Studies in the Azadispiro[5.1.5.2]pentadecene Series. III. Cyclizations and Other Reactions

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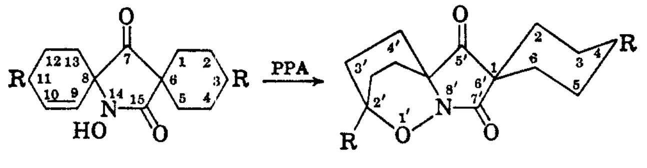
When 14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (**4**) was heated with polyphosphoric acid at 55–60° or with concentrated sulfuric acid at 50°, the 14-hydroxyl group cyclized at the 11-carbon to form 3′,4′-dihydrospiro[cyclohexane-1,6′(7′H)-[5H-2,4a]ethano(2H)pyrrolo[1,2-*b*]-1,2-oxazine]-5′,7′-dione (**5**). During the bromination of **4** in ether and acetic acid, the 14-hydroxyl group cyclized at the 10-carbon rather than at the 11-carbon to form **16**, along with the expected 9,10-addition product. When **3**, the oxime of **4**, reacted with bromine in carbon tetrachloride, the oxime hydroxyl cyclized at the 10-carbon to form **21**. The Beckmann rearrangement of the oxime **3** with polyphosphoric acid at 55–65° formed a normal product **32**. At 140°, the product was a mixture of two rearranged products, **34** and **36**, in which cyclization had also taken place. Compound **32** cyclized at 130° to form these same two products. The 7-carbonyl group of **4** reacted with representative RLi compounds and with methyl- and allylmagnesium bromide to form tertiary alcohols. With other Grignard reagents, the ketone was either reduced to secondary alcohol or did not react.

The unique azadispiro compounds which are obtained from the base-catalyzed condensation of nitromethane with alicyclic ketones show interesting interactions between functional groups of adjacent rings. In a previous publication,[2a] the acid-catalyzed cyclization of the 14-hydroxyl group of 3,11-dimethyl-14-hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (**1**, R = CH_3) with the olefinic double bond was described.



1, R = CH_3
4, R = H

2, R = CH_3
5, R = H

The structure of the tetracyclic product **2** was readily established by nmr spectra, but this technique was not applicable to **5** (R = H) owing to ambiguity of the spectra. In the present investigation, this cyclization has been further investigated and the structure of **5** has been established by chemical means.

The Acid-Catalyzed Cyclization of 4.—Compound **4** cyclized to form **5** in the presence of either polyphosphoric acid or dilute sulfuric acid. Structure **5** for the product was anticipated by analogy with **2**, since both infrared and nmr spectra and chemical reactions are compatible with it. The infrared spectrum has a five-membered-ring ketone carbonyl band at 1740 cm^{-1} and an amide carbonyl band at 1670 cm^{-1} but no absorption for hydroxyl, -NH, or olefinic groups. These data were substantiated by the formation of a 5′-ketoxime and a negative ferric chloride test. Further evidence for this structure was afforded by the reactions shown in Scheme I.

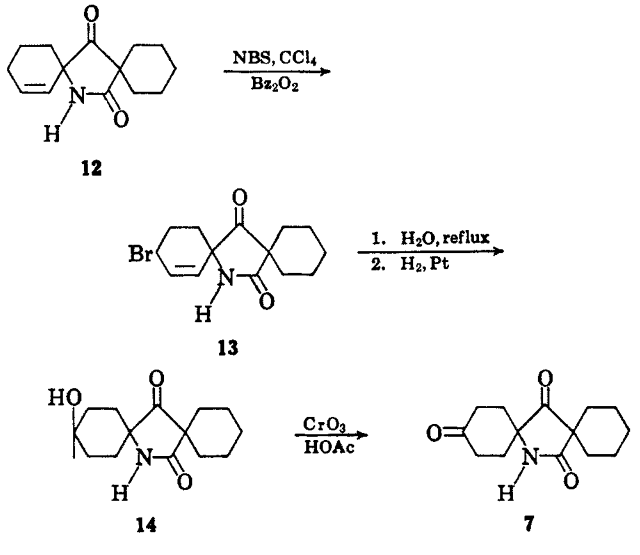
Cleavage of the O–N bond of **5** with hydriodic acid yielded the iodo compound **9**, which was dehydrohalogenated with sodium hydroxide to form **10** in good yield, along with some **5**. Compound **10** cyclized more readily than **4** with polyphosphoric acid to form **5**.

Lithium aluminum hydride reduced both the ketone and amide carbonyl groups, leaving the tetrahydrooxazine ring intact in **11**.

Hydrogenation of **5** at high pressure with Raney nickel formed the diol **8** by hydrogenolysis of the O–N ring system and hydrogenation of the 5′-carbonyl group.

Hydrogenation of **5** at low pressure over Raney catalyst or palladium on carbon formed **6** by reductive cleavage of the O–N bond of the oxazine ring. This type of cleavage takes place readily when isoxazolines and isoxazoles are hydrogenated in the presence of these catalysts.[3] The infrared spectrum of **6** shows both OH and NH absorption.

The structure of the 11-hydroxy ketone **6** was established by chromic acid oxidation of **6** to the 7,11-diketone **7**, which was obtained by an independent synthesis.



12

13

14

7

The hydroxy ketone **14** formed in this series of reactions was not identical with **6** obtained by the reduction of **5**, as shown by differences in melting points and infrared spectra, but the fact that they were each

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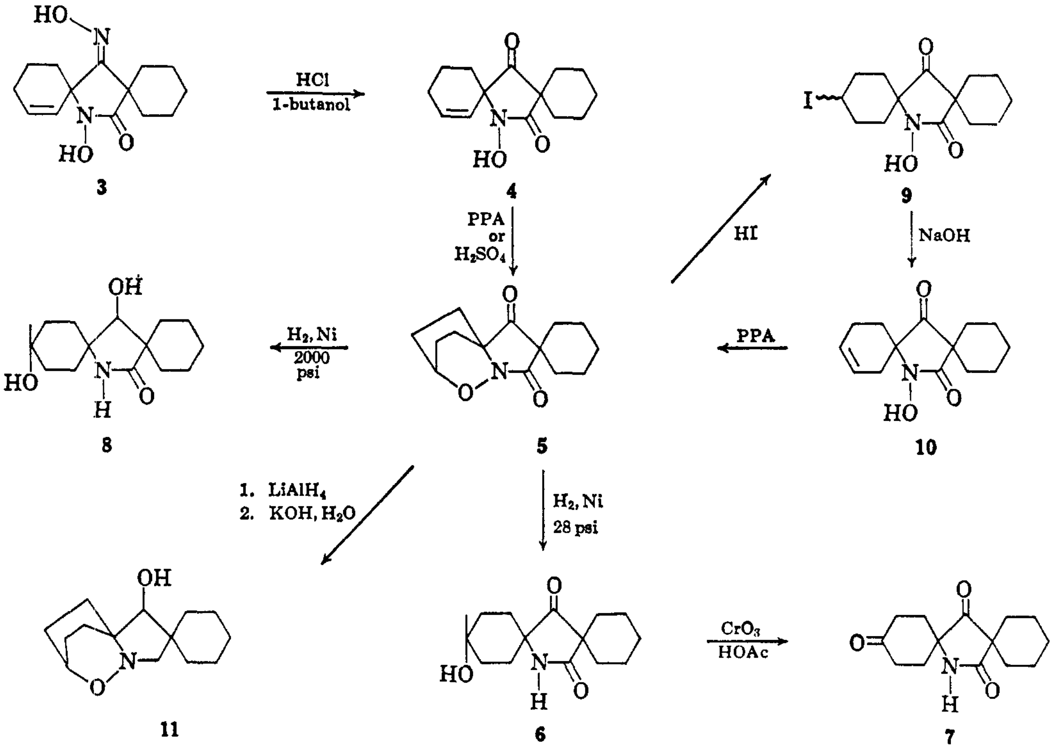
[1] Abstracted from the Ph.D. Dissertations of D. N. Heintz, University of Missouri, June 1965, and J. E. Johnson, University of Missouri, Aug 1966.

[2] (a) D. V. Nightingale and D. N. Heintz, *J. Org. Chem.*, **31**, 361 (1966); (b) D. V. Nightingale and J. E. Johnson, *J. Heterocyclic Chem.*, **4** 102 (1967).

[3] (a) A. H. Lindemann and W. Pickert, *Ann.*, **456**, 275 (1927); (b) W. Stuhmer, and W. Heinrich, *Ber.*, **84**, 224 (1951).

SCHEME I



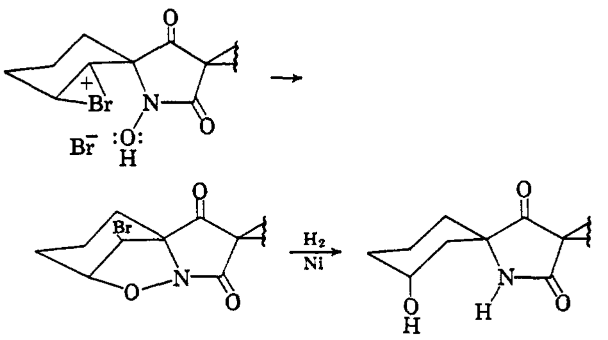
oxidized in good yields to the same diketone **7** indicated that they are stereoisomers rather than position isomers. The ring structure in **5** requires that the hydroxyl group formed by reductive cleavage be *cis* to the nitrogen. Consequently, the hydroxyl group in **14** must be *trans* to the nitrogen.

