimum volume of hot water and dried at 110°, m.p. 176–178°.

6-Hydroxy-4-nitrobenzimidazole (VIII).—A solution of 2.39 g. (12.4 mmoles) of 6-methoxy-4-nitrobenzimidazole[2] in 15 ml. of hydrobromic acid (48%) was refluxed for 5 hours, diluted with 140 ml. of hot water and clarified with Darco. The hot filtrate was adjusted to *p*H 5 by addition of 28% ammonium hydroxide solution and cooled. The precipitated 6-hydroxy-4-nitrobenzimidazole was collected, washed with water and dried in a vacuum oven at 70° overnight. The yield was 1.56 g. (70%; crystallized from 25% ethanol (125 ml.), m.p. 288°.

4-Amino-6-hydroxybenzimidazole (IX).—The reduction of 300 mg. of 6-hydroxy-4-nitrobenzimidazole in 100 ml. of ethanol was conducted in the same manner as II. The crude 4-amino-6-hydroxybenzimidazole was crystallized from a small volume (6–10 ml.) of water, m.p. 250° dec.

5-Methoxy-7-nitroquinoxaline (X).—A solution of 1.04 g. (6 mmoles) of 2,3-diamino-5-nitroanisole in 75 ml. of ethanol was treated with 4 ml. of a 30% aqueous solution of glyoxal. After refluxing for 2 hours, the solution was cooled and 672 mg. (58%) of 5-methoxy-7-nitroquinoxaline separated. It was recrystallized from ethanol (50 ml.) with the aid of Nuchar, m.p. 177–179°.

This compound was also obtained when an aqueous solution of equimolar quantities of the base and glyoxal bisulfite was heated on the steam-bath for 30 min. The hot reaction mixture was filtered by gravity through coarse filter paper to remove a resinous by-product. The filtrate was made slightly basic by addition of 28% ammonium hydroxide solution in order to precipitate the quinoxaline.

7-Amino-5-methoxyquinoxaline (XI).—This compound was obtained by reduction of 410 mg. (2 mmoles) of 5-methoxy-7-nitroquinoxaline (X) as described for II. It was recrystallized from a minimum volume of hot water (Darco), m.p. 199–201°.

2,3-Dimethyl-5-methoxy-7-nitroquinoxaline (XII).—A mixture of 1.83 g. (10 mmoles) of 2,3-diamino-5-nitroanisole and 3.4 g. (40 mmoles) of diacetyl in 175 ml. of ethanol was refluxed for one hour. The dimethylquinoxaline separated as light brown needles on cooling; crystallized from ethanol (Nuchar), m.p. 218–220°.

7-Amino-2,3-dimethyl-5-methoxyquinoxaline (XIII).—By reduction of 466 mg. (2 mmoles) of 2,3-dimethyl-5-methoxy-7-nitroquinoxaline in 80 ml. of ethanol in the manner described for II, 421 mg. of 7-amino-2,3-dimethyl-5-methoxyquinoxaline was obtained. This was recrystallized from 10% ethanol solution, m.p. 226–229°.

2,3-Dimethyl-7-methoxy-5-nitroquinoxaline (XIV).—A suspension of 549 mg. (3 mmoles) of 3,4-diamino-5-nitroanisole[6] in 50 ml. of 10% acetic acid was stirred and heated on the steam-bath. A solution of 260 mg. of diacetyl in 2 ml. of 10% acetic acid was added dropwise. Heating and stirring were continued for 30 min. after all of the diacetyl had been added. The resulting solution was cooled. The precipitate (652 mg., 93%) of 2,3-dimethyl-7-methoxy-5-nitroquinoxaline was collected, washed with water and dried. It was recrystallized from 50% ethanol, m.p. 155–156°.

Acknowledgments.—The authors are indebted to the Damon Runyon Memorial Fund and the American Cancer Society for support of this work.

