7-Substituted 2,3-Diazabicyclo[2.2.1]heptane Derivatives. Synthesis of a Stable Ketone Hydrate

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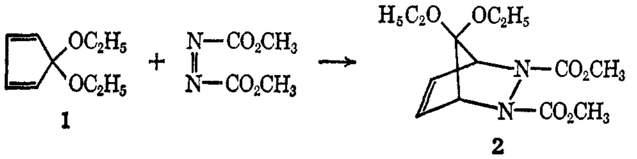
Received September 12, 1967

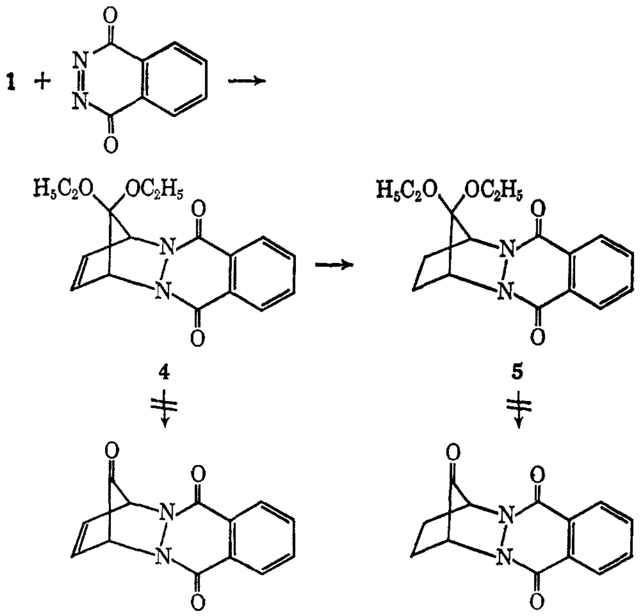
The synthesis of 2,3-phthalyl-7,7-diethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene (**4**) and its saturated analog (**5**) is described. These ketals are inert toward hydrolysis. Ozonolysis of 2,3-dicarbethoxy-7-isopropylidene-2,3-diazabicyclo[2.2.1]heptane (**10**), prepared by hydrogenation of the Diels–Alder product of dimethylfulvene and diethyl azodicarboxylate, results in formation of the stable ketone hydrate 2,3-dicarbethoxy-7,7-dihydroxy-2,3-diazabicyclo[2.2.1]heptane (**13**).

The work reported here is concerned with attempts to provide synthetic routes to 7-substituted 2,3-diazabicyclo[2.2.1]heptanes. After completion of this work, Allred and Anderson[2] reported the first successful preparation of this type of compound by the Diels–Alder reaction of the diethyl ketal of cyclopentadienone (**1**) and dimethyl azodicarboxylate (Scheme I). We had unsuccessfully attempted the same route. In the presence of a 1 *M* excess of diethyl azodicarboxylate (**3**) we were unable to trap **1**. However, the more reactive dienophile, 1,4-phthalazinedione, readily intercepted **1** to give a good yield of the expected adduct **4** which gave the corresponding dihydro compound **5** upon hydrogenation (Scheme II). Although a variety of conditions were employed (see Experimental Section) ketals **4** and **5** were inert toward hydrolysis and formation of the corresponding 7-keto derivatives. This was an unexpected result since 7,7-dimethoxybicyclo[2.2.1]hept-2-ene, its saturated analog, and the dimer of the diethyl ketal of cyclopentadienone are readily hydrolyzed at room temperature by dilute mineral acids.[3,4] The unreactivity of **4** and **5** toward hydrolysis, however, is in agreement with the results of Allred and Anderson.[2] They found that the ketal **2**, its saturated analog, and the corresponding 2,3-dimethyl compound are also inert toward hydrolysis.