This acid-catalyzed cyclization is interesting because the new ring is formed at a site adjacent to the double bond. The formation of **4** may proceed as follows: protonation of the double bond to form a secondary carbonium ion on the 10-carbon followed by a 1-2 hydride shift to give a secondary carbonium ion on the 11-carbon. The boat conformation of the latter, which would be in equilibrium with the chair conformer, is in an ideal position to cyclize by nucleophilic attack of the HO–N group to form **5**.

Cyclization during the Bromination of 4 (Scheme II).—When **4** was treated with bromine in ether and acetic acid, cyclization apparently occurred without a hydride shift to form **16**. The structure of this compound is based on infrared, nmr, and analytical data and on its reduction to a keto alcohol **17**, which was oxidized to a diketone **20** that was different from the diketone **7**.

Since there was no reason to expect any change in the 7-carbonyl group, this product could be either the 7,9- or the 7,10-diketone. The former, however, would necessarily be derived from a four-membered-ring structure, which would be greatly strained if fused to a five- and six-membered ring in the tetracyclic system.

It would seem reasonable that cyclization during the bromination of **4** could be explained as being due to attack of the hydroxyl group of the hydroxamic acid on the 10-carbon atom during the intermediate bromonium ion stage. The bromine in the resulting monobromo compound **16** would consequently be axial. It should be noted also that the ring system sets the configuration of the hydroxyl group in the reduction product **17**.

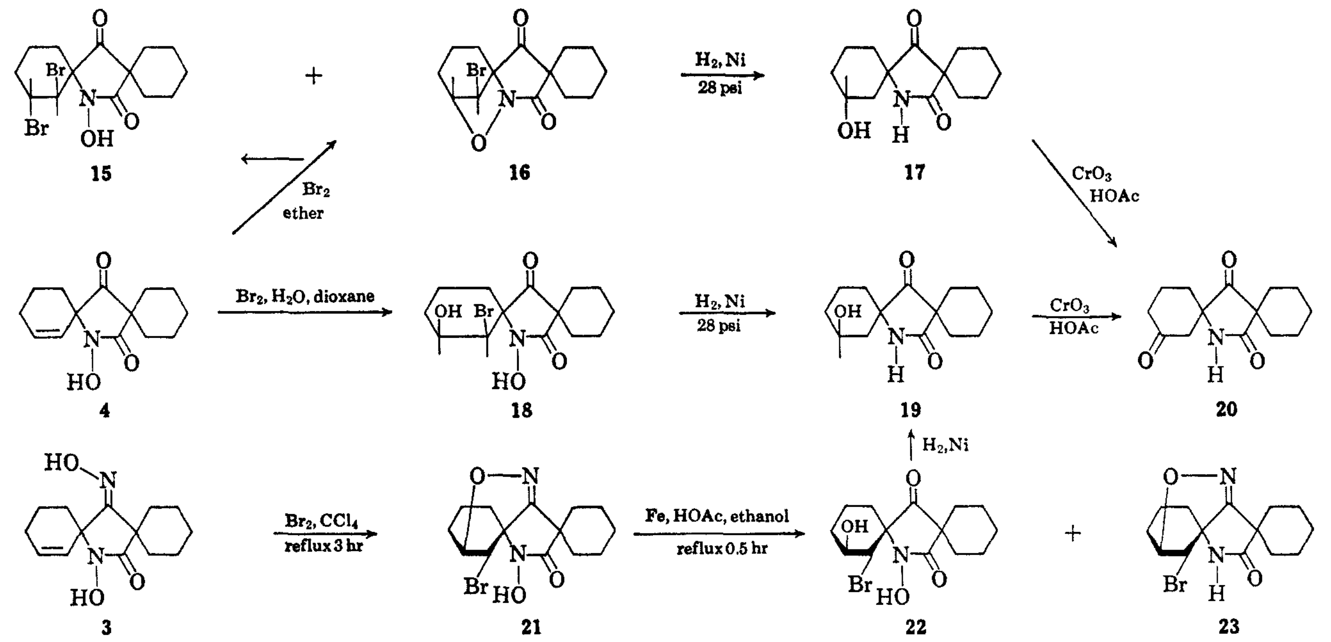


16 17

A second product obtained from the bromination of **4** was the dibromide **15**. This structure is supported by analytical and spectral data and by the quantitative debromination with zinc to give the olefinic compound **12**, which is also obtained in this manner from **16**. It is likely that **15** is the *trans*-9,10-dibromide with the 9-bromine atom *trans* to the adjacent nitrogen atom. Compound **15** would logically be formed by attack of bromide ion on the bromonium ion formed in initial step of the reaction. It is of interest that **15** is unaffected by boiling 30% aqueous sodium hydroxide.

Synthesis of the 7,10-Diketone.—This diketone was obtained from **4** by a second sequence of reactions shown in Scheme II. The addition of hypobromous acid to an unsymmetrical olefinic double bond can give a mixture of position isomers and it is possible that **18** is a mixture in which the 10-hydroxy isomer predominates. The orientation shown should be favored by electronic factors noted below for the hydroboration of **12**.

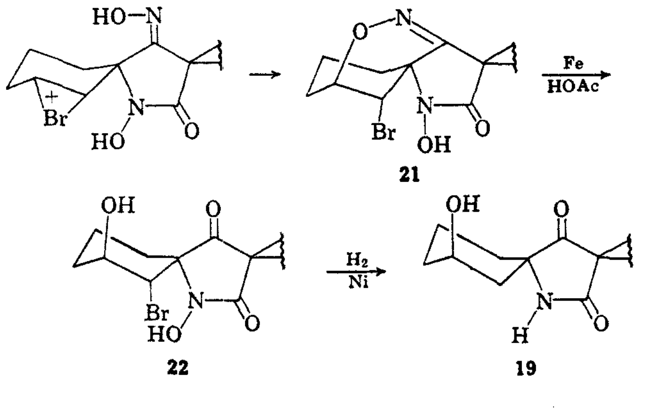
SCHEME II



Bromine in aqueous dioxane gave a bromohydrin **18**, which was reduced to a keto alcohol **19** that was different from **17**. Both keto alcohols were oxidized in good yield to the same 7,10-diketone **20**. This would indicate that the hydroxyl group in **19** must have a configuration opposite that of **17**.

Cyclization during the Bromination of the Oxime 3.—It had been reported earlier from this laboratory[4] that the bromination of **3** yielded a monobromo compound **21**, the structure of which was not determined. Noland and Michaelson[5] have investigated the reaction and concluded that cyclization had occurred, either on the 9- or 10-carbon, by means of the oxime hydroxyl.

Compound **3** contains two nitrogen–hydroxyl groups, either one of which could interact with an intermediate bromonium structure as postulated for the formation of **16**. Cyclization by the hydroxamic acid hydroxyl should lead to an oxime of **16**. However, reduction of **21** with iron and acetic acid[5] yielded a bromohydrin **22** which is isomeric with **18**, accompanied by **23** in which the hydroxamic acid hydroxyl has been removed. The infrared spectra of the two bromohydrins both show the 7-ketone band at 1750 cm^{-1} and the spectrum of **23** showed no hydroxyl absorption. These data indicate that cyclization proceeded *via* the oxime hydroxyl group.



If it is assumed that the reaction of **3** with bromine involves an intramolecular attack of the oxime hydroxyl group on the intermediate bromonium ion, the resulting product **21** would have the stereochemistry shown, with the bromine and the cyclic oxygen in a *trans* diaxial relationship.

The stereochemistry of the hydroxyl group in **22** is set by the ring system of **21**; so it should have a configuration opposite to that of the hydroxyl group in the bromohydrin **18** obtained from compound **4** as shown.

The bromohydrins **18** and **22** were converted into the same keto alcohol **19** by means of hydrogen and Raney nickel and these two samples were oxidized in good yield to the 7,10-diketone **20**.

The isomeric alcohols **17** and **19** should have opposite configurations as shown, since they are derived from cyclized compounds in which the stereochemistry is fixed. They have notably different melting points and different infrared spectra; yet both are oxidized in good yield to the same ketone **20**. The two samples of the two ketones obtained by these two different routes also have different melting points; yet their nmr and infrared solution spectra are identical. These two solids appear to be dimorphic forms of **20** and, in the two alcohols from which they are prepared, the hydroxyl must be on the 10-carbon. Thus, cyclization during the bromination of the oxime **3** and the keto-hydroxamic acid **4** must have occurred predominately in that position.

An attempt to cleave the dihydro-1,2-oxazine ring system of **21** by low-pressure hydrogenation over Raney nickel resulted only in the hydrogenolysis of the bromine atom and the hydroxyl group of the hydroxamic acid to form **26**. The reaction of **21** with zinc and ethanol opened the ring to form **25**, which is also readily obtained from **3** with this reagent.

