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# Diazirines. II.[1] Synthesis And Properties of Small Functionalized Diazirine Molecules. Some Observations on The Reaction of a Diaziridine with the Iodine–Iodide Ion System

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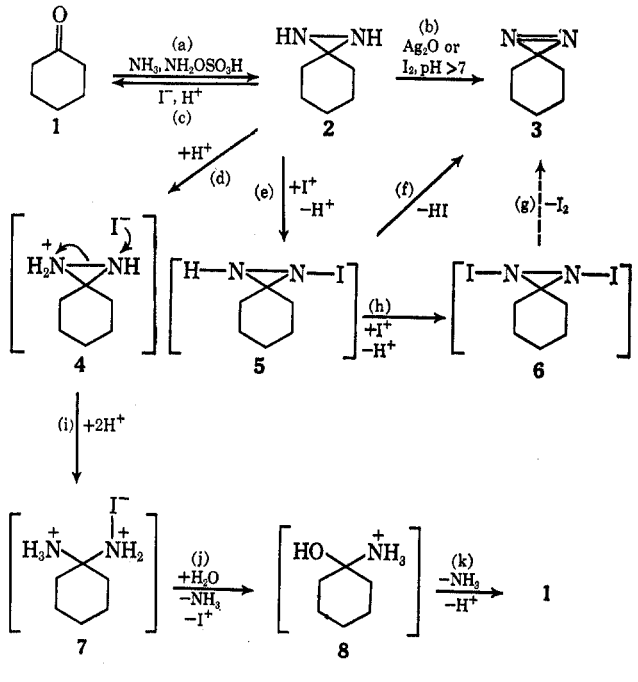
The use of iodine in triethylamine is presented as a superior alternative to the commonly used silver oxide procedure for the oxidation of diaziridines to diazirines. However, in acidic media this oxidation is not stoichiometric. A study of the iodine–iodide ion redox system with 1,1-hydrazicyclohexane disclosed that a catalytic cyclic process is operative and leads to disproportionation of the diaziridine. Conversely, overconsumption of iodine under conditions of rapid titration is also possible, perhaps owing to the formation of an N,N′-diiododiaziridine intermediate. A variety of simple diazirine-containing aliphatic acids, acid chlorides, esters, alcohols, acetals, aldehydes, amines, amides, etc., were prepared either from the corresponding ketone or by subsequent transformations. The diazirine group was stable to a variety of reagents. The physical properties ($pK_a$, uv, ir, nmr) of some of these functionalized diazirine-containing molecules are discussed. The effect of the diazirine function on $pK_a$ is approximately comparable with that exerted by a keto group or a chlorine atom, but it is less diminished by increasing distance.

Considerable interest has been generated by the diazirine and diaziridine groups since their unequivocal discovery about ten years ago.[2] In continuation of our study concerning the effect of the diazirine group on biological activity,[1] we have found it necessary to prepare a variety of small, otherwise functionalized molecules which contain this group. In addition to the preparation of some of these compounds, we report herein our observations concerning the compatibility of the diazirine group with a number of common chemical reagents and certain interactions between the diazirine group and neighboring functions. A subsequent report[3] will describe some of the biological properties of these and derived compounds.

The diazirine group is generally introduced by oxidation of the diaziridine obtained from the corresponding ketone by treatment with ammonia and hydroxylamine-O-sulfonic acid or chloramine (Scheme I). Usually, the oxidation (reaction b) is effected by silver oxide which, however, is not an entirely satisfactory reagent for this purpose. Certain functional groups, amines in particular, interfere with the reagent. Furthermore, preprepared silver oxide which is sufficiently active is rather difficult to obtain and, when prepared *in situ* (addition of sodium hydroxide to a solution of silver nitrate and the diaziridine in water or aqueous methanol), several competing side reactions are possible. This oxidation is often sluggish and, since water appears to be the most appropriate solvent, the recovery of

SCHEME I




(1) Diazirines. I: R. F. R. Church, A. S. Kende, and M. J. Weiss, *J. Amer. Chem. Soc.*, **87**, 2665 (1965).

(2) (a) H. J. Abendroth and G. Henrich, *Angew. Chem.*, **71**, 283 (1959); (b) S. R. Paulsen and G. Huck, *Chem. Ber.*, **94**, 869 (1961); (c) E. Schmitz and R. Ohme, *ibid.*, **94**, 2166 (1961).

(3) R. F. R. Church, H. J. Albers, D. Blickens, W. P. Cekleniak, R. Maleike, S. Riggi, and M. J. Weiss, unpublished work.

water-soluble products is troublesome. Probably the most pressing argument against the use of silver oxide is the potential explosive character of the silver mirror formed on the reaction vessel as the oxidation proceeds.[4]

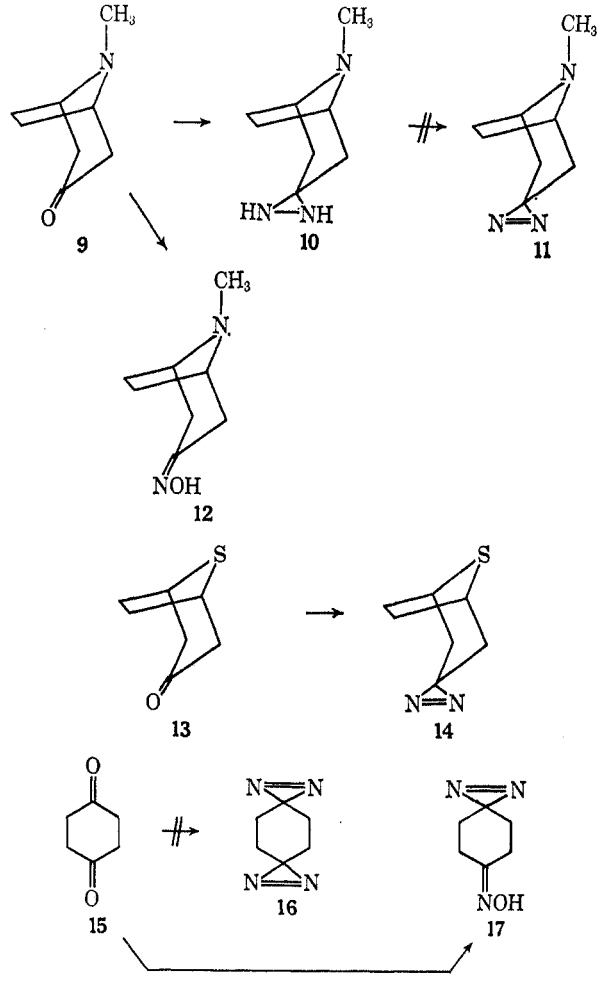
There is a report describing the use of bromine in basic media for this oxidation,[5] and we have found iodine to be at least as useful. This reaction (b in Scheme I, pH >9), which is quantitative and nearly instantaneous, can be carried out by the addition of solid iodine to a methanolic solution of the diaziridine which contains at least one equivalent of triethylamine. After the red color of iodine has persisted for a few seconds, the oxidation is completed by titration with a saturated methanolic solution of iodine (about 0.4 *M*). An important advantage of this method is the apparent absence of side reactions. The method can be used not only in the presence of virtually all functional groups, but the intermediate diaziridine need not be purified or even isolated from the methanolic reaction medium in which it is formed. The only precaution necessary is the complete removal of ammonia prior to adding iodine in order to avoid formation of nitrogen triiodide.[6]

