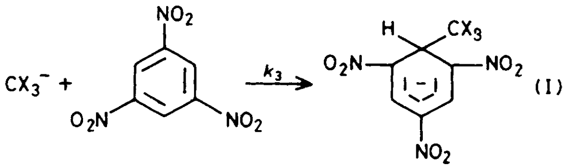
The Reaction of Trihalogenomethyl Anions with Carbonyl Compounds: Competitive Reactivity Comparisons and Applications to the Synthesis of α-Trihalogenomethyl Alcohols

Paul J. Atkins, Victor Gold,* and Wasfy N. Wassef
King's College London, Strand, London WC2R 2LS

Trihalogenomethyl anions, generated by decarboxylation of trichloro- and tribromo-acetic acid in dimethyl sulphoxide solution, react with added aldehydes. In the presence of 1,3,5-trinitrobenzene, the reaction with aldehydes competes with the formation of the coloured Meisenheimer adduct. The reduction in absorbance from the value in the absence of aldehyde has been used to measure the reactivity of trihalogenomethyl anions towards a series of aldehydes relative to their reactivity towards trinitrobenzene. For 4-substituted benzaldehydes, the reactivities obey a linear ρσ− relationship. The most reactive aldehyde used is only two times less reactive towards CCl_3^- or CBr_3^- than hydrogen ions, and it is concluded that, in dimethyl sulphoxide solutions, the reaction between trichloromethyl anions and hydrogen ions is not encounter-controlled. The reactions with aldehydes have been used to prepare several new compounds of the formula $RCH(OY)CX_3$ where R = aryl or pyridyl, X = Br or Cl, and Y = H or $COCH_3$.

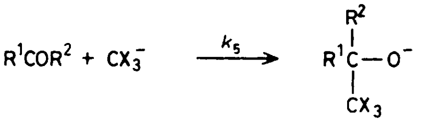
$$CX_3CO_2H \rightleftharpoons CX_3CO_2^- + H^+_{solv} \qquad (1)$$

$$CX_3CO_2^- \xrightarrow{k_2} CX_3^- + CO_2 \qquad (2)$$

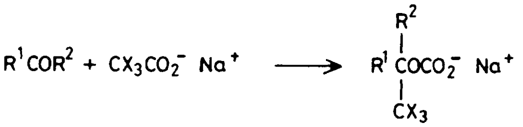


(I) (3)

$$CX_3^- + H^+_{solv} \xrightarrow{k_4} HCX_3 \qquad (4)$$



$$R^1COR^2 + CX_3^- \xrightarrow{k_5} R^1\overset{R^2}{\underset{CX_3}{C}}{-}O^- \qquad (5)$$



$$R^1COR^2 + CX_3CO_2^-\ Na^+ \longrightarrow R^1\overset{R^2}{\underset{CX_3}{C}}OCO_2^-\ Na^+ \qquad (6)$$

It has recently been shown that trichloro- and tribromoacetic acid (and their sodium salts) rapidly decompose when dissolved in dimethyl sulphoxide (DMSO).[1] The rate-limiting step of the overall reaction is the unimolecular heterolysis of the trihalogenoacetate ion [equation (2)] with liberation of the unstable trihalogenomethyl anion, which can be efficiently trapped with 1,3,5-trinitrobenzene (TNB) [equation (3)]. The yield of the coloured Meisenheimer adduct anion formed in the trapping reaction[2] is reduced if other reactants with a high reactivity towards trihalogenomethyl anions are present. This has been demonstrated by the addition of hydrochloric acid to the reaction medium so that solvated hydrogen ions compete with TNB for the trihalogenomethyl anions [equation (4)].[1] The effect has been used to determine the ratio of the rate constants for reactions (3) and (4) and is now applied to reactivity comparisons involving the reaction of carbonyl compounds with trihalogenomethyl anions.

Carbonyl compounds are known to be reactive towards anionic nucleophiles, and it was therefore expected that reaction (5) would occur when the decomposition of the trihalogenoacetic acids takes place in their presence, leading (in experiments on a preparative scale) to isolation of the corresponding trihalogenomethyl-substituted alcohols.

The present work shows that these expectations are fulfilled and reports the application of these principles (a) to the determination of the reactivity ratio k_5/k_3 for a series of substituted benzaldehydes (R^1 = aryl, R^2 = H), with evaluation of the Hammett ρ value for reaction (5), and (b) to the preparation of several 1-trihalogenomethyl alcohols and of some of their derivatives.