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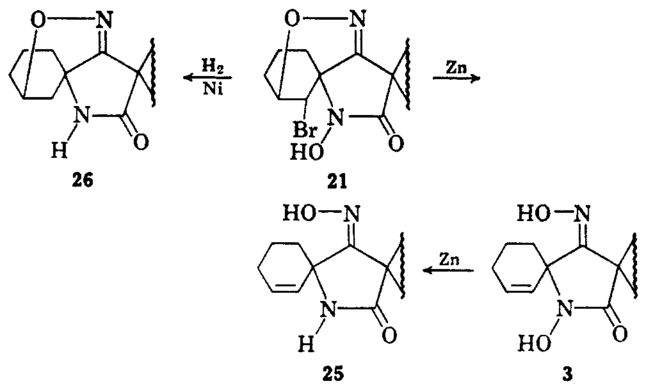
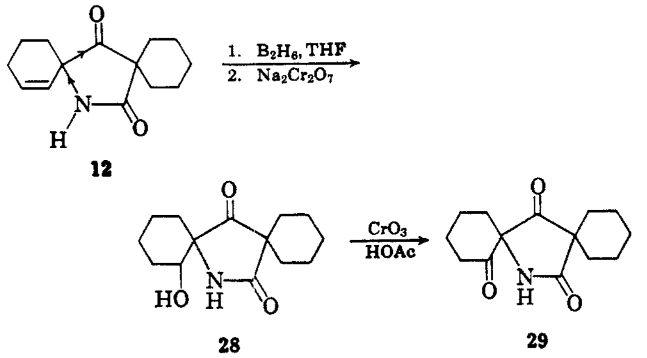
(4) D. V. Nightingale, D. A. Reich, and F. B. Erickson, *J. Org. Chem.*, **23**, 236 (1958).

(5) W. E. Noland and M. L. Michaelson, personal communication.



By contrast, the ring system of **16** is readily opened with hydrogen and Raney nickel to form **17** as noted above (Scheme II) and it yields **12** when refluxed with zinc and ethanol. This latter compound is also obtained from **4** and this reagent.

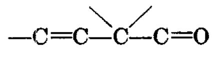
The Synthesis of the 7,9-Diketone 29.—The only feasible route to this diketone appeared to be *via* the hydroboration of **12**. It was recognized that borane



could attack either the 9- or the 10-carbon, but the latter should be favored.

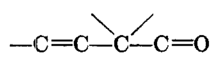
Considerable evidence has been accumulated to show that the addition of this reagent is influenced more by electronic factors than by steric factors.[6] Recently, Klein and coworkers[7] have reported that hydroboration of methyl cyclohexene-3-carboxylate yielded a mixture of position isomers in which the 3-hydroxy ester predominated. They explain this preferred boron attack as being due to a polar factor, stating "it is reasonable that the partial positive charge developed on the olefinic carbon next to the one forming a bond with boron should tend to be as remote as possible from the electron-attracting carboxylate group."

In **4**, the portion



$$-C=C-\overset{\diagdown\;\diagup}{C}-C=O$$

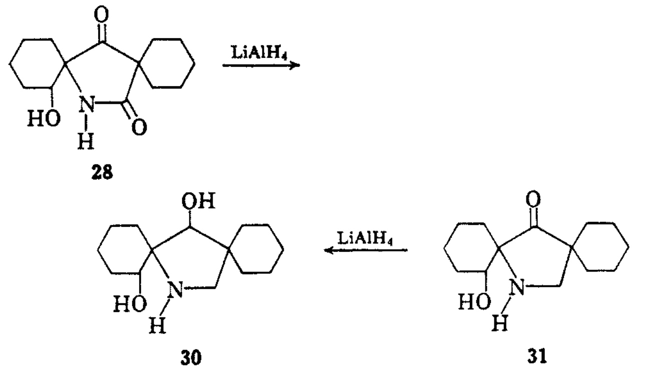
of the dispiro ring system is analogous to the same system



$$-C=C-\overset{\diagdown\;\diagup}{C}-C=O$$

present in methyl cyclohexene-3-carboxylate; so similar electronic factors should be operative. Also, the additional inductive effect of the nitrogen atom should tend to polarize the double bond in the same direction.

The use of a large excess of diborane generated *in situ* and a longer reaction time resulted in the reduction of the amide carbonyl group to methylene to yield **31**. This is in agreement with the report by Brown and Heim[8] of the reduction of amides to amines. Reduction of **28** and **31** with lithium aluminum hydride yielded the same 7,9-diol **30**.



The Beckmann Rearrangements (Scheme III).—The Beckmann rearrangement of the oxime **3** with polyphosphoric acid at 55–65° for 7 hr yielded a normal product, 7-hydroxy-7,15-diazadispiro[5.2.5.2]hexadec-1-ene-8,16-dione (**32**). This compound is soluble in base, gives a purple color with ferric chloride, and shows N–OH absorption in its infrared spectrum.

When **3** was heated with polyphosphoric acid at 140° for 10 min, two cyclized compounds were formed, **36** not previously reported, and **34** reported by Sundberg.[9] The reaction of **32** with this reagent under these same conditions also yielded **36** and **34** in nearly the same proportions. Both compounds were insoluble in base, gave no color with ferric chloride, and showed no N–OH absorption in their infrared spectra, which were identical in the 3300–1500-cm^{-1} region and differed very little in the fingerprint region.

The rearrangement product of the oxime **38** proved to be **36**, which established that **36** had the same nitrogen–oxygen ring system present in **5**.

At first it was thought that **3** might have isomerized during the reaction to form the isomeric *anti* oxime **39**, which could give rise to a 2,4-pyrimidinedione ring system in **34** rather than the 2,5-piperazinedione system. If so, then **34** could be formed by the rearrangement of **39**. The reaction of **39** with polyphosphoric acid at 140° yielded **41**, the infrared absorption spectrum of which showed aromatic absorption and indicated that it obviously was not structurally related to either **34** or **36**. A molecular formula, $C_{14}H_{18}N_2O_2$, was calculated for **41** from the elemental analyses but it was not investigated further. The reaction of **39** with polyphosphosphoric acid at 55–65° for 8 hr formed **32** in low yield.

High-pressure hydrogenation of **32** over Raney nickel formed 7,15-diazadispiro[5.2.5.2]hexadecane-8-16-dione (**33**), which was also obtained by rearrangement of the oxime **40**. The structure of **33** was confirmed by synthesis from 1-aminocyclohexanecarboxylic acid. The infrared spectra of these three samples of **33** were identical.

High-pressure hydrogenation of **34** and **36** over Raney nickel formed **35** and **37**, respectively. The similarity of the infrared spectra of these two com-

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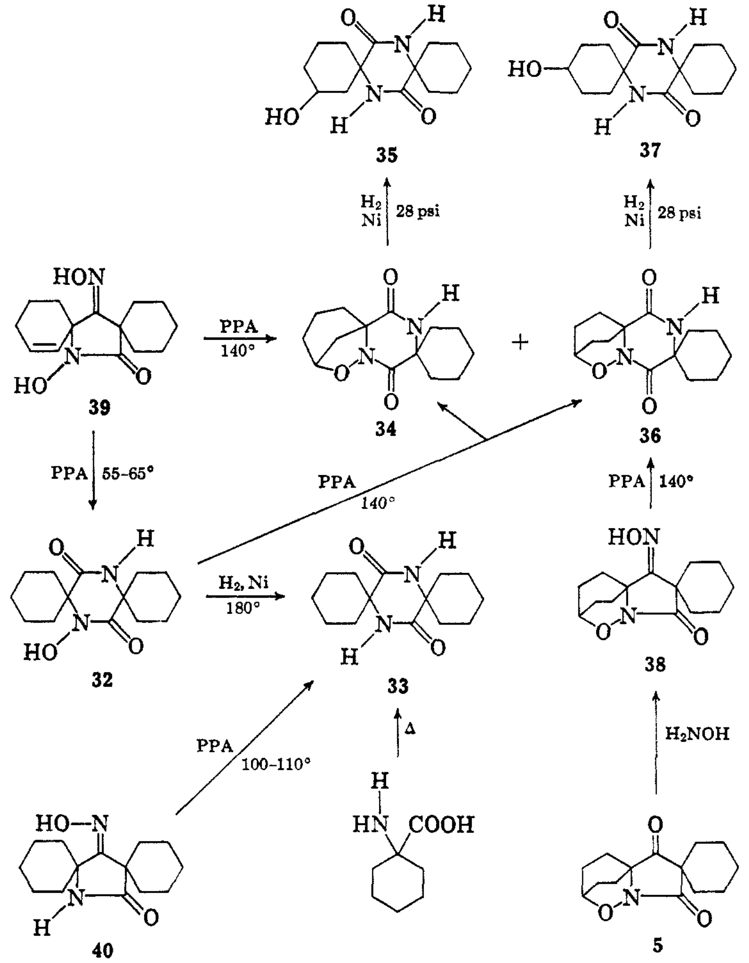
[6] G. Zweifel and H. C. Brown, *Org. Reactions*, **13**, 1 (1963).

[7] J. Klein, E. Dunkelblum, and D. Avraham, *J. Org. Chem.*, **32**, 935 (1967).

[8] H. C. Brown and P. Heim, *J. Am. Chem. Soc.*, **86**, 3566 (1964).