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[CONTRIBUTION FROM THE OHIO STATE UNIVERSITY RESEARCH FOUNDATION]

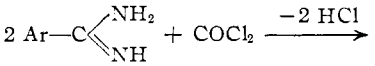
Triazines. XIV. The Extension of the Pinner Synthesis of Monohydroxy-*s*-triazines to the Aliphatic Series. 2,4-Dimethyl-*s*-triazine[1-3]

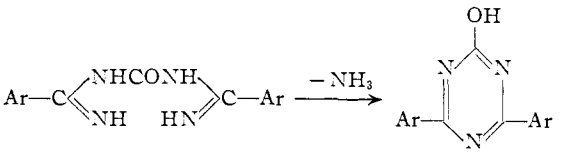
BY HANSJUERGEN SCHROEDER AND CHRISTOPH GRUNDMANN

RECEIVED DECEMBER 5, 1955

Hitherto the Pinner synthesis of monohydroxy-*s*-triazines has been limited to the preparation of 2,4-diaryl-6-hydroxy-triazines. This reaction has now been extended to the aliphatic series using α-chlorinated amidines. By hydrogenolysis dialkyl-hydroxy-triazines are obtained which are converted into a series of derivatives. From 2-chloro-4,6-dimethyl-*s*-triazine 2,4-dimethyl-*s*-triazine, the first known dialkyl-triazine, is obtained.

The synthesis of 2,4-diaryl-6-hydroxy-*s*-triazines from two moles of an arylamidine and one mole of phosgene has been described by Pinner and coworkers.[4-6] In the first step of this reaction an N,N′-bisimidylurea is formed which when heated above its m. p. undergoes ring closure to the desired hydroxy-*s*-triazine with elimination of ammonia.





It has now been found in a more detailed study of the reaction of benzamidine that the intermediate urea is obtained exclusively only when working with ice–salt cooling. However, if the reaction is carried out without cooling, the reaction product contains, beside the intermediate urea, some 2,4-diphenyl-6-hydroxy-*s*-triazine, the amount of the latter increasing with the reaction temperature. In the case of *p*-chlorobenzamidine only the hydroxy-*s*-triazine has been obtained even at a temperature of −10°.[7]

(1) This article is based on work performed under project 116-B of The Ohio State University Research Foundation sponsored by the Olin Mathieson Chemical Corporation, Baltimore, Md.

(2) Presented before the Organic Division of The American Chemical Society at the 128th Meeting at Minneapolis, Minn., Sept. 12, 1955.

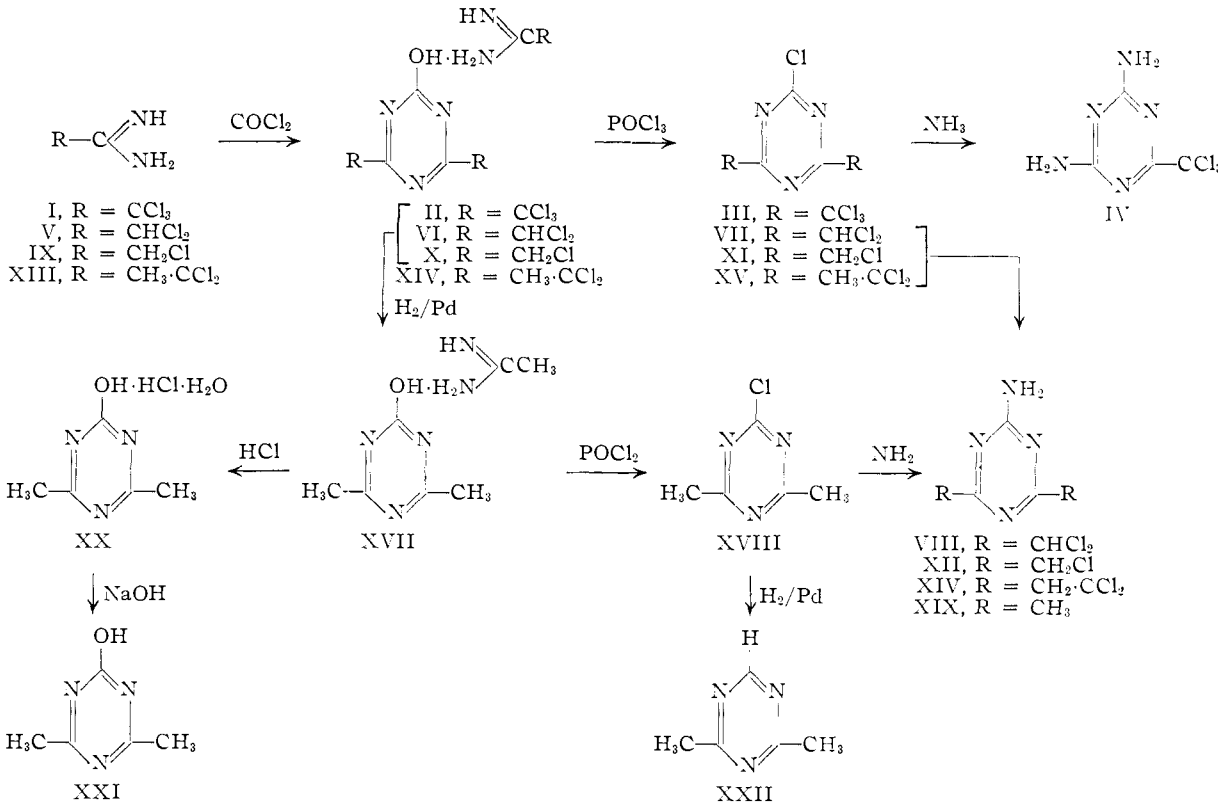
(3) Preceding communication: Ch. Grundmann and A. Kreutzberger, THIS JOURNAL, **77**, 6559 (1955).

