INVESTIGATIONS IN THE FIELD OF PYRAZOLIDINE CHEMISTRY XVIII.* SYNTHESIS, SPECTRAL CHARACTERISTICS, AND BEHAVIOR TOWARD A RANEY NICKEL CATALYST OF 2,4,6,8-TETRAOXO-1,5-DIAZABICYCLO[3.3.0]OCTANES

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Symmetrical and unsymmetrical di-, tri-, and tetrasubstituted 2,4,6,8-tetraoxo-1,5-diazabicyclo[3.3.0]octanes were synthesized, and their IR and UV spectra were examined. The N-N bond undergoes hydrogenolysis and the C-N bond is cleaved when ethanol solutions are refluxed in the presence of a Raney nickel catalyst. The N-N bond is more resistant to hydrogenolysis than is the case for 3,5-dioxopyrazolidines.

We have previously shown that the enclates of 1,2,4-trisubstituted 3,5-dioxopyrazolidines (3,5-DOP) are not changed by catalytic hydrogenation in the presence of a Raney nickel catalyst. The N-N bond of the heterocycle undergoes hydrogenolysis on hydrogenation in neutral media; 1,2,4,4-tetrasubstituted 3,5-DOP, which are in a fixed diketo form [2], behave in the same way.

It seemed of interest to use this reaction for the hydrogenolysis of the N-N bond in 2,4,6,8-tetraoxo-1,5-diazabicyclo[3.3.0]octanes (I) to obtain the corresponding tetraoxo-1,5-diazocines (II). For this, we synthesized symmetrical and unsymmetrical di-, tri-, and tetrasubstituted derivatives of this series (Table 1).



These compounds (Ia-k) were obtained primarily by the reaction of equimolecular amounts of the acid dichlorides of variously substituted malonic acids with 4,4-disubstituted 3,5-DOP [3-5], and also by the condensation of the acid dichlorides of disubstituted malonic acids with benzal semicarbazone [6], and by the reaction of monosubstituted malonic ester with hydrazine hydrochloride in the presence of sodium ethoxide [7]. The best yields were observed when the first method was used (Table 1). Compounds Ia-k are colorless, crystalline, chromatographically homogeneous substances that are quite soluble in organic solvents.

*See [1] for communication XVII.

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		U		53,29	60,57	58,91			36,58	56,43	33,67	33,22	38,02	38,10	
Em pirical formula			C ₁₀ H ₁₂ N ₂ O ₄	$C_{10}H_{12}N_2O_4^*$	C14H20N2O4*	C ₁₃ H ₁₇ N ₂ O ₄ *		$C_{14}H_{20}N_2O_4$	C20H32N2O4	C20H32N2O4	C17H26N2O4	C ₁₇ H ₂₆ N ₂ O ₄	$C_{21}H_{26}N_2O_4$	$C_{21}H_{26}N_2O_4$	
Mp, deg C (crystallization solvent)			249-2507	(dloxane) 250 ⁵	(acetic acid) 110-112 (ethanol-henzene)	1 : 1) 148-149	acetic acid)	$201-202^{6}$	(methanol) 145-147	(ctnanot) 128—130	(ethanol) 9596	(methanol) 118119	(methanol) 134-136	(absolute ethanol)	(apsoince channi)
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TABLE 1. 2,4,6,8-Tetraoxo-1,5-diazabicyclo[3.3.0]octanes

* The equivalents (titration by alkali) of Ib-d were 218, 267, and 264. The calculated values were 224, 280, and 266.

Regardless of the number and character of the substituents in the 3- and 7-positions, two absorption bands are observed in the IR spectra of the compounds in the region of the C=O valence vibrations: one with a maximum at 1760-1774 cm⁻¹ (intense), and the other at 1730-1750 cm⁻¹ (medium intensity). The difference in the position of the maxima is 29-37 cm⁻¹. A shift of the first band to 1792 cm⁻¹ is noted only in the case of the 7-unsubstituted compound (b). Thus replacement of the two phenyl groups of 1,2-diphenyl-3,5-DOP, in the IR spectra of which a doublet at 1720-1750 cm⁻¹ is constantly observed [8], by the electronacceptor residue of malonic acid leads, as expected, to a shift in the doublet to the high-frequency region. The IR spectra of all of the compounds (Ia-k) also contain an intense absorption band at 1240-1275 cm⁻¹, which can be ascribed to the valence vibrations of the C-N bond.

