[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE COLLEGE OF ARTS AND SCIENCES OF THE UNIVERSITY OF LOUISVILLE]

Dimethylhydrazones of Aliphatic, Aromatic, and Heterocyclic Aldehydes and Their Infrared Absorption Characteristics

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A series of 37 aldehyde dimethylhydrazones have been prepared as isosteres of the tumor-growth retardant 3,3-dimethyl-2-phenyltriazene. Infrared absorption data clearly establish a band at 1640–1590 cm.$^{-1}$ characteristic of the C=N linkage and, as the strongest absorption in the spectra, a band at 1070–960 cm.$^{-1}$ which can be correlated with the electron releasing or electron attracting character of the substituents in the benzene ring of the aromatic aldehyde dimethylhydrazones.

The observation that 3,3-dimethyl-1-phenyltriazene, $C_6H_5N{=}N{-}N(CH_3)_2$, is an effective material for the retardation of tumor growth[1] suggested that the isosteric grouping, $>C{=}N{-}N(CH_3)_2$, might confer a similar activity on the aldehyde dimethylhydrazones in which the group is found. This class of compounds is practically completely unknown. The only previously recorded examples are the dimethylhydrazones of benzaldehyde,[2] *p*-isopropylbenzaldehyde,[2] furfural,[2] cyclohexanal,[2] formaldehyde,[3] and acetaldehyde.[3] Thirty-seven additional derivatives have now been prepared and their properties are described in the tables along with infrared absorption characteristics.

The availability of infrared data for these compounds makes it possible to establish new structural correlations for the atomic groups present. The series of aliphatic aldehyde dimethylhydrazones all show an absorption in the 1610 cm.$^{-1}$ region which is attributable to the C=N stretching vibrations. This is apparently the first location of the frequency (C=N) in compounds containing the $>C{=}N{-}N<$ group. In the series of dimethylhydrazones of formaldehyde-acetaldehyde-acetone the band shifts from 1585 cm.$^{-1}$ to 1610 cm.$^{-1}$ to 1639 cm.$^{-1}$. A similar shift occurs with increasing methyl substitution on the C=C band and can be attributed to either a weighting effect or the electron release characteristics of the methyl group. For the glyoxal derivative, the band is split into bands at 1678 cm.$^{-1}$ and 1550 cm.$^{-1}$, presumably as a result of mechanical interaction or resonance between the two identical C=N bonds in which one band is raised, the other lowered with the average at 1614 cm.$^{-1}$.[4] Conjugation with the benzene ring would probably place this absorption band in the 1590 cm.$^{-1}$ region which is intermediate between the 1600 cm.$^{-1}$ and 1580 cm.$^{-1}$ benzene C=C absorption bands. As a result the C=N band is obscured in the aromatic aldehyde derivatives, and a similar situation exists in the heterocyclic series. These types show two characteristic absorption bands at 1613–1587 cm.$^{-1}$ and 1580–1555 cm.$^{-1}$ and, in about a fourth of the examples, a third band at 1681–1616 cm.$^{-1}$.

The presence of two absorption bands centered at about 1471 cm.$^{-1}$ and 1450 cm.$^{-1}$ in nearly all of the dimethylhydrazones are characteristic carbon-hydrogen deformation modes associated with methyl (and methylene where present) groupings. These along with strong, characteristic C—H absorption bands in the 2941–2778 cm.$^{-1}$ range are of confirmatory interest. Additional characteristic bands occurring in spectra of all types of dimethylhydrazones are found near 1282 cm.$^{-1}$, 1136 cm.$^{-1}$, and 870–905 cm.$^{-1}$. The last probably results from contributions from the C—H out of plane deformation also characteristic of the aldehyde CHO group[5] and the N—N stretching band,[6] both of which are known to occur in this region. It is present in 36 out of 38 compounds. The two exceptions are the acetaldehyde derivative and the acetone derivative.

