An N.m.r. Study of Hydroxymethylation of Some Substituted Amides

JOHN P. CHUPP AND A. J. SPEZIALE

The Research Department, Agricultural Chemicals Division, Monsanto Chemical Company, St. Louis, Missouri

Received March 21, 1963

A proton n.m.r. method has been developed for the assay of materials arising from the N-hydroxymethylation of several N-methylamides. The extent and nature of the reaction and products under both anhydrous and aqueous conditions are discussed and the results compared with previous work in the field.

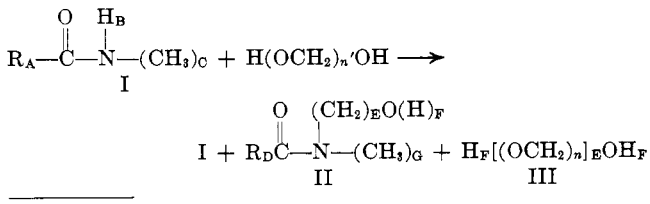
The hydroxymethylation of nitrogen in unsubstituted amides is well described.[1,2] The reaction of formaldehyde with N-alkylamides has been reported only recently and found, despite earlier opinions to the contrary,[1-3] to give N-hydroxymethyl-N-alkylamides.[4,5]

The thermal instability of simple N-hydroxymethyl-N-alkylamides makes it impossible to isolate the pure liquids by distillation. Consequently, the existence of N-hydroxymethyl-N-methylamides has recently been shown only by the isolation of crystalline derivatives,[4] distillable acetate esters,[6] or titrations for remaining formaldehyde in aqueous mixtures of formaldehyde and N-alkylamide solutions.[5]

Thus, the quantitative yields of methylol compounds reported by Böhme[4] on heating equimolar quantities of certain N-alkylacetamides and -benzamides with paraformaldehyde at 120–145° were based on the conversion of the viscous or sirupy liquids to certain crystalline derivatives in nearly quantitative yields.

Vail[5] studied the methylolation reaction at 60° in 20% formalin solution, using a 1:1.5 molar excess of formaldehyde. He found that the reaction did not proceed to completion; only 63% of N-methylformamide reacted, while N-methylacetamide gave a 79% conversion, as determined by titration with sodium sulfite.

A study of these methylolation reactions might be advantageously carried out using proton n.m.r. as an aid in determining the nature and extent of reaction. This method would obviate the disadvantages inherent in chemical transformations to crystalline derivatives where unchanged formaldehyde and amide might possibly enter reaction to give the chemical derivative as well as the methylol compound. The titration of excess formaldehyde[5] is open to criticism because of the doubt existing that only pure formaldehyde is titrated and that the equilibrium is stable under conditions of increasing pH. N.m.r. spectra, if amenable to interpretation, would give, with no external influences, an accurate representation of the reaction mixture. Table I shows the results obtained in the hydroxymethylation of various amides, utilizing both Böhme's and Vail's



reaction conditions. A typical n.m.r. spectrum (material 2) is shown in Fig. I. If we consider the generalized reaction as representing the hydroxymethylation reaction, Table I is interpreted as follows: The peaks A, B, and C represent the hydrogens attached to unchanged amide as shown in I. These peaks are also present in the reaction mixtures, thus indicating that the reactions did not proceed to completion. The peak assignments were confirmed by adding the pure amides to the reaction mixtures and noting the increase in A, B, and C. Moreover, peak C showed the characteristic doublet when the reaction was carried out under essential anhydrous conditions.[7] The remaining peaks (D, E, F, G) were consequently assigned to the reaction products and unreacted formaldehyde (II and III).

We wished to demonstrate that only methylolation occurred in these reactions, and that the reaction mixtures contained no confusing complex aggregate of condensation products. Materials 2, 4, and 8 were passed through a vapor phase chromatography column at 200°. The only peaks obtained were assignable to formaldehyde and I. Moreover, the fraction of I observed in the chromatogram from each mixture was equal to the fraction of I employed in the preparation of the respective mixtures. This observation agrees with the known instability of certain methylol compounds, wherein formaldehyde and amide can be quite easily obtained on heating. On the other hand, when an aqueous solution of methylenebisacetamide was subjected to the same v.p.c. treatment at 200°, no acetamide was obtained, showing the irreversible character of thermal treatment of formaldehyde–amide condensation products. We may conclude, therefore, that no products incapable of quantitative thermal reversal to amides arose in our methylolation studies.

