2,3,7,8-Tetraazaspiro[4.4]nonane, 2,3,7,8-Tetraazaspiro-[4.4]nona-2,7-diene and Derivatives

Arnold T. Nielsen

Organic Chemistry Branch, Chemistry Division, Research Department, Naval Weapons Center
Code 6056, China Lake, California 93555

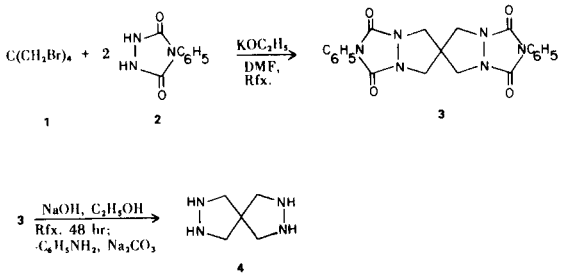
Received September 11, 1975

Synthetic routes to the title compounds (**4**, **12**) are described. Chiral derivatives of these, 2,7-*bis*(phenylcarbamoyl)-2,3,7,8-tetraazaspiro[4.4]nonane (**7**) and 3,8-dicarbomethoxy-2,3,7,8-tetraazaspiro[4.4]nona-1,6-diene (**10**) were prepared. Synthetic routes to diketo derivatives of other tetraazaspiro[4.4]nonanes were explored. 3,3-Dicarbethoxy-1-pyrazoline (**24**) and 3,3-dicarbethoxypyrazolidine (**25**) were prepared and their reactions with hydrazine examined. Proton and ^{13}C nuclear magnetic resonance spectra of new compounds, including some 5-substituted 3-hydroxypyrazoles, are discussed in relation to structure.

As part of a study of new polycyclic and macrocyclic polyhydrazines this report describes the first synthesis of unsubstituted spiranes incorporating hydrazino or azo groups. Few synthetic routes to spiranes with two or more hydrazino or azo groups have been described (1-4). These methods lead to substituted derivatives and most are not readily adaptable to a synthesis of the parent unsubstituted compounds.

2,3,7,8-Tetraazaspiro[4.4]nonane (**4**) was synthesized from pentaerythrityl tetrabromide and 4-phenylurazole by the reaction sequence **1** → **4** (Scheme 1). Reaction

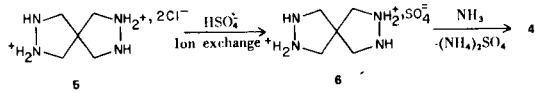
Scheme 1



of 4-phenylurazole potassium salt with pentaerythrityl tetrabromide in refluxing dimethylformamide leads to spirane **3** in 26% yield. Replacing *N,N'*-diisobutyryl-hydrazine for 4-phenylurazole in the reaction gave an oily product which failed to crystallize. [4-Butylurazole undergoes this reaction under different conditions to yield a spirane (**3**, C_6H_5 = *n*-C_4H_9, 8.5% yield (1))].

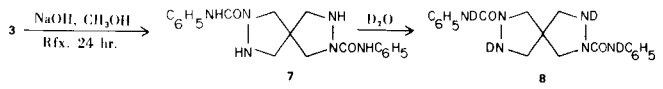
Saponification of spirane **3** occurs slowly in refluxing ethanolic sodium hydroxide (48 hours, oxygen-free nitrogen atmosphere) leading to 2,3,7,8-tetraazaspiro[4.4]-nonane (**4**), aniline (two mole-equivalents isolated) and sodium carbonate. The pure base **4** is very soluble in water and saturated potassium carbonate solution. It is a waxy, crystalline solid whose melting point depends on the rate of heating. It slowly reacts with oxygen of the air at ambient temperature, but may be stored in a well-sealed container at -15°. The structure of **4** is supported by its simple nmr spectrum which shows two singlets corresponding to the methylene and NH protons (deuterium oxide solvent).

Salts of **4** have been prepared in a procedure developed to isolate pure, salt-free **4**. The compound was initially isolated as its *bis*-hydrochloride salt (**5**, crystallized from hydrochloric acid).



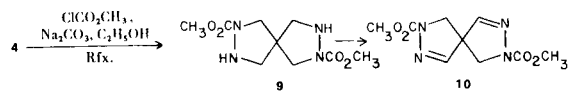
The sulfate salt (**6**) was prepared from **5** by ion exchange and the free base **4** liberated in liquid ammonia. The separation of pure **4** from ammonium sulfate was easily effected in absolute ethanol. More conventional methods of isolating **4** were ineffective owing to the very high solubility of **4** in aqueous solutions of high ionic strength. A stable *bis*-picrate salt of **4** forms readily.

