From the filtrate 0.63 g of crude **16** was obtained.

[1.2.5]Oxadiazolo[3,4-*d*]pyrimidine-5(4H),7(6H)-dione 1-Oxide (26).—A solution of **24**[17] (2.0 g) in THF (100 ml) containing NaN_3 (1.0 g) was stirred at room temperature for 3 hr. The residue was collected by filtration, washed with water (10 ml), and dissolved in 2 *N* HCl (25 ml). After 3 hr this solution was evaporated to dryness, and the solid was recrystallized from a mixture of THF–petroleum ether (bp 85–105°) and dried *in vacuo* over P_2O_5 at 78° to yield 510 mg (29%). This sample melted with decomposition at about 260°: λ_{max} in mμ ($\epsilon \times 10^{-3}$),[18d] pH 7, 272 (9.15), 346 (3.65); $\bar{\nu}_{max}$ in cm^{-1}, 3300, 3190, 3105 (NH), 1740, 1715 (CO), and 1640, 1600, 1530 (C=C, C=N).

Anal. Calcd for $C_4H_2N_4O_4$: C, 28.24; H, 1.18; N, 32.94. Found: C, 28.11; H, 1.37; N, 32.92.

Registry No.—Sodium azide, 12136-89-9; **3**, 16206-18-1; **4**, 16206-19-2; **13**, 16206-20-5; **14**, 16206-21-6; **15**, 16214-85-0; **16**, 16206-22-7; **17**, 16206-23-8; **21**, 16206-24-9; **26**, 16206-25-0.

Acknowledgments.—The authors are indebted to Dr. W. J. Barrett and the members of the Analytical and Physical Chemistry Division of Southern Research Institute for the spectral and microanalytical determinations. Some of the analyses reported were performed by the Galbraith Microanalytical Laboratories, Knoxville, Tenn.

Oxidations with Lead Tetraacetate. II. Δ^3-1,3,4-Oxadiazolines from Ketocarbohydrazones and a Δ^3-1,3,4-Thiadiazoline from Acetone Thiocarbohydrazone[1]

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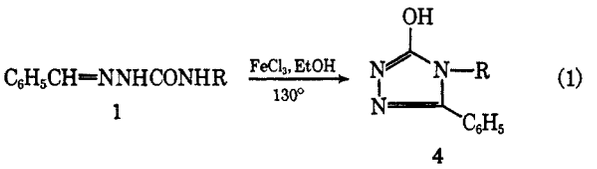
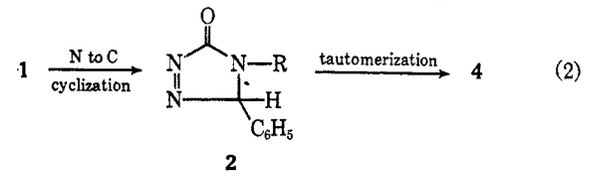
Acetone thiocarbohydrazone is cyclized by lead tetraacetate (LTA), in low yield, to 2-isopropylidenehydrazono-5,5-dimethyl-Δ^3-1,3,4-thiadiazoline (**10**). Spectra of **10** led to reassignment of the structures of the products obtained from oxidation of ketocarbohydrazones with LTA. Those products, which were earlier thought to be 4-ketimino-Δ^1-1,2,4-triazolin-3-ones (**7**), are shown to be 2-alkylidene-hydrazono-Δ^3-1,3,4-oxadiazolines (**8**). Spectra and some reactions of **8** are reported. Carbohydrazones of dialkyl ketones are shown to be much more reactive toward LTA than those of diaryl ketones. As a consequence the mixed carbohydrazone from acetone and benzophenone is cyclized primarily to the isopropylidene carbon rather than to the benzhydrylidene carbon. Diphenylmethylene diacetate is a by-product of oxidation of benzophenone carbohydrazone with LTA.

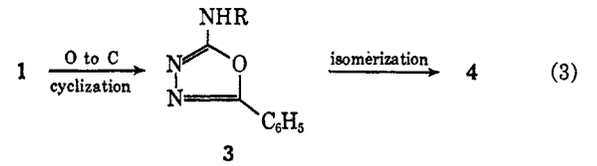
Oxidation of benzaldehyde semicarbazones with alcoholic $FeCl_3$ leads to cyclized products, *i.e.*, the 1,2,4-triazoles of eq 1.[3–6] Two ways in which the process can be formulated are shown in eq 2 and 3. Although



(1)

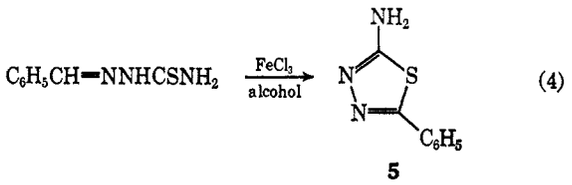


(2)



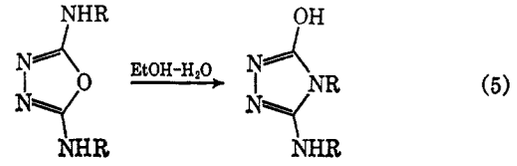
(3)

triazolinones (**2**) have not been isolated we do not know of any evidence which rules out the intermediacy of such compounds in the reaction. On the other hand, there is precedent for formation of products like **3**. A 1,3,4-thiadiazole (**5**) has been isolated from the reaction of benzaldehyde thiosemicarbazone with $FeCl_3$[7] (eq 4). Moreover, some oxadiazoles[8,9] are known to



(4)

isomerize to triazoles (eq 5) under conditions like those used in oxidation with $FeCl_3$.[9] It is possible then, that, where a five-membered ring can be formed



(5)

to either nitrogen or oxygen (eq 2 and 3), cyclization to oxygen is kinetically favored.