SCHEME I

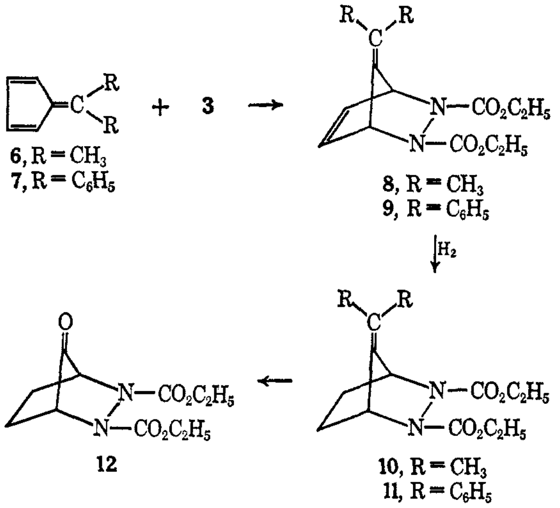


SCHEME II



In view of the inability to generate a keto function at the 7 position by the above synthetic route an alternate procedure was examined. This procedure has as its starting point a Diels–Alder reaction of a fulvene with **3** and is outlined in Scheme III. Both **6** and **7** reacted with **3** exothermally and quantitatively, as evidenced by dissipation of the orange color of the reactants. The infrared and nmr spectra of the reaction mixture showed only trace amounts of residual starting materials.

SCHEME III



The Diels–Alder adduct **8** was isolated as a pale yellow oil which had an infrared and nmr spectrum consistent with the assigned structure. Efforts to purify this oil by column chromatography, gas chromatography, molecular distillation, and crystallization were unsuccessful and instead resulted in its decomposition or conversion to other materials. This was evidenced by the increasing orange color of the oil, the appearance of N–H stretching in the infrared spectrum, and changes in the nmr spectrum to one of greater complexity. It appears that **8** undergoes slow Diels–

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[1] Abstracted from the thesis of J. A. Alford, submitted in partial fulfillment of the M.S. degree requirements at Clemson University, May 1966.

[2] E. L. Allred and C. Anderson, *J. Org. Chem.*, **32**, 1874 (1967).

[3] P. G. Gassman and P. G. Pope, *ibid.*, **29**, 160 (1964).

[4] P. E. Eaton and R. A. H. Hudson, *J. Amer. Chem. Soc.*, **87**, 2769 (1965).

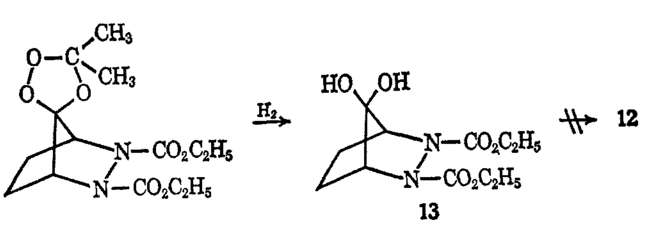
Alder reversal at room temperature followed by an abstraction–addition reaction to give a substituted hydrazide. Similar behavior has been previously reported for the Diels–Alder adduct of 3,6-pyridazinedione and **6**.[5]

Freshly prepared **8** rapidly absorbed 1 molar equiv of hydrogen, in which the endocyclic double bond was preferentially reduced to give **10**. Compound **10** was ozonized in a methanolic solution and the intermediate ozonide was catalytically hydrogenated[6] with palladium. Subsequent nonaqueous work-up gave an oil which upon prolonged standing deposited a white crystalline solid. This solid was found to be very water soluble, a property unexpected for the presumed product **12**. The water-soluble ozonolysis product is not the 7-keto compound **12** but is instead the corresponding *gem*-diol **13**. The infrared, nmr, and elemental analysis data are all consistent with structure **13**. The infrared spectrum showed strong O–H stretching and lacked carbonyl absorption at 5.6 which is characteristic of 7-ketobicycloheptanes.[7] The nmr spectrum ($CDCl_3$) consisted of a six-proton triplet (CH_3) at 1.3 ppm, a four-proton quartet (CH_2) centered at 4.3 ppm, a four-proton broadened quartet (ring CH_2) centered at 1.95 ppm, a two-proton singlet (bridgehead C–H) at 4.12 ppm, and a two-proton broad singlet at 5.1 ppm (OH). Positive assignment of the O–H and its distinction from that of the bridgehead protons was accomplished by deuterium exchange with D_2O containing a small amount of HCl. The nmr spectrum of deuterium exchanged **13** was exactly the same as that of unexchanged **13** except that the signal at 5.1 ppm was considerably diminished.

Subsequent preparations of **13** took advantage of its water solubility by extracting the ether solution of the reduced ozonide with water. The water extracts were then evaporated to give crude **13**.