Chiral derivatives of **4** have been prepared. Partial saponification of the tetraoxo derivative **3** was realized in refluxing methanolic sodium hydroxide (24 hours reaction time). The *bis*(phenylcarbamoyl) derivative **7** was isolated in 52% yield. Structure **7** is supported by its nmr spectrum. Separate signals are observed for the two ring methylenes; those adjacent to the carbamoyl nitrogen appear as a singlet, while those adjacent to the ring NH

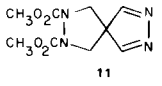


group are coupled to the ring NH proton and appear as a doublet of doublets (J 8.2, 9.7 Hz) owing to the chirality of the molecule. The ring NH proton signal also appears as a doublet of doublets with the same coupling constants. Replacement of the NH proton by deuterium (to form the tetradeuterio derivative **8**) results in singlet peaks for both ring methylene signals. The acidic carbamoyl proton signal which appears as a sharp singlet at δ 9.00 in **7** is absent in **8** (dimethylsulfoxide-d_6 solvent).

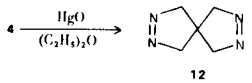
Reaction of tetraazaspirononane (**4**) with two mole-equivalents of methyl chloroformate and sodium carbonate in refluxing ethanol gave the tetraazaspironona-1,6-diene derivative **10** (9% yield) as the ultimate crystalline product. The intermediate spirononane derivative **9** could



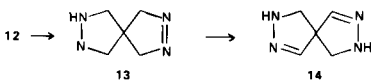
not be obtained in crystalline form. It evidently oxidized during workup despite precautions. Structure **10** is supported by its molecular formula and spectral data; infrared bands appear at 1720 cm^{-1} (C=O) and 1590 cm^{-1} (C=N). The nmr spectrum reveals a sharp singlet corresponding to the ring vinyl proton and an AB quartet for the ring methylene protons owing to the molecular chirality. This observation excludes the alternative achiral 4*H*- pyrazole structure **11** for the reaction product.



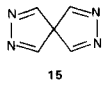
The cyclic dihydrazine **4** was readily oxidized to the tetraazaspironona-2,7-diene **12** (100% yield) by reaction with mercuric oxide in ether. The product structure is supported by molecular formula and spectra. The infrared



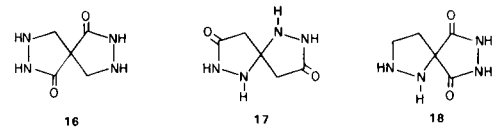
spectrum reveals absence of NH bands; an azo band is found at 1520 cm^{-1}. The nmr spectrum is characterized by a single line representing eight equivalent ring protons (deuteriochloroform solvent). On standing in air one vinyl singlet appears in the nmr spectrum suggesting tautomerization to products such as **13** and/or **14**.



Further oxidation to a dispiro-4*H*-pyrazole (**15**) is not observed in these experiments since a second vinyl signal is absent in the nmr spectrum.

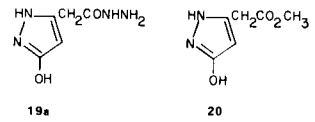


Synthetic routes to selected diketo derivatives of tetraazaspirononanes (compounds **16**, **17** and **18**) were studied.

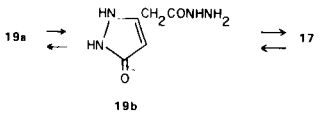


It was found that reaction of hydrazine with suitable precursors gave none of these substances in pure form under the conditions examined. Generally, the isolated products showed the properties of amorphous polymers. For example, reaction of diethyl *bis*(hydroxymethyl)-malonate (5) with hydrazine (two mole-equivalents) in refluxing ethanol gave unidentified amorphous products; compound **16** was not isolated.

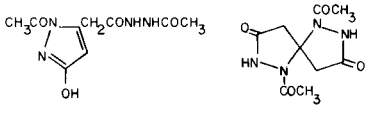
Reaction of dimethyl acetonedicarboxylate with two mole-equivalents of hydrazine in refluxing ethanol gave 5-(3-hydroxypyrazolyl)acethydrazide (**19a**) (73% yield).



[With one mole-equivalent of hydrazine in methanol at 0° 5-carbomethoxymethylpyrazolin-3-one (**20**) was obtained (6).] In one of two keto tautomeric forms (**19b**) an intramolecular Michael addition of the terminal amino group at the ring C-5 position would lead to 3,7-dioxo-1,2,5,6-tetraazaspiro[4.4]nonane (**17**). Heating **19** in



refluxing dimethylformamide led to an unidentified amorphous solid melting above 360°; **17** was not isolated. The diacetyl derivative of **19a**, **21** was prepared by reaction of **19** with excess acetic anhydride at 25°. It was not converted into the 1,6-diacetyl derivative of **17**, **22** by heating in water or in dimethyl formamide containing

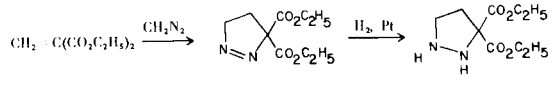


potassium *t*-butoxide catalyst, but was recovered unchanged.