In contrast to this reaction, in which iodine in alkaline media oxidizes the diaziridine function, is the reaction in which iodide ion in acidic media reduces this group.[2a] The latter reaction (c in Scheme I) is typical of diaziridines and is the basis for the standard qualitative test for the group.

We carried out a brief investigation of these reactions with 1,1-hydrazicyclohexane[7] (**2**) as model substrate. When **2** was titrated with iodine the oxidation reaction b (to the diazirine **3**) was rapid and stoichiometric at pH values above *ca.* 9. On the other hand, the reaction was not stoichiometric at pH 7 or below, the amount of iodine consumed being dependent upon the rate of iodine addition. If titrated rapidly (within 1.5 min) at pH 5.0, the consumption of iodine exceeded (up to 15%) the stoichiometric requirement. When the titration was carried out slowly, less than stoichiometric quantities of iodine were consumed. In fact, in acidic media, catalytic quantities (0.05–0.1 mol equiv) of iodine *or* iodide ion caused complete disappearance of the diaziridine if the reaction mixture was allowed to stand sufficiently long (*e.g.*, *ca.* 30 min, pH 5.0, 24°).

These results can be rationalized as follows. In basic media the oxidation proceeds as pictured in Scheme I, *via* steps e and f, and involves the consumption of one iodine molecule and the generation of two iodide ions. Step f requires proton elimination and thus it should be favored in basic media and inhibited in acidic media. We suggest that in the latter circumstance a second iodination reaction, h, to form **6**, may participate, resulting in the overconsumption of iodine, as was observed in the rapid-titration experiment at pH 5. However, when the titration at acid pH is carried out slowly, an additional pathway, which is opposed to iodine overconsumption, becomes operative. Thus, the iodide ion generated by steps e and f can, at acid pH, attack the protonated diaziridine **4** resulting in ring scission to **7** with ultimate hydrolysis through **8** to cyclohexanone **1**, and the concommitant generation of iodonium ion. The formation of iodonium ion establishes a catalytic process (reactions e and f, then d, i, and j) and, to the extent that this process can assert itself, underconsumption of iodine will result.

SCHEME II




Although no concrete evidence can be presented for the existence of **6**,[8] its presence for a finite time would allow overconsumption of iodine to occur as long as iodine elimination from it is sufficiently slower than the rate of its formation. However, the lifetime of **6** must be relatively short under the conditions of the cyclic process; otherwise iodine concentration would be reduced and the catalytic reaction would be slowed or stopped.

We have previously noted that the conversion of ketones to N,N′-unsubstituted diaziridines is subject to

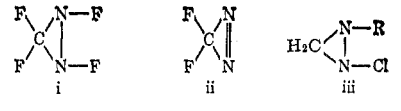
(4) Silver mirrors produced by Tollens reagent, as well as the reagent itself, are notoriously explosive, probably owing to reaction of silver ion and ammonia. Since similar conditions are potentially present in diazirine preparations with silver oxide, prudence dictates that they be avoided, particularly on a large scale.

(5) H. Kato and M. Ohta, *Bull. Chem. Soc. Jap.*, **35**, 2048 (1962).

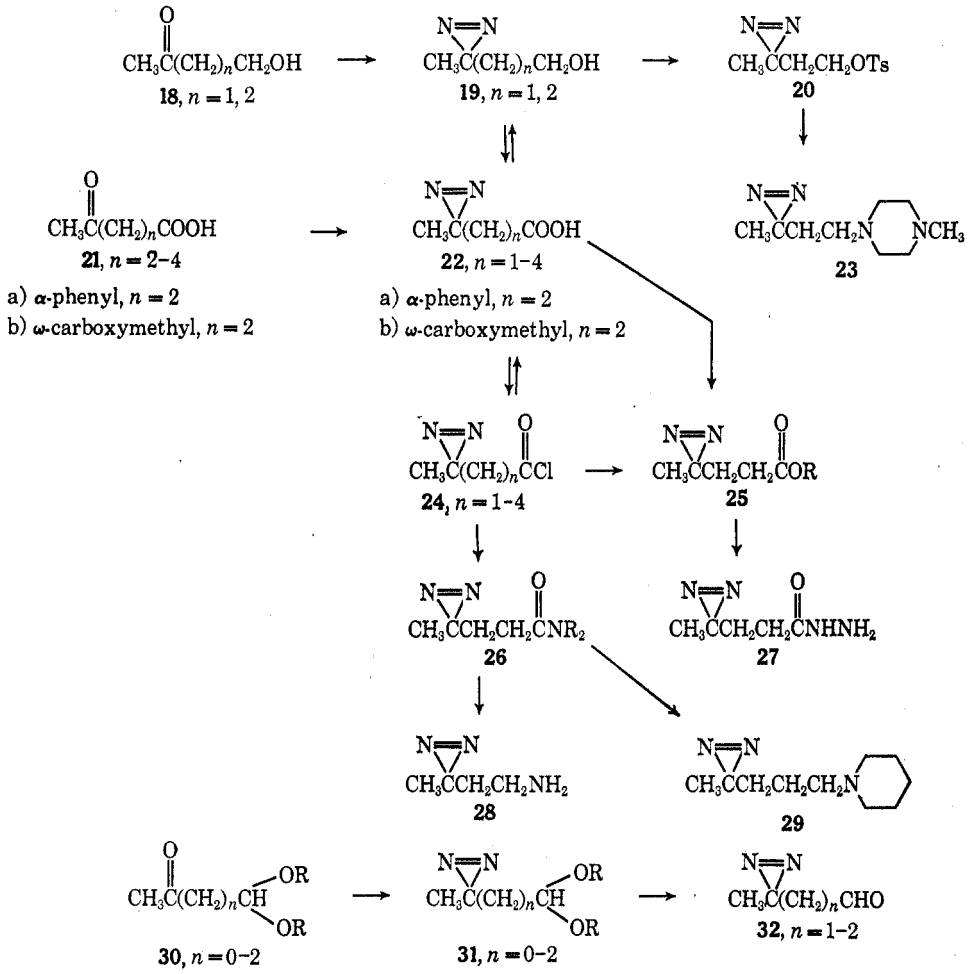
(6) Ammonia can be removed completely by partial evaporation of the methanolic reaction medium (in the case of carboxylic acids, one equivalent of triethylamine is added prior to evaporation of ammonia). If nitrogen triiodide is indeed formed as a result of incomplete removal of ammonia, it can be detected as an insoluble silvery black precipitate.

