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The Preparation of 5-(2-Aminophenyl)-1,3,4-oxadiazole-2(3*H*)-one and Its Rearrangement to 3-Amino-2,4(1*H*,3*H*)-quinazolinedione

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When anthranilic acid hydrazide is reacted with 1,1′-carbonyldiimidazole in *THF* 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3*H*)-one (**4**) is formed. It can also be prepared from 1-*o*-aminobenzoyl-4,4-dimethylsemicarbazide which eliminates methylamine when boiled with *DMF*. On heating the 5-(2-aminophenyl)-1,3,4-oxadiazole above its melting point it rearranges to 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**5**).

(Keywords: 3,4-Dihydro-1H-1,3,4-benzotriazepine-2,5-dione; Oxadiazoles)

Die Darstellung von 5-(2-Aminophenyl)-1,3,4-oxadiazol-2(3H)-on und dessen Umlagerung in 3-Amino-2,4(1H,3H)-chinazolindion

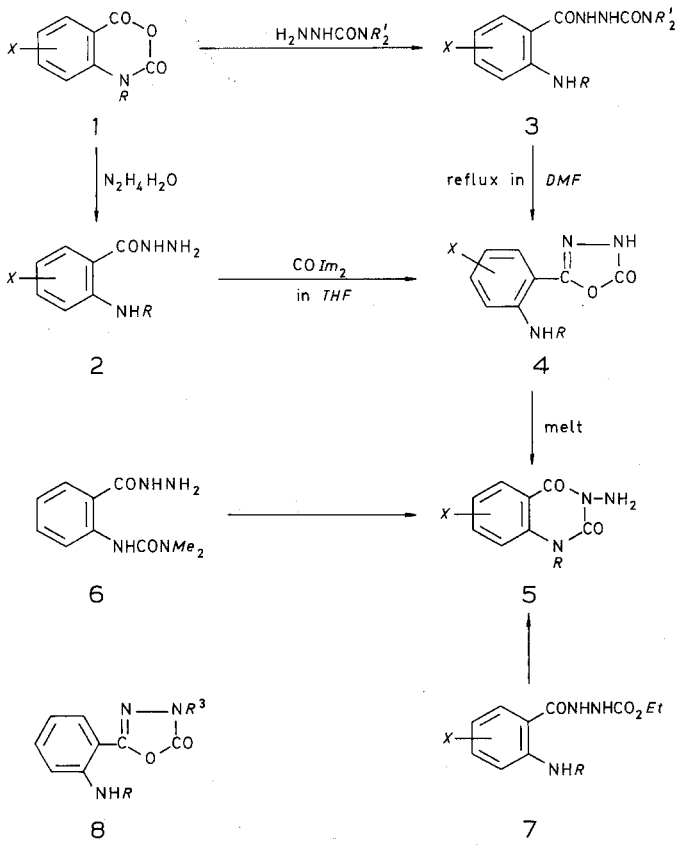
Bei der Reaktion von Anthranilsäurehydrazid mit 1,1′-Carbonyldiimidazol in *THF* wird 5-(2-Aminophenyl)-1,3,4-oxadiazol-2(3*H*)-on (**4**) gebildet. Dieses kann auch aus 1-*o*-Aminobenzoyl-4,4-dimethylsemicarbazid dargestellt werden, welches beim Kochen mit *DMF* Methylamin eliminiert. Beim Erhitzen von 5-(2-Aminophenyl)-1,3,4-oxadiazol über seinen Schmelzpunkt tritt Umlagerung zu 3-Amino-2,4(1*H*,3*H*)-chinazolindion (**5**) ein.

Recently[1,2] it was found that anthanilic acid hydrazide reacted with 1,1′-carbonyldiimidazole to afford a compound $C_8H_7N_3O_2$ (**4**), m.p. 175–176°. The melt soon resolidified as the isomeric 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**5**) was formed. At first the compound, m.p. 175–176°, was considered to be 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-dione. Then it was suggested[3], on spectroscopic evidence, that it was 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3*H*)-one, and this structure has now been verified by preparing **4** by reduction of 5-(2-nitrophenyl)-1,3,4-oxadiazole-2(3*H*)-one.

