Products from Lactones and Hydrazines: Hydroxyalkanohydrazides and Pyrazolidones

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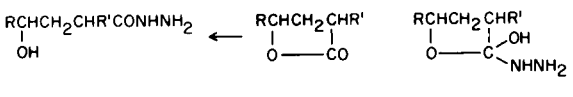
Saturated aliphatic lactones and dihydrocoumarins have been characterized by the formation of their crystalline 1:1-adducts (hydroxyalkanohydrazides) with hydrazine hydrate. A new procedure, which involves the use of azeotropic distillation to remove the water present, greatly facilitates the reaction by reducing the time required. Three macrocyclic lactones, that did not react in either of two short procedures, readily formed the same type of 1:1-adducts after several hours of refluxing of the components in alcoholic solution. The unsaturated macrocyclic lactone gave two products of cleavage; one was the expected ω-hydroxyalkenohydrazide, but the other was its saturated analog, in which the double bond had been reduced by the excess hydrazine employed. β-Lactones are a special case, requiring variations in conditions; the yield of the simplest adduct was more than doubled by a new procedure. In one instance products in which the lactone ring had been opened in both possible ways were obtained for the first time. A "stream-lined extracter" was useful with the low melting adducts. Coumarins themselves gave either 1:2 adducts or pyrazolidones. The latter could also be prepared from the adducts.

A study of 4-hydroxybutanohydrazide in a mass spectrometer showed that both γ-butyrolactone and 5-methyl-3-pyrazolidone are thermal products. Pure 5-methyl-3-pyrazolidone has now been isolated from the syrupy reaction product of ethyl crotonate and hydrazine. It has been converted to benzylidene derivatives; spectral data of the latter are consistent with their polarized structures.

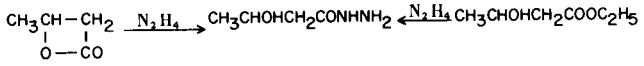
Our original purpose was to devise a simple, rapid, and reliable procedure of general applicability for the preparation of solid reference compounds from lactones which are mostly liquids, and to determine its limits. This aim has been realized by using hydrazine hydrate which forms 1:1-adducts (hydroxyalkanohydrazides (**1**)). The results are described in this communication.

Structure.

During the literature survey, (1-6) it was found that the structure of the adducts, now written as hydroxyalkanohydrazides (**1**), had never been unequivocally established, so the settlement of this point became a first aim. This has been accomplished in this laboratory in the classical way, by obtaining 3-hydroxybutanohydrazide (**2**) from β-butyrolactone, which had the same properties as the substance previously prepared from ethyl β-hydroxybutyrate (7). The infrared and N.M.R. spectra of the adduct (**2**) are in agreement with this structure.



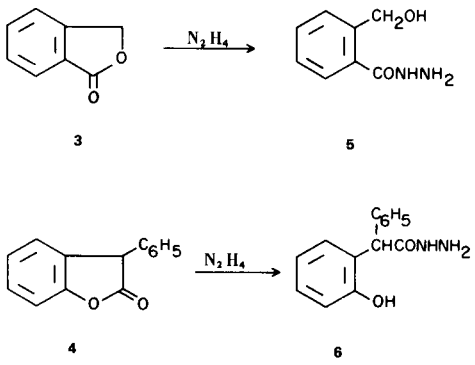
1 **1a**



2

Wedel (1) first examined the behavior of the γ-lactones, phthalide **3** and 3-phenyl-2-coumaranone (**4**) (the lactone of 2-hydroxydiphenylacetic acid), with hydrazine. In each instance solid adducts were obtained, to which he assigned the open chain structures **5** and **6**, (a) on account of the phenolic properties of the latter, particullarly its solubility in alkali and reprecipitation by carbon dioxide, (b) by the loss of hydrazine on being heated with

acidic reagents, and (c) by analogy with the behavior of lactones with ammonia, which gives rise to open chain amides.



3 5

4 6

Blaise and Luttringer (2) found that when 4-hydroxybutanohydrazide was heated, hydrazine was evolved, and the lactone from which it had been made was reformed; this was identified by remaking the adduct using fresh hydrazine. Less convincing was the non-formation of a benzylidene derivative of the adduct. Although aware of Wedel's work, they interpreted their results as favoring the cyclic structure (**1a**). However, the presence of a carbonyl group (I.R. 6.1 and 6.5 μ) in all the hydroxyalkanohydrazides examined by us (of which **2** is an example) definitely excludes the form (**1a**), advocated by Blaise and Luttringer, accepted by the editors of Beilstein (27), and in use for about 30 years.

Their observations on the lactone regeneration have been checked, but, in addition, a second major product has been identified, by examining the behavior of 4-hydroxybutanohydrazide in the mass spectrometer, having an all-glass heated inlet (235°). Its mass spectrum clearly indicated the presence of at least two components, as judged by the change in ratios of peak intensities with time. One of the components present is undoubtedly the adduct, even though there is no molecular ion of m/e 118. The highest mass peak (exclusive of isotope peaks) is at m/e 100, which suggests the loss of water. There are numerous aliphatic alcohols which lose water under electron impact to yield a large peak at M-18, and no molecular ion peak (M). In this instance the most likely possibility would be 5-methyl-3-pyrazolidone (see below), which could be formed by an intramolecular cyclization of the, as yet unknown, crotonohydrazide. Use of authentic 5-methyl-3-pyrazolidone (as a reference sample) showed that its mass spectrum strongly supports the identification of the substance m/e 100 as this compound.

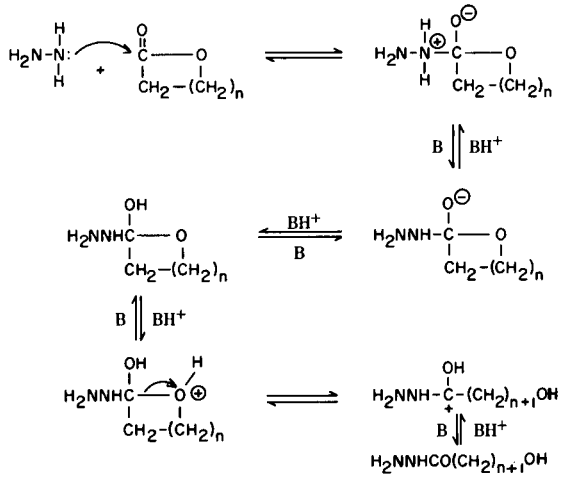
The other component present gave a mass spectrum identical with that of γ-butyrolactone (used as a reference compound). The rate of rise of its peak intensities is greater than that for the peak intensities for the 4-hydroxybutanohydrazide. This substantiates the identity of γ-butyrolactone. Both main components are thermal products, formed at the heated inlet of the mass spectrometer.

Also present was a trace of compound, the highest mass of which appears at m/e 172, presumably of molecular weight 172. The authentic sample of 5-methyl-3-pyrazolidone contained only a little of this component when first examined, but after several weeks the same sample showed an abundance of 172 in the mass spectrum. After isolation this compound was identified as 1,2-dibutyrylhydrazine by comparison with an authentic specimen (26) and by its I.R. and N.M.R. spectra. It was not a thermal product in the mass spectrometer because its pattern was the same whether the sample was introduced *via* the 230° inlet system or *via* the direct insertion probe at 100°.

In 1934, the reaction product of ϵ-caprolactone and hydrazine was given the open chain name, "hydrazide of ϵ-hydroxycaproic acid and hydrazine" (3). With one exception (9) this type of structure has been used ever since. In 1936, Darapsky carried out a careful investigation of the adduct from hydrazine and γ-valerolactone, prepared the benzal derivative that had eluded Blaise, and pointed out the correctness of Wedel's formulation (4).

Mechanism.

Because lactones are cyclic esters and for the most part give the same characteristic reactions as their open-chain analogs, it is possible to extend the mechanism of the cleavage of the latter by ammonia to the substituted ammonia, hydrazine. The reaction of lactones with hydrazine can, therefore, be considered to be analogous to ester hydrolysis.



