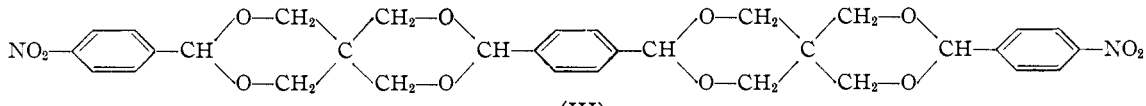


(III)

Experimental

The displacement reactions are summarized in Table I. As an example, the reaction of (I, X = NO_2) with *o*-nitrobenzaldehyde may be described *in extenso:* A mixture of 2.6 g. of (I, X = NO_2), 0.8 g. of *o*-nitrobenzaldehyde, 0.2 g. of naphthalene-2-sulfonic acid and 20 cc. of benzene was refluxed for 4 hours. The dark-brown solution was concentrated to about half its volume. Upon standing, (*o*-nitrobenzylidene) - pentaerythritol di - (*p* - nitrobenzoate) separated. It was filtered, washed with methanol and water and recrystallized from benzene. It then melted at 133°; yield 2.5 g. (89%).

(*o*-Nitrobenzylidene)-pentaerythritol.—The preceding substance (1 g.) was refluxed for one hour with a solution of sodium hydroxide (0.8 g.) in 80% ethyl alcohol (15 cc.). The sodium *p*-nitrobenzoate, which separated, was filtered off and the mother liquor evaporated to dryness. The solid residue was washed with, and subsequently recrystallized from, water (10 cc.). The product, which formed needles of m.p. 148°, was identical with the substance obtained by Tanasescu and Iliescu[6] by a photochemical method (m.p. 145°); yield quantitative.

Anal. Calcd. for $C_{12}H_{15}O_6N$: C, 53.5; H, 5.6. Found: C, 53.7; H, 5.7.

Terephthalylidene-bis-(*p*-nitrobenzylidene-pentaerythritol) (III).—When a solution of *p*-nitrobenzylidene-pentaerythritol[2] (1.3 g.) and terephthalaldehyde (0.5 g.) in alcohol, containing concentrated hydrochloric acid (0.5 cc.), was kept at room temperature for 12 hours, colorless crystals separated. Recrystallization from toluene gave star-like clusters of needles of m.p. 179°; yield, 1.5 g. (50%).

Anal. Calcd. for $C_{32}H_{32}O_{12}N_2$: N, 4.4. Found: N, 4.4.

(6) Tanasescu and Iliescu, *Bull. soc. chim. France*, [5], **5**, 1446 (1938).

REHOVOTH, ISRAEL RECEIVED OCTOBER 12, 1950

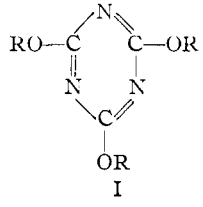
[CONTRIBUTION FROM ABBOTT LABORATORIES]

Anticonvulsant Drugs. V. Some Cyanurates[1]

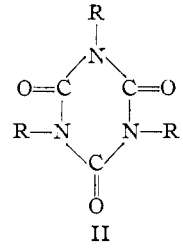
BY M. A. SPIELMAN, W. J. CLOSE AND I. J. WILK

Some alkyl esters of cyanuric acid have been synthesized by the reaction between cyanuric chloride and sodium alkoxides. Tests for possible anti-epileptic activity have shown that several members of the series are able to antagonize the convulsant effect of Metrazol.

In the search for anti-epileptic drugs, any substance known to have a mild depressant effect upon the central nervous system is worthy of consideration. Fränkel[2] has stated without reference to any original literature that triethyl cyanurate has hypnotic properties and, following this lead, we prepared a sample of trimethyl cyanurate which was subjected to routine testing for anticonvulsant action. Its ability to antagonize the convulsing effect of electroshock and Metrazol (pentamethylenetetrazole) led us to synthesize a number of other cyanurates with the results given in Table I.