(4) A. Pinner, *Ber.*, **23**, 2919 (1890).

(5) T. Rappetort, *ibid.*, **34**, 1990 (1901).

(6) A. Pinner, *ibid.*, **28**, 473 (1895).

(7) Ch. Grundmann and H. Schroeder, *Ber.*, **87**, 747 (1954).



Pinner attempted to extend this method to the synthesis of 2,4-dialkyl-6-hydroxy-*s*-triazines, but his experiments using propionamidine and caproamidine failed.[4] The same negative result was obtained with acetamidine hydrochloride which failed to react at all with phosgene. This method then appeared to be strictly limited to the preparation of 2,4-diaryl-6-hydroxy-*s*-triazines.

However, it was supposed that alkanamidines could be employed successfully if their alkyl groups are converted to electron-attracting groups by introduction of certain polar atoms. In this investigation we selected chloro-substituted alkylamidines for study since we anticipated that the inductive effect of the chlorinated methyl group would be strong enough to facilitate cyclization reaction of the amidine with phosgene to the desired triazine derivative.

Trichloroacetamidine (I) was selected as a model compound. Its reaction with phosgene was carried out in water at *p*H 8. As expected two moles of the amidine reacted with one mole of phosgene to form the desired 6-hydroxy-2,4-bis-(trichloromethyl)-*s*-triazine. However, in contrast to the 2,4-bis-aryl-6-hydroxy-*s*-triazines,which are weaker acids, it separated from the reaction mixture in form of its salt with one mole of trichloroacetamidine (II).

The presence of a triazine ring in our product was demonstrated by conversion of the 6-hydroxy-2,4-bis-(trichloromethyl)-*s*-triazine trichloroacetamidine salt (II) to the 6-chloro-2,4-bis-(trichloromethyl)-*s*-triazine (III) in 98% yield by refluxing with phosphorus oxychloride. Amination of this product not only exchanged an amino group for the chlorine in the 6-position but also for one of the trichloromethyl groups. The product, 4,6-diamino-2-trichloromethyl-*s*-triazine (IV), had been previously prepared by Weddige[8] from 2,4,6-tris-trichloromethyl-*s*-triazine and ammonia. A mixed melting point of an authentic sample with the compound obtained by our procedure proved its assumed structure.

In order to establish the scope of this reaction, we tried the same synthesis with dichloroacetamidine (V). Unlike the trichloroacetamidine it could not be obtained directly from the corresponding nitrile and liquid ammonia; the reaction in this case produced only dark resins. But we succeeded in obtaining its hydrochloride, which was phosgenated to the expected reaction product, the dichloroacetamidine salt of 2,4-bis-(dichloromethyl)-6-hydroxy-*s*-triazine (VI). The chlorination of this salt produced 6-chloro-2,4-bis-(dichloromethyl)-*s*-triazine (VII). When the same treatment with alcoholic ammonia was applied to this compound, only the ring chlorine was replaced by ammonia; both dichloromethyl groups remained unattacked.

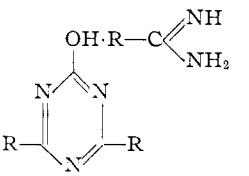
An analogous series of reactions was carried out using monochloroacetamidine hydrochloride (IX) to see if a single chlorine atom on the methyl group would produce the cyclization reaction of an alkanamidine with phosgene. In this case the expected hydroxy-*s*-triazine salt X was obtained in an even higher yield than in the corresponding reaction of dichloroacetamidine hydrochloride.

That in general aliphatic amidines with at least one chlorine atom on the carbon atom adjacent to the amidine group would react with phosgene in the same manner was shown by the reaction of α,α-di-

(8) A. Weddige, *J. prakt. Chem.*, [2] **33**, 8 (1886).