Perhaps the strongest, and therefore most characteristic, band observed with every one of the 38 derivatives prepared is the 1066–963 cm.$^{-1}$ region. Shifts in this band can be correlated with the electron releasing and attracting nature of the substituents in the aryl groups. Such correlations have been recorded relating shifts in the carbonyl absorption band to Hammett *sigma* values for substituted benzoic acid,[7] dibenzoyl peroxides,[8] and acetophenones.[9] Fig. 1 shows a plot of the wave length at which this absorption band occurs *vs.* Hammett *sigma* values for fifteen *m*- and *p*-substituted aryl and the pyridine aldehydes. The

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TABLE I

DIMETHYLHYDRAZONES OF ALIPHATIC CARBONYL COMPOUNDS

Carbonyl Compound	Yield, %	B.P. (°C.)	n_D/T	Nitrogen Analysis		Principal Infrared Absorption Bands[a]								
				Calcd.	Found									
Formaldehyde[b]	70	69–71	1.4266/27	—[b]	—	1585s[c]	1477m	1451m	1393w	—	1261m	1135m	1008vs	887s
Acetaldehyde[b]	44	90–93	1.4326/28	32.53	31.28[d]	1610m[e]	1471s	1447s	1379s	1348m	1255s	1142s	1017vs	855s
Isobutyraldehyde	64	125–127	1.4355/27	24.53	24.43	1613m	1473s	1449m	1385m	1366m	1256s	1142m	1020vs	887m
Hexanal	60	181–184	1.4452/27	19.70	19.67	1608w	1468s	1445m	1379w	—	1252m	1136m	1015s	879m
Octanal	65	114–115/3	1.4489/29	16.45	16.67	1610w[f]	1471s	1447m	1395w	1357w	1255m	1139m	1031s	874m
Decanal	66	113–115/2	1.4517/29	14.12	14.29	1613m[g]	1471s	1447m	1379w	1357w	1256m	1139m	1031s	870m
Glutaraldehyde	64	113–6/3	1.4903/26	30.41	30.15	1613m[h]	1475s	1449s	1404w	1364w	1258s	1143s	1033s	877m
Acetone	75	92–94	1.4255/27	27.97	27.93	1639s[i]	1473s	1451s	1370m	1361s	1256m	1153m	1020s	852m
Acetylacetone	72	76–79/5	1.4728/27	30.41	29.22[d]	1616s[j]	1468s	1453m	—	1359m	1290m	1153m	1020s	894w
Glyoxal	60	105/10	1.5626/27	39.40	39.35	1678w 1527s	1468s	1443s	1420s	1379w	1259s	1133s	1013s	892s

[a] In the 1660–850 cm.$^{-1}$ range. All measured in carbon tetrachloride solution. [b] F. Klages *et al.*, *Ann.*, **547**, 1–38 (1941). [c] Also 1410w, 1170m, 1036m. [d] The low nitrogen values are attributed to the presence of traces of water which could not be removed by techniques successfully used with others in this series which are also hygroscopic and form constant boiling mixtures. The acetylacetone product rapidly turns colored on exposure to air, apparently undergoing oxidation. [e] Also 1404w, 935m. [f] Also 1412w. [g] Also 1404w, 1010m, 893m. [h] Also 1010 m. [i] Also 1610m, 1439s, 1220w, 1198m, 1081m, 964s. [j] Also 1570m, 1437m, 1190m, 1087w, 1058m, 986w, 977w, 919w.

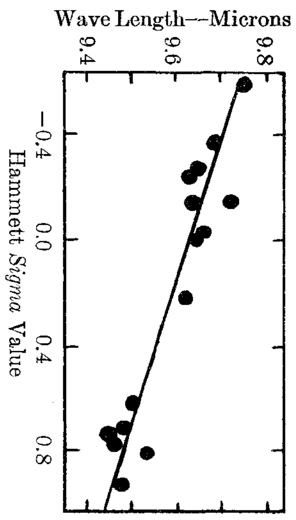

FIG. 1. INFRARED ABSORPTION *vs.* HAMMETT *sigma* VALUE FOR SUBSTITUTED ARYL DIMETHYLHYDRAZONES.

presence of this strong band at 965 cm.$^{-1}$, the highest value of the entire series, in acetone dimethylhydrazone, can be attributed to the electron release characteristics of the two methyl groups indicating the importance of hyperconjugation structures. This is not, however, consistent with the observation that this band occurs at 1008 cm.$^{-1}$ in formaldehyde dimethylhydrazone and 1028 cm.$^{-1}$ in acetaldehyde dimethylhydrazone. One would expect a value for the formaldehyde derivative below that for the acetaldehyde derivative.