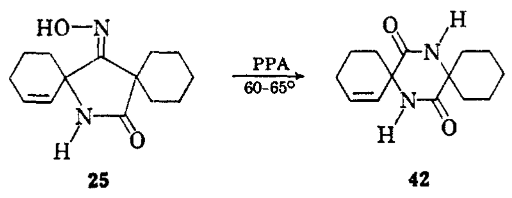
[9] R. J. Sundberg (with W. E. Noland), Ph.D. Dissertation, University of Minnesota, 1962.

SCHEME III
BECKMANN REARRANGEMENT PRODUCTS

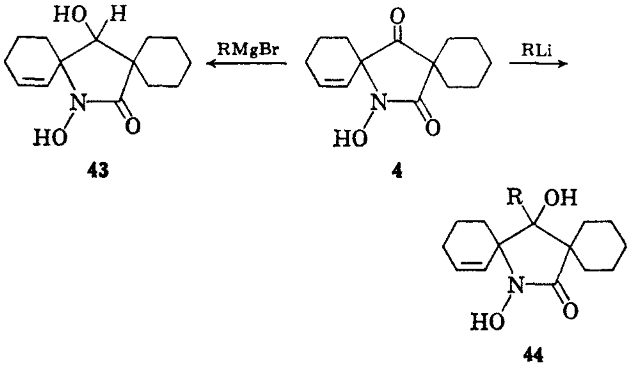


pounds and of **33** in the 3500–1500-cm^{-1} region and in the fingerprint region indicates that they contain the same heterocyclic ring system. Since the ring system of **38** has been established, the hydroxyl group of **37** must be in the 11 position and in **35** it should be in the 10 position. The very similar infrared spectra of **34** and **36** noted above suggested that in **36** cyclization has occurred at the 2 position of **32** rather than at the 3 position.

Rearrangement of **25** with polyphosphoric acid at 60–65° gave **42**. Since **25** was obtained from **3** by reduction with zinc and ethanol, the stereochemistry of the oximino group should be the same in both compounds and **42** should have the same ring system as **32**.



Reactions of 4 with Organometallic Compounds.—The 7-ketone group of **2** and **4** reacted with representative RLi compounds and Grignard reagents in a manner typical of hindered ketones. The RLi compounds added to the ketones to form tertiary alcohols. Allylmagnesium bromide and methylmagnesium iodide were the only Grignard reagents which formed tertiary alcohols. The other Grignard reagents either reduced the carbonyl group to secondary alcohol or did not react. The products from these reactions are listed in Table I.



All efforts to replace the secondary alcohol group with halogen by conventional methods were unsuccessful. The reagents used were 48% hydrobromic acid alone or with a little concentrated sulfuric acid, phosphorus tribromide, and thionyl chloride. With phosphorus trichloride, **43** formed **45**, apparently a phosphite.

The reaction of **46** (R = C$_6$H$_5$) with aluminum chloride or aluminum bromide in nitromethane resulted in a skeletal rearrangement.[10] When R is

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(10) D. V. Nightingale and H. A. Parish, Jr., 154th National Meeting of the American Chemical Society, Chicago, Ill., Sept 1967.

TABLE I

REACTIONS WITH RLi AND RMgBr REAGENTS

Compd	Reagent	Type of reaction	Yield, %	Mp, °C	Formula	Calcd, % C	Calcd, % H	Calcd, % N	Found, % C	Found, % H	Found, % N
4	CH_3Li[a]	Addn	84	194–195	$C_{15}H_{23}NO_3$	67.89	8.74	5.28	67.86	8.57	5.28
4	CH_3MgI	Addn		194–195							
4	C_2H_5MgBr	Reducn	58	175–177	$C_{14}H_{21}NO_3$	66.90	8.42	5.57	67.13	8.41	5.85
4	i-C_3H_7MgBr	Reducn	75	178–179							
4	n-C_4H_9MgBr	Reducn	56	173–173							
4	n-C_4H_9Li[b]	Addn	83	206–208	$C_{18}H_{29}NO_3$	70.32	9.51	4.56	70.31	9.53	4.31
4	C_3H_5MgBr[c]	Addn	29	189–190	$C_{17}H_{25}NO_3$	70.07	8.67	4.84	70.26	8.91	4.46
4	$C_6H_5CH_2Li$[d]	Addn	31	244–245	$C_{21}H_{27}NO_3$	73.87	7.97	4.10	73.77	7.97	3.98
4	C_6H_5Li[e]	Addn	80	239–240	$C_{20}H_{25}NO_3$	73.36	7.70	4.28	73.63	7.91	4.21
2	i-C_3H_7MgBr[f]	Reducn	87	196–198							
2	n-C_4H_9Li[g]	Addn	83	203–205	$C_{20}H_{33}NO_3$	71.60	9.92	4.18	71.61	10.12	3.92
2	C_6H_5Li[h]	Addn	71	221–225	$C_{22}H_{29}NO_3$	74.33	8.22	3.94	74.36	8.23	4.22

Registry no.: [a] 15025-54-4; [b] 15077-34-6; [c] 15026-38-7; [d] 15025-55-5; [e] 15026-37-6; [f] 4880-71-1; [g] 15025-51-1; [h] 15025-52-2.

methyl, the product is 7-methylene-11-chloro- (or bromo-) 14-azadispiro[5.1.5.2]pentadecan-15-one. These and related reactions will be described in a subsequent publication.

Experimental Section[11]

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione 7-oxime (**3**) was prepared as previously described,[12] using piperazine as the catalyst.

14-Hydroxy-14-azadispiro[5.1.5.2]pentadec-9-ene-7,15-dione (**4**) was more conveniently prepared by the hydrolysis of **3** with hydrochloric acid in 1-butanol rather than with dilute aqueous sulfuric acid. Compound **3** (9.0 g), 150 ml of concentrated hydrochloric acid, and 125 ml of 1-butanol were refluxed for 1.3 hr. The solvent was removed by distillation until crystals began to separate. Water (150–200 ml) was added to the residue and after the mixture had cooled, the solid was collected on a filter to yield 6.4 g (74%) of **4**, mp 170–171° after crystallization from aqueous ethanol (lit.[4] 170–172°).

3′,4′-Dihydrospiro[cyclohexane-1,6′(7′H)-[5H-2,4a]ethano-(2H)pyrrolo[1,2-*b*]-1,2-oxazine]-5′,7′-dione (**5**).—With stirring, 20 g of **4** was heated with 400 g of polyphosporic acid at 70–80° for 7.5 hr and then allowed to stand overnight at room temperature. With stirring, cold water was added to the mixture until the polyphosphoric acid had dissolved. The cold solution was extracted with chloroform and the chloroform extracts were washed with 10% sodium hydroxide to remove any **4**. The solution was washed with water, dried, and evaporated nearly to dryness. Petroleum ether (bp 30–60°) was added to the warm, viscous residue until crystals began to separate. After the solution had cooled, the solid was collected on a filter and recrystallized from methanol to yield 12.5 g (62.5%) of **5**: mp 247–248°; infrared bands at 1740 and 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$; C, 67.44; H, 7.68; N, 5.62. Found: C, 67.08; H, 7.37; N, 5.69.

Formation of 5 in Sulfuric Acid.—Compound **4** (5 g) in 25 ml of concentrated sulfuric acid was heated to 50° and the temperature held at 45–50° for 1.5 hr. The cooled mixture was poured slowly onto ice and the product extracted with chloroform. The chloroform solution was washed with 10% sodium hydroxide, then with water and dried and the solvent removed by evaporation. The yield of **5** was 1.39 g (27%), mp 247–248° after recrystallization of the residue from ethanol. The infrared spectrum of this compound was identical with that of **5** obtained from the above reaction in polyphosphoric acid.

Reaction of 5 with Hydriodic Acid.—The procedure is essentially that of Perold and von Reiche[13] for the cleavage of 3,5-diphenyl-2-isoxazoline.

Compound **5** (3.0 g) and 100 ml of 47% hydriodic acid were refluxed with stirring for 7 hr. After 2.5 hr a solid began to separate. The solution was cooled, diluted with water, and extracted with benzene. The benzene layer was washed as quickly as possible with 5% sodium hydroxide solution and then with water. The basic wash solution and the water washings were immediately acidified with 1:1 hydrochloric acid and the solid which separated was extracted with benzene. After this benzene extract was washed, dried, and evaporated to dryness, the residue was crystallized from benzene–petroleum ether to yield 1.05 g (23%) of **9**, mp 202–203°. This solid was soluble in dilute sodium hydroxide solution and gave a violet color with ferric chloride.

Anal. Calcd for $C_{14}H_{20}NO_3I$: C, 44.57; H, 5.34; N, 3.72; I, 33.64. Found: C, 44.58; H, 5.34; N, 3.77; I, 33.70.

Formation of 10 from 9.—Compound **9** (0.4 g) and 30 ml of 30% sodium hydroxide solution were allowed to stand overnight at room temperature, then heated on a steam bath for 40 min. The solution was diluted with water and the insoluble material was collected on a filter. Crystallization of this solid from benzene–petroleum ether gave 0.04 g (15%) of **5**, mp 247–248°, the infrared spectrum of which was identical with that of **5** obtained from **4**.

