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

Methyl and Dimethylhydrazones

RICHARD H. WILEY AND GETHER IRICK

Received June 12, 1959

The ultraviolet and infrared absorption characteristics and the tumor growth retardation properties of a series of methyl- and dimethyl-hydrazones have been studied. Characteristic absorption is observed at 232–234 mμ and 1604–1637 cm.$^{-1}$ for the methylamino or dimethylamino substituted carbon-nitrogen double bond. Several aromatic types show a weak but non-reproducible tumor growth retardation in Sarcoma 180 tests.

Previous tumor-growth retardation studies[1] with dimethylhydrazones suggested the desirability of further study of this structural type. Several additional dimethylhydrazones and a series of methylhydrazones have been prepared and characterized. The data describing these compounds and some related acyl derivatives are given in Tables I–IV.

TABLE I

DIMETHYLHYDRAZONES

Carbonyl Compound[a]	Yield, %	B.P. or[b] M.P., °C.	N_D[c]	*N* Analysis Calcd.	*N* Analysis Found	Ultraviolet Absorption[d]	
1-Butanal	54	134	1.4390/24	24.53	24.73	240/3.86	
2-Ethylbutanal	69	83/45	1.4442/24	19.70	19.91	241/3.86	
Citronellal	83	65/0.1	1.4695/24	14.27	14.35	242/3.72	
1-Allylcyclohexane-C	60	73/0.8	1.4883/26	14.42	14.41	239/3.82	
2-Ethyl-1-hexanal	87	62/0.5	1.4473/26	16.45	16.42	239/4.01	
2-Ethyl-1-hexenal	62	100/27	1.4482/23	16.65	16.65	241/3.86	
3-Ethoxypropanal	50	109/24	1.4470/24	19.43	19.48	242/3.87	
2-Phenyl-1-propanal	79	67/0.1	1.5308/24	15.90	16.10	245/4.03	269/3.43
4-Methyl-2-pentanone	55	68/42	1.4320/23	19.70	19.91		269/2.95
Cyclopentanone	48	86/61	1.4690/24	22.20	22.05		
3-Methylcyclohexanone	58	89/24	1.4673/26	18.16	18.43		272/2.85
3-Chloro B	83	132/3	1.6118/23	15.34	15.26	232/3.98	303/4.35
3,4,5-Trimethoxy B	88	m75W		11.75	11.57	227/4.27	303/4.38
9-Anthraldehyde	91	m85MW		11.24	11.01	219/4.33	255/4.96
Dehydroacetic acid	52	m84BP		13.33	13.19	233/4.16	310/4.15
Isatin	42	m124EW		22.20	22.20	260/3.81[e]	281/3.95
Indole-3-C	96	m102TP		22.44	22.45	273/4.18[f]	296/4.25

[a] C = carboxaldehyde; B = benzaldehyde. [b] M, melting point; recrystallized from W, water; M, methanol; B, benzene; P, petroleum ether; E, ethanol; T, toluene. [c] Reading/°C. [d] Absorption maximum mμ/log extinction coefficient. [e] Shoulder 228–255 mμ/log e 3.73. [f] Maximum at 234 mμ/log e 4.3.

The infrared absorption characteristics for this group of methyl and dimethylhydrazones provide further data for evaluation of the group assignments for such structural types previously discussed.[1] The absorption associated with the carbon-nitrogen double bond stretching vibration occurs in the saturated aliphatic types as a weak band in the 1604–12 cm.$^{-1}$ region for the aldehyde dimethylhydrazones; in the 1634–47 cm.$^{-1}$ region for the ketone dimethylhydrazones; in the 1625–1631 cm.$^{-1}$ region for the aldehyde methylhydrazones; and in the 1624–1652 cm.$^{-1}$ region for the ketone methylhydrazones. The relative positions of the bands for the aldehyde and ketone derivatives are in the reverse order to that observed for the carbonyl compounds themselves. The cyclopentanone methylhydrazone absorbs at 1652 cm.$^{-1}$ and the dimethylhydrazone at 1647 cm.$^{-1}$ the highest values observed. This represents a shift similar in magnitude and direction to that observed for the carbonyl group stretching absorption in cyclopentanone itself. The presence of either aliphatic or aromatic carbon-carbon double bonds complicates this assignment. The absorption bands in the 865 cm.$^{-1}$ and 1000 cm.$^{-1}$ regions, useful in previous correlations, do not appear with any regularity in the methylhydrazones. The absorption in the 1100–1140 cm.$^{-1}$ region does, however, appear in the methylhydrazones and, as noted previously, also in the dimethylhydrazones. Often with the methylhydrazones this is the only band in this region of the spectrum and is nearly always strong and well-defined. This can be tentatively assigned to a carbon-nitrogen stretching vibration in the methylhydrazone unit. It has been suggested before that aliphatic amines show absorption bands,

(1) R. H. Wiley, S. C. Slaymaker, and H. Kraus, *J. Org. Chem.*, **22**, 204 (1957).

