The Reaction of Carboxylic Acid Hydrazides with Formaldehyde

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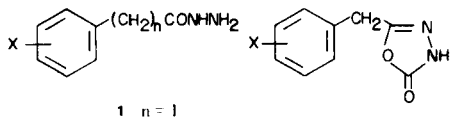
The hydrazides of benzoic, phenyacetic, and 3-phenylpropionic acids react with an acidic solution of formaldehyde to give **15**. Similar treatment of the corresponding methylhydrazides gave **16**. The ethers **15** can be cleaved to give, after methylation, **16**. Spectral data for **15** and **16** are presented.

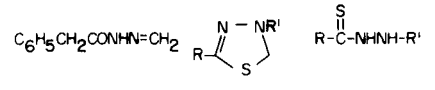
It is well known that carboxylic acid hydrazides and phosgene react to give a five-membered ring, 1,3,4-oxadiazolin-5-one. Thus, for example, we recently reported (1) that phenylacethydrazides (**1**) and phosgene gave rise to 2-benzyl-1,3,4-oxadiazolin-5-ones (**2**). The reaction of carboxylic acid hydrazides with formaldehyde, however, has received much less attention.



1 n = 1
10 n = 2
11 n = 0

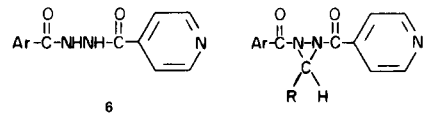
2

In 1898 Curtius (2) reported that the reaction of phenylacethydrazide and formaldehyde gave the simple product **3**. Wuyts and Lacourt (3) have reported that thiohydrazides (**4**, R′ = C_6H_5) and formaldehyde in ethanol containing hydrochloric acid give **5** (R′ = C_6H_5) or under certain conditions 1,2,4,5-tetrazines. Holmberg reported a study of the reactions of benzthiohydrazides and claimed the formation of **5** (R = C_6H_5, R′ = CH_3) from the reaction of **4** with formaldehyde. In 1964 vonPlessing (5) claimed that diacylhydrazines (**6**) and aldehydes gave diaziridines (**7**). More recently Kametani and co-workers (6) have reported that hydrazine **8** with formaldehyde and hydrochloric acid in ethanol gave the 1,2,4,5-tetrazine **9**.

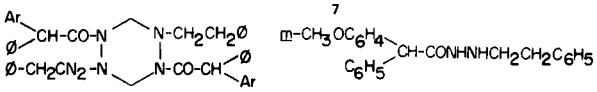


3 **5** **4**

We have found that the reaction of the hydrazide of phenylacetic acid (**1**, X = H) with an acidic solution of 37% formaldehyde gave a white solid, $C_{20}H_{22}N_4O_3$, to which we have assigned structure **15** (Ar = C_6H_5, n = 1). Analogous products were obtained from **1** (X = *p*-CH_3O, *p*-NO_2, *p*-Br, *p*-Cl, *o*-CH_3, *m*-CH_3, and *p*-CH_3) and from 2-naphthylacetylhydrazide. Similar reactions of the hydrazides

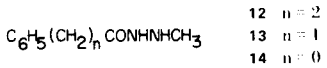


6 **7**



9 **8**

of hydrocinnamic acid (**10**) and of benzoic acid (**11**) gave **15** (Ar = C_6H_5, and n = 2 and 0 respectively). Reaction of the methylhydrazides of hydrocinnamic (**12**), phenylacetic (**13**), and benzoic (**14**) acids with an acidic solution of formaldehyde under the same conditions gave white solids to which we have assigned structure **16** (Ar = C_6H_5, and n = 2, 1, and 0 respectively). Ring substituted analogues of **12** gave similar products. Examination of the molecular formulas and of some of the data presented below indicates that analogous products are being obtained from the hydrazides and the methylhydrazides except that a dimethylene ether bridge (-CH_2-O-CH_2-) is formed in the unmethylated case.

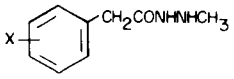


12 n = 2
13 n = 1
14 n = 0

Compound **15** (Ar = C_6H_5, n = 1) exhibited the spectral data shown in Table II which is consistent with the structure shown. The compound was unreactive towards sodium hydroxide but underwent a facile acid-hydrolysis to give phenylacetic acid. This latter observation together with the occurrence of an A_2B_2 splitting pattern in the aromatic region of the nmr spectrum of products derived from **1** with X as a *p*-substituent eliminated any possibility of cyclization onto the aromatic ring to give a seven-membered ring product. Compound **15** and its analogues all exhibit strong ($ArCH_2^+$) and ($\frac{M^+ - 16}{2}$) peaks in the mass spectra.

