from 250 cc. of hot ethanol. The yield of pure product was 1 g., m. p. 185–188° dec.

Anal. Calcd. for $C_{22}H_{39}O_6NS$: N, 3.14. Found: N (Dumas), 2.84, basic N (perchloric acid titration in acetic acid), 2.76.

The product was soluble in sodium bicarbonate solutions and in hot dilute hydrochloric acid solution. Alkaline titration indicated the presence of one carboxyl and one lactone group. The reaction product obtained from cysteme and $\Delta^{\beta,\gamma}$-angelicalactone[11] when titrated with perchloric acid showed the absence of a basic amino group; protolichesterinic acid appears to have added cysteine through the —SH group without secondary involvement of the amino group.

Antibacterial Tests.—Tests against the *Streptococcus, Staphylococcus* and *Bacillus typhi* were conducted in tryptose phosphate medium. The inoculum was a 1:1000 dilution of a twenty-four-hour culture of the organism and incubation was for eighteen hours at 37°. The anaerobe was tested in Bacto-Anaerobe Medium with Dextrose. The acid-fast organisms, *B. tuberculosis ranae* and the human tuberculosis strain H37Rv were grown in submerged culture in Youmans' modification[14] of Proskauer–Beck synthetic medium. The inoculum with *ranae* was a 1:100 dilution of a forty-eight hour culture in Long's synthetic medium; incubation was for forty-eight hours at 37°. An inoculum of 0.02 mg. of fresh bacteria per cc. of test medium was used with H37Rv; incubation at 37° was for fourteen days, excellent growth being evidenced after eight days.

(14) Composition: Asparagin, 0.5%; primary potassium acid phosphate, 0.5%, potassium sulfate, 0.05%; magnesium citrate, 0.15%; and glycerol, 2% in distilled water.

Acknowledgment.—We are indebted to M. E. Auerbach and Staff for analytical data, to Dr. F. C. Nachod for surface-tension measurements, and John W. Klimek for antifungal tests.

Summary

The antibacterial activity of *l*-protolichesterinic acid is related to its effect on surface tension and not to any significant extent to the unsaturated system. A series of synthetic lactone aliphatic acids of the approximate molecular size of the lichesterinic acids also demonstrate antibacterial activity, particularly against acid-fast bacteria. The lactone aliphatic acids are more compatible with complex media than are the aliphatic monocarboxylic and malonic acids and are more soluble at neutrality.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF PARKE, DAVIS AND CO.]

Substituted Chlorodiamino-*s*-triazines[1]

BY WILLIAM M. PEARLMAN AND C. K. BANKS

Previous studies have described a number of compounds of pharmacological interest containing the *s*-triazine nucleus.[2-5] Most of these compounds were 2-substituted 4,6-diamino-*s*-triazines. Since unsubstituted amino- and hydroxy-*s*-triazines are theoretically capable of existence in more than one tautomeric form (I–IV), substitution of hydrogen atoms by alkyl groups should alter or completely inhibit the equilibrium of certain of the tautomers and thereby alter the pharmacological properties of the resulting compounds.

As most of the previous compounds had been derived from 2-chloro-4,6-diamino-*s*-triazine, it was considered of interest to prepare representative chlorodiaminotriazines in which the hydrogen atoms of the amine groups had been substituted by alkyl or alkylene groups. Very few compounds of this type had been described, and several of these, on reexamination were found to be mixtures of related products. Cyanuric chloride (2,4,6-trichloro-*s*-triazine) was used as the starting material for the preparation of the desired substituted chlorodiaminotriazines. Fierz-David and Matter[6] had shown that the three halogens of cyanuric chloride were hydrolyzed stepwise depending upon the temperature of the hydrolytic mixture and Diels[7] had demonstrated the stepwise replacement by reaction with amines and ammonia.