Preliminary incomplete data on the evaluation of these materials in tumor growth retardation studies have shown that pyridine-3-carboxaldehyde dimethylhydrazone has a ±, − rating at a dose level of 30 mg./kg. in tests on experimental mouse sarcoma 180.[10] Tests with pyridine-2,6-dicarboxaldehyde dimethylhydrazone and with pyridine-4-carboxaldehyde methylhydrazone have shown ± (250 mg./kg.), − (125 mg./kg.) and ±, ? (125 mg./kg.) ratings, respectively. Many of the others are toxic. These results do not establish either strong or consistent activity and additional testing to determine the meaning of these results is necessary.

EXPERIMENTAL[11]

Details of typical preparations of materials listed in the tables are given. The aldehydes, dimethylhydrazine, and methylhydrazine were obtained from commercial sources.[12] Most of the heterocyclic hydrazones were unstable and turned dark on standing.

Isobutyraldehyde dimethylhydrazone. A solution of 7.0 g. (0.1 mole) of isobutyraldehyde and 7.0 g. (0.116 mole) o dimethylhydrazine was heated to reflux and cooled. Solid sodium hydroxide was added to induce the separation of two layers. The nonaqueous layer was separated and the treatment with solid sodium hydroxide was repeated until no aqueous layer separated. Distillation from sodium hydroxide gave 7.0 g., 64%, of isobutyraldehyde dimethylhydrazone, b.p. 125–127°.

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(10) The authors are indebted to Dr. C. C. Stock and Dr. D. A. Clarke, Sloan-Kettering Institute, for conducting these evaluations. The testing procedure and rating scale have been described by Stock *et. al.*, *Cancer Research, Suppl. No. 1*, p. 91 (1953) and *Suppl. No. 2*, p. 179 (1955).

(11) Analyses by Micro Tech Laboratories, Skokie, Ill.

(12) The authors acknowledge with thanks the gift of samples of acetylacetone and glutaraldehyde from Carbide and Carbon Chemicals Corp. and of 2,5-diethoxyterephthalaldehyde from Tennessee Eastman Co.