Oxidative cyclization of symmetrical ketocarbohydrazones (**6**) could, by analogy, occur in either sense

(1) (a) Acknowledgment is made to the donors of The Petroleum Research Fund, administered by the American Chemical Society, for support of this research; (b) taken from the Ph.D. Thesis of P. R. West, McMaster University, 1967.

(2) Holder of a National Research Council of Canada studentship, 1962–1966; presently at the Department of Chemistry, York University, Heslington, York, England.

(3) G. Young and E. Witham, *J. Chem. Soc.*, **77**, 224 (1900).

(4) G. Young and W. H. Oates, *ibid.*, **79**, 659 (1901).

(5) J. R. Bailey and A. T. McPherson, *J. Amer. Chem. Soc.*, **39**, 1322 (1917).

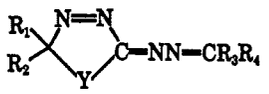
(6) M. Busch and A. Walter, *Ber.*, **36**, 1357 (1903).

(7) R. Duschinsky and H. Gainer, *J. Amer. Chem. Soc.*, **73**, 4464 (1951).

(8) The oxadiazoles were not prepared by oxidative cyclization but by a dehydration process.[9]

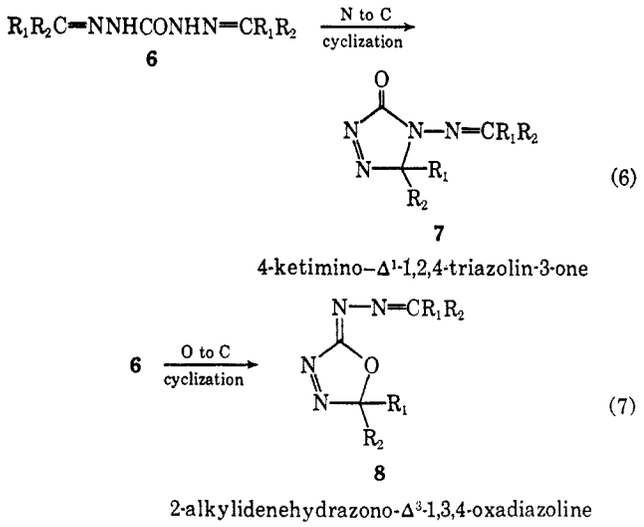
(9) H. Gehlen and K. Moekel, *Ann.*, **685**, 176 (1965).

TABLE I

SPECTRA OF 

Compound[a]						Ir, cm^{-1}				Uv, mμ[b]		Pmr, ppm[c,d]	
No.[f]	Y	R_1	R_2	R_3	R_4	C=N stretch	Skeletonal i	Skeletonal ii	Skeletonal iii	λ_{max}	Log ϵ_{max}	R_1 and R_2	R_3 and R_4
1	O	Me	Me	Me	Me	1669	1224	1133	986			1.62 s (6 H)	2.01 s (3 H)
									962	291	3.74		1.95 s (3 H)
2	O	Me	Et	Me	Et	1669	1206	1138	960			1.53 s (3 H)	1.90 s
									942	295	3.73	0.73 t (3 H)	1.10 t
												1.91 q	2.28 q
3	O	Me	Ph	Me	Ph	1664	1202	1030	763	245	3.88	1.95 s (3 H)	2.48 s (3 H)
								952	692	314	3.91	8.0–7.3 m	8.0–7.3 m
4	O	Ph	Ph	Ph	Ph	1661	1200	1045	751	252	4.08	7.8–7.1 m	7.8–7.1 m
								1022	692	322	3.96		
5	O	Me	Me	Ph	Ph	1675	1232	1134	970	251	3.98	1.62 s (6 H)	7.8–7.2 m (10 H)
									952	322	4.03		
6	S	Me	Me	Me	Me	1621			961	210[e]	3.97[e]	1.83 s (6 H)	2.17 s (3 H)
									671	335[e]	3.67[e]		2.12 s (3 H)

[a] The first four compounds, which are not named in the Experimental Section are, in order of listing: 2-isopropylidenehydrazono-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline; 2-(2-butylidenehydrazono)-5-ethyl-5-methyl-Δ^3-1,3,4-oxadiazoline; 2-(1-phenylethylidenehydrazono)-5-methyl-5-phenyl-Δ^3-1,3,4-oxadiazoline; and 2-diphenylmethylenehydrazono-5,5-diphenyl-Δ^3-1,3,4-oxadiazoline. Names are assigned according to Rule C-923 in "Nomenclature of Organic Chemistry, Section C," International Union of Pure and Applied Chemistry, Butterworth and Co., Ltd., London, 1965. [b] In 95% ethanol, unless otherwise indicated. [c] CCl_4 or $CDCl_3$ solvent; internal TMS. [d] Individual areas of overlapping peaks are not given. The total integrals of such peaks were satisfactory. [e] In hexane. [f] Registry no. are as follows: 1, 16199-20-5; 2, 16199-14-7; 3, 16199-15-8; 4, 16199-16-9; 5, 16199-17-0.



according to eq 6 and 7. For an unsymmetrical ketocarbohydrazone, RRC=NNHCONHN=CR′R′ (**9**), two each of structures **7** and **8** can be written in which the groups R′ are on the ring in the one case and in which the ketimino part of the side chain in the other.[10,11]

In this report we present evidence for O to C cyclization of ketocarbohydrazones, and for S to C cyclization of a ketothiocarbohydrazone, by oxidation with lead tetraacetate. The triazolinone structure (**7**), favored in our earlier communication,[11] is shown to be incorrect. A comparison of the relative reactivities of the two "halves" of **9** (R = CH_3, R′ = C_6H_5), in oxidative cyclization to carbonyl oxygen, has been obtained from product studies and from qualitative rate relationships.

