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THE SYNTHESIS OF ALKYLATED PENTAMETHYLENE-TETRAZOLE CARBOXYLIC ACIDS

CARLETON W. ROBERTS,[1] ROBERT M. HERBST,[2] AND EDWARD K. HARVILL[3]

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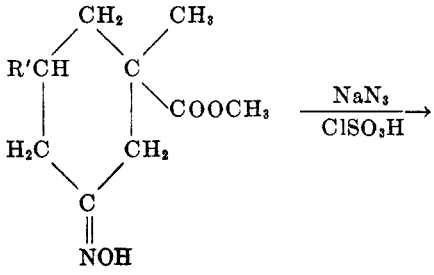
In a previous paper the preparation of a series of alkylated pentamethylene-tetrazole derivatives was described (1). Although the parent pentamethylene-tetrazole is very easily soluble in water, the substitution of even a single methyl group on the pentamethylene carbon skeleton caused a profound decrease in water-solubility, while larger alkyl groups and di- or tri-methyl substitution caused almost complete disappearance of water-solubility. Since the pentamethylenetetrazole structure, as a 1,5-dialkylated tetrazole derivative, has an essentially neutral reaction and fails to form stable salts with acids or alkalies, it became desirable to attempt the preparation of such bicyclic structures incorporating a salt-forming group to insure the probability of water-solubility. Furthermore, the possibility existed that some of the polyalkylated structures previously prepared owed their lack of pharmacologic action to their insolubility in water. Although the introduction of a carboxyl group frequently serves to reduce the toxicity of the parent structure, this appeared to be the simplest method of incorporating a salt-forming group in the alkylated pentamethylenetetrazole structure.

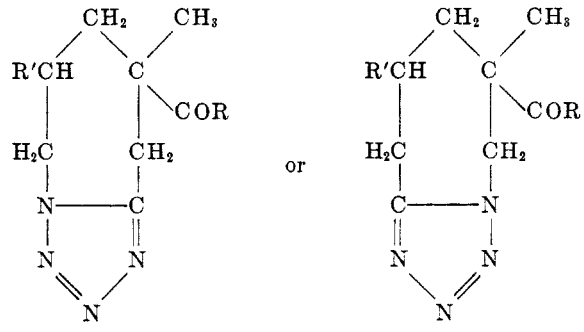
Suitable intermediates for the synthesis of the desired structures have recently been prepared in this laboratory and described by Whitmore and Roberts (2), who reported the preparation of the esters of a number of 3,5-dialkyl- and 3,5,5-trialkyl-cyclohexanone-3-carboxylic acids. The synthesis of these esters was based upon Knoevenagel's observation (3, 4) that ring-alkylated derivatives of Δ^2-cyclohexenone readily undergo addition of sodium bisulfite at the carbon-carbon double bond, and that the sulfonic acid group so introduced could be replaced by a cyanide group by interaction with sodium or potassium cyanide. Simultaneous hydrolysis and esterification of the cyanoketones led to esters of the polyalkylcyclohexanone carboxylic acids.

The keto esters so obtained were converted into the corresponding pentamethylenetetrazole derivatives by the procedure outlined previously (1), namely, formation of the oxime and treatment of the latter with sodium azide and chlorosulfonic acid in an inert solvent. Since the oximes were usually liquids that solidified only slowly to give products having a rather broad melting range even after several recrystallizations, attempts to purify the oximes were omitted and the crude intermediates were used directly in the second step of the procedure.

[1] Present address: Department of Chemistry, University of Illinois, Urbana, Illinois.
[2] Present address: Kedzie Chemical Laboratory, Michigan State College, East Lansing, Michigan.
[3] Present address: Ernst Bischoff Company, Inc., Ivoryton, Connecticut.

The presence of diastereoisomeric forms could account for the difficulty in purifying the oximes.





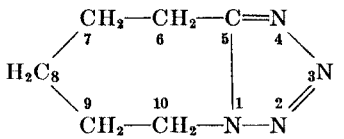
Ia R = OCH_3 Ib R = OCH_3
II R = OH
III R = $N(C_2H_5)_2$; R'H = $(CH_3)_2$

Depending upon the configuration of the individual oximes, the reaction employed in the formation of the tetrazole derivatives could conceivably lead to either of two isomeric structures. The configuration favoring rupture of the bond between C_1 and C_6 of the cyclohexanone ring would form a tetrazole of structure Ia, while the oxime configuration favoring rupture of the bond between C_1 and C_2 would initiate rearrangement and cyclization leading to form Ib. Since no steps were taken to separate the isomeric oximes, it was to be anticipated that mixtures of the configurations I (a and b) might be formed. Although the tetrazole esters appeared to be pure, homogeneous entities, which exhibited constant melting points on recrystallization from several different solvents, the two possible structures could not be distinguished by any simple expedient. For the sake of uniformity the structure Ia has been assigned arbitrarily to all of the new compounds. Employing the same numbering scheme previously suggested for pentamethylenetetrazole derivatives (1), the compounds are methyl esters of 7-methyl-9-alkyl-pentamethylenetetrazole-7-carboxylic acids (Formula Ia), or in the other instance esters of 7-alkyl-9-methyl-pentamethylenetetrazole-9-carboxylic acids.