The nmr spectra of pyrazolinones **19**, **20**, and **21** in dimethyl sulfoxide and pyridine solvents indicate the presence of one hydroxyl-substituted tautomer; a sharp ring methine signal (one proton) is observed near 5.0-5.5

δ in each spectrum. Based on other studies (7-13) hydroxyl structures **19a**, **20**, and **21** are favored for these species in basic aprotic solvents. All ring protons are rapidly exchanged upon addition of deuterium oxide to dimethyl sulfoxide solutions of **19** and **20** indicating rapid equilibria involving ring tautomers. The C-4 ring methine in **21**, however, is not exchanged rapidly; complete exchange of the α-methylene protons of the C-5 substituent occurs during one hour without any exchange of the ring protons.

3,3-Dicarbethoxypyrazolidine (**25**) was prepared from 1,1-dicarbethoxyethene (**23**) by the reaction sequence **23** → **25**. Reaction of a dilute absolute ethanolic solution



23 **24** **25**

of it with hydrazine, followed by sodium ethoxide (one mole equivalent of each) and heating under reflux gave amorphous products, not identified; none of the desired 1,4-diketo-2,3,5,6-tetraazaspiro[4.4]nonane **18** could be isolated. 3,3-Dicarbethoxy-1-pyrazoline (**24**) was extensively decomposed by this treatment in a parallel experiment.

EXPERIMENTAL

Infrared spectra were determined on a Perkin Elmer Model 137, ^{1}H nmr spectra on a Varian A-60 or XL-100, and ^{13}C nmr spectra on a Varian XL-100 spectrometer with Transform Technology TT-100 pulsed Fourier transform system; ^{1}H and ^{13}C chemical shift measurements were determined at *ca.* 30° and are referenced to tetramethylsilane internal standard [sodium 3-(trimethylsilyl)-1-propanesulfonate in deuterium oxide]. Melting points were determined on a Kofler hot stage, unless otherwise stated, and are corrected. Elemental analyses and molecular weights were determined by Galbraith Laboratories, Knoxville, Tennessee.

Methyl 3-(phenylcarbamoyl)carbazate.

A solution of methyl carbazate [91.9 g., 1.02 moles (14)] in 450 ml. of benzene was added dropwise with stirring during 45 minutes to phenyl isocyanate (122 g., 1.02 moles); a temperature rise to near 80° is observed. After addition of the ester solution the mixture was heated under reflux, with stirring, for 45 minutes. Stirring was continued at ambient temperature for 15 hours. Removal of volatiles under reduced pressure gave 210.6 g. (99%) of product ester, as long prisms, m.p. 154-155°. Recrystallization from isopropyl alcohol/ethanol (4/1) gave a polymorph as chunky crystals, m.p. 166-168°.

Anal. Calcd. for $C_9H_{11}N_3O_3$: C, 51.67; H, 5.30; N, 20.09. Found: C, 51.54; H, 5.45; N, 20.03.

4-Phenylurazole (**2**).

A mixture of methyl 3-(phenylcarbamoyl)carbazate (209.2 g., 1.0 mole), 4*N* aqueous potassium hydroxide solution (500 ml., 2.0 moles) and 100 ml. of ethanol was heated with stirring under reflux for 5.5 hours. The chilled mixture was treated with 12 *N* hydrochloric acid (170 ml.) to adjust the solution to *p*H 1 and precipitate the product. The mixture was filtered and the product washed with water. The dried solid was extracted with 1300 ml. of boiling ethanol and filtered hot to remove some insoluble material. Concentration of the filtrate to dryness gave 146.4 g. of 4-phenylurazole, m.p. 208-210° [lit. (15) m.p. 209-210°]; a second crop was isolated from the aqueous filtrate, 7.4 g., m.p. 208-210°; total yield 153.8 g. (87%).

2,2′-Diphenyl-1,1′,3,3′-tetraoxo-6,6′-spirobi[hexahydropyrazolo-[1,2-*a*]-*s*-triazole] (**3**).