(7) E. Schmitz, R. Ohme, and R. D. Schmidt, *Chem. Ber.*, **95**, 2714 (1962).

(8) See R. A. Mitsch, *J. Heterocycl. Chem.*, **3**, 245 (1966), for the preparation of 3,3-difluorodiazirine (ii) from bis(difluoramino)difluoromethane through related intermediate i. Also see W. H. Graham, *J. Org. Chem.*, **30**, 3108 (1965), for a discussion of species such as iii, which are postulated as intermediates, for example, in the reaction of dichloramine with imines to prepare diazirine.



SCHEME III




serious electronic and steric restrictions.[1] For example, $\alpha,\beta$ unsaturation, or an adjacent *gem*-dimethyl group, prevents reaction with steroid 3-ketones,[1] and acetophenone affords a diaziridine by an indirect reaction in only 9% yield.[2c,9,10] The present investigation further confirms the observation that this reaction of ketones with ammonia and hydroxylamine-O-sulfonic acid is not generally applicable. Thus, we were unable to effect the transformation of cyclopentanone,[11] quinuclidin-3-one, and dicyclopropyl ketone to the corresponding diazirines. Furthermore, attempts to convert tropinone (**9**, X = $NCH_3$) to the diazirine (**11**, X = $NCH_3$) gave only the oxime **12**, despite the fact that the 8-thia analog **13** (X = S) is reported[12] to afford the diazirine **14** (X = S) in relatively good yield (Scheme II). Also, the reaction with cyclohexane-1,4-dione **15** failed to yield the bisdiazirine **16**; after numerous attempts we could isolate only 4,4-azocyclohexanone oxime (**17**) in 1–2% yield.

Nevertheless, a considerable variety of relatively simple ketones bearing other functional groups can be smoothly converted to the corresponding diazirines (see Scheme III and Table I). The homologous series of keto alcohols **18**[13] and keto acetals **30** readily undergo this transformation. The homologous series of keto acids **21** ($n > 1$) also afford the diazirines **22** ($n > 1$), but, when the conversion of **21** ($n = 1$) was attempted, no diazirine was obtained. This diazirine acid (**22**, $n = 1$) is, however, available by chromic acid oxidation[14] of the diazirine alcohol **19** ($n = 1$).

The diazirine function is compatible with a variety of reagents, so that transformation of the other functional group proceeds cleanly affording additional types of diazirine-containing molecules. Thus, the azobutanol **19** ($n = 1$) was converted to the tosylate **20**, which in turn reacted smoothly with N-methylpiperazine to give amine **23**. Similarly, the acids **22** provided the corresponding acid chlorides **24**,[15] useful for the preparation of esters, *e.g.*, **25** (R = benzyl) and amides **26**. Fisher esterification of acid **22** ($n = 2$) afforded ester **25** (R = methyl).[15] Incidentally, the acid chlorides could be obtained directly from crude diazirine acid preparations. They constituted useful intermediates for the purification of the diazirine acids, since the boiling ranges of the acid chlorides allowed lower distillation temperatures and, therefore, much less thermal decomposition. Recovery of the acid by

(9) Extensive review: E. Schmitz, *Advan. Heterocycl. Chem.*, **2**, 83 (1963).

(10) Schiff base iv reacts with monomethylamine and hydroxylamine-O-sulfonic acid to yield 1-methyl-3-phenyldiaziridine in 77% yield,[3a] but this compound is not a diazirine intermediate.

$$PhCH{=}N{-}CH_3$$
iv

(11) This observation parallels our finding[1] that certain steroid 17-ketones are unreactive.

(12) J. J. Eubel and J. C. Martin, *J. Amer. Chem. Soc.*, **86**, 4618 (1964).

(13) See E. Schmitz, C. Horig, and C. Grundemann, *Chem. Ber.*, **100**, 2093 (1967), for the preparation and properties of a series of α-hydroxydiazirines.

(14) F. L. M. Pattison, J. B. Stothers, and R. B. Woolford, *J. Amer. Chem. Soc.*, **78**, 2255 (1956).

(15) For additional examples, see ref 3.

