

conditions for 5 hr over 70 mg of platinum dioxide. The catalyst was filtered and the solvent was concentrated to a small volume. A solution of sodium bicarbonate was added and the neutral mixture was extracted with ethyl acetate. The organic layer was dried and evaporated to dryness, yielding 410 mg of desoxyisohysterin, mp 91–92°. Recrystallization from isopropyl ether-hexane raised the melting point to 103–104°:  $[\alpha]_D -15.6^\circ$  (*c* 1.0);  $\lambda_{\max}$  222  $m\mu$  ( $\epsilon$  16,000); infrared bands at 1748, 1660, and 1225  $cm^{-1}$ .

*Anal.* Calcd for  $C_{17}H_{24}O_4$ : C, 69.83; H, 8.27; O, 21.89. Found: C, 69.80; H, 8.30; O, 21.83.

**Dihydroisoambrosin from Hysterin (VIII).**—A solution of 100 mg of desoxyisohysterin and 100 mg of potassium bicarbonate in 20 ml of methanol was refluxed for 45 min. The methanol was removed under vacuum and the residue was acidified with acetic acid. The mixture was diluted with water and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated to dryness affording an oily product which did not crystallize. This alcohol without further purification was dissolved in 6 ml of acetic acid and to this solution was added dropwise with stirring a solution of 100 mg of chromic oxide in 2 ml of water. Stirring was continued for 3 hr. The mixture was poured into water and extracted with ethyl acetate. The organic layer was washed, dried, and evaporated to dryness. Crystallization from ethyl acetate-isopropyl ether afforded 20 mg of dihydroisoambrosin: mp 165°;  $[\alpha]_D -9.3^\circ$  (*c* 1.0). This compound was compared with an authentic sample of dihydroisoambrosin and was found to be identical in all respects.

**4-Epidesoxyisohysterin (XIIb).**—A solution of 200 mg of ambrosin in 15 ml of acetic acid and 2 drops of perchloric acid was hydrogenated under normal conditions for 24 hr in the presence of 20 mg of platinum dioxide. The reaction mixture was filtered, neutralized with sodium bicarbonate solution, and

extracted with ethyl acetate. The oily residue was acetylated in the usual manner, yielding 85 mg of 4-epidesoxyisohysterin, mp 93–95°. The mother liquors (90 mg) contained approximately 70% of 4-epidesoxyisohysterin (tlc).

**Dehydrohysterin (X).**—To an ice-cold solution of 310 mg of hysterin in 10 ml of pyridine was added dropwise with stirring a solution of 210 mg of chromic oxide in 15 ml of pyridine. Stirring was continued for 6 hr at 37°. The excess of chromic oxide was destroyed with 10 ml of methanol and the solvents were evaporated to dryness. The oily residue was extracted with ethyl acetate and the organic layer was washed with water, dried, and evaporated to dryness. Recrystallization from isopropyl ether afforded 95 mg of dehydrohysterin (X): mp 154–155°;  $[\alpha]_D -65.5^\circ$  (*c* 1.0);  $\lambda_{\max}$  213  $m\mu$  ( $\epsilon$  10,000); infrared bands at 2860, 1710, 1245, 1045, and 885  $cm^{-1}$ .

*Anal.* Calcd for  $C_{17}H_{22}O_6$ : C, 66.65; H, 7.24; O, 26.11. Found: C, 65.94; H, 7.26; O, 26.93.

**4-Epidesoxyisohysterin (XIIb) from Dihydroisoambrosin (VIII).**—To a solution of 280 mg of dihydroisoambrosin in 15 ml of methanol was added 250 mg of  $NaBH_4$ . The mixture was refluxed for 2 hr. The reaction product was acidified with acetic acid and the solvent was evaporated under vacuum to dryness. The residue was extracted with ether. The organic layer was washed, dried, and evaporated to dryness. The oily residue was acetylated in the usual manner. The resulting product was chromatographed over alumina (Alcoa F-20) yielding 180 mg of 4-epidesoxyisohysterin (XIIb). This compound was compared with a sample of 4-epidesoxyisohysterin obtained by catalytic hydrogenation of ambrosin and was found to be identical in all respects.

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## Synthesis of Simple Hydrazones of Carbonyl Compounds by an Exchange Reaction

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Simple N-unsubstituted hydrazones of most aldehydes or ketones, usually difficult to obtain in good yields and high purity, may be so prepared from the corresponding N,N-dimethylhydrazones by exchange with anhydrous hydrazine. Since azine formation is nil under these conditions, the reaction can be followed by observing loss of color. Hydrazones prepared in this manner are stable for long periods when stored as crystalline solids. The N,N-dimethylhydrazones used as reagents are prepared in high yields directly from aldehydes or ketones and *unsym*-dimethylhydrazine. Exceptions to this occur only if the carbonyl compound is sterically hindered or possesses a labile group (toward nucleophilic substitution) *ortho* to the carbonyl function on an aromatic ring. In the latter instance, derivatives of 1H-indazole are formed.