In attempting the preparation of unsymmetrically substituted triazines it was found that while stepwise substitution could be achieved, the nature of the reacting group and the order of entry of the groups were highly important in the preparation of unique products. While reaction of ammonia with cyanuric chloride would replace only one chlorine below 0° and two below 100°, interaction with dimethylamine replaced all three halogens at 25°. The behavior of morpholine and piperidine also indicated that the basicity of the amine was not the only factor, since both were practically as reactive as dimethylamine and more reactive than the monoalkyl amines. It was found that only one halogen would be replaced by an amino group if a sufficiently low temperature was maintained during reaction. The second amino group was then introduced at a higher temperature. When mixed diamines were desired, it was found to be more practical to introduce the basic radical of the less reactive amine first, and then that of the more reactive amine. Organic solvents were used in the synthesis of monoaminodichlorotriazines but most of the diamines were prepared in aqueous suspensions. Alcohols, acids and other

(1) Presented before the Division of Medicinal Chemistry, Chicago, Ill., April 20, 1948.

(2) (a) Banks, THIS JOURNAL, **66**, 1127 (1944); (b) Banks, *et al.*, *ibid.*, **66**, 1771 (1944).

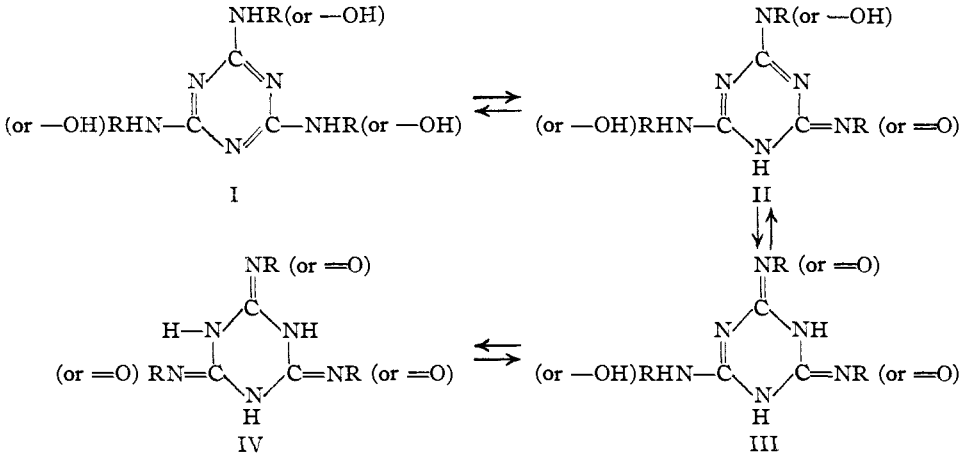
(3) Controulis and Banks, *ibid.*, **67**, 1946 (1945).

(4) Friedheim, *ibid.*, **66**, 1776 (1944).

(5) Witt and Hamilton, *ibid.*, **67**, 1078 (1945).

(6) Fierz-David and Matter, *J. Soc. Dyers Colourists*, **426** (1937).

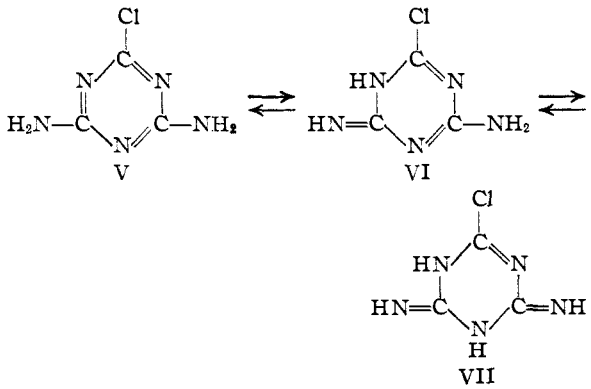
(7) Diels, *Ber.*, **32**, 697 (1899).



solvents which contain reactive hydroxyl groups were avoided during these preparations since the second halogen tended to react with them. Dioxane was also found to cause difficulty in that solvent complexes were formed which were difficult to free from excess solvent.

Ammonia, methylamine, ethylamine and dimethylamine reacted with cyanuric chloride to obtain 2-amino-4,6-dichloro-*s*-triazines. These triazines, in turn, reacted with a number of amines of various types. 2,4-bis-Substituted-6-chloro-*s*-triazines were obtained by direct reaction of the amine with cyanuric chloride.