Cases are, however, known where substituted anthranilic acid hydrazides react with carbonyldiimidazole to give 3,4-dihydro-1*H*-1,3,4-benzotriazepine-2,5-diones or 3-amino-2,4(1*H*,3*H*)-quinazolinediones.

Thus 1-(*o*-aminobenzoyl)-1-methylhydrazine[4] reacts with 1,1′-carbonyldiimidazole to afford 3,4-dihydro-4-methyl-1*H*-1,3,4-benzotriazepine-2,5-dione, and when 2-(*o*-aminobenzoyl)-1-phenylhydrazine is treated with 1,1′-carbonyldiimidazole 3-anilino-2,4(1*H*,3*H*)-quinazolinedione is obtained.

It was found[6] that when a solution of 2-dimethylcarbamoylanthraniloylhydrazide (**6**) in dimethylformamide was boiled, methylamine was eliminated and 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**5**) was formed. It has now been found that 1-



anthraniloyl-4,4-dimethylsemicarbazide (**3**), in boiling dimethylformamide, cyclises to 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3*H*)-one (**4**). *Heller*[7] obtained **5** by heating **7** ($R = H$, $X = H$). It has now been found that **7** ($R = Me$, $X = H$) behaves similarly. When **7** was boiled in *DMF*, in an attempt to prepare **4**, unchanged **7** was recovered.

All the compounds **4** showed a strong C=O absorption near 1 790 cm^{-1} whereas **5** absorbed at 1 730 cm^{-1} and 1 650 cm^{-1}.

When 5-(2-methylaminophenyl)-1,3,4-oxadioazole-2(3*H*)-one (**4f**) was reacted with sodium methoxide and methyl iodide it afforded 3-methyl-5-(2-methylaminophenyl)-1,3,4-oxadiazole-2(3*H*)-one.

The mechanism of the rearrangement of 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3*H*)-one (**4**) to 3-amino-2,4(1*H*,3*H*)-quinazolinedione (**5**) has not been studied. A recent paper[9], however reported the ring opening of oxadiazolones by aromatic amines and recyclization of the products to quinazolinediones. In the case of **4**, the structure includes both an oxadiazolone ring and an aromatic amino group. The rearrangement was not observed in compounds **8**, with an alkyl group on N3 of the oxadiazolone ring.

Experimental

5-(2-Aminophenyl)-1,3,4-oxadiazole-2(3H)-ones (**4**) *from anthranilic acid hydrazides and 1,1-carbonyldiimidazole*

The anthranilic acid hydrazide **2** (0.01 mol) was dissolved in *THF* (ca. 30 ml) and 1,1-carbonyldiimidazole (1.78 g, 0.011 mol) added. The mixture was heated under reflux for several hours. Then the bulk of the tetrahydrofuran was distilled off, and water added to afford the 5-(2-aminophenyl)-1,3,4-oxadiazole-2(3*H*)-one **4** which was recrystallised from ethanol or aqueous ethanol (Table 1).

3-Amino-2,4(1H,3H)-quinazolinediones (**5a–e**)

On heating above their melting points compounds **4a–e** rearrange to the corresponding 3-amino-2,4(1*H*,3*H*)-quinazolinediones (**5a–e**) (Table 2) which were purified by washing the ground solid with isopropanol, and crystallising from glacial acetic acid.

5f *and* **5g**

5-(2-Methylaminophenyl)-1,3,4-oxadiazole-2(3*H*)-one (**4f**) is more stable, it can be recovered unchanged after being kept molten (190–200°) for 30 minutes, but rearranges if heated to a higher temperature. When **4f** (2 g) was heated to 240–250° for 1 hour, the melt cooled, and the solid product recrystallised from pyridine, it afforded **5f**, 1.16 g (58%), m.p. 241–242° (Lit.[5] m.p. 240–241°). Benzylidene derivative, m.p. 167–168°.

Similarly **4g** gave 1-ethyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (**5g**) (55%), m.p. 153–154°, from ethanol (Lit.[10] m.p. 152–158°). Benzylidene derivative, m.p. 115–116°.

As compounds **4h–l** could not be isomerised without heating to destructively high temperatures they were not investigated further.