Preparation in good yield of pure unsubstituted hydrazones of the more reactive aldehydes and ketones has been generally reported as difficult. Azine formation, hard to prevent during direct reactions between hydrazine and the carbonyl compounds (particularly aliphatic aldehydes and ketones or mixed alkaryls), is catalyzed by acids or is the principle reaction when the system is not quenched.<sup>3–5</sup> The hydrazones themselves may spontaneously decompose to tars<sup>6</sup> or azines with water or catalysts.<sup>5,7</sup>

In contrast, the few reported reactions of aldehydes or ketones with N-alkyl- and N,N-dialkylhydrazines to give the corresponding hydrazones indicate that these are uncomplicated by side reactions.<sup>7c,8–10</sup> The product N-substituted hydrazones are variously reported as oils of high refractive index obtained in yields from 20 to 80%. The most extensive preparative investigations of these compounds are those of Wiley and co-workers,<sup>11</sup> who prepared N-methyl- and N,N-dimethylhydrazones of a number of aldehydes and ketones as potential tumor growth retardants. Dialkylhydrazones have also been prepared from geminal dihalides instead of the corresponding carbonyl compounds.<sup>12</sup>

Preliminary to a study of subsequent reactions of pure aldehyde and ketone hydrazones now underway

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TABLE I  
 N,N-DIMETHYLHYDRAZONES OF SUBSTITUTED ACETOPHENONES

Substituted acetophenone	% yield	Bp, °C (mm)	$n_D^{25}$	% C		% H		% N	
				Calcd	Found	Calcd	Found	Calcd	Found
-H <sup>a</sup>	92	55-56 (0.15)	1.5443	74.03	74.02	8.70	8.90	17.27	17.43
2'-Methyl-	75	51-52 (0.2)	1.5228	74.96	75.09	9.15	9.02	15.90	15.84
3'-Methyl-	98	65-66 (0.1)	1.5383	74.96	75.11	9.15	9.00	15.90	15.96
4'-Methyl-	90	64-65 (0.15)	1.5424	74.96	75.02	9.15	9.04	15.90	15.84
2'-Hydroxy-	60	74-75 (0.15)	1.5649	67.39	67.36	7.92	7.96	15.72	15.75
3'-Hydroxy-	62	149-151 (2.3)	1.5795 (21°)	67.39	67.70	7.92	8.04	15.72	15.74
4'-Hydroxy-	95	<i>b</i>	...	67.39	67.36	7.92	7.84	15.86	15.86
2'-Bromo-	53	70-71 (0.2)	1.5563	49.80	49.80	5.44	5.44	11.62	11.61
3'-Bromo-	93	76-77 (0.05)	1.5780	49.80	49.78	5.44	5.38	11.62	11.80
4'-Bromo-	73	78-80 (0.15)	1.5809	49.80	49.80	5.44	5.44	11.62	11.66
2'-Chloro-	84	55-56 (0.1)	1.5382	61.06	60.86	6.66	6.64	14.24	14.48
4'-Chloro-	87.5	68-69 (0.2)	1.5601	61.06	61.04	6.66	6.69	14.24	14.30
2'-Iodo-	<i>c</i>	88-89 (0.2)	1.5903						
4'-Fluoro-	93	49 (0.20)	1.5248	66.64	66.60	7.27	7.37	15.54	15.73
2'-Methoxy-	75	65-66 (0.1)	1.5343	68.72	68.81	8.39	8.30	14.57	14.25
4'-Methoxy-	83.5	<i>d</i>	1.5486 (41°)	68.72	69.07	8.39	8.49	14.57	14.69
4'- <i>t</i> -Butyl-	70	78-79 (0.1)	1.5266	77.02	77.13	10.16	10.06	12.83	13.00
4'-Phenyl-	92	<i>e</i>	...	80.64	80.46	7.61	7.55	11.75	11.90
3'-Amino-	89	112-114 (0.1)	1.5929	67.76	67.82	8.53	8.52	23.71	23.63
3'-Nitro-	93.5	134-136 (1.0)	1.5738	57.95	57.97	6.32	6.27	20.27	19.74
4'-Nitro-	87	122-124 (0.2)	1.6057	57.95	58.36	6.32	6.60	20.27	20.11
4'-Cyano-	93.5	96-98 (0.2) <sup>f</sup>	...	70.56	70.45	7.00	7.09	22.44	22.68
4'-Carbomethoxy-	91	121-123 (0.2)	1.5591	65.42	65.73	7.32	7.52	12.72	12.73
2,6'-Dimethyl-	<i>g</i>								

<sup>a</sup> See ref 10; lit. bp 100.5-102° (10 mm),  $n_D^{25}$  1.5455. <sup>b</sup> Mp 133.5-134.5°. <sup>c</sup> 2'-Iodoacetophenone underwent internal aromatic nucleophilic displacement with formation of crystalline N,N,N-trimethylhydrazinium iodide and 1,3-dimethyl-1H-indazole; the yield was not calculated (see text). <sup>d</sup> Mp 41-42°, bp 88-90° (0.5 mm). <sup>e</sup> Mp 65-66°. <sup>f</sup> Mp 46-47°. <sup>g</sup> No reaction, even with acid catalysis.