TABLE II.—DIMETHYLHYDRAZONES OF SUBSTITUTED BENZALDEHYDES

Substituent	Yield, %	B.P. or M.P. (°C.)	Physical Data[a]	Nitrogen Analysis		Principal Infrared Absorption Bands[b]												
				Calcd.	Found													
—[c]	71	b100/3	1.5930/29	—	—	—	1595s	1570s	—	1475s	1449s	1404w	1370s	1276s	1136s[d]	1036S	885m	T
2-Hydroxy	59	b128/4	1.6078/23	17.06	17.16	1629m	1603s	1575m	1502m	1488s	1453m[e]	1408m	1374m[f]	1282[g]	1143m[d]	1036S[h]	897m	L
4-Hydroxy	50	m153	EW	17.27	17.18	1616s	1600m	1580m	1520s	1477m	1451s	1410w	1379m[f]	1277s[g]	1140m[d]	1031S[h]	898s	K
2-Methoxy	71	b118/3	1.6065/11	15.72	15.63	—	1610s	1567m	1497s	1475s	1445s	1410w	1368w[f]	1259s[g]	1139m[d]	1036S[h]	893m	L
4-Methoxy	70	b120/3	1.6048/11	15.72	15.60	1616s	1603m	1572m	1517s	1475s	1449s[e]	1408w	1372m[f]	1247S[g]	1142m[d]	1036S[h]	894s	L
2-Ethoxy	66	b136/4	1.5863/13	14.57	14.80	—	1610s	1570m	1499s	1479s	1466s[e]	1401w	1368w[f]	1253S[g]	1143m[d]	1049S[h]	893s	L
4-Chloro	83	m72	EW	15.38	15.37	—	1595s	1555w	1493s	1473s	1445m[e]	1401m	1362m	1279m[g,i]	1134s[d]	1038s[h]	885s	T
3-Nitro	63	m45	M	21.75	21.70	—	1597m	1572m[j]	1538S	1479s	1449m[e]	1412w	1362S[f]	1259w	1138m[d]	1055S[h]	866m	T
4-Nitro	78	m112	E	21.75	21.88	—	1603m	1563s	1522s	1477m	1447w[e]	1387w	1348S[f]	1261w[g,i]	1135m[d]	1056S[h]	880m	T
4-Dimethylamino	26	m74	EW	21.97[k]	22.06	1616s	—	—	1524m	1475w	1449m	—	1355s	1266w[g,i]	1136m	1025S[h]	889m	T
4-Isopropyl[c]	90	b131/6	1.5665/29			1618w	1597m	1563w	1515w	1477s	1451m[e]	1389w	1368m	1280m	1142s	1037S[h]	892s	L
4-Acetamido	25	m166	EW	20.47	20.63	1681s	1600m	1572m	1513s	1466m	1447w[e]	1404m	1368m[f]	1244m	1131m	1035S	887m	L
2,4-Dihydroxy	39	m149	MW	15.55	15.48	1623s	1608s	1575m	1513s	1466m	1445sh	—	1344s	1250s[g,i]	1149s[d]	1022m[h]	878s	K
2-Hydroxy-3-methoxy	51	m88	EW	14.42	14.23	1647w	1605w	1572s	—	1473s	1453m[e]	1410m	1372w	1264S	1143m[d]	1050s[h]	900	L
3-Methoxy-4-hydroxy	89	m88	EW	14.42	14.58	—	1613m	1582m	1515s	1453s	1433s[e]	1385m	1362m	1276S[g,i]	1136m[d]	1037S[h]	894s	T
2-Hydroxy-5-nitro	50	m168	N	20.09	19.98	1623w	1587m	1558m	—	1464s	1433m	1397m	1348s	1282s[g,i]	1124m[d]	1048m[h]	905s	K
3,4-Dimethoxy	45	m40	D	13.45	13.34	—	1608m	1572m	1515s	1471s	1449m[e]	—	1370ws	1274s	1142s	1029s[h]	894s	L
2,3-Dimethoxy	62	b130/2	1.5942/11	13.45	13.53	—	1600s	1572m	1488S	1453s	1410m[e]	1404m	1362s[f]	1285s[gi]	1139s[d]	1042S[h]	894m	L
3,4-Diethoxy	30	m64	M	11.86	11.91	—	1608m	1572m	1520S	1488s	1453m[e]	1399s	1374m[f]	1272S[g,i]	1144s[d]	1037S[h]	896s	T
4-Aldehydo[l]	76	m182	E	25.67	25.36	—	1592m	1580m	1548m	1471s	1445m	1408w	1366m	1277m	1134s[d]	1033S	883s	L
4-Aldehydo-2,5-Diethoxy[l]	22	m147	MW	18.29	18.07	—	—	1577m	1502m	1475s	1453s	1397m	1366w	1272m[g,i]	1136m[d]	1024s[h]	905s	T

[a] n_D for liquids—solvents for recrystallization of solids; E, ethanol; W, water; M, methanol; N, nitromethane; D, diethyl ether. [b] In the 1680–870 cm.$^{-1}$ range. Medium: T, CCl_4; L, $CHCl_3$; K, KBr. [c] D. Todd, *J. Am. Chem. Soc.*, **71,** 1353 (1949). [d] Additional bands at 1115–1053. [e] Additional bands at 1445–1406. [f] Additional bands at 1333–1304. [g] One to three additional bands 1212–1157. [h] One to three additional bands at 1013–909. [i] Additional bands at 1263–1229. [j] Additional bands at 1553s. [k] Calcd. C, 69.07; H, 8.96. Found, C, 69.12; H, 8.90. [l] bis(Dimethylhydrazone).