In contrast to the IR spectra, the UV spectra of Ia-k in neutral, acidic, and alkaline ethanol enable one to distinguish tetrasubstituted from trisubstituted and symmetrical and unsymmetrical disubstituted compounds. In neutral and acidic ethanol, one absorption band with a maximum at 232-235 nm is characteristic for all of the tetrasubstituted Ie-k. Two intense absorption bands are observed in the spectra of the tri- (Ic, d) and disubstituted (Ia, b) compounds: one is found at 245 nm, and the second, broader band of about the same intensity is situated in the longer wavelength region. It is characteristic that the absorption maximum of this band is at 286-289 nm for the 7-monosubstituted compounds (Ia, c, d), compared with 274 nm for the 7-unsubstituted compound (Ib). The position of the band with a maximum at 232-235 nm of the tetrasubstituted compounds (Ie-k), which are not capable of enolization, does not change in alkaline ethanol, but a second band with a maximum at 300 nm appears. Considering the ease of cleavage of tetrasubstituted 2,4,6,8-tetraoxo-1,5-diazabicyclo[3.3.0]octanes in alkaline media at the C-N bond to form N-malonated 3,5--DOP (III) and, subsequently, also N,N'-dimalonylhydrazines (IV) [6, 9], this band can be ascribed to the absorption of the lactim form of III. The short-wave band in the spectra of alkaline solutions of the trisubstituted compounds (Ic, d), which are capable of enolization, does not change position, but the long-wave band is shifted hypsochromically.

The catalytic hydrogenation of Ia-k in the presence of a Raney nickel catalyst under the standard conditions (at 20 deg and atmospheric pressure) at which the N-N bond of 3,5-DOP is cleaved [2] does not lead to new compounds; the bulk of the starting material is recovered unchanged, and a portion is irreversibly adsorbed on the catalyst. Under more severe conditions (refluxing of an ethanol solution in the presence of a Raney nickel catalyst without feeding in hydrogen), chromatographically homogeneous 3,3-7,7-tetraethyl-2,4,6,8-tetraoxo-1,5-diazocine (II) can be isolated in 17% yield in the case of Ie. Absorption bands are displayed at 3370 and 3245 cm⁻¹ ($\nu_{\rm N-H}$) in the IR spectrum of II. Instead of a doublet at 1767 and 1730 cm⁻¹, two bands with maxima at 1731 and 1700 cm⁻¹, which are characteristic for cyclic imides [10], appear in the spectrum of the starting compound. As in the case of malonic acid diamides, the absorption maximum in the UV spectrum in neutral and acidic ethanol lies in the short-wave region below 220 nm. In contrast to malonic acid diamides, however, an intense absorption band with a maximum at 243 nm appears in the spectrum of an alkaline solution. During potentiometric titration in dimethylformamide, II ties up 2 equivalents of tetraethylammonium hydroxide. All of the data presented are evidence in favor of the 1,5-diazocine structure ascribed to II.

In addition to II, a complex containing nickel, which could not be recrystallized, was isolated from the reaction solution. According to the results of elemental analysis for N and Ni, its composition is very close to $(IIe)_2Ni$.

The corresponding II could not be obtained when di- and trisubstituted azabicyclooctanes Ia-d were refluxed with the Raney nickel catalyst. 4,4-Diethyl-3,5-DOP was isolated in the case of Ib while ethyl-malonic acid diamide was isolated in the case of Ia. Two parallel reactions apparently take place when I are refluxed with the Raney nickel catalyst: hydrogenolysis of the N-N bond and hydrolysis of the C-N of both the starting compounds (I) and of the 1,5-diazocines (II) formed. The latter is confirmed by the fact that the formation of diethylmalonic acid diamide was also observed in separate experiments with Ie.

EXPERIMENTAL

2,4,6,8-Tetraoxo-1,5-diazabicyclo[3.3.0]octanes (Ia-k). A) Preparation of Ib-e and Ii-k. Equimolecular amounts (0.01 mole) of 4,4-disubstituted 3,5-DOP and malonyl chloride were heated to 160-170 deg and held at this temperature for 30 min. The liquid, homogenous, yellow reaction mass began to crystallize on cooling and was then recrystallized from an appropriate solvent (Table 1).

B) Preparation of Ie, f, g. Equimolecular amounts (0.01 mole) of disubstituted malonyl chloride and benzal semicarbazone were heated to 170 deg and held at this temperature for 30 min. The reaction mass was cooled, and the thickened mass was recrystallized from an appropriate solvent.

C) Preparation of Ia. Ethyl malonate (0.5 mole) and 0.25 mole of hydrazine hydrochloride were added with stirring to sidum ethoxide (1 mole), and the reaction mass was heated to the boiling point. The mixture was refluxed for 15 min, the alcohol was removed by distillation, and the residual mixture was heated at 115-130 deg for 5 h. The reaction mass was cooled and dissolved in water. The solution was extracted with ether. Acidification of the water layer gave a crystalline precipitate.