To 4-phenylurazole (53.1 g., 0.3 mole) in 700 ml. of absolute ethanol was added an ethanolic solution of potassium ethoxide, prepared from potassium (23.5 g., 0.6 mole) and 300 ml. of absolute ethanol (calcium chloride tube attached). After warming on the steam bath for 1 hour, the solution was concentrated to dryness. The residue was treated with dry dimethylformamide (1 l.) and the mixture distilled until the still head temperature reached 135° (9 ml. of distillate removed). A solution of pentaerythrityl tetrabromide (58.2 g., 0.15 mole) in 250 ml. of warm, dry dimethylformamide was placed in a heated dropping funnel (wrapped with heating tape) maintained sufficiently warm to keep the solid in solution. This warm solution was added dropwise to the refluxing, stirred reaction mixture during 8 hours; heating at reflux and stirring were continued for an additional 14 hours. The reaction mixture was then chilled in an ice bath and the precipitated potassium bromide removed by filtration. After washing the precipitate with dimethylformamide the filtrate was concentrated to near dryness under reduced pressure while heating on the steam bath. Water (1 l.) was added to the residue and the mixture warmed on the steam bath. The water layer was removed by decantation and the residue triturated with water and the washings discarded. The residue was digested with 200 ml. of boiling ethanol; after cooling, filtering and washing the residual product with ethanol there was obtained 23.4 g. of crude **3**, m.p. 325-335°; this material was digested with 500 ml. of boiling ethanol for 1.5 hours and filtered hot to yield 16.0 g. of **3**, m.p. 336-345° (an additional 0.6 g., m.p. 341-348°, was isolated from the filtrates, total yield 16.6 g., 26%); recrystallization from boiling dimethylformamide yields tiny prisms, mp. 349-350° (55% recovery). Parallel runs gave comparable results.

Anal. Calcd. for $C_{21}H_{18}N_6O_4$: C, 60.28; H, 4.34; N, 20.09, mol. wt. 418.4. Found: C, 60.29; H, 4.49; N, 20.08, mol wt. 423 (dimethylformamide).

Pentaerythritol tetrabenzenesulfonate was substituted for pentaerythrityl tetrabromide in one run using the above procedure to provide a 16% yield of **3**. In another run mesitylene was substituted for dimethylformamide solvent resulting in recovered reactants and no **3**.

2,3,7,8-Tetraazaspiro[4.4]nonane Bishydrochloride (**5**).

A mixture of spirane **3** (16.75 g., 0.040 mole), sodium hydroxide (40 g., 1.0 mole) and 400 ml. of oxygen-free 95% ethanol (degassed by bubbling in oxygen-free nitrogen) was heated under reflux in an oxygen-free nitrogen atmosphere with stirring (magnetic) for 48 hours. The mixture, after chilling at 0° for 1 hour, was filtered by suction and the solid washed with oxygen-free ethanol. The filtrate was immediately acidified to *p*H 1 by adding concentrated hydrochloric acid (80 ml.) and concentrated to dryness under reduced pressure on the steam bath. Water (130 ml.) was added to the residue to dissolve all but *ca.* 0.5 g. of dark gummy material. The solution was filtered by suction and the solid washed with water. Aqueous sodium hydroxide solution (50 ml. of 20%) was added to make the solution

alkaline (*p*H 12, nitrogen atmosphere maintained) and the solution extracted three times with ether (50 ml. portions); the extracts were dried and concentrated to yield 6.0 g. (80%) of aniline.

The aqueous alkaline solution remaining from the ether extraction was immediately acidified to *p*H 1 with concentrated hydrochloric acid (15 ml.). After filtration to remove traces of gummy material the filtrate was concentrated to dryness under reduced pressure. Concentrated hydrochloric acid (150 ml.) was added to the residue and the mixture stirred magnetically for 1 hour at 60-90° (water bath temperature). After cooling the mixture was filtered through a sintered glass filter to remove sodium chloride and washed with concentrated hydrochloric acid. Concentration of the filtrate to dryness gave a gummy residue (10.0 g.) which was redissolved in 75 ml. of hot concentrated hydrochloric acid and cooled to 25° to deposit more sodium chloride (0.7 g. removed by filtration and washed with concentrated hydrochloric acid). The filtrate (*ca.* 100 ml.) was chilled to 0° and seeded to yield, in successive crops, 5.63 g. (70%) of dihydrochloride **5**, m.p. 192-200°; recrystallization from concentrated hydrochloric acid, followed by drying in air at 25°, gave crystals, mp. 208-210° without decomposition (on cooling to 140° the material recrystallized as long needles, m.p. 150-155°); ir (potassium bromide): 3170 cm^{-1} (NH); nmr deuterium oxide: δ 3.58 (s, 8, CH_2).

Anal. Calcd. for $C_5H_{14}Cl_2N_4$: C, 29.86; H, 7.02; N, 27.86; Cl, 35.26. Found: C, 29.76; H, 7.03; N, 27.89; Cl, 35.46.

2,3,7,8-Tetraazaspiro[4.4]nonane Sulfate (**6**).