(Table I)

Phenylacetyl-2-methylhydrazides

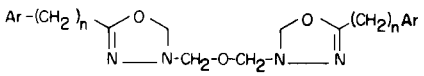


X	Yield	M.p. (a)	Analyses Calcd. C	Calcd. H	Found C	Found H
m-CH_3	72	88-89	67.38	7.92	67.04	8.03 (b)
o-CH_3	82	118-121	67.38	7.92	67.23	7.78
p-CH_3	71	123-124	67.38	7.92	67.39	7.99 (c)
3,4-$(CH_3O)_2$	63	106-108	58.91	7.19	58.91	7.17
p-CH_3O	78	116-117 (d)	61.83	7.27	61.70	7.26
p-Br	78	148-150 (d)	44.49	4.56	44.43	4.49
p-Cl	72	140-141 (d)	54.41	5.58	54.34	5.53

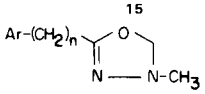
(a) Recrystallized from benzene-hexane unless otherwise noted. (b) Calcd.: N, 15.72. Found: N, 15.63. (c) Calcd.: N, 15.72. Found: N, 15.78. (d) Recrystallized from benzene.

In addition to similar spectral properties, the other analogues also underwent acid-hydrolysis to the parent carboxylic acid. The compound **16** (Ar = C_6H_5, n = 1) underwent a similar acid hydrolysis to phenylacetic acid. With the exception of a very intense peak at m/e = 85 ($C_2H_5N_2O$), the mass spectrum of the compound **15** exhibits all of the major peaks, below mk = 176, given by the compound **16**.

Hydrolysis of the dimethylene ether **15** (Ar = C_6H_5, n = 1) with dilute acid causes cleavage to give a compound $C_9H_{10}N_2O$. Alkylation of this cleavage product with methyl iodide or with dimethyl sulfate gave the same compound **16** (Ar = C_6H_5, n = 1) obtained from the reaction of the methylhydrazide of phenylacetic acid (**13**) with formaldehyde. Although sodium hydroxide did not react with the dimethylene ether **15**, treatment with sodium hydride in dimethylformamide with an excess of either methyl iodide or dimethyl sulfate gave the *N*-methyl compound **16**.



15



16

EXPERIMENTAL

All melting points are corrected. Analyses by Spang Microanalytical Laboratory, Ann Arbor, Mich., Mass Spect. by Morgan-Schaeffer, Montreal.

Preparation of Hydrazides.

Hydrazides were prepared by reaction of the appropriate esters with hydrazine or with methylhydrazine (1). See Table I for previously unreported hydrazides.

Reaction of Hydrazides (**1**, **10**, **11**) with Formaldehyde.

In a typical preparation 10 ml. of 37% formaldehyde and 5 ml. of concentrated hydrochloric acid was added to 2.0 g. (0.0133 mole) of phenylacethydrazide (**1**, X = H) in 25 ml. of glacial acetic acid. The mixture was heated on a steam bath until the solution became deep yellow and then poured onto crushed ice and filtered to give 3.52 g. (73%) of white solid (**15**, Ar = C_6H_5, n = 1), m.p. 139-140° from benzene. Analytical data for this and related compounds is included in Table II.

Reaction of *N*-Methylhydrazides (**12** - **14**) with Fromaldehyde.

In a similar manner the methylhydrazides were reacted with formaldehyde solution to give the products (**16**) indicated in Table III.

Reaction of Dimethylene Ether **15** (Ar = C_6H_5, n = 1) with Sodium Hydroxide.

A mixture of 1 g. (0.00274 mole) of the compound **15** (Ar = C_6H_5, n = 1) and 10% sodium hydroxide was heated for 2 hours to give after cooling and filtration 0.82 g. of starting material. No other crystalline products could be isolated from the reaction. similar results were obtained with 25% sodium hydroxide.

Reaction of Methyl Compound **16** (Ar = C_6H_5, n = 1) with Sodium Hydroxide.

A mixture of 1 g. (0.00558 mole) of the compound **16** (Ar = C_6H_5, n = 1) and 10 ml. of 10% sodium hydroxide was heated for 3 hours. After cooling the solution was extracted with chloroform and the dried extract was evaporated to give 0.86 g. of starting material.