 TABLE II  
 N,N-DIMETHYLHYDRAZONES OF VARIOUS CARBONYL COMPOUNDS

Parent carbonyl compound	% yield	Bp (mm) or mp, °C	$n_D^{25}$	% C		% H		% N	
				Calcd	Found	Calcd	Found	Calcd	Found
2-Butanone	80	113-115 (740)	1.4236	63.10	63.30	12.36	12.30	24.54	24.39
Benzaldehyde <sup>a</sup>	93.5	54-56 (0.1)	1.5953						
2-Chloro-	95	77-78 (0.1)	1.6096	59.18	58.93	6.07	5.97	15.34	15.50
4-Chloro- <sup>b</sup>	80	68	...						
4-Nitro- <sup>c</sup>	98+	112-113	...						
Cyclohexanone <sup>d</sup>	73	60 (11.5)	1.4698						
2-Methyl-	80	31-32 (0.2)	1.4648	70.08	70.23	11.76	11.81	18.17	18.02
2-Phenyl-	95	92-93 (0.1)	1.5382	77.74	77.48	9.32	9.11	12.95	13.07
Benzylacetone	82	68-69 (0.2)	1.5104	75.84	76.00	9.55	9.46	14.74	14.06
Benzophenone <sup>e</sup>	98	101-103 (0.3)	1.6048						
Fluorenone	98	127-128 (0.1)	1.684 <sup>f</sup>	81.05	81.13	6.35	6.27	12.60	12.63
$\alpha$ -Tetralone	95	76-78 (0.1)	1.5718	76.56	76.40	8.57	8.33	14.88	14.70
1-Indanone	95	73-75 (0.2)	1.5817	75.82	75.80	8.10	8.04	16.08	16.19
5-Acetylindan	86	88-90 (0.2)	1.5616	77.18	77.27	8.97	8.81	13.85	13.68

<sup>a</sup> See ref 9; lit. bp 127-128° (20 mm),  $n_D^{25}$  1.5920. <sup>b</sup> See ref 11a; lit. mp 72° in 83% yield. <sup>c</sup> See ref 11a; lit. mp 112°. <sup>d</sup> Lit.<sup>10</sup> bp 59-60 (11.5 mm),  $n_D^{25}$  1.4728. <sup>e</sup> Lit.<sup>10</sup> bp 101° (0.3 mm),  $n_D^{25}$  1.6057. <sup>f</sup> Fluorenone dimethylhydrazone was highly colored (orange) and the refractive index was difficult to obtain.

in our laboratory we have investigated methods for their preparation. The possibility of exchange reactions in an anhydrous medium between the relatively easily prepared N,N-dimethylhydrazones and hydrazine suggested itself as a means of elimination of azines as impurities. We have found that this is indeed a satisfactory method for preparation of simple hydrazones in good yield and high purity.

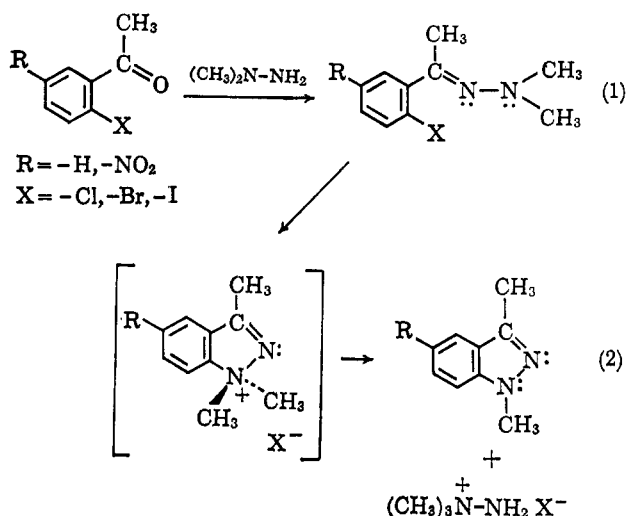
### Discussion of Results

Most ketones and aldehydes react directly and rapidly with *unsym*-dimethylhydrazine to give high yields of the N,N-dimethylhydrazones (Tables I and II). Unlike the hydrazones themselves, the N,N-

dimethylhydrazones are easily purified by distillation and cannot give azine formation. They are stable over long periods of time at room temperature.

Catalysts other than an excess of *unsym*-dimethylhydrazine are generally unnecessary for preparation of N,N-dimethylhydrazones although it was found that a few drops of mineral acid prevented formation of side products with 4'-nitroacetophenone. Difficulty was otherwise experienced only for attempted reactions of highly hindered ketones (*e.g.*, 2',6'-dimethylacetophenone is unreactive under the conditions used) or for *ortho*-substituted acetophenones which could undergo intramolecular cyclization of the N,N-dimethylhydrazone.