I



II

The 2,4,6-trialkoxy-1,3,5-triazines (I) which appear in all but the oldest literature as esters of cyanuric acid have been prepared by the reaction between a cyanogen halide and a sodium alkoxide,[3] from cyanuric halides and sodium alkoxides,[4] in poor yield from silver cyanurate and alkyl halides,[4b,5] from alcohols and 2,4,6-tricyano-1,3,5-triazine,[6] by the alcoholysis of cyanogen[3d] and by the pyrolysis of ethyl iminocarbonate.[7] The commercial availability of cyanuric chloride makes the use of that intermediate the method of choice.

Our first experiments were carried out by adding cyanuric chloride to the sodium alkoxide in a large excess of the corresponding alcohol. The yields were generally only 25–35%. It was found that the use of any considerable excess of alcohol was undesirable, possibly because free alcohols react with cyanuric chloride to form alkyl chlorides.[8] When the reaction was carried out in dry benzene, and a good grade of cyanuric chloride was used, the yields were 65–90%.

The possibility that the products were N-substituted derivatives (II) of isocyanuric acid (1,3,5-trialkyl-2,4,6-triazinetriones) had to be considered, since it is known that lower members of the O-alkyl series rearrange to N-alkyl products under the influence of heat,[3b,4b] and high temperatures were often involved in the distillation of our compounds. It was hoped that ultraviolet spectroscopy would provide a useful tool for differentiating between the two species. Typical esters from our work showed no selective ultraviolet absorption but did reveal

(1) Preceding paper, W. J. Close, THIS JOURNAL, **73**, 95 (1951).

(2) S. Fränkel, "Die Arzneimittelsynthese," Julius Springer, Berlin, 1927, p. 525.

(3) (a) S. Cloëz, *Ann.*, **102**, 355 (1857); (b) A. W. Hofmann and O. Olshausen, *Ber.*, **3**, 269 (1870); (c) E. Mulder, *ibid.*, **15**, 69 (1882); **16**, 390 (1883); *Rec. trav. chim.*, **1**, 63, 191 (1881); **2**, 133 (1883); **3**, 287 (1884); (d) J. Ponomarev, *ibid.*, **15**, 513 (1882); (e) E. V. Zappi and J. A. Cagnoni, *Anales asoc. quim. Argentina*, **36**, 58 (1948); *C. A.*, **43**, 9034 (1949); (f) For the effect of temperature on this reaction see J. U. Nef, *Ann.*, **287**, 313 (1895).

(4) (a) A. W. Hofmann, *Ber.*, **19**, 2063 (1886); (b) P. Klason, *J. prakt. Chem.*, [2] **33**, 130 (1885); (c) J. Ponomarev, *Ber.*, **18**, 3261 (1885); (d) W. W. Cuthbertson and J. S. Moffatt, *J. Chem. Soc.*, 561 (1948).

(5) E. Biilmann and J. Bjerrum, *Ber.*, **50**, 503 (1917).

(6) E. Ott, *ibid.*, **52**, 656 (1919).

(7) A. Hantzsch and L. Mai, *ibid.*, **28**, 2466 (1895).

(8) P. Klason, *J. prakt. Chem.*, [2] **34**, 152 (1886).