Various authentic materials containing groups corresponding to D, E, F, and G were shown to have respective chemical shifts of similar magnitude.[8] Examining Fig. 1, it can be seen that the chemical shift for D is close to A, and G has a chemical shift similar to C, while the chemical shift for E includes the methylene groups from both II and III. Similarly the somewhat broad F peak is assigned to the OH groups from II and III.

If these assignments are correct, then the areas under G + C should be, respectively, 1, 1.5, 3, and 0.6 times area of A + D in mixtures arising from methylolation

(1) H. Einhorn, *Ann.*, **343**, 207 (1905).

(2) J. F. Walker, "Formaldehyde," 2nd Ed., Reinhold Publishing Corp., New York, N. Y., 1953, p. 290.

(3) B. R. Schröter in "Methoden d. Organ. Chemie (Houben-Weyl) 4. Aufage," Bd. XI/1, Verlag Georg Thieme, Stuttgart, 1957, p. 795.

(4) H. Böhme, A. Dick, and G. Driesen, *Ber.*, **94**, 1879 (1961).

(5) S. L. Vail, C. M. Moran, and H. B. Moore, *J. Org. Chem.*, **27**, 2067 (1962).

(6) W. Walter, M. Steffen, and K. Heyns, *Ber.*, **94**, 2462 (1961).

(7) This doublet is due to coupling of the N–CH_3 group with the amidic hydrogen. In even slightly alkaline aqueous solutions the doublet becomes a single peak owing to rapid exchange of the amidic hydrogen [see A. Berger, A. Loewenstein, and S. Meiboom, *J. Am. Chem. Soc.*, **81**, 62 (1959)].

(8) Thus, with respect to tetramethylsilane, *s*-trioxane showed a peak at 5.28 −p.p.m. for $-OCH_2O-$ and IV had the following peak assignments (−p.p.m.): $CH_3C{=}O$ (−2.15, −2.19); $N-CH_3$ (−3.01, −3.21); $-N-CH_2O-$ (−5.44, −5.49). Small amounts of water added to the reaction mixtures increased the intensity of the F peak and it was also moved upfield, substantiating the correct assignment of this peak.

TABLE I

PROTON N.M.R. DATA ON SOME HYDROXYMETHYLATED AMIDES[a]

	Materials[d]	Chemical shift (−p.p.m.)[b] A	D	B	C	E	F	G	Relative area[c] A	D	B	C	E	F	G
1.	Pure N-methylacetamide in CCl_4	1.93		8.18	2.72[e]				4.7		1.2	4.8			
2.	N-Methylacetamide–paraformaldehyde, 1:1 mole ratio at 145°	2.15	2.38	8.08	2.91[e]	5.08–5.10	5.67	3.18 3.30	4.6	10.1	1.25	4.5	9.35	3.4	6.5 3.6
3.	N-Methylformamide (pure)	8.30		...	2.94[e]				9.6 (A + B)		See A	16.19			
4.	N-Methylformamide–paraformaldehyde, 1:1 mole ratio at 100°	8.39	8.53	...	3.11[e]	5.19	6.24	3.26 3.40	0.31	1.97	...	0.63	4.68	1.78	6.52
5.	N-Methylbenzamide in CCl_4	8.4–8.5, 7.8–7.9		8.88	3.45[e]				13.7 (A + B)		See A	6.48			
6.	N-Methylbenzamide–paraformaldehyde, 1:1 mole ratio at 140–160°[f]	← 7.55–8.13 →			3.10[e]	5.05	5.47	3.20 3.40	← 17.52 →			7.55	5.3	1.15	2.40
7.	N-Methyl α-chloroacetamide in CCl_4	4.67		8.32	3.5[e]										
8.	N-Methyl α-chloroacetamide–paraformaldehyde, 1:1 mole ratio at 100°	4.72	5.02	8.31	3.42[e]	← 5.5 →		3.7	1.92	5.02	0.75	2.91	← 6.68 →		5.45
9.	N-Methylformamide in water (pH 8.3–8.8)	8.56		...	3.28				3.3		...	9.5			
10.	N-Methylformamide–20% formalin, 1:1.5 mole ratio at 60°	8.58	8.71	...	3.33	← 5.39 →		[g] 3.48 3.62	0.55	3.0	...	0.3		[g]	10.7
11.	N-Methylformamide–20% formalin, 1:0.5 mole ratio at 60°	8.58	8.71	...	3.33	← 5.40 →		[g] 3.47 3.63	3.25	2.35	...	7.4		[g]	8.0
12.	N-Methylacetamide in water (pH 8.3–8.8)	2.52		...	3.25				3		...	3			
13.	N-Methylacetamide–20% formalin, 1:1.5 mole ratio at 60°	2.52	2.69 2.73	...	3.27	← 5.35 →		[g] 3.51 3.65	5.90	2.30 5.70	...	6.20		[g]	5.55 2.53
14.	N-Methylacetamide–20% formalin, 1:0.5 mole ratio at 60°	2.52	2.69 2.73	...	3.27	← 5.3 →		[g] 3.51 3.65	7.31	0.80 2.45	...	7.30		[g]	3.15 0.85