*o*-Haloacetophenones give *N,N,N*-trimethylhydrazinium halide as a by-product during the preparation of the dimethylhydrazone using excess *unsym*-dimethylhydrazine. This is presumed to arise by elimination of methyl halide from an intermediate cyclization product that is first formed from the normal *N,N*-dimethylhydrazone (eq 1 and 2).



Evidence for this reaction sequence rather than initial nucleophilic displacement are the observations that (1) freshly distilled 2'-bromoacetophenone *N,N*-dimethylhydrazone slowly deposits a water-soluble solid quaternary salt after standing several days; and (2) if 2'-bromoacetophenone *N,N*-dimethylhydrazone and anhydrous *unsym*-dimethylhydrazine are heated (~120°) in a sealed tube for several days, *N,N,N*-trimethylhydrazinium bromide<sup>13</sup> and 1,3-dimethyl-1H-indazole are the exclusive products. 1,3-Dimethyl-1H-indazole<sup>14</sup> has methyl resonances at  $\tau$  6.12 (N-CH<sub>3</sub>) and 7.53 (conjugated C-CH<sub>3</sub>) besides aromatic protons at  $\tau$  3. *N,N,N*-Trimethylhydrazinium bromide has proton singlets at  $\tau$  5.4 (N-H) and 6.55 (N-CH<sub>3</sub>).

The rapid quantitative precipitation of 1,3-dimethyl-5-nitro-1H-indazole by reaction of 2'-chloro-5'-nitroacetophenone with a fourfold excess of *unsym*-dimethylhydrazine was, therefore, not surprising. The excess of the strong base, *unsym*-dimethylhydrazine, would convert a quaternary salt intermediate of the indazole into its free base. The identical indazole was obtained with 2'-chloro-5'-nitroacetophenone and an excess of anhydrous methylhydrazine. It is apparent that hydrogen chloride is more readily eliminated than methyl chloride, which is to be expected if a quaternary intermediate cyclization product is first formed. 3-Methyl-5-nitro-1H-indazole as well as 1-phenyl-3-methyl-5-nitro-1H-indazole has been prepared by Borsche<sup>15</sup> by the analogous reaction of 2'-bromo-5'-nitroacetophenone with aqueous hydrazine and phenylhydrazine, respectively. There was an internal nucleophilic displacement with elimination of hydrogen bromide for each reaction.

(13) F. Klager and H. Wolf, *Ber.*, **92**, 1842 (1959).

(14) (a) E. Fischer and J. Tafel, *Ann.*, **227**, 303 (1885); (b) K. Auwers and M. Duesburg, *Ber.*, **53**, 1179 (1920).

(15) (a) W. Borsche and W. Schriba, *Ann.*, **541**, 283 (1939); (b) W. Borsche and A. Herbert, *ibid.*, **546**, 293 (1941).

The conversion of aldehyde or ketone *N,N*-dimethylhydrazones into the corresponding unsubstituted hydrazones by direct exchange with hydrazine occurs smoothly and in high yield (Tables III and IV). The reaction is conducted by refluxing the *N,N*-dimethylhydrazones with a 2-3-fold excess of anhydrous hydrazine, and results in practically complete conversions. Reaction times beyond those required for complete conversion to hydrazone did *not* result in formation of azine, which is usually yellow as are *N,N*-dimethylhydrazones. A convenient "end point," therefore, for the termination of the reaction was observation of the color change from light yellow of the *N,N*-dimethylhydrazones to colorless for most of the hydrazones. Only those hydrazones with a strong electron-withdrawing substituent (*e.g.*, nitro) on an aromatic ring or the more highly conjugated ones (*e.g.*, fluorenone hydrazone) are not colorless.

TABLE III  
HYDRAZONES OF ACETOPHENONES PREPARED BY EXCHANGE  
WITH DIMETHYLHYDRAZONES

Substituted acetophenone	% yield	Mp, °C	
		Obsd <sup>a</sup>	Lit.
-H	96	25	24 <sup>b</sup>
2'-Methyl-	86.5	<i>c</i>	...
3'-Methyl-	83.5	<i>d</i>	...
4'-Methyl-	90	34	34 <sup>b</sup>
2'-Hydroxy-	97	84	84, <sup>b</sup> 86 <sup>e</sup>
3'-Hydroxy-	56	143-144	<i>f</i>
4'-Hydroxy-	97 <sup>g</sup>	155	155 <sup>b</sup>
2'-Bromo-	82	<i>h</i>	...
3'-Bromo-	84	<i>i</i>	...
4'-Bromo-	89	84	164, <sup>j</sup> 73, <sup>k</sup> 84 <sup>l</sup>
2'-Chloro-	82	~5	...
4'-Chloro-	89	56	55 <sup>b</sup>
2'-Methoxy-	95.5	<i>m</i>	...
4'-Methoxy-	96	122-123	117, <sup>n</sup> 118.5 <sup>o</sup>
4'- <i>t</i> -Butyl-	92	81-82	<i>p</i>
4'-Phenyl-	91.5 <sup>q</sup>	155	<i>q</i>
3'-Amino-	85	81-82	98 <sup>r</sup>
3'-Nitro-	86	86-87	84-86, <sup>s</sup> 88 <sup>t</sup>
4'-Nitro-	87	148	149-151 <sup>t</sup>