TABLE I

DIAZIRINES PREPARED DIRECTLY FROM KETONES

| Compd no. | Structure | Method of oxidation[a] | Yield from ketone | bp (mm) or mp (solvent) | Calcd, % C | Calcd, % H | Calcd, % N | Found, % C | Found, % H | Found, % N | Principal ir bands,[b] μ | Uv bands,[c] mμ (ε) | Nmr terminal methyl absorption, δ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 22, $n = 2$ | $CH_3C(N{=}N)(CH_2)_2COOH$ | A[d]<br>B | 42<br>43 | 66 (0.12)<br>8.5–10 (hexane) | 46.87 | 6.29 | 21.87 | 46.76 | 6.38 | 21.94 | 3.30 (m), 5.83 (s), 6.32 (w), A | 347 (64), 363 (52) | 1.05 |
| 22, $n = 3$ | $CH_3C(N{=}N)(CH_2)_3COOH$ | B | 38 | 14–16 (hexane) | 50.69 | 7.09 | 19.71 | 51.06 | 7.26 | 19.52 | 3.25 (s), 5.84 (s), 6.26 (m), A | 348 (57), 365 (50) | |
| 22, $n = 4$ | $CH_3C(N{=}N)(CH_2)_4COOH$ | A[d] | 30 | 8–10 (hexane) | 53.84 | 7.74 | 17.94 | 54.15 | 7.40 | 17.58 | 3.3 (s, broad), 5.85 (s), 6.30 (m), B | 350 (66), 366 (59) | |
| 22a | $CH_3C(N{=}N)CH_2CH(C_6H_5)COOH$ | B | 47 | 73.5–75 (methanol–water) | 64.69 | 5.92 | 13.72 | 64.64 | 6.20 | 13.56 | 3.4 (m), 5.95 (s), 6.30 (w), C | 346 (66), 361 (51) | |
| 22b | $HOOCCH_2CH_2C(N{=}N)CH_2CH_2COOH$ | B | 28 | 121–123 (water) | 45.16 | 5.41 | 15.05 | 45.03 | 5.49 | 15.01 | 3.3 (s), 5.80 (vs), 5.85 (vs), 6.30 (m, sharp), 7.82 (s, sharp), 10.7 (s), D | 345 (58), 362 (39) | |
| 31, $n = 0$ | $CH_3C(N{=}N)CH(OC_2H_5)_2$ | A<br>B | 41<br>40 | 37 (8) | 53.14 | 8.92 | 17.71 | 53.48 | 9.12 | 18.30 | 3.47 (m), 6.25 (w), 9.0 (m), 9.4 (m, broad), A | 331 (40), 341 (35) | 1.07 |
| 31, $n = 1$ | $CH_3C(N{=}N)CH_2CH(OCH_3)_2$ | A<br>B | 22<br>26 | 45 (12) | 49.98 | 8.38 | 19.44 | 50.48 | 8.77 | 19.44 | 3.55 (m, sharp), 6.30 (m), 8.90 (s), 9.3–9.5 (s, broad), B | 347 (58), 361 (46) | 1.07 |
| 31, $n = 2$ | $CH_3C(N{=}N)CH_2CH_2CH(OC_2H_5)_2$ | A | 40 | 43 (2.5) | 58.03 | 9.75 | 15.04 | 58.22 | 10.12 | 14.46 | 3.45 (s), 6.3 (m), 8.85 (s), 9.35 (s), B | 348 (72), 365 (56) | |
| 19, $n = 1$ | $CH_3C(N{=}N)CH_2CH_2OH$ | A<br>B | 35<br>40 | 32 (3)<br>44 (6) | 47.98 | 8.06 | 27.98 | 48.24 | 8.75 | 27.54 | 3.0 (s), 6.28 (s), 9.5 (s), B | 347 (55), 365 (40) | 1.04 |
| 19, $n = 2$ | $CH_3C(N{=}N)CH_2CH_2CH_2OH$ | A | 39 | 42 (2.5) | 52.61 | 8.83 | 24.55 | 52.78 | 8.96 | 23.93 | 2.9 (s, broad), 6.28 (s), 9.5 (broad) 9.5, B | 348 (63), 365 (51) | |

[a] A, iodine–triethylamine oxidation; B, silver oxide oxidation. [b] A, $CHCl_3$ solution; B, film; C, Nujol mull; D, KBr disk. [c] In methanol solution. [d] In at least one experiment, the crude diazirine prepared by iodine oxidation was purified through the acid chloride. See text.

hydrolysis of the acyl halide was thence straightforward.

Amines could be obtained not only by displacement of the tosylate as previously mentioned, but also by application of the Hofmann hypobromite reaction (synthesis of **28**) and by diborane reduction of disubstituted amides (synthesis of **29**). However, diborane reduction of the unsubstituted amide **26** (R = H) was not successful because of concommitant reduction of the diazirine function. On the other hand, diborane reduction of the carboxylic acid group was sufficiently rapid to allow the clean reduction of **22** ($n = 2$) to the diazirine alcohol **19** ($n = 2$).

The homologous series of acetals **31** could be transformed to the corresponding diazirine aldehydes **32** when $n > 0$. However, **31** ($n = 0$) was inert to dilute acid, as in the corresponding keto acetal **30** ($n = 0$).

In general, the various diazirines were found to be stable to storage of several months or longer, the only exceptions being the $C_4$ and $C_5$ acids **22** ($n = 1, 2$), which darkened considerably and partially liquefied even when stored at $-10°$ in the solid state.

The electron-withdrawing character of the diazirine group is apparent when the $pK_a$ of a series of diazirine acids is considered (see Table II). The effect on the carboxylic acid proton is roughly comparable with that exerted by a keto group or a chlorine atom, and is still detectable through three and possibly four intervening methylene groups. (It is interesting that, in one instance, 4,4-azo-2-phenylpentanoic acid (**22a**), a cumulative effect obtains when the acid is substituted by both an $\alpha$-phenyl and a $\gamma$-azo function.) A further manifestation of this electron-withdrawing effect is observed by comparison of 1-amino-3,3-azobutane hydrochloride (**28** HCl salt, $pK_a = 9.35$) with 1-aminobutane hydrochloride ($pK_a = 10.7$). Probably the inability to hydrolyze the azo acetal **31** ($n = 0$) in the presence of dilute acid can also be attributed to this effect.