TABLE I

ALKYL CYANURATES

Alkyl	M.p., °C.[a]	B.p., °C.	Mm.	$n^{25}D$	Formula	Nitrogen, % Calcd.	Nitrogen, % Found	Anticonvulsant potency Electro-shock	Anticonvulsant potency Metrazol
CH_3–[b]	130–132							++	+
C_2H_5–[b]		135	5.0					0	0
CH_2=$CHCH_2$–		161–162	2.5	1.5037	$C_{12}H_{15}N_3O_3$	16.9	16.7	++	++
n-C_3H_7–[c]	33–34	130–133	0.6		$C_{12}H_{21}N_3O_3$	16.5	16.5	+	0
i-C_3H_7–[d]	102–103				$C_{12}H_{21}N_3O_3$	16.5	16.4	0	0
n-C_4H_9–[d]		155–156	0.5	1.4733	$C_{15}H_{27}N_3O_3$	14.1	14.1	0	++
i-C_4H_9–	44–45				$C_{15}H_{27}N_3O_3$	14.1	14.4	0	++
s-C_4H_9–[d]		168	5.0	1.4736	$C_{15}H_{27}N_3O_3$	14.1	14.0	0	++
n-C_5H_{11}–[d]		210–213	5.0	1.4726	$C_{18}H_{33}N_3O_3$	12.4	12.5	0	++
i-C_5H_{11}–[d,e]		165–167	0.6	1.4700				0	+++
s-C_5H_{11}–		147–150	0.4	1.4704	$C_{18}H_{33}N_3O_3$	12.4	12.4	0	++
t-C_5H_{11}–[f]		150 (dec.)	3.0	1.4776	$C_{18}H_{33}N_3O_3$	12.4	12.8	0	0
$(C_2H_5)_2CH$–		155	0.8	1.4737	$C_{18}H_{33}N_3O_3$	12.4	12.7	0	+
n-$C_3H_7CH(CH_3)$–		175–178	0.9	1.4716	$C_{18}H_{33}N_3O_3$	12.4	12.5	0	+
n-C_6H_{13}–		210	1.7	1.4739	$C_{21}H_{39}N_3O_3$	11.0	11.4	0	0
s-C_6H_{13}–		195	2.2	1.4728	$C_{21}H_{39}N_3O_3$	11.0	10.9	0	0
$C_6H_5CH_2$–[g]	101–102							0	0

[a] Temperatures are uncorrected. [b] Reference 4a. [c] Reported without analysis in reference 4a. [d] Reported in reference 3c with properties differing from those here reported. [e] Reference 4b. [f] The best yield was 11%. Cyanuric acid was found in the distilling flask and the trap contained mixed isoamylenes, b.p. 34–40°. [g] Reference 5.

a general end absorption at the lower wave lengths (250–220 mμ). This was fairly conclusive evidence of structure, for the known trimethylisocyanuric acid was completely transparent in this region, and other N-alkyl derivatives would be expected to behave similarly.[9]

A more definite method of distinguishing between O- and N-substitution was found in alkaline hydrolysis, and this method has shown that our compounds are true cyanuric esters. Representative members of the series gave the proper alcohol rather than the amine when hydrolyzed.

The physical properties of several of our cyanurates differ considerably from those reported recently by Zappi and Cagnoni.[3e] For example, these authors give the boiling point of *n*-butyl cyanurate as 75° at 1–2 mm., whereas our sample boiled at 155–156° at 0.5 mm. Their results recall the alleged iso(?)amyl cyanurate of Hofmann and Olshausen[3b] which boiled at 200° at atmospheric pressure, while a subsequent preparation[4b] boiled with some decomposition at 360°. As explained above, we are satisfied that our compounds are true O-alkyl cyanurates, and therefore the authors cited must have had something else in hand.[10]

Pharmacology.—We are indebted to Dr. R. K. Richards and Dr. G. M. Everett for the evaluation of our compounds. The methods of the earlier work[11] were employed in testing for ability to abolish or modify convulsive seizures provoked in mice by electroshock or by injection of Metrazol. Graded, oral doses were given, usually 200, 400 and 800 mg./kg. The principal side effect noted was depression, for the cyanurates proved to be moderately hypnotic.

Results are shown in Table I. The scale of activity is expressed as follows: +++, complete protection without side effects; ++, complete protection, but with some alteration in normal behavior such as ataxia or depression; +, partial protection with central nervous changes. It may be seen that nearly all cyanurates show some activity against Metrazol. The peak seems to be reached in the C_5 series with isoamyl cyanurate the most active of all. Allyl and butyl cyanurate are the most potent hypnotics.

Experimental[12]

Preparation of Cyanuric Esters.—With the exception of certain compounds from early experimental runs, the cyanurates were synthesized as described below. The yields varied from 65% for the isopropyl and allyl esters to 90% for the *n*-butyl derivative. Pertinent physical data for the new compounds involved are included in Table I.