The postulated keto–enol tautomerism for hydroxy and amino triazines (I–IV) can be extended to the chlorodiaminotriazines (V–VII). The sub-



stitution of hydrogen atoms by alkyl radicals should similarly alter this equilibrium. While one alkyl group, or two alkyl groups symmetrically placed, do not eliminate any of the tautomeric forms, two alkyl groups asymmetrically substituted or three alkyl groups result in the elimination of VII. Four groups eliminate all but V. The substituted chlorodiaminotriazines had physical properties (melting points, solubilities) and chemical reactivities which indicated a remarkable agreement with this theory. The tetraalkyl compounds are distinctly different from the mono-, di- and trialkyl compounds, which is consistent with the elimination of the imino forms (VI and VII). Other structural comparisons are also apparent. Since melamine has been tentatively assigned the amino structure (I) on the basis of crystallographic[8] and ultraviolet absorption spectra data,[9] the variations here indicated are worthy of further investigation.

Experimental

2-Amino-4,6-dichloro-*s*-triazine.—The amount of redistilled cyanuric chloride necessary to yield the desired amount of product was dissolved in a volume of hot acetone slightly in excess of the minimum for complete solution, the solution chilled in a Dry Ice-bath to −40° and anhydrous ammonia passed into the suspension at a rapid rate. There was a tendency for the temperature to rise and the rate of ammonia addition was regulated so that the temperature did not exceed 0°. When the odor of ammonia above the reaction vessel was pronounced or when the temperature began to fall, the reaction vessel was removed from the bath and its contents poured over five volumes of finely crushed ice. When all of the ice had just melted, the product was filtered off and used immediately. This product could be dissolved in ether, dried with anhydrous calcium chloride and crystallized by concentration of the dry ether solution. Although this triazine could be isolated and dried, it was prepared fresh for subsequent use since it decomposed on storage, and the impurities formed made the isolation of subsequent products difficult.

2-Substituted-Amino-4,6-dichloro-*s*-triazines.—Cyanuric chloride (0.5 mole) was dissolved in a minimum of hot acetone and cooled in a Dry Ice-bath with stirring. When the temperature reached −30°, the liquid amine or an aqueous solution of the amine (1 mole) was added at such a rate so that the temperature did not exceed −20°. When all of the amine had been added, the temperature was allowed to rise slowly to −10° and held there for thirty minutes. The acetone mixture was poured over 2 kg. of crushed ice, and the acetone evaporated by blowing air over the surface, maintaining the solution at 0°. The triazine 2-methyl- or 2-ethylamino-4,6-dichloro-*s*-triazine[6] was filtered off and recrystallized from appropriate solvents.

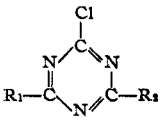
2,4-Dichloro-6-dimethylamino-*s*-triazine.—The 6-dimethylamino compound was obtained by the procedure above with the following alterations. An excess of 10 *N* sodium hydroxide was added at 0° to precipitate the product. It was recrystallized from petrolic ether; 38% yield; m. p. 122.5–123.5°.

Anal. Calcd. for $C_5H_6Cl_2N_4$: C, 31.11; H, 3.13. Found: C, 31.40; H, 3.22.

Chlorodiamino-*s*-triazines.—Cyanuric chloride or a 2-substituted amino-4,6-dichlorotriazine in acetone or moist

(8) Hughes, THIS JOURNAL, **63**, 1737 (1941).
(9) Klotz and Askounis, *ibid.*, **69**, 801 (1947).