The basic filtrate was acidified with 1:1 hydrochloric acid and the solid which separated was collected on a filter. Crystallization of this material from petroleum ether yielded 0.18 g (66%) of **10**: mp 179–180°; infrared bands 3025, 2670, 1750, and 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.40; H, 7.86; N, 5.62. Found: C, 67.32: H, 7.85; N, 5.84.

Cyclization of 10.—Compound **10** (0.6 g) was heated with 40 g of polyphosphoric acid at 60–65° for 19 hr to yield 0.32 g (53%) of **5**, mp 246–248° after one crystallization from benzene. The infrared spectrum of this compound was identical with that of **5** obtained by the cyclization of **4**.

Reduction of 5 with Lithium Aluminum Hydride.—To a solution of 1.5 g of lithium aluminum hydride in 50 ml of dry ether was added with stirring a suspension of 1.0 g of **5** in 150 ml of dry ether. After the solution had refluxed for 24 hr the excess hydride was decomposed with 30% potassium hydroxide. Chloroform was added to the mixture, the aluminate was separated by filtration, and the chloroform–ether layer was dried and evaporated nearly to dryness. Petroleum ether was added to the residue and the separated solid was recrystallized from methanol to yield 0.6 g (60%) of **11**: mp 191.5–193°; infrared band at 3300 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 71.00; H, 9.81; N, 6.02.

Hydrogenation of 5.—All of the catalytic hydrogenations were carried out in conventional equipment for either high- or low-pressure reactions. After the mixture was removed from the container, the catalyst was separated by filtration from the solvent, heated if necessary, and the filtrate was evaporated,

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[11] All melting points were taken in an open capillary tube in a metal block and are corrected. For compounds which melted with decomposition, the block was heated to within 20° of the melting point before inserting the tube. The microanalyses were performed at the Weiler–Strauss Laboratories, Oxford, England. Unless otherwise specified, the drying agent for organic solutions was anhydrous magnesium sulfate and the petroleum ether had bp 60–70°. Most of the infrared spectra were determined in Nujol mulls with a Perkin-Elmer 237B. The nmr spectra were determined with a Varian A-60.

[12] D. V. Nightingale, S. Miki, D. N. Heintz, and D. A. Reich, *J. Org. Chem.*, **28**, 462 (1963).

[13] G. W. Perold and F. V. K. von Reiche, *J. Am. Chem. Soc.*, **79**, 465 (1957).

leaving a residue which was purified by crystallization from a suitable solvent.

A. High Pressure.—A solution of 1.8 g of **5** in 60 ml of ethanol was hydrogenated over 1 g of Raney nickel at an initial pressure of 2000 psi and a final temperature of 195° and 2550 psi. The product was washed with hot benzene, then crystallized from methanol to yield 6.5 g (30%) of **6**: mp 230–231°; infrared bands at 3350, 3200, and 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_3$: C, 66.37; H, 9.15; N, 5.53. Found: C, 66.28; H, 9.02; N, 5.51.

B. Low Pressure.—A solution of 2.1 g of **5** in 100 ml of ethanol was hydrogenated over 0.75 g of Raney nickel at room temperature and 28 psi. The residue was washed with benzene, then recrystallized from methanol to yield 1.8 g (85%) of **6** as fine white needles: mp 254–255°; infrared bands at 3500, 3150, 3060, and 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 67.14; H, 8.48; N, 5.56.

C. Low Pressure. Palladium on Carbon.—A solution of 0.8 g of **5** in 40 ml of ethanol was hydrogenated over 0.5 g of 5% palladium on carbon at room temperature and 38 psi. Compound **6**, mp 253–254°, was isolated as described above. The infrared spectra of the two samples of **6** were identical.

Oxidation of 6.—The oxidations of the secondary alcohols were all carried out and the product isolated by the same general procedure. The crude ketone was recrystallized from a suitable solvent.

To a solution of 1.0 g of **6** in 20 ml of acetic acid was added dropwise and with stirring a solution of 560 mg of potassium dichromate and 0.3 ml of concentrated sulfuric acid in 4.6 ml of water. The mixture was stirred overnight at room temperature, then diluted with water and extracted with ether. The combined ether extracts were washed with 10% sodium hydroxide, dried, and evaporated to dryness. Fractional crystallization of the residue from benzene–petroleum ether yielded 0.24 g of impure **7**.

The benzene–petroleum ether filtrate was concentrated and the solid which separated was collected on a filter. Two crystallizations of this material from benzene–petroleum ether gave 0.29 g (29%) of **7**: mp 227–229°; infrared bands at 3210, 3170, 3100, 1760, 1730, and 1680 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.68; H, 8.01; N, 5.71.

Synthesis of the 7,11-Diketone (7). Preparation of 12.—A solution of 32 g (0.13 mole) of **4** in 700 ml of ethanol and 48.0 g of zinc dust was refluxed and stirred for 6 hr. The mixture was allowed to stand overnight at room temperature, then filtered and the residue washed with hot ethanol. The combined filtrates were evaporated nearly to dryness and 200 ml of water was added to the residue. The mixture was extracted with chloroform and the chloroform extracts were washed with 10% sodium hydroxide and with water, then dried and the solvent removed by evaporation. The residue was recrystallized from benzene to give 21.7 g (73%) of **12**: mp 203–205°; infrared bands at 3130, 3030, 1751, 1680, and 1640 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_2$: C, 72.07; H, 8.21; N, 6.00. Found: C, 71.85; H, 8.43; N, 5.93.

Allylic Bromination of 12.—In a 500-ml round-bottom flask fitted with a stirrer, nitrogen inlet tube, and a reflux condenser were placed 10.0 g (0.042 mole) of **12**, 7.7 g (0.04 mole) of N-bromosuccinimide, 0.2 g of benzoyl peroxide, and 25 ml of reagent grade carbon tetrachloride. After the mixture had been stirred and refluxed in a nitrogen atmosphere for 2 hr it was cooled to room temperature and stirred overnight, then filtered to remove a white precipitate. This material was washed with carbon tetrachloride and the combined filtrates were evaporated to give a semisolid product which was dissolved in hot benzene. Petroleum ether was added to the warm benzene solution until it became cloudy and the mixture was kept overnight at room temperature. The separated crystals were collected on a filter and crystallized from benzene–petroleum ether to give 4.29 g (32%) of **13**, mp 157–160° dec. Two more recrystallizations from this solvent pair gave white needles: mp 170–172° dec; infrared bands at 3160, 3060, 1760, 1690, and 1640 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}NO_2Br$: C, 53.85; H, 5.81; N, 4.49; Br, 25.60. Found: C, 53.68; H, 5.93; N, 4.50; Br, 26.21.

Hydrolysis of 13.[14]—A mixture of 4.3 g (0.014 mole) of **13** and 150 ml of water was refluxed for 24 hr. The resulting solution was filtered while hot, then cooled to room temperature and the separated crystals (2.5 g 72%) were collected on a filter. After several recrystallizations from chloroform–petroleum ether, the white crystals of the unsaturated alcohol melted at 246–247°: infrared bands at 3450, 3240, 3150, 1780, 1700, and 1650 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.59; H, 7.64; N, 5.24.

Hydrogenation of the Unsaturated Alcohol.—A suspension of 1.36 g of the above unsaturated alcohol and 0.50 g of platinum oxide in 100 ml of ethanol was shaken for 24 hr at room temperature with hydrogen at 32 psi.

The mixture was filtered thru Filter-Cel and the solid washed with methanol. The combined filtrates were evaporated to yield 1.34 g (96%) of **14**, mp 211–219°, which after two recrystallizations from chloroform–methanol–petroleum ether gave small white needles: mp 228–229°; infrared bands at 3490, 3430, 3240, 3110, 1760, and 1690 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C. 66.62; H, 8.64; N, 5.67.

Oxidation of 14 (from 13).—To a solution of 0.83 g (0.003 mole) of **14** in 15 ml of glacial acetic acid were added dropwise and with stirring a solution of 0.5 g (0.0017 mole) of potassium dichromate in 6 ml of water and 0.5 g of concentrated sulfuric acid. The mixture was stirred for 24 hr at room temperature, diluted with 100 ml of water, and extracted with three 100-ml portions of ether. The ether extracts were washed with saturated aqueous sodium bicarbonate, dried, and evaporated to dryness to give 0.37 g (46%) of **7** as white crystals, mp 227–229°.

One crystallization from benzene–petroleum ether gave small white needles, mp 227–229°, which did not depress the melting point of **7** prepared in two steps from **5** (Scheme I). The infrared spectra of these two samples of **7** each showed bands at 3210, 3170, 3100, 1760, 1730, and 1680 cm^{-1} and were also identical in the fingerprint region.

Synthesis of the 7,10-Diketone (20). Reaction of 4 with Bromine in Ether and Acetic Acid.—A solution of 1.5 ml of bromine and 0.15 g of sodium acetate in 25 ml of acetic acid was added slowly to 5 g of **4** in 200 ml of ether. The mixture was heated on a steam bath until all of the ether had evaporated and the bromine color had disappeared, then 200 ml of water was added to the residue. The oil which separated was extracted with ether, the ether extract was washed with water, dried, and evaporated to dryness under reduced pressure, yielding another oily residue which would not solidify. The residue was dissolved in chloroform and the solution was first washed with aqueous sodium hydroxide then the chloroform layer was separated and washed with 2 l. of water. Evaporation of the dried solution yielded a yellow residue which was crystallized from ethanol to give 0.90 g (13%) of **16** as long white needles, mp 194–196°, which gave no color with ferric chloride: infrared bands at 1760, 1710, and 3000 cm^{-1}.