[a] All n.m.r. spectra obtained on the Varian A-60 at ambient temperature with exception noted. [b] Chemical shifts with respect to tetramethyl silane contained within a sealed capillary tube. [c] Areas are not relative between different materials. [d] See Experimental for preparation of these materials. [e] Taken as the mid-point in a symmetrical doublet. [f] N.m.r. obtained at 55°. [g] The E and F peaks obscured by water.

of N-methylacetamide, N-methyl α-chloroacetamide, N-methylformamide, and N-methylbenzamide, respectively. Likewise the area of E, when not obscured by water, should be 0.66 times area of G + C. Examination of Table I reveals that within experimental error, these relationships are borne out. It is possible to calculate the extent of hydroxymethylation by either the ratio D/(A + D) or G/(G + C). Table II gives the extent of reaction for the various materials listed in Table I. With N-methylbenzamide only the G/(G + C) ratio was used to calculate the per cent reaction inasmuch as the phenyl hydrogens from A and D were indistinguishable. Theoretically it should be possible to calculate the extent of reaction by the value 1 − 3B/(C + G), but the ill-defined area achieved with even the pure N-methylamides for N–H(B) negates this possibility.

TABLE II

EXTENT OF HYDROXYMETHYLATION OF SOME AMIDES

Material	% Conversion[a] Area $\frac{G}{G+C}$ × 100	Area $\frac{D}{D+A}$ × 100
2[b]	69.1	68.7
4[c]	91.2	86.4
6	24.1	[d]
8	65.0	65.8
10[c]	97.5	84.5
11[c]	52.0	42.0
13	56.6	57.5
14	30.1	30.8

[a] Per cent II formed from amount of I charged. [b] Conversions of 63.4 and 64.8%, respectively, were obtained when equimolar amounts of N-methylacetamide and paraformaldehyde were heated at 100°. [c] The conversion calculated from the ratio G/G + C should be more accurate than from D/D + A because of the inability to obtain complete resolution of the formyl protons. [d] The complex phenyl hydrogens made this ratio impossible to discern.

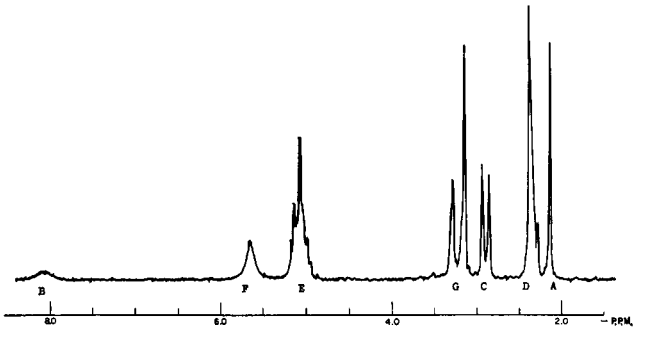
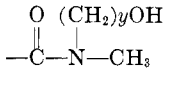
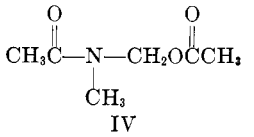


Fig. 1.—Proton n.m.r. spectrum of material 2, at room temperature, referenced to tetramethylsilane contained within a sealed capillary. See Table I for peak assignments.

