encountered in again obtaining a crystalline sample of 2-chloroadenosine.

2-Chloroadenine has now been obtained by amination of 2,6-dichloropurine.[7,8] Aqueous ammonia, with which only the 6-position of 2,6,8-trichloropurine is aminated,[9] led to 2,6-diaminopurine. However, with methanolic ammonia only the 6-position was aminated and nearly quantitative yields of 2-chloroadenine were obtained.

The chloromercuri salt of 2-chloroadenine was condensed with 2,3,5-tri-*O*-acetyl-D-ribosyl chloride.[6] A crystalline product was obtained only after fractionation of solutions in 50% methanol over Dowex-1-chloride. From water the crystals separated slowly as a mass of well formed needles, *ca.* 0.01 to 0.10 mm. long, which entrain 2 to 5 times their weight of water when collected. Several recrystallizations are necessary to eliminate impurities retained in the water trapped in each filter cake. When dried in air, or *in vacuo*, at temperatures as low as 4°, an anhydrous, but amorphous, product is obtained. Maximum biological activities[2,4] were found[10] with such samples. The anhydrous product will not serve as seed crystals, but crystalline material can so serve after storage for up to two years under water at 4°.[11] It is suggested that the crystalline material may be a hydrate which loses water easily. Up to 50% solutions of the anhydrous material can be prepared, but these will not crystallize until seeded with the above "hydrate," after which almost complete recovery can be obtained.

EXPERIMENTAL

2-Chloroadenine. One gram of 2,6-dichloropurine[8] per 50 cc. of methanol, saturated with ammonia at 0°, was heated in a sealed tube 17 hr. at 100°. Crystals were present in the cooled tube. The supernatant was evaporated and the residue and crystals were dissolved in 9 cc. of 1*N* NaOH per gram of starting material. The solution was immediately filtered and acidified with acetic acid. Yields of from 0.7 to 0.85 g. (77 to 96%) were obtained.

Anal. Calcd. for $C_5H_5N_5Cl$: N, 41.3; Cl, 20.9. Found: N, 41.0; Cl, 21.0.

The ultraviolet absorption in 0.1*N* HCl showed a maximum at 265 mμ (ϵ_M 12 × 10^3), a minimum at 230 mμ; and in 0.1*N* NaOH a maximum at 270–272 mμ (ϵ_M 12 × 10^3), and a minimum at 240–242 mμ. The ϵ_M values were slightly lower than those previously found[6] on a sample known to contain some adenine.

2-Chloro-9-β-D-ribofuranosyladenine. Three grams of 2-chloroadenine in 100 cc. of water were warmed and 18.2 cc. of 1*N* NaOH, about 3 g. of Celite and a solution of 5.6 gm. of mercuric chloride in 100 cc. of warm ethanol were added successively with continuous stirring. The solution was cooled and the dense, slightly gelatinous precipitate was collected immediately. The material was dried *in vacuo* over P_2O_5 in the funnel and the hard cake was pulverized. In experiments where the Celite was omitted the yield was 77 to 90%.

The powdered chloromercuri salt was condensed[6] with 2,3,5-tri-*O*-acetyl-D-ribosyl chloride prepared from 4.5 g. (0.8 of an equivalent based upon the 2-chloroadenine) of tetraacetylribofuranose[12], and the mixture was refluxed two hours. The oily triacetyl derivative obtained was deacetylated with methanolic ammonia, the solution concentrated to dryness and dissolved in 50 cc. of water. When seeded with the "hydrate" crystals slowly separated. After three recrystallizations from water of the first crop, and four of the second, a total of 1.2 g. (29%) of the dried product, m.p. 147–149° was obtained. Davoll and Lowy[6] previously reported m.p. 135°. The ultraviolet absorption maxima, at 265 mμ in acid and alkali, agreed with those previously[6] observed.

Anal.[13] Calcd. for $C_{10}H_{12}O_4N_5Cl$: N, 23.2; Cl, 11.7. Found: N, 22.8, 23.1, 22.7; Cl, 12.1, 11.2, 11.5, on three preparations.

With the use of 1.0 or more equivalents of the triacetylribosyl chloride the product was difficult to crystallize.

