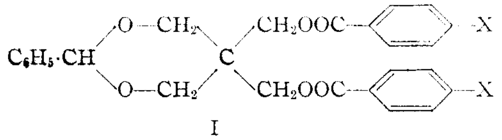
[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

Experiments with Acetals of Pentaerythritol. II

BY ERNST D. BERGMANN AND ELIAHU BOGRACHOV[1]

Additional exchange reactions have been investigated between **benzylidene-pentaerythritol dibenzoates** (I) and various **aldehydes and ketones**. The exchange ability is a specific property of the carbonyl compounds and is not influenced by the **operating** conditions. Of the ketones, only cyclopentanones and cyclohexanones displace the benzaldehyde radical in (I), **forming** spiranes.

In a previous communication,[2] it has been shown that dibenzylidene-pentaerythritol and benzylidene-pentaerythritol dibenzoate (or di-*p*-nitrobenzoate) (I, X = H or NO_2) exchange the benzylidene against the *p*-nitrobenzylidene group, when treated with *p*-nitrobenzaldehyde in presence of an acidic catalyst.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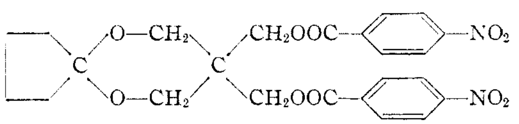
II

An attempt was made to determine whether there exists a gradation of affinity of carbonyl compounds to the pentaerythritol system or whether the above exchange reaction is governed by factors such as the relative quantities of the reactants and the solubilities of the products. The compounds obtained by interaction of various aldehydes and ketones with benzylidene-pentaerythritol dibenzoate or di-*p*-nitrobenzoate (I) are listed in Table I. The following carbonyl compounds could not be induced to react, even if applied in large excess: *o*- and *p*-methoxybenzaldehyde, *p*-dimethylaminobenzaldehyde, methyl isobutyl ketone, ethyl acetoacetate, camphor, acetophenone, fluorenone, cinnamic aldehyde, citral and β-ionone.

TABLE I

DISPLACEMENT REACTIONS OF (I) WITH VARIOUS CARBONYL COMPOUNDS

Solvent, benzene; catalyst, naphthalene-2-sulfonic acid

No.	Carbonyl compound	I, X =	Duration, hour	Yield, %	M.p., °C.	Product Formula	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	*o*-Nitrobenzaldehyde	NO_2	4	89	133[a]	$C_{26}H_{21}O_{12}N_3$			7.5			7.7
2	*m*-Nitrobenzaldehyde	NO_2	1	88	141.5[b]	$C_{26}H_{21}O_{12}N_3$			7.5			7.4
3	*m*-Chlorobenzaldehyde	NO_2	4	65	115[c]	$C_{26}H_{21}O_{10}N_2Cl$			5.0			5.0[c]
4	Heptaldehyde	H	5	90	94.5[d]	$C_{26}H_{32}O_6$	70.9	7.3		71.0	7.6	
5	Cyclohexanone	H	3	75	124[d]	$C_{25}H_{28}O_6$	70.7	6.6		70.4	6.9	
6	Cyclohexanone	NO_2	3	90	147[e]	$C_{25}H_{26}O_{10}N_2$	58.4	5.1		58.6	5.1	
7	3-Methylcyclohexanone	NO_2	3	90	98[a]	$C_{26}H_{28}O_{10}N_2$			5.3			5.4
8	Cyclopentanone	NO_2	3	90	92[a]	$C_{24}H_{24}O_{10}N_2$	57.6	4.8	5.6	57.5	5.0	5.6

[a] Recrystallized from benzene. [b] Recrystallized from toluene. [c] Calcd.: Cl, 6.3. Found: Cl, 6.4. [d] Recrystallized from ethyl alcohol. [e] Recrystallized from isobutanol.

If it is permissible to draw a general conclusion from this limited number of experiments, one may state: (a) Aliphatic aldehydes and those substituted benzaldehydes which are not inactivated by alkoxy- or dimethylamino- radicals, displace the benzylidene group. For *p*-dimethylaminobenzaldehyde, this is in keeping with the observation of Fairbourne and Woodley[3] that benzaldehyde displaces the *p*-dimethylaminobenzylidene group in mono-(*p* - dimethylaminobenzylidene) - pentaerythritol. (b) Ketones do not displace the benzylidene radical in (I), with the exception of cyclopentanone, cyclohexanone and 3-methylcyclohexanone which form *spiranes* of type (II). There appears[4] to be a definite tendency to form such spiranes, *e.g.*, in the reaction of cyclohexanone with ethylenediamine while aliphatic and aromatic ketones yield double Schiff bases with the diamine.[5]

The ability to displace the benzylidene group in (I) is, therefore, a specific property of certain aldehydes and ketones: it does not depend on the relative concentration of the reactants. This is in accord with the observation that benzaldehyde, even if used in excess, did not react with heptylidene-pentaerythritol dibenzoate or *p*-nitrobenzylidene-pentaerythritol di-(*p*-nitrobenzoate).

The exchange reactions require an acidic catalyst: aromatic sulfonic acids are most effective; but trichloroacetic acid can often be used to advantage, especially in the case of sensitive carbonyl compounds.

From terephthalaldehyde and *p*-nitrobenzylidene-pentaerythritol, an interesting seven-ring compound (III) has been synthesized.

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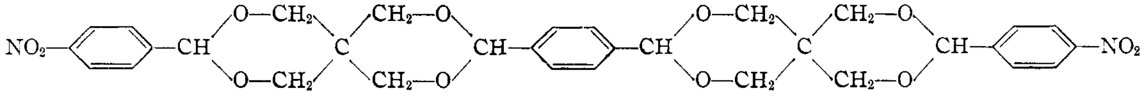
(1) Division of Plant Protection, Ministry of Agriculture, Tel-Aviv, Israel.

(2) Bograchov, THIS JOURNAL, **72**, 2268 (1950).

(3) Fairbourne and Woodley, *J. Chem. Soc.*, 3240 (1926).

(4) E. Bergmann, Meeron, Hirshberg and Pinchas, *Rec. trav. chim.*, in press (1951). Compare E. Bergmann, Fischer, Zimkin and Pinchas, *ibid.*, in press (1951).

(5) A similar observation has been made in the condensation of salicylamide with aldehydes and ketones. Ketones are, on the whole, refractory; however, cyclopentanone and cyclohexanone show the same response as aldehydes (Horrom and Zaugg, THIS JOURNAL, **72**, 721 (1950)).



(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.

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

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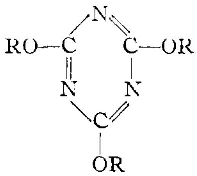
[CONTRIBUTION FROM ABBOTT LABORATORIES]

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.



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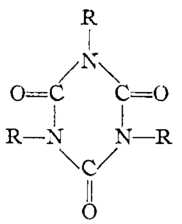

II

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).