Experimental

Methyl 3β-Hydroxy-Δ⁴-etiocholenate (III).—The starting material for this synthesis was methyl 3β-hydroxy-Δ⁵-etiocholenate (I) which was converted by an Oppenauer oxidation[4] to methyl 3-oxo-Δ⁴-etiocholenate (II). To a solution of 990 mg. (3.0 mmoles) of the latter in 40 ml. of methanol and 10 ml. of ethyl acetate was added a solution of 228 mg. (6.0 mmoles) of sodium borohydride in 40 ml. of methanol and 10 ml. of ethyl acetate and the mixture allowed to stand at room temperature for 16 hours under exclusion of moisture. At the end of this time, 1.0 ml. of water was added and the solution adjusted to *p*H 7 with acetic acid. The solvent was then evaporated *in vacuo* at 40–45° to near-dryness, the residue taken up with 15 ml. of warm methanol and transferred quantitatively to 150 ml. of water. After refrigeration for one hour, the separating crystalline material was filtered by suction and allowed to dry. This dry material was dissolved in 100 ml. of absolute ethanol, added to a solution of 3100 mg. of digitonin in 170 ml. of absolute ethanol and 40 ml. of water and allowed to stand under refrigeration for 20 hours. The resulting digitonide was filtered by suction, washed with two 15-ml. portions of absolute ether, then transferred to a mortar and pulverized. This was extracted thoroughly with 200 ml. of absolute ether, filtered and washed several times with the same solvent. The digitonide thus treated was transferred to a 500-ml. erlenmeyer flask, covered with 93 ml. of pure pyridine and allowed to dissolve.

In the meantime, the alcoholic filtrate, combined with the ether washings, was evaporated *in vacuo* at 40–45°. When the volume had diminished to about 100 ml. a further, small quantity of the digitonide separated. This was filtered, washed with absolute ether and transferred to the flask containing the main bulk of the digitonide. The pyridine solution of the now decomposed digitonide was diluted with 800 ml. of absolute ether, centrifuged and filtered. The separating digitonin was washed with the same solvent and the washings combined with the filtrate, all of which was evaporated to dryness *in vacuo*. This treatment resulted in 906 mg. (91%) of methyl 3β-hydroxy-Δ⁴-etiocholenate which, when recrystallized twice from methanol, gave needles, m.p. 209–211° (Fisher–Johns block), $[\alpha]^{26}D$ +92° (*c* 1.98, $CHCl_3$).

Anal. Calcd. for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 75.64; H, 9.58.

Methyl Δ³,⁵-Etiocholadienate (IV).—The alcoholic filtrate from the preceding preparation, reduced in volume and combined with the ether washings, was evaporated to dryness *in vacuo* at 50°, leaving a residue consisting of material not precipitable with digitonin plus a small amount of unused digitonin. This was taken up with ether, filtered, evaporated and dried for 15 minutes at 50° under a reduced pressure of 0.1 mm. This resulted in a light yellow oil which was placed on a column of Fisher reagent grade silicic acid and chromatographed. Benzene and benzene–ether (99.5–0.5) eluates gave 60 mg. (6%) of crude methyl Δ³,⁵-etiocholadienate which, when recrystallized three times from methanol, gave long, fine needles, m.p. 141–142° (Fisher–Johns block), λ_{max}^{alc} 234 (4.3).

Anal. Calcd. for $C_{21}H_{30}O_2$: C, 80.21; H, 9.61. Found: C, 79.77; H, 9.50.

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Dialkoxyalkanenitriles. II.[1] Reaction of Dialkoxyacetonitriles with Dicyanodiamide

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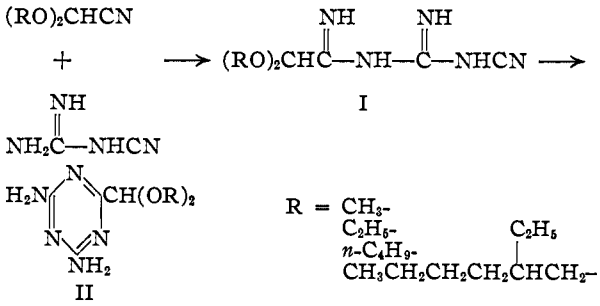
The base-catalyzed reaction of dialkoxyacetonitriles with dicyandiamide in 2-methoxyethanol or 1-butanol solution produces dialkoxyacetoguanamines (II), acetals of 4,6-diamino-2-*s*-triazinecarboxaldehyde. The reactions take place very rapidly, and excellent yields of pure materials are obtained. The first step in the reaction probably involves the formation of dialkoxyacetimidodicyandiamides (I), followed by cyclization to the triazine.



