A New Ring Opening Reaction of *N*-Aminophthalimide Hydrazones [1]

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Araldehyde hydrazones III of *N*-aminophthalimide underwent rapid ring opening reactions initiated by the addition of excess base to their refluxing methanolic solutions. The products were conveniently isolated through liquid-liquid extraction as the stable sodium salts V, and acidification precipitated the resulting phthalic acid congeners VI from aqueous solution. Compounds III readily exchanged one hydrazine moiety for another. For example, IIId reacted with 2,4-dinitrophenylhydrazine to give the 2,4-dinitrophenylhydrazone of 4-chlorobenzaldehyde (VIId, 93%). Nonetheless, IIIg reacted exclusively at the carboxaldehyde function to give products VIIIa and VIIIb.

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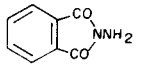
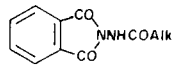
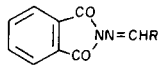
We have previously reported examples of the unusual reactivity of *N*-aminophthalimide (I) and its derivatives II-IV [2-4]. In view of recently renewed interest in the lability of the phthalimide group with lysing reagents [5,6], we would now like to discuss a new and very rapid ring opening reaction of *N*-aminophthalimide araldehyde hydrazones III under basic conditions. Thus we found that the addition of solid sodium methylate (2 equivalents) to a refluxing methanolic solution of IIIa occasioned a vigorous



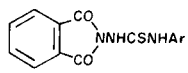
I



II



IIIa, R = p-$CH_3C_6H_4$
b, R = p-$CH_3OC_6H_4$
c, R = m-ClC_6H_4
d, R = p-ClC_6H_4
e, R = o-ClC_6H_4
f, R = p-$NO_2C_6H_4$
g, R = p-$CHOC_6H_4$
h, R = $CH{=}CHC_6H_5$

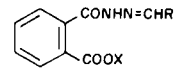


IV

and surprisingly rapid reaction, leading to the formation of the sodium salt Va (60%), characterized by its intense red-orange flame test and infrared bands appropriate to the carboxylate and hydrazide functions. Careful adjustment of the *p*H of an aqueous solution of Va led to exhaustive precipitation of the carboxylic acid VIa. Our results on the formation of the acids VI are summarized in Table I, and representative procedures are given below for their preparation (*vide infra*). We found the sodium salts V to be stable materials which could be conveniently stored in a dessicator for months without decomposition. Although our methods of analysis were capable of their detection in comparatively small proportions (*ca.* 5%), we did not observe formation of nitriles in the product mixtures, a result consistent with the ascription of *anti*-stereochemistry to the starting materials [3].

Table I

Benzals of *o*-Phthalic Acid Monohydrazide



V, X = Na
VI, X = H

Entry	Compound	Yield %	Analysis % Calcd./Found C	H	N
1	VIa	60 [a]	68.08	5.00	9.92
			67.79	5.00	9.86
2	VIb	79	64.44	4.79	9.39
			64.26	4.83	9.46
3	VIc	79	59.52	3.66	9.25
			59.40	3.70	9.12
4	VIe	12	59.52	3.66	9.25
			59.57	3.61	9.27
5	VIf	92	57.50	3.55	13.42
			57.42	3.65	13.35

[a] Yield data for isolated sodium salts V.

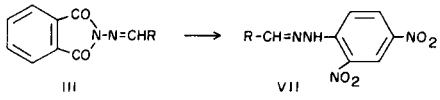
Treatment of the progenitor hydrazones III with 2,4-dinitrophenylhydrazine reagent led readily to the collection of the material resulting from interchange of the hydrazine residue as the only isolable solid product. In a typical example, *p*-chlorobenzylidenaminophthalimide (IIId) was warmed for a few minutes with 2,4-dinitrophenylhydrazine reagent [7] and rapidly gave rise to the 2,4-dinitrophenylhydrazone of *p*-chlorobenzaldehyde (VIId, Table II, entry 3, 93%), identical to an authentic sample prepared directly from the aldehyde. Interestingly, in both the ring-opening reaction and the hydrazine exchange reaction, compound IIIe, bearing an *ortho* substituent, remained relatively inert to the prevailing reaction conditions, a fact from which we infer the very crowded nature of the needed transition states.

On the other hand, compound IIIg did not experience hydrazine exchange but instead reacted exclusively at the free carboxaldehyde function. In this vein, warming phen-

ylhydrazine reagent [7] with IIIg in ethanol gave the clean formation of a canary yellow precipitate (VIIIa, 67%), the result of hydrazone formation. Similarly formed was the yellow unsymmetrical dihydrazone VIIIb (82%).

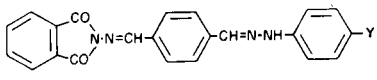
Table II

Hydrazine Exchange Reactions



III VII

Entry	Compound	Yield %
1	VIIa	89
2	VIIc	59
3	VIId	93
4	VIIe	5
5	VIIf	95



VIIIa, Y = H

b, Y = Cl

EXPERIMENTAL

Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tennessee, and were obtained for all new compounds. Melting points were taken in open capillary tubes using a Mel-Temp apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 1310 spectrophotometer as mineral oil mulls. *N*-Aminophthalimide was used as received from Fluka A.G. or conveniently prepared by the standard method of Drew and Hatt [8]. Reagent grade solvents were purchased from Baker.

o-Phthalic Acid Monohydrazide *p*-Tolual (VIa).