Anal. Calcd for $C_{14}H_{18}NO_3Br$; C, 51.23; H, 5.52; N, 4.26; Br, 24.35. Found: C, 51.14; H, 5.45; N, 4.11; Br, 24.50.

The above water wash solution and the basic wash solution were combined and acidified with concentrated hydrochloric acid and extracted with chloroform. The chloroform extract was washed, dried, and evaporated to dryness. The oily residue was triturated with 40 ml of boiling petroleum ether and the solid which slowly separated was collected on a filter, then refluxed with petroleum ether. The insoluble material was recrystallized from benzene–petroleum ether to give finally 1.38 g (17%) of **15** as a white powder, mp 180–182°, which gave a violet color with ferric chloride and was soluble in sodium hydroxide: infrared bands at 3050, 2680, 1750, and 1680 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3Br_2$: C, 41.10; H, 4.68; N, 3.42; Br, 39.07. Found: C, 41.19; H, 4.91; N, 3.33; Br, 38.95.

The Reaction of 15 and 16 with Zinc.—The reaction of 0.40 g of **15** or **16** and 2.0 g of zinc dust in 70 ml of ethanol as described above for the preparation of **12** from **3** gave 0.28 g (97%) of **12**, mp 203–204°. The infrared spectra of the two samples were identical.

Hydrogenation of 16.—A solution of 1.0 g of **16** and 1 g of sodium acetate in 100 ml of ethanol was hydrogenated over 1.0 g of Raney nickel at 32 psi. Removal of the catalyst and evaporation of the solvent gave a white solid which, after fractional crystallization from benzene–petroleum ether, yielded

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[14] This experiment was carried out by H. A. Parish, Jr., University of Missouri.

0.42 g (56%) of **17**: mp 166–168°; infrared bands at 3500, 3350, 3310, 3225, 1755, and 1665 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.81; H, 8.40; N, 5.61.

Oxidation of 17.—To a solution of 0.7 g of **17** in 20 ml of acetic acid was added, dropwise and with stirring, a solution of 560 mg of potassium dichromate and 0.3 ml of sulfuric acid in 4.6 ml of water. The mixture was stirred overnight at room temperature, then diluted with water and extracted with three 150-ml portions of ether. The ether extracts were combined and washed with 10% sodium hydroxide solution and evaporated to dryness. The white residue was recrystallized from benzene–petroleum ether to yield 0.53 g (76%) of **20** as white needles: mp 216–218°; infrared bands (Nujol) 3150, 3050, 1775, 1725, and 1670, and (chloroform) 3370, 1760, and 1690 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.78; H, 7.66; N, 5.58.

Reaction of 4 with Aqueous Bromine.[5]—To a warm solution of 20.0 g (0.08 mole) of **4** in 150 ml of dioxane and 50 ml of water was added 30 g (0.188 mole) of bromine in 200 ml of water. A yellow precipitate separated, which dissolved when the mixture was heated and stirred for 20 min at 80–90°. The solution was cooled to room temperature and diluted with 300 ml of water, then extracted with chloroform and the chloroform extracts were washed with 10% sodium thiosulfate solution. The chloroform layer was dried and evaporated to leave a viscous, oily residue which was dissolved in warm ether and the solution cooled in a refrigerator. The crystals which separated during 3 days were combined and recrystallized from aqueous methanol to yield 5.19 g (19%) of **18** as white crystals, mp 250–252° dec, which gave a light reddish brown color with ferric chloride: infrared bands at 3440, 3360, 3190, 1760, and 1660 cm^{-1}, identical with the infrared spectrum of Michaelson's analytical sample of **18**.

Hydrogenation of 18.—A suspension of 1 g of **18**, 1 g of sodium acetate and 0.5 g of Raney nickel in 100 ml of ethanol was hydrogenated at 39 psi for 2 days at room temperature. The mixture was filtered thru Filter-Cel and the filtrate evaporated to dryness; then the residue was triturated with water and filtered. The solid was recrystallized from aqueous methanol to yield 0.57 g (79%) of **19**, mp 224–225°, which gave no color with ferric chloride: infrared bands at 3490, 3420, 3160, 3040, 1740, and 1675 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 66.63; H, 8.45; N, 5.62.

Oxidation of 19.—A solution of 0.30 g of potassium dichromate in 3 ml of water and 0.30 g of concentrated sulfuric acid was added dropwise with stirring to a solution of 0.50 g of **19** in 10 ml of glacial acetic acid. The crude product (0.29 g, 58%), isolated as described above, was crystallized from benzene–petroleum ether to yield **20** as white needles: mp 199–200°; infrared bands (Nujol) 3120, 3040, 1760, 1720, and 1680, and (chloroform) 3370, 1760, and 1690 cm^{-1}.

The infrared spectrum of this sample in chloroform was identical with the spectrum in that solvent of **20** prepared from **16**. The nmr spectra of these two samples were also identical.

Anal. Calcd for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.07; H, 7.67; N, 5.68.

The Reaction of 21 with Iron and Acetic Acid.—The procedure is that of Noland and Michaelson.[5] To a solution of 2 g of **21**, prepared as previously described,[4] in 30 ml of ethanol and 2 ml of acetic acid was added 1.4 g of iron powder (reduced by hydrogen, Mallinckrodt Chemical Works, St. Louis, Mo.). The mixture was refluxed for 30 min, then cooled to room temperature, and diluted with 100 ml of water and 10 ml of sulfuric acid. After standing at room temperature for 5 min, the mixture was filtered. The filtrate was kept at room temperature for 24 hr, during which time 0.20 g (10%) of **22**, mp 224–226° dec, separated. The infrared spectrum of this compound was identical with that of **22** prepared in this manner by Noland and Michaelson,[5] with bands at 3120, 1750, and 1680 cm^{-1}.

The residue from the filtration of the original reaction mixture was triturated with ethanol and filtered again. Dilution of this filtrate with water yielded 0.58 g (30%) of a white solid, mp 200–204°. Three crystallizations from methanol gave **23** as white needles, mp 211–212°, which did not depress the melting point of **23**, mp 212–213°, prepared from **25**. The infrared spectra of the two samples were identical.

Hydrogenation of 22.—A mixture of 2.0 g of **22**, 2.0 g of sodium acetate, and 0.5 g of Raney nickel in 200 ml of ethanol was hydrogenated at 40 psi for 2 days at room temperature. The mixture was filtered through Filter-Cel and the filtrate evaporated to dryness. The residue was triturated with water and filtered. The solid was recrystallized from benzene to yield 0.53 g (27%) of white crystals of **19**, mp 215–218°, which did not depress the melting point (221–222°) of **19** prepared from **18**. The infrared spectra of the two samples were identical.

Hydrogenation of 21.—A mixture of 2.0 g of **21**, 1.0 g of sodium acetate, and 0.5 g of Raney nickel in 150 ml of ethanol was hydrogenated at 30 psi for 24 hr. The product, isolated as described above, was triturated with water, filtered, and dried to yield 1.04 g of crude product, mp 241–243° dec. Two crystallizations from ethanol–petroleum ether gave **26** as white platelets, mp 270–271° dec, which gave no color with ferric chloride: infrared bands at 3100, 1690, 1655, and 1645 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 63.61; H, 7.63; N, 10.60. Found: C, 63.71; H, 7.64; N, 10.65.

Formation of 25. A. From 3.—A suspension of 15 g of **3** and 20 g of zinc dust in 1 l. of ethanol was refluxed for 3 hr. The excess zinc and some suspended white solid was separated by filtration of the hot solution. The zinc was dissolved by reaction with dilute hydrochloric acid and the remaining solid was collected on a filter. The ethanol filtrate was evaporated to dryness under reduced pressure leaving a white residue which was combined with the solid separated from the zinc, then extracted with 10% sodium hydroxide to remove any unchanged **3**. Crystallization of the base insoluble material from ethanol yielded 10.97 g (77%) of **25**, mp 299–300° dec, as needles which gave no color with ferric chloride: infrared bands at 3265, 1695, 3130, 3000, 1645, and 1665 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}NO_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.93; H, 8.13; N, 11.17.

B. From 21.—A suspension of 2 g of **21** and 2.0 g of zinc in 150 ml of ethanol was refluxed and stirred for 1 hr. The crude product was isolated as described above and crystallized from ethanol to give 0.48 g (33%) of **25**, mp 297–299° dec, which did not change the decomposition point of **25** obtained from **3**. The infrared spectra of the two samples were identical.

Bromination of 25.—A solution of 16.6 g (0.104 mole) of bromine in 25 ml of carbon tetrachloride was added to a suspension of 10.0 g (0.04 mole) of **25** in 250 ml of carbon tetrachloride. After the mixture had refluxed on a steam bath for 3 hr the solution was cooled to room temperature and kept overnight, then diluted with chloroform, washed with water and with 10% aqueous sodium thiosulfate and again with water. The organic solution was dried and then evaporated to dryness. The oily residue was dissolved in benzene–petroleum ether and left overnight at room temperature. The pale yellow crystals were separated and recrystallized to give 4.76 g (36%) of **23**: mp 212–213°; infrared bands at 3150, 3050, 1710, and 1620 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}N_2O_2Br$: C, 51.39; H, 5.85; N, 8.56; Br, 24.42. Found: C, 51.10: H, 5.87; N, 8.44; Br, 24.22.