TABLE II

METHYLHYDRAZONES

Carbonyl Compound[a]	Yield, %	B.P. or[b] M.P., °C.	N_D[c]	N Analysis Calcd.	N Analysis Found	Ultraviolet Absorption[d]	
1-Hexanal	68	110/20	1.4544/24	21.86	22.10	235/3.62	
1-Heptanal	55	62/0.2	1.4555/26	19.70	19.71	233/3.72	
1-Octanal	33	112/20	1.4551/24	17.93	17.72	236/3.61	
1-Nonanal	50	72/0.3	1.4574/26	16.45	16.53	235/3.84	
1-Decanal	58	90/0.2	1.4593/23	15.20	15.01	233/3.76	
Citral	66	86/0.2	1.5210/27	15.54	15.50	270/3.95	
Cyclopentanone	70	87/26	1.4936/24	24.98	25.28	269/3.00	
Cyclohexanone	78	117/50	1.4998/24	22.20	22.44	234/3.72	
3-Methylcyclohexanone	49	99/20	1.4906/25	19.98	20.05	235/3.74	
Benzaldehyde	91	81/0.8	1.6140/24	20.88	20.98	217/4.23	283/4.34
3-Chloro B	34	92/0.3	1.6245/25	16.61	16.62	228/3.9	293/4.39
2-Methoxy B	50	130/0.6	1.6115/24	17.06	17.07	232/3.17	314/4.13
2-Ethoxy B	70	118/1.8	1.5918/25	15.72	15.91	225/3.98	312/4.08[e]
2-Hydroxy B	28	m46MW		18.65	18.80	220/4.07	308/4.05[h]
2-Hydroxy-5-nitro B	92	m148EW		21.55	21.51		289/4.14
2,4-Dihydroxy B	65	m148TP		16.86	17.09		306/4.22[f]
3-Nitro B	75	m67MW		23.45	23.36		295/4.29
9-Anthraldehyde	90	m100EW		11.97	11.76	218/4.37	255/5.04
Isatin	83	m179EW		23.98	24.01	239/3.9	335/4.19[j]
Pyridine-3-C	94	107/0.2[e]		31.09	31.09	229/3.55	293/4.07
6-Methylpyridine-2-C	80	95/1	1.6020/25	28.17	28.17		308/4.51
Thiophene-2-C	87	150/18	1.6489/24	19.98	20.22		306/4.44

[a,b,c,d] See footnotes a–d, Table I. [e] M.p. 35°. [f] Additional maximum: 281/3.95. [g] 280/4.04. [h] 281/4.13. [i] 289/4.24. [j] 252/3.07 and 278/4.19.

TABLE III

1,2-DIACYL DERIVATIVES OF METHYLHYDRAZINE

Acyl Group	Yield, %	M.P., °C.	Solvent[a]	N Analysis Calcd.	N Analysis Found
Cinnamoyl	76	170	MW	9.15	9.33
2-Furoyl	78	88	W	11.96	11.83
2-Methoxybenzoyl	69	134	TP	8.92	9.20
4-Methoxybenzoyl	80	90	MW	8.92	8.79
1-Napthoyl	78	185	TP	7.91	7.74
3-Nitrobenzoyl	76	164	EW	16.28	16.24
Phenoxyacetyl	83	138	MW	8.92	8.86

[a] See footnote b, Table I.

TABLE IV

1-METHYL-1-ACYLHYDRAZONES

Compound	Yield, %	M.P., °C.	Solvent[a]	N Analysis Calcd.	N Analysis Found
3-Chlorobenzaldehyde, 1-methyl-1-phenoxyacetylhydrazone	63	140	TP	9.25	9.22
3-Methoxybenzaldehyde, 1-methyl-1-phenoxyacetyl-hydrazone	93	109	EW	9.39	9.52
3-Nitrobenzaldehyde, 1-benzenesulfonyl-1-methylhydrazone	67	125	MW	13.16	12.94
Citronellal, 1-methyl-1-phenoxyacetylhydrazone	56	201	MW	13.59	13.52
Isatin, 1-methyl-1-phenoxyacetylhydrazone	35	137	E	8.85	8.92

[a] See footnote b, Table I.

although of low intensity, in the 1220–1020 cm.$^{-1}$ region assignable to this vibration. The variability is presumably eliminated in this series of structurally related derivatives. The absorption bands in the 860–920 cm.$^{-1}$ region show little regularity and it is not possible to state with certainty that a band in this region can be assigned to the aldehyde carbon-hydrogen[2] or the nitrogen-nitrogen stretching frequency.[3] Within the narrow range of 870–910 cm.$^{-1}$ there are a few aldehyde derivatives which show no absorption and a few ketone derivatives which do. The long chain aldehyde methylhydrazones show very weak, if any, absorption. Both the methyl- and dimethylhydrazones with-

(2) N. B. Colthup, *J. Opt. Soc. Amer.*, **40**, 397 (1950).