TABLE I

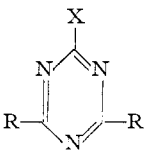
MONOHYDROXY-*s*-TRIAZINE-AMIDINE SALTS



	R	M.p., °C.	Yield, %	Formula	Molecular weight	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
II	CCl_3	222–224	75	$C_7H_4N_5Cl_9O$	493.3	17.04	17.63	0.82	1.22	14.20	14.36	64.69	63.52
VI	$CHCl_2$	241–245	40	$C_7H_7N_5Cl_6O$	389.9	21.56	21.70	1.81	2.04	17.96	17.63	54.56	54.04
X	CH_2Cl	150	63	$C_7H_{10}N_5Cl_3O$	286.6	29.34	29.35	3.51	3.54	24.44	24.06	37.12	36.89
XVII	CH_3	212–213	60–70	$C_7H_{13}N_5O$	183.2	45.88	45.83	7.15	7.06	38.23	38.30		
XIV	CH_3CCl_2	212–214	51	$C_{10}H_{13}N_5OCl_6$	432.0	27.80	28.27	3.03	3.32	16.21	16.22	49.25	49.05

TABLE II

6-CHLORO-*s*-TRIAZINES AND THEIR AMINATION PRODUCTS



R	X	M.p., °C.	Yield, %	Formula	Molecular weight	Carbon, % Calcd.	Carbon, % Found	Hydrogen, % Calcd.	Hydrogen, % Found	Nitrogen, % Calcd.	Nitrogen, % Found	Chlorine, % Calcd.	Chlorine, % Found
CCl_3	Cl	56	98	$C_5N_3Cl_7$	350.2	17.04	17.10			12.00	11.97	70.86	70.83
$CHCl_2$	Cl	114	72	$C_5H_2N_3Cl_5$	281.4	21.35	21.40	0.72	0.77	14.94	14.99	63.02	62.75
CH_2Cl	Cl	33.5	53	$C_5H_4N_3Cl_3$	212.5	28.26	28.35	1.89	2.23	19.77	19.74	50.06	49.75
CH_3	Cl	64	35	$C_5H_6N_3Cl$	143.6	41.82	41.76	4.21	4.30	29.27	29.21	24.70	24.65
CH_3CCl_2	Cl	104–105	89	$C_7H_6N_3Cl_5$	309.4	27.17	27.15	1.96	1.77	13.58	13.48	57.29	57.30
$CHCl_2$	NH_2	142	81	$C_5H_4N_4Cl_4$	261.9	22.93	23.14	1.53	1.62	21.39	20.69	54.15	53.88
CH_2Cl	NH_2	105	75	$C_5H_6N_4Cl_2$	193.1	31.11	31.32	3.13	3.35	29.03	28.25	36.74	36.82
CH_3	NH_2	171	90	$C_5H_8N_4$	124.2	48.37	48.43	6.50	6.59	45.13	44.89		
CH_3CCl_2	NH_2	162	90	$C_7H_8N_4Cl_4$	290.0					19.32	19.39		
CCl_3	$N(CH_3)_2$	120	89	$C_7H_6N_4Cl_6$	358.9	23.43	22.98	1.68	1.85	15.61	15.44	59.28	59.72
$CHCl_2$	$N(CH_3)_2$	78	82	$C_7H_8N_4Cl_4$	290.0	29.00	29.36	2.78	2.82	19.32	19.18	48.91	48.87
CH_2Cl	$N(CH_3)_2$	34	77	$C_7H_{10}N_4Cl_2$	221.1	38.02	37.90	4.56	4.85	25.32	24.82	32.07	31.98
CCl_3	$N(CH_2CH_2)$	99	86	$C_7H_4N_4Cl_6$	356.9	23.56	23.56	1.13	1.07	15.70	15.65	59.61	59.52
CH_2Cl	$N(CH_2CH_2)$	60	83	$C_7H_8N_4Cl_2$	219.1	38.37	38.47	3.68	3.76	25.58	25.65	32.37	32.22
CH_3	$N(CH_2CH_2)$	94	81	$C_7H_{10}N_4$	150.2	55.98	56.04	6.71	6.90	37.31	37.35		

chloropropionamidine hydrochloride (XIII) with phosgene to give the expected hydroxy-*s*-triazine salt (XIV) in a satisfactory yield. Chlorination of XIV and amination of the monochloro-*s*-triazine (XV) thus obtained proceeded without difficulty.