Although the method is essentially an extension of a reaction already reported in the patent literature[3] for the preparation of simple guanamines, the products represent a new series of *s*-triazine derivatives. A survey of the literature has shown that the only *s*-triazinecarboxaldehyde derivatives reported heretofore are the oximinoacetoguanamides prepared by Ostrogovich and co-workers.[4]

In earlier work,[5] it had been found that dialkoxyacetonitriles are easily cleaved by solutions of ammonia in alcohols. The successful preparation of these guanamines from dialkoxyacetonitriles in alcoholic solutions containing much stronger bases than ammonia was, accordingly, unexpected. Apparently, the reactions of dialkoxyacetonitriles with dicyandiamide are much faster than the cleavage reactions. We have observed that dialkoxyacetonitriles are considerably more reactive toward dicyandiamide, as well as other reagents, than are simple aliphatic nitriles. On the other hand, α,α-dimethoxypropionitrile does not react in the same manner with dicyandiamide. With this compound, apparently, the cleavage reaction predominates over the reaction with dicyandiamide.

Acknowledgment.—Analyses were performed by the Microanalytical Group of the Stamford Research Laboratories.

Experimental[6]

The preparation of the dialkoxyalkanenitriles from hydrocyanic acid and the alkyl esters of ortho acids has already been reported.[1]

Dimethoxyacetoguanamine.—A mixture of dimethoxyacetonitrile (30.3 g., 0.3 mole), dicyandiamide (27.7 g., 0.33 mole), potassium hydroxide (85% pure, 1.0 g., 0.015 mole) and 2-methoxyethanol (75 ml.) was stirred and heated in a suitably equipped three-necked flask. At 60°, the source of heat was removed and the temperature of the solution rose rapidly to 132°, where the mixture refluxed vigorously. After the exothermic reaction had subsided, the mixture was refluxed 15 minutes longer, cooled to 15°, filtered, washed with ethanol and dried. This gave 49.6 g. (89.4%) of guanamine as white prisms, m.p. 207–210°. It was recrystallized twice from water (decolorized with charcoal); m.p. 208–209°.

(1) Previous paper in this series, John G. Erickson, THIS JOURNAL, **73**, 1338 (1951).

(2) Research Dept., General Mills, Inc., Minneapolis, Minn.

(3) W. Zerweck and W. Brunner, U. S. Patent 2,302,162 (Nov. 17, 1942); J. E. Castle, U. S. Patent 2,548,772 (April 10, 1951); J. K. Simons, U. S. Patent 2,522,419 (Dec. 5, 1950); D. W. Kaiser and B. C. Redmon, U. S. Patent 2,510,981 (June 13, 1950); D. W. Kaiser, U. S. Patent 2,606,904 (Aug. 12, 1952).

(4) A. Ostrogovitch and V. Crasu, *Gazz. chim. ital.*, **64**, 800 (1934); **66**, 653 (1936); A. Ostrogovitch and J. Cadariu, *ibid.*, **71**, 505, 515, 524 (1941).

(5) To be reported elsewhere.

(6) Melting points are not corrected.

Anal. Calcd. for $C_6H_{11}N_5O_2$: C, 38.91; H, 5.99; N, 37.80; CH_3O, 33.53. Found: C, 38.92; H, 5.93; N, 37.72; CH_3O, 33.78.

An attempt to carry out this reaction in water solution was unsuccessful. Refluxing began around 80°, the solution turned progressively darker, and the temperature dropped to 60°. Apparently the methoxyl groups of the nitrile are easily hydrolyzed by aqueous alkali, but not by alcoholic alkali, before reaction with dicyandiamide takes place.

Diethoxyacetoguanamine.—A mixture of the diethoxyacetonitrile (25.8 g., 0.2 mole), dicyandiamide (18.6 g., 0.22 mole), potassium hydroxide (0.66 g., 0.01 mole) and 2-methoxyethanol (30 ml.) was heated as described above and worked up in the same manner, giving 40 g. (94%) of white crystalline product, m.p. 195–197°. It was recrystallized from 60% aqueous ethanol; m.p. 194–194.5°. It is thermally stable at least to 260°.

Anal. Calcd. for $C_8H_{15}N_5O_2$: C, 45.04; H, 7.09; N, 32.83; C_2H_5O, 42.25. Found: C, 45.26; H, 7.23; N, 32.72; C_2H_5O, 42.17.

When the quantities of reagents were tripled in this reaction, the exothermic reaction became so violent that half of the contents of the flask were expelled. Attempts to moderate the violence of this reaction were only partially successful. Portionwise addition of the dicyandiamide to the other reagents gave a 48% yield of the guanamine. Addition of the nitrile to the hot mixture of dicyandiamide and alkali gave an 84% yield on a 0.1-mole scale but only 38% on a 0.35-mole scale. When 2-methoxyethanol was replaced by 1-butanol, the reaction rate was decreased (probably because of lower boiling point and lower solubility of dicyandiamide) without impairing the yield; foaming, however, was troublesome. Weaker bases such as piperidine and potassium carbonate gave only dark, tarry products. Use of water as solvent caused hydrolysis of the nitrile.