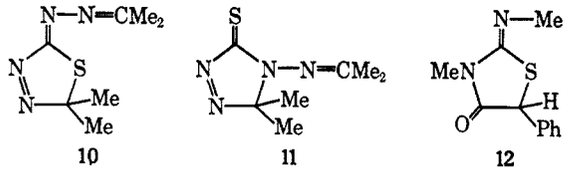
(10) Additional structures can be written if geometric isomerism is considered. In an earlier report[11] it was shown that, where such isomerism is possible, one isomer predominates in both the carbohydrazone and its oxidation product. The question of geometric isomerism is considered more fully below, after discussion of the evidence for the type of ring present.

(11) J. Warkentin and P. R West, *Tetrahedron Lett.*, 5815 (1966).

Discussion

Evidence for the cyclic, monomeric nature of the oxidation products of ketocarbohydrazones has been presented earlier.[11] In this report we show that the spectra and chemical properties of the compounds can be accommodated only in terms of an oxadiazoline ring system. In the discussion, arguments for the structure assignment follow immediately after citation of a property of the products. Spectra are recorded in Table I.

The infrared spectra (Table I) are considered first. If the product of oxidation of acetone thiosemicarbazone were triazolinthione **11**, rather than thiadiazoline **10**, one would expect to see both a broad thioureide band[12] at 1475–1550 cm^{-1} and an intense C=S band[13]



near 1025–1225 cm^{-1}. Neither is observed, but the strongest band is at 1621 cm^{-1}. The position of the band is correct for **10**, based on the structure **12**[14] which absorbs strongly at 1621 cm^{-1}. High intensity is also expected, for, although many C=N absorptions are quite weak, it has been shown that the stretching absorption of exocyclic C=N is greatly enhanced in intensity.[15] Thus the infrared spectrum is incompatible with structure **11** and completely in accord with structure **10**.

The infrared of the oxygen analogs is not interpreted as readily. A strong band near 1680 cm^{-1} could be

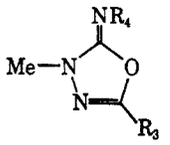
(12) Acetone thiocarbohydrazone absorbs strongly at 1470 and 1235 cm^{-1}.

(13) G. D. Thorn, *Can. J. Chem.*, **38**, 2349 (1960).

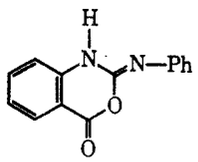
(14) H. Najer, R. Giudicelli, C. Morel, and J. Menin, *Bull. Soc. Chim. Fr.* 1022 (1963).

(15) M. Kurihara and N. Yoda, *Tetrahedron Lett.*, 2597 (1965).

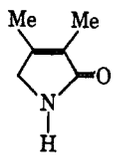
assigned to either α,β-unsaturated carbonyl of **7** or to exocyclic C=N of **8**, as indicated by the spectra of model compounds **13**, **14**, and **15**. However, there is evidence that the α azo function raises the CO stretching frequency above that for the carbon analog. This is illustrated with the pair **16**[20] and **17**[21] and with the pair **18** and **19**.[22] One might therefore expect the products of cyclization of carbohydrazones to absorb strongly at 1700 cm^{-1}, or more, if they were triazolinones (**7**).



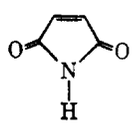
13a, R_3 = Ph; R_4 = Me; 1710 cm^{-1} [16]
b, R_3 = R_4 = Ph; 1660–1680 cm^{-1} [17]
c, R_3 = H; R_4 = Ph; 1675 cm^{-1} [18]



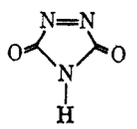
14, ν_{CN} 1644 cm^{-1} [15]



15, ν_{CO} 1680 cm^{-1} [19]



16, ν_{CO} 1675 cm^{-1}

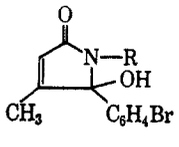


17, ν_{CO} 1760–1780 cm^{-1}

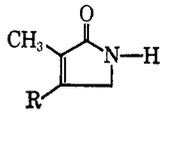
$C_6H_5CH{=}CHCONH_2$
18, ν_{CO} 1666 cm^{-1}

$C_6H_5N{=}NCONH_2$
19, ν_{CO} 1702 cm^{-1}

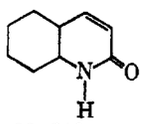
Ultraviolet spectra of model Δ^3-1,3,4-oxadiazolines or of Δ^1-1,2,4-triazolin-3-ones do not seem to be recorded in the literature.[23] Analogs, with a C=C group instead of the azo function, are known and there is evidence that they are good models for predicting the ultraviolet spectra of corresponding azo systems.[24] Thus compounds **20–22** [λ_{max}^{EtOH} (ϵ)] are models for the ring chromophore of a triazolinone (**7**). All indicate that the α,β-unsaturated lactam chromophore absorbs at low wavelength, unless there is extended conjugation.[28]