TABLE II

EFFECT OF THE DIAZIRINE GROUP AND OTHER REPRESENTATIVE FUNCTIONAL GROUPS ON THE $pK_a$[a] OF ALIPHATIC ACIDS

$CH_3—X—(CH_2)_n—COOH$

| X | $pK_a$ $n = 1$ | 2 | 3 | 4 |
|---|---|---|---|---|
| $CH_2$ | 4.8 | 4.8 | 4.8 | 4.8 |
|  | 3.9 | 4.4[b] | 4.5 | 4.7 |
|  | 3.6 | 4.6 | 4.8 | |
|  | 4.2 | 4.4 | 4.6 | |
|  | 4.4 | 4.7 | 4.8 | |

[a] The $pK_a$'s were determined by titration in aqueous solution at 25°. [b] The $pK_a$ of compound **22a**, containing an $\alpha$-phenyl group, is 3.9. [c] The $pK_a$ of $\alpha$-phenylpropionic acid is 4.3.

The weak, but characteristic, ultraviolet absorption of the diazirine group occurs as a double peak at 351 ± 1 mμ and 368 ± 2 mμ.[1] We have noted a hypsochromic shift of up to 27 mμ in the presence of neighboring electron-withdrawing groups, the effect diminishing rapidly as more than one methylene group intervenes between the functions. In the infrared, these groups cause a weak hypsochromic shift (at most 0.04 μ) of the diazirine absorption. The reciprocal effect by the diazirine function on the neighboring groups is even weaker. These infrared effects disappear entirely with the intervention of more than one methylene group.

In previous reports,[1,12] it was shown that the diazirine group exhibits a very high degree of magnetic anisotropy. This effect does not carry over to the more flexible noncyclic aliphatic series. In fact, relative to methylene, the diazirine function exhibits virtually no shielding or deshielding effect on adjacent methyl groups, resonance for the protons of which was noted at δ 1.05 ± 0.02 [four out of five examples; in the fifth, 3,3-azobutanal (**32**, $n = 1$), it was at 1.15].

## Experimental Section

**General.**—Melting points were measured in a Mel-Temp apparatus in open capillary tubes and are corrected. Ultraviolet spectra were determined with a Cary recording spectrophotometer (Model 14), and infrared spectra were determined on a Perkin-Elmer spectrophotometer (Model 21). Nmr spectra were obtained on a Varian Model A-60 spectrometer in deuteriochloroform using tetramethylsilane as internal standard. Solutions were dried with anhydrous sodium sulfate except where noted and evaporations were carried out at reduced pressure. Boiling points are uncorrected.

**Oxidation of 1,1-Hydrazicyclohexane (2). Titration with Iodine.**—The direct titrations of 1,1-hydrazicyclohexane were carried out in appropriately buffered aqueous solutions using 0.094 *N* methanolic iodine solution at 24°. The pH's of the solutions were determined at the beginning and end of the titrations and were found to vary not more than 0.4 pH units, becoming progressively more acidic. The titrations were followed either by the appearance of a persistent iodine color (using starch indicator) or potentiometrically using a platinum electrode *vs.* a calomel electrode.

For the study of the catalytic process, appropriately buffered aqueous solutions of 1,1-hydrazicyclohexane were treated with 0.05 mol equiv of iodine at 24°, aliquots were removed and made strongly basic with aqueous sodium hydroxide, and the remaining diaziridine was titrated potentiometrically using 0.094 *N* methanolic iodine solution. After correction for the immediate rapid consumption of 0.05% of the initial diaziridine, the disappearance of diaziridine follows first-order kinetics. The results are summarized in Tables III and IV.

TABLE III

TITRATION OF 1,1-HYDRAZICYCLOHEXANE (2)

| Expt no. | pH | Elapsed time for titration, min | Mol equiv of $I_2$ consumed |
|---|---|---|---|
| 1 | 11.0 | 30+ | 0.99 |
| 2 | 11.0 | 3 | 1.00 |
| 3 | 8.9 ± 0.1 | 30+ | 1.00 |
| 4 | 8.9 ± 0.1 | 3 | 1.01 |
| 5 | 6.5 ± 0.2 | 30+ | 0.85 |
| 6 | 5.0 ± 0.1 | 7 | 0.62 |
| 7 | 5.0 ± 0.1 | 5 | 0.77 |
| 8 | 5.0 ± 0.1 | 2.0 | 1.10 |
| 9 | 5.0 ± 0.1 | 1.5 | 1.15 |

**General Method for the Synthesis of Diazirines. Synthesis of 3,3-Hydrazibutanol-1.**—A solution of 11.2 g (0.13 mol) of 3-ketobutanol-1 (**18**, $n = 1$) in 200 ml of liquid ammonia was stirred for a 5-hr period at reflux temperature. The solution was then cooled in a Dry Ice–acetone bath and a solution of 16 g (0.15 mol) of hydroxylamine-O-sulfonic acid in 100 ml of methanol was added over a 30-min period. The cooling bath was removed, the mixture was stirred at reflux (Dry Ice condenser) for about an hour, and the ammonia was allowed to evaporate overnight. The

TABLE IV

RATE OF DISAPPEARANCE OF DIAZIRIDINE AT 24° USING 0.05 MOL EQUIV OF $I_2$

| Expt no. | pH | Catalyst | Mol equiv | Time, min | Mol of diaziridine remaining |
|---|---|---|---|---|---|
| 1 | 2.6 ± 0.1 | $I_2$ | 0.05 | 0.0 | 0.585 |
| | | | | 0.7 | 0.36 |
| | | | | 1.5 | 0.25 |
| | | | | 2.5 | 0.17 |
| | | | | 5.0 | 0.055 |
| | | | | 10.0 | 0.01 |
| 2 | 5.0 ± 0.2 | $I_2$ | 0.05 | 0.0 | 0.59 |
| | | | | 2 | 0.47 |
| | | | | 5 | 0.38 |
| | | | | 10 | 0.24 |
| | | | | 20 | 0.132 |
| | | | | 30 | 0.06 |
| 3 | 6.8 ± 0.1 | $I_2$ | 0.05 | 0 | 0.59 |
| | | | | 5 | 0.56 |
| | | | | 20 | 0.55 |
| | | | | 80 | 0.52 |
| | | | | 125 | 0.50 |
| 4 | 9.1 | $I_2$ | 0.05 | 0 | 0.58 |
| | | | | 10 | 0.56 |
| | | | | 20 | 0.56 |
| | | | | 100 | 0.55 |
| 5 | 5.0 ± 0.2 | KI | 0.8 | 0 | 0.54 |
| | | | | 5 | 0.03 |
| 6 | 5.0 ± 0.2 | KI | 0.1 | 0 | 0.54 |
| | | | | 5 | 0.26 |
| | | | | 20 | 0.03 |

resulting slurry was filtered and the filter cake was washed with several portions of methanol. All washings were combined with the original filtrate and the solution (about 200 ml) was concentrated to about 60 ml; no odor of ammonia could be detected. The 3,3-hydrazibutanol thus prepared was oxidized without further work-up.