Compound IIIa (1.0184 g, 3.85 mmoles) was suspended in absolute methanol (15 ml) and heated with stirring to reflux. Solid sodium methylate (0.416 g, 7.70 mmoles) was added directly through the reflux condenser, and the reaction mixture was refluxed a further 2.5 hours. The condenser was removed, and the solvent was allowed to evaporate to approximately half volume. To the cooled reaction mixture was then added distilled water (10 ml). The solution was extracted with ether (2 × 10 ml), and the aqueous portion was allowed to evaporate to give large well-formed white prisms (Va, 60%, ir 1650, 1590 cm^{-1}). This material gave an intense red-orange flame when tested in the usual manner for the presence of a sodium salt.

The solid was taken up in a small volume of water and the *p*H was carefully adjusted to 1 using 6*N* hydrochloric acid causing the immediate precipitation of VIa, which was collected by filtration *in vacuo*, mp 159-164°; ir: 3420, 3190, 1690, 1620, 1580, 1300 cm^{-1}; hrms: Calcd. for $C_{16}H_{14}N_2O_3$: m/z 264.0899. Found: 264.0889.

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.08; H, 5.00; N, 9.92. Found: C, 67.79; H, 5.00; N, 9.86.

In a similar manner, the following compounds were also prepared.

o-Phthalic Acid Monohydrazide *p*-Methoxybenzal (VIb).

The sodium salt Vb was obtained in 79% yield, precipitation from dilute hydrochloric acid gave VIb, mp 178-181°; ir: 3230, 1740, 1650, 1610, 1595, 1570, 1500, 1330, 1300 cm^{-1}.

o-Phthalic Acid Monohydrazide *m*-Chlorobenzal (VIc).

The sodium salt Vc was prepared in 79% yield, precipitation from hydrochloric acid gave VIc, phase change 152-155° to yellow semisolid, mp 270°; ir: 3235, 1725, 1630, 1560, 1410, 1320 cm^{-1}.

o-Phthalic Acid Monohydrazide *o*-Chlorobenzal (VIe).

Isolation of the sodium salt occurred in 12% yield; treatment of an aqueous solution of the salt with dilute hydrochloric acid to *p*H 1 gave the benzal VIe, phase change to yellow semisolid 151-153°, mp 260° dec; ir: 3230, 1708, 1650, 1600, 1575, 1420, 1365, 1315 cm^{-1}.

o-Phthalic Acid Monohydrazide *o*-Nitrobenzal (VIf).

Evaporation of the solvent from the reaction mixture gave the sodium salt Vf (92%), from which was then derived by the usual adjustment of *p*H to 1 the corresponding acid VIf as a yellow crystalline solid, phase change to orange semisolid, mp 241-244°.

p-Chlorobenzaldehyde 2,4-Dinitrophenylhydrazone (VIId).

Compound IIId (0.22 g, 0.77 mmole) was suspended in 95% ethanol (10 ml) and warmed on a hot water bath. The addition in one portion of standard 2,4-dinitrophenylhydrazine reagent [7] caused the suspension to clear. The solution was heated and stirred a further 5 minutes, then allowed to cool. The yellow-orange solid (93%) was collected, washed with hot 95% ethanol (35 ml) and permitted to dry thoroughly. The sample thus obtained was shown to be identical to authentic material (mp, ir) prepared independently by the direct reaction of *p*-chlorobenzaldehyde with 2,4-dinitrophenylhydrazine reagent according to the conventional technique [7]. In an analogous way, conversions of compounds IIIa, IIIc, IIIe and IIIf to hydrazones VIIa, VIIc, VIIe and VIIf were also observed. In each case, the material so obtained was identified by comparison with an authentic sample prepared independently (Table II).

Representative Procedure for Dihydrazones VIII. Phenylhydrazonoterephthalilydenaminophthalimide (VIIIa).

Compound IIIg (0.278 g, 1.00 mmole) was suspended in 95% ethanol (35 ml) and heated on a boiling water bath. Phenylhydrazine reagent [7] (10 ml) was added and occasioned the immediate formation of a canary yellow precipitate. The reaction mixture was returned to the boil with stirring, the mixture cooled and the crystalline product filtered and washed with hot ethanol. After standing overnight, the product was washed with a further portion of hot ethanol and refiltered to obtain the analytical sample, 67%, mp 189° dec; ir: 3290, 1770, 1720, 1600, 1580, 1535, 1495 cm^{-1}.

Anal. Calcd. for $C_{22}H_{16}N_4O_2$: C, 71.73; H, 4.38; N, 15.21. Found: C, 71.93; H, 4.42; N, 15.50.

p-Chlorophenylhydrazonoterephthalilydenaminophthalimide (VIIIb).

The yellow unsymmetrical dihydrazone was obtained in 82% yield, mp 220° dec; ir: 3260, 1770, 1714, 1600, 1545, 1500, 1485 cm^{-1}; hrms: Calcd. for $C_{22}H_{15}ClN_4O_2$: m/z 402.0884. Found: 402.0918.

Anal. Calcd. for $C_{22}H_{15}ClN_4O_2$: C, 65.60; H, 3.75; N, 13.91. Found: C, 65.46; H, 3.96; N, 13.75.

Acknowledgments.

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REFERENCES AND NOTES

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