The spectra assigned to the N–CH_3 group of the methylolated compounds (G) always appear as two nonequivalent peaks. In the absence of spin–spin coupling, it might be expected that only one peak should be present. There might be a possibility that these peaks are identified with the N–CH_3 grouping from two or more different chemical entities, for instance,



where $y = 1$ and $y > 1$; in such a case these two peaks represent real chemical shifts, and the mixture is more complex than first anticipated. The alternative interpretation is that the two peaks represent nonequivalence of the N–CH_3 group in the single compound II. Walter[6] published the n.m.r. spectra for



IV

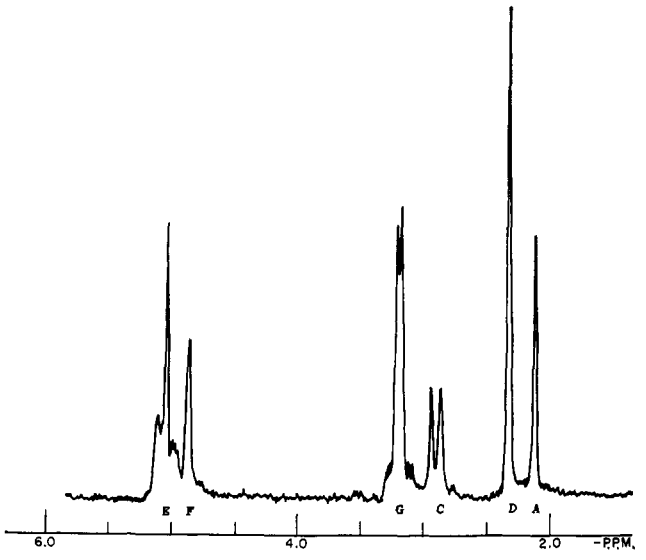


Fig. 2.—Proton n.m.r. spectrum of material 2 at 80° ± 5°. The chemical shifts are referenced with respect to the symmetrical doublet C assigned to 2.91 − p.p.m. On cooling to room temperture the spectrum of the sample was identical to that given in Fig. 1.

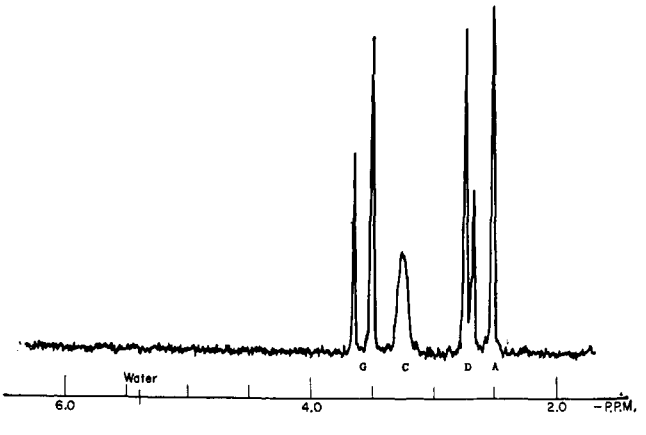
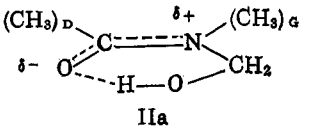


Fig. 3.—Proton n.m.r. spectrum of material 13, at room temperature, referenced to tetramethylsilane contained within a sealed capillary. The water–formaldehyde peak (E and F) at *ca.* 5.35 − p.p.m. is not shown. See Table I for peak assignments.

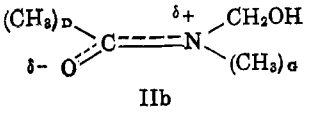
prepared by both peracetic acid oxidation of N,N-dimethylacetamide and by acetylation of the methylol compound obtained *via* a modified Böhme procedure. The pure distilled material showed two nonequivalent peaks at 3.01 −p.p.m. and 3.21 −p.p.m. for the N–CH_3 group, and in our hands, on heating to 55°, the two peaks merged to one sharp peak at 3.07 −p.p.m. Thus, the two peaks are caused at room temperature by nonequivalence arising from restricted rotation about the C–N bond.[9]

In similar manner material 2, containing the methylol compound from N-methylacetamide was heated to 75–80° (see Fig. 2) where the two peaks G at 3.18 and 3.30 were transformed to a very close doublet at 3.20 − p.p.m. The similarity of the n.m.r. spectra of IV to our methylol compound from material 2 plus the behavior on heating confirms that G arises from only one chemical entity. On heating material 2 (Fig. 2), the F peak moves upfield, indicating greater shielding due to decreased hydrogen bonding.[10] Dilution of material 2 with water or carbon tetrachloride has a similar effect.