This same reaction sequence was tried using diphenylfulvene as the diene. The adduct **9** crystallized out of the reaction mixture as a stable white solid. Ozonolysis of **11** and work-up in a manner identical with that described for **10** did not give any detectable quantity of **13**.

Formation of diol **13** by catalytic reduction of the ozonide is explained by the reaction



13

However, it is surprising that **13** does not undergo spontaneous dehydration to give the 7-keto compound **12** or exchange with solvent methanol to give what is usually the more thermodynamically favored dimethyl ketal. The extraordinary and unexpected stability of the hydrate **13** is further evidenced by the fact that it is unchanged when heated at 100° at 0.005 mm as determined by elemental analysis.

As previously mentioned, a variety of dimethyl and diethyl ketals of 7-keto-2,3-diaza[2.2.1]bicycloheptanes are inert toward hydrolysis. Allred and Anderson[2] have suggested that the reason for the stability of these ketals toward hydrolysis is due to ineffective acid catalysis as a result of preferential protonation of nitrogen. It is difficult to invoke this argument to explain the remarkable stability of **13**. Unlike ketals, ketone hydrates, in the absence of special stabilizing effects, suffer spontaneous dehydration without the necessity of acid catalysis. Furthermore, **13** undergoes rapid exchange with D_2O containing a small amount of HCl. This result suggests that **13** does indeed undergo rapid protonation at the hydroxyl group. It therefore appears that the stability of **13** and corresponding ketals must be attributed to some other effect.

Experimental Section

Melting points were taken by the capillary tube method and are corrected. Nmr spectra were obtained with a Varian Model A-60 spectrometer using tetramethylsilane as an internal standard. Elemental analyses were performed by Galbraith Laboratories.

2,3-Phthalyl-7,7-diethoxy-2,3-diazabicyclo[2.2.1]hept-5-ene (4).—To a solution of 1,4-phthalazinedione[5] (prepared from 29.04 g (0.16 mol) of the sodium salt of phthalhydrazide and 0.16 mol of *t*-butyl hypochlorite) at −77° was added a solution of 5,5-diethoxycyclopentadiene (prepared from 50.56 g (0.16 mol) of the dibromo ketal and 50.0 g (0.446 mol) of potassium *t*-butoxide, which had been precooled to −77°). The two phase system was stirred rapidly at −70°. After 30 min a white precipitate began to form and the green color had completely disappeared. The reaction mixture was filtered at −70° to give 31.3 g (61.7%) of **4**, mp 185–188°. Recrystallization from benzene afforded an analytical sample, mp 188–189°.

Anal. Calcd for $C_{17}H_{18}N_2O_4$: C, 64.96; H, 5.77; N, 8.91. Found: C, 65.02; H, 5.78; N, 9.02.

The infrared spectrum (KBr) contained absorption maxima at 6.05 and 6.17 μ (C=O). The nmr spectrum (CCl_3D) contained a multiplet centered at 1.12 ppm composed of two triplets (CH_3), an octet centered at 3.58 ppm composed of two quartets (CH_2), a triplet at 5.70 ppm (C–H bridgehead), a triplet at 6.71 ppm (vinyl=CH), and two multiplets at 7.80 and 8.30 ppm (aromatic).

2,3-Phthalyl-7,7-diethoxy-2,3-diazabicyclo[2.2.1]heptane (5).—A solution of 4.0 g (0.0127 mol) of **4** in 200 ml of ethyl acetate was hydrogenated over 100 mg of Adams catalyst. After the uptake of hydrogen ceased, the solution was filtered and the solvent removed under vacuum. The remaining white solid, 3.95 g (99%), was recrystallized from benzene, mp 183–184.5°. The nmr spectrum was essentially the same as that for **4** with the exception that it now contained a multiplet centered at 2.2 ppm (ring CH_2) and the vinyl CH at 6.71 ppm was no longer present.

Anal. Calcd for $C_{17}H_{20}N_2O_4$: C, 64.54; H, 6.37; N, 8.85. Found: C, 64.68; H, 6.51; N, 9.10.

