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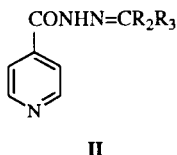
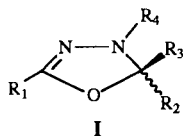
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1,3,4-Oxadiazolines **I**, in which substituent groups R_1 through R_4 may be varied through appropriate choice of precursor reactants, can be prepared in good yields and purity by convenient cyclizations of acyl-hydrazones with anhydrides. The reactions can be effectively monitored by salient changes in the infrared spectra. The oxadiazolines are stable materials and thus serve as suitable derivatives for the chemical characterization of such tuberculostatic Schiff bases as **IIa-c**.

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Oxadiazolines **I** represent an interesting and less common class of five-membered ring heterocycles. With a high ratio of heteroatoms to carbons, they possess the potential for high lability and novel reactions [1-3]. Since a report on these compounds appeared in the literature some time ago [5], not much further work has been done in a systematic way on the preparation of 3-acyl-1,3,4-oxadiazolines, their reactivity or their determination by reliable spectrometric methods. As heterocyclic systems which have not been investigated in depth, these materials are of theoretical appeal in their own right; but they may also serve as sources *in situ* of acid hydrazides in certain



synthetic procedures [1]. Our regard for this family of compounds came about as the result of our need for dependable chemical characterization data on tuberculostatic Schiff base derivatives of isonicotinic acid hydrazone, such as **II**, for which melting point determinations are often complicated by the effects of polymorphism or solvents of crystallization [4].

We now report that such Schiff bases may be readily converted to their congener oxadiazolines in good yield by treatment with an appropriate anhydride followed by a simple work-up procedure. Our results on the preparation of these materials are summarized in the Table. We found, for example, that the reaction of **IIa** ($R_2 = R_3 = \text{CH}_3$) with neat propionic anhydride under reflux for an hour produced **Ib** in 85% yield. The pattern of substitution at each of the positions available for variation on the five-membered ring may be controlled by choosing the appropriate progenitor reactants: the anhydride (3-substitution), the acid hydrazone (5-substitution) and the carbonyl compound (2-substitutions).

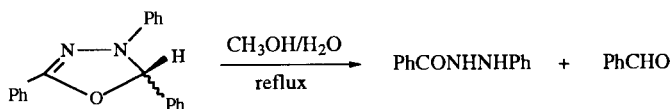
Of particular interest was the convenience with which the progress of the reaction could be monitored using infrared

Table
Preparation of Oxadiazolines

Entry	Compound	R_1	R_2	R_3	R_4	% Yield
1	Ia	4-pyr	CH_3	CH_3	COCH_3	99
2	Ib	4-pyr	CH_3	CH_3	COCH_2CH_3	85
3	Ic	4-pyr	--- $(\text{CH}_2)_5$ ---		COCH_3	87
4	Id	Ph	CH_3	CH_3	COCH_3	96
5	Ie	Ph	CH_3	CH_3	COCH_2CH_3	95
6	If	Ph	Ph	H	COCH_3	98
7	Ig	CH_3	Ph	H	COCH_3	96

spectroscopy. Thus the conversion of **IIa** (*Anal.* Calcd. for $\text{C}_9\text{H}_{11}\text{N}_3\text{O}$: C, 61.00; H, 6.25. Found: C, 60.95; H, 6.21.) to **Ib** (*Anal.* Calcd. for $\text{C}_{12}\text{H}_{15}\text{N}_3\text{O}_2$: C, 61.79; H, 6.48. Found: C, 62.16; H, 6.67.) was accompanied by several dramatic changes in the infrared spectrum, making it possible to readily assess preparative reactions. These diagnostic changes included the disappearance of the N-H stretch near 3180 cm^{-1} , loss of the intense hydrazone carbonyl band near 1654 cm^{-1} , loss of the unusually strong N-H bend near 1535 cm^{-1} , and the production of a strong new band at 1675 cm^{-1} in the oxadiazoline. These spectrometric data facilitate the characterization of difficult Schiff bases in the presence of the effects noted above (see Experimental).