Since a particular object of this investigation was the preparation of dialkyl-*s*-triazine derivatives, the dehalogenation of the 2,4-bis-(chloroalkyl)-6-hydroxy-*s*-triazines was then investigated. All three hydroxy-*s*-triazine salts (II, VI, X) obtained by phosgenation of the different chloroacetamidines were dechlorinated readily by hydrogenation with a palladium–carbon catalyst in the presence of triethylamine. In each case the desired 2,4-dimethyl-6-hydroxy-*s*-triazine acetamidine salt (XVII) was obtained. Table I lists the physical and analytical data of the hydroxy-*s*-triazine salts. When XVII was carried through the same sequence of reactions as the 2,4-bis-(chloroalkyl)-6-hydroxy-*s*-triazine salts, some difficulty was encountered in obtaining the monochloro-*s*-triazine. When refluxed with thionyl chloride and a catalytic amount of phosphorus pentachloride, XVII gave only high melting decomposition products. Boiling phosphorus oxychloride produced only traces of the desired compound. However, the use of phosphorous oxychloride and triethylamine led to a moderate yield of 6-chloro-2,4-dimethyl-*s*-triazine (XVIII). This compound is a lachrymator with a strong mouse odor and was aminated easily to the known 2-amino-4,6-dimethyl-*s*-triazine (XIX).[9]

A final proof for our assignment of a salt structure to the reaction products of the phosgenation of chloroalkanamidines was provided by conversion of the dehalogenated hydroxy-*s*-triazine salt XVII in two steps to the free 2,4-dimethyl-6-hydroxy-*s*-triazine (XXI). Hydrogen chloride precipitated the hydrochloride XX of the dimethyl-hydroxy-*s*-triazine from an alcoholic solution of XVII, demonstrating the amphoteric character of the hydroxy-*s*-triazine. Treatment of XX with an equimolar amount of alcoholic sodium hydroxide produced the desired 2,4-dimethyl-6-hydroxy-*s*-triazine (XXI).

The preparation of 2-chloro-4,6-dimethyl-*s*-triazine (XVIII) led us to attempt its dechlorination to one of the unknown simple triazine derivatives, 2,4-dimethyl-*s*-triazine (XXII). This was accomplished successfully by hydrogenation with a 10% palladium–carbon catalyst in the presence of triethylamine, after preliminary experiments with magnesium, calcium or barium oxides had failed. Ether was used as the solvent because of the high vapor pressure of the 2,4-dimethyl-*s*-triazine (XXII). It formed an extremely hygroscopic dihydrochloride which could be isolated only as its monohydrate. All five monochloro-*s*-triazines re-

(9) N. Tscherven-Iwanoff, *J. prakt. Chem.*, [2] **46**, 146 (1892).

acted readily with ammonia as shown above and with amines such as dimethylamine and ethylenimine to give the corresponding amino-*s*-triazines. Physical and analytical data for the chloro compounds and the products of the performed reactions are compiled in Table II.

Acknowledgment.—We are very much indebted to the Olin Mathieson Chemical Corporation for their generous support of this work.

Experimental[10]

Starting Materials. Nitriles.—Trichloroacetonitrile[11] was prepared from commercial trichloroacetamide by dehydration with P_2O_5. Dichloroacetonitrile[12] was obtained from commercial ethyl dichloroacetate *via* dichloroacetamide.[13] α,α-Dichloropropionitrile was obtained from commercial sodium α,α-dichloropropionate by conversion through the acid and the ethyl ester to the amide which was dehydrated with P_2O_5.[14]

Imidic Acid Ester Hydrochlorides.—Ethyl dichloroacetimidate[15] and ethyl chloroacetimidate[16] were obtained as hydrochlorides from the ether solutions of the required nitrile and an equimolar amount of ethanol by saturating with HCl. This method failed in the case of ethyl α,α-dichloropropionimidate hydrochloride which was formed in a 99% yield by reaction of the equimolar amounts of α,α-dichloropropionitrile, ethanol and HCl, m.p. 71°. Analytical data could not be obtained because it was extremely hygroscopic and decomposition took place after a short period of time at room temperature. It was utilized immediately for the preparation of α,α-dichloropropionamidine-HCl.