Reaction of Dimethylene Ether **15** (Ar = C_6H_5, n = 1) with Acid.

A mixture of 1 g. (0.00274 mole) of the compound **15** (Ar = C_6H_5, n = 1) and 10% hydrochloric acid was heated for 2 hours.

(Table II)

$Ar(CH_2)_nCONHNH_2 + CH_2O \rightarrow$ **15**

Ar	n	M.p. (a)	Yield	Formula	Anal. Calcd. / Found C	H	N	Ir (KBr)
C_6H_5	1	139-140 (b)	73	$C_{20}H_{22}N_4O_3$	65.56 / 65.86	6.05 / 6.08	15.29 / 15.29	1650 (c)
p-$CH_3OC_6H_4$	1	132-134	62	$C_{22}H_{26}N_4O_5$	61.99 / 61.94	6.10 / 6.14	13.14 / 13.22	1650 (d)
p-$NO_2C_6H_4$	1	225-226	86	$C_{20}H_{20}N_6O_7$	52.62 / 52.27	4.41 / 4.42	18.41 / 18.11	1650 (e)
p-BrC_6H_4	1	193-194	89	$C_{20}H_{20}Br_2N_4O_3$	45.82 / 45.95	3.85 / 3.87	10.69 / 10.81	1650 (f)
p-ClC_6H_4	1	183-187	93	$C_{20}H_{20}Cl_2N_4O_3$	55.18 / 55.08	4.63 / 4.66	12.87 / 12.83	1650
o-$CH_3C_6H_4$	1	164-165	92	$C_{22}H_{26}N_4O_3$	66.98 / 67.02	6.64 / 6.64	14.20 / 14.21	1650
m-$CH_3C_6H_4$	1	150-151	62	$C_{22}H_{26}N_4O_3$	66.98 / 66.61	6.64 / 6.57	14.20 / 13.89	1650 (g)
p-$CH_3C_6H_4$	1	191-192	94	$C_{22}H_{26}N_4O_3$	66.98 / 66.71	6.64 / 6.59	14.20 / 14.17	1660 (h)
2-$C_{10}H_7$	1	185-187	82	$C_{28}H_{26}N_4O_3$	72.08 / 72.48	5.61 / 5.65	12.02 / 12.13	1650 (i)
1-$C_{10}H_7$	1	148-151 (j)	50	$C_{28}H_{26}N_4O_3$	72.08 / 70.85	5.62 / 5.55	12.01 / 11.78	1650 (k)
C_6H_5	2	124-126 (l)	80	$C_{22}H_{26}N_4O_3$	66.98 / 67.02	6.64 / 6.59	14.20 / 14.30	1670 (m)
C_6H_5 (n)	0	146-148 (l)	76	$C_{18}H_{18}N_4O_3$	63.89 / 63.71	5.36 / 5.25	16.56 / 16.51	1640 (o)

