EXPERIMENTAL

Diethyl p-methoxybenzylidenemalonate. This substance was prepared from anisaldehyde and diethylmalonate using diethylamine as a condensing agent. The method of synthesis is similar to that described by Knoevenagel and Groos.[9] The product had a melting point of 39°, yield 49%.

Anal. Calcd. for $C_{15}H_{18}O_5$: C, 64.73; H, 6.52. Found: C, 65.14; H, 6.38.

5-(p-Methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3. This compound was prepared from diethyl *p*-methoxybenzylidenemalonate and ethyl acetoacetate using sodium ethoxide as condensing agent. The method used has been described[4,5] previously. The product melted at 157°, yield 60%.

Anal. Calcd. for $C_{19}H_{22}O_7$: C, 62.97; H, 6.12. Found: C, 63.11; H, 6.16.

5-(p-Methoxyphenyl)cyclohexanedione-1,3. This substance was prepared by hydrolysis and decarboxylation of 5-(*p*-methoxyphenyl)-4,6-dicarbethoxycyclohexanedione-1,3 according to the method previously described.[4,5] It dissolves in boiling water and recrystallizes at lower temperatures, m.p. 178°.

Anal. Calcd. for $C_{13}H_{14}O_4$: C, 71.54; H, 6.46. Found: C, 71.38; H, 6.34.

This compound was prepared also from 5-(*p*-methoxyphenyl)-4-carbethoxycyclohexanedione-1,3 using similar procedure to that of Lespagnol and Schmitt.[6]

5-(p-Methoxyphenyl)-2-(3,3-diethoxypropyl)cyclohexanedione-1,3. Potassium (2.8 g.) was added to 400 ml. of dry xylene and the mixture heated with stirring in a 1000-ml. three-neck flask equipped with a condenser, dropping funnel, and mercury sealed stirrer. The air in the apparatus was displaced with nitrogen. When the potassium had melted, 18 g. of 5-(*p*-methoxyphenyl)cyclohexanedione-1,3 suspended in 200 ml. of xylene was added over a period of 2 hr. After all the potassium had reacted 11 g. of β-chloropropionaldehyde diethyl acetal[10] was added in 50 ml. of xylene and the mixture refluxed for 16 hr. at an oil bath temperature of 155°. The resulting red product was filtered and washed with ether. From the residue a brownish-orange colored *bisphenylhydrazone* derivative was prepared under alkaline conditions, m.p. 87°.

Anal. Calcd. for $C_{32}H_{40}N_4O_3 \cdot 2H_2O$: N, 9.91. Found: N, 9.92; 10.03.

This experiment was repeated later with some modifications. The crude red material was washed with ether. The residue was dissolved in an alcohol-water mixture and heated with excess phenylhydrazine. The osazone formed was soluble in the alkaline solution. The solution was heated in a water bath to remove some of the alcohol. After cooling, addition of water caused the separation of 4 ml. of viscous red liquid which was kept for the treatment described in the following paragraph. The rest of the cold alkaline water solution was made nearly neutral by the addition of dilute acetic acid. The precipitate formed was washed, filtered, and dried in a desiccator. It had brownish-orange color and melted at 86°. The analytical results indicate that it is the *bisphenylhydrazone derivative of* (II). This compound is identical with the one obtained above.

Anal. Calcd. for $C_{32}H_{40}N_4O_3 \cdot 2H_2O$: N, 9.91. Found: N, 9.82, 10.00. One OCH_3 and $2(OC_2H_5)$, 21.45. Found: 21.24.

The 4 ml. of viscous red liquid was heated on a water bath to evaporate the solvents. A little brownish-orange colored hydrazone of (IV) was obtained; it sintered at 90 and melted at 142°.

Anal. Calcd. for $C_{26}H_{34}O_4N_2 \cdot H_2O$: N, 6.14. Found: N, 6.06.

Two grams of the red material was dissolved in distilled water. The solution was cooled and then neutralized with dilute acetic acid. A white precipitate formed which was filtered and recrystallized from dilute methyl alcohol; m.p. 170° (II).

Anal. Calcd. for $C_{20}H_{28}O_5$: C, 68.40; H, 8.04. Found: C, 68.55; H, 8.40.

Bis-2,4-dinitrophenylhydrazine derivative of (II). The procedure followed is described by Shriner and Fuson.[11] The derivative was purified by recrystallization from ethyl alcohol-ethyl acetate mixture; m.p. 207°–207.5°.

Anal. Calcd. for $C_{32}H_{36}O_{11}N_8 \cdot H_2O$: C, 52.89; H, 4.95; N, 15.42. Found: C, 53.15; H, 4.69; N, 15.17.

8-(p-Methoxyphenyl)-2-hydroxybicyclo[3.3.1]nonan-6,9-dione (III). To a mixture of 16 ml. glacial acetic acid, 4 ml. concentrated HCl and 8 ml. water, 5 g. of 5-(*p*-methoxyphenyl)-2-(3,3-diethoxypropyl)cyclohexanedione-1,3 was added. The mixture was heated until all the material dissolved and then allowed to stand for 30 hr. The crude product was filtered and recrystallized from dilute methyl alcohol. Yield 30%, m.p. 174–175°. It does not give Schiff's test.

Anal. Calcd. for $C_{16}H_{18}O_4$: C, 69.79; H, 6.09. Found: C, 69.73, 69.87, 69.72; H, 6.44, 6.32, 6.38.

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2-Chloroadenine and 2-Chloroadenosine[1]

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Biological interest in the potent hypotensive[2] and ulcerigenic[3] activities, and the effects on smooth muscle[4] of 2-chloroadenosine prompted further investigation of its preparation. The nucleoside was originally prepared by partial reduction of 2,8-dichloro-9-β-D-ribofuranosyladenine[5] and, when the chloromercuri method became available,[6] by the direction condensation of the chloromercuri derivative of 2-chloroadenine with 2,3,5-tri-*O*-acetyl-D-ribosyl chloride. At that time 2-chloroadenine was available only through the partial reduction of 2,8-dichloroadenine, followed by separation from admixed adenine and 2,8-dichloroadenine.[6] Considerable difficulty was also

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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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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.

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