Amidines.—Trichloroacetamidine (I) was obtained according to Dachlauer[17] by the reaction of trichloroacetonitrile and liquid ammonia in 99% yield, m.p. 44° after recrystallization from petroleum ether. Dichloroacetamidine hydrochloride (V), monochloroacetamidine hydrochloride (IX)[18] and α,α-dichloropropionamidine hydrochloride (XIII) were synthesized by treatment of the corresponding imidic acid ester with 5% alcoholic ammonia as follows. To 400 ml. of 5% alcoholic ammonia was added with stirring at −5° one mole of the required ethyl imidate. The mixture was then kept for 4 hr. at 40° and the precipitate of NH_4Cl was filtered off. The filtrate was evaporated almost to dryness and the amidine hydrochloride was precipitated by addition of 500 ml. of ether. For purification the products were dissolved in ethanol and precipitated with ether.

Monochloroacetamidine.—HCl, m.p. 101–103°, yield 30%.

Dichloroacetamidine.—HCl, m.p. 133°, yield 60%. *Anal.* Calcd. for $C_2H_5N_2Cl_3$ (163.5): C, 14.71; H, 3.08; N, 17.14; Cl, 65.08. Found: C, 14.74; H, 3.13; N, 17.08; Cl, 64.92.

α,α-Dichloropropionamidine.—HCl, m.p. 132°, yield 10%. *Anal.* Calcd. for $C_3H_7N_2Cl_3$ (177.5): C, 20.30; H, 3.98; N, 15.78; Cl, 59.94. Found: C, 20.17; H, 4.33; N, 15.81; Cl, 59.49.

The following procedures are representative of the syntheses performed.

Phosgenation of Chloroalkanamidines. 6-Hydroxy-2,4-bis-(trichloromethyl)-*s*-triazine Trichloroacetamidine Salt (II).—An amount of 54 g. (0.33 mole) of trichloroacetamidine (I) was added with stirring to 400 ml. of water at 25°. The amidine dissolved completely upon the addition of approximately one-fourth of a solution of 20 g. (0.5 mole of NaOH in 50 ml. of water. The solution was cooled to and maintained at 5–10° throughout the course of the reaction. A solution of 25 g. (0.25 mole) of $COCl_2$ in 120 ml. of toluene was added dropwise with efficient stirring until the *p*H reached a value of 6. By alternate addition of phosgene and more of the above-mentioned NaOH solution, the *p*H was maintained at 8–9. Finally, the *p*H was brought to 6, and the separated product II was filtered by suction and dried *in vacuo* over P_2O_5; yield 41 g. (74%), m.p. 218–224°. Purification for analysis was accomplished by dissolving the product in ethanol with subsequent addition of cold water; m.p. 222–224°.

2,4-Bis-(dichloromethyl)-6-hydroxy-*s*-triazine dichloroacetamidine salt (VI) and 2,4-bis-(α,α-dichloroethyl)-6-hydroxy-*s*-triazine α,α-dichloropropionamidine salt (XIV) separated from their reaction mixture as viscous resins which were dried *in vacuo* over P_2O_5 and then recrystallized from benzene. **6-Hydroxy-2,4-bis-(monochloromethyl)-*s*-triazine monochloroacetamidine salt (X)** is soluble in water. Therefore it was crystallized from the reaction mixture at −5° and then recrystallized from ethanol. For physical and analytical data see Table I.

Chlorination of Monohydroxy-*s*-triazine Salts. 6-Chloro-2,4-bis-(trichloromethyl)-*s*-triazine (III).—The crude 6-hydroxy-2,4-bis-(trichloromethyl)-*s*-triazine trichloroacetamidine salt (II, 30 g.) and $POCl_3$ (75 g.) were refluxed at a bath temperature of 125° for 3 hr., after which excess $POCl_3$ was removed by distillation *in vacuo*. The remaining viscous residue was triturated with a mixture of ice and water whereupon it formed a solid. The product was dried over P_2O_5 *in vacuo* and then extracted with petroleum ether. The solution was filtered, concentrated to about 30 ml. and cooled to −15° to recrystallize 21 g. of III, m.p. 56°. 6-Chloro-2,4-bis-(monochloromethyl)-*s*-triazine (XI) was prepared similarly and recovered by distillation from the reaction mixture at 120° and 0.1 mm. after removal of the excess $POCl_3$.

The chlorination of 2,4-dimethyl-6-hydroxy-*s*-triazine acetamidine salt (XVII) (1 g.) with $POCl_3$ (8 g.) required the addition of triethylamine (1 g.). After the mixture was refluxed for 0.5 hr. the excess $POCl_3$ and the 2-chloro-4,6-dimethyl-*s*-triazine (XVIII) were removed by distillation *in vacuo*. XVIII crystallized in the condenser and, after cooling, in the distilled $POCl_3$ and was recrystallized from ligroin.