Synthesis of the 7,9-Diketone (29). Hydroboration of 12. A. With Diborane in THF.—In a 500-ml round-bottomed flask fitted with a reflux condenser and with a side arm capped with a rubber septum was placed 10.0 g (0.042 mole) of **12** and 50 ml of anhydrous THF. The mixture was cooled in an ice bath and stirred with a magnetic bar. To the cold suspension was added slowly, *via* a hypodermic syringe through the rubber septum, 80 ml (0.08 mole) of an approximately 1 *M* solution of diborane in THF prepared by the procedure of Zweifel and Brown.[8] After the solution had stirred for 2 hr at room temperature, the excess hydride was decomposed by the careful addition of 30 ml of water.

A solution of 20.5 g (0.068 mole) of sodium dichromate in 29.7 g (0.03 mole) of concentrated sulfuric acid in 125 ml of water, cooled below 20°, was added slowly with stirring. The temperature of the reaction mixture was maintained at 15–20° during the reaction.

After the addition was complete, the mixture was stirred 23 hr. Water (200 ml) was added and the mixture was extracted with two 100-ml portions of chloroform and the combined extracts were washed with water and dried. Evaporation of the solvent at aspirator pressure gave a semisolid residue which was triturated with benzene–petroleum ether. Filtration of the crystals yielded 3.56 g (33%) of crude product, mp 246–251°. Three crystallizations from methanol gave **28** as white needles: mp 268–270°; infrared bands at 3440, 3160, 1760, and 1690 cm^{-1}.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 67.17; H, 8.72; N, 5.51.

B. With Diborane Generated *in Situ*.—A 1-l. three-necked round-bottom flask was fitted with a stirrer, condenser, drying tube and a dropping funnel fitted with a gas inlet. The system was flushed with dry nitrogen and in the flask 10 g (0.042 mole) of **12** was suspended in 100 ml of diglyme. A solution of 3.93 g (0.104 mole) of sodium borohydride in 75 ml of diglyme was added and the flask was immersed in water at 15°. Boron trifluoride etherate (19.65 g, 0.138 mole) was added with stirring over 0.5 hr during which time the **12** went into solution. After the addition was complete, the solution was stirred for 3 hr at 15–29°. After the excess hydride was decomposed by the addition of water, an oxidizing solution, cooled below 20°, was added dropwise with stirring during 0.5 hr.

The oxidizing solution contained 20.5 g (0.067 mole) of sodium dichromate dihydrate in 29.7 g of concentrated sulfuric acid and 125 ml of water.

After the solution had stirred at room temperature for 15 hr, 200 ml of water was added, the mixture was extracted with four 200-ml portion of ether, and the extracts were discarded. The aqueous layer was made basic to litmus with 10% sodium hydroxide solution and 200 ml of ether was added. After shaking in a separatory funnel, the mixture was filtered to remove the precipitated inorganic salts. The ether layer was then separated and the aqueous layer again extracted with 200 ml of ether. The combined ether extracts were evaporated at aspirator pressure to a small residue containing diglyme, which was diluted with water and cooled. The resulting crystals (1.29 g, 13%), mp 153–155°, were separated and recrystallized from petroleum ether to give white crystals of **31**: mp 149–151°; infrared bands at 3250, 3060, and 1725 cm^{-1}.

Anal. Calcd for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77; N, 5.90. Found: C, 70.87; H, 10.07; N, 6.07.

Lithium Aluminum Hydride Reduction of 31.—To a stirred suspension of 1 g of lithium aluminum hydride in 25 ml of anhydrous ether was added a solution of 0.62 g of **31** in 50 ml of anhydrous ether and 25 ml of anhydrous THF. After the mixture had stirred and refluxed 4.5 hr, the excess hydride was decomposed with 30% potassium hydroxide solution. The coagulated inorganic salts were separated by filtration and washed with ether, the combined filtrates were evaporated to dryness at aspirator pressure, and the residue was crystallized from benzene–petroleum ether to yield 0.40 g (64%) of **30**, mp 177–180°. Two recrystallizations from this solvent gave white plates: mp 181–182°; infrared bands at 3410, 3270, 3000, and 2690 cm^{-1}.

Anal. Calcd for $C_{14}H_{25}NO_2$: C, 70.25; H, 10.53; N, 5.85. Found: C, 70.38; H, 10.76; N, 5.91.

Lithium Aluminum Hydride Reduction of 28.—In the same manner, 2 g of **28** in 100 ml of THF were reduced with 1 g of lithium aluminum hydride in 50 ml of THF. The mixture was stirred and refluxed for 24 hr and finally yielded 1.26 g (66%) of product, mp 170–173° after one crystallization from benzene–petroleum ether. One recrystallization from this solvent pair gave **30**, mp 177–180°, which did not depress the melting point of **30** prepared by the reduction of **31**. The infrared spectra of the two samples were identical.

Oxidation of 28.—To a solution of 2.0 g of **28** in 40 ml of glacial acetic acid was added dropwise and with stirring a solution of 1.18 g of potassium dichromate and 1.18 g of concentrated sulfuric acid in 10 ml of water. The solution was stirred for 24 hr at room temperature and then diluted with 200 ml of water. The mixture was extracted with chloroform and the chloroform extracts were washed with saturated sodium bicarbonate solution. The chloroform layer was dried and evaporated to dryness at aspirator pressure. A solution of the residue (1.58 g) in a 1:1 mixture of benzene and petroleum ether was chromatographed on 40 g of aluminum oxide with this solvent pair. After an initial fraction (0.23 g, mp 177–186°), a second fraction (0.32 g, 16%), mp 137–140°, was obtained. One crystallization of the latter from benzene–petroleum ether gave **29** as clusters of white needles: mp 143–144°; infrared bands at 3170, 3030, 1760, 1720, and 1690 cm^{-1}.

Anal. Calcd for $C_{14}H_{19}NO_3$: H, 7.68; N, 5.62. Found: C, 67.83; H, 7.75; N, 5.72.

The Beckmann Rearrangements. Preparation of the Oxime 38.—The procedure was essentially that of Noland and Sundberg[15] for the preparation of their oximes. The crude oxime was washed with water and recrystallized from methanol to yield 3.9 g (94%) of **38**: mp 288–289° dec; infrared bands at 3340, 3260, 1720, and 1670 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 65.62; H, 8.27; N, 9.58. Found: C, 65.72; H, 8.35; N, 9.83.

The Beckmann Rearrangement of 38.—The procedure for all of the Beckmann rearrangements is essentially that of Horning, Stromberg, and Lloyd.[16] The reaction of **38** is described in detail. With stirring, 2.0 g of **38** and 50 g of polyphosphoric acid were heated to 140° and kept at this temperature for 10 min. The brown solution was cooled to room temperature and cold water added until the polyphosphoric acid had dissolved. The solution was extracted with chloroform, the extract was washed until neutral, dried, and the solvent evaporated until crystals began to separate. The product was collected on a filter and recrystallized from petroleum ether to yield 1.0 g (50%) of **36**: mp 297–299° dec; infrared bands at 3270, 3200, 3050, and 1660 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.61; H, 7.63; N, 10.60. Found: C, 63.34; H, 7.53; N, 10.78.

The Beckmann Rearrangement of 3. At 55–65°.—With stirring, a mixture of 9.9 g of **3** and 200 g of polyphosphoric acid was heated at 55–65° for 7 hr. Water was added as described above and the chloroform solution was extracted with 5% sodium hydroxide. The basic solution was acidified and the solid which separated was collected on a filter to yield 4.2 g (24%) of **32**: mp 268–269° dec after recrystallization from methanol; infrared bands at 3150, 3050, 2650, and 1675 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.61; H, 7.63; N, 10.60. Found: C, 63.93; H, 7.76; N, 10.81.

Compound **32** formed a monoacetate, mp 177–178°.

Anal. Calcd for $C_{16}H_{22}N_2O_4$: C, 62.72; H, 7.24; N, 9.14. Found: C, 62.39; H, 7.20; N, 9.10.

B. At 140°.—A mixture of 8.6 g of **3** and 150 g of polyphosphoric acid was heated with stirring at 140° for 10 min. The cooled solution, diluted with water, was extracted with chloroform, and the chloroform solution was washed with 10% sodium hydroxide to remove unreacted **3**, then dried and evaporated. The residual reddish brown oil was dissolved in 30 ml of 1:2 benzene–chloroform and chromatographed on alumina to yield finally 2.9 g of white solid, mp 233–242° dec, which when recrystallized from chloroform–petroleum ether gave 0.4 g (4.7%) of **36** as shiny white needles, mp 294–296°. The infrared spectrum of this compound was identical with that of **36** obtained from the rearrangement of **38**.

The filtrates from the separation of **36** were combined and concentrated to yield 1.5 g (17.4%) of **34**: mp 248–249° dec (lit.[9] mp 249–250° dec); infrared bands at 3280, 3200, and 3060 cm^{-1}.