The free acids were obtained by saponification of the methyl esters with aqueous sodium hydroxide. The yields of acids and the ease with which products of constant melting point were obtained might be considered as further evidence

TABLE I

Pentamethylenetetrazole Carboxylic Acid Derivatives



Code No.[a]	Substituted Pentamethylene Tetrazole[b]	Yield, %	M.P., °C.	Crystals	Solvent	Molecular Formula	Analysis					
							Calc'd			Found		
							C	H	N	C	H	N
TT-8	7,9-Dimethyl-7-carbomethoxy	48	114–115	Prisms	Methanol ether	$C_{10}H_{16}N_4O_2$	53.5	7.1	25.0	53.6	7.0	25.1
TT 54	7,9-Dimethyl-7-carboxy	90	238 (d.)	Small needles	Water	$C_9H_{14}N_4O_2$	51.4	6.7	26.7	51.5	6.6	26.8
TT-63	7-Methyl-9-ethyl-7-carbomethoxy	40	68–69	Needles	Ether-pet. ether	$C_{11}H_{18}N_4O_2$	55.5	7.6	23.5	55.5	7.5	23.7
TT-64	7-Methyl-9-ethyl-7-carboxy	60	161–162	Needles	Water	$C_{10}H_{16}N_4O_2$	53.6	7.1	25.0	53.8	7.1	24.8
TT 59	7-Methyl-9-*n*-propyl-7-carbomethoxy	83	(B.p. 163–165°/1)	—	—	$C_{12}H_{20}N_4O_2$	—	—	—	—	—	—
TT-60	7-Methyl-9-*n*-propyl-7-carboxy	85	174.5–175.5	Prisms	Water	$C_{11}H_{18}N_4O_2$	55.4	7.6	23.5	55.2	7.6	23.4
TT-55	7-Methyl-9-isopropyl-7-carbomethoxy	62	76.5–77.5	Prisms	Ether-pet. ether	$C_{12}H_{20}N_4O_2$	57.1	7.9	22.2	57.2	7.7	22.2
TT-57	7-Methyl-9-isopropyl-7-carboxy	90	201–201.5	Needles	Water	$C_{11}H_{18}N_4O_2$	55.5	7.6	23.5	55.2	7.7	23.1
TT-2	7,9,9-Trimethyl-7-carbomethoxy	43	131–132	Needles	Heptane-benzene	$C_{11}H_{18}N_4O_2$	55.4	7.6	23.5	55.6	7.4	23.6
TT-53	7,9,9-Trimethyl-7-carboxy	75	263–264 (d.)	Leaflets	Water	$C_{10}H_{16}N_4O_2$	53.5	7.1	25.0	53.5	7.0	25.0
TT-56	7,9,9-Trimethyl-7-diethylcarboxamide	67	140–141	Prisms	Water	$C_{14}H_{26}N_6O$	60.2	9.0	25.1	60.2	8.8	25.3

[a] Compounds were identified by these code numbers in the communications of Gross and Featherstone (5). [b] By application of Chemical Abstracts usage the compounds may also be named as 8,6-dialkyl-8-carboxy-6,7,8,9-tetrahydro-5-azepotetrazole derivatives, for example, TT-63 is 8-methyl-6-ethyl-8-carbomethoxy-6,7,8,9-tetrahydro-5-azepotetrazole. Other compounds would be named in an analogous manner.

for the homogeneity of the esters. In one instance the acid was further converted into the diethylamide by way of the acid chloride, which formed readily upon interaction of the acid with thionyl chloride, followed by treatment of the acid chloride with diethylamine. The possibility of isomeric structures is recognized in the arbitrary assignment of formulas for the acids (II) and the diethylamide of 7,9,9-trimethylpentamethylenetetrazole-7-carboxylic acid (III).

Pertinent data regarding the new tetrazole esters and acids are summarized in Table I, where the naming of the compounds as 6,7,8,9-tetrahydro-5-azepotetrazoles according to Chemical Abstracts usage is included.

The pharmacologic actions of these compounds have been described by Gross and Featherstone (5). Neither the esters nor the acids showed profound effects upon rats. Introduction of the carboxyl groups, even in esterified form, markedly decreased the stimulatory action of the compounds on the central nervous system. Toxicity also appeared to be reduced.

EXPERIMENTAL[4]

Methyl 3,5-dialkylcyclohexanone-3-carboxylates. The preparation of the dialkylcyclohexanone carboxylic acid esters used as intermediates was described in an earlier communication by Whitmore and Roberts (2).

Methyl 7,9-dialkylpentamethylenetetrazole-7-carboxylates. The tetrazole esters were prepared by a method analogous to that employed for the synthesis of alkylated pentamethylenetetrazoles (1). The preparation of methyl 7,9-dimethylpentamethylenetetrazole-7-carboxylate may serve as a typical example.