Attempted Hydrolysis of Ketal 5.—Hydrolysis of 1.0-g samples of **5** under a variety of conditions shown in Table I was unsuccessful. In all cases the reaction mixture was poured into ice water after the specified reaction time. The acid was neutralized with sodium bicarbonate and the mixture was extracted several times with methylene chloride or chloroform and dried over magnesium sulfate. The solution was filtered and solvent removed under vacuum. In all cases except the last, a yield of greater than 90% of starting material was recovered. Melting points, mixture melting points, and infrared spectra were all identical with that of starting material. In concentrated sulfuric acid at 70° complete decomposition occurred and no starting material or product was isolated.

2,3-Dicarbethoxy-7-isopropylidene-2,3-diazabicyclo[2.2.1]hept-5-ene (8).—To a solution of 2.12 g (0.02 mol) of **6**[8] in 20 ml of tetrahydrofuran was added 2.92 g (0.02 mol) of ethyl azodicarboxylate. The reaction was exothermic and after 2 hr the orange color was completely dissipated. The infrared and inte-

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[5] T. J. Kealy, *J. Amer. Chem. Soc.*, **84**, 966 (1962).

[6] P. S. Bailey, *Chem. Rev.*, **58**, 925 (1958).

[7] F. H. Allen, *ibid.*, **62**, 653 (1962).

[8] J. Thiele, *Ber.*, **33**, 666 (1900).

TABLE I

EXPERIMENTAL CONDITIONS USED IN ATTEMPTED HYDROLYSIS OF **5**

Expt	Reaction medium	Temp, °C	Time, hr
1	25 ml of 5% H_2SO_4–25 ml of dioxane	Room temperature	24
2	66 ml of 10% H_2SO_4–33 ml of dioxane	Reflux	24
3	20 ml of 47% HI–10 ml of acetic acid	Room temperature	24
4	25 ml of 90% acetic acid	Reflux	24
5	25 ml of 70% perchloric acid	0	0.25
6	25 ml of concentrated sulfuric acid	Room temperature	1
7	30 ml of 70% sulfuric acid	Room temperature	1.5
8	25 ml of methylene chloride and 1.0 g of $AlCl_3$	Room temperature	0.5
9	25 ml of concentrated sulfuric acid	70	24

grated nmr spectra taken at this time were consistent with structure **8**. The nmr spectrum showed a triplet at 1.18 ppm (CH_3), a singlet at 1.68 ppm (CH_3), a quartet at 4.1 ppm (CH_2), a broad singlet at 5.22 ppm (bridgehead), and a triplet at 6.6 ppm (vinyl). Attempts to crystallize the yellow oil from a variety of solvents were unsuccessful. Distillation resulted in decomposition and polymerization, whereas column chromatography on Bio-Rad activity one neutral alumina resulted in reverse Diels–Alder reaction and some apparent decomposition of the azo compound as evidenced by the evolution of a gas. Elution with a benzene–ether mixture and evaporation of solvent gave an orange oil which appeared to be identical with that obtained by "aging" the original mixture for several days.

2,3-Dicarbethoxy-7-isopropylidene-2,3-diazabicyclo[2.2.1]heptane (10).—A solution containing 0.4 mol of freshly prepared **8** dissolved in 350 ml of tetrahydrofuran was catalytically reduced with 1 g of 10% palladium on charcoal. Absorption of about 1.1 molar equiv of hydrogen proceeded very rapidly. The reaction mixture was filtered and the solvent was removed *in vacuo*. Distillation of the residual oil gave an 80% yield of product, bp 113–115° (0.04 mm).

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.56; H, 7.85; N, 9.92. Found: C, 59.45; H, 7.89; N, 10.12.

The nmr spectrum ($CDCl_3$) consisted of a triplet at 1.28 ppm (CH_2), a singlet at 1.75 ppm (CH_3), a broad singlet at 1.82 ppm (ring CH_2), a quartet at 4.25 ppm (CH_2), and a broad singlet at 4.85 ppm (bridgehead).