20a, R = CH_3; 230 mμ (12,700)[25]
b, R = Ph; 230–280 mμ (16,800–3,000) (no maximum)[25]



21a, R = CH_3; 216 mμ (14,000)[19]
b, R = Ph; 258 mμ (15,000)[26]



22, 210 mμ (11,000)[27]

The ultraviolet spectra (Table I) of compounds **8** and **10** show absorption maxima at much longer wavelength than those of the model compounds **20–22** for the alternative, triazolinone structure. It is unlikely that it is extended conjugation, through what would be the lactam nitrogen of a triazolinone series, which gives the compounds the long-wavelength maxima. Such extended conjugation is unimportant in shifting the uv of lactams, relative to the effect of conjugation through the double bond (compare **20b** with **21b**). The available models for triazolinones indicate, therefore, that our oxidation products are not triazolinones.

On the other hand, the oxadiazoline or thiadiazoline structure may be regarded as a semicyclic diene with extended conjugation in the acyclic portion and with a β OR or SR substituent. Although prediction of the absorption maximum from rules for diene or enone models can not be expected, the shift in the maximum, accompanying substitution of SR for OR, should be about the same as that observed in such models. From the first and last rows of Table I, it is seen that SR causes a bathochromic effect of 44 mμ, relative to OR. This value is intermediate to the difference between the effects of β OR and SR in enones (55 mμ) and in dienes (24 mμ), quoted by Scott.[29] The ultraviolet spectra then, are readily accommodated in terms of the structure assigned in Table I, but not in terms of the alternative structure. The n–π^* absorption of the azo function, expected at longer wavelength, is probably obscured by the more intense π–π^* band.

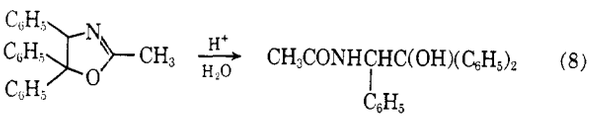
Proton magnetic resonance spectra (Table I) also support the oxadiazoline structure for the oxy systems. The basis of that support is again, in part, in the comparison of products of oxidation of acetone carbohydrazone and of acetone thiocarbohydrazone. That the latter probably is **10** comes from the infrared evidence (*vide supra*). If the former is structure **8**, then the difference in chemical shift of the ring methyls should agree with the difference in shielding constants of β OR and SR groups. This difference is about 0.18 ppm,[30] close to the observed increment (Table I) of 0.21 ppm. If structure **7** were correct for the oxy systems, the relative shielding constants of β NR and SR should apply, approximately, and the chemical shifts of ring methyls should differ by about 0.35 ppm.[30] Additional support for structure **8** comes from comparison with a good model, $(CH_3)_2C(OAC)$-$N{=}NC_6H_5$. In the nmr spectrum of that compound, the *gem*-dimethyl singlet appears at 1.62 ppm.[31] With this last piece of evidence, the nmr spectra provide strong support for both assignments, **10** and **8**.

Chemical reactions of the cyclized compounds are in accord with expectation for the oxadiazoline structure. Both catalytic hydrogenation and treatment with

(16) H. Najer, J. Menin, and J. F. Giudicelli, *Compt. Rend.*, **258**, 4579 (1964).
(17) H. Najer, J. Menin, and J. F. Giudicelli, *ibid.*, **259**, 2868 (1964).
(18) J. Giudicelli, J. Menin, and H. Najer, *ibid.*, **260**, 4538 (1965).
(19) H. Plieninger and M. Decker, *Ann.*, **598**, 198 (1956).
(20) Sadtler Standard Spectra, Sadtler Research Laboratories, Inc., Philadelphia, Pa., 1965, spectrum no. 6225.
(21) R. C. Cookson, S. S. H. Giliani and I. D. R. Stevens, *Tetrahedron Lett.*, 615 (1962).
(22) E. Fahr and H. Lind, *Angew. Chem. Intern. Ed. Engl.*, **5**, 372 (1966).
(23) An oxadiazoline in the same oxidation state as **8** had been reported but was not useful as a model because of extended conjugation involving phenyl substituents. See W. Kirmse, *Ber.*, **93**, 2357 (1960).
(24) B. T. Gillis and J. D. Hagarty, *J. Amer. Chem. Soc.*, **87**, 4576 (1965).
(25) R. E. Lutz, C. T. Clark, and J. P. Feifer, *J. Org. Chem.*, **25**, 346 (1960).
(26) J. A. Moore and J. Binkert, *J. Amer. Chem. Soc.*, **81**, 6029 (1959).
(27) G. DiMaio and P. A. Tardella, *Gazz. Chim. Ital.*, **94**, 584 (1964).
(28) Attention should be drawn to a high value (λ_{max} 250 mμ) reported for dihydropyridones, similar to **22**, by O. E. Edwards and T. Singh, *Can. J. Chem.*, **32**, 683 (1954).
(29) A. I. Scott, "Interpretation of the Ultraviolet Spectra of Natural Products," Pergamon Press Ltd., Oxford, England, 1964, p 58.
(30) L. M. Jackman, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," Pergamon Press Ltd., Oxford, England, 1959, p 53.
(31) P. R. West and J. Warkentin, unpublished data.

lithium aluminum hydride afforded starting carbohydrazone as major product. Facile ring opening through catalytic hydrogenation has been reported for other Δ^3-1,3,4-oxadiazolines.[23,32] Ring opening with $LiAlH_4$ can be rationalized in terms of hydride attack either at the terminus of the conjugated system or at the azo function.