This appears to be valid for α- and larger lactones, which give the expected γ-hydroxyalkanohydrazides. The β-lactones, however, could give two types of products,

TABLE I

Properties of Newly Prepared Compounds

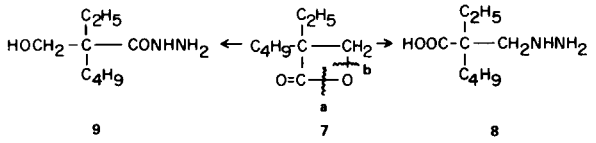
Compound Number	Molecular Formula	M.p., °C	Analyses % Calcd. C	H	N	Found C	H	N	Notes
2	$C_4H_{10}N_2O_2$	119-120	40.7	8.5	23.7	40.8	8.6	23.8	
8	$C_9H_{20}N_2O_2$	147-149	57.4	10.6	14.9	57.2	10.5	14.7	(a)
9	$C_9H_{20}N_2O_2$	69-70	57.4	10.6	14.9	57.8	10.2	14.7	
11	$C_{16}H_{32}N_2O_2$	131	67.6	11.3	9.9	67.3	11.4	9.9	(n)
12	$C_{16}H_{34}N_2O_2$	143	67.1	11.9	9.8	67.4	12.0	9.8	(n)
14	$C_{12}H_{12}N_4O_2$	161-162	46.7	3.9	18.2	46.6	3.9	18.3	
18	$C_9H_{14}N_4O_2$	136-137	51.4	6.7	26.7	51.4	6.8	26.8	(b,e)
18g	$C_{10}H_{16}N_4O_2$	145-146	53.6	7.1	25.0	53.4	7.1	24.8	(g)
20	$C_9H_{10}N_2O_2$	100±	60.7	5.6	15.7	60.8	5.7	16.0	(c,h)
20i	$C_{12}H_{16}N_2O_3$	159-160	61.0	6.8	11.8	60.8	6.9	11.9	(i)
22	$C_9H_9N_3O_3$	146-147	52.2	4.3	20.2	52.2	4.5	19.7	(p)
26	$C_4H_8N_2O$	32-35	48.0	8.0	28.0	48.1	8.0	28.0	(t)
28f	$C_{11}H_{12}N_2O$	149-150	70.2	6.4	14.9	70.1	6.5	15.0	(f)
28l	$C_{12}H_{18}N_2O_4$	61	56.6	7.1	11.0	56.7	6.9	11.0	(i,r)
28q	$C_{13}H_{17}N_3O$	200-201	67.5	7.4	18.1	67.3	7.6	18.1	(q)
30	$C_9H_{20}N_2O_2$	79-80	57.4	10.6	14.9	57.6	10.4	14.7	(j)
31	$C_{11}H_{24}N_2O_2$	99-100	61.1	11.1	13.0	61.3	10.9	13.0	(d)
32	$C_6H_{14}N_2O_2$	119	49.3	9.6	19.2	49.2	9.6	19.5	(k)
33	$C_{14}H_{30}N_2O_2$	141	65.1	11.6	10.9	65.3	11.3	11.1	(o)
34	$C_{15}H_{32}N_2O_2$	145-146	66.2	11.8	10.3	66.3	11.8	10.6	(o)
35	$C_{11}H_{16}N_2O_2$	123-124	63.5	7.7	13.5	63.5	7.7	13.6	(m)
36	$C_{10}H_{14}N_2O_2$	157-158	61.9	7.2	14.4	61.7	7.2	14.6	
37	$C_{12}H_{18}N_2O_3$	158-159	60.5	7.7	11.7	60.5	7.6	11.9	
41	$C_{18}H_{24}N_6O_4$	gum	55.7	6.2	21.6	54.8	6.4	22.0	(u)
44	$C_{11}H_{13}N_3OS$	161-162	56.2	5.5	17.9	56.2	5.4	18.2	(s)

(a) mol. wt., calcd: 188; found (boiling alcohol) 192; (b) mol. wt., calcd: 210; found (boiling alcohol) 222. (c) mol. wt., calcd: 178; found (boiling alcohol) 192; (d) no previous analysis found; (e) lit. m.p., 128-129° (f) R = H; (g) 6-CH_3 derivative; (h) R,R′ = H; (i) R = CH_3, R′ = C_2H_5O; (j) only N% in lit; (k) lit. m.p. ranges, 114-119°; (l) R = CH_3O; a dihydrate; (m) *as*-dimethylhydrazide of 17; (n) mixed m.p. 118-119°; (o) mixed m.p. 126-128°; (p) lit. m.p. 126°; (q) R = $(CH_3)_2N$; (r) dihydrate; (s) %S, calcd. 13.3; found, 13.2; (t) mol. wt, calcd: 100; found (boiling alcohol) 93; (u) dried 117 hours (60°).

the expected β-hydroxyalkanohydrazides as well as β-hydrazinoalkano acids. Such a behavior with other nucleophiles has been reported previously, but Testa (5) did not find a single instance of a second product among eighteen lactones investigated.

Unsubstituted propiolactone reacts very vigorously. This high reactivity has been attributed (10) to the deformation of the bond angle from its usual tetrahedral value to the 90° value required by the geometry of the small ring. Alkyl substituents, particularly in the α-position, decrease the rate of addition due to their bulk. This ring-strain tends to make a saturated carbon atom in some respects like an unsaturated one. The difference in reactivity of a nucleophilic reagent at alkyl versus acyl carbon normally results in preferential if not exclusive attack at the acyl carbon. In these lactones, however, this difference is so far reduced as to facilitate nucleophilic attack at either position.

Our results are in agreement with this conclusion. Whereas most β-lactones gave only β-hydroxyalkanohydrazides (5,11), α-butyl-α-ethylpropiolactone (**7**) gave both isomers, the expected hydroxyhydrazide (**9**) by acyl-oxygen cleavage at **a** and the hydrazino acid (**8**) by alkyl-oxygen cleavage at **b**.



9 **7** **8**

The Hydroxylkanohydrazides.

The new procedure (A) of general applicability for rapidly preparing hydroxyalkanohydrazides from most lactones depends upon removing the water as an azeotrope, b.p., 64° (12), from the mixture of reagents, as described in the experimental part. The adducts formed crystallize better because ***all*** the water is removed. The time limit specified is more than ample to allow completion of the reaction. Since commercial technical specimens were used successfully, extreme purity is not essential. Two other procedures that have been employed are B, heating the lactone and hydrazine hydrate without a solvent on a steam bath "until the water is removed" (2), and C, a customary refluxing period of the components in alcoholic solution for several hours. The least quantity of lactone used by us in procedure A and C was one-half gram. The second, B, has been reported (6) to have been successful with one-tenth gram.

Scope of the Reaction, and Limits.

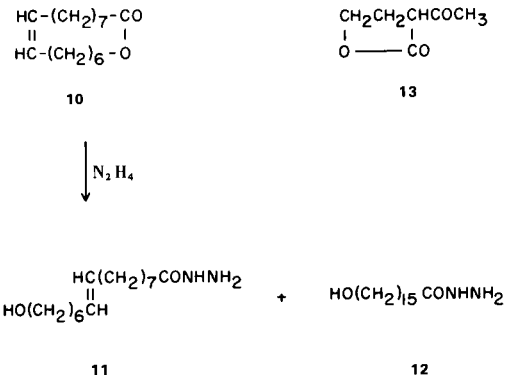
The Procedure A has been employed successfully with all classes of saturated lactones, with the exception of two β-lactones which vary greatly in reactivity, and two coumarins which are unsaturated lactones. The third, C, is advisable for use with larger sized runs, or in instances in which the first two fail; for instance, macrocyclic lactones such as cyclopentadecanolide, which has been reported (9) as failing to give an adduct, did so easily in six to eight hours.

Modification of Procedure A: β-Lactones.

In our limited experience each of the available lactones (propio-, β-butyro-, α-butyl-α-ethylpropio-) which were employed required modifications. The new, general azeotroping procedure was useful only with the disubstituted derivative (**7**). The first product that separated from the reaction mixture was the β-hydrazinopropionic acid (**9**). The hydroxyhydrazide (**8**) was then obtained from the residual solution. This is the first reported instance of the isolation of both isomers from the interaction of hydrazine and a β-lactone. The structures of both adducts were shown by the spectral data.

Modification of Procedure C.

The unsaturated macrocyclic 9-cyclohexadecenolide (**10**) resembled the saturated analogs; there was no apparent reaction, using the azeotropic procedure A. On account of the high molecular weight of the lactone the amount of hydrazine specified in the general procedure C (2 ml., 8 equivalents per g.) was so large a secondary reaction caused a complication; the ethylenic linkage was reduced, so that a mixture containing 16-hydroxy-9-hexadecenohydrazide (**11**) and the saturated 16-hydroxyhexadecanohydrazide (**12**) was formed. Accordingly the use of much less hydrazine and a shorter reflux time has been specified to minimize extensive fractional crystallization (see Experimental). The similar behavior of a number of saturated acids are reported in the literature (13). However, it has also been noted that 9-*cis*-dodecen-5-olide gave 5-hydroxy-9-*cis*-dodecenohydrazide, in which the double bond was still present (14).