**Preparation of Diazirines by Oxidation of Diaziridines. Method A. With Iodine–Triethylamine. Synthesis of 3,3-Azobutanol-1** (19, $n$ = 1).—The crude methanolic solution of 3,3-hydrazibutanol-1 (prepared as described above from 40 g, 0.45 mol, of 3-ketobutanol-1) was diluted with 200 ml of methanol, cooled in an ice bath, and treated with 60 ml of triethylamine; this was followed by addition of solid iodine at a rate of ~1 g/min. Iodine reduction was virtually instantaneous. After 68 g (0.27 mol) of iodine had been added, the red color of excess iodine persisted. The solution was concentrated to about 250 ml and then diluted to about 800 ml with brine. The solution was extracted with several portions of ether, and the combined extracts were dried and concentrated to about 50 ml. The residue was distilled, yielding 16.0 g (35%) of 3,3-azobutanol-1 (19, $n$ = 1) with bp 32° (0.3 mm).

**Method B. Oxidation with Silver Oxide.**—The methanolic solution of 3,3-hydrazibutanol-1, prepared as described above, was added with stirring and ice cooling during 10 min to a suspension of silver oxide in water (freshly prepared by the addition of a solution of 34 g of silver nitrate in 100 ml of water to 200 ml of 4% aqueous sodium hydroxide). The resulting slurry was filtered through Celite[16] and the filtrate was treated with brine. The precipitated silver chloride was removed by a second filtration through Celite.[16] The colorless solution was extracted with several portions of ether and methylene chloride. The combined extracts were concentrated to about 40 ml and the residue was distilled, yielding 5.14 g (40%) of 3,3-azobutanol-1 with bp 42.5–44° (5.5–6 mm). This material was spectroscopically identical with that prepared by method A.

**Tropinone Oxime** (12). **Attempted Preparation of 5,5-Azotropane** (13, X = $NCH_3$).—A solution of 6.21 g of tropinone (11, X = $NCH_3$) in 20 ml of methanol was added to 40 ml of liquid ammonia and stirred at reflux for 1.5 hr. The solution was then treated with 13.2 g of hydroxylamine-O-sulfonic acid as described above for the preparation of diaziridines to give a brown oil which on partition chromatography afforded 740 mg of a single crystalline product, recrystallized from methylene chloride–hexane to yield 592 mg of tropinone oxime as short blunt needles: mp 111–113°;[17] uv end absorption only; ir (KBr) 3.38, 3.55, 6.04 (weak), 9.94, 10.70, 13.25 μ.

*Anal.* Calcd for $C_8H_{14}N_2O$: C, 62.31; H, 9.14; N, 18.17; mol wt, 154. Found: C, 61.98; H, 9.42; N, 17.94; mol wt, 170 ($CHCl_3$).

A 3-g sample of the crude mixture oxidized by method B of the general procedure afforded 8 mg of tropinone, mp 40–41°, as the only characterizable product.

**4,4-Azocyclohexanone Oxime** (17).—A solution of 890 mg of cyclohexane-1,4-dione (15) was added to 100 ml of methanol saturated at 0° with ammonia, and the solution was stirred 1.5 hr at 0° ± 2°. A solution of 1.80 g of hydroxylamine-O-sulfonic acid in 10 ml of methanol was added dropwise and the resulting solution was stirred 2.5 hr at 0° and filtered. The filtrate was evaporated to a volume of about 50 ml and oxidized according to oxidation method B. The oily residue obtained after evaporation of the solvent was chromatographed on 7 g of silica gel. Elution with 150 ml of 5% ether in benzene afforded 66 mg (5.4%) of product, which was recrystallized from ether–hexane in fine needles, 23 mg, mp 88–89°. The compound is polymorphic, the needles initially obtained slowly changing to sugar-like crystals: mp 87–98°; uv $\lambda_{max}^{MeOH}$ 347 mμ (ε 97), 362 (83); ir (KBr) 3.15, 3.25, 6.0, 6.34 μ.

*Anal.* Calcd for $C_6H_9N_3O$: C, 51.78; H, 6.52; N, 30.20. Found: C, 52.15; H, 6.57; N, 30.30.

**4,4-Azopentanol-1** (19, $n$ = 2) **(by Diborane Reduction of 4,4-Azopentanoic Acid).**—A stirred solution of 918 mg of 4,4-azopentanoic acid (22, $n$ = 2) in 35 ml of dry tetrahydrofuran was treated dropwise with 5 mmol of diborane in tetrahydrofuran. The resulting solution was stirred at room temperature for 0.5 hr, water was added cautiously to destroy excess reagent, and the solution was diluted with brine. The layers were separated and the aqueous layer was extracted with two small portions of ether. The combined organic portions were washed with aqueous sodium bicarbonate and brine, then dried, and evaporated. The residue was distilled, yielding 306 mg of a colorless, mobile liquid with bp 61° (5 mm). This product was spectroscopically identical with that prepared from 4-ketopentanol-1 (18, $n$ = 2) by the general method described for the preparation of diazirines (Table I).

**3,3-Azo-1-(*p*-toluenesulfonyloxy)butane** (20).—A solution of 10.1 g of 3,3-azobutanol-1 (19, $n$ = 1) in 80 ml of pyridine was cooled and 20 g of *p*-toluenesulfonyl chloride was added in portions. The solution was stirred at 0–10° for 2 hr and allowed to stand at 4° for 16 hr, and poured into a mixture of 150 ml of concentrated hydrochloric acid and 600 g of ice. The oily layer was extracted into ether and the ethereal extract was washed with cold dilute hydrochloric acid, cold dilute sodium hydroxide, and brine and then dried. After evaporation of the ether, the residue was recrystallized from ether–petroleum ether to afford 17.55 g (70%) of product with mp 25.5–28°; uv $\lambda_{max}^{MeOH}$ 225 mμ (ε 1200), 256–273 (multiplet, 400–550), 342 (75), 360 (57); ir (KBr) 6.25, 8.42, 8.5, 10.3, 11.1, 15.2 μ.