Ion exchange resin, polystyrene quaternary ammonium chloride type (Biorad AG1X-10, 200-400 mesh, 150 g.), was thoroughly exchanged with aqueous saturated potassium bisulfate solution until tests for chloride ion were negative. To this bisulfate resin in a column was introduced a solution of 2.50 g. of bishydrochloride **5** in 20 ml. of water. Concentration of the eluate to dryness gave 2.8 g. of crystalline solid which was dissolved in water (10 ml.) and diluted with 60 ml. of ethanol to precipitate the sulfate salt after chilling at 0°. The crystals were filtered and washed with ethanol to yield 2.51 g. (89%) of sulfate **6**, as small prisms, m.p. 231-234° dec.

Anal. Calcd. for $C_5H_{14}N_4O_4S$: C, 26.54; H, 6.24; N, 24.76, S, 14.17. Found: C, 26.53; H, 6.25; N, 24.73; S, 14.24.

2,3,7,8-Tetraazaspiro[4.4]nonane (**4**).

The sulfate salt **6** (4.0 g.) was placed in a 3-necked flask flushed with oxygen-free dry nitrogen and equipped with a dry-ice-acetone condenser, *ascarite* tube and magnetic stirrer and surrounded by a dry-ice acetone cold bath. Ammonia (100 ml.) was condensed into the apparatus during 3 hours with stirring. The ammonia inlet was replaced by oxygen-free dry nitrogen and the cold bath was removed. The ammonia was allowed to evaporate completely at ambient temperature with stirring. To the residue was added 50 ml. of oxygen-free absolute ethanol (degassed by passing through oxygen-free nitrogen) and the mixture stirred at ambient temperature for 3 hours. The mixture was filtered (to remove ammonium sulfate) into a distilling flask equipped with an oxygen-free nitrogen capillary inlet. Solvents were removed at 30 mm. pressure keeping the bath temperature below 50°. A white solid precipitates from the ethanol solution as the distillation proceeds; after all solvents are removed there remians 2.17 g. (95%) of the amine **4**, clusters of flat waxy crystals, m.p. 140-170° (open or sealed capillary, slow heating from bath temperature 25°), m.p. 180-190° (open capillary, rapid heating from bath temperature 150°; a clear liquid results on melting with no gassing and on cooling the sample recrystallizes; d_4^{25} 1.21 (compression at 40,000 psi); ir (potassium bromide): 3400, 3200 cm^{-1} (NH); nmr (deuterium oxide): δ, 3.0 (s, 8, CH_2), 4.78 (s, 4, OH from NH exchange).

Anal. Calcd. for $C_5H_{12}N_4$: C, 46.85; H, 9.44; N, 43.71; mol. wt. 128.2. Found: C, 46.63; H, 9.19; N, 43.47; mol. wt. 128 (mass spectrum), 132 (osmometry, dimethylformamide).

A bispicrate salt was prepared by reaction of 0.128 g. (1.0 mmole) of **4** with picric acid (0.458 g., 2.0 mmoles) in 5 ml. of oxygen-free warm ethanol to yield 0.49 g. (84%) of the picrate salt after crystallization from 50% aqueous ethanol, m.p. 182-184°. Recrystallization gave rectangular yellow prisms, m.p. 185-186° dec.

Anal. Calcd. for $C_{17}H_{18}N_{10}O_4$: C, 34.82; H, 3.09; N, 23.89. Found: C, 35.06; H, 2.96; N, 24.02.

2,7-*Bis*(phenylcarbamoyl)2,3,7,8-tetraazaspiro[4.4]nonane (**7**).

A mixture of spirane **3** (1.77 g., 4.1 mmoles), sodium hydroxide (3.2 g., 80 mmoles) and 50 ml. of methanol was heated under reflux (nitrogen atmosphere) for 24 hours. After chilling at 0° the mixture was filtered and the solid washed with methanol. The solid was treated with dilute hydrochloric acid to dissolve the sodium carbonate present leaving the product which was filtered off and washed with water; 0.77 g. (52% of **7**, m.p. 227°); recrystallization from ethanol gave long prisms; m.p. 230-231°; ir (potassium bromide): 3330, 3230 cm^{-1} (NH), 1660 (C=O); nmr (dimethyl sulfoxide-d_6): δ 9.0 (s, 2, N*H*CO; signal disappears on addition of deuterium oxide), 6.8-7.8 (m, 10, C_6H_5), 5.67, 5.80 (d, d, J = 9.7, 8.2 Hz, 2, CH_2NH; signals disappear on addition of deuterium oxide), 3.57 (broad singlet, 4, CH_2NCO; on addition of deuterium oxide the signal shifts to 3.72 δ), 2.97, 3.00 (doublets, J = 9.7, 8.2 Hz, respectively, 4, CH_2NH; signal becomes a singlet on addition of deuterium oxide, 2.92 δ).