10 **13**

11 **12**

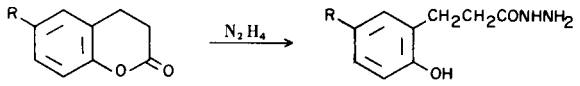
The infrared spectra of both adducts (**11** and **12**) show the usual amide bands at 6.1 and 6.5 μ; a band at 10.45 μ confirms the *trans* double bond in **11**; (the latter is also present in the lactone (**10**)).

The bifunctional saturated α-acetyl-γ-butyrolactone (**13**) was so easily identified as its 2,4-dinitrophenylhydrazine (**14**) that its behavior with hydrazine was not studied.

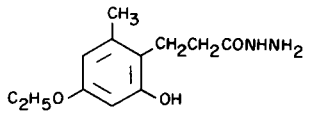
Benzolactones.

Since most lactones which are fused on one side to a benzene ring are crystalline, their conversion to solid derivatives is less urgent than with the aliphatic types already considered. However, some new facts have been discovered in our work, and are included herewith. The behavior of the two γ-benzolactones, phthalide (**3**), and 3-phenyl-2-coumaranone (**4**) and their conversion to the hydroxyhydrazides (**5** and **6**) has already been recounted.

The δ-benzolactones may be either saturated or unsaturated. Representatives of the first type are three dihydrocoumarins (**15**, **16**) which resemble aliphatic lactones; when treated with hydrazine they give 3-(*ortho*-hydroxyphenyl)propanohydrazides, e.g., **17** (15).



15 **17**



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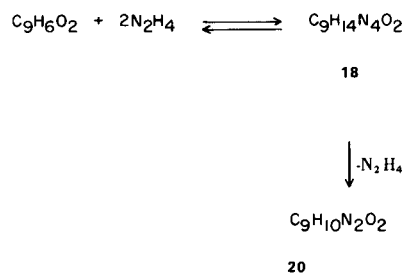
Coumarins are unsaturated δ-lactones and offer more possibilities. Coumarin itself reacts readily with an excess of hydrazine and forms, reversibly, an adduct (**18**) containing two molecules of hydrazine. The generally accepted structure of this type of adduct is that of a hydrazinohydrazide (**21**, R,R′ = H) (17). In this particular instance, partial evidence consists of (a) the empirical analyses which show the composition to be in agreement with **18**, (b) the infrared spectrum, in which, as in all other hydroxyhydrazides, the two usual amide carbonyl bands are present at 6.1 and 6.5 μ, and (c) the reversibility of the addition, which is shown by partial reformation of the components upon distillation *in vacuo* (4).



The most characteristic property of this adduct is the ease with which half of the hydrazine is lost irreversibly as the free base (see Experimental). All chemical reactions employed to show this are ambiguous because the same reagents that attack the hydrazine also react with the carbohydrazido group.

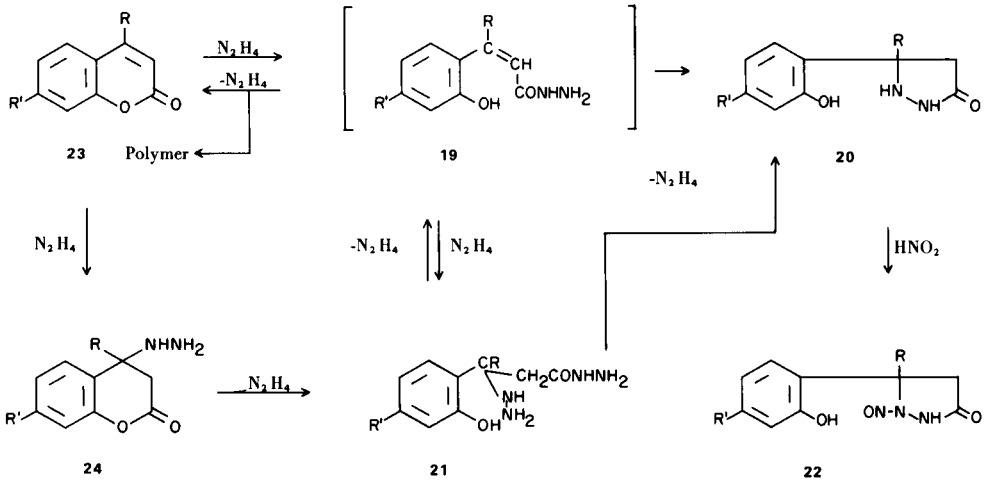
The mass spectrum obtained during temperature programming of the hydrazinohydrazide (**18**, from coumarin) had peaks at m/e 178 (parent peak M of the pyrazolidone **20**), (R,R′ = H), *147* (M-N_2H_3), *136* (M-CH_2CO), *135*, *120* (M-NHNHCO), *91* and *32* (probably M of NH_2NH_2). The major peaks are italicized. It may be concluded that the hydrazine is lost as a molecule during heating.

In addition, a photographic process was also successfully employed for this purpose.

The nmr spectrum of **18** was ambiguous. Owing to its insolubility in the usual solvents the hydrazinohydrazide from coumarin (and its 6-methyl derivative) was dissolved in dimethylsulfoxide at ambient temperature. Interpretation of the spectrum led to the conclusion that a pyrazolidone, $C_9H_{10}N_2O_2$ (**20**, R,R′ = H) had been formed irreversibly by loss of a molecule of hydrazine. Although the heterocycle was not previously isolated, its presence was inferred (17) because the structure of the nitroso derivative (**22**, R,R′ = H), which resulted from the action of nitrous acid on the adduct (**18**) was carefully proved (4).

After appropriate manipulation of a solution of the hydrazinohydrazide (**21**, R,R′ = H) in dimethylsulfoxide the (new) 5-(2-hydroxyphenyl)-3-pyrazolidone (**20**, R,R′ = H) was isolated in poor yield, and converted to the known *N*-nitroso derivative (**22**, R,R′ = H) (4).

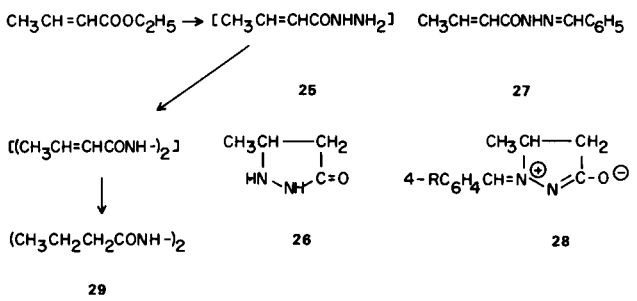
The assumed path of reaction to the pyrazolidone (**20**) is **23, 24, 21, 20**. A saturated hydrazinodihydrocoumarin (**24**) is first formed by addition of hydrazine to the conjugated system. The ring is then opened as with the dihydro analog (**15**-17) to give the hydrazinohydrazide (**21**). The latter now loses a molecule of hydrazine by an intramolecular cyclization to give the pyrazolidone (**20**). This conclusion is in accord with that postulated by Godtfredson and Vangedal (17), who reinvestigated and corrected earlier work (18, 19) on unrecognized pyrazolidones. An alternate path **23, 19, 20**, may be visualized as occurring



by a direct ring opening to give the unsaturated hydrazide (**19**), which could cyclize directly to the pyrazolidone, or add a second molecule of hydrazine to give the hydrazinohydrazide (**21**). Evidence favoring this was obtained by employing a coumarin containing a 4-methyl group (**23**, R = CH_3, R′ = C_2H_5O) which would be expected to hinder addition at that point. In this instance the pyrazolidone (**20**, R = CH_3, R′ = C_2H_5O) was isolated directly, there being no evidence for the formation of a hydrazinohydrazide.

With regard to the behavior of 4-hydroxybutanohydrazide in the mass spectrometer, it was shown that the thermal product (m/e 100) formed by its loss of water was, in all likelihood, 5-methyl-3-pyrazolidone (**26**) not yet described in the literature. Because Muckermann's "cinnamic acid hydrazide" (18) has since been shown (17) to be 5-phenyl-3-pyrazolidone (**43**) it seemed reasonable to assume that the "syrup" he obtained by treating ethyl crotonate with hydrazine (19), instead of being "crotonic acid hydrazide" (**25**) might well contain the isomeric, missing 5-methyl-3-pyrazolidone (**26**). His evidence for the open chain structure rested on an analogy to the "cinnamic acid hydrazide", formation of a benzylidene derivative (**27**), and production of a hydrochloride, which, with nitrous acid, yielded 5-methyl-1-nitroso-3-pyrazolidone. However, since the assumed cinnamic acid hydrazide is now known (17) to be the heterocyclic compound, 5-phenyl-3-pyrazolidone, the analogy must also be changed.