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(7) J. A. Montgomery, *J. Am. Chem. Soc.*, **78**, 1928 (1956).
(8) G. B. Elion and G. H. Hitchings, **78**, 3508 (1956).
(9) E. Fischer, *Ber.*, **30**, 2226 (1897).
(10) Assayed through the courtesy of Dr. D. A. Clarke, see footnote 2, ref. 4.
(11) Some supplies of 2-chloroadenosine were kindly furnished for biological studies by Drs. Karl Folkers and C. H. Skunk, Merck and Co., Rahway, N. J. Crystallization of a portion of that material was induced by the crystals described here.
(12) G. B. Brown, J. Davoll, and B. A. Lowy, *Biochemical Preparations*, **IV**, 70 (1955), John Wiley and Sons, Inc., New York, N.Y., 1955, Vol. IV, p. 70.
(13) Analyses by J. F. Alicino, Metuchen, N. J.

3,3-Disubstituted Tetronic Acids

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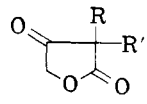
Among the compounds prepared and tested in our laboratory for hypnotic and anticonvulsant activities were several 3,3-disubstituted tetronic acids. These were prepared by modifications of methods previously reported by others for the synthesis of 3,3-dimethyl[1] and 3,3-diethyltetronic[1a] acids. The reaction sequence consisted of preparing the appropriate α,α-disubstituted acetoacetic esters,[2] brominating to yield the γ-bromo compounds, converting to the γ-acetoxy derivatives with potassium acetate, and cyclizing to the tetronic acids. The cyclization step was carried out using a trace of sulfuric acid as described below and appeared to be a distinct improvement over the earlier procedures.

These tetronic acids had hypnotic and anticonvulsant activities only at very high doses. The properties of the compounds are described in Table I.

(1) (a) M. Conrad and R. Gast, *Ber.*, **31**, 2954 (1898); (b) C. F. Koelsch, *J. Am. Chem. Soc.*, **66**, 306 (1944); (c) E. B. Reid, R. B. Fortenbaugh, and H. R. Patterson, *J. Org. Chem.*, **15**, 572 (1950).

TABLE I

3,3-DISUBSTITUTED TETRONIC ACIDS



R	R′	B.p. °C./Mm.	n_D^{25}	Yield, %	Empirical Formula	Analyses, C and H Calcd.		Found	
CH_3	CH_3	42–44/0.5	1.4468	85	$C_6H_8O_3$[1]	56.24	6.29	55.98	6.36
C_2H_5	C_2H_5	219/760	1.4463	79	$C_8H_{12}O_3$[1a]	61.52	7.75	61.27	7.89
CH_3	n-C_4H_9	240–244/760	1.4475	75	$C_9H_{14}O_3$	63.51	8.29	63.28	8.34
C_2H_5	sec-C_5H_{11}	255/760	1.4655	68	$C_{11}H_{18}O_3$	66.64	9.15	66.55	9.19
CH_3	C_6H_5	292/760	1.5341	67	$C_{11}H_{10}O_3$	69.46	5.30	69.51	5.42

EXPERIMENTAL

Ethyl α,α-disubstituted acetoacetates. These esters were prepared according to a method recently described from this laboratory.[2] *Ethyl α,α-dimethylacetoacetate*[3] was obtained in 65% yield; b.p. 180–184°; n_D^{25} 1.4162. *Ethyl α,α-diethylacetoacetate*[4] was prepared in 79% yield; b.p. 99–103° (14 mm.); n_D^{25} 1.4300. *Ethyl α-methyl-α-n-butylacetoacetate* was prepared with a yield of 82%; b.p. 119–120° (16 mm.); n_D^{25} 1.4295.

Anal. Calcd. for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.85; H, 9.88.

Ethyl α-ethyl-α-(1-methylbutyl)acetoacetate was obtained in a yield of 66%; b.p. 107° (5 mm.); n_D^{25} 1.4418.

Anal. Calcd. for $C_{13}H_{24}O_3$: C, 68.38; H, 10.59. Found: C, 68.54; H, 10.65.

Ethyl γ-bromo-α,α-disubstituted acetoacetic esters. The preparation of these compounds was according to the method of Conrad and Gast.[5] *Ethyl γ-bromo-α,α-dimethylacetoacetate*[5] was obtained in 73% yield; b.p. 117–119° (12 mm.); n_D^{25} 1.4651. *Ethyl γ-bromo-α,α-diethylacetoacetate*[1a] was prepared with a yield of 77%; b.p. 80° (1 mm.); n_D^{25} 1.4713. *Ethyl γ-bromo-α-methyl-α-n-butylacetoacetate* was obtained in 79% yield; b.p. 133° (4 mm.); n_D^{25} 1.4665.