<u>General Method of Hydrogenation</u>. The hydrogenation of 0.001 mole of Ia-k in 20 ml of ethanol in the presence of 1.0 g of W-5 Raney nickel catalyst was carried out under the standard conditions [2] for 4 h. The substances isolated after the hydrogenation (~60%) were identical to the starting materials with respect to melting points and R_f values.

3,3,7,7-Tetraethyl-2,4,6,8-tetraoxo-1,5-diazocine (II, $R' = R'' = R''' = C_2H_5$). A solution of 4.48 g (0.016 mole) of Ie in 300 ml of 50% ethanol was refluxed in the presence of 8 g of W-5 Raney nickel catalyst with stirring for 4 h. The catalyst was removed by filtration, and the filtrate was vacuum evaporated to give 3.0 g (67%) of an oily green residue. Treatment of the residue with ether gave 0.8 g (17.7%) of a color-less, crystalline substance with mp 140-142 deg (from 50% ethanol). Found: N 9.81%. $C_{14}H_{22}N_2O_4$. Calculated: N 9.93%. IR spectrum (ν , cm⁻¹): 3370, 3245, 1731, 1700, 1637, 1362, 1318, 1300, 1218. The substance was soluble in ethanol and methanol, slightly soluble in chloroform, dichloroethane, and dioxane, and insoluble in ether and aqueous alkalis and acids. One spot with R_f 0.85 was displayed during chromatography in a thin layer of activity II aluminum oxide with an ethanol-25% ammonium hydroxide system (5:1). Two equivalents of tetraethylammonium hydroxide were consumed in the potentiometric titration in dimethylformamide. An oily green residue that gave a positive test for nickel remained after evaporation of the ether mother liquor. Found: N 8.69; Ni 7.90%, ($C_{12}H_{22}N_2O_4$)₂Ni. Calculated: N 9.05; Ni 9.50%.

<u>Cleavage of le to Diethylmalonic Acid Diamide</u>. A mixture of 4.0 g (0.014 mole) of le and 14 g of Raney nickel catalyst in 15 ml of 50% ethanol was refluxed for 50 h with stirring. The catalyst was removed by filtration, and the filtrate was vacuum evaporated to give 3.0 g (75%) of a solid residue. Treatment of this residue with ether and recrystallization from 50% ethanol gave a colorless, crystalline precipitate with mp 217-218 deg that was identical to diethylmalonic acid diamide [11].

Reaction of Ia with a Raney Nickel Catalyst on Refluxing in Ethanol. A mixture of 2.0 g (0.01 mole) of Ia and 8.0 g of a Raney nickel catalyst in 50 ml of 50% ethanol was refluxed for 6 h. The catalyst was removed by filtration, and the filtrate was vacuum evaporated to give 1.5 g (75%) of a solid residue, which, after recrystallization from 50% ethanol, melted at 215 deg [12]. Found: N 21.87%. $C_5H_9N_2O_2$. Calculated: N 21.54%. IR spectrum (ν , cm⁻¹): 3344, 3194, 3153, 1675, 1650, 1558, 1540, 1521, 1505, 1260, 1150.

Reaction of Ib with a Raney Nickel Catalyst in Refluxing Ethanol. A mixture of 0.22 g (0.001 mole) of Ib and 1.0 g of a Raney nickel catalyst in 30 ml of 50% ethanol was refluxed for 4 h. The catalyst was removed by filtration, and the filtrate was evaporated in vacuo to give 0.2 g (90%) of a white residue with mp 258 deg (from ethanol). The substance was identical to the known 4,4-diethyl-3,5-DOP with respect to melting point and R_f value.

The UV spectra of solutions in neutral ethanol, 0.01 N ethanolic HCl, and 0.025 N ethanolic NaOH $(2 \cdot 10^{-4} \text{ and } 2 \cdot 10^{-5} \text{ mole/liter})$ were recorded with an SF-4A spectrometer.

The IR spectra of mineral oil suspensions were recorded with an IKS-14 spectrometer with NaCl and LiF prisms.

Compounds Ia-k were chromatographed in a thin layer of activity III aluminum oxide on 12 by 12 cm glass plastes in an ethanol-25% ammonium hydroxide system (5:1). The spots were detected in UV light (with a UI-1 ultrachemiscope with emission maximum at 254 nm).

The equivalents of Ib-d were determined in ethanol solution by titration with 0.1 N aqueous NaOH with phenolphthalein and bromthymol blue as the indicators.

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