When the "syrup", that resulted upon repetition of the crotonic ester work, was distilled *in vacuo*, the principal component was 5-methyl-3-pyrazolidone (**26**). Traces of an impurity were found to be the bisbutyroamide (1,2-dibutyrylhydrazine) (**29**). Its formation can be accounted for by assuming that one molecule of the, as yet unisolated, crotonhydrazide (**25**) reacts with a second molecule of ethyl crotonate, to give an unsaturated biscrotonamide; the ethylenic linkage of the latter is then reduced by the hydrazine present to the saturated bisbutyramide. The alternative possibility, that reduction occurs first, cannot be excluded. It has been known for a long time that unsaturated acids (e.g., crotonic) are reduced by hydrazine (13).



As reference compounds for the 5-methyl-3-pyrazolidone (**26**) the known (25) 1-phenylthioureido-5-methyl-3-pyrazolidone (**44**), and four benzylidene derivatives were prepared. Muckermann's open-chain derivative (**27**) has already been excluded from consideration (17), and replaced by the charged cyclic structure (**28**, R = H). The solubility of these substances in benzene renders a betaine structure unlikely.

EXPERIMENTAL

The starting materials were obtained from the following sources: γ-Butyro-, γ-valero- (P6123, optically inactive), and propiolactone, coumarin and the hydrazines from Distillation Products Industries; three other β-lactones from the Tennessee Eastman Co. (28); γ-octano- and 2-acetylbutyro-lactones, phthalide and dihydro-

coumarin from Aldrich; ϵ-caprolactone from Union Carbide (28); γ-*n*-amyl- and γ-*n*-heptylbutyrolactones from Compagnie Parento (28); 6-methyl-, 6-methyldihydro- and 7-ethoxy-4-methylcoumarins and 8-hexadecenolide from Givaudan (28); cyclotetradecanolide from E. W. Spanagel (28); and cyclopentadecanolide from Polak and Schwartz (28).

Although the α,α-dimethylpropiolactone, as received, contained a small amount of white solid the N.M.R. spectrum indicated only a trace of impurity; the bottle was opened only long enough to remove a sample, yet some catalyst must have been present in the laboratory air, because the entire material solidified before it could be used.

In our work the homogeneity of the lactones used, and the open-chain structure for the hydroxyalkanohydrazides formed from them, was shown by an examination of their infrared and N.M.R. spectra. All the previously known hydroxyalkanohydrazides used for the determination of spectral data were samples the analyses and melting points of which were satisfactory and in agreement with those in the literature. These data are included in Table I. Attempts to apply vapor phase chromatography to these adducts were unsuccessful, since they decompose, even when in methanolic solution.

The infrared spectra were obtained using a Baird Atomics spectrometer, Model NK-1. Most samples were prepared as pressed plates in potassium bromide. In all instances of hydroxyalkanohydrazides the amide I bands were in the range 6.0-6.2 μ, and the amide II bands were at 6.5-6.6 μ. In a very few instances (2-hydroxymethyl-2-butylhexano-, 4-hydroxyoctano-, 4-hydroxynonanohydrazides, and dihydrocoumarin) two bands were noted between 6.0 and 6.2 μ. The first is attributed to the amide carbonyl, and the second to an amine peak arising from splitting between the two hydrazino nitrogens. A broad band centering at 3 μ reasonably includes both hydroxyl and amine absorption. The amide band in the infrared at 1650 cm^{-1} (6.1 μ) has been noted previously (5) in adducts derived from β-lactones only. The amide bands were absent in the hydrazino acid (**8**) which, however, had a band at 6.43 μ, characteristic of the carboxylate ion.

In the hydrazinohydrazides (**18**) (from coumarin and its 6-methyl derivative) the two usual amide bands were found, as well as the amine and hydroxyl band at 3 μ. Furthermore, a small, broad absorption at approximately 4 μ may be assigned to a hydroxyl group with strong hydrogen bonding; a more definite statement is unwarranted.

The ring carbonyl absorption in all the pyrazolidones was in the range 5.8-6.0 μ, whether in a potassium bromide pressing, Nujol suspension, or chloroform solution.

In the infrared spectrum of the benzylidene derivatives (**28**) there were two bands in the double bond region at 5.98 and 6.25 μ. Both were at a higher wavelength than would normally be assigned to a lactam having a five-membered ring-carbonyl. The N.M.R. excluded a possible condensation product through the methylene group.

All N.M.R. spectra were measured on a Varian A 60 spectrometer. The chemical shifts are reported in p.p.m. downfield from tetramethylsilane. In the N.M.R. of all the ω-hydroxyalkanohydrazides having very long chains the area of the large peaks is approximately proportional to the number expected from the analytical data; the proof of structure rests on the presence of the peaks at the correct chemical shifts. The solvent used was dimethylsulfoxide-d_6 unless otherwise stated. Although none of the lactones are new, their N.M.R. spectra except for propiolactone (21, *409*, γ-butyrolactone *63*, phthalide *496*, coumarin *225*, and 7-ethoxy-4-methylcoumarin *294*), could not be located. The N.M.R. of γ-heptylbutyrolactone, made by a new method (22) had just appeared. Most of the spectra are given below.

N.M.R. Spectra.

β-Butyrolactone.

The spectrum (deuteriochloroform) is a typical $ABMX_3$, the M multiplet centered at δ 4.72 (1H, -O-CH), the AB pattern centered at 3.30 with $J_{AB} \cong 16$ Hz, $J_{AM}+J_{BM}=10.6$. (Further analysis is difficult because of the poorly resolved M part of this spectrum. The X_3 portion consists of a doublet at 1.56, $J_{MX} = 7$ Hz).

α,α-Dimethyl-β-propiolactone.

This compound shows (deuteriochloroform) δ 4.10 (s, 2H, $-OCH_2$), 1.39 (s, 6H, CH_3).

α-*n*-Butyl-α-ethyl-β-propiolactone (**7**).

This compound shows (deuteriochloroform) δ 4.10 (s, 2H, $-OCH_2-$), 2.0-0.8 (m, 14H, C_2H_5, C_4H_9).

γ-*n*-Heptyl-γ-butyrolactone.

This compound shows (carbon tetrachloride) δ 4.4 (m, 1H, CH-O-), 2.35 (m, 2H, $-CH_2CO-$), (m, 1.1-2.0, ~14H, $-(CH_2)_n-$), 0.9 (t, 3H, $-CH_3$). The spectrum of γ-*n*-amyl-γ-butyrolactone is exactly analogous except for the appropriate area ratios.

Cyclopentadecanolide ("Muscolactone").

This compound shows (deuteriochloroform) δ 4.16 (t, 2H, $-OCH_2-$), 2.32, (t, 2H, $-CH_2CO$), (s, 1.4, base 1.3 to 2.1, area ~ 24H, $-(CH_2)_n-$).

9-Cyclohexadecenolide ("Ambrettolide") (**10**).

This compound shows (deuteriochloroform) δ 5.34 (t, 2H, CH=CH), 4.1, (t, 2H, OCH_2), 1.2-2.5 (m, 24H).

3-Hydroxypropanohydrazide (**38**).

This compound shows δ 2.26 (t, 2H), 3.68 (t, 2H), 4.37 (s, 3H, exch), 8.9 (s, 1H, exch).

3-Hydroxybutanohydrazide (**2**).

This compound shows δ 1.05 (d, 3H, J $\cong$ 6Hz, CH_3) 2.12 (d, 2H, J $\cong$ 6Hz, CH_2CO), 3.97 (five peaks of the expected multiplet for the CH-O-) are superimposed on the side of a broad 3H peak at 4.3 (total area 4H, N_2H_3), 9.1 (s, H, OH). The broad peaks at 4.3 and 9.1 are exchangeable. The chemical shift of the methine proton (at 3.97) is good evidence for the presence of the CH-O- group as distinguished from a CH-N group which would be present in an isomeric hydrazino acid.

2-*n*-Butyl-2-ethyl-3-hydroxypropanohydrazide (**9**).

This compound shows δ 0.5 to 1.8 (m, 14H, C_2H_5, C_4H_9), 3.46 (s, 2H, CH_2O), 4.3 (s, 3H, exch N_2H_3), 8.7 (s, H, exch, OH). The chemical shift of the OCH_2 singlet supports the hydroxyhydrazide structure.

2-*n*-Butyl-2-ethyl-3-hydrazinopropionic acid (**8**).

This compound shows δ 0.6-1.7 (m, 14H, C_2H_5, C_4H_9), 2.82 (s, 2H, CH_2N), 6.75 (s, 4H, exch, N_2H_3, OH). The chemical shift of the CH-N singlet supports the assignment as the hydrazinocarboxylic acid. The rapid exchange between the labile protons makes them all equivalent.