Table 1. *5-(2-Aminophenyl)-1,3,4-oxadiazole-2(3H)-ones* (**4**)

	X	*R*	Yield (%)	m.p. (°C)	Mol. formula[a]	M^+
a	H	H	75	175–176	$C_8H_7N_3O_2$	177
b	5′-Cl	H	83	211–212	$C_8H_6ClN_3O_2$	211
c	4′-Cl	H	87	219–221	$C_8H_6ClN_3O_2$	211
d	5′-Br	H	87	220–221	$C_8H_6BrN_3O_2$	
e[b]	5′-*Me*	H	60	191–193	$C_9H_9N_3O_2$	
f[b]	H	*Me*	86	187–189	$C_9H_9N_3O_2$	191
g	H	*Et*	95	174–175	$C_{10}H_{11}N_3O_2$	205
h	H	*Ph*	85	211–212[c]	$C_{14}H_{11}N_3O_2$	253
i	H	*m*-$CF_3C_6H_4$	50	179–180	$C_{15}H_{10}F_3N_3O_2$	321
j	H	*Ph*CH_2	71	189–190	$C_{15}H_{13}N_3O_2$	267
k	H	*Ph*CH_2CH_2	64	146–147	$C_{16}H_{15}N_3O_2$	281
l	H	C_6H_{11}	86	165–166	$C_{14}H_{17}N_3O_2$	259

[a] Analytical data (C, H, N) agree very well with calculated values.
[b] NMR (in pyridine-d_5): **4e** δ 2.11 (3H, s, *Me*); **4f** δ 2.73 (3H, d, *Me*).
[c] This is the same compound as was described by *Langis* and *Charest*[8]. 1-Phenyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione m.p. 239–240° was prepared by an unequivocal route (see text).

Table 2. *3-Amino-2,4(1H,3H)-quinazolinediones* (**5**)

	X	Yield (%)	m.p. (°C)	Mol. formula[a]
a	H	86	293–295[b]	$C_8H_7N_3O_2$
b	6-Cl	73	311–313	$C_8H_6ClN_3O_2$
c	7-Cl		306–307	$C_8H_6ClN_3O_2$
d	6-Br	82	304–306	$C_8H_6BrN_3O_2$
e	6-*Me*	43	265–266	$C_9H_9N_3O_2$

[a] Analytical data (C, H, N) agree very well with the calculated values.
[b] Lit.[5] m.p. 291.5–293°.

1-Phenyl-3-amino-2,4(1H,3H)-quinazolinedione

1-Phenyl-2,4(1H,3H)-quinazolinedione (1 g) was suspended in a solution of sodium hydroxide (1 g) in water (25 ml). Hydroxylamine-*O*-sulphonic acid (1.1 g) was added and the mixture kept with occasional stirring for a few days. The product was then extracted with hot ethanol, filtered from unchanged 1-phenyl-2,4(1*H*,3*H*)-quinazolinedione (0.25 g), and the ethanol solution cooled. The product was triturated with 5% sodium hydroxide solution to remove any 1-phenyl-2,4(1*H*,3*H*)-quinazolinedione and then recrystallised from ethanol to afford 1-phenyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (0.1 g) as needles, m.p. 239–240° (Found: C 66.55, H 4.24, N 16.35, M^+ 253. $C_{14}H_{11}N_3O_2$ requires C 66.39, H 4.38, N 16.59%, M^+ 253).

1-Ethoxycarbonyl-2-o-methylaminobenzoylhydrazine (**7** $R = Me$, $X = H$)

N-Methylisatoic anhydride was warmed with a solution of ethoxycarbonylhydrazine (Cf11) till evolution of carbon dioxide ceased. On cooling 1-ethoxycarbonyl-2-*o*-methylaminobenzoylhydrazine (35%), m.p. 168–169° (Found: C 55.59, H 6.44, N 17.65. $C_{11}H_{15}N_3O_3$ requires C 55.68, H 6.37, N 17.71%) was obtained. This was heated to 230–245° for 45 minutes, cooled, the solid product washed with ethanol and then recrystallised from ethanol to give 1-methyl-3-amino-2,4(1*H*,3*H*)-quinazolinedione (66%), m.p. 240–241°.