*Anal.* Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.96; H, 5.55; N, 11.02; S, 12.59. Found: C, 51.65; H, 5.70; N, 11.02; S, 12.26.

**N-Methyl-N′-(3,3-azobutyl)piperazine** (23).—A solution of 5 g of 3,3-azo-1-(*p*-toluenesulfonyloxy)butane (20) and 4 ml of N-methylpiperazine in 40 ml of dimethylformamide was heated at 82° ± 2° for 6 hr, then held 16 hr at room temperature. The solution was diluted with 150 ml of water, acidified (HCl) to congo red, and extracted with ether. The aqueous phase was made strongly basic (NaOH) and extracted with several portions of ether. The combined extracts were dried (KOH), the ether was evaporated, and the residue was distilled, the fraction boiling at 33–50° (2–15 mm) being collected. Redistillation, 47° (2 mm), afforded 1.48 g (40%) of amine 23: uv $\lambda_{max}^{MeOH}$ 349 mμ (ε 55), 364 (37); ir (neat) 3.40, 3.56, 6.26, 7.80, 8.60, 9.90 μ.

*Anal.* Calcd for $C_9H_{18}N_4$: C, 59.34; H, 9.89; N, 30.86. Found: C, 59.64; H, 9.70; N, 30.08.

**3,3-Azobutyric Acid** (22, $n$ = 1).—To a solution of 16 g of chromic acid in 180 ml of acetic acid–water (5:1) at 3° was added dropwise 7.0 g of 3,3-azobutanol-1 (19, $n$ = 1). The solution was stirred 45 min at 3°, then at room temperature overnight. The solution was diluted with 500 ml of brine and extracted with

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(17) Lit. 110–111°: E. Otiai, K. Tuda, and K. Murakami, *J. Pharm. Soc. Jap.*, **57**, 407 (1937).

several portions of ether. The combined extracts were washed once with brine and the solvent was evaporated. The residue was distilled to afford 2.8 g (35.1%) of product with bp 44° (0.15 mm) as a yellow liquid. Redistillation, 48° (0.18 mm), afforded a colorless oil that crystallized at −20°: mp −2–3°; uv $\lambda_{max}^{MeOH}$ 343 mμ (ε 66), 359 (51); ir (neat) 3.3, 5.80, 6.26 μ. This material is unstable, becoming yellow after standing at room temperature for several hours. Storage for several weeks in the solid state at −10° affords a bright yellow oily solid.

*Anal.* Calcd for $C_4H_6N_2O_2$: C, 42.10; H, 5.30; N, 24.55. Found: C, 43.88; H, 6.19; N, 23.48.

**4,4-Azopentanoyl Chloride (24, $n$ = 2).**—A solution of 12.4 g of 4,4-azopentanoic acid (**22**, $n$ = 2) and 15.4 g of oxalyl chloride was allowed to stand for 16 hr protected from atmospheric moisture. The solution was distilled, affording 12.4 g (88%) of product with bp 38° (5 mm); uv $\lambda_{max}^{hexane}$ 341 mμ (ε 84), 358 (80); ir (neat) 5.57, 5.78, 6.3 μ.

*Anal.* Calcd for $C_5H_7ClN_2O$: C, 40.97; H, 4.81; Cl, 24.17; N, 19.11. Found: C, 41.11; H, 4.90; Cl, 24.15; N, 19.28.

Basic aqueous hydrolysis of this acyl halide afforded a 90% yield of 4,4-azopentanoic acid, identical by boiling point, melting point, and spectral data with the starting 4,4-azopentanoic acid.

**Methyl 4,4-Azopentanoate (25, R = $CH_3$).**—A solution of 8.0 g of 4,4-azopentanoic acid (**22**, $n$ = 2) in 50 ml of methanol was treated with hydrogen chloride and allowed to stand for 16 hr. The solution was poured into dilute sodium bicarbonate solution and extracted with ether. The combined extracts were washed ($NaHCO_3$) and dried. After evaporation of the solvent, the residue was distilled to afford 6.26 g of ester having bp 45° (5.5 mm); uv $\lambda_{max}^{MeOH}$ 346 mμ (ε 60), 362 (50); ir (neat) 5.75, 6.32, 8.35, 8.50 μ.

*Anal.* Calcd for $C_6H_{10}N_2O_2$: C, 50.69; H, 7.09; N, 19.71. Found: C, 51.03; H, 7.36; N, 19.46.

**4,4-Azopentanamide (26, R = H).**—To 160 ml of concentrated ammonium hydroxide at 0° was added slowly with good stirring 17.5 g of 4,4-azopentanoyl chloride (**24**, $n$ = 2), the temperature being kept below 10°. The resulting mixture was extracted with methylene chloride; the extracts were washed with brine and evaporated. The crystalline residue was recrystallized from methylene chloride–hexane to afford 11.9 g of the product: mp 89.5–91°; uv $\lambda_{max}^{MeOH}$ 348 mμ (ε 64), 363 (55); ir (KBr) 2.97, 6.02, 6.11, 6.35 μ (shoulder).

*Anal.* Calcd for $C_5H_9N_3O$: C, 47.23; H, 7.13; N, 33.06. Found: C, 47.04; H, 7.12; N, 33.11.

**N-(4,4-Azopentanoyl)piperidine [26, $(R)_2$ = $(CH_2)_5$].**—To an ice-cooled solution of 5 g of 4,4-azopentanoyl chloride (**24**, $n$ = 2) in 300 ml of benzene was added dropwise 10 ml of piperidine with the temperature maintained below 25°. The mixture was stirred 16 hr, then treated with 60 ml of water, and shaken well; the layers were separated. The organic phase was washed twice with 2 *N* hydrochloric acid and once with dilute sodium bicarbonate and dried. After evaporation of the solvent, the residue crystallized at Dry Ice temperature and was recrystallized from petroleum ether at −20 to −60° to afford 5.25 g of fine needles, with mp 9–11° after drying at high vacuum.