4-Hydroxybutanohydrazide (**39**).

This compound shows δ 1.85 (p, 2H), 2.1-2.9 (m, 2H), 3.62 (t, 2H), 4.2 (s, 2H, exch), 9.2-10.0 (s $\cong$ 1H each, exch).

4-Hydroxypentanohydrazide (**40**).

This compound shows (deuteriochloroform) δ 0.85 (d, 3H, J ≅ 6Hz), 1.73 (m, 2H), 2.30 (t, 2H), five peaks of the expected sextuplet at 3.76 (1H, J ≅ 6Hz), partially obscured by a broad singlet at 4.13 (3H, exch), 8.9 (s, 1H, exch).

4-Hydroxyoctanohydrazide (**42**).

This compound shows (deuteriochloroform) δ 3.5 (s, 1H, CH-O), 2.34 (t, 2H, $-CH_2CO-$), 0.6-2.1 (m, 11H, C_4H_9 and $-(CH_2)_n-$). A very broad 2H peak centered at 4.2, which broadens further on heating, is assigned to the NH and/or OH absorption; the remaining OH and/or NH is apparently too broad to be detected.

4-Hydroxynonanohydrazide (**30**).

This compound shows (deuteriochloroform), δ 0.6 to 2.0 (complex 13H), 2.35 (t, 2H), 3.6 (s, 1H), 4.2 (s, 2H, exch), 8.7 (s, 1H, exch.).

4-Hydroxyundecanohydrazide (**31**).

This compound shows (deuteriochloroform) δ 0.7 to 2.0 (complex 17H), 2.35 (t, 2H), broad s at δ 3.5 (not exch), merged with broad s at 4.1 (exch), total area +3H. No other peaks visible in spectrum. Presumably the low field CH and NH were too broad to be detected.

6-Hydroxyhexanohydrazide (**32**).

This compound shows δ 1.0-1.8 (m, 6H) and 1.8-2.3 (m, 2H), 3.43 (t, 3H), 4.2 (s, 3H, exch), 9.0 (s, 1H). A total of 4 exchangeable protons confirms the expected open-chain structure.

14-Hydroxytetradecanohydrazide (**33**).

This compound shows (100°) δ 1.3 (s, 22H), 2.1 (t, 2H $COCH_2$), 3.0 (m, 1H, OH), 3.4 (m, 2H, $-OCH_2-$), 4.0 (s, 2H, NH_2). The peaks at 4.0 and 3.0 shift to lower field on cooling, and are, thus, identified as the exchangeable protons.

15-Hydroxypentadecanohydrazide (**34**).

This compound shows (90°) δ 1.22 (s, 24H), 2.0 (t, 2H, $COCH_2$), 3.8 (t, 2H, $-OCH_2-$). Two broad peaks at 3.0 and 3.9 (of ~2H area each) sharpen and shift upfield as the temperature is raised; they are assigned to the NH and OH.

16-Hydroxyhexadecanohydrazide (**12**).

This compound shows only a trace of absorption at δ 5.4, and, therefore, there are no olefinic protons. δ 1.25 (s, ~32H), 2.0 (m, 2H, $COCH_2$), 3.42 (t, 2H, $-OCH_2-$), 3.8 (s, 2H, NH and/or OH). The area of methylene chain absorption is higher than the expected 26H.

16-Hydroxy-8-hexadecenohydrazide (**11**).

This compound shows (90°) δ 1.3 (s, 18H, $-(CH_2)-$), 2.0 (m, 6H, CH_2CO, $-CH_2-CH=$), 3.4 (t, 2H, $-OCH_2-$), 4.0 (s, 3H, exch, NH_2 and OH), 5.36 (t, 2H, CH=CH).

3-(2-Hydroxyphenyl)propanohydrazide (**17**, R = H).

This compound exhibits a typical symmetrical A_2B_2 pattern centered at δ 2.48 and extending from δ 2.1-2.9; the complex aromatic multiplet (4H) is centered at δ 6.7. Broad peaks for the exchangeable protons occur at δ 4.2 (2H) and ~8.6 (~2H). The absorption at δ 8.9 consists of a fairly sharp peak superimposed on the side of a broad absorption ($w\frac{1}{2}_h \cong 30$ Hz); a broad peak at δ 3.3 is ascribed to the presence of adventitious water since the total deuterum hydroxide peak, after exchange with deuterium oxide, has an area greater than 4H.

5-Methyl-3-pyrazolidone (**26**).

The spectrum of this compound has the characteristic $ABMX_3$ pattern. The methyl absorption (X_3) is a doublet at δ 1.23 (J = 6Hz), the methylene AB pattern is centered at δ 2.35 and the methine proton (M) is a complex multiplet centered at δ 3.76. The NH protons (exchangeable with deuterium oxide) are in a broad singlet at δ 6.2.

5-Phenyl-3-pyrazolidone (**43**) (17).

This spectrum consists of an ABX pattern with the AB portion centered at δ 2.60 and the X portion as a triplet at δ 4.62. The 5-aromatic protons fall in a multiplet centered at δ 7.33. The two NH protons are at δ 5.48 and 11.0.

5-(2-Hydroxyphenyl)-3-pyrazolidone (**20**, R,R′ = H).

The AB part of the ABX pattern is centered at δ 2.50, the X part appears as a triplet at 4.73. The 4-aromatic protons give rise to a complex multiplet from 6.6-7.5. The area of the deuterum hydroxide peak, (δ = 4.1) after exchange with deuterium oxide corresponds to 3H, confirming the existence of the cyclic structure.

5-(4-Ethoxy-2-hydroxyphenyl)-5-methyl-3-pyrazolidone (**20**, R = CH_3, R′ = C_2H_5O).

This compound shows (deuterioacetonitrile) triplet at δ 1.30 (3H) and a quartet at δ 3.95 (2H) for the ethoxy group, an AB pattern centered at δ 2.73 (J = 16 Hz, 2H) for the pair of non-equivalent protons *alpha* to the carbonyl, a multiplet from δ 6.25-6.50 (2H) and a doublet of multiplets at δ 7.03 and 7.18 (1H) for the aromatic protons. A single NH in a broad peak at δ 8.65 (1H, exch.). Addition of deuterium oxide gives a large deuterum hydroxide peak at 2.5 H area, suggesting a slight amount of water was present.

Hydrazinohydrazide from Coumarin (**21**, R,R′ = H).

This compound shows absorption at δ 2.46 (m, AB part of ABX, 2H, $-CH_2CO-$), 4.24 (t, X part of ABX, 1H, Ar-$\underset{\underset{N}{|}}{C}$H-), 5.2 v. broad s, 4.5 H, NH), 6.6-7.2 (m, 4H, ArH), ~5.3 (vv broad s, non-integral, OH). Addition of deuterium oxide gave rise to an 7 + H signal at 4.5, the total exchangeable H content. The initial dissolution of the compound in dimethylsulfoxide-d_6 was accompanied by gas evolution and had a distinct odor of dimethyl sulfide, presumably arising form the reaction:

$$N_2H_4 + 2DMSO\text{-}d_6 \longrightarrow 2H_2O + N_2 + 2DMS\text{-}d_6$$

The N.M.R. data alone do not permit a distinction between an open chain hydrazide structure and that of a pyrazolidone.

5-(2-Hydroxy-5-methyl)-3-pyrazolidone (from **18g**).

This compound shows δ 2.15 (s, 3H, CH_3), 2.43 (m, 2H, four lines superimposed on the dimethylsulfoxide-d_6 multiplet, the center lines of an AB part of an ABX spectrum, assigned to the non-equivalent hydrogens *alpha* to the CO function), 4.17 (t, H of the ABX, ArCH-N), 5.0 (very broad s, 8H exch., NH, OH), 6.5-7.0 (d, 3H, aromatic). The 8H area of the exchangeable hydrogen absorption (7H expected) suggests that some water is present in the sample.

Benzylidene Derivative (**28**, R = H).

This spectrum has a characteristic $ABMX_3$ pattern. The methyl

doublet at δ 1.12 (J ≅ 6Hz) establishes that the methyl is substituted on a *saturated* carbon (*i.e.*, it is not allylic). The methylene AB patterns are centered at δ 2.08. The methine proton, a broad complex multiplet, is at δ 4.3. The chemical shift indicates that the methyl is next to a N+. The aromatic protons fall at δ 7.05 (m, 3H, the *meta* and *para* protons), and 7.9 (m, 2H, the *ortho* protons). The imino proton (-CH=N-) is a singlet at δ 7.29. In addition, with *both* this and the following, there is a 2-proton-broad singlet at δ 3.0, indicating the presence of one mole of water.

