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Preparation of Aliphatic *gem*-Dinitro Monoisocyanates and Derivatives

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The first aliphatic *gem*-dinitro diisocyanate was reported by Herzog, Gold, and Geckler.[3] This paper describes the preparation of the first aliphatic *gem*-dinitro monoisocyanates by modifications of the original procedure. In general the starting materials were derived from a Michael addition of a *gem*-dinitroalkane[4] to acrylic acid. The nitro acid (I) was converted by the Curtius reaction into the corresponding isocyanate (IV), *via* the respective acid chloride (II) and azide (III).

$$\underset{\text{I}}{RC(NO_2)_2CH_2CH_2CO_2H} \longrightarrow \underset{\text{II}}{RC(NO_2)_2CH_2CH_2COCl} \longrightarrow \underset{\text{III}}{RC(NO_2)_2CH_2CH_2CON_3} \longrightarrow \underset{\text{IV}}{RC(NO_2)_2CH_2CH_2NCO}$$

$$R = NO_2,\ CH_3,\ CH_3O_2CCH_2CH_2$$

The nitro isocyanates obtained by these means were isolated from the acid chlorides in over-all yields of 60–71% as viscous distillable liquids. They were characterized by conversion into carbamates (V), hydrolysis of the carbamates or the isocyanates with hydrochloric acid gave the corresponding amine hydrochlorides (VI), while treatment of the isocyanates with water yielded the ureas (VII).

$$\underset{\text{IV}}{RC(NO_2)_2CH_2CH_2NCO} \xrightarrow{R'OH} \underset{\text{V}}{RC(NO_2)_2CH_2CH_2NHCO_2R'}$$

$$\underset{\text{IV}}{RC(NO_2)_2CH_2CH_2NCO} \xrightarrow{H_2O} \underset{\text{VII}}{[RC(NO_2)_2CH_2CH_2NH]_2C{=}O}$$

$$\underset{\text{IV}}{RC(NO_2)_2CH_2CH_2NCO} \xrightarrow{HCl} \underset{\text{VI}}{RC(NO_2)_2CH_2CH_2NH_2\cdot HCl}$$

The physical properties of these compounds are listed in Table I.

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EXPERIMENTAL[5,6]

Nitro acids (I) 4,4-Dinitropentanoic acid was prepared as reported by Shechter[4] and 4,4,4-trinitrobutyric acid was made by the hydrolysis of methyl 4,4,4-trinitrobutyrate.[7] The synthesis of 4,4-dinitro-6-carbomethoxyhexanoic acid is described below. A slurry of 107 g. (0.51 mole) of the sodium salt of methyl 4,4-dinitrobutyrate[8] and 500 ml. of water was warmed to 45° and 180 g. (2.5 moles) of acrylic acid was added. The reaction mixture was stirred at 45° for 3 hr., cooled, and extracted with methylene chloride. The extracts were washed with water and concentrated leaving an oily residue which solidified upon standing at −20°. Recrystallization of the product from isopropyl ether gave 84.5 g. (63.1%) of white crystals, m.p. 92–93°.

Anal. Calcd. for $C_8H_{12}N_2O_8$: C, 36.38; H, 4.58; N, 10.61. Found: C, 37.02; H, 4.53; N, 10.62.

Nitro acid chlorides (II). The acid chlorides were prepared by refluxing the acids with thionyl chloride for 4–6 hr. Generally the crude acid chlorides were not purified but converted directly to the isocyanates. It was found that refluxing 4,4,4-trinitrobutyric acid with thionyl chloride for 4 hr. gave the anhydride while the acid chloride was only obtained after 20 hr., of refluxing.

A mixture of 8.9 g. (0.04 mole) of 4,4,4-trinitrobutyric acid and 10 ml. (0.138 mole) of redistilled thionyl chloride was refluxed for 4 hr. and concentrated *in vacuo*. The residual oil crystallized and was dissolved in 8.5 ml. of benzene. Addition of 30 ml. of hexane caused 2.8 g. (33%) of white solid to separate, m.p. 107–108.5°. Recrystallization from methylene chloride raised the melting point to 109.5–110°.

Anal. Calcd. for $C_8H_3N_6O_{15}$: C, 22.44; H, 1.88; N, 19.63. Found: C, 22.60; H, 2.06; N, 19.44.