TABLE I



R_1	R_2	M. p., °C.	Recrystallization solvent	Yield, % (Calcd. from $C_3Cl_3N_3$)	Empirical formula	Analyses, %[a] Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$N(CH_3)_2$	Cl	122.5–123.5	Petrolic ether	38	$C_5H_6Cl_2N_4$	31.11	31.40	3.13	3.22
NH_2[b]	$NHCH_3$	244–246	Water	76	$C_4H_5ClN_6$	30.10	30.44	3.79	4.07
NH_2[c]	NHC_2H_5	177–179	Water	85	$C_5H_7ClN_6$	34.59	34.88	4.65	4.55
NH_2	NHC_7H_7-*n*	169–171	Benzene	76	$C_8H_{10}ClN_5$	38.40	38.50	5.37	5.37
NH_2	NHC_4H_9-*n*	142–144	Tetrohydrofuran–water	74	$C_7H_{12}ClN_5$	41.69	41.53	6.00	6.25
NH_2	NHC_5H_{11}-*n*	148–150	Water	84	$C_8H_{14}ClN_5$	44.55	44.65	6.54	6.17
NH_2	NHC_6H_{13}-*n*	149–151	Benzene	75	$C_9H_{16}ClN_5$	47.05	47.08	7.02	7.00
NH_2	NHC_6H_{11}[d]	185–187	Ethyl cellosolve	67	$C_9H_{14}ClN_5$	47.47	47.92	6.20	6.10
NH_2	$NHCH_2CH{=}CH_2$	168–170	Water	79	$C_6H_8ClN_5$	38.82	38.84	4.34	4.18
NH_2	$NHCH_2C(CH_3){=}CH_2$	168–170	Ethanol–water	79	$C_7H_{10}ClN_5$	42.11	42.13	5.05	5.04
NH_2[b]	$NHCH_2CH_2OH$	187–189	Water	76	$C_5H_8ClN_5O$	31.67	32.00	4.25	4.25
NH_2[b]	$NHCH_2CHOHCH_3$	192–194	Water	41	$C_6H_{10}ClN_5O$	35.39	35.25	4.95	5.05
NH_2	$N(CH_3)_2$	220–222	Ethanol	95	$C_5H_8ClN_5$	34.59	34.78	4.65	4.95
NH_2	$N(C_2H_5)_2$	123–125	Ethanol–water	66	$C_7H_{12}ClN_5$	41.69	41.95	6.00	5.78
NH_2	$N(CH_2CH{=}CH_2)_2$	78–80	Ethanol–water	63	$C_9H_{12}ClN_5$	47.90	47.92	5.36	5.35
NH_2	$N[CH_2C(CH_3){=}CH_2]_2$	114–116	Ethanol–water	79	$C_{11}H_{16}ClN_5$	52.07	52.33	6.36	6.20
NH_2	NC_5H_{10}[e]	180–182	Ethyl cellosolve[f]	53	$C_8H_{12}ClN_5$	44.97	45.03	5.66	5.47
NH_2	NC_4H_8O[g]	189–191	Water	35	$C_7H_{10}ClN_5$	38.99	38.72	4.67	4.88
NH_2	$N(C_2H_5)CH_2CH_2OH$	136–138	Water	75	$C_7H_{12}ClN_5O$	38.62	38.65	5.56	5.41
NH_2	$N(C_6H_5)CH_2CH_2OH$	188–189	Methyl cellosolve	72	$C_{11}H_{12}ClN_5O$	49.72	49.74	4.55	4.35
$NHCH_3$	$NHCH_3$	>335	Insol.[h]	98	$C_4H_5ClN_6$	34.59	35.10	4.65	4.88
$NHCH_3$	$N(CH_3)_2$	207–209	Chloroform	75	$C_6H_{10}ClN_5$	38.40	38.43	5.37	5.27
NHC_2H_5	NHC_2H_5	228–229	Ethanol[f]	82	$C_7H_{12}ClN_5$	41.69	41.95	6.00	6.03
NHC_2H_5	$N(C_2H_5)_2$	100–102	Propanol	70	$C_9H_{16}ClN_5$	47.05	47.22	7.02	6.83
$NHCH_2CH{=}CH_2$	$NHCH_2CH{=}CH_2$	203–205	Methyl cellosolve	85	$C_9H_{12}ClN_5$	47.90	47.90	5.36	5.32
$NHCH_2C(CH_3){=}CH_2$	$NHCH_2C(CH_3){=}CH_2$	209–211	Ethyl cellosolve	91	$C_{11}H_{16}ClN_5$	52.07	52.04	6.36	6.24
$N(CH_3)_2$	$N(CH_3)_2$	66–68	Propanol–water	41	$C_7H_{12}ClN_5$	41.69	41.90	6.00	5.87
$N(C_2H_5)_2$	$N(C_2H_5)_2$	B. p. 154–156 (4 mm.)		87	$C_{11}H_{20}ClN_5$	51.25	51.53	7.82	7.73
NC_5H_{10}[e]	NC_5H_{10}[e]	117–119	Ethanol–water, benzene	75	$C_{12}H_{20}ClN_5$	55.41	55.74	6.99	6.96
NC_4H_8O[g]	NC_4H_8O[g]	172–174	Ethanol[f]	87	$C_{11}H_{16}ClN_5O_2$	46.24	46.54	5.65	5.57
$N(CH_2CH{=}CH_2)_2$	$N(CH_2CH{=}CH_2)_2$	B. p. 147–150 (1.2 mm.)		81	$C_{15}H_{20}ClN_5$	58.91	59.42	6.59	6.72
$N[CH_2C(CH_3){=}CH_2]_2$	$N[CH_2C(CH_3){=}CH_2]_2$	B. p. 175–179 (2 mm.)		79	$C_{19}H_{28}ClN_5$	63.05	63.11	7.80	7.97
$NH(CH_2CH{=}CH_2)$	$N(CH_2CH{=}CH_2)_2$	72	Ethanol–water	70	$C_{12}H_{15}ClN_5$	54.23	54.50	6.06	6.04
$NH[CH_2C(CH_3){=}CH_2]$	$N[CH_2C(CH_3){=}CH_2]_2$	87	Ethanol–water	79	$C_{15}H_{22}ClN_5$	58.52	58.50	7.21	7.23