Anal. Calcd. for $C_{11}H_{19}BrO_3$: C, 47.32; H, 6.85. Found: C, 46.95; H, 7.07.

Ethyl γ-bromo-α-ethyl-α-(1-methylbutyl)acetoacetate was obtained in 55% yield; b.p. 131° (4 mm.); n_D^{25} 1.4671.

Anal. Calcd. for $C_{13}H_{23}BrO_3$: C, 50.82; H, 7.54. Found: C, 50.07; H, 7.64.

Ethyl γ-bromo-α-methyl-α-phenylacetoacetate was prepared in 51% yield; b.p. 165° (4 mm.); n_D^{25} 1.5306.

Anal. Calcd. for $C_{13}H_{15}BrO_3$: C, 52.18; H, 5.05. Found: C, 51.76; H, 5.43.

Ethyl γ-acetoxy-α,α-disubstituted acetoacetates. These esters were prepared by reaction of the above γ-bromo compounds with potassium acetate in alcohol.[5] *Ethyl γ-acetoxy-α,α-dimethylacetoacetate*[1b] was obtained in 80% yield; b.p. 89° (0.5 mm.); n_D^{25} 1.4319. *Ethyl γ-acetoxy-α,α-diethylacetoacetate*[1a] was obtained in 63% yield; b.p. 92° (0.25 mm.); n_D^{25} 1.4415. *Ethyl γ-acetoxy-α-methyl-α-n-butylacetoacetate* was prepared in 55% yield; b.p. 126° (1.5 mm.); n_D^{25} 1.4398.

Anal. Calcd. for $C_{13}H_{22}O_5$: C, 60.44; H, 8.59. Found: C, 60.24; H, 8.85.

Ethyl γ-acetoxy-α-ethyl-α-(1-methylbutyl)acetoacetate was obtained in 46% yield; b.p. 153° (5 mm.); n_D^{25} 1.4500.

Anal. Calcd. for $C_{15}H_{26}O_5$: C, 62.91; H, 9.15. Found: C, 63.08; H, 8.95.

Ethyl γ-acetoxy-α-methyl-α-phenylacetoacetate was obtained in 47% yield; b.p. 171° (5 mm.); n_D^{25} 1.5002.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 65.03; H, 6.66.

3,3-Disubstituted tetronic acids. The preparation of 3-methyl-3-phenyltetronic acid will illustrate the method used for the synthesis of the compounds listed in Table I.

In a small distillation apparatus was placed 26 g. of ethyl γ-acetoxy-α-methyl-α-phenylacetoacetate. To this was added five drops of concentrated sulfuric acid and the flask was placed in an oil bath at 125°. The odor of ethyl acetate became noticeable after about 15 min. The mixture was held at 125° for 24 hr. During this time a small volume of distillate was collected and was identified as ethyl acetate. The remaining material was distilled under reduced pressure and that portion boiling at 145–150°/5 mm. was collected. A small sample on redistillation boiled at 292°/atm.

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(2) F. J. Marshall and W. N. Cannon, *J. Org. Chem.*, **21**, 245 (1956).
(3) E. Frankland and B. F. Duppa, *Ann.*, **138**, 328 (1866).
(4) E. Frankland and B. F. Duppa, *Ann.*, **138**, 204 (1866).
(5) M. Conrad and R. Gast, *Ber.*, **31**, 2726 (1898).

Reduction of the Azido Group with Sodium Borohydride[1]

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Pyridinium salts, azomethine derivatives, and diazonium salts represent functional groups that have been reduced by sodium borohydride.[2] Nitro,[3] amide, imide, and nitrile groups are not generally attacked by this metal hydride[2] and its effect on other functional groups containing nitrogen has not been established. An extension of the selectivity of this reagent to organic azides is described here.

Both aliphatic and aromatic azides were reduced by lithium aluminum hydride (LAH) in good yields to the corresponding primary amines.[4] In

(1) Financial support by the Office of Ordnance Research, U. S. Army, under contracts No. DA-01-ORD-331 and DA-01-ORD-428.
(2) N. G. Gaylord, *Reduction with Complex Metal Hydrides*, Interscience Publishers, Inc., New York (1956), pp. 100, 750, 760, 773, 776, 781, 789, 806.
(3) C. E. Weill and G. S. Panson, *J. Org. Chem.*, **21**, 803 (1956) reported the reduction of nitrobenzene with sodium borohydride to azoxybenzene.
(4) J. H. Boyer, *J. Am. Chem. Soc.*, **73**, 5865 (1951).