A mixture of 49.0 g. (0.22 mole) of 4,4,4-trinitrobutyric acid and 100 ml. (1.38 moles) of thionyl chloride was refluxed for 20 hr. and concentrated *in vacuo*. The residual oil was distilled yielding 44.0 g. (82%), b.p. 65–66°/0.5 mm., n_D^{25} 1.4835, d^{25} 1.5669.

Anal. Calcd. for $C_4H_4ClN_3O_7$: C, 19.89; H, 1.67; N, 17.40 Found: C, 20.28; H, 1.74; N, 17.45.

Nitro isocyanates (IV). The preparation of 3,3-dinitrobutyl isocyanate is given as typical. A mixture of 50 g. (0.26 mole) of 4,4-dinitropentanoic acid and 300 ml. of thionyl chloride was refluxed for 6 hr. and concentrated *in vacuo* to give 55.0 g. (100%) of 4,4-dinitropentanoyl chloride. A solution of the acid chloride in 75 ml. of acetone was added dropwise to a solution of 27.9 g. (0.43 mole) of sodium azide in 279 ml. of water, at a temperature of 10–20°. The solution became cloudy and deposited crystals of the azide. The reaction mixture was stirred for 30 min. and extracted with 500 ml. of chloroform. The chloroform solution was washed with water, dilute sodium bisulfite solution, water, and dried over sodium sulfate. The solution was partially concentrated *in vacuo* to remove the last traces of water and then heated to reflux until the evolution of nitrogen had ceased. The solution was then concentrated *in vacuo* and the residual oil was distilled to give 31.7 g. (63.0%), b.p. 106–110°/1 μ, n_D^{25} 1.4708.

Carbamates (V). The carbamates were prepared in quantitative yields by refluxing the isocyanates with methanol or ethanol.

Amine hydrochlorides (VI). The preparation of 3,3-dinitrobutylamine hydrochloride from 3,3-dinitrobutyl isocyanate and methyl *N*-(3,3-dinitrobutyl)-carbamate is given as typical.

From 3,3-dinitrobutyl isocyanate. A 450-g. (2.38 moles) quantity of 3,3-dinitrobutyl isocyanate was added dropwise with good agitation to 2250 ml. of concentrated hydrochloric

(5) All melting points are uncorrected.

(6) Microanalyses by Elek microanalytical Laboratories, Los Angeles, Calif.

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TABLE I

Compound	B.P. °C/ micron	n_D^{25}	M.P.	Recryst. Solvent	Yield, %	Formula	Calcd. C	Calcd. H	Calcd. N	Calcd. Cl	Calcd. OCH_3	Found C	Found H	Found N	Found Cl	Found OCH
Isocyanates																
3,3-Dinitrobutyl	106–110	1.4708			63.0	$C_5H_7N_3O_5$			22.22					21.98		
5-Carbomethoxy-3,3-dinitrobutyl	140–150	1.4793			60.8	$C_8H_{11}N_3O_7$	36.78	4.25	16.09			37.37	4.58	16.40		
3,3,3-Trinitropropyl	73–75	1.4805			71.2	$C_4H_4N_4O_7$	21.83	1.83	25.41			21.94	1.76	25.52		
Carbamates																
Methyl *N*(3,3-dinitrobutyl)			48–49	Diethyl ether	[a]	$C_6H_{11}N_3O_6$			19.00					19.13		
Methyl *N*-(5-carbomethoxy-3,3-dinitropentyl)			74–75	Diisopropyl ether		$C_9H_{15}N_3O_8$	36.86	5.15				37.10	5.22			
Ethyl *N*-(3,3,3-trinitropropyl)			65.5–66	Cyclohexane		$C_6H_{10}N_4O_8$	27.07	3.79	21.05			27.63	3.94	21.56		
Amine Hydrochlorides																
3,3-Dinitrobutyl			220–230	Methanol-ether		$C_4H_{10}ClN_3O_4$			21.05	17.76				21.46	17.49	
5-Carboxy-3,3-dinitropentyl			180–182	Methanol-ether		$C_6H_{12}ClN_3O_6$			16.31	13.76				16.30	13.87	
3,3,3-Trinitropropyl			161–163	Nitromethane–ethylene dichloride		$C_3H_7ClN_4O_6$	15.63	3.06	24.40	15.38		16.04	3.05	24.34	15.57	
Ureas																
Bis(3,3-dinitrobutyl)			120–121	Chloroform		$C_9H_{16}N_6O_9$			23.86					23.82		
Bis(5-carbomethoxy-3,3-dinitropentyl)			159–160	Ethylene dichloride		$C_{15}H_{24}N_6O_{13}$	36.29	4.87	16.93		12.61	36.71	4.92	17.36		12.12
Bis(3,3,3-trinitropropyl)			170–171	Chloroform		$C_7H_{10}N_8O_{13}$	20.30	2.43	27.05			20.44	2.35	27.04		