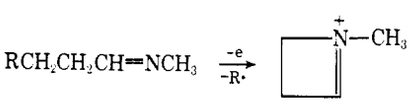
The carbohydrazone oxidation products are hydrolyzed rapidly at room temperature by aqueous acid and more slowly by *p*-toluenesulfonic acid hydrate in ether. Similar, acid-catalyzed, ring opening of imidic esters is known to occur under mild conditions (eq 8).[33] We have not yet studied the products of



(8)

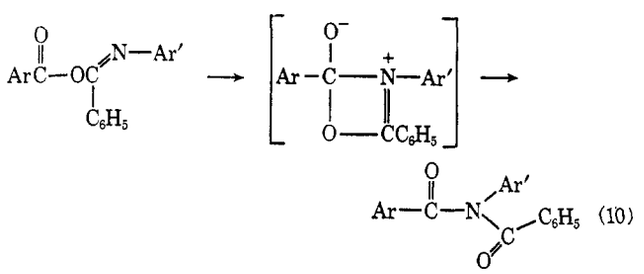
hydrolysis in any detail but two materials from reaction of **8** ($R_1 = R_2 =$ Ph) with toluenesulfonic acid hydrate in ether are benzophenone and benzophenone hydrazone. Although such products could conceivably come from the isomeric triazolinone, it is less likely that it (a lactam) would hydrolyze so readily.

One of the stronger reasons for favoring the triazolinone structure in our initial communication[11] was the absence of M − 28 peaks in the mass spectra, all of which had the highest significant peak at M − 56. It was easy to see that a triazolinone (**7**) might go directly to the M − 56 ion by loss of N_2 and CO but it was not obvious that an oxadiazoline (**8**) might be able to by-pass the expected M − 28 ion resulting from loss of N_2. In view of the evidence that our products are indeed oxadiazolines we sought precedent for the observed fragmentation. Studies of the mass spectra of azomethines[34] indicate formation of a cyclic, four-membered ion as shown in eq 9. A similar



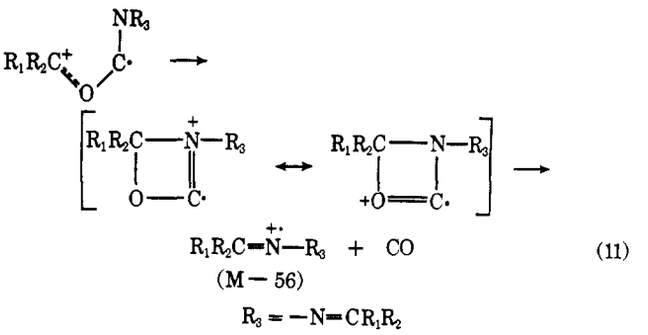
(9)

four-membered ring may be involved in the thermal rearrangements of arylisoimides in solution[35] (eq 10).



(10)

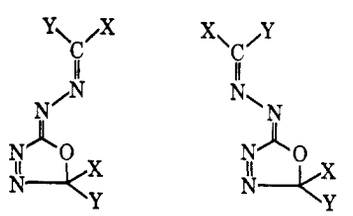
An analogous, short-lived intermediate could account for the M − 56 peaks, and the absence of M − 28 peaks, in the mass spectra of the oxadiazoline systems (eq 11).[36]



(11)

With the type of ring present firmly established, some consideration is given to structural detail and possible mechanisms of formation of the oxadiazolines. If the only large barrier to rotation is at the C=N bonds, the carbohydrazone of acetone can have only one structure whereas that of 2-butanone has three possibilities: *syn,syn* (methyl); *syn,anti* (methyl); and *anti,anti* (methyl).

For the oxadiazolines, configurational isomers are possible even in the simplest cases. There are two and four possibilities, respectively, for the oxadiazolines derived from acetone (**23** and **24**, X = Y = Me) and from 2-butanone (**23** and **24**, X = Me, Y = Et or X = Et, Y = Me).



23 **24**

Not all isomers can be expected, however. In the parent carbohydrazones, that isomer in which the smaller group is *syn* (*i.e.*, *cis* to nitrogen) can be expected to predominate, for it has been demonstrated that such a preference exists in the formation of semicarbazones,[37] 2,4-dinitrophenylhydrazones,[37,38] and phenylhydrazones.[39] From our nmr spectra, we estimated[11] that crude carbohydrazones of unsymmetrical ketones (2-butanone and acetophenone) are more than 90% configurationally pure. By analogy, the predominating isomer is assigned the *syn,syn* (methyl) structure.

The oxadiazolines appear to be at least 90% configurationally pure also, even in the crude state. Most likely the configuration at the hydrazono C=N group is retained and the exocyclic C=N bond is formed with high stereospecificity but we have no information at this time as to which geometry is preferred at the latter.[40] Azines of unsymmetrical ketones exist preferentially in the least hindered (*syn,syn*) configuration.[41] Models of the oxadiazolines suggest, however, that the steric requirement of azo nitrogen is comparable to that of oxygen in **8**. In any case, there is no way of

