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Aryl Alkanehydrazonates and Their Thio Analogs. Synthesis of Some 2-Alkyl Derivatives of 4*H*-1,3,4-Benzoxadiazines and 4*H*-1,3,4-Benzothiadiazines

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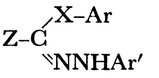
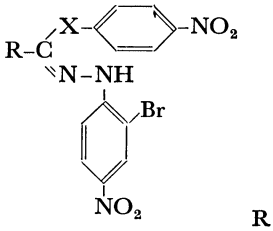
Synopsis. Synthesis of some *p*-nitrophenyl alkanethiohydrazonates, $RC(SC_6H_4NO_2\text{-}p)=NNHC_6H_3BrNO_2(2,4^-)$, and *p*-nitrophenyl alkanehydrazonates, $RC(OC_6H_4NO_2\text{-}p)=NNHC_6H_3BrNO_2(2,4^-)$ is described. Upon treatment with triethylamine in ethanol at reflux the thiohydrazonates give directly 2-alkyl-4-(*p*-nitrophenyl)-7-nitro-4*H*-1,3,4-benzothiadiazines, whereas the hydrazonates yield the hydrazides, $RCONHN(C_6H_4NO_2\text{-}p)C_6H_3BrNO_2(2,4^-)$. The latter hydrazides can be cyclized, under stronger basic conditions, into 2-alkyl-4-(*p*-nitrophenyl)-7-nitro-4*H*-1,3,4-benzoxadiazines by displacement of the 2-bromine atom.

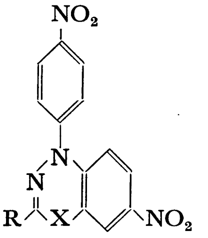
We have been exploring the synthesis and thermal rearrangement of several hydrazonate esters of type I (Z=aryl, C_2H_5OOC, C_6H_5NHCO, and $X=O$ or S).[3–6] We wish now to describe the synthesis of some alkanethiohydrazonates (II, R=alkyl and X=S) and the use of such esters in the synthesis of 2-alkyl derivatives of 4*H*-1,3,4-benzoxadiazines (III, X=O) and the thiadiazine analogs (III, X=S) respectively.



I

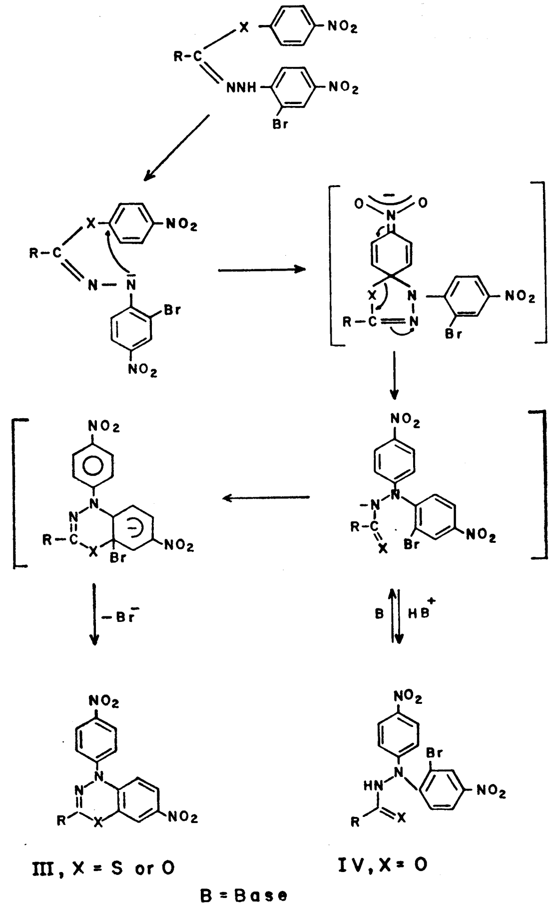


II



III

a, X=S; R=CH_3
b, X=S; R=CH_3CH_2
c, X=S; R=$(CH_3)_2CH$
d, X=O; R=$(CH_3)_2CH$
e, X=O; R=CH_3



Scheme 1.

The required *S*-*p*-nitrophenyl alkanethiohydrazonates, IIa to IIc, were obtained by treating the corresponding alkanehydrazonoyl bromides with *p*-nitrobenzenethiol in ethanol in the presence of triethylamine at room temperature. The other alkanehydrazonates, IId and IIe, were similarly prepared using *p*-nitrophenol in place of *p*-nitrobenzenethiol. The structures of these esters were confirmed by their elemental analysis and the spectral data. For example, esters IId and IIe exhibited in infrared spectra bands at 1250 and 1065 cm^{-1} assignable to an aryl ether linkage. Their electronic absorption pattern in ethanol was of typical hydrazones.