4-Methoxy Homolog of **28**, (R = CH_3O).

This spectrum is also consistent with the structure given. The $ABMX_3$ pattern for the CH_3CHCH_2 entity has the methyl doublet at δ 1.06 (J_{MX} = 6.5 Hz); δ_A = 1.74, δ_B = 2.38 (J_{AB} = 16Hz, $J_{AM} \cong$ 4.5 Hz, $J_{BM} \cong$ 9Hz), and the methine multiplet is centered at 4.27. The methoxyl CH_3 is at 3.36 and the imino proton at 7.27. The typical *para*-disubstituted pattern falls at 6.67 and 7.83.

Benzylidene derivative (**28**, R = $(CH_3)_2N$).

This spectrum shows (deuteriochloroform), δ 1.70 (d, 3H, J = 7Hz, CH_3); 3.15 (s, 6H, $N(CH_3)_2$; 4.7 (m, 1H, C-CH-N+); 6.77 (d, 2H, J = 9Hz, ArH *ortho* to N); 8.36 (d, 2H, J = 9Hz, ArH *ortho* to CN); 7.22 (s, 1H, imino proton); the AB part (2H) of the ABXM pattern is centered at 2.75 (J_{AB} = 16.5 Hz, $\delta_{AB} \cong$ 0.57 ppm, $J_{AX} \cong$ 9Hz, $J_{BX} \cong$ 4.5 Hz).

Derivatives.

As a class hydroxyalkanohydrazides (29) are very soluble in water, but somewhat less so in the alcohols, so the latter, if anhydrous, are useful for recrystallization. Unless otherwise specified *absolute* alcohol was always employed, and, when chilled, for rinsing. The rinse removed traces of a sticky, yellowish impurity. For recrystallization a minimum amount of solvent was taken; in most instances the same reagent was employed both for the purification and the rinse. It should be noted that the strength of hydrazine hydrate solution used in preparing the adducts has not usually been specified in the literature; this may account for the numerous discrepancies reported. An excess of hydrazine is essential to minimize the formation of by-products (*e.g.*, RCONHNHCOR).

Examples of Procedure A.

Example 1.

(As suggested for Qualitative Organic Analysis, and employed in this paper). In the hood a mixture of 2 ml. of the lactone, 1 ml. of 95% ethyl alcohol, 3 ml. of benzene, and 2 ml. of 85-95% hydrazine hydrate, in a 50 ml. beaker, was heated on the steam bath for 10 minutes. The cloudy mixture, which soon separated into two layers, cleared up very shortly. The beaker was then placed in the freezer. The solidified product was pulverized with 5 ml. of chilled absolute alcohol, and collected on a filter. Since most of the hydrazides are very soluble in cold water, and moderately soluble in alcohol, recrystallization was accomplished using a minimum (not over 5 ml.) of absolute alcohol (or larger amounts of ethyl acetate, chloroform, methylene chloride, or acetonitrile).

This procedure was successfully employed with γ-butyro-, γ-valero-, γ-butylbutyro- (octano), γ-amylbutyro-, γ-heptylbutyro-, and ε-capro-lactones, phthalide, three dihydrocoumarins (one with both hydrazine and 1,1-dimethylhydrazine), two coumarins, and with two β-lactones (the latter with some modifications). In the case of the γ-valerolactone, the adduct was extremely soluble in alcohols; furthermore, although it dissolved completely in 10 ml. of hot chloroform, it oiled out on cooling, and, on standing, solidified into a lump, along with a few crystals. The use of a "stream-lined extracter," described by Pingert (23), and 45 ml. of a low boiling solvent such as methylene chloride produced excellent results, with one extraction. The product had a melting point of 69-70°.

Example 2.

6-Hydroxyhexanohydrazide (**32**).

A 10 g. portion of technical ε-caprolactone was distilled, 8 g. being collected at 236-237°, a yellow oil remaining. The adduct was obtained in a 90% yield after one crystallization and decantation of the solution from a small amount of polymer. The analytical sample had a melting point of 119° after three recrystallizations. There was no difference in the adducts prepared from the material "as received" or after distillation. The "purified" lactone formed a solid polymer after standing at room temperature for 5 months.

Example 3.

3-(4-Ethoxy-2-hydroxyphenyl)butanohydrazide (**37**).

7-Ethoxy-4-methyldihydrocoumarin was obtained by catalytic reduction of 7-ethoxy-4-methylcoumarin ("Maraniol"), and, without isolation, was converted to the hydrazide by reaction with hydrazine, using procedure A.

Reduction: A mixture of 5 g. of the coumarin (m.p. 114-115°), 180 ml. of 95% alcohol, and 0.5 g. of platinum oxide catalyst was shaken for 6 hours at room temperature; the initial hydrogen pressure (60 lb.) dropped to 17 lb. (43 lb.; theory, 42 lb.). After removing the catalyst, aliquots of the colorless solution were used directly. On evaporation of a 25 ml. portion, 0.7 g. of a spicy viscous oil remained.

Hydrazinolysis: This oil was taken in 10 ml. of absolute alcohol, 3 ml. of benzene and 5 drops of 95% hydrazine hydrate, warmed on a steam bath for 15 minutes (about one-half evaporated), and allowed to stand overnight. The solid was taken up in 6 ml. of hot absolute alcohol, chilled, and the product was collected on a filter, and rinsed. The melting point of the adduct was raised from 157-158° to 158-159° by two recrystallizations. It reduced a hot Benedict's solution rapidly.

Example 4. 3-Hydrazino-5-(2-hydroxyphenyl)propanohydrazide (**21**, R,R′ = H).

The yields from 10 g. of coumarin were 13-13.1 g. (90-91%) of once-recrystallized hydrazinohydrazide. The homologous 6-methyl derivative (**18g**) was similarly prepared. Both were also obtained by Procedure C (3 hours). Although no crystalline product could be isolated from the residual gum, after drying to constant weight, analyses gave values agreeing with those calculated for a *bis*-derivative (**41**) (RCONHNHCOR).

Both hydrazinohydrazides reduced hydrogen peroxide and copper solutions (*e.g.*, Benedict's solution, copper acetate) with gas evolution and formation of copper derivatives. An aqueous solution reduced silver nitrate to the metal, and gave a red-violet color with ferric chloride; these results may be ambiguous, since they could be attributed to the phenolic hydroxyl group.

One of the principal arguments in favor of Blaise's cyclic structure was the ease of loss of hydrazine, which occurred on heating of the butyrolactone adduct; the lactone was isolated by distillation (2). Blaise (2) gave no indication as to the temperature

at which the hydrazine actually appeared. All of the hydroxyhydrazides gave off hydrazine when heated in a test tube, considerably above their melting point. It is known that both salicylhydrazide and benzohydrazide also evolve hydrazine when similarly heated; that is, the latter is a heat artifact.

A rough, qualitative trial was devised, using the aliphatic adducts, C_4, C_5, C_9, C_{11}, in aqueous solution testing with universal indicator paper; the latter was sensitive to small amounts of hydrazine, turning green. In no single instance was there any color change with the aliphatic hydrazides, even at the boiling point of the solution. Wedel's adduct (5) did give a slight color change. A photographic test was then employed; hydrazine is known to be a weak developer of silver emulsions. When Wedel's compound was so used, the developing action was practically negligible, even in a hot solution. The only positive indication of the presence of free hydrazine occurred with the coumarin adduct (**21**, R = H). When aqueous or alcoholic solutions were warmed on the steam bath, the indicator paper held in the vapor was quickly colored green. However, the action of a developing solution at 20° containing this adduct and enough dimethylsulfoxide to aid solubility was exactly the same as that of a control, using an equivalent quantity of pure hydrazine. That is, free hydrazine appears to be present at ambient temperatures.

Modified Procedure A.

It has been reported that the greater activity of β-lactones, indicated by their strong exothermic reaction when treated with hydrazine, required that each case needed individual study (5, 11). The yields of adducts varied from 18-82% with changes in conditions, such as temperature, solvent, order of mixing (11), and degree of substitution (5). Each of the three available lactones required different conditions; in all instances, the time had to be reduced to a minimum, and with the first one ice-cooling and reverse addition were essential to keep the vigorous reaction under control. (If the hydrazine was added last, polymerization, with much heat evolution, occurred. The adduct did not separate for a week or more, was very difficult to separate and purify, and the yield was low. The reaction was very vigorous, even with 64% hydrazine hydrate; the higher concentration is preferable for it contains much less water.)