<sup>a</sup> Melting points and yields were of the crude products (in text). <sup>b</sup> See ref 4a. <sup>c</sup> Bp 90-94° (0.55 mm), *n*<sub>D</sub><sup>20</sup> 1.5573. <sup>d</sup> Bp 112-113° (0.15 mm), *n*<sub>D</sub><sup>20</sup> 1.5860. <sup>e</sup> H. Wolf and O. Westphal, *Ann.*, **657**, 39 (1962). <sup>f</sup> *Anal.* Calcd for C<sub>8</sub>H<sub>10</sub>N<sub>2</sub>O: C, 63.97; H, 6.71; N, 18.65. Found: C, 63.95; H, 6.67; N, 18.81. <sup>g</sup> Owing to insolubility of 4'-hydroxyacetophenone hydrazone in either diethyl ether or chloroform, it was isolated by pouring into ice-water, filtering, and drying. <sup>h</sup> Bp 92-93° (0.15 mm), *n*<sub>D</sub><sup>20</sup> 1.5826. <sup>i</sup> Bp 132° (0.2 mm), *n*<sub>D</sub><sup>20</sup> 1.6294; owing to the high boiling point, the hydrazone decomposed upon distillation to give exclusively the corresponding azine (mp 105-106°, lit.<sup>40</sup> mp 102.5°). <sup>j</sup> H. J. Barber and R. Slack [*J. Chem. Soc.*, 612 (1944)] reported a melting point of 164°. This constant is more than likely that for the azine. L. N. Ferguson and T. C. Goodwin [*J. Am. Chem. Soc.*, **71**, 633 (1949)] reported the azine to melt at 159-160°. <sup>k</sup> J. Barrott, M. I. Gillibrand, and A. H. Lamberton [*J. Chem. Soc.*, 1282 (1951)] reported a melting point of 73°, which they assign to the hydrazone. <sup>l</sup> B. L. Hawbecker, private communication. <sup>m</sup> Bp 95-96° (0.1 mm), *n*<sub>D</sub><sup>20</sup> 1.5641. <sup>n</sup> J. G. Bennett, Jr., and S. C. Bunce, *J. Org. Chem.*, **25**, 73 (1960). <sup>o</sup> M. Oki and Y. Urushibara, *Bull. Chem. Soc. Japan*, **25**, 109 (1952); *Chem. Abstr.*, **48**, 4486 (1954). <sup>p</sup> *Anal.* Calcd for C<sub>12</sub>H<sub>18</sub>N<sub>2</sub>: C, 75.73; H, 9.54; N, 14.54. Found: C, 75.70; H, 9.63; N, 14.86. <sup>q</sup> *Anal.* Calcd for C<sub>14</sub>H<sub>14</sub>N<sub>2</sub>: C, 79.96; H, 6.71; N, 13.31. Found: C, 79.87; H, 6.64; N, 13.27. <sup>r</sup> F. Mayer and F. A. English, *Ann.*, **417**, 83 (1918). *Anal.* Calcd for C<sub>8</sub>H<sub>11</sub>N<sub>2</sub>: C, 64.41; H, 7.43; N, 28.16. Found: C, 64.41; H, 7.46; N, 28.24. <sup>s</sup> Y. Nagai, *Yuki Gosei Kagaku Kyokai Shi*, **19**, 470 (1961); *Chem. Abstr.*, **55**, 18662 (1961). <sup>t</sup> See ref 7d.

TABLE IV  
HYDRAZONES OF SELECTED CARBONYL COMPOUNDS PREPARED  
BY EXCHANGE WITH DIMETHYLHYDRAZONES

Parent carbonyl compound	% yield	Mp, °C, or bp (mm)	
		Obsd <sup>a</sup>	Lit.
Benzaldehyde	93	16	16 <sup>b</sup>
2-Chloro-	82	28	33-34 <sup>c</sup>
4-Nitro-	51	134	136 <sup>c</sup>
Cyclohexanone	59	55-59 (1.0)	<i>d</i>
2-Phenyl-	60	65-66	...
Benzophenone	80	99	99 <sup>e</sup>
Fluorenone	90	149	148-149 <sup>f</sup>
$\alpha$ -Tetralone	96	38-40	<i>g</i>
1-Indanone	79	77-78	<i>g</i>
5-Acetylindan	86	57-58	<i>g</i>

<sup>a</sup> Melting points and yields were of the crude products. <sup>b</sup> See ref 7a. <sup>c</sup> See ref 7b. <sup>d</sup> W. H. Perkin and S. G. P. Plant [*J. Chem. Soc.*, 127, 1138 (1925)] reported bp 105-110° (22 mm). <sup>e</sup> L. I. Smith and K. L. Howard, "Organic Syntheses," Coll. Vol. II, John Wiley and Sons, Inc., New York, N. Y., 1955, p 352. <sup>f</sup> See ref 25. <sup>g</sup> Products identified from nmr and infrared spectra by similarity to known compounds.