*Anal.* Calcd for $C_{10}H_{17}N_3O$: C, 61.51; H, 8.77; N, 21.53. Found: C, 61.16; H, 8.95; N, 21.14.

**4,4-Azopentanoyl Hydrazide (27).**—A solution of 4.5 g of hydrazine hydrate in 25 ml of methanol was refluxed while 6.8 g of methyl 4,4-azopentanoate (**25**, R = $CH_3$) was added dropwise over a 40-min period. The solution was stirred 30 min at reflux and concentrated at 85° (0.5 mm) to a yellow oil. Upon cooling, the oil solidified to a waxy solid with mp 39–40° (no satisfactory solvent for recrystallization was found); uv $\lambda_{max}^{MeOH}$ 346 mμ (ε 57), 363 (43); ir (KBr) 3.30, 3.40, 6.0 μ (broad).

*Anal.* Calcd for $C_5H_{10}N_4O$: C, 42.24; H, 7.09; N, 39.42. Found: C, 41.56; H, 7.23; N, 36.85.

The maleate salt was recrystallized from ethanol–ether to afford white crystals, mp 90–92°.

*Anal.* Calcd for $C_9H_{14}N_4O_5$: C, 41.85; H, 5.47; N, 21.70. Found: C, 42.18; H, 5.77; N, 21.23.

**1-Amino-3,3-azobutane HCl (28).**—To a solution of sodium hypobromite (prepared by adding 12.50 g of bromine to 100 ml of 3 *N* sodium hydroxide at 5°) was added 6.22 g of 4,4-azopentanamide (**26**, R = H). The solution was stirred 2.5 hr at 0–20°, then warmed slowly to 45°, at which temperature a mild exothermic reaction began, the temperature rising to 60°. The solution was distilled and the distillate (about 20 ml) was collected in 20 ml of 3 *N* hydrochloric acid. The distillate was made strongly basic (NaOH) and extracted with several portions of ether. Treatment of the dried ethereal solution with hydrogen chloride afforded the product as thin glistening plates, 2.49 g (34%), with mp 170–172°; uv $\lambda_{max}^{MeOH}$ 344 mμ (ε 58), 360 (48); ir (KBr) 3.35, 6.3 μ.

*Anal.* Calcd for $C_4H_{10}ClN_3$: C, 35.43; H, 7.43; N, 30.99. Found: C, 35.84; H, 7.81; N, 30.61.

**N-(4,4-Azopentyl)piperidine (29).**—To 16.7 ml of 1 *M* sodium borohydride in tetrahydrofuran cooled in Dry Ice–acetone was added 1.95 g of N-(4,4-azopentanoyl)piperidine [**26**, $(R)_2$ = $(CH_2)_5$] in 10 ml of dry tetrahydrofuran. The temperature remained between 0 and 6° throughout. When the addition was complete, the solution was refluxed 20 min, then cooled in ice, and treated carefully with 2.5 ml of 6 *N* hydrochloric acid. The solution was warmed briefly, diluted with 50 ml of water, made strongly acidic (HCl), and extracted with several small portions of ether. After evaporation of the solvent, the residue was added to 40 ml of 1 *N* hydrochloric acid and the solution was heated on the steam bath for 1.5 hr. The cooled solution was extracted with ether, then made strongly basic with solid sodium hydroxide, and extracted with ether. The dried ethereal extracts were evaporated, and the residue was distilled, yielding 338 mg of the product (18.6%): bp 60–62° (3 mm); uv $\lambda_{max}^{MeOH}$ 349 mμ (ε 59), 365 (95).

*Anal.* Calcd for $C_{10}H_{19}N_3$: C, 66.25; H, 10.57; N, 23.18. Found: C, 66.66; H, 10.78; N, 23.07.

**3,3-Azobutyraldehyde (32, $n$ = 1).**—A solution of 4.86 g of 3,3-azo-1,1-dimethoxybutane (**31**, $n$ = 1) and 0.5 ml of concentrated hydrochloric acid in 30 ml of acetone–water (3:1) was allowed to stand 16 hr at room temperature. The solution was saturated with salt and extracted with ether. The extracts were washed with brine, dried, and evaporated. The residue was distilled, affording 2.0 g (65.2%) of aldehyde, bp 45–56° (35 mm). Redistillation at 49–49.5° (37 mm) afforded a pure sample: uv $\lambda_{max}^{MeOH}$ 344 mμ (ε 25), 360 (20); ir (neat) 5.77, 6.27 μ; nmr δ 1.15 ($CH_3$–).

*Anal.* Calcd for $C_4H_6N_2O$: C, 48.97; H, 6.16; N, 28.55. Found: C, 49.64; H, 7.36; N, 26.30.

The semicarbazide of 3,3-azobutyraldehyde had mp 103–104.5°.

*Anal.* Calcd for $C_5H_9N_5O$: C, 38.70; H, 5.85; N, 45.14. Found: C, 38.73; H, 6.00; N, 45.24.

**Registry No.**—**12**, 1515-26-0; **17**, 25055-81-6; **19**, $n$ = 1, 25055-82-7; **19**, $n$ = 2, 16297-94-2; **20**, 25055-84-9; **22**, $n$ = 1, 16297-95-3; **22**, $n$ = 2, 25055-86-1; **22**, $n$ = 3, 16297-97-5; **22**, $n$ = 4, 25080-63-1; **22a**, 16297-96-4; **22b**, 16297-98-6; **23**, 25055-89-4; **24**, $n$ = 2, 25055-90-7; **25**, R = $CH_3$, 25055-91-8; **26**, R = H, 25055-92-9; **26**, $(R)_2$ = $(CH_2)_5$, 25055-93-0; **27**, 25055-94-1; maleate salt of **27**, 25062-48-0; **28**, 25055-95-2; **29**, 25055-96-3; **31**, $n$ = 0, 25055-97-4; **31**, $n$ = 1, 25055-98-5; **31**, $n$ = 2, 23902-18-3; **32**, $n$ = 1, 25056-00-2; semicarbazide of **32**, $n$ = 1, 25056-01-3.

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