Similarly 6-chloroisatoic anhydride reacted with ethoxycarbonylhydrazine to afford *1-ethoxycarbonyl-2-(2-amino-5-chlorobenzoyl)hydrazine* (70%), m.p. 154–155° (Found: C 46.79, H 4.70, N 16.27. $C_{10}H_{12}ClN_3O_3$ requires C 46.61, H 4.69, N 16.31%) which on heating eliminated ethanol to give 3-amino-6-chloro-2,4(1*H*,3*H*)-quinazolinedione, m.p. 309–310° (Found: C 45.61, H 2.86, N 19.42. $C_8H_6ClN_3O_2$ requires C 45.41, H 2.86, N 19.86%).

1-Aminobenzoyl-4,4-dialkylsemicarbazides

4,4-Dimethylsemicarbazide was obtained as described by *Vogelesang*[12]. Similarly diethylcarbamoyl chloride was reacted with hydrazine hydrate to afford 4,4-diethylsemicarbazide as an oily liquid [benzylidene derivative m.p. 133–134° (Found: C 65.77, H 7.88, N 19.31, $C_{12}H_{17}N_3O$ requires C 65.73, H 7.81, N 19.16%)] which was used without further purification to prepare **3** ($R^1 = Et$).

1-o-Aminobenzoyl-4,4-dimethylsemicarbazide (**3**)

Isatoic anhydride (8.15 g, 0.05 mol) was suspended in ethanol, 4,4-dimethylsemicarbazide (5.4 g, 0.052 mol) added, and the mixture warmed till no more carbon dioxide was evolved and nearly all the solid had dissolved, filtered, and water added to the filtrate to give **3** (8.8 g, 79%), m.p. 171–172° (Found: C 54.16, H 6.36, N 25.01. $C_{10}H_{14}N_4O_2$ requires C 54.04, H 6.35, N 25.21%). NMR (p.p.m.) δ 2.90 (6 H, s, Me_2).

MS (*m/e*): M^+ 222 (23%), 177 (14), 120 (100), 92 (12), 72 (18).

The other 1-aminobenzoyl-4,4-dialkylsemicarbazides were prepared similarly (Table 3). In each case the M^+ peak was observed in the mass spectrum as well as peaks corresponding to $(M^+—R_2NH)$ and $(R_2NCO)^+$.

Similarly 4,4-diphenylsemicarbazide reacted with 6-chloroisatoic anhydride to afford 1-(2-amino-5-chlorobenzoyl)-4,4-diphenylsemicarbazide, felted needles from aqueous methanol, m.p. 117–118° (Found: C 62.92, H 4.44, N 14.86, M^+ 380. $C_{20}H_{17}ClN_4O_2$ requires C 63.08, H 4.50, N 14.71%, M^+ 380).

5-o-Aminophenyl-1,3,4-oxadiazole-2(3H)-one (**4a**) *from 1-o-aminobenzoyl-4,4-dimethylsemicarbazide* (**3**)

1-*o*-Aminobenzoyl-4,4-dimethylsemicarbazide (1.11 g, 0.005 mol) was dissolved in dimethylformamide (11 ml) and the mixture heated under reflux for 2 hours, cooled somewhat and water (50 ml) added. The mixture was then cooled in an ice bath for 1 hour and the 5-*o*-aminophenyl-1,3,4-oxadiazole-2(3*H*)-one filtered off (0.62 g, 70%), needles from aqueous ethanol, m.p. 174–175° (Found: C 54.59, H 4.12, N 24.0. $C_8H_7N_3O_2$ requires C 54.23, H 3.98, N 23.72%). The m.p. was not depressed on admixture with **4a** and comparison of the infra-red spectra confirmed the identity.

MS (*m/e*): $(M^+ + 1)$ 178 (10%), M^+ 177 (100), 146 (66), 120 (98), 93 (12), 92 (25), 90 (12), 65 (17).

Table 3. *1-o-Aminobenzoyl-4,4-dialkylsemicarbazides* (**3**)

X	*R*	*R'*	yield (%)	m.p. (°C)	Mol. formula[a]
H	H	*Me*	79	171–172	$C_{10}H_{14}N_4O_2$
Me	H	*Me*	59	171–173	$C_{11}H_{16}N_4O_2$
Cl	H	*Me*	52	187–189	$C_{10}H_{13}ClN_4O_2$
H	*Me*	*Me*	20[b]	157–158	$C_{11}H_{16}N_4O_2$
H	*Ph*	*Me*	35	200–201	$C_{16}H_{18}N_4O_2$
H	*m*-$C_6H_4CF_3$	*Me*	14[c]	163–164	$C_{17}H_{17}F_3N_4O_2$
H	H	*Et*	77	141–142	$C_{12}H_{18}N_4O_2$
Me	H	*Et*	55	145–146	$C_{13}H_{20}N_4O_2$
Cl	H	*Et*	50	196–197	$C_{12}H_{17}ClN_4O_2$

[a] Analytical data (C, H, N) agree very well with the calculated values.
[b] Low yield largely due to losses during purification of very soluble product.
[c] Overall yield from flufenamic acid.