The usual procedure for purification of the hydrazones consisted in stripping excess anhydrous hydrazine and exchanged *unsym*-dimethylhydrazine along with solvent on a vacuum evaporator. This can be accomplished at room temperature for thermally sensitive hydrazones. Most hydrazones prepared in this manner were sufficiently pure for further reactions or characterization without additional treatment. Freeze recrystallization was also used when feasible. This afforded material which appears to be stable as a crystalline solid for long periods of time. It was observed that liquid hydrazones investigated were actually less pure owing to azine formation during attempted distillation than when isolated without heating.

Spontaneous decomposition of the hydrazone samples prepared in our laboratory occurred only in the undiluted liquid state. Thus, acetophenone and *p*-methylacetophenone hydrazones decomposed into azines at room temperature in a few days, whereas, when stored as crystalline solids at ~0°, there was no apparent change after 2-3 months.

In one preparation of fluorenone hydrazone by the exchange reaction, the reaction mixture was allowed to reflux for an extended period of time (~2 days) beyond that required for hydrazone formation (~12 hr). Appreciable quantities of fluorene were isolated, probably resulting from a modification of Wolff-Kishner reduction of the hydrazone with excess anhydrous hydrazine present.

### Experimental Section

Melting points were taken in capillaries with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra were determined with a Perkin-Elmer 237-B spectrometer. Nmr spectra were obtained with a Varian Associates A-60 pmr spectrometer; tetramethylsilane was used as the internal standard. Refractive indices were obtained with a Bausch and Lomb Abbe-type refractometer. Microanalyses were done by Spang Microanalytic Laboratory, Ann Arbor, Mich., and Galbraith Laboratory, Inc., Knoxville, Tenn.

Anhydrous *unsym*-dimethylhydrazine (99+%) and 97% anhydrous hydrazine were obtained from Matheson Coleman and Bell. Indanone and 5-acetylindane were obtained from Neville Chemical Co., Pittsburgh, Pa. Aldehydes and other ketones were obtained from commercial sources or synthesized by procedures analogous to that for 2'-iodoacetophenone.

**2'-Iodoacetophenone.**<sup>16</sup>—2-Iodobenzoyl chloride, prepared by refluxing 2-iodobenzoic acid with an excess of thionyl chloride, was added to ethyl magnesium malonate in ether. The crude product was hydrolyzed and decarboxylated to give 2'-iodoacetophenone in 78.5% over-all yield: bp 86-88° (0.5 mm),  $n_D^{20}$  1.6148; lit.<sup>17</sup> bp 112° (4 mm),  $n_D^{20}$  1.6180.

2'-Bromo-5'-nitroacetophenone, 84%, mp 86° (lit.<sup>18</sup> mp 89°), 2'-chloro-5'-nitroacetophenone, 80%, mp 62° (lit.<sup>19</sup> mp 62°), and 2'-methoxy-5'-nitroacetophenone, 52%, mp 92° (lit.<sup>20</sup> mp 98°), were prepared by the same method as was 2'-iodoacetophenone.

2-Bromo-5-nitrobenzoyl chloride, mp 60° (lit.<sup>21</sup> mp 63°), was prepared by treating the product from direct nitration of 2-bromobenzoic acid with thionyl chloride.

**General Procedure for the Preparation of Dimethylhydrazones.**—The method was similar to that described by Smith and Most,<sup>10</sup> except for the ratio of carbonyl compound to *unsym*-dimethylhydrazine, and is illustrated for 4'-chloroacetophenone dimethylhydrazone.

A mixture of 4'-chloroacetophenone (50 g, 0.324 mole), and anhydrous dimethylhydrazine (77.7 g, 1.3 moles) in absolute ethanol (75 ml) was refluxed 24 hr. Excess dimethylhydrazine and ethanol were removed by evaporation at reduced pressure. The crude product was fractionally distilled, giving 4'-chloroacetophenone dimethylhydrazone (55.5 g, 0.282 mole) in 87.5% yield: bp 77-78° (0.4 mm),  $n_D^{20}$  1.5601.

**General Procedure for Hydrazone Syntheses.**—The synthesis of 4'-chloroacetophenone hydrazone illustrates the general method used for the exchange conversion of dimethylhydrazones to hydrazones.

A mixture of 4'-chloroacetophenone dimethylhydrazone (5 g, 0.0254 mole) and anhydrous hydrazine (3.25 g, 0.102 mole) in anhydrous ethanol (10 ml) was refluxed until colorless or just pale yellow (~24 hr). The mixture was poured into ice-water (25 ml), extracted with diethyl ether (two 25-ml portions), and dried with magnesium sulfate. The ether was stripped by vacuum evaporation at room temperature to give white crystalline 4'-chloroacetophenone hydrazone (3.8 g, 0.0226 mole) in 89% yield, mp 56°. Recrystallization from benzene-petroleum ether (bp 30-60°) gave mp 56° (lit.<sup>4a</sup> mp 55°).