Since the submission of the preliminary publication[3] of some of our preparative results a patent specification has appeared which claims that the reaction of trihalogenoacetate salts in dimethylformamide (and in related solvents, including DMSO) with carbonyl compounds leads to the formation of the corresponding carbonates.[4] That reaction could be looked upon as the addition of CX_3^- and CO_2 across the carbonyl group [equation (6)]. In our experiments we have obtained no evidence for the formation of the carbonate.

In the light of our kinetic study of the reaction mechanism of the decomposition of trichloroacetic acid and of sodium trichloroacetate in DMSO, the formation of the carbonate, if it does occur, would be a subsequent reaction between dissolved carbon dioxide and the alkoxide ion formed in reaction (5). The effectiveness of such a secondary process would depend on the concentrations and on the solubility of carbon dioxide in the particular solvent used. In any case it would not affect the validity of the determination of the rate constant ratio k_5/k_3 by competition experiments, nor that of our method for the one-step preparation of 1-trihalogenomethyl alcohols from carbonyl compounds.

Experimental

The aromatic aldehydes used in competition experiments were washed with an aqueous alkaline solution to remove carboxylic acids, dried ($CaSO_4$ or $MgSO_4$), and either freshly distilled or, in the case of solids, crystallised from a recommended solvent. Pyridine-4-carbaldehyde and chloral hydrate were commercial samples and used without purification.

Solvents and other materials were treated as previously described.

Competition Experiments.—Measurements of the rate of formation of the coloured Meisenheimer adduct anion were

Table 1. Final absorbance results for experiments with trichloroacetic acid and added aldehydes

(A) Aromatic aldehydes XC_6H_4CHO

10^3 [C] *	$(A^0 - A)/A$ for X =						
	p-NO_2	*m*-NO_2	*m*-Cl	*p*-Cl	H	*p*-CH_3	*p*-OCH_3
2	0.442	0.398	0.212	0.043			
3		0.580					
4	1.053	0.770	0.371	0.173			
5	1.287	0.993	0.475	0.253	0.067		
8	1.976	1.627	0.705	0.429			
10	2.440	1.892	0.878	0.557	0.223		
15		3.151					
20	4.80		1.850	1.120	0.446	0.183	
25					0.478		
30			2.449	1.648			
40					0.842	0.397	
50					1.037	0.548	0.174
60					1.242	0.622	
100					2.273	1.159	0.439
150							0.738
200							0.935
250							1.176
300							1.459

(B) Other aldehydes

10^3 [C] *	$(A^0 - A)/A$ for		
	Pyridine-4-carbaldehyde	Chloral hydrate	Furfural
2	1.535		
4	1.105		
5	1.351	0.121	
10	2.715	0.280	
20	5.405	0.613	0.185
30		0.836	
40		1.264	0.401
50		1.557	0.542
100			1.245
150			1.905

* [C] = Concentration of carbonyl compound; [TNB] = 2×10^{-3}M; $[CCl_3CO_2H]_0 = 5 \times 10^{-5}$M.

Table 2. Final absorbance results for experiments with tribromoacetic acid and aromatic aldehydes XC_6H_4CHO

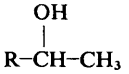
10^3 [C] *	$(A^0 - A)/A$ for X =					
	p-NO_2	*m*-NO_2	*m*-Cl	*p*-Cl	H	*p*-CH_3
2	0.414	0.305				
3	0.605					
4	0.878	0.540	0.177	0.061		
5	1.061	0.850	0.269	0.100		
8	1.493	1.269	0.453	0.226		
10	1.950	1.430	0.486	0.247		
20		2.716	1.049	0.513		
25					0.158	
40					0.244	0.088
50					0.339	0.157
60					0.350	
75						0.323
100					0.704	0.382

* [C] = Concentration of aldehyde; [TNB] = 2×10^{-3}M; $[CBr_3CO_2H]_0 = 5 \times 10^{-5}$M.