Treatment of thiohydrazonate IIa with triethylamine in ethanol at reflux gave the corresponding thiadiazine, IIIa. The other thiohydrazonates, IIb and IIc, similarly gave the thiadiazines, IIIb and IIIc, respectively. The structures of the latter products were evidenced by their elemental analysis and spectra (see Experimental). To account for this, it is assumed that the reaction proceeds through the formation of the anionic species of the rearranged thiohydrazide (IV, X=S), which undergoes cyclization to thiadiazine (III, X=S) as it is formed (Scheme 1). This is analogous to the reaction of arenehydrazonoyl bromides with thioacetate ion[7] and the recently reported rearrangement of aryl thiohydrazonates.[8]

In contrast to thiohydrazonates IIa to IIc, hydrazonates IId and IIe rearranged to the corresponding hydrazides (IV, X=O) in refluxing ethanol–triethylamine generally within 100 min. The structures of the latter hydrazides,

$$\underset{\text{IV}}{R\text{-}CX\text{-}NHN(C_6H_4NO_2\text{-}p)C_6H_3BrNO_2(2,4^-)}$$

were evidenced by the appearance of bands at 1680 cm^{-1}

Table 1. *p*-Nitrophenyl alkanehydrazonates and their thio analogs

Compd No.	Mp, °C	Molecular formula	C, %		H, %		N, %	
			Found	(Calcd)	Found	(Calcd)	Found	(Calcd)
IIa[a]	156	$C_{14}H_{11}N_4O_4BrS$	41.05	(40.88)	2.76	(2.69)	13.60	(13.62)
IIb	132	$C_{15}H_{13}N_4O_4BrS$	42.50	(42.36)	2.87	(3.08)	13.31	(13.17)
IIc	113	$C_{16}H_{15}N_4O_4BrS$	43.74	(43.74)	3.33	(3.44)	12.65	(12.75)
IId[b]	151	$C_{16}H_{15}N_4O_5BrS$	45.44	(45.40)	3.59	(3.57)	13.43	(13.24)
IIe	188	$C_{14}H_{11}N_4O_5Br$	42.39	(42.54)	2.87	(2.80)	14.29	(14.28)

a) λ_{max}^{EtOH} (log ε) 363 (4.383); 320 (4.156) b, nm; $\bar{\nu}$ (KBr) 3297 (NH); 1344 (C–S–C) cm^{-1}; δ(CDCl$_3$) 2.14 (s, 3H, CH$_3$), 7.0—8.40 (m, 8H, ArH and hydrazone NH) ppm. b) λ_{max}^{EtOH} (log ε) 363 (4.321), 325 sh (4.156), 260 sh (4.010) nm; $\bar{\nu}$(KBr) 3375 (NH), 1336, 1038 (aryl ether linkage) cm^{-1}; δ(CDCl$_3$) 1.28 (d, 6H, J=7 Hz, (CH$_3$)$_2$CH), 2.75 (septet, 1H, J=7 Hz, (CH$_3$)$_2$CH), 7.0—8.6 (m, 8H, ArH and hydrazone NH) ppm.

(CO) and the absence of the Ar–O–C bands in their infrared spectra. This base catalyzed rearrangement of II to IV (X=O) appears to follow nucleophilic substitution mechanism (Scheme 1) rather than the free radical sequence proposed for the thermally induced rearrangement of aryl arenecarbohydrazonates to *N*-aroyl-*N′*,*N′*-diarylhydrazines.⁹⁾ The *p*-nitro substituent in the *O*-aryl moiety probably increases the stability of the five-membered cyclic transition state. In this respect the present O→N aryl migration can be seen as a Smiles-type rearrangement;¹⁰⁾ in agreement with the views of Elliott *et al.*¹¹⁾ who indicated that aryl arenecarbohydrazonates substituted such that the *O*-aryl ring is sufficiently electron deficient, undergo a facile base-catalyzed Smiles rearrangement to give the corresponding hydrazides.