(32) R. W. Hoffman and H. J. Luthardt, *Tetrahedron Lett.*, 411 (1966).
(33) E. M. Fry, *J. Org. Chem.*, **15**, 802 (1950).
(34) D. Goldsmith, D. Becker, S. Sample, and C. Djerassi, *Tetrahedron Suppl.*, **7**, 145 (1966).
(35) D. Y. Curtin and L. L. Miller, *Tetrahedron Lett.*, 1869 (1965).
(36) Molecular ion peaks and M − 28 peaks would probably be recorded if low ionizing voltages were used. The mass spectrum of the oxadiazoline derived from acetone-4-phenylsemicarbazone, when run at 11 eV, includes peaks corresponding to the molecular ion and to an ion of mass M − 28.[31]
(37) G. J. Karabatsos, J. D. Graham, and F. M. Vane, *J. Amer. Chem. Soc.*, **84**, 753 (1962).
(38) G. J. Karabatsos, B. L. Shapiro, F. M. Vane, J. S. Fleming, and J. S. Rakta, *ibid.*, **85**, 2784 (1963).
(39) G. J. Karabatsos and R. A. Taller, *ibid.*, **85**, 2326, 2327 (1963).
(40) If the products are actually *syn,anti* mixtures, the isomers must be inseparable by tlc and must have superimposable nmr spectra.
(41) E. Arnal, J. Elguero, R. Jacquier, C. Marzin, and J. Wylde, *Bull. Soc. Chim. Fr.*, 877 (1965).

predicting the importance of steric effects in the cyclizations without knowing the mechanism.[42,43]

Carbohydrazones of dialkyl ketones undergo facile oxidation with LTA at 0° in CH_2Cl_2 to give yields reaching 80%. Those of diaryl ketones react slowly, if at all, at 0° and they give lower yields (*ca.* 20%) at higher temperatures. The rate differences probably arise out of both steric and polar effects,[43] and they are large enough so that the unsymmetric carbohydrazone, $Me_2C{=}NNHCONHN{=}CPh_2$, is cyclized very selectively to the isopropylidene carbon (see Experimental Section).

Little is known about the reactions which compete with oxadiazoline formation. From benzophenone carbohydrazone, diphenylmethylene diacetate was isolated. It could arise from further reaction of a first-formed azo acetate, $Ph_2C(OAc)N{=}NCONHN{=}CPh_2$.

Experimental Section[44]

Preparation and properties of the first four compounds of Table I were reported earlier,[11] although the structures assigned there are incorrect.

Acetone Thiocarbohydrazone.—This compound was prepared by the method of Stephen and Wilson.[45] Thiosemicarbazide (Eastman, Reagent Grade; 12.0 g, 0.117 mol) was added to 150 ml of dry acetone and the mixture was refluxed for 12 hr after which time all but a small amount of white solid remained undissolved. Excess acetone was distilled and the residual white solid was extracted with a 1:1 solution of chloroform in petroleum ether (30–60°). The resulting solution was concentrated to crystallize the product. Two additional recrystallizations from petroleum ether–chloroform gave white needles (7.3 g, 33.5%). When these were heated on a hot stage and viewed through a polarizing microscope, softening and resolidification was observed at 144–145°, followed by melting at 185° (lit.[45] mp 192° dec).

2-Isopropylidenehydrazono-5,5-dimethyl-Δ^3-1,3,4-thiadiazoline.—Acetone thiocarbohydrazone (6.8 g, 0.037 mol) in 75 ml CH_2Cl_2 was added gradually to a stirred solution of 1 equiv (6.8 g, 0.0365 mol) of $Pb(OAc)_4$ in 200 ml of CH_2Cl_2, kept near 0° by cooling with ice. A precipitate (presumably $Pb(OAc)_2$) was formed rapidly and the solution became red-brown in color. Dropwise addition of the oxidizing solution to thiosemicarbazone in CH_2Cl_2 gave the same result.

Addition of the last of the thiosemicarbazone was followed after a few minutes by addition of water and separation of the methylene chloride layer. The latter was washed three times with 100-ml portions of cold water, once with 100 ml of bicarbonate solution, and again with water. After drying, solvent was removed at about 0°, under vacuum, leaving 6.0 g of red-brown oil. The latter was extracted with low-boiling petroleum ether from which was obtained 1.3 g of red oil which had a complex (ten line) nmr spectrum in the region 2.5–1.5 ppm. The oil was chromatographed on Florisil (5 × 10 cm column) with low-boiling petroleum ether. Evaporation of the first, bright yellow eluant left an orange oil (0.2 g) which contained about 50% of the desired product (nmr estimate). Repeated crystallization from petroleum ether (bp 30–60°) gave yellow, rhombic crystals, mp 65.0–65.5°. Spectra of the product are given in Table I (see Discussion). No attempt was made to improve the yield.

Anal. Calcd for $C_7H_{12}N_4S$: C, 45.65; H, 6.46; N, 30.44. Found: C, 45.95; H, 6.55; N, 30.51.

1-Diphenylmethylene-5-Isopropylidene Carbohydrazide.—Benzophenone 4-aminosemicarbazone (1.0 g, 3.9×10^{-3} mol), prepared by the method by Brown, Pickering, and Wilson,[46] mp 221–223°, was heated on a steam bath for 3 hr with 80 ml of acetone. During that time, the 4-aminosemicarbazone slowly dissolved. Cooling led to separation of a mass of white needles which, after drying, weighed 1.0 g (86% yield) and melted at 200–202°. The compound was characterized by its spectra. The nmr spectrum ($CDCl_3$) showed singlets at 1.88 (3 H) and at 1.85 (3 H) as well as a multiplet at 7.5–7.2 ppm (10 H). Absorption due to NH was not discernible in the nmr, but the infrared spectrum showed N–H absorption at 2.98 as well as typical carbohydrazone C=O stretching at 5.86 μ.