Example 1. 3-Hydroxypropanohydrazide (**38**).

To a mixture of 3 ml. of benzene, 1 ml. of absolute alcohol, and 2 ml. of 95% hydrazine hydrate in a flask fitted with a stirrer and surrounded by ice-water, was added, *dropwise*, 2 ml. of propiolactone. At first each drop sputtered; the addition was done slowly until the noise moderated, and then was no longer noticeable. The flask and contents were then warmed on a steam bath for six minutes and allowed to stand until cold, when the solution solidified. The solid was extracted by heating on a steam bath with 25 ml. of acetonitrile, and decanted; the adduct crystallized almost at once. Several more extractions, using 16 ml. portions of acetonitrile, gave small additional amounts. The combined yields of several runs were 70-80% (30%, Reference 11).

Owing to the toxicity of the reagents (30), the use of a *hood* is essential. Gloves are also desirable, for propiolactone is a skin irritant.

Example 2. 3-Hydroxybutanohydrazide (**2**).

A mixture of 4 ml. of 95% alcohol, 8 ml. of benzene, and 5.5 ml. of β-butyrolactone boiled on the addition of 5 ml. of 85% hydrazine hydrate. The clear solution was allowed to stand after heating for 2 minutes on the steam bath; crystallization began shortly. The next day 6.6 g. of crude adduct was collected on a filter; after two recrystallizations from absolute alcohol, the analytically pure adduct, m.p. 119-120°, was collected.

Example 3. Use of α-butyl-α-ethylpropiolactone.

There was no reaction on mixing 4.9 g. of the lactone, 4 ml. of absolute alcohol, 8 ml. of benzene and 5 ml. of 85% hydrazine hydrate. It was therefore warmed on the steam bath until reaction set in; the two layers disappeared after 1 minute. After an additional 1.5 minutes, heating was discontinued and the viscous syrup was inoculated with a small amount of previously prepared hydrazino acid. After a slow (3 days) crystallization it was stirred with absolute alcohol and the solid (1 g.) was collected on a filter. Two recrystallizations from a large amount of absolute alcohol have an analytical sample of the hydrazino acid (**8**), m.p. 147-149°.

In a check run crystals were not deposited for a month; 20 ml. of *dry* ether was added to the viscous mass and 1 g. of the hydrazino acid (**8**) was collected on a filter. On standing, the filtrate deposited 1.4 g. of the hydroxyhydrazide (**9**), m.p., 68-69°. It was analyzed directly because no suitable solvent for recrystallization was discovered. This adduct is insoluble in hexane, ligroine, ether, acetonitrile and methylene chloride, but extremely soluble in water and the alcohols. A similar run, using 95% hydrazine hydrate exhibited the same behavior, the yields being 1 g. of **8** and 1.1 g. of **9**.

Procedure A failed when 1,1-dimethylhydrazine was used with coumarin and γ-butyrolactone. The coumarin was recovered, unchanged. With the lactone a strong odor of butyric acid was evident indicating hydrolysis.

Procedure B (no solvent) (2).

A mixture of 2 g. each of the lactone and 85% hydrazine hydrate was heated in an evaporating dish on the steam bath until the reaction was "complete." This point was judged to have been reached if the oil solidified when cold, or the next day. With γ-butyro- and γ-valerolactones solidification occurred after 75 minutes; with *n*-amyl-γ-butyro-, 100 minutes; with *n*-heptyl-γ-butyro-, 45 minutes. It failed with cyclopentadecanolide, and was abandoned, once the superiority of Procedure A had been discovered.

Procedure C (long period of refluxing).

Example 1.

Although coumarin and its 6-methyl derivatives gave adducts readily by procedure A, it was convenient, if larger sized runs were to be made, to employ this modification. The adduct often separated in a finely-divided condition, rendering filtration slow. As soon as the 95% hydrazine hydrate became available it was always used. This could have been a factor in obtaining a favorable result with the macrocyclic lactones, which were refluxed from 8 to 16 hours (the latter period being a safety precaution when the available amount of lactone was small). The observation that the hydrazinolysis of the macrocyclic lactones takes longer agrees with the conclusion reached by Huisgen and Ott (10) who reported on a study of ring opening and other properties of a series of homologous cyclic lactones.

Example 2. 15-Hydroxypentadecanohydrazide (**34**).

A mixture of 0.5 g. of cyclopentadecanolide ("Muscolactone," "Exaltolide," m.p., 32-33°), 10 ml. of absolute alcohol, and 1 ml. of 95% hydrazine hydrate was refluxed for 8 hours and allowed to cool. The adduct crystallized at once. It was collected on a filter, and rinsed with cold, absolute alcohol, yield 1.5 g. Since it is

almost insoluble in cold alcohol there is little loss on recrystallization. Furthermore, sufficient material for a melting point specimen can be obtained after only one hour's heating. This procedure was used with cyclotetradecanolide, and, with some modifications, cyclohexadecanolide, and 9-cyclohexadecenolide.

Example 3. 16-Hydroxyhexadecanohydrazide (**12**).

The necessary cyclohexadecanolide was obtained by catalytic reduction of cyclohexadecenolide, essentially by the procedure described on page 357, by employing 2 g. of catalyst the reduction was completed in 10 minutes. The *hydrazinolysis* was performed by Procedure C, using the residue from a 25 ml. aliquot in 10 ml. of absolute alcohol, and 10 drops of 95% hydrazine hydrate for 5 hours. The yield was 1.2 g. which melted sharply at 143° after two recrystallizations. The residue contained more adduct as well as unchanged lactone.

Example 4. The ω-Hydroxy-9-hexadeceno- and -Decanohydrazides, (**11** and **12**).

A mixture of 1 g. of 9-cyclohexadecenolide ("Ambrettolide") (**10**) 5 ml. of absolute alcohol, and 6 drops (0.25 g., 2 equivalents) of 95% hydrazine hydrate was refluxed for 3 hours. The adduct (**11**) was collected from the cooled solution, and, after two recrystallizations from absolute alcohol, amounted to 0.13 g., m.p. 131°. When 2 ml. (8 equivalents) of hydrazine was used and heating was continued for 5 hours, 0.7 g. of the mixed adducts were obtained, but the filtrate then deposited the slightly impure saturated adduct (**12**), m.p. 141-142°, after being warmed with a little benzene. A 3 g. run, inadvertently left over the week-end, gave mainly the saturated adduct; a very small amount (0.2 g.) of **11**, the unsaturated adduct, was isolated, from the filtrate. It was difficult to separate the adducts by fractional crystallization; most of the saturated derivative (**12**) came out first, and later fractions were contaminated by this as an impurity. They are moderately soluble in hot absolute alcohol, less so in chloroform, but insoluble in water, carbon tetrachloride, methylene chloride, and acetonitrile. A chloroform solution of **11** instantly decolorizes bromine, whereas the latter did not affect the saturated **12**.

The 2,4-dinitrophenylhydrazone (**14**) of α-acetyl-γ-butyrolactone was prepared, quantitatively, by the preferred procedure (24).

The Pyrazolidones.

5-(2-Hydroxyphenyl)-3-pyrazolidone (**20**, R, R′ = H).

A warm solution of 5 g. of freshly prepared adduct (**21**, R, R′ = H) in 10 ml. of dimethylsulfoxide was fractionally distilled *in vacuo*. The large volume of gas, which came off ar toom temperature as soon as the pressure was reduced, was mostly hydrazine, and was collected in the sulfuric acid trop. A non-condensable gas passed through the pump; a strong odor of dimethyl sulfide was noticable. It was difficult to remove all of the dimethylsulfoxide. The clean, pale yellow fraction (1 g.) b.p. 53-58°/6 mm. (91-93°/13 mm.) was collected. As the temperature during the distillation was increased, the higher boiling portions were mainly coumarin (20-40%), probably arising from thermal decomposition of the adduct. The pyrazolidone solidified to a brittle, electrostatic resin, which had no melting point but softened at about 100°. It was sparingly soluble in boiling water, but dissolved slowly in boiling alcohol; the solution became cloudy on cooling. The hot aqueous solution gave no color with silver nitrate, but was quickly reduced, changing from a deep red color to black metallic silver.

5-(4-Ethoxy-2-hydroxyphenyl)-5-methyl-3-pyrazolidone (**20**, R = CH_3, R′ = C_2H_5O).