The cyclization of IV (X=O) into III (X=O) was effected only by boiling with an equivalent amount of sodium hydroxide in *N*,*N*-dimethylformamide–triethylamine mixture for 10 h. The structure of the benzoxadiazines prepared followed their elemental analysis and was confirmed by the absence of NH and CO absorption bands in their infrared spectra. The mechanism favoured for this cyclization seems to be analogous to that proposed for the cyclization of IV—III (X=S); *i.e.*, the anionic species derived from the hydrazide is thought to attack the 2-position of the 2-bromo-4-nitrophenyl group to form the heterocyclic ring by nucleophilic displacement of bromine.

Experimental

All melting points are uncorrected. Microanalyses were performed by Alfred Berhardt, Mikroanalytische Laboratorium, West Germany. The IR and UV spectra were recorded with Pye-Unicam SP 1000 and SP 8000 spectrophotometers respectively. PMR spectra were recorded on a Varian T60A spectrometer using tetramethylsilane as an internal reference.

Alkanehydrazonoyl bromides were prepared by literature method;¹²⁾ their physical constants (mp.s) corresponded with data reported.¹²⁾

p-Nitrophenyl *N*-(2-bromo-4-nitrophenyl)alkanehydrazonates (IId—e) and their thio analogs (II—ac). General Procedure. A mixture of hydrazonoyl bromide (0.01 mol), *p*-nitrophenol (or *p*-nitrobenzenethiol) (0.01 mol) and triethylamine (0.02 mol) in ethanol (50 ml) was stirred at room temperature for 1 h. The product that precipitated was collected, washed with water and purified by crystallization from ethanol. The results are summarized in Table 1.

N-Isobutyryl-N′-(2-bromo-4-nitrophenyl)-N′-(p-nitrophenyl)-hydrazine (IVd). The hydrazonate IId in 1: 1 (v/v) ethanol–triethylamine mixture was refluxed for 1 h. The reaction mixture was then concentrated, diluted with water and the solid formed was collected. Crystallization from methanol gave the hydrazide IVd, mp 168 °C. Found: C, 45.41; H, 3.50: N, 13.20%. Calcd for $C_{16}H_{15}N_4O_5Br$: C, 45.40; H, 3.57; N, 13.24%. $\bar{\nu}$(KBr) 1680 (CO); 3250 (NH) cm^{-1}; λ_{max}^{EtOH} (log ε) 363 (4.274); 325 (3.997) sh; 260 (3.912) sh; δ (CDCl$_3$) 1.22 (d, 6H, J=7 Hz, (CH$_3$)$_2$CH) 2.58 (septet, 1H, J=7 Hz, Me$_2$CH); 7.0—8.6 (m, 8H, ArH and hydrazide NH) ppm.

2-Isopropyl-4-(p-nitrophenyl)-7-nitro-4H-1,3,4-benzoxadiazine, IIId. Equivalent amounts of the hydrazide IVd and sodium hydroxide were dissolved in a mixture of *N*,*N*-dimethylformamide and triethylamine and refluxed for 10 h. The solution was then cooled, poured into excess of 5% acetic acid. The solid that precipitated was collected and washed with water. Crystallization from methanol gave IIId in 50% yield, mp 165 °C. Found: C, 55.98; H, 4.20; N, 16.20%. Calcd for $C_{16}H_{14}N_4O_5$: C, 56.14; H, 4.12; N, 16.36%. $\bar{\nu}$(KBr) 1350, 1040 (cyclic ether).

2-Alkyl-4-(p-nitrophenyl)-7-nitro-4H-1,3,4-benzothiadiazines, IIIa—c. The appropriate thiohydrazonate (0.5 g) was refluxed in a 1: 1 (v/v) mixture of ethanol and triethylamine (40 ml) for 4 h. The solution was then concentrated and the solid that separated on cooling was collected. Crystallization from dioxane gave the following benzothiadiazines.

Compound IIIa, mp 240 °C. Found: C, 50.90; H, 3.13; N, 16.59%. Calcd for $C_{14}H_{10}N_4O_4S$: C, 50.90; H, 3.05; N, 16.96%. λ_{max}^{EtOH} (log ε) 410 (4.163); 295 sh (3.833) nm; δ(CDCl$_3$) 2.40 (s, 3H, 2-CH$_3$); 7.0—8.4 (m, 7H, ArH) ppm.

Compound IIIb, mp 180 °C. Found: C, 51.95; H, 4.10; N, 16.23%. Calcd for $C_{15}H_{12}N_4O_4S$: C, 52.32; H, 3.51; N, 16.27%.

Compound IIIc, mp 160 °C. Found: C, 53.41; H, 3.78; N, 15.41%. Calcd for $C_{16}H_{14}N_4O_4S$: C, 53.62; H, 3.93; N, 15.63%.

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