(a) Recrystallized from ethanol unless otherwise noted. (b) Recrystallized from benzene. (c) Nmr (DMSO-d_6): 7.18 (10 Ar), 4.8-4.3 ($4CH_2$), 3.68 δ ($2CH_2$); Mass Spectrum: 366 (3%), 336 (3%), 308 (2), 175 (22), 162 (25), 145 (6), 118 (16), 117 (11), 116 (5), 92 (20), 91 (100), 90 (11), 89 (8), 71 (4), 65 (18), 63 (7), 57 (17), 51 (7). (d) Nmr (DMSO-d_6): 7.2-6.8 (8Ar, A_2B_2), 4.8-4.3 ($4CH_2$), 3.7 ($2CH_3$), 3.65 δ ($2CH_2$); Mass Spectrum: 426 (11%), 368 (1), 206 (8), 205 (60), 204 (23), 192 (4), 175 (2), 148 (26), 147 (2), 122 (9), 121 (100), 91 (4), 78 (6), 77 (6). (e) Nmr (DMSO-d_6): 8.07-8.93 (8Ar, A_2B_2), 5.1-5.0 ($4CH_2$), 4.1 δ ($2CH_2$); Mass Spectrum: 456 (2.5%), 426 (8), 398 (2), 221 (18), 220 (82), 219 (5), 207 (16), 206 (6), 204 (5), 191 (5), 190 (29), 189 (15), 181 (11), 180 (7), 164 (8), 163 (9), 162 (3), 151 (6), 148 (6), 147 (6), 137 (13), 136 (58), 133 (20), 120 (13), 118 (7), 107 (13), 106 (90), 105 (6), 90 (29), 89 (14), 85 (10), 78 (25), 77 (8), 58 (7), 57 (100). (f) Nmr (DMSO-d_6): 7.5-7.05 (8Ar, A_2B_2), 4.85-4.4 ($4CH_2$), 3.70 δ ($2CH_2$). (g) Nmr (DMSO-d_6): 7.75-7.57 (8Ar), 5.27-4.75 ($4CH_2$), 4.0 ($2CH_2$), 2.47 δ ($2CH_3$). (h) Mass Spectrum: 394 (28%), 364 (3), 336 (3), 190 (17), 189 (95), 188 (21), 176 (25), 159 (8), 132 (40), 131 (3), 106 (14), 105 (100), 79 (10), 77 (12), 57 (20), 42 (40). (i) Nmr (DMSO-d_6): 7.87-7.2 (14Ar), 4.8-4.35 ($4CH_2$), 3.83 δ ($2CH_2$). (j) Recrystallized from ethanol-ethyl acetate. (k) Nmr (DMSO-d_6): 8.87-7.97 (14Ar), 5.3-5.1 ($4CH_2$), 4.6 δ ($2CH_2$). (l) Recrystallized from benzene-hexane. (m) Nmr (DMSO-d_6): 7.87 (10Ar), 5.27-4.78 ($4CH_2$), 3.18 δ ($4CH_2$); Mass Spectrum: 394 (16%), 364 (6), 336 (3), 216 (7), 190 (20), 189 (96), 188 (5), 177 (8), 176 (37), 175 (8), 161 (6), 159 (8), 133 (23), 131 (5), 130 (9), 106 (13), 105 (82), 104 (13), 92 (8), 91 (100), 79 (8), 77 (8), 65 (5), 57 (19). (n) Prepared using 100% formic acid in place of acetic acid-hydrochloric acid. (o) Nmr (deuteriochloroform): 8.1-7.5 (10Ar), 5.5-4.9 ($2CH_2$), 4.8 δ ($2CH_2$); Mass Spectrum: m/e 338.

After cooling the solution was extracted with methylene chloride and the dried extract evaporated to give 0.6 g. (81%) of phenylacetic acid identical in every respect with an authentic sample. Analogous ethers (**15**) prepared from the hydrazides of benzoic, p-chlorophenylacetic, p-bromophenylacetic, and hydrocinnamic acids gave good yields of the carboxylic acids when treated with 10% of hydrochloric acid.

Reaction of the Methyl Compound **16** (Ar = C_6H_5, n = 1) with Acid.

A solution of 1 g. (0.00658 mole) of the compound **16** (Ar = C_6H_5, n = 1) in 10 ml. of 10% hydrochloric acid was heated for 3 hours. Upon cooling the solution was extracted with chloroform and the dried extract evaporated to give 0.6 g. (78%) of phenylacetic acid identical in every respect with an authentic sample. Similar results were obtained with the products (**16**) derived from the methylhydrazides of benzoic and hydrocinnamic acid.

Reaction of the Dimethylene Ether **15** (Ar = C_6H_5, n = 1) with Acid in DMF.

To 0.5 g. (0.00136 mole) of the compound **15** (Ar = C_6H_5, n = 1) in 40 ml. of dimethylformamide was added 1 ml. of concentrated hydrochloric acid and the solution was heated for one hour and poured onto ice. The solution was extracted with ether and

(Table III)