[a] The yields of carbamates, amine hydrochlorides, and ureas were essentially quantitative.

acid. Carbon dioxide was evolved immediately and a temperature rise was observed. After 45 min. all the isocyanate had been added. The temperature of the reaction mixture was then raised from 45° to 85° and held at 85° for one hr. The reaction mixture was then concentrated to dryness *in vacuo* leaving 468 g. (98.5%) of white solid. Recrystallization from methanol-ether gave white crystals, m.p. 220–230° (dec.).

From methyl N-(3,3-dinitrobutyl)carbamate. A mixture of 160 g. (0.72 mole) of methyl *N*-(3,3-dinitrobutyl)carbamate and 480 ml. of concentrated hydrochloric acid was heated on the steam bath overnight. Then 480 ml. of water was added and the mixture cooled to 10°. A portion of unchanged starting material crystallized and was collected. The mother liquor was evaporated to yield the desired amine hydrochloride. The recovered starting material was hydrolyzed again with 200 ml. of concentrated hydrochloric acid for 10 hr. and worked up as before. A total of 127 g. (88.0%) of product was obtained, m.p. 220–230° (dec.).

Ureas (VII). The preparation of bis(5-carbomethoxy-3,3-dinitropentyl)-urea is given as typical. To 60 g. (0.23 mole) of 5-carbomethoxy-3,3-dinitropentyl isocyanate was added a solution of 180 ml. of acetone and 60 ml. of water. The mixture warmed up immediately and was refluxed until crystals precipitated. Upon cooling the whole mass solidified. The product was collected and recrystallized from ethylene dichloride to give 60.0 g. (93.4%), of white solid, m.p. 159–160°.

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Preparation of 2-Fluoro-9,10-phenanthrenequinone[1,2]

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Takizawa[5] has demonstrated that β-benzoquinone and α-naphthoquinone are carcinogenic and that phenanthrenequinone will produce papillomas of the skin, on mice. Frequently, the addition of a fluorine atom to a molecule that is already physiologically active will enhance its activity. For example, it is known that fluorination increases the tumor-producing effects of *N,N*-dimethylaminoazobenzene.[6] Also the 6-α-fluoro substituted steroids[7] show increased progestational, androgenic, and corticoid activity. Further, 7-fluoro-2-acetamidofluorene[8] is more carcinogenic in the liver of the rat than 2-acetamidofluorene.[9] Therefore, in selecting a project for an undergraduate research problem, it was deemed of interest to prepare the 2- and 4-fluoro derivatives of phenanthrenequinone, since these compounds are not listed in the literature, to see if their potency would be thereby increased. The preparation of the 2-isomer is herewith described. Work is in progress on the preparation of the 4-fluoro compound.

Starting with phenanthrene, the synthesis involved first, oxidation to phenanthrenequinone, then nitration of the quinone and separation of the resulting 2- and 4-nitro isomers. Reduction of the 2-nitro compound to the 2-amino compound was immediately followed by diazotization and addition of fluoboric acid to give the fluoborate. Finally, the fluoroborate was decomposed by heating at reduced pressure and the fluoro compound separated from the resulting tarry mixture by sublimation at reduced pressure. This method of introducing a fluorine atom into an aromatic nucleus was first described by Balz and Schiemann.[10] The general method has been reviewed by Roe.[11]

The reduction of the 2-nitro compound was effected by tin and hydrochloric acid as described by Schmidt and Spoun.[12] In our hands the method of Brass and Ferber[13] using sodium hydrosulfite did not give consistent results, so the former method was used even though it was longer and involved decomposing the resulting tin double salt with hydrogen sulfide.

Because of the poor solubility of the 2-amino compound for diazotization, it was decided to carry out the reduction of the 2-nitro compound in such a manner as to keep the resulting amine in solution and proceed to the diazotization directly. It was noticed by Goldberg *et al.*,[14] in the preparation of 9-fluorophenanthrene, that the presence of dioxane was essential to the formation of the diazonium salt and the subsequent fluoborate. Therefore when the amine salt was found to be soluble in dioxane, it was decided to precipitate the tin sulfide in a water-dioxane mixture, leaving the amine salt in solution. After the tin sulfide was removed, the solution was cooled and diazotized and fluoboric acid added to

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