To a solution of 8 g. (0.049 mole) of hydroxylamine sulfate, 3.9 g. (0.098 mole) of sodium hydroxide, and 8 g. (0.098 mole) of anhydrous sodium acetate in 75 ml. of water there was added 16 g. (0.088 mole) of methyl 3,5-dimethylcyclohexanone-3-carboxylate. After thorough shaking at frequent intervals during three hours, the oxime layer was taken up in ether and the aqueous layer was twice extracted with 30-ml. portions of ether. The combined ether solutions were dried over sodium sulfate, and after removal of the solvent, the residual oxime was distilled under reduced pressure. A fraction (13 g., 76%) distilling at 156–158°/11 mm. was collected. The crude oxime was a viscous, colorless liquid. (In some instances the oxime solidified slowly during the preparation and was used in the subsequent step without further purification.)

The conversion of the oxime into the tetrazole was carried out in a good hood. A suspension of 10.8 g. (0.17 mole) of powdered sodium azide in 200 ml. of propylene dichloride (ethylene dichloride may also be used) was prepared in a 1-liter three-necked flask equipped with a stirrer, dropping-funnel, thermometer, and exit tube. An alcohol thermometer is preferable. The bulb of the thermometer and the tip of the dropping-funnel should extend below the surface of the reaction mixture. Provision should be made for the absorption of the hydrogen chloride and hydrazoic acid evolved during the course of the reaction. To the vigorously stirred suspension 116 g. (0.99 mole) of chlorosulfonic acid was added dropwise at such a rate that the temperature of the mixture did not rise above 35°. After complete addition of the chlorosulfonic acid, a solution of 16.5 g. (0.083 mole) of methyl 3,5-dimethylcyclohexanone-3-carboxylate oxime in 25 ml. of propylene dichloride was added with continued vigorous stirring at such a rate that a reaction temperature of 40–45° was maintained. Stirring was continued until the reaction mixture had cooled to room temperature when it was surrounded by an ice-bath, cooled to 5°, and the excess chlorosulfonic acid decomposed by the slow addition of 50 ml. of water taking care that the temperature did not rise above 10°. The propylene dichloride layer was separated

[4] Microanalyses were performed on all compounds by Mr. William Saschek.

from the acid layer and the latter was diluted with 800 ml. of ice and water before extraction with two 250-ml. portions of propylene dichloride. The combined propylene dichloride solutions were washed with 10% potassium carbonate solution and dried over potassium carbonate. After removal of the solvent under reduced pressure on a water-bath, the residue was treated with petroleum ether. On standing, the *7,9-dimethylpentamethylenetetrazole-7-carboxylic acid methyl ester* crystallized and was obtained in the form of colorless, dense prisms on recrystallization from ether-methanol mixtures. Yield, 9 g. (48%); m.p. 114–115°.

The esters of the other dialkyl- and trimethyl-pentamethylenetetrazole carboxylic acids were obtained in an analogous manner. The products are described in Table I where analytical data are also recorded. The 7-methyl-9-*n*-propyl analog failed to crystallize but could be distilled under reduced pressure to effect partial purification. No analyses were carried out on this compound.

7,9-Dialkylpentamethylenetetrazole-7-carboxylic acids. The preparation of 7,9-dimethylpentamethylenetetrazole-7-carboxylic acid is described as typical of the procedure used for the saponification of the esters. A suspension of 9 g. of the methyl ester in 100 ml. of 5% sodium hydroxide was boiled under reflux for 30 minutes during which time the ester dissolved completely. After the hot solution was decolorized with charcoal, it was acidified to Congo Red with hydrochloric acid. On cooling the tetrazole acid crystallized as small, colorless needles. Recrystallization from water gave 8.5 g. (90%) of *7,9-dimethylpentamethylenetetrazole-7-carboxylic acid;* m.p. 238° (d.).

Other acids were prepared in an analogous manner. Analytical data and physical constants of the products are recorded in Table I. All of the acids are moderately soluble in hot water and almost completely insoluble in cold water in which they dissolve readily, however, upon addition of sodium or potassium hydroxide.

7,9,9-Trimethylpentamethylenetetrazole-7-carboxylic acid diethylamide. A suspension of of thionyl chloride in 50 ml. of benzene was boiled under reflux for 2½ hours. Neither the acid nor the acid chloride was completely soluble in benzene, but the character of the solid changed from a light bulky material to a rather dense, heavy, granular product. The benzene and excess thionyl chloride were removed under reduced pressure; then the crude acid chloride was suspended in 50 ml. of dry benzene and treated with an excess of diethylamine. After the suspension had been heated on a water-bath for an hour and allowed to stand at room temperature for 24 hours, the diethylamide was separated from the accompanying diethylammonium chloride by extraction with hot benzene. After recrystallization from water, 9.5 g. of pure diethylamide, melting at 140–141° was obtained. Analytical data are recorded in Table I.

SUMMARY

The preparation of the methyl esters of five di- and tri-alkylpentamethylenetetrazole carboxylic acids and the corresponding free acids has been described. In one instance the diethylamide of the acid was prepared. None of the compounds exhibited marked pharmacologic activity. Evidenty the introduction of the carboxyl group, although it permits the formation of water-soluble salts, severely reduces the activity of the resulting products.

ORANGE, NEW JERSEY

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