Examining Fig. 3, it can be seen that unchanged N-methylacetamide in 20% alkaline formalin from material 13 shows, as expected,[7] only a single peak C. The N–CH_3 group in the methylol compound still shows, however, two peaks due to restricted rotation. An interesting feature of Fig. 3 as contrasted with Fig. 1 is the more highly resolved doublet D that appears at 2.69 and 2.73 −p.p.m. This doublet corresponds then, as do the G peaks, to the *cis* and *trans* isomers caused by restricted rotation about the C–N bond,[11] and indeed the respective areas found in D and G (Table I) are approximately equal.



IIa



IIb

It is interesting to speculate upon the assignment of the D and G peaks to IIa and IIb. Thus, if IIa is assumed to be present in higher amount because of increased stability arising from internal hydrogen bonding, then the N–CH_3 in IIa is more shielded (higher field) than in the *trans* IIb. Conversely, the CH_3–C in IIa is less shielded (lower field) than in IIb.

On the other hand, it has been postulated[12] that the N–CH_3 group *cis* to the carbonyl oxygen in dimethylacetamide is the more highly shielded. If this is also true for the methylol compounds, then IIb should be the predominant isomer. The unknown effects of hydrogen bonding in the materials plus the difficulty of predicting shielding effects in unsymmetrically disubstituted amides make it difficult, at this time, to assign definitely with any assurance structures IIa and IIb to the nonequivalent forms in mixtures 2 and 13 as manifested by peaks D and G.

Examination of Table II reveals an obvious disagreement with previous investigations. Thus, N-methylformamide shows a greater degree of reaction by far with aqueous formalin than does N-methylacetamide, a finding entirely consistent with our hydroxymethylation results on these two amides employing paraformaldehyde. Vail, *et al.*, pointed out that the greater ease of hydroxymethylation of bisformamides over bisacetamides, and we might add, of formamide over acetamide, conflicted with their finding of greater reactivity of N-methylacetamide over N-methylformamide. Our results with these amides in both aqueous, and under relatively anhydrous conditions, obviate this apparent contrast.

Experimental

Hydroxymethylation of Amides. A. Anhydrous Conditions.—The method of Böhme[4] was followed, wherein the appropriate amide was heated for several hours in a sealed glass pressure flask. The following conditions are given.

Material 2.—Equimolar amounts of N-methylacetamide (Eastman White Label) and paraformaldehyde were heated in an oil

(9) J. H. Pople, W. G. Schneider, and H. J. Bernstein, "High Resolution Nuclear Magnetic Resonance," McGraw-Hill Book Co., Inc., New York, N. Y., 1959, p. 366.

(10) Ref. 9, p. 400.

(11) Although a partial double bond between carbon and nitrogen is shown to explain nonequivalence, a referee has suggested that hydrogen bonding alone may contribute significantly to the energy barrier between the two forms.

(12) M. T. Rogers and J. C. Woodbury, *J. Phys. Chem.*, **66**, 540 (1962). We are indebted to one of the referees for pointing out this recent reference.

bath at 145° for 1 hr. longer than necessary for the complete dissolution of paraformaldehyde. A portion of the resulting cooled oil could then be transferred to the n.m.r. tube.

Materials 4 and 8.—Equimolar amounts of the amide and paraformaldehyde were treated at 100° for 1 hr. longer than necessary for complete dissolution of the paraformaldehyde. The resulting products were colorless and yellow oils.

Material 6.—Equimolar amounts of N-methylbenzamide and paraformaldehyde containing 0.05% by weight of dry potassium carbonate were heated at 140–160° for 1 hr. longer than necessary for complete dissolution of the paraformaldehyde. On cooling, a salve-like material was obtained, which necessitated measuring its n.m.r. spectra at *ca.* 55° in order to obtain satisfactory resolution.

B. Aqueous Conditions. Materials 10, 11, 13 and 14.—The method of Vail[5] was followed, wherein a fresh 20% solution of formaldehyde was prepared by dissolving the appropriate amount of paraformaldehyde in water in a pressure flask at 60–70° (pH 8–9 maintained by a trace of sodium bicarbonate). To this solution was added the appropriate amount of amide, and the mixture was heated in a closed glass vessel with an oil bath for 2 hr. at 60°. The n.m.r. spectra of the cooled clear solution was then obtained.

Vapor Phase Chromatography of Mixtures 2, 4, and 7.—A known amount of material 2 (20 μl.) was passed through a chromatography column at 200° (15% butenediol succinate on Chromosorb P-2). The amount of N-methylacetamide recovered in this mixture as determined by the area of the amide peak was 70.5% by weight of the injected mixture. The calculated amount of changed and unchanged N-methylacetamide in material 2 was 71%.