[a] Analyses performed by A. W. Spang and Patricia Keller. [b] Prepared by Mr. D. F. Walker. [c] The product was digested with carbon tetrachloride to remove impurities prior to recrystallization. [d] Insoluble in water, ethanol, propanol, methyl and ethyl cellosolves, tetrahydrofuran, ether, benzene, petrolic ether, chloroform and carbon tetrachloride. Hofmann, *Ber.*, 18, 2766 (1885), assigned this structure to a product, m. p. 241°, obtained from the reaction of cyanuric chloride and methylamine and crystallized by dissolving it in glacial acetic acid and pouring the solution into boiling water. Repeating this procedure yielded a compound free of halogen and believed to be an acetate ester. [e] Hofmann, *Ber.*, 18, 2755 (1885), assigned this structure to a compound for which no melting point or analyses were given. [f] Ref. 5. [g] Cyclohexyl. [h] Piperidino. [i] Morpholino.

2-amino-4,6-dichloro-*s*-triazine from the procedure above (0.1 mole of either) was added to 500 g. crushed ice and the required amine added all at one time with stirring (0.4 mole with cyanuric chloride or 0.2 mole with aminodichlorotriazine). The mixture became thick almost immediately. It was heated on a steam-bath with continued stirring to 45° and then allowed to cool to room temperature for most of the amines used. In the case of the more reactive amines, the maximum temperature allowable was for dimethylamine, 20°; morpholine, 25°; and piperidine, 30°. The product was filtered off and recrystallized from a suitable solvent.

2-Allylamino-4-diallylamino-6-chloro-*s*-triazine.—Cyanuric chloride (0.1 mole) was dissolved in a minimum of hot acetone, cooled to −50° in a Dry Ice-bath and allylamine (0.2 mole) added portionwise, with stirring, so as to maintain a temperature below −30°. The reaction mixture was stirred for fifteen minutes after all of the amine had been added, and then sufficient ice added directly to the acetone to precipitate the dichloroamino compound. The ice mixture was stirred until nearly all of the ice had melted and the product then filtered off. The monoamino product was washed with ice water, resuspended in a mixture of ice and water (500 ml.), diallylamine (0.2 mole) added all at once and the mixture stirred and heated to 45° for one-half hour. The reaction mixture was cooled to 0° and the product filtered off and recrystallized from 50% ethanol.

2-Methallylamino-4-dimethallylamino-6-chloro-*s*-triazine was prepared by a similar procedure.

Summary

1. Cyanuric chloride was reacted with ammonia, methylamine, ethylamine and dimethylamine to yield aminodichloro-*s*-triazines.

2. Unsymmetrical diaminochloro-*s*-triazines were obtained by treating the monoamino compounds with other amines at regulated temperatures.

3. Symmetrical diaminochloro-*s*-triazines were obtained from cyanuric chloride and amines under controlled conditions of temperature.

DETROIT 32, MICHIGAN RECEIVED MAY 1, 1948