An almost colorless mixture of 5 g. of 7-ethoxy-4-methylcoumarin, 25 ml. of absolute ethyl alcohol, and 3 ml. of 95% hydrazine hydrate was refluxed for 10 hours and allowed to stand over night. After removal of the unchanged coumarin the solvent was removed on the steam bath, and the filtrate was placed in the refrigerator for a second night. Upon the addition of 2 ml. of water to the oily residue, followed by warming, and addition of 2 ml. of alcohol with frequent stirring, crystals formed on cooling. The solid was stirred with 4 ml. of 50% alcohol-water, collected on a filter, and rinsed once with 1-2 ml. of chilled absolute alcohol. Additional solid separated over another night and was handled in the same way. For recrystallization, the combined products were suspended in 13 ml. of chloroform, and 2 ml. of absolute alcohol was added to obtain a clear solution. After partial evaporation and standing over night, crystallization occurred. Repeated treatments were needed to get a product having the m.p. 158-160°. Decolorizing carbon removed a part, but not all, of the color; the latter ranged from off-white to a light brownish-yellow. Some of the surface color could be removed by a chilled alcohol rinse, but the product dissolved very readily.

The unsubstituted 1-nitrosopyrazolidone (**22**) was obtained easily by the described procedure (4) but the melting point of the analytical sample was 20° higher. Both the methylated adduct (**18**, R = CH_3) and the disubstituted pyrazolidone (**20**, R = CH_3, R′ = C_2H_5O) gave black tars under the same conditions.

5-Methyl-3-pyrazolidone (**26**).

Four runs were made, one without refluxing, and three by heating 14 g. (16 ml.) of ethyl crotonate, 15 ml. of absolute alcohol, and 5 ml. (20% excess) of 95% hydrazine hydrate, for times ranging from 8 to 70 hours. (Muckermann stated "a few hours"). In each instance the solvent was removed in an open flask on the steam bath over night, and the residual "syrup" was distilled at reduced pressure (Muckermann used the crude syrup, which had 28.7, 27.4% nitrogen (calcd., 28.0%)). Any residual hydrazine was absorbed in a sulfuric acid trap. The mean, distilled yield of the four runs was 10.1 g. (76.3%; the highest, with no refluxing, was 88%). Fractions from all four runs were essentially the same; they set to a glass in the refrigerator. 5-Methyl-3-pyrazolidone retains water tenaciously. Upon redistillation of combined middle fractions, the portion boiling at 154-158°/0.8 mm. (mainly 156-157°), after six days had set to a massive, largely crystalline solid. Because of its hygroscopic nature its melting point could only roughly be obtained; however, after a week in a desiccator over phosphorus pentoxide, by rapid manipulation, samples of a white crust could be collected between two microscope cover glasses, and the melting point of 32-35° was observed. The extremely viscous, water-white pyrazolidone dissolves readily in water and the lower alcohols, but is much less soluble in other common organic solvents. It was used to prepare the following derivatives.

1-Phenylthioureido-5-methyl-3-pyrazolidone (**44**) resulted on rubbing (25) a mixture of the pyrazolidone (**26**) with phenyl isothiocyanate, and set to a hard cake. Recrystallization could be accomplished by the use of either methyl or ethyl alcohols; the former is preferable for small amounts, because the recovery is greater.

The benzylidene derivatives (**28**, R = H, Cl, CH_3O, $(CH_3)_2N$) were readily obtained, the best yield being 81%. Only the one from freshly prepared acid-free benzaldehyde formed readily at room temperature (the components were rubbed with a glass rod). The others required a few minutes' heating on a steam bath. The dimethylamino derivative was anhydrous, the others contained

water of crystallization. The unsubstituted derivative lost the water on air drying, leaving the anhydrous compound, m.p. 149-150°. All the derivatives were recrystallized from hot benzene (the dimethylamino derivative was also crystallized from ethyl acetate. It may also be recrystallized in small amounts from hot water by working rapidly; it then separates in small yellow crystals, "gold dust.") The crude *p*-chloro derivative (**28**, R = Cl), m.p., 75-78°, was not analyzed. All these substances dissolved in hot water, lose their yellow color (due to an impurity, except the dimethylamino derivative) in alkali, and the solutions decompose rapidly; they are also destroyed by sulfuric acid. The odor of butyric acid was noticeable in most residual solutions of the various substances mentioned under methylpyrazolidone.

1,2-Dibutyrylhydrazine (**29**).

This substance was found in all fractions of the distilled 5-methyl-3-pyrazolidone, as though it had co-distilled; it crystallized after standing from 6 days to 3 months. The solid that had formed was separated from the very viscous material by the use of ethyl formate by rinsing and repeated crystallization from this solvent which is preferable to alcohol for small amounts (other suitable solvents are acetonitrile, ethyl acetate and (V.s.s.) chloroform). The yield was 0.3%. This substance might have been formed by the action of adsorbed water on the hygroscopic pyrazolidone. The identity of the isolate with an authentic specimen prepared according to Stolle (26) was shown by melting point, infrared, and N.M.R. spectra. The latter spectrum shows the presence of a butyryl group with the CH_2CO at δ 2.15, the $-C-CH_2-C$ at δ 1.61, and the terminal methyl at δ 0.92.

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REFERENCES

(1) J. Wedel, *Ber.*, 33, 768 (1900).

(2) E. E. Blaise and A. Luttringer, *Bull. Soc. Chim.*, [3], 33, 1095 (1905).

(3) F. J. Van Natta, J. W. Hill, and W. H. Carothers, *J. Am. Chem. Soc.*, 56, 455 (1934).

(4) A. Darapsky, H. Berger, and A. Neuhas, *J. Prakt. Chem.*, 147, 145-160 (1936).

(5) E. Testa, L. Fontanella, G. Cristiani, and L. Mariani, *Ann. Chim.*, 639, 166-180 (1961).

(6) G. Lardelli, V. Lambert, W. T. Weller, and A. P. de Jonge, *Rec. Trav. Chim.*, T86, No. 5, 481-503 (1967).

(7) P. A. Levene, and J. Scheideger, *J. Biol. Chem.*, 60, 180 (1924).

(8) E. Carrière, *Ann. Chim.*, [9], 17, 78 (1922).

(9) B. Rothstein, *Bull. Soc. Chim.*, [5], 2, 1936-1942 (1935).

(10) R. Huisgen and H. Ott, *Tetrahedron*, 6, 253-267 (1959).

(11) T. L. Gresham, J. E. Jansen, F. W. Shaver, R. A. Bankert, and F. F. Fiedorek, *J. Am. Chem. Soc.*, 73, 3168 (1951).

(12) M. S. Bains and C. L. Jain, *Indian J. Technol.*, 2, 109 (1964); *Chem. Abstr.*, 61, 81d (1964).

(13) F. Aylward and M. Sawistowska, *Chem. Ind.*, 404 (1961).

(14) P. H. Begemann, V. Lamberti, and W. T. Weller, *Rec. Trav. Chim.*, 86, 1335 (1967).

(15) R. Pschorr and H. Einbeck, *Ber.*, 38, 2070 (1905).

(16) T. Posner and R. Hess, *ibid.*, 46, 3816 (1913).

(17) W. O. Godfredsen and S. Vangedal, *Acta. Chem. Scand.*, 9, 1498 (1955).

(18) E. J. Muckermann, *J. Prakt. Chem.*, [2], 83, 523 (1911).

(19) T. Curtius and P. A. Bleicher, *ibid.*, [2], 107, (1924).

(20) E. J. Muckermann, *Ber.*, 42, 3449 (1909).

(21) Varian High Resolution N.M.R. Spectra Catalog.

(22) D. Elad, G. Friedman, and R. D. Youssefyek, *J. Chem. Soc.*, (1968) C 870.

(23) F. P. Pingert, *Synthetic Organic Chemicals.*, Vol. 18 (1) (1946).

(24) C. F. H. Allen, *J. Am. Chem. Soc.*, 52, 2955 (1930).

(25) J. M. Adduci, Private Communication.

(26) R. Stollé, *J. Prakt. Chem.*, [2], 69, 489 (1904).

(27) In the Fourth Edition (1921) both open chain and cyclic structures are named (the latter as derivatives of tetrahydrofuran) in this order. In the supplement the order is reversed. The adduct from butyrolactone itself, written as cyclic by Carrière (8), is corrected to open chain in the second supplement [E 11, (1920-1929; out in 1951; Band 3/4, p. 871, Nachtrage und Berichtungen, but was omitted under "γ-oxybutyric hydrazide"].

(28) We are greateful for these gifts.

(29) All the hydroxyalkanohydrazides prepared from lactones, as found in the literature, are collected in six tables of a Thesis, submitted by the junior author for the degree of Master of Science from the Rochester Institute of Technology, June, 1968.

(30) G. D. Byrkit and G. A. Michalek, *Ind. Eng. Chem.*, 42, 1872 (1950).

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