Amination of Monochloro-*s*-triazines.—A solution of 1 g. of 2,4-bis-(dichloromethyl)-6-chloro-*s*-triazine (VII) in 20 ml. of 8% alcoholic ammonia reacted rapidly at 5° to form 2,4-bis-(dichloromethyl)-6-amino-*s*-triazine (VIII). The ethanol was evaporated and the product was recrystallized from water.

A solution of 2 g. of 2,4-bis-(trichloromethyl)-6-chloro-*s*-triazine (III) in 20 ml. of ether was added at 0° to 1 g. of dimethylamine dissolved in 25 ml. of ether. Dimethylamine hydrochloride separated and was filtered off. The filtrate was evaporated *in vacuo* and the 2,4-bis-(trichloromethyl)-6-dimethylamino-*s*-triazine was recrystallized from petroleum ether.

A solution of 0.3 g. of ethylenimine and 1.19 g. of triethylamine in 10 ml. of petroleum ether was added with stirring to a solution of 0.27 g. of dimethyl-chloro-*s*-triazine (XVIII) in 10 ml. of petroleum ether. The reaction took place at room temperature and after 10 minutes the precipitate of triethylamine hydrochloride was filtered off. The filtrate was evaporated *in vacuo* and the 2,4-dimethyl-6-aziridino-*s*-triazine obtained was recrystallized from petroleum ether.

2,4-Dimethyl-6-hydroxy-*s*-triazine Acetamidine Salt (XVII).—A mixture of 4.0 g. of 2,4-bis-(monochloromethyl)-6-hydroxy-*s*-triazine monochloroacetamidine salt (X), 4.3 g. of triethylamine, 4 g. of 2% palladium-on-carbon catalyst and 150 ml. of methanol was shaken at room temperature with hydrogen. The absorption of 3.0 molar equivalents of hydrogen was completed in 40 minutes. The catalyst was filtered off by suction and a solution of 1.65 g. of NaOH in 15 ml. of methanol was added to the filtrate in order to convert the triethylamine hydrochloride to triethylamine and sodium chloride. After the precipitated sodium chloride was filtered off, the filtrate was evaporated to dryness at reduced pressure. The residue was taken up with ethanol and precipitated again with ether. The yield of crude XVII was 87.5%. The material was purified by sublimation at 160° and 0.1 mm. followed by dissolution in ethanol and precipitation with ether. The yield was 1.75 g. (68%) of product, m.p. 212–213°. The analytical data are given in Table I. XVII was also prepared by the above procedure

(10) Melting points are uncorrected (Fisher–Johns); analyses are by Galbraith Microanalytical Laboratories, Knoxville, Tenn.

(11) L. Bisschopinck, *Ber.*, **6**, 731 (1873).

(12) W. Steinkopf and L. Bohrmann, *ibid.*, **40**, 1638 (1907).

(13) A. Geuther, *Jahresber. Fortschr. Chem.*, **17**, 317 (1864).

(14) H. Backuntz and R. Otto, *Ber.*, **9**, 1593 (1876).

(15) German Patent 830,640 (1952); Swiss Patent 282,380 (1952).

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from 2,4-bis-(dichloromethyl)-6-hydroxy-*s*-triazine dichloroacetamidine salt (VI) in 63% yield and from 6-hydroxy-2,4-bis-(trichloromethyl)-*s*-triazine trichloroacetamidine salt (II) in 60% yield.

2,4-Dimethyl-6-hydroxy-*s*-triazine Hydrochloride Monohydrate (XX).—Hydrogen chloride was bubbled into a cold solution of 2.5 g. of 2,4-dimethyl-6-hydroxy-*s*-triazine acetamidine salt (XVII) in 15 ml. of 96% ethanol for about 15 minutes. The crystalline reaction product was filtered off and washed with 10 ml. of cold 96% ethanol to remove traces of acetamidine hydrochloride. The yield was 1.7 g. (70%) of product, m.p. 177–179°.

Anal. Calcd. for $C_5H_7N_3O\cdot HCl\cdot H_2O$ (179.6): C, 33.43; H, 5.61; N, 23.40; Cl, 19.74. Found: C, 34.21; H, 5.41; N, 23.79; Cl, 19.71.

2,4-Dimethyl-6-hydroxy-*s*-triazine (XXI).—A solution of 1.17 g. of 2,4-dimethyl-6-hydroxy-*s*-triazine hydrochloride monohydrate (XX) in 15 ml. of methanol was treated with 2.6 ml. of a 10% solution of NaOH in methanol. The methanol was then evaporated *in vacuo* and the residue was sublimed at 150° and 0.05 mm. Recrystallization of the sublimate from acetone gave 0.49 g. of product, m.p. 230–231°.