(3) D. W. Scott, G. D. Oliver, M. E. Gross, W. N. Hubbard, and H. M. Huffman, *J. Am. Chem. Soc.*, **71**, 2293 (1949).

out exception, show an absorption band at 1475±5 cm.$^{-1}$ attributable to the carbon-hydrogen deformation modes of the methyl groups. The strong methyl group absorption near 2850 cm.$^{-1}$ obscures the carbon-hydrogen stretching absorption, if any, often found in the aldehyde at 2720 cm.$^{-1}$

The ultraviolet absorption data for a series of the methyl and dimethylhydrazones is recorded in Table I and II. The statement is often found in discussions of the characteristic ultraviolet chromophores that the isolated, unconjugated carbon-nitrogen double bond has no absorption maximum in the ultraviolet range above 220 mμ. Our data show that the saturated aliphatic dimethylhydrazones have a characteristic absorption maximum of moderate intensity (log ε, 3.7–4.0) at 239–242 mμ. The saturated aliphatic aldehyde monomethylhydrazones have a similar maximum at 232–6 mμ (log ε, 3.6–3.8). Conjugated unsaturation shifts this to 270 mμ (log ε 3.95) in the citral derivative. Absorption in this series must be attributed to the bathochromic effect of the methyl or dimethyl amino group attached to the carbon-nitrogen double bond as the chromophore. The benzaldehyde derivatives absorb at 283 mμ (log ε, 4.34) and 217 mμ (log ε, 423). Substituted aromatic types show two or three maxima between 233 and 310 mμ. The principal maxima at 280–315 mμ (log ε, 4.05–4.39) is attributable to the hydrazone chromophore shifted approximately 60 mμ on conjugation with the aromatic ring. The reports that the eneamine from acetone and methylamine has an absorption maximum at 230 mμ,[4] suggest that other similar types may absorb in the ultraviolet range above 220 mμ. The corresponding oximes, in which the methylamino- or dimethylamino-group of the hydrazines is replaced by hydroxyl, absorb at significantly lower wave lengths with maxima at approximately 190 mμ for saturated aldehyde oximes and 229.5 mμ (log ε, 2.28) for α,β-unsaturated aldehyde oximes.[5]

Preliminary screening data[6] have shown the following tumor growth retardation effects for compounds described in this report: 2,3-dimethoxybenzaldehyde dimethylhydrazone ±(250), −(125); pyridine-3-carboxaldehyde methylhydrazone ?, ±(125), −(30); 2,4-dihydroxybenzaldehyde methylhydrazone ±, −(250), —, −(125); indole-3-carboxaldehyde dimethylhydrazone —, −(500), ±, −(250), −(125). The values in parentheses are the dose levels in mg./kg. in tests at different levels. The significance of the ± rating has been stated elsewhere.[6] These results do not establish either strong or consistent activity.

During the course of this study several diacyl derivatives of methylhydrazine were prepared. Physical properties and analytical data for these are given in Table III. These were obtained using the acyl chloride under reaction conditions which indicate a 1,2-diacyl structure. Apparently, the only previously known[7,8] derivatives of this type are the dibenzoyl and diacetyl compounds which have also been assigned the 1,2-diacyl structure. The structural assignment is based on the observation[7,8] that the monobenzoyl derivative of methylhydrazine gives a hydrazone derivative with benzaldehyde. This indicates that the first acylation occurs at the more basic methylated nitrogen to leave an amino group to form the hydrazone or react with the second acyl halide to give the 1,2-diacyl structure. The reaction of methylhydrazine with esters is known to give the 1-methyl-2-acyl structure.[9] Several acylated derivatives of the *N*-methyl-hydrazones are described in Table IV.

EXPERIMENTAL[10]

The aldehydes, ketones, and dimethyl- and methylhydrazines were commercial materials. The dimethylhydrazones were prepared as described previously.[1] Typical preparations for methylhydrazones and the acyl derivatives are given in detail. Data for all of the hydrazones are given in Table I and II. The methylhydrazones were acylated readily to give solid derivatives. Data for several of these are given in Table III and IV. The liquid hydrazones are colorless and remain so if stored under nitrogen. They become colored on exposure to air.