performed as before.[1] A stock solution of trihalogenoacetic acid was added last to the thermostatted reaction medium containing TNB and aldehyde. The initial concentration of trihalogenoacetic acid was 5×10^{-5}M throughout. The observed rate constants at 25 °C were found to be independent both of the concentration of trinitrobenzene (over the range 5×10^{-4}—0.1M) and of the concentration of added aldehyde. The infinity readings did not depend on the concentration of TNB, but decreased with increasing concentration of added aldehyde. These final absorbances did not change over a time interval corresponding to several reaction half-lives, indicating that under the conditions of our experiments the adduct anion (I) does not react with aldehyde either directly or *via* the reverse reaction of step (3). Results for the reduction in final absorbance are given in the form $(A^0 - A)/A$, where A^0 and A are the observed final absorbances at the absorption maximum near 430 nm without and with added aldehyde, respectively (Tables 1 and 2). The corresponding values of A^0 were 1.345 in the case of trichloroacetic acid and 1.334 for tribromoacetic acid. For all the examples listed in Table 1,

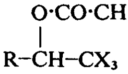
Table 3. Formulae and names of 1-trihalogenomethyl alcohols and corresponding acetate esters

Compound	R	X	Systematic name
(IIa)	4-Nitrophenyl	Cl	2,2,2-Trichloro-1-(4-nitrophenyl)ethanol
(IIb)	4-Pyridyl	Cl	2,2,2-Trichloro-1-(4-pyridyl)ethanol
(IIc)	4-Nitrophenyl	Br	2,2,2-Tribromo-1-(4-nitrophenyl)ethanol
(IId)	4-Pyridyl	Br	2,2,2-Tribromo-1-(4-pyridyl)ethanol
(IIe)	2-Nitrophenyl	Br	2,2,2-Tribromo-1-(2-nitrophenyl)ethanol
(IIf)	2-Pyridyl	Br	2,2,2-Tribromo-1-(2-pyridyl)ethanol
(IIg)	4-Chlorophenyl	Br	2,2,2-Tribromo-1-(4-chlorophenyl)ethanol
(IIIa)	3-Chlorophenyl	Br	2,2,2-Tribromo-1-(3-chlorophenyl)ethyl acetate
(IIIb)	3-Nitrophenyl	Br	2,2,2-Tribromo-1-(3-nitrophenyl)ethyl acetate



$$R{-}\overset{\overset{\displaystyle OH}{|}}{C}H{-}CH_3$$

(II)



$$R{-}\overset{\overset{\displaystyle O{\cdot}CO{\cdot}CH_3}{|}}{C}H{-}CX_3$$

(III)

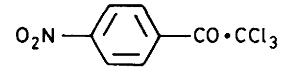
the first-order rate constants for the appearance of the absorbance due to the anion (I) were also measured and found to have the same value (±15% in extreme cases) as in the absence of aldehyde. In experiments with even larger concentrations of added aldehyde the final absorbance at 430 nm was very small.

Preparative Experiments.—2,2,2-*Trichloro*-1-(4-*nitrophenyl*)-*ethanol* (IIa). Trichloroacetic acid (2.4 g, 0.015 mol) was added with stirring to a solution of 4-nitrobenzaldehyde (1.5 g, 0.01 mol) in DMSO (50 cm^3). After being allowed to react for *ca.* 50 min at room temperature, the solution was poured into ice-cold water (400 cm^3) and the mixture was extracted with ether. The ethereal extract was washed successively with sodium hydrogencarbonate solution (5%) and water and then dried ($MgSO_4$). The solid product left after removal of ether under reduced pressure was crystallised from n-heptane, to give crystals of (IIa), m.p. 107—108 °C (lit.,[5] 109 °C).

The trihalogenoethanols (IIb—g) (see Table 3) were prepared by corresponding procedures, except that the addition of the trihalogenoacetic acid was in small portions over 1—3 h and that other solvents (dichloromethane–tetrachloromethane, trichloromethane–n-hexane, or trichloromethane–n-heptane) were in some cases preferred for crystallisation. In most preparations dilution with cold water after reaction yielded a solid product which was filtered off, rendering extraction with ether unnecessary. Yields were in the range 50—80%. M.p.s and n.m.r. spectra of compounds (II) are tabulated (Table 4). The ^{13}C n.m.r. spectrum of (IIa) is in agreement with one previously reported.[6]

2,2,2-*Tribromo*-1-(3-*chlorophenyl*)*ethyl acetate* (IIIa). The same procedure as for (II) was followed up to the isolation of the crude alcohol. This product (3 g) was dissolved in a small volume of acetyl chloride (2 cm^3) and heated under reflux (2 h). The solid ester produced separated when the mixture was poured onto ice. It was crystallised from light petroleum (b.p. 60—90 °C), m.p. 102 °C, yield 43%. An identical procedure was used for the preparation of (IIIb), m.p. 145 °C, yield 57%. N.m.r. spectra of (IIIa and b) are included in Table 4.