**Attempted Synthesis of 2',6'-Dimethylacetophenone Dimethylhydrazone.**—An attempt to prepare 2',6'-dimethylacetophenone dimethylhydrazone from the ketone by refluxing the reagents for 2 weeks gave only recovered starting materials (quantitative).<sup>22</sup>

**4'-Nitroacetophenone Dimethylhydrazone.**—A mixture of 4'-nitroacetophenone (15 g, 0.091 mole), anhydrous dimethylhydrazine (25 g, 0.415 mole), and 1 drop of concentrated sulfuric acid<sup>23</sup> in anhydrous ethanol (50 ml) was refluxed 48 hr. The mixture was stripped at reduced pressure and the residue was fractionally distilled, giving pure 4'-nitroacetophenone dimethylhydrazone (16.3 g, 0.079 mole) in 87% yield: mp 122-124° (0.2 mm),  $n_D^{20}$  1.6057.

**2'-Bromoacetophenone Dimethylhydrazone.**—The same general procedure used for the preparation of 4'-chloroacetophenone dimethylhydrazone was used for 2'-bromoacetophenone dimethylhydrazone. Fractional distillation at reduced pressure gave 2'-bromoacetophenone dimethylhydrazone in 53% yield, bp 70-71° (0.2 mm). A solid residue, which remained after distillation, was washed with absolute ethanol-ethyl acetate and gave N,N,N-trimethylhydrazinium bromide (0.85 g), mp 248° dec (lit.<sup>13</sup> mp 242° dec). The pmr spectrum in deuterium oxide as solvent has singlets at  $\tau$  4.60 (N-H) and 6.53 (N-CH<sub>3</sub>) with an integration ratio of 2:9.

**Attempted Synthesis of 2'-Chloro-5'-nitroacetophenone Dimethylhydrazone.**—A mixture of 2'-chloro-5'-nitroacetophenone

(16) The procedure described is that used for 2'-nitroacetophenone by G. A. Reynolds and C. R. Hauser, "Organic Syntheses," Coll. Vol. IV, John Wiley and Sons, Inc., New York, N. Y., 1963, p 708.

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(22) The sample of 2',6'-dimethylacetophenone was kindly donated by Dr. Harold Shechter of The Ohio State University.

(23) If acid catalysis is not used, the yield of this dimethylhydrazone decreases owing to the formation of an undetermined red solid. This has a melting point of 215-216°. *Anal.* Found: C, 71.45; H, 5.51; N, 10.87.

(10 g, 0.054 mole) and anhydrous *unsym*-dimethylhydrazine (10 g, 0.167 mole) in anhydrous ethanol was refluxed 4 hr. Excess dimethylhydrazine and ethanol were removed with a vacuum evaporator to give a yellow solid residue. This was recrystallized from ethyl acetate to give 1,3-dimethyl-5-nitro-1H-indazole (8.1 g, 0.0425 mole) in 78% yield, mp 164.5–165.5°. The pmr spectrum shows phenyl protons at  $\tau \sim 3$  and two singlets at  $\tau$  5.95 and 7.28 with equal intensities.

*Anal.* Calcd for  $C_9H_9N_3O_2$ : C, 56.53; H, 4.75; N, 21.98. Found: C, 56.66; H, 4.77; N, 22.08.

**1,3-Dimethyl-5-nitro-1H-indazole (from Methylhydrazine).**—A mixture of 2'-chloro-5'-nitroacetophenone (1.0 g, 0.0054 mole) with anhydrous methylhydrazine (5 ml) in absolute ethanol (15 ml) was refluxed 5 hr. Excess methylhydrazine and ethanol were removed at reduced pressure to give a yellow solid residue. Recrystallization from ethyl acetate gave 1,3-dimethyl-5-nitro-1H-indazole (700 mg) in 80% yield; mp 164–165°. A mixture melting point determination with the 1,3-dimethyl-5-nitro-1H-indazole prepared by using *unsym*-dimethylhydrazine showed no depression; the infrared spectra were identical.

**5-Amino-1,3-dimethyl-1H-indazole.**—A mixture of 1,3-dimethyl-5-nitro-1H-indazole (2.0 g, 0.0105 mole), 10% palladium on carbon (0.01 g), and 95% ethanol (20 ml) was heated to 50° with stirring and slow addition of anhydrous hydrazine (3 ml) in 1 hr. The catalyst was filtered from the solution and washed with hot ethanol (10 ml). The filtrate was concentrated on a rotary evaporator to give a white solid. Recrystallization from ethanol gave 5-amino-1,3-dimethyl-1H-indazole (1.4 g, 0.0087 mole) in 83.5% yield; mp 170°.