Anal. Calcd. for $C_5H_7N_3O$ (125.1): C, 47.99; H, 5.64; N, 33.57. Found: C, 47.95; H, 5.73; N, 33.52.

2,4-Dimethyl-*s*-triazine (XXII).—A mixture of 300 mg. of 6-chloro-2,4-dimethyl-*s*-triazine (XVIII), 211 mg. of triethylamine, 1 g. of 10% palladium-on-charcoal catalyst and 20 ml. of anhydrous ether was shaken at 20° with hydrogen. The absorption of the theoretical amount of hydrogen was completed in 5 minutes. The catalyst and the formed triethylamine hydrochloride were filtered off, and the filtrate was evaporated under mild vacuum; yield 120 mg. (52%) of product, m.p. 46°.

Anal. Calcd. for $C_5H_7N_3$ (109.1): C, 55.03; H, 6.47; N, 38.51. Found: C, 54.99; H, 6.50; N, 38.37.

XXII was characterized as the dihydrochloride salt by passing HCl into its ethereal solution. The precipitate is extremely hygroscopic and immediately forms a monohydrate, m.p. 148–150°. *Anal.* Calcd. for $C_5H_7N_3\cdot 2HCl\cdot H_2O$: Cl, 35.62. Found: Cl, 36.12.

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The Synthesis of Desoxycarpyrinic and Carpyrinic Acids

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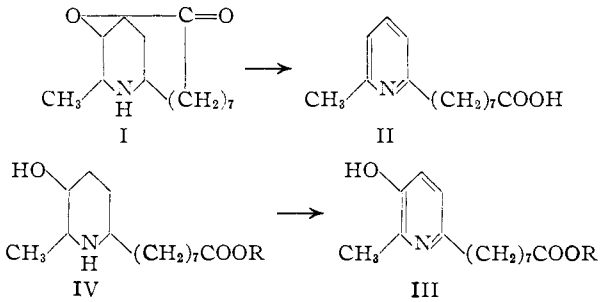
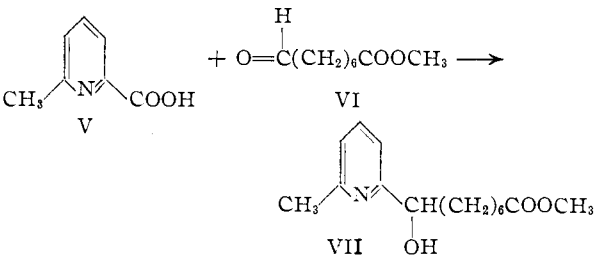
Desoxycarpyrinic acid and carpyrinic acid, degradation products of carpaine, have been synthesized by application of the Hammick reaction (decarboxylation of a picolinic acid in the presence of a carbonyl compound) to the half-ester aldehyde of suberic acid. The intermediate carbinol group in the one case was converted to the chloride and thence reduced to methylene, while in the other case it was oxidized to the ketone and then converted to methylene. The 5-hydroxy-6-methylpicolinic acid needed for the synthesis of carpyrinic acid was prepared by carboxylation of 3-hydroxy-2-methylpyridine.

As a result of a recent reinvestigation, the structure of carpaine, the chief papaya alkaloid, has been established[2] by degradative methods as I, containing the rather unique thirteen-membered lactone ring fused 2,5- to the piperidine nucleus. In considering synthetic approaches to this and related structures, two compounds seemed most attractive as the objectives of initial synthetic efforts. These compounds are desoxycarpyrinic acid (II) and carpyrinic acid (III), the products of catalytic dehydrogenation, under relatively mild conditions, of carpaine[3] and methyl or ethyl[4] carpamate (IV), respectively. The present report is a description of the synthesis of these two acids.



The synthesis of desoxycarpyrinic acid was investigated first, and the various methods for preparing 2,6-disubstituted pyridines commencing from the readily available 2,6-lutidine were examined. Particularly attractive from the standpoint of economy of steps was the Hammick reaction in which a pyridylcarbinol is formed by decarboxylation of a picolinic acid in the presence of a carbonyl compound.[5] The application of this reaction to the synthesis of desoxycarpyrinic acid (II) would involve the use of 6-methylpicolinic acid (V), easily prepared by oxidation of 2,6-lutidine,[6] and the half-ester aldehyde of suberic acid (methyl 7-formylheptanoate) (VI).



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