Anal. Calcd. for $C_{19}H_{22}N_6O_2$: C, 62.28; H, 6.05; N, 22.94; mol. wt. 366.4. Found: C, 62.80; H, 6.38; N, 23.23; mol. wt. 325 (dimethylformamide).

The methanolic filtrate remaining from removal of product **7** and sodium carbonate was acidified with concentrated hydrochloric acid to *p*H 1. The filtrate was concentrated to dryness, triturated with methanol (25 ml.) and filtered to remove sodium chloride. The filtrate was concentrated to dryness and dissolved in 2 ml. of water and made basic with 10% aqueous sodium hydroxide solution. The resulting mixture was extracted with ether and the extracts dried with magnesium sulfate; removal of solvent under reduced pressure gave amiline, 0.26 g. (35%); its benzoyl derivative was prepared, m.p. 163-165°. Some **4** picrate, m.p. 174-178°, was also ultimately isolated from the reaction mixture.

3,8-Dicarbomethoxy-2,3,7,8-tetraazaspiro[4.4]nona-1,6-diene (**10**).

To a solution of spirononane **4** (0.64 g., 5 mmoles) in 20 ml. of oxygen-free ethanol was added sodium carbonate (0.56 g., 10.6 mmoles) and, during 2 minutes, methyl chloroformate (1.0 g., 10.6 mmoles). The mixture was heated under reflux (oxygen-free nitrogen atmosphere) with stirring for 2.5 hours. The mixture was concentrated to dryness, the residue extracted with boiling 2-propanol and filtered hot to remove sodium chloride. Concentration of the filtrate to dryness gave 1.17 g. of gum which was crystallized from 2-propanol to yield **10** (0.11 g., 9%, m.p. 185-190°); recrystallization from 2-propanol gave small crystals, m.p. 195-197°; ir (potassium bromide): 1720 cm^{-1} (C=O), 1590 (C=N); nmr (deuteriochloroform): δ, 7.10 (s, 2, CH=), 4.20 (q, 4, CH_2), 4.10 (s, 6, CH_3).

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.33;

mol. wt. 240.22. Found: C, 44.84; H, 4.88; N, 23.32; mol. wt. 235.

2,3,7,8-Tetraazaspiro[4.4]nona-2,7-diene (**12**).

A mixture of spirononane **4** (0.64 g., 5 mmoles), mercuric oxide (2.17 g., 10 mmoles) and ether (50 ml.) was stirred magnetically at ambient temperature in a nitrogen atmosphere (oxygen not rigorously excluded) for 11 hours. The mixture was filtered to remove a gray solid, and the filtrate concentrated to yield 0.52 g. of **12**, as needle-shaped prisms (m.p. 125-137°, Kofler, with change to rosettes near 110°; m.p. 122-125° in open capillary to clear liquid with previous sintering near 110°, followed by slow gas evolution at 150-220° and rapid gas evolution at 220°). Recrystallization from cyclohexane gave feathery prisms, m.p. 113-119° (capillary). The gray solid containing mercury was extracted with warm 2-propanol and filtered; concentration of the extracts gave additional **12**, 0.10 g., m.p. 100-101° (capillary), having an infrared spectrum identical to the principal fraction; total yield 0.62 g. (100%); d^{25}_4 1.28 (pressed pellet at 40,000 psi); ir (potassium bromide): 1520 cm^{-1} (N=N); NH bands absent; nmr (deuteriochloroform): δ, 4.62 (s, 8, CH_2); on standing a small singlet appears at δ 7.57 (CH=).

Anal. Calcd. for $C_5H_8N_4$: C, 48.37; H, 6.50; N, 45.13; mol. wt. 124.15. Found: C, 48.57; H, 6.74; N, 45.34; mol. wt. 124 (mass spectrum); 130 (osmometry, chloroform).

5-(3-Hydroxypyrazolyl)acethydrazide (**19**).

To dimethyl acetonedicarboxylate (3.48 g., 0.02 mole) in 100 ml. of ethanol was added dropwise 2.2 g. (0.044 mole) of hydrazine hydrate. The mixture was heated under reflux for 21 hours (nitrogen atmosphere). The resulting solution was concentrated to dryness and the residue crystallized from water to yield, in successive crops, 2.28 g. (73%) of **19**, m.p. 198-200° dec.; recrystallization from water (*Darco* treatment) gave tiny crystals (86%) recovery), m.p. 204-206° dec.; ir (potassium bromide): 3330 cm^{-1} (sharp, NH), 2000-3500 (broad OH, NH), 1630 (C=O); nmr (dimethylsulfoxide-d_6): δ 8.0 (broad, s, 5, OH, NH), 5.68 (s, 1, CH= ring), 3.58 (s, 2, CH_2CO).