The 3-acyl-1,3,4-oxadiazolines appear to be stable substances and could be maintained on the shelf in pure form for months without serious decomposition. Previous reports have indicated the ready ring-opening reaction of at least one member of this class under hydrolytic conditions. In this way, treatment of **I** ($R_1 = R_2 = R_4 = \text{Ph}$, $R_3 = \text{H}$) with boiling aqueous methanol led to rapid formation of the related phenylhydrazone [6]. On the other hand, the



present compounds appear not to experience ring-opening in aqueous methanol. In a representative example, compound **Ia** was mixed with aqueous methanol and refluxed

for an hour. Work-up of the reaction gave only recovery of the starting material (see Experimental).

In summary, 3-acyl-1,3,4-oxadiazolines can be prepared conveniently and in good yield by the reactions of acylhydrazones with anhydrides. This process can be monitored effectively by clear-cut changes in the infrared spectra during reaction. The acyloxadiazolines appear to be stable compounds, less sensitive to hydrolysis than their unacylated counterparts, and are in this way suitable for chemical characterization of their Schiff base precursors.

EXPERIMENTAL

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee. Melting points were taken in open capillary tubes using a Mel-Temp apparatus and are corrected. Infrared spectra were recorded on a Perkin-Elmer Model 1600 Fourier transform spectrophotometer as Nujol mulls. Anhydrides were obtained from Aldrich Chemical Company and were used as received. Acylhydrazones were available from literature methods, as cited in the individual procedures which follow, or as more generally described in Vogel [10]. **Safety Notes:** Gloves were worn, and the reactions were performed in the hood. In general, any scale-up of preparations of compounds with relatively high proportions of nitrogen was done with due caution. No specific safety problems were associated with the methods given below.

2,2-Dimethyl-3-acetyl-5-(4-pyridyl)-1,3,4-oxadiazoline (**Ia**).

To the isonicotinoylhydrazone of acetone (**IIa**, 0.417 g, 2.36 mmoles, mp 161-162°, lit mp [7] 160-161°. *Anal.* Calcd. for $C_9H_{11}N_3O$: C, 61.00; H, 6.25. Found: C, 60.95; H, 6.21.) was added acetic anhydride (10 ml). The mixture was brought to the boiling point, and refluxing was continued for an hour. The hot mixture was turned out onto a watchglass and allowed to air dry in the hood overnight to give 0.511 g (99%) of **Ia**, hexagonal plates, mp 117-118°, lit mp [9] 109-111°; ir (Nujol): ν 3032, 1665, 1625, 1598, 1550, 1505, 1085, 1047, 1039, 968, 945, 839, 826, 735 cm^{-1} .

2,2-Dimethyl-3-propionyl-5-(4-pyridyl)-1,3,4-oxadiazoline (**Ib**).

To the isonicotinoylhydrazone of acetone (**IIa**, 0.355 g, 2.01 mmoles) was added propionic anhydride (10 ml). The mixture was brought to the boiling point, and refluxing was continued for an hour. After 45 minutes of reflux, the sample had become a deep orange color. The hot mixture was turned out onto a watchglass and allowed to air dry in the hood overnight. The material thus obtained (100% of theory) showed the expected infrared bands, and only a small amount of the anhydride remained. The material was taken up in ether (30 ml), and the ether solution was stirred vigorously over 10% aqueous sodium bicarbonate solution for 90 minutes, during which time a substantial amount of the color passed into the aqueous layer. The ether was drawn off, and the aqueous portion was extracted with 3 x 15 ml portions of ether. The combined ether layers were dried over anhydrous magnesium sulfate, filtered and evaporated on a watchglass in the hood to give 0.397 g (85%) of **Ib**, semisolid mass, not improved in crystallinity by difficult recrystallizations from

aqueous ethanol; ir (Nujol): ν 3030, 1676, 1625, 1597, 1551, 1498, 1093, 840, 826 cm^{-1} .

Anal. Calcd. for $C_{12}H_{15}N_3O_2$: C, 61.79; H, 6.48. Found: C, 62.16; H, 6.67.

2,2-Pentamethylene-3-acetyl-5-(4-pyridyl)-1,3,4-oxadiazoline (**Ic**).

Cyclohexanone isonicotinoylhydrazone (**IIb** ($R_2, R_3 = (CH_2)_5$), 0.502 g, 2.31 mmoles), prepared according to the method of Shchukina [7], was placed in a reflux apparatus with toluene (10 ml). Acetic anhydride (1 ml, 11 mmoles) in toluene (5 ml) was added, and the mixture was brought to the boil, giving a clear yellow solution. Refluxing was continued for a total of 8.5 hours, at which point the hot mixture was turned out onto a watchglass. After evaporation, compound **Ic** was obtained (0.52 g, 87%), mp 106-107° (from petroleum ether), lit mp [5] 104-105°; ir (Nujol): ν 3030, 1678, 1628, 1598, 1552, 1504, 892, 846, 827, 734, 665 cm^{-1} .