α,α,α-*Trichloro*-4-*nitroacetophenone* (IV). Trichloroacetic acid (1.7 g, 0.01 mol) was added with stirring to a solution of 4-nitrobenzaldehyde (1.5 g, 0.01 mol) in DMSO (20 cm^3). After several hours at room temperature, acetic anhydride (5 cm^3) was added and, after being left for a day at room temperature, the solution was poured into ice-cold water. An oil separated which solidified on standing. Crystallisation of the solid product from ethanol gave (IV), m.p. 118—120 °C (lit.,[5] 104—106 °C) in 70% yield. The product was identified by its n.m.r. spectrum (see Table 4). Its melting point was depressed to 75 °C on admixture of 4-nitrobenzaldehyde, m.p. 106 °C. On being heated with 6% sodium hydroxide solution at 90 °C, followed by acidification, the compound yielded 4-nitrobenzoic acid, m.p. 242 °C.



(IV)

The reaction scheme represented by equations (1)—(5) requires that the relative yields of products in steps (3)—(5) should be in the ratio k_3[TNB] : $k_4[H^+_{solv.}]$: k_5[C] (where [C] is the concentration of the carbonyl compound). In experiments without added mineral acid, reaction (4) is relatively unimportant. The final absorbance (A^0) in a cell of 1 cm path-length when there is no added carbonyl compound will be given by equation (7) and not very different from the product ε_{431}[TXAA] (where [TXAA] is the stoicheiometric initial concentration of trihalogenoacetic acid), as expressed in equation (8). The numerical factor p, given by equation (9),

$$A^0 = \varepsilon_{431}[\text{TXAA}]\cdot\frac{k_3[\text{TNB}]}{k_3[\text{TNB}] + k_4[\text{H}^+_{\text{solv.}}]} \qquad (7)$$

$$A^0 = p\,\varepsilon_{431}[\text{TXAA}] \qquad (8)$$

$$p = k_3[\text{TNB}]/\{k_3[\text{TNB}] + k_4[\text{H}^+_{\text{solv.}}]\} \qquad (9)$$

has a value of *ca.* 0.9 for experiments at the concentrations of trihalogenoacetic acid used. This value is obtained by comparison of the ratio A^0/[TXAA] in the present series of experiments (26 900) with the value of ε_{431} deduced from earlier experiments in which the adduct ion was formed *via* the decomposition of sodium trichloroacetate. In the presence of added carbonyl compound, the final concentration of the Meisenheimer adduct (I) will be reduced by the amount of CX_3^- that adds to the carbonyl compound instead of to TNB. On the assumption that the light absorption at 431 nm is under all conditions due only to (I) [and that, for example, the alkoxide ion formed in step (5) is not itself trapped by TNB with formation of a coloured adduct], the final absorbance is given by equation (10). From equations (7), (8), and (10) equation (11) is obtained.

$$A = \varepsilon_{431}[\text{TXAA}]\cdot\frac{k_3[\text{TNB}]}{k_3[\text{TNB}] + k_4[\text{H}^+_{\text{solv.}}] + k_5[\text{C}]} \qquad (10)$$

$$(A^0 - A)/A = pk_5[\text{C}]/k_3[\text{TNB}] \qquad (11)$$

Table 4. Characterisation of compounds (II) and (III) *

	M.p. (°C)		^{1}H n.m.r. (δ) *C*HOH	CHO*H*	J_{CHOH}	2,6	3,5	4
(IIa)	107—109		5.26	3.44		← 8.02m	→	
(IIb)	136—138	D	5.32d	7.59d †	6.0	7.60—7.63m(2)	8.59—8.61m(2)	
(IIc)	118—120	C	5.31s			7.91—7.95m(2)	8.22—8.27m(2)	
(IId)	162—163	D	5.22d	7.54d	5.8	7.69—7.72m(m)	8.59—8.61m(2)	
(IIe)	99—100	D	6.1d		5.5	← incl. O*H*,	7.64—8.17m(5)	→
(IIf)	132—133	DM	5.14d	7.35	6.4	7.78—7.90m(2)	8.57m(1)	7.39—7.44m(1)
(IIg)		N	5.1			← incl. O*H*,	7.14—8.0m	→
				CH_3				
(IIIa)	102	D	6.38	2.22(3)		←	7.44—7.81(4)	→
(IIIb)	145	D	6.60	2.25(3)		8.62s(2)	7.76t(2)	