Di-*n*-butoxyacetoguanamine.—A mixture of dibutoxyacetonitrile (13.0 g., 0.07 mole), dicyandiamide (6.7 g., 0.08 mole), sodium hydroxide (0.3 g., 0.007 mole) and 2-methoxyethanol (35 ml.) was heated to 110°. A mildly exothermic reaction caused the temperature to rise to 130°. The mixture was refluxed for 15 minutes, cooled and poured into water. The filtered and dried product was a white, crystalline material, 16.4 g. (87.2%), m.p. 165–168°. It was recrystallized from methanol; m.p. 166.5–167.5°.

Anal. Calcd. for $C_{12}H_{23}N_5O_2$: C, 53.50; H, 8.61; N, 25.97. Found: C, 53.62; H, 8.35; N, 25.91.

The reaction proceeded similarly when larger amounts of material were used.

Bis-(2-ethyl-1-hexyloxy)-acetoguanamine.—A mixture of bis-(2-ethyl-1-hexyloxy)-acetonitrile (38.2 g., 0.13 mole), dicyandiamide (16.0 g., 0.19 mole), potassium hydroxide (1.0 g., 0.015 mole) and 2-methoxyethanol (50 ml.) was heated as described above for the butyl analog. Ammonia was evolved and insoluble material (melamine[7] and similar materials) formed. The insoluble material was removed by filtration and the filtrate was poured into several volumes of water. The guanamine precipitated as an oil which rapidly hardened to a white, waxy solid. This was washed with water in a Waring blendor and dried. The weight of the crude product was 47.5 g. (96%), m.p. *ca.* 100°. It was recrystallized from hexane; m.p. 115–116°.

Anal. Calcd. for $C_{20}H_{39}N_5O_2$: C, 62.97; H, 10.31; N, 18.34. Found: C, 62.91; H, 10.26; N, 18.43.

Attempted Experiments.—α,α-Dimethoxypropionitrile did not give a guanamine under the conditions used in this study. It did not react exothermically with dicyandiamide and, after refluxing, a very dark solution was obtained which apparently contained none of the desired guanamine.

Heating dialkoxyacetoguanamines in the presence of an acidic condensing agent, such as zinc chloride, transformed them into brittle resins with the loss of the etherifying alcohol.

(7) Dicyandiamide, when heated under alkaline conditions, loses ammonia to form melamine and more complex triazine condensation products. This is especially true in the guanamine synthesis when relatively unreactive nitriles are used. See, for example, D. W. Kaiser, U. S. Patent 2,606,904 (Aug. 12,1952).

AMERICAN CYANAMID CO.
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COMMUNICATIONS TO THE EDITOR

A POLAROGRAPHIC INVESTIGATION OF THE MECHANISM OF MUTAROTATION OF *d*-GLUCOSE

Sir:

It has been shown previously[1] that the polarographic reduction of equilibrium *d*-glucose is a completely rate-controlled process in a 10^{-2} molar solution of LiOH and in a phosphate buffer.

In the present case a solution which was 0.655 molar in *d*-glucose, 0.0183 molar in NaH_2PO_4, 0.0458 molar in Na_2HPO_4 and 0.0916 molar in LiCl gave a wave height of the limiting current of glucose of 57 mm. These current–voltage curves were recorded with a Sargent–Heyrovsky Model XII polarograph at 25°, some 40 minutes after the α-glucose was dissolved, and at $1/5$ of the maximum galvanometer sensitivity (0.0052 μa./mm.). Within the limits of the accuracy obtained this wave height was independent of the height of the mercury level. Immediately after dissolving the α-glucose a current–voltage wave was obtained with a limiting current considerably higher than 57 mm. This limiting current decreased with time, approaching the equilibrium value of 57 mm. The change in wave height was recorded as a function of time, yielding a continuous current–time curve of glucose in the phosphate buffer at 25°.

If the mechanism of mutarotation is considered to be essentially

$$\alpha \underset{k_1'}{\overset{k_1}{\rightleftarrows}} \mu \underset{k_2}{\overset{k_2'}{\rightleftarrows}} \beta \qquad (1)$$

where μ presumably is the aldehyde form, then the kinetic current due to α- and β-glucose separately is given by (*cf.*[2,3])

$$i_k(\alpha) = nF \times 10^{-3} \times 3/5 \times 0.85(mt)^{2/3} \sqrt{D}(k_1/\sqrt{k_1' + k_2'})C_\alpha \qquad (2)$$

and

$$i_k(\beta) = nF \times 10^{-3} \times 3/5 \times 0.85(mt)^{2/3} \sqrt{D}(k_2/\sqrt{k_1' + k_2'})C_\beta \qquad (3)$$

where all symbols have their conventional meaning (mt = 0.00475 g., $D = 6.16 \times 10^{-6}$ cm.^{2}/sec.)[4].

(1) K. Wiesner, *Collection Czechoslov. Chem. Commun.*, **12**, 64 (1947).

(2) K. Wiesner, *Chem. Listy*, **41**, 6 (1947).

(3) J. Koutecky and R. Brdicka, *Collection Czechoslov. Chem. Commun.*, **12**, 337 (1947).

(4) L. Friedman and P. G. Carpenter, THIS JOURNAL, **61**, 1745 (1939).