Procedure.—A suspension of the appropriate sodium alkoxide was prepared by refluxing and stirring overnight 1.05 moles of sodium hydride in 1.5 moles of the alcohol mixed with an equal volume of dry benzene. One-third of a mole of cyanuric chloride (must be of good quality) dissolved in a minimum quantity of dry benzene was added dropwise while cooling in ice. After the addition the mixture was refluxed for one hour, cooled, acidified with acetic acid, diluted with water, filtered and separated. The organic phase was washed with water and dried over anhydrous potassium carbonate before distillation under reduced pressure.

Hydrolysis of Cyanuric Esters.—Five grams (19.6 millimoles) of triisopropyl cyanurate was refluxed for three days with a solution of 5 g. of potassium hydroxide dissolved in 10 cc. of diethylene glycol and 20 cc. of water. A suitable water trap was connected to the condenser to prevent loss of volatile products. At the end of the hydrolysis, the water in the trap was added to the reaction mixture which was then distilled into water through a short column. Distillation was continued until pure water began coming over. Titration of the distillate with 0.1 *N* hydrochloric acid to a methyl orange end-point showed the presence of 12.7 millimoles of

(9) Compare W. N. Hartley, J. J. Dobbie and A. Lauder, *J. Chem. Soc.*, **79**, 848 (1901).

(10) In this connection it may be of interest that Ponomarev, *Ber.*, **15**, 515 (1882), found that when the cyanogen chloride reaction was carried out in ethanol and the product exposed to water, urethan could be isolated. It is improbable, however, that Zappi and Cagnoni had carbamates because of the melting points and the excellent analyses which they give.

(11) G. M. Everett and R. K. Richards, *J. Pharmacol.*, **81**, 402 (1944).

(12) Microanalysis by E. F. Shelberg and staff. Ultraviolet spectra by Charles Savidas.

basic material. The neutralized solution was then distilled until all of the isopropyl alcohol had been removed. The distillate was assayed for the alcohol by comparison of its refractive index with that of mixtures of known composition. It was found to contain 3.1 g. (51.7 millimoles) of the alcohol. The excellent yield (88%) of alcohol demonstrates that the starting material was O-substituted. The basic fraction (22%) must have consisted, at least in part, of ammonia derived from the breakdown of cyanuric acid, although it may have contained a maximum of 12% of isopropylamine resulting from rearrangement during the prolonged heating period.

Similar results were obtained with *n*-propyl and *s*-amyl cyanurates. In these instances refluxing was continued for shorter periods of time and only traces of base were found. In a 10-g. run of *s*-amyl cyanurate, distillation of ether-extracted material gave 4.8 g. of *s*-amyl alcohol, b.p. 110–118°, $n^{20}D$ 1.4052 (lit. b.p. 119°, $n^{20}D$ 1.4053).

NORTH CHICAGO, ILLINOIS RECEIVED OCTOBER 9, 1950

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

Partial Synthesis of Reichstein's Substance E[1]

BY L. H. SARETT, MAX FEURER AND KARL FOLKERS

The partial synthesis of Reichstein's Substance E, 4-pregnene-11β,17α,20β,21-tetrol-3-one, has been accomplished *via* two routes: A, from pregnane-3α,17α,20β,21-tetrol-3-one 20,21-acetonide by reduction of the 11-ketone with lithium aluminum hydride, partial oxidation by the Oppenauer method and introduction of the 4,5-double bond; B, by reduction of the 3-enol ether of cortisone acetate.

The characterization of 4-pregnene-11β,17α,20β,-21-tetrol-3-one (VI), Reichstein's Substance E, and its isolation from the adrenal glands of cattle have been reported by Reichstein[2] and Reichstein and von Euw.[3] The present paper describes the partial synthesis of this compound from pregnane-3α,17α,-20β,21-tetrol-11-one[4] and also from cortisone acetate. The former route proceeded *via* the 20,21-acetonide[4] (I) which with lithium aluminum hydride was reduced with a high degree of stereospecificity to pregnane-3α,11β,17α,20β,21-pentol 20,21-acetonide (II). The steric course of this reduction is thus the same as that of catalytic hydrogenation.[5] Extending the views of Trevoy and Brown[6] on the mechanism of reduction with lithium aluminum hydride to the present case, it is apparent that the reagent finds free entrance to the C-11 position only from the rear of the molecule. This result parallels the findings of Ott and Murray[7] who obtained estradiol-17β from estrone in high yield and those of Shoppee and Summers[8] who noted that coprostanone and cholestanone are reduced in a sterically unique sense. In contrast, cholestane-3β-ol-7-one showed no steric selectivity on reduction to the diol with lithium aluminum hydride.[9]