		^{13}C n.m.r. (δ) *C*X$_3$	*C*HOH	Aromatic	*C*H$_3$	*C*O
(IIa)	C	102.09	83.53	122.86, 130.42, 141.44, 148.8		
(IIb)	D	102.54	81.43	124.14, 145.67, 148.87		
(IIc)	D	52.16	84.64	122.65, 130.94, 141.84, 148.43		
(IId)	D	52.73	82.58	124.53, 146.6, 148.53		
(IIe)	D	52.67	76.84	124.01, 130.06, 130.51, 131.71, 132.51, 149.71		
(IIf)	D	52.37	85.04	123.60, 123.70, 136.03, 147.67, 175.08		
(IIIa)	D	44.13	136.15	128.47, 129.40, 129.52, 129.57, 132.40,		
(IIIb)	D	43.54	136.35	124.18, 124.41, 129.35, 135.92, 136.35, 147.15, 136.15	20.46	169.23

* N.m.r. spectra taken on a Bruker WM 250 spectrometer (250 MHz for ^{1}H; 62.89 MHz for ^{13}C); the letters C, D, DM, N refer to the solvents used [C = $CDCl_3$; D = $(CD_3)_2SO$; N = CD_3CN; DM = mixture of $(CD_3)_2SO$ and CD_3OD] [except ^{1}H spectra of (IIa and IIg), taken at 60 MHz]. † Assignment confirmed by H–D exchange on addition of D_2O.

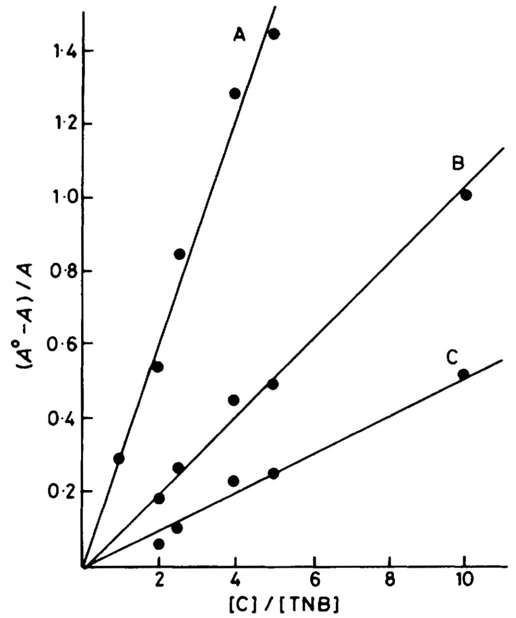


Figure 1. Graphical evaluation of pk_5/k_3 according to equation (10). (A, 4-chlorobenzaldehyde; B, 3-chlorobenzaldehyde; C, 3-nitrobenzaldehyde)

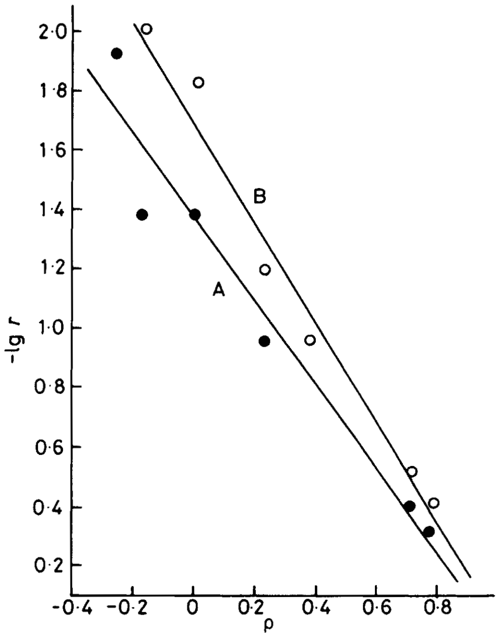


Figure 2. ρσ$^-$ Correlations for reactions of trihalogenomethyl anions with aromatic aldehydes (A, CCl_3^-; B, CBr_3^-)