Anal. Calcd. for $C_5H_8O_2N_4$: C, 38.46; H, 5.16; N, 35.88; mol. wt. 156.2. Found: C, 38.34; H, 5.35; N, 35.71; mol. wt. 166 (osmometry, dimethylformamide).

A solution of hydrazide **19** (0.35 g., 2.0 mmoles) in 500 ml. of dimethylformamide was heated under reflux in a nitrogen atmosphere for 64 hours. Concentration of the dark mixture to dryness, followed by dilution with ethanol gave a dark red solid, 0.22 g., m.p. above 360°.

N-[5-(1-Acetyl-3-keto-4-pyrazolinyl)acetyl]-*N'*-acetylhydrazine (**21**).

5-(3-Hydroxypyrazolyl)acethyrazide (**19**, 1.56 g., 0.01 mole) was stirred with acetic anhydride (25 ml.) at 25° for 17 hours (an initial temperature rise to a maximum of 44° during 15 minutes was noted). The viscous mixture was diluted with 100 ml. of water, filtered, and the precipitate washed with water to yield 1.28 g. of **21**, m.p. 229-232°, dec.; concentration of the filtrate gave an additional 1.15 g. of **21**, m.p. 215-232°; total yield 2.43 g. (100%); recrystallization from dimethylformamide gave small crystals, m.p. 226-231°, dec.; ir (potassium bromide): 3120 cm^{-1} (sharp, NH), 1680, 1660 (C=O); nmr (dimethylsulfoxide-d_6): δ 9.45, 9.32 (s, 2, NH), 4.93 (s, 1, CH=), 3.20 (s, 2, CH_2), 1.8-2.4 (broad s, 1, OH), 2.32 (s, 3, CH_3), 1.72 (s, 3, CH_3).

Anal. Calcd. for $C_9H_{12}N_4O_4$: C, 45.00; H, 5.04; N, 23.33; mol. wt. 240.22. Found: C, 45.25; H, 4.96; N, 23.15; mol. wt. 241 (dimethylformamide).

A mixture of hydrazide **21** (0.48 g., 2 mmoles) and potassium *t*-butoxide (0.02 g.) in 50 ml. of dimethylformamide was heated on the steam bath for 5.5 hours. The cooled solution was treated with 4 drops of acetic acid and concentrated to dryness to yield recovered **21**, 0.48 g., m.p. 225-234°. Heating a 0.48 g. sample of **21** in water (50 ml.) on the steam bath for 21.5 hours gave recovered **21** (100%).

5-Carbomethoxymethyl-4-pyrazolin-3-one. (3-Hydroxy-5-carbomethoxymethylpyrazole) (**20**).

To dimethyl acetonedicarboxylate (3.48 g., 0.02 mole) in methanol (5 ml.) at 0° was added hydrazine hydrate (1.0 g., 0.02 mole). After standing at 0° for 4.5 hours the mixture was filtered to yield 1.29 g. of **20**, m.p. 135-140°; concentration of the filtrate to dryness, followed by trituration with 2-propanol, gave an additional 0.74 g., m.p. 136-141° (total yield of **20**, 2.03 g., 65%). Recrystallization from ethanol gave flat prisms, m.p. 145-147°; ir (potassium bromide): 2000-3500 cm^{-1} (broad OH, NH) 1740 (C=O, ester), 1650, 1630, 1620 (C=O, amide); nmr (dimethyl sulfoxide-d_6): δ 9.8 (very broad, s, 2, OH, NH), 3.63 (s, 3, CH_3O), 3.57 (s, 2, CH_2C=O); 5.40 (s, 1, CH=@ C-4), addition of deuterium oxide to the dimethyl sulfoxide-d_6 solution of **20** reduces the spectrum to two lines: δ 5.2 (s, OH), 3.73 (s, CH_3O); nmr (pyridine-d_5): δ 10.5 (broad, s, 2, OH, NH), 6.0 (s, 1, CH=@ C-4), 3.88 (s, 2, CH_2CO), 3.60 (s, 3, CH_3O).

Anal. Calcd. for $C_6H_8N_2O_3$: C, 46.15; H, 5.16; N, 17.94; mol. wt. 156.14. Found: C, 46.43; H, 5.17; N, 18.06; mol. wt. 165 (osmometry, dimethylformamide).

3,3-Dicarbethoxypyrazolidine (**25**).

To 1,1-dicarbethoxyethene (14.7 g., 0.085 mole) (16) in 40 ml. of ether was added slowly an ethereal solution of diazomethane (keeping the reaction temperature below 10°) until a pale yellow color persisted in the solution. Removal of volatiles under reduced pressure gave 18.5 g. of crude 3,3-dicarbethoxy-1-pyrazoline (**24**) as a colorless liquid; ir (neat): 1740 cm^{-1} (C=O), 1550 (N=N).