The methylhydrazone of benzaldehyde has previously been reported[11] as a solid, m.p. 179°, with analytical data which were not in good agreement with calculated values, and as a liquid N_D 1.6053/21.5°, with analysis only for a derivative.[12] The product we have obtained, from the reaction in methanol, is a liquid, N_D 1.6140/24°, and has physical, analytical, and spectroscopic properties in accord with the assigned structure. The reaction of methylhydrazine with 2,4-dichlorobenzaldehyde gave a variety of products. At least four different products were obtained depending on reaction time, solvent, and concentrations. The usual product, obtained in 23% yield, was a yellow, crystalline solid, m.p. 217–218° which gave a nitrogen analysis (8.37, 8.41%) in agreement with the theory (8.21%) for the 1-methyl-1-(3′-chloro-4′-formylphenyl)hydrazone of 2,4-dichlorobenzaldehyde. The methylhydrazone of β-ethoxypropanal was very unstable and darkened in a few hours even when placed under nitrogen. Two layers were present after several days. A sample was sealed under nitrogen immediately following distillation and gave a nitrogen analysis 0.66% below theory. It apparently was undergoing decomposition prior to the analysis. The methylhydrazone of veratraldehyde (m.p. 103–105°) decomposes to an oil

(4) F. A. Miller in H. Gilman, "Organic Chemistry—An Advanced Treatise," J. Wiley and Sons, New York, 1953, Vol. III, p. 166.

(5) L. K. Evans and A. E. Gillam, *J. Chem. Soc.*, **1943**, 565.

(6) C. C. Stock, F. S. Philips, Alice E. Moore, Sonja M. Buckley, D. A. Clarke, R. K. Barclay, and K. Sugiura, Cancer Research Suppl. No. 1, p. 91 (1953); Suppl. No. 2, p. 179 (1955). The authors are indebted to Drs. C. C. Stock, Ralph K. Barclay, and D. A. Clarke, Sloan-Kettering Institute, for conducting these tests.

(7) A. Michaelis and E. Hadanck, *Ber.*, **41**, 3285 (1908).

(8) R. L. Hinman, *J. Am. Chem. Soc.*, **78**, 2463 (1956).

(9) R. L. Hinman and D. Fulton, *J. Am. Chem. Soc.*, **80**, 1895 (1958).

(10) Analyses by Micro Tech Laboratories, Skokie, Illinois.

(11) C. Harries and T. Haga, *Ber.*, **31**, 62 (1898).

(12) D. Todd, *J. Am. Chem. Soc.*, **71**, 1353 (1949).

on standing a few hours. The methylhydrazone of indole-3-carboxaldehyde was obtained in large colorless crystals from ethanol, but turned pink after a few hours. Chromatography removed the color, but it returned rapidly. The methylhydrazone of 2-hydroxy-1-naphthaldehyde (m.p. 70–73° crude) decomposed upon attempted recrystallization and could not be obtained pure. Most of the pure aliphatic methyl and dimethylhydrazones were tested with acidic ethanolic 2,4-dinitrophenylhydrazine reagent and gave immediate precipitation of the corresponding 2,4-dinitrophenylhydrazone.

Pyridine-3-carboxaldehyde methylhydrazone. Nine grams (0.085 mole) of the aldehyde were cooled in a dry-ice acetone bath during the addition of 4.0 g. (0.087 mol.) of methylhydrazine. The reaction mixture was heated on a water bath for one hour and fractionated to give 8.4 g., 73.9%, of product, b.p. 107°/0.2 mm. The distillate solidified in the receiver.

Cyclohexanone methylhydrazone Nine and eight tenths grams (0.1 mol.) of cyclohexanone were cooled in a dry-ice acetone bath as 4.6 grams (0.1 mol.) of methylhydrazine were added dropwise. The mixture was heated to reflux for 0.5 hr., 25 ml. of water were added and the product extracted with 100 ml. of ether. The ether extracts were dried over magnesium sulfate, the ether removed, and the residue fractionated to give 9.8 g., 77.7%, of the product, b.p. 117°/50 mm. Unless ether-extracted from an aqueous solution, the product foams uncontrollably on distillation.