The predicted linear dependence of the ratio $(A^0 - A)/A$, listed in Tables 1 and 2, upon the concentration ratio [C]/[TNB] is obeyed, as illustrated by the graphs of Figure 1. The slopes, corresponding to the proportionality constant $r = pk_5/k_3$, are summarised in Table 5. The values show that the carbonyl compounds studied span a *ca.* 40-fold range of reactivity towards trihalogenomethyl anions, with the more reactive carbonyl compounds being only about two times less reactive than TNB.

The aromatic aldehydes were chosen as a reaction series

Table 5. Reactivity ratios r, pk_5/k_3 for different aldehydes with trichloro- and tribromo-methyl anions

	CCl_3^-		CBr_3^-		Hammett σ
Aldehyde	r	lg r	r	lg r	
4-$(NO_2)C_6H_4$	0.49	−0.31	0.39	−0.41	0.78
3-$(NO_2)C_6H_4$	0.40	−0.40	0.31	−0.51	0.71
3-ClC_6H_4	0.164	−0.79	0.113	−0.95	0.37
4-ClC_6H_4	0.111	−0.95	0.064	−1.19	0.23
C_6H_5	0.042	−1.38	0.015	−1.82	0.00
4-$(CH_3)C_6H_4$	0.024	−1.62	0.010	−2.00	−0.17
4-$(CH_3O)C_6H_4$	0.012	−1.92			−0.27
Pyridine-4-carbaldehyde	0.554	−0.26			0.76—0.96
Chloral hydrate	0.061				
Furfural	0.02				

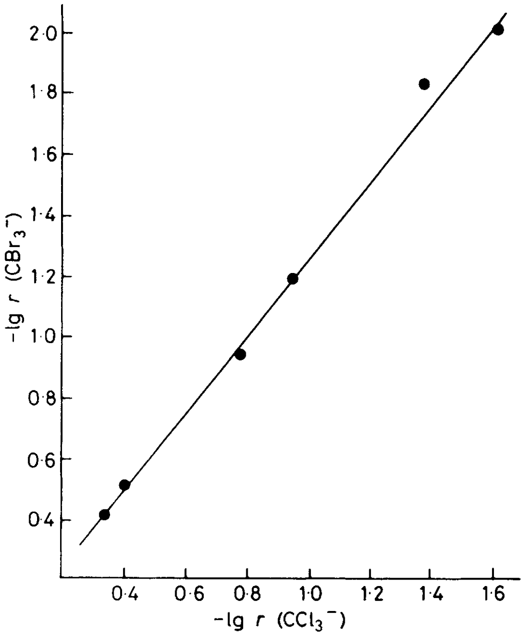


Figure 3. Illustration of linear relationship between lg r values for CCl_3^- and CBr_3^- anions

with known Hammett substituent constants. The suspected correlation of lg r and σ [which is effectively the correlation of lg k_5 with σ, since the factor (p/k_3) is constant throughout the series] is demonstrated by Figure 2. The value of ρ thus deduced for the reaction of trichloromethyl anions is 1.2. The more rapidly formed (and hence presumably more stable) tribromomethyl anion is slightly more selective, with a σ value of 1.4. As is to be expected from these results, a plot of lg r for CBr_3^- against lg r for CCl_3^- (Figure 3) is closely linear. The slope (1.2) is not far from the slope of unity consistent with Ritchie's N_+ relationship,[7] although the difference appears to be outside the limits of error.

The linear correlation suggests that the reaction with aldehydes is not encounter-controlled and hence that the reaction between trichloromethyl anions and hydrogen ions in DMSO is also not encounter-controlled.

There is strong evidence that in aqueous solution the reaction between hydrogen ions and trichloromethyl anions is encounter-controlled.[8] Our results suggest that other factors raise the energy barrier for proton transfer in DMSO solution.

The Gibbs energy correlations also serve as a guide for the preparation of compounds (II)—(IV) (see Table 3) by trihalogenomethyl anion attachment to the corresponding aldehydes, as detailed in the Experimental section. With the exception of (IIa) and (IV) the compounds have not previously been reported.

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