TABLE III.—DIMETHYLHYDRAZONES OF HETEROCYCLIC ALDEHYDES

Aldehyde	Yield, %	B.P. or M.P. (°C.)	Nitrogen Analysis		Principal Infrared Absorption Bands[a]									
			Calcd.	Found										
Pyridine-2	77	b128/13[b]	28.17	28.32	1595sh	1575s	1468s	1439s	1427m	1361m	1285m	1135m[c]	1048S[d]	892s[e]
Pyridine-3	82	b138/10[f]	28.17	28.17	1595s	1565m	1477s	1453m	1422m	1372m	1285m	1136m[c]	1042s[d]	886m
Pyridine-4	73	m65–6	28.17	27.87	1600s	1582s	1477m	1449m	1418m	1370s	1295s	1134m[c]	1053S[d]	876s
6-Methylpyridine-2	94	m51–3	25.75	25.40	1600s	1577S	1460s		1412m	1359m	1279s	1157m[c]	1057S[d]	899s[e]
Pyridine-2,6-di	82	m125–6	31.94	32.01		1575s	1460s	1431m	1414m	1351s	1279s	1136s	1058S[d]	890s[e]
Thiophene-2	87	b125/7[g]	18.17	18.31		1575m	1477s	1449m	1427m	1366m	1282s	1139s[c]	1042S[d]	878s
3,4-Dihydro-2H-pyran-2	88	b98/8[h]	18.17	18.13	1647s	1613m	1475m	1449m		1389w	1266sh[i]	1140m[c]	1066S[d]	903w
Furan-2	87[j]	b82/4.5	—	—	1603w	1582m	1486m	1466s 1445m	1420w	1342s	1266s	1130m[c]	1034S[d]	883s[e]

[a] In the range 1680–870 cm.$^{-1}$ All run in carbon tetrachloride. [b] n_{D}^{28} 1.6038; picrate, m.p. 185°. [c] Additional bands at 1136–1066. [d] Additional band at 1026–926. [e] Additional bands at 890–870. [f] n_{D}^{28} 1.6048; picrate, m.p. 180°. [g] n_{D}^{27} 1.6284. [h] n_{D}^{27} 1.4970. [i] Additional bands at 1241 vs. [j] n_{D}^{26} 1.5753, D. Todd, *J. Am. Chem. Soc.*, **71,** 1353 (1949).

o-Ethoxybenzaldehyde dimethylhydrazone. A solution of 15 g. (0.1 mole) of *o*-ethoxybenzaldehyde and 7.0 g. (0.116 mole) of dimethylhydrazine was refluxed 3 hr. Distillation of the reaction mixture, after evaporation of the excess hydrazine, gave 12.6 g., 66%, of the product, b.p. 136–138°/4 mm.

2,5-Diethoxyterephthalaldehyde bis(dimethylhydrazone). A solution of 6.6 g. (0.03 mole) of 2,5-diethoxyterephthalaldehyde and 5.0 g. (0.083 mole) of dimethylhydrazine in 25 ml. of alcohol was refluxed for 3 hr. The solid which precipitated on cooling was recrystallized from methanol-water to give 2.0 g., 22%, of the product, m.p. 147–148°.

p-Dimethylaminobenzaldehyde dimethylhydrazone. A solution of 15 g. (0.1 mole) of *p*-dimethylaminobenzaldehyde and 7.0 g. (0.116 mole) of dimethylhydrazine in 30 ml. of concentrated hydrochloric acid and 25 ml. of ethanol was refluxed for 3 hr. The solution was made basic with concentrated ammonium hydroxide, filtered hot, and cooled to precipitate the crude product. Recrystallization from ethanol-water gave 5.0 g., 26%, of the product, m.p. 74–75°.