The unpurified pyrazoline **24** (7.5 g., 0.035 mole) in absolute ethanol (100 ml.) and platinum oxide catalyst (0.3 g.) were shaken in a Parr apparatus with hydrogen (25°, 30 psi) until hydrogen uptake ceased (10 minutes). The catalyst was filtered and the filtrate concentrated and distilled to yield 3.6 g. of colorless ester **23** (48% from 1,1-dicarbethoxyethene), b.p. 110-112° (1 mm): n^{25}_4 1.4568; d^{25}_4 1.14; ir (neat): 3330 cm^{-1} (NH), 1785 (C=O); a forerun (0.85 g.) and residue (2.36 g.) were also obtained; redistillation of the ester gave 2.1 g. of **25**, b.p. 110° (1 mm), n^{25}_D 1.4573 and undistillable residue (1.0 g.).

Anal. Calcd. for $C_9H_{16}N_2O_4$: C, 49.99; H, 7.46; N, 12.96; mol. wt. 216.23. Found: C, 50.40; H, 7.53; N, 13.22; mol. wt. 240 (osmometry, chloroform).

A solution of the distilled ester **25** (0.87 g., 4.0 mmoles) and hydrazine (0.135 g. of 95%, 4.0 mmoles) in 100 ml. of absolute ethanol was heated under reflux for 1.5 hours. The cooled solution was treated with 4.0 ml. of 1*N* methanolic sodium methoxide and stored at 25° for 19 hours, followed by heating under reflux for 24 hours. The cooled solution was treated with 4.0 ml. of 1*N* hydrochloric acid to yield a gummy water soluble precipitate; concentration of the filtrate gives additional gummy material. No pure crystalline product or picrate derivative could be isolated from the reaction products. A parallel experimnet with ester **24** gave similar results except that the products evolved gas on heating.

Acknowledgment.

The author is indebted to D. W. Moore for assistance in securing some of the experimental data and for helpful discussions.

REFERENCES AND NOTES

(1) G. Zinner and W. Deucker, *Arch. Pharm.*, **296**, 13 (1963); *Chem. Abstr.*, **59**, 5151 (1963).

(2) J. P. Davreux and A. Bruylants, *Bull. Cl. Sci. Acad. Roy. Belg.*, **54**, 823 (1968); *Chem. Abstr.*, **71**, 112857g (1969).

(3) A. Aspect, P. Battioni. L. Vo-Quang and Y. Vo-Quang, *C. R. Acad. Sci. Ser. C*, **269**, 1063 (1969).

(4) S. D. Andrews, A. C. Day and R. N. Inwood, *J. Chem. Soc. (C)*, 2443 (1969).

(5) P. Block, Jr., *Organic Syntheses*, Collective Vol. **5**, 381 (1973); John Wiley and Sons, New York.

(6) 5-Carboethoxymethyl-4-pyrazolin-3-one has been prepared from diethyl acetonedicarboxylate; T. Ishimura, *Yakugaku Zasshi*, 77, 803 (1957); *Chem. Abstr.*, **51**, 17893 (1957).

(7) A. R. Katritzky, *Chimia*, **24**, 134 (1970).

(8) R. Jacquier, C. Petrus, F. Pétrus and J. Verducci, *Bull. Soc. Chim. France*, 247 (1970).

(9) A. Maquestiau, Y. Van Haverbeke, R. Jacquerye, *Bull. Soc. Chim. Belges.*, **80**, 17 (1971).

(10) M. J. Nye and W. P. Tang, *Tetrahedron*, **28**, 455 and 463 (1972).

(11) J. Feeney, G. A. Newman and P. J. S. Pauwels, *J. Chem. Soc. (C)*, 1842 (1970).

(12) J. Deschamps, H. Sauvaitre, J. Arriau, A. Maquestiau, Y. Van Haverbeke and R. Jacquerye, *Tetrahedron Letters*, 2929 (1971).

(13) G. A. Newman and P. J. S. Pauwels, *Tetrahedron*, **26**, 1571 and 3429 (1970).

(14) O. Diels, *Chem. Ber.*, **47**, 2183 (1914).

(15) R. C. Cookson, S. S. Gupte, I. D. R. Stevens and C. T. Watts, *Organic Syntheses*, **51**, 212 (1971); John Wiley and Sons, New York.

(16) A. Sakurai, H. Midorikawa and S. Aoyama, *J. Sci. Res. Inst. (Tokyo)*, **52**, 112 (1958); *Chem. Abstr.*, **53**, 15961 (1959).