2-Diphenylmethylenehydrazone-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline.—A slightly yellow solution of $Pb(OAc)_4$ (0.71 g, 1.6×10^{-3} mol) in 10 ml of methylene chloride was cooled to about 0° in a three-necked flask equipped with stirrer and dropping funnel. Purified-grade nitrogen was admitted to purge the vessel of air before 1-diphenylmethylene-5-isopropylidene carbohydrazide (0.440 g, 1.51×10^{-3} mol) in 5 ml of methylene chloride was added over a period of 15 min. The reaction mixture was stirred and cooled for 15 min after completion of the addition. Ice–water (about 2 ml) was added and stirring was continued for 10 min more. After addition of 50 ml of CH_2Cl_2 the dark slurry was filtered through Celite and the pale yellow methylene chloride solution was separated. It was washed three times with water, once with saturated $NaHCO_3$ solution, and again with water before it was dried over sodium sulfate. Evaporation of the solvent gave 0.361 g (82%) of the title compound as a yellow oil. It was crystallized from petroleum ether to mp 110–111°. In the nmr spectrum of the crude oil there was a singlet at 1.62 (6 H) and a multiplet at 7.8–7.2 ppm (10 H) but no other absorptions. The singlet at 1.62 ppm must be due to the *gem* dimethyl substituents on the oxadiazoline ring (*vide supra*). In view of the high yield and the absence of other methyl signals in the nmr, it can be concluded that cyclization is highly selective.

Infrared and ultraviolet spectra of the product are entered in Table I.

Benzophenone Carbohydrazone.—Three approaches to the title compound were explored.

Heating carbohydrazide with 3 equiv of benzophenone in ethanol, as described in the literature,[46] gave mainly benzophenone 4-aminosemicarbazone (50%), mp 221–223° (lit.[46] mp 223–224°).

Use of dimethyl sulfoxide solvent gave better results, although the yields remained low. Carbohydrazide (5.0 g, 0.06 mol) was heated on a steam bath for 48 hr with benzophenone (25.0 g, 0.14 mol) in 150 ml of dimethyl sulfoxide. The bright yellow solution was cooled and poured into a mixture of ice and water (500 ml). A yellow, oily solid separated, from which the supernatant liquid was decanted. Trituration of the oily mass with cold ethanol (25 ml) and filtration gave crude benzophenone carbohydrazone (6.0 g, 26%). After two recrystallizations from ethanol there remained 4.1 g of white needles, mp 224–225° (lit.[46] mp 222–223°). The best yields by this method were 20–30%. Extension of the heating period led to increased decomposition of the product to a major contaminant, diphenylketazine.

The recommended reaction for synthesis of benzophenone carbohydrazone is that of benzophenone hydrazone[47] with phosgene in pyridine, as described below.

A solution of benzophenone hydrazone (61.0 g, 0.311 mol) in 300 ml pyridine (Fisher Certified Reagent, distilled from barium oxide, bp 113–114°) was cooled to 0° in a 1-l., three-necked flask equipped with a mechanical stirrer, condenser ($CaCl_2$ tube), and gas inlet. Phosgene gas from a cylinder was condensed into a second flask by means of a Dry Ice condenser. The liquid phosgene (16.9 g, 0.17 mol) was allowed to distil into the reaction vessel holding the stirred pyridine solution, with the inlet tube above the surface of the solution. Stirring and cooling was continued for 30 min after distillation of phosgene. The orange-brown solution as then poured into 1.5 l. of 10% acetic acid solution, containing crushed ice. Filtration of the voluminous, white precipitate left 61.0 g (94%) of crude benzophenone carbohydrazone, with infrared spectrum nearly identical with that of a pure sample. After two recrystallizations from ethanol–water (decolorizing carbon) the product was obtained as white needles, mp 224–225°.

Deliberate treatment of benzophenone carbohydrazone with phosgene in pyridine at 0°, led to an unidentified, water-soluble product. It is important, therefore, to use no more than 1 equiv of phosgene in the synthesis described above.

(42) There is evidence for organolead intermediates in oxidation of ketone arylhydrazones with LTA.[43] Perhaps carbohydrazones react *via* related intermediates, with lead bonded to carbohydrazone oxygen.

(43) M. J. Harrison, R. O. C. Norman, and W. A. F. Gladstone, *J. Chem. Soc., Sect. C.*, 735 (1967).

(44) Melting points were determined with capillary tubes and an oil bath, unless otherwise indicated. They are uncorrected.

(45) H. W. Stephen and F. J. Wilson, *ibid.*, 2531 (1926).

(46) A. C. Brown, E. C. Pickering, and F. J. Wilson, *ibid.*, 106 (1927).

(47) S. G. Cohen and C. H. Wang, *J. Amer. Chem. Soc.*, **77**, 2457 (1955).

2-Diphenylmethylenehydrazono-5,5-diphenyl-Δ^3-1,3,4-oxadiazoline.—The oxidation procedure was similar to that outlined above except that the temperature was raised to 30° for 15 min after the reagents were mixed at about 0°. From 28.8 g (0.07 mol) of benzophenone carbohydrazone and 67.2 g (0.15 mol) of LTA was obtained a red-orange oil from which 10.5 g (36.5%) of the title compound was isolated by crystallization from chloroform–petroleum ether. The shiny, yellow plates melted at 113–114° with decomposition. Analyses and molecular weight were reported earlier[11] and spectra are recorded in Table I.