2,2-Dimethyl-3-acetyl-5-phenyl-1,3,4-oxadiazoline (**Id**).

Freshly prepared acetone benzoylhydrazone (0.61 g, 3.47 mmoles) was mixed with an excess (10 ml) of acetic anhydride in an apparatus fitted for reflux. The mixture was boiled for an hour, turned out onto a watchglass and allowed to air dry to give **Id** (0.73 g, 96%), mp 48-49°, lit mp [5] 49-50°; ir (film): ν 3061, 1666, 1632, 1578, 1241, 1083, 1049, 1024, 967, 854, 771, 692, 668, 626 cm^{-1} .

Anal. Calcd. for $C_{12}H_{14}N_2O_2$: C, 66.04; H, 6.47. Found: C, 66.08; H, 6.57.

2,2-Dimethyl-3-propionyl-5-phenyl-1,3,4-oxadiazoline (**Ie**).

Freshly prepared acetone benzoylhydrazone (1.19 g, 6.76 mmoles) was mixed with an excess (10 ml) of propionic anhydride in an apparatus fitted for reflux. The mixture was boiled for an hour and then allowed to evaporate on a watchglass to give tan crystals of **Ie** (1.49 g, 95%). The crystals were washed with sparing amounts of petroleum ether to obtain the analytical sample: mp 69-70°; ir (Nujol): ν 3060, 1667, 1632, 1578, 1241, 1060, 848, 773, 695, 667 cm^{-1} .

Anal. Calcd. for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.94. Found: C, 67.48; H, 7.21.

2,5-Diphenyl-3-acetyl-1,3,4-oxadiazoline (**If**).

Benzaldehyde benzoylhydrazone (0.902 g, 4.03 mmoles) was mixed with acetic anhydride (10 ml) and refluxed for an hour. The mixture was then evaporated on a watchglass in the hood to give **If** (1.05 g, 98%); the analytical sample was obtained by washing the product with sparing amounts of absolute ethanol, mp 91-92° (from aqueous ethanol), lit mp [5] 92-94°; ir (Nujol) ν 3060, 1663, 1624, 1576, 1330, 1289, 1262, 1217, 1062, 1022, 961, 882, 837, 761, 688, 666 cm^{-1} .

2-Phenyl-3-acetyl-5-methyl-1,3,4-oxadiazoline (**Ig**).

To benzaldehyde acetylhydrazone (0.71 g, 4.38 mmoles) was added acetic anhydride (5 ml), and the mixture was refluxed for 45 minutes. The reaction mixture was evaporated to dryness on a watchglass in the hood to give **Ig** (0.85 g, 96%), mp 93°, lit mp [5] 90-92°; ir (Nujol) ν 3060, 1722-1698 (broad), 1615, 1604, 1575, 1415, 1315, 1267, 1227-1210 (broad), 1110, 1052, 1037, 966, 866, 756, 738, 687 cm^{-1} .

Attempted Ring-Opening Reaction of Ia.

The oxadiazoline Ia (0.191 g) was weighed into a flask fitted for reflux, and aqueous methanol (methanol:water as 1:1, 10 ml) was added. The clear colorless solution was boiled for an hour, then allowed to air dry over several days, giving a white crystalline solid (0.144 g), the infrared spectrum of which was identical to that of Ia, as described above.

REFERENCES AND NOTES

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- [4] The same compound is often reported in multiple literature sources with satisfactory analytical data but with substantially different melting points. As an example, in careful reports from two different laboratories, compound II ($R_2 = H$, $R_3 = p\text{-CH}_3\text{OPh}$), is stated to have mp 126-127°C [7] and mp 171.5-173.5°C [8]. In numerous preparative methods in the literature, the Schiff bases have been formed in different solvents and by divergent techniques from the reactions of isonicotinic acid hydrazide with carbonyl compounds. The problems associated with use of melting points to characterize hydrazones have been the subjects of previous commentary: M. J. Hearn and K. G. Sy, *Bull. Soc. Chim. Belg.*, **98**, 339 (1989); M. Behforouz, J. L. Bolan and M. S. Flynt, *J. Org. Chem.*, **50**, 1186 (1985).
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