*Anal.* Calcd for  $C_9H_{11}N_3$ : C, 67.06; H, 6.88; N, 26.07. Found: C, 66.95; H, 6.75; N, 26.13.

**1,3-Dimethyl-1H-indazole. A. Reduction of 5-Amino-1,3-dimethyl-1H-indazole.**—A mixture of 5-amino-1,3-dimethyl-1H-indazole (500 mg, 0.0031 mole) in warm dilute hydrochloric acid (5.0 ml,  $\sim 5$  N) was dissolved, then cooled to  $\sim 10^\circ$ . Additional concentrated hydrochloric acid (0.40 ml) was added, followed by a solution of sodium nitrite (1 ml, 30%) over 10 min. The reaction mixture was poured into cold 50% hypophosphorous acid solution (5 ml) and allowed to stand at  $\sim 0^\circ$  for several

hours. The solution was made basic with dilute aqueous sodium hydroxide and extracted with diethyl ether (two 50-ml portions). The ether extract was dried with magnesium sulfate and stripped to give 1,3-dimethyl-1H-indazole (200 mg, 0.0013 mole) in 42% yield; mp 34°, bp 58–60° (0.3 mm) (lit.<sup>14</sup> mp 35.5°, bp 240°).

**B. From 2'-Bromoacetophenone.**—A mixture of 2'-bromoacetophenone (2.0 g, 0.0101 mole) and anhydrous *unsym*-dimethylhydrazine (5 ml, excess) was heated at 80° in a sealed tube for 6 days. The contents were poured into absolute ethanol; a white insoluble solid was filtered, washed with anhydrous ether, and dried, giving N,N,N-trimethylhydrazinium bromide (mp  $\sim 250^\circ$  dec). The filtrate was stripped, giving a pale yellow oil. Fractional distillation gave 1,3-dimethyl-1H-indazole (1.35 g, 0.0092 mole) in 92% yield; bp 59–61° (0.3 mm),  $n_D^{20}$  1.5679.

The nmr spectrum exhibited phenyl hydrogens as a complex region at  $\tau$  2.8; the methyl groups appeared as two singlets at  $\tau$  6.12 (N-CH<sub>3</sub>) and 7.53 (conjugated C-CH<sub>3</sub>). The nmr and infrared spectra and physical properties were identical with those obtained above.

**Fluorenone Hydrazone.**—A mixture of fluorenone dimethylhydrazone (2.0 g, 0.009 mole) in absolute ethanol (10 ml) was refluxed with anhydrous hydrazine (3 g, 0.094 mole) for 12 hr.<sup>24</sup> The mixture was poured into ice-water (10 ml), extracted with diethyl ether (two 20-ml portions), and dried with magnesium sulfate. The solvent was stripped *in vacuo*, giving yellow crystalline fluorenone hydrazone (1.57 g, 0.0081 mole) in 90% yield; mp 146° (lit.<sup>25</sup> mp 148–149°). Recrystallization from ethyl acetate gave mp 149°.

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(24) If the reflux time was extended to 48 hr, the yield of the fluorenone hydrazone was drastically reduced. The major isolated product was fluorene in as high as 96% yield; mp 102–103° (recrystallization from benzene). A mixture melting point with an authentic sample of fluorene was undepressed; the infrared spectra were identical.

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## The Structure of Ambrosiol.

### A New Sesquiterpene Lactone from *Ambrosia psilostachya*

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The structure of ambrosiol, the major sesquiterpene lactone in an Austin, Texas, collection of *Ambrosia psilostachya*, DC., is shown to be **11**.

The sesquiterpene lactones of *Ambrosia psilostachya*, DC., a common ragweed of the United States, are being analyzed as part of a chemosystematic investigation of *Ambrosia* and related *Compositae* genera. Coronopilin (**1**) was the only sesquiterpene lactone reported by Herz and Högenauer<sup>2</sup> from *A. psilostachya* obtained in Kansas and by Geissman and Turley<sup>3</sup> from *A. psilostachya* collected in the western United States. Our investigation of *A. psilostachya* from Galveston Island, Texas, resulted in the isolation of three structurally closely related sesquiterpenes which belonged to a new class of sesquiterpene dilactones. The structure of one of them, psilostachyin (**2**), has already been described.<sup>4</sup>

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No coronopilin (**1**) was detected in the extracts of the Galveston Island material. In view of these differences in the sesquiterpene lactone content of *A. psilostachya* collected from different locations, we initiated a phytochemical survey of a number of widely separated populations of the species. We now report the sesquiterpene lactone constituents of *A. psilostachya* collected near Austin, Texas.

Extraction of the Austin collection of *A. psilostachya* furnished in about 1% yield a new substance, which we have named ambrosiol, and smaller amounts of coronopilin (**1**) and parthenin (**3**). This is the first report of parthenin from this species. Parthenin, whose structure has been previously established,<sup>5</sup> is the major sesquiterpene lactone in *Parthenium hysterophorus*. The presence of parthenin in *A. psilostachya* provides further chemical evidence to

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