The partial oxidation of the pentol acetonide (II) to the desired tetrol-3-one acetonide (III) was accomplished through an Oppenauer oxidation.[10] It is interesting parenthetically that the rate of oxidation of the 11β-hydroxyl group with substances capable of liberating hypobromous acid, such as N-bromoacetamide, is greater than that of the 3α-hydroxyl (A/B *cis*). This result may be compared with the recorded observation[9] that the rate of oxidation of an hydroxyl group at the 11β-position with chromic acid is much greater than that at the 20β-position. It appears probable from these results and from those of Fieser and Rajagopalan,[11] who investigated the partial oxidation of various polyhydroxy steroids with N-bromosuccinimide that the oxidation rate of a given secondary hydroxyl group is far more dependent on the stability of the intermediate hypobromite ester (or chromic ester) than on the degree of steric hindrance of the hydroxyl group, as measured by its accessibility to acylating agents.

Hydrolysis of the acetonide (III) with warm dilute acetic acid yielded the free tetrolone (IV), from which the diacetate (V) was readily prepared. Bromination of the latter afforded an amorphous 4-bromo derivative, condensation of which with dinitrophenylhydrazine gave the dinitrophenylhydrazone[12] of Substance E diacetate, also an amorphous powder. However, chromatography of the crude pyruvic acid[12] hydrolysis product yielded a compound the properties of which agreed with those of Substance E diacetate (VII).

Substance E could also be obtained from cortisone acetate in three steps. The α,β-unsaturated carbonyl group was protected by formation of an enol ether[13] (VIII). Reduction with lithium aluminum hydride then afforded $\Delta^{3,5}$-3-ethoxypregnadiene-11β,17α,20β,21-tetrol, acid hydrolysis of which gave a hydrated pregnanetetrolone which from its physical constants and its method of preparation must be identical with the hydrate of Substance E. On acetylation this material yielded the same diacetate obtained by the first-described method.

Experimental[14]

Pregnane-3α,11β,17α,20β,21-pentol 20,21-Acetonide (II).—To a solution of 3.78 g. of pregnane-3α,17α,20β,21-tetrol-11-one 20,21-acetonide (I) in 40 cc. of absolute

(1) The substance of this paper was presented at the 118th Meeting of the American Chemical Society, September 5, 1950.

(2) Reichstein, *Helv. Chim. Acta*, **19**, 29 (1936); **20**, 953 (1937).

(3) Reichstein and von Euw, *ibid.*, **24**, 247E (1941).

(4) Sarett, THIS JOURNAL, **71**, 1169 (1949).

(5) See, for example, Lardon and Reichstein, *Helv. Chim. Acta*, **27**, 713 (1944). The 11β-hydroxyl group is designated 11α in the cited reference, according to the convention of that period.

(6) Trevoy and Brown, THIS JOURNAL, **71**, 1675 (1949).

(7) Abstracts of American Chemical Society, 113th Meeting (1948).

(8) Shoppee and Summers, *J. Chem. Soc.*, 687 (1950).

(9) Fieser, Fieser and Chakravarti, THIS JOURNAL, **71**, 2226 (1949).

(10) *Cf.* Reich and Reichstein, *Arch. Inst. Pharmacodyn. Therap.*, **68**, 415 (1943); von Euw, Lardon and Reichstein, *Helv. Chim. Acta*, **27**, 821 (1944).

(11) Fieser and Rajagopalan, THIS JOURNAL, **71**, 3935, 3938 (1949).

(12) The procedure of Mattox and Kendall, *ibid.*, **70**, 882 (1948); *J. Biol. Chem.*, **188**, 601 (1950).

(13) *Cf.* Serini and Koster, *Ber.*, **71**, 1766 (1938).

(14) Melting points were taken on the Kofler micro hotstage.