In one experiment the filtrate (chloroform–petroleum ether) remaining from oxidation of 0.615 g of benzophenone carbohydrazone, after removal of 0.283 g (46%) of the oxadiazoline, was examined. Evaporation of the solvent left 0.280 g of a pale red oil. Thin layer chromatography indicated only two major components. Crystallization from petroleum ether gave 0.1 g (25%) of diphenylmethylenediacetate as white needles, mp 120–122° (lit.[48] mp 121°). The nmr spectrum ($CDCl_3$) showed a singlet at 1.96 (6 H) for the acetoxy groups and a multiplet centered at 7.34 ppm (10 H). In the infrared spectrum there was no NH or OH absorption and a single C=O absorption at 5.75 μ. Treatment of the compound with 2,4-dinitrophenylhydrazine in ethanol–phosphoric acid gave a red, crystalline product identical with authentic benzophenone 2,4-dinitrophenylhydrazone.

Catalytic Hydrogenation.—All catalytic hydrogenations were carried out as described below for one member of the series.

To a solution of 0.980 g of 2-isopropylidenehydrazono-5,5-dimethyl-Δ^3-1,3,4-oxadiazoline (**8**, $R_1 = R_2 = CH_3$) in 200 ml of ethanol was added 0.588 g of 5% palladium on charcoal. The mixture, in a 500-ml hydrogenation bottle, was shaken at room temperature for 3 hr under hydrogen at 48 psi. The mixture was filtered twice and the colorless filtrate was evaporated to leave a light gray powder (0.733 g, 74.8%) which gave an infrared spectrum identical with that of authentic acetone carbohydrazone. One recrystallization gave material melting at 160° (lit.[46] mp 160°).

Analogous reduction gave, from **8** ($R_1 = CH_3$; $R_2 = C_2H_5$), 2-butanone carbohydrazone (81.5%), mp 110–113° (lit.[46] mp 110–113°), with infrared and nmr spectra identical with those of authentic material prepared from ketone and carbohydrazide. Similarly, **8** ($R_1 = R_2 = C_6H_5$) gave crude benzophenone carbohydrazone (75.7%) as a clear oil, with an infrared spectrum identical with that of an authentic sample. The oil crystallized from CCl_4 to give white needles, mp 224–225° (lit.[46] mp 223–224°).

Reduction with Lithium Aluminum Hydride.—A solution of **8** ($R_1 = R_2 = CH_3$) (1.442 g, 0.0086 mol) in 75 ml of absolute ether was added, by drops, to $LiAlH_4$ (0.33 g, 0.0088 mol) in 200 ml of ether. A yellow color developed at once. The mixture was refluxed for 12 hr before it was cooled to room temperature for gradual addition of saturated aqueous sodium sulfate until gas evolution ceased. The ether layer was decanted from the grey solid in the flask; it left 0.1 g of an unidentified white solid on evaporation. Extraction of the gray solid with boiling chloroform and evaporation of the chloroform gave 0.979 g (61.1%) of a clear, colorless oil. Its infrared spectrum matched that of acetone carbohydrazone. Crystallization from ethanol–water gave 0.423 g (30%) of pure, crystalline product.

Reduction of **8** ($R_1 = CH_3$, $R_2 = C_2H_5$; 1.244 g, 0.0064 mol) with $LiAlH_4$ (0.48 g, 0.0128 mol) in an analogous manner gave 0.997 g (80%) of slightly yellow oil. The complex nmr spectrum (CCl_4) indicated a mixture. A white solid that separated from the CCl_4 in the nmr tube was identified by infrared and nmr spectra as 1,5-di-(2-butyl) carbohydrazide, $[CH_3(C_2H_5)CHNH\text{-}NH]_2$ C=O. With that information, the nmr spectrum of the original mixture could be resolved in terms of a 70:30 mixture of the above carbohydrazide and of 2-butanone carbohydrazone. Since a large excess of $LiAlH_4$ was used, it is likely that the former product arose from reduction of the latter.

Treatment of **8** ($R_1 = R_2 = C_6H_5$; 0.400 g, 0.96×10^{-3} mol) with a large excess of $LiAlH_4$ (0.095 g, 2.53×10^{-3} mol) for 12 hr at the temperature of refluxing ether left at least 0.192 g of starting material unreacted. In addition to starting material, benzophenone carbohydrazone (0.098 g, 52% based on reacted material) was recovered. Identity was again established by comparison of infrared spectrum and melting point with those of an authentic specimen.

Acid Hydrolysis.—To 15 ml of ether, saturated with *p*-toluenesulfonic acid monohydrate, was added 0.1 g of **8** ($R_1 = R_2 = C_6H_5$). During 2 hr at room temperature the initial yellow color faded and a white precipitate was deposited. The ether layer was filtered, washed with saturated aqueous bicarbonate and with water, dried, and evaporated. The colorless, oily residue had the same infrared spectrum as benzophenone. An infrared spectrum (KBr) of the white solid left on the filter showed broad, salt-like absorption at 2.9–4.0 μ. Treatment of the solid with saturated sodium acetate solution gave a new solid which was identical (infrared, KBr) with benzophenone hydrazone.

Registry No.—**10**, 16199-18-1; acetone thiocarbohydrazone, 16199-19-2; 1-diphenylmethylene-5-isopropylidene carbohydrazide, 16240-67-8; benzophenone carbohydrazone, 16240-68-9; lead tetraacetate, 546-67-8.

(48) H. R. Hensel, *Ber.*, **88**, 527 (1955).