Cyclization of 32.—Compound **32** (5 g) was added to 140 g of polyphosphoric acid and the mixture was heated to 140° and held at this temperature for 10 min. The products were isolated as described for the preparation of **36** from **38**. The residual brown oil from the evaporation of the chloroform was dissolved in a 1:2 benzene–chloroform solution and chromatographed on alumina. Chloroform–benzene solutions containing 50–75% chloroform eluted 1.5 g of a white solid, which, when recrystallized from chloroform–petroleum ether, yielded 0.3 g (6%) of **36**, mp 294–296°. The infrared spectrum of this compound was identical with that of **36** from **38**.

The remaining filtrates were concentrated and the solid so obtained was fractionally crystallized from chloroform–petroleum ether to yield 1.0 g (20%) of **34**, mp 248–250° dec. The infrared spectrum of this compound was identical with that of **34** obtained from **3**.

Hydrogenation of 32.—A solution of 3.3 g of **32** in 100 ml of ethanol was hydrogenated over 1.5 g of Raney nickel at a final temperature of 180° and a final pressure of 1325 psi. Dimethylformide was added to the contents of the liner and the alcohol–amide solution was heated to boiling. The catalyst was separated from the hot solution and the crystals which formed from the cooled solution were collected on a filter and the filtrate was concentrated to yield some additional solid.

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The combined product was recrystallized from dimethylformamide to yield 1.2 g (40%) of **33**: mp 380–383° dec; infrared bands at 3200, 3199, and 1675 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.10; H, 8.78; N, 11.29.

Rearrangement of 40.—A mixture of 5 g of the oxime **40**[14] and 140 g of polyphosphoric acid was stirred at 100–110° for 7 hr. The yield of **33**, isolated as described above, was 1.07 g (21%), mp 382–386° dec after crystallization from dimethylformamide. The infrared spectrum of this product and **33** obtained from the hydrogenation of **32** were identical.

Synthesis of 33.—The procedure is similar to that of McElvain and Pryde[17] for the preparation of 2,5-piperazinediones. 1-Aminocyclohexane-1-carboxylic acid (10 g) and 85 ml of β,β'-dihydroxy ethyl ether were refluxed for 4 hr in a 200-ml round-bottomed flask having a 4-in. neck. After the brown solution had cooled, the solid which slowly separated was collected on a filter and washed with ethanol and with water. Crystallization of the product from dimethylformamide gave 0.48 g (5.7%) of **33** as a white granular solid, mp 382–385° dec. The infrared spectrum of this compound was identical with the spectrum of **33** from the hydrogenation of **32**.

Anal. Calcd for $C_{14}H_{22}N_2O_2$: C, 67.17; H, 8.86; N, 11.19. Found: C, 67.22; H, 8.89; N, 10.95.

Hydrogenation of 34.—A solution of 0.6 g of **34** in 100 ml of absolute ethanol was hydrogenated over 0.5 g of Raney nickel as described above. Recrystallization of the product from aqueous ethanol gave a white solid, mp 330–334°, which when recrystallized from chloroform–petroleum ether gave **35** as a white powder: mp 329–331°; infrared bands at 3500, 3200, and 1660 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.31; H, 8.33; N, 10.52. Found: C, 62.91; H, 8.00; N, 10.51.

Hydrogenation of 36.—A solution of 0.4 g of **36** in 150 ml of absolute ethanol was hydrogenated over 0.5 g of Raney nickel at an initial pressure of 2 atm. After shaking for 23 hr at room temperature, dimethylformamide was added and the solution heated to boiling. The catalyst was removed by filtration, water was added to the filtrate, and the solid which separated was collected on a filter. Recrystallization of this material from dimethylformamide yielded 0.32 g (80%) of **37** which decomposed at 400°: infrared bands at 3420, 3275, 3160, 3060, 3025, and 1660 cm^{-1}.

Anal. Calcd for $C_{14}H_{22}N_2O_3$: C, 63.13; H, 8.33; N, 10.52; Found: C, 63.13; H, 8.41; N, 10.48.

Rearrangement of 25.—Compound **25** (2.0 g) was stirred with 100 g of polyphosphoric acid at 60–65° for 16 hr. After decomposition of the reagent, the solid which separated was collected on a filter and recrystallized from ethanol to give 0.84 g (42%) of **42** which began to decompose around 380° without melting: infrared bands at 3250, 3150, 3000, and 1665 cm^{-1}.

Anal. Calcd for $C_{14}H_{20}N_2O_2$: C, 67.71; H, 8.12; N, 11.28. Found: C, 67.42; H, 8.24; N, 11.28.

Reactions with Organometallic Compounds. Reactions of 4 with RLi and RMgBr Reagents.—A typical reaction of **4** with each type of organometallic compound is described in detail. The physical constants, yields, and analyses of the products are listed in Table I. The three-necked reaction flask was fitted with a condenser, a stirrer, and a separatory funnel.

Reaction of 4 with Isopropylmagnesium Bromide.—With stirring, 5 g (0.02 mole) of **4** in 375 ml of dry ether was added to the Grignard reagent from 12.3 g (0.10 mole) of isopropyl bromide in 20 ml of ether contained in a three-necked reaction flask. A black precipitate separated after about one-sixth of the **4** had been added. The mixture was refluxed with stirring for 3 hr and then poured into iced 10% sulfuric acid. The ether layer was separated, washed until neutral, and dried. The solvent was removed by evaporation and the white solid so obtained was recrystallized from benzene to yield 3.04 g (60%) of the reduction product, **43**, mp 178–179°.

Anal. Calcd for $C_{14}H_{21}NO_3$: C, 66.90; H, 8.42; N, 5.57. Found: C, 67.13; H, 8.41; N, 5.85.

Reaction of 4 with Allylmagnesium Bromide.—The allymagnesium bromide was prepared from 24.4 g of (0.2 mole) of allyl bromide by the procedure of Henze, Allen, and Leslie.[18] The ether solution of the reagent was filtered through glass wool into the three-necked reaction flask and 10.0 g (0.04 mole) of **4** in 650 ml of dry ether was added during 45 min. Stirring was continued for 2 hr.

The complex was decomposed with cold saturated ammonium chloride solution. The ether layer was separated, washed until neutral, and dried. The ether was removed by distillation until an oil began to separate. When petroleum ether (bp 30-60°) was added to the oily material, crystals formed slowly. This solid was collected on a filter and washed with two 10-ml portions of boiling ether to remove unreacted **4**. The yield of tertiary alcohol was 3.3 g (29%), mp 189–190° after recrystallization from benzene.

The Reaction of 4 with Benzyllithium.—The benzyllithium was prepared by the procedure of Gilman and McNinch.[19] The reagent from 10.4 g (1.5 moles) of lithium and 18.3 g (0.09 mole) of dibenzyl ether in tetrahydrofuran was filtered through glass wool into the three-necked reaction flask.

A solution of 7 g (0.03 mole) of **4** in 100 ml of tetrahydrofuran was slowly added in an atmosphere of nitrogen. The mixture was stirred an additional 2 hr, then poured into ice. The cold solution was acidified with dilute hydrochloric acid and extracted with benzene. The benzene extracts were washed, dried, and evaporated nearly to dryness. Petroleum ether was added and the solid which separated was collected on a filter. The yield of tertiary alcohol was 3 g (31.1%), mp 242–243.5°, after recrystallization from benzene–methanol.

The Reaction of 4 with Other Lithium Reagents.—Methyllithium was prepared by the procedure of Van Dorp and Arens.[20] *n*-Butyllithium and phenyllithium were prepared by the method of Jones and Gilman.[21] The additions were carried out as described for benzyllithium.

Reaction of 43 with Phosphorous Trichloride.—Compound **43** (3.0 g) was added slowly with stirring to 3 g of phosphorus trichloride during 5 min. The mixture was refluxed for 1 hr and then cooled and diluted with 50 ml of water. The cold solution was extracted with chloroform and the extract was washed with sodium carbonate solution. The separated carbonate layer was acidified with dilute hydrochloric acid and the solid collected on a filter paper to yield 3.1 g (72%) of **45**, mp 192–195° after crystallization from methanol.

Anal. Calcd for $C_{14}H_{24}NO_4P$: C, 55.81; H, 8.02; N, 4.65; P, 10.28. Found: C, 56.09; H, 7.91: N, 4.93; P, 10.56.

Registry No.—**5**, 15025-33-9; oxime of **5**, 15026-34-3; **6**, 15026-25-2; **7**, 15026-26-3; **9**, 15025-34-0; **10**, 15025-35-1; **11**, 15025-36-2; **12**, 15025-37-3; **13**, 15025-38-4; **14** (unsaturated), 15026-27-4; **14**, 15026-28-5; **15**, 15026-29-6; **16**, 15026-30-9; **17**, 15025-39-5; **19**, 15025-40-8; **20**, 15025-41-9; **23**, 15025-42-0; **25**, 15025-43-1; **26**, 15025-44-2; **28**, 15026-31-0; **29**, 15026-32-1; **30**, 15043-50-2; **31**, 15026-33-2; **32**, 15025-45-3; monoacetate of **32**, 15025-46-4; **33**, 4507-65-7; **34**, 15025-47-5; **35**, 15025-48-6; **36**, 15025-49-7; **37**, 15077-33-5; **42**, 15025-53-3; **43**, 15026-36-5.

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