2,3-Dicarbethoxy-7,7-dihydroxy-2,3-diazabicyclo[2.2.1]heptane (13).—A solution of 28.2 g (0.1 mol) of **10** in 500 ml of absolute methanol was ozonized at −30° in the usual way. After reaction was complete the reaction mixture was catalytically reduced with 1 g of 10% palladium on charcoal. Approximately 70% of theoretical hydrogen was consumed very rapidly. The catalyst was filtered and solvent removed *in vacuo* to give a light yellow residual oil. The product, **13**, can be crystallized from this residual oil by trituration with ether; however, a much more convenient isolation procedure was to dissolve the oil in ether and extract with water. Removal of water *in vacuo* gave 14 g of a residual white solid, mp 129–133°. Recrystallization from acetone–cyclohexane gave 12 g (44%) of **13**, mp 131–133°. See discussion for spectral data.

Anal. Calcd for $C_{11}H_{18}N_2O_6$: C, 48.17; H, 6.62; N, 10.21. Found: C, 48.39; H, 6.80; N, 10.18.

6,6-Diphenylfulvene (7) was prepared by a modification of the method of Thiele.[8] To 1 l. of tetrahydrofuran, which had been distilled over lithium aluminum hydride, was added 24 g (1 mol) of sodium hydride, followed by the slow addition of 66.1 g (1 mol) of freshly distilled cyclopentadiene. After the evolution of hydrogen had ceased, a solution of 182.2 g (1 mol) of benzophenone in 800 ml of tetrahydrofuran was added over a period of 1 hr. The solution was stirred for 1 additional hr and poured into 2 l. of ice water and extracted with four 500-ml portions of 30–60° petroleum ether. The combined extracts were washed with water and saturated sodium chloride solution and dried over magnesium sulfate. The drying agent was removed by filtration and the solvent was removed by evaporation. The remaining red solid was recrystallized from 30–60° petroleum ether to give 199 g (86%) of red solid, mp 81–82° (lit.[8] mp 82°).

2,3-Dicarbethoxy-7-diphenylmethylene-2,3-diazabicyclo[2.2.1]hept-5-ene (9).—To a solution of 3.31 g (0.0144 mol) of **7** in 40 ml of cyclohexane was added 2.50 g (0.0144 mol) of ethyl azodicarboxylate and the deep red solution was stirred for 24 hr at room temperature. The resulting white precipitate was filtered and washed with cold cyclohexane to give 4.74–5.51 g (81–95%) of product. Recrystallization from hexane afforded an analytical sample, mp 76–78°.

Anal. Calcd for $C_{24}H_{24}O_4N_2$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.18; H, 6.04; N, 6.75.

The infrared spectrum (liquid film) showed absorption maxima at 5.74 and 5.90 μ (C=O). The nmr spectrum (CCl_4) showed a triplet at 1.1 ppm (CH_3), a quartet at 4.1 ppm (CH_2), a triplet at 5.34 ppm (bridgehead), a triplet at 6.75 ppm (vinyl), and a singlet at 7.2 ppm (aromatic).

2,3-Dicarbethoxy-7-diphenylmethylene-2,3-diazabicyclo[2.2.1]-heptane (11).—A 4.04-g (0.01 mol) sample of **9** was reduced over 100 mg of Adams catalyst in 100 ml of ethyl acetate at atmospheric pressure. The uptake of hydrogen was extremely slow after 1 equiv had been consumed (1.4 hr). The reaction mixture was filtered and concentrated under vacuum, and the remaining oil was crystallized from pentane. Recrystallization from pentane gave 3.3 g (81.5%) of product, mp 89–90.5°.

Anal. Calcd for $C_{24}H_{26}O_4N_2$: C, 70.92; H, 6.45; N, 6.89. Found: C, 70.71; H, 6.48; N, 6.88.

The infrared spectrum (liquid film) showed absorption maxima at 5.74 and 5.90 μ (C=O). The nmr spectrum (CCl_4) showed a triplet at 1.12 ppm (methyl), a singlet at 1.95 ppm (ring methylene), a quartet at 4.10 ppm (methylene), a triplet at 4.77 ppm (bridgehead), and a singlet at 7.2 ppm (aromatic).

Ozonolysis of 11.—Ozonolysis of **11** and work-up of the reduced ozonide in a manner identical with that described for **10** gave no water soluble material.

Registry No.—**4**, 16425-73-3; **5**, 16462-52-5; **7**, 2175-90-8; **8**, 16425-69-7; **9**, 16425-70-0; **10**, 16425-71-1; **11**, 16425-67-5; **13**, 16425-72-2.