$Ar(CH_2)_nCONHNHCH_3 + CH_2O \rightarrow$ **16**

Ar	n	M.p. (a)	Yield	Formula	Anal. Calcd. / Found C	H	N	Ir (KBr)
C_6H_5 (b)	1	200-202	83	$C_{10}H_{12}N_2O$	68.16 / 68.21	6.86 / 6.83	15.90 / 15.81	1655 (c)
3,4-$(CH_3O)_2C_6H_3$	1	142-144	42	$C_{12}H_{16}N_2O_3$	61.00 / 60.95	6.83 / 6.71	11.86 / 11.66	1660
m-$CH_3C_6H_4$	1	173-175	48	$C_{11}H_{14}N_2O$	69.44 / 69.25	7.42 / 7.26	14.73 / 14.70	1650
p-$CH_3C_6H_4$	1	158-160 (d)	42	$C_{11}H_{14}N_2O$	69.44 / 69.27	7.42 / 7.52	14.73 / 14.63	1655
o-$CH_3C_6H_4$	1	172-173	48	$C_{11}H_{14}N_2O$	69.44 / 69.26	7.42 / 7.30	14.73 / 14.51	1660
p-$NO_2C_6H_4$	1	244-246 (e)	44	$C_{10}H_{11}N_3O_3$	54.24 / 54.34	5.01 / 5.12	19.00 / 18.65	1655
p-BrC_6H_4	1	170-172	40	$C_{10}H_{11}BrN_2O$	47.08 / 47.14	4.35 / 4.57	10.98 / 10.91	1655
p-ClC_6H_4	1	180-182	44	$C_{10}H_{11}ClN_2O$	57.04 / 57.05	5.27 / 5.28	13.31 / 13.22	1660
p-$CH_3OC_6H_4$	1	143-145	41	$C_{11}H_{14}N_2O_2$	64.06 / 64.27	6.84 / 6.84	13.58 / 13.79	1650
C_6H_5 (f)	2	157-158	51	$C_{11}H_{14}N_2O$	69.44 / 69.35	7.42 / 7.39	14.73 / 14.73	1670 (g)
C_6H_5 (f)	0	235-237	46	$C_9H_{10}N_2O$	66.64 / 66.74	6.21 / 6.27	17.28 / 17.39	1660 (h)

(a) Recrystallized from benzene-hexane unless otherwise noted. (b) Also prepared using 100% formic acid in place of acetic acid-hydrochloric acid. (c) Nmr (DMSO-d_6): 7.35 (5Ar), 3.85 (CH_2), 4.38-4.67 (CH_2), 3.3 δ (CH_3). Mass Spectrum: 176 (27%), 175 (12), 162 (1), 118 (3), 117 (6), 116 (5), 92 (9), 91 (55), 90 (6), 89 (6), 85 (100), 71 (14), 65 (14), 63 (5), 51 (6). (d) Recrystallized from hexane. (e) Recrystallized from ethanol. (f) Prepared using 100% formic acid in place of acetic acid-hydrochloric acid. (g) Nmr (deuteriochloroform): 7.5 (5Ar), 5.1-4.0 (CH_2), 3.2-2.8 ($2CH_2$), 2.5 δ (CH_3); Mass Spectrum: m/e 190. (h) Nmr (deuteriochloroform): 7.7-7.3 (5Ar), 5.0-4.6 (CH_2), 2.8 δ (CH_3); Mass Spectrum: m/e 162.

the dried extract was evaporated to give 0.41 g. (93%) of a compound $C_9H_{10}N_2O$, m.p. 225-227° from benzene; ir (potassium bromide): 3250, 1650 cm^{-1}; nmr (DMSO-d_6): 7.25 (5), 6.0-5.7 (1), 4.5-4.3 (2), 3.7 δ (2).

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.65; H, 6.21; N, 17.27. Found: C, 66.78; H, 6.24; N, 17.35.

Methylation of the Compound $C_9H_{10}N_2O$.

To a solution of 1 g. (0.00615 mole) of the compound $C_9H_{10}N_2O$, obtained in the above reaction, was added 0.28 g. (0.00615 mole) of 50% sodium hydride in oil. The mixture was stirred at room temperature and 10 ml. of methyl iodide was added (a similar reaction took place when the methyl iodide was replaced with dimethyl sulfate). After stirring for 1 hour, the solution was poured onto ice and 0.66 g. (61%) of the *N*-methyl compound **16** (Ar = C_6H_5, n = 1) m.p. 200-202° from hexane-benzene, was obtained. This compound was identical in every respect with compound **16** (Ar = C_6H_5, n = 1) included in Table III.

Cleavage and Methylation of the Dimethylene Ether **15** (Ar = C_6H_5, n = 1).

To a warm solution of 1 g. (0.00272 mole) of the ether **15** (Ar = C_6H_5, n = 1) in 10 ml. of dimethylformamide was added 0.25 g. (0.00545 mole) of 50% sodium hydride in oil and then 10 ml. of methyl iodide (a similar reaction took place when the methyl iodide was replaced with dimethyl sulfate). The solution was heated for 1 hour, cooled, and poured onto ice. Filtration and recrystallization from hexane-benzene gave 0.59 g. (61%) of the *N*-methyl compounds **16** (Ar = C_6H_5, n = 1), m.p. 200-202°. This compound was identical in every respect with the compound reported above and with the compound listed in Table III. Extraction with ether of the solution remaining after isolation of **16** (Ar = C_6H_5, n = 1) gave 0.1 g. of unreacted starting ether.

Acknowledgment.

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