1-Methyl-2-phenoxyacetylhydrazine. A mixture of 6.8 g. (0.0377 mole) of ethyl phenoxyacetate and 3 g. (0.0653 mol.) of methylhydrazine was allowed to stand at room temperature 24 hr. The crystals which formed were collected and recrystallized twice from toluene–petroleum ether to give 5.1 g. 75.2%, of the product, m.p. 86–89°. This compound is recovered unchanged after attempted reaction with 3-nitrobenzaldehyde or 5-nitrosalicylaldehyde establishing the 1,2-structure.

Anal. Calcd. for $C_9H_{12}O_2N_2$: N, 15.55. Found: N, 15.57.

1-Methyl-1,2-di(1-naphthoyl)-hydrazine. A solution of 4 g. (0.021 mol.) of 1-naphthoyl chloride in 50 ml. of benzene was cooled to approximately 10° prior to the dropwise addition of 1 g. (0.217 mol.) of methylhydrazine. The solvent was then removed and the residue recrystallized from toluene-petroleum ether to give 2.9 g., 78%, of the product, m.p. 185°.

Isatin, 1-methyl-1-phenoxyacetylhydrazone. To 1.75 g. (0.01 mol.) of isatin methylhydrazone in 25 ml. of benzene was added dropwise 1.7 g. of phenoxyacetyl chloride. This mixture was heated at 60° on a water bath for 15 min. and evaporated to dryness. After being washed with 10% sodium bicarbonate and water, the red residue was recrystallized from methanol-water to give 1.74 g., 56.3%, of the product, m.p. 201–202°.

N-Phenoxyacetyl citronellal methylhydrazone. To 3.0 g. (0.0165 mol.) of citronellal methylhydrazone dissolved in 15 ml. of toluene was added 3.0 g. (0.0176 mol.) of phenoxyacetyl chloride. Evaporation of the solvent and recrystallization of the residue from ethanol gave 1.8 g., 34.6%, of the product, m.p. 137–139°.

The infrared absorption data were obtained using chloroform or carbon tetrachloride solutions or potassium bromide pellets and a Baird double beam recording spectrophotometer. The ultraviolet absorption data were obtained using a Beckman DK-2 recording ultraviolet spectrophotometer using methanol (Baker, purified) as solvent.

Acknowledgment. The authors wish to acknowledge partial support of this research through grant C-2457 from the National Cancer Institute of the National Institutes of Health and to the Research Corporation and the Brown-Forman Company for grants for the purchase of the infrared spectrophotometer.

LOUISVILLE, KY.

[CONTRIBUTION FROM THE LABORATORIES OF LEPETIT S.P.A.]

5,5-Disubstituted Dihydro-1,3-oxazine-2,4-diones. Research on Compounds Active on Central Nervous System. XII[1a]

EMILIO TESTA, LUIGI FONTANELLA, GIANFRANCO CRISTIANI, AND GIANGUALBERTO GALLO[1b]

Received June 15, 1959

A number of 5,5-dialkyl-, alkyl- aryl-, alkyl-cycloalkyl-, and polymethylene-, dihydro-1,3-oxazine-2,4-diones (I)[1c] have been synthesized by treating the suitable α,α-disubstituted β-hydroxypropionic acids (V) with sodium cyanate and hydrochloric acid to give α,α-disubstituted β-carbamyloxypropionic acids (VI); the latter are cyclized to I by treatment with thionyl chloride and pyridine. From compounds I the corresponding 3-methyl derivatives (XI) have been obtained as well as some dihydro-1,3-oxazine-2,4-dithiones (XII) which by oxydation with hydrogen peroxide yield the original oxazine-2,4-diones (I). Some examples of the ring opening of compounds I by alkaline hydrolysis and by reduction with $LiAlH_4$ present evidence for the assigned structure I. The 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones and some derivatives thereof show promising activity on central nervous system (CNS).

As a part of our studies on CNS-acting substances we have synthesized a number of 5,5-disubstituted dihydro-1,3-oxazine-2,4-diones (I) which represent a class of compounds[1d] of potentially great pharmacological interest. Actually, oxazinediones I are structurally related to some heterocyclic rings, whose basic features are common to a number of clinically useful hypnotic, narcotic, sedative, and anticonvulsant agents; namely barbiturates, glutarimides, and oxazolidinediones. Furthermore,

(1) (a) E. Testa, L. Fontanella, and G. F. Cristiani, *Ann.*, **626**, 114 (1959).

(1) (b) Physical chemical department of Lepetit S.p.A.

(1) (c) It is to note that the described new heterocyclic compounds may also be named tetrahydro-1,3-oxazine-2,4-diones.

(1) (d) Recently R. S. Safir and R. J. Lopresti briefly described various 5,6-substituted dihydro-1,3-oxazine-2,4-diones (U. S. Patent **2,797,217**) with possible sedative action on CNS.