Pyridine-2-carboxaldehyde dimethylhydrazone. A mixture of 5.35 g. (0.05 mole) of pyridine-2-carboxaldehyde and 4.0 g. (0.067 mole) of dimethylhydrazine was fractionated after standing 1 hr. to give 5.7 g., 77%, of the crude product, b.p. 128–132°/13 mm. Refractionation gave the pure product, b.p. 128–130°/13 mm., n_{D}^{25} 1.6038. The picrate prepared from this product melts at 185–186°.

Pyridine-4-carboxaldehyde dimethylhydrazone. This product was prepared by the procedure given for the isomeric 2-carboxaldehyde. The fraction b.p. 136–149°/21 mm. solidified in the receiver. Recrystallization from petroleum ether gave 73% of the product, m.p. 60–64°. Additional recrystallization from petroleum ether and from water gave the pure product, m.p. 65–66°.

Infrared spectra were determined using a Baird double beam recording spectrophotometer with sodium chloride optics. All measurements were calibrated against the 3.419μ band for polystyrene. The medium used is given in the tables of data. Solutions were run at approximately 5% concentrations. The abbreviations used signify w (weak), m (medium), s (strong), S or vs (very strong), sh (shoulder)

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LOUISVILLE, KY.

[CONTRIBUTION NO. 996 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

Infrared Spectra of Allenic Compounds

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From the inspection of the infrared spectra of 58 allenic compounds, 48 of them from the literature, 2 resynthesized, and 8 synthesized for this study, it was concluded that the bands at 1950 and 850 cm.$^{-1}$ are characteristic of the allene bond system with certain variations due to substitution. The antisymmetrical stretching frequency at 1950 cm.$^{-1}$ appears as a doublet when the allene group is terminal and is substituted by an electron-attracting group (CO_2H, CO_2R, $CONH_2$, COCl, COR, CF_3, CN). Its intensity decreases with increasing substitution of electronically similar groups. The band at 850 cm.$^{-1}$ is characteristic of the terminal $=CH_2$ group and its absence is good evidence for the absence of terminal allenes. It has an overtone at 1700 cm.$^{-1}$ of low intensity. The synthesis of the new allenes is described.

Because of the increasing interest in allenic compounds it became important to develop fast and safe methods for their identification. The present paper deals with the application of infrared spectroscopy to this problem. Certain empirical rules became apparent which were successfully tested and applied to all available allenic compounds. Some allenic compounds were especially synthesized for this study; other data were collected from the literature or obtained by personal communications with other investigators. In some cases infrared spectra of the allenic compounds prepared by other workers was determined in our laboratories.[2]

For the identification of allenes two bands are of special interest. In the 1950 cm.$^{-1}$ region, ν_1 (due to the antisymmetrical C=C=C stretching vibration) sometimes appears as a doublet,[3] and ν_2 (due to torsional motion of an allenic terminal methylene) in the 850 cm.$^{-1}$ region. The latter band has an overtone, $2\nu_2$ at 1700 cm.$^{-1}$ The presence of ν_1 and ν_2 and their relative intensities clearly differentiates between allenes containing various substituents. Tables I to V list the allenic compounds available for this study and the position and intensities of the ν_1, ν_2 and $2\nu_2$ bands.

Explanation of Tables I to V. Tables I to V contain pertinent infrared data collected during this study for allenic compounds. These data were obtained from many different sources, under diversified conditions and using many different instruments. Therefore, the actual frequencies of the absorption bands listed in these tables are quite uncertain.

Frequencies are in reciprocal centimeters (cm.$^{-1}$). The frequency of a band is followed by an intensity description. The usual terms (v = very, s = strong, m = medium, w = weak) are used.

The meanings of other terms are: — = no appreciable absorption band; na = information for this frequency range is not available; [] = "ac-

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[1] Abstracted from the Ph.D. thesis of D.E.M., University of Pittsburgh, 1956. The authors wish to acknowledge the financial support of the Air Reduction Company.

[2] We wish to thank Dr. Foil A. Miller and his coworkers for all the determinations and for the fruitful discussions.

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