A similar experiment using dimethylacetamide as solvent gave a 65% yield of **4a**. The other compounds **3** similarly afforded the corresponding compounds **4** when boiled in dimethylformamide. If boiling was continued for too long some isomerisation to the 3-amino-2,4(1*H*,3*H*)-quinazolinedione was observed. The reaction also occurred with 1-(2-amino-5-chlorobenzoyl)-4,4-diphenylsemicarbazide but in this case the 5-(2-amino-5-chlorophenyl)-1,3,4-oxadiazole-2(3*H*)-one (**4b**) obtained was contaminated with diphenylamine, which could be removed by recrystallisation from *n*-butanol, or by triturating the mixture with sodium hydroxide solution, filtering through celite, and precipitation of the **4b** from the filtrate by acidification with acetic acid.

Alkylation to compounds **8**

5-*o*-Methylaminophenyl-1,3,4-oxadiazole-2(3*H*)-one (**4a**, 1 g) was added to a solution from sodium (0.46 g) and methanol (25 ml). Excess alkyl iodide was added and the mixture refluxed for 3 hours, some of the alkyl iodide and methanol was distilled off. On cooling the product separated and was recrystallised from ethanol (Table 4).

5-(2-Nitrophenyl)-1,3,4-oxadiazole-2(3H)-one

2-Nitrobenzoylhydrazine (5 g) was dissolved in warm water. A solution of phosgene (40 ml, 12% in toluene) was added to the rapidly stirred solution. Solid began to separate as the phosgene solution was added. Stirring was continued while the mixture cooled. The product was then filtered off and washed with water, to give 4.43 g (77%), m.p. 159–161° (Lit.[9] m.p. 161–162°).

The same compound was obtained by reacting 2-nitrobenzoylhydrazine with carbonyldiimidazole in *THF* (33%), m.p. 159–160°.

Reduction of 5-(2-nitrophenyl)-1,3,4-oxadiazole-2(3H)-one to **4a**

5-(2-Nitrophenyl)-1,3,4-oxadiazole-2(3*H*)-one (1.035 g, 0.005 mol), and *Adams* platinum oxide (60 mg), was suspended in alcohol (20 ml) and

Table 4. *3-Alkyl-5(2-alkylaminophenyl)-1,3,4-oxadiazole-2(3H)-ones* (**8**)

R	R^3	Yield (%)	m.p. (°C)	Mol. formula[a]
Me	*Me*	78	175–176[b]	$C_{10}H_{11}N_3O_2$
Me	*Et*	64	92–93	$C_{11}H_{13}N_3O_2$
Me	*n-Pr*	59	82–83	$C_{12}H_{15}N_3O_2$
Me	*i-Pr*	37	69–70	$C_{12}H_{15}N_3O_2$
Me	$PhCH_2$	44	126–127	$C_{16}H_{15}N_3O_2$
$PhCH_2$	*Me*	30	106	$C_{16}H_{15}N_3O_2$
Et	*Me*	47	143–144	$C_{11}H_{13}N_3O_2$
Et	*Et*		77–78	$C_{12}H_{15}N_3O_2$

[a] Analytical data (C, H, N) agree very well with the calculated values.
[b] NMR (in pyridine-d_5): δ 2.80 (3 H, d, *Me*); 3.25 (3 H, s, *Me*).

hydrogenated at atmospheric pressure. After 30 minutes, when the theoretical volume of hydrogen had been absorbed, the catalyst was filtered off, the filtrate concentrated, and diluted with water. On cooling the solution afforded 0.78 g **4a** (88%), needles from aqueous ethanol, m.p. 174–176°; a mixed m.p., and the infrared spectrum showed identity with the product from anthranilic acid hydrazide and carbonyldiimidazole.

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