In similar fashion, 75% of N-methyl α-chloroacetamide was recovered from material 7 *vs.* the calculated amount of 78%, while 70% of N-methylformamide was recovered from 4 *vs.* the calculated 66%.

Preparation of IV.—The procedure was based upon the method given by Walter,[6] wherein an excess of acetic anhydride was added to material 2 and stirred at 20–25° for 3 days, then heated to 40° for 6 hr. The excess acetic anhydride and acetic acid were then removed under vacuum and the resulting mixture was distilled to give product at 45° (0.05 mm.); $n^{25}D$ 1.4470. This material was further purified by passing a portion of it through a v.p.c. column at 200° (previously described) and recovering, at the appropriate retention time, the purified product, $n^{25}D$ 1.4445, with infrared and n.m.r. spectra identical to that given by Walter.

Acknowledgment.—The authors wish to express their appreciation to Dr. C. C. Tung for stimulating discussions during the course of this work.

A Novel Elimination Reaction of *o*-Acylaminobenzenesulfonamides

JOHN G. TOPLISS, LEROY M. KONZELMAN, AND ELIZABETH P. SHAPIRO

Medicinal Chemical Research Department, Schering Corporation, Bloomfield, New Jersey

Received March 27, 1963

The action of heat on some *o*-acylaminobenzenesulfonamides has been shown to give the corresponding acylaminobenzenes in addition to the expected benzothiadiazines. The dependence of the reaction on various structural factors was investigated. A mechanism for the reaction is proposed.

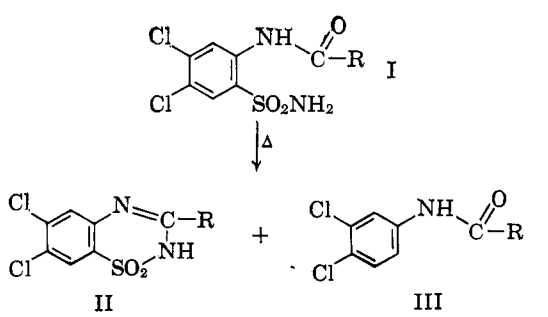
In connection with another program[1] we have been engaged in the synthesis of various 3-substituted 2*H*-1,2,4-benzothiadiazine 1,1-dioxides utilizing the known method[2] of fusing the appropriately substituted *o*-acylaminobenzenesulfonamides. During the course of the preparation of 3-(α-cyclohexyl)benzyl-6,7-dichloro-2*H*-1,2,4-benzothiadiazine 1,1-dioxide [II, R = $CH(C_6H_{11})C_6H_5$], another product was isolated in approximately the same yield as the benzothiadiazine (35–37%). This additional compound did not contain sulfur and was shown to be α-cyclohexyl-3,4-dichloro-α-phenylacetanilide [III, R = $CH(C_6H_{11})C_6H_5$] by comparison with an authentic sample. Careful examination of the fusion products of other substituted *o*-acylaminobenzenesulfonamides showed that the reaction is a general one and that the yield of the acylaminobenzene varies markedly with the structure of the acyl group. The yields of benzothiadiazine and acylaminobenzene obtained from the fusion of a number of substituted *o*-acylaminobenzenesulfonamides are given in Table I. It is apparent from these results that the yield of the acylaminobenzene (III) is greatest in those cases where the group R has a high steric requirement.

TABLE I

YIELDS OF BENZOTHIADIAZINES (II) AND ACYLAMINOBENZENES (III) OBTAINED FROM VARIOUS *o*-ACYLAMINOBENZENESULFONAMIDES (I)

R	% Yield of II	III	Total
n-C_3H_7	87	0.9	88
i-C_3H_7	89	3.0	92
sec-C_4H_9	79	0.6	80
$CH(C_2H_5)_2$	65	24	89
C_5H_9	87	5.4	92
$CH(n\text{-}C_3H_7)C_5H_9$	47	26	73
$C(CH_3)_3$	80	13	93
$CH(C_6H_5)_2$	73	17	90
$CH(C_6H_{11})C_6H_5$[a]	35	37	72
$CH(C_6H_{11})_2$	54	38	92

[a] In the corresponding example where the chlorine atoms on the phenyl nucleus of I are replaced by hydrogen (*i.e.*, compound V) the yields of benzothiadiazine and acylaminobenzene were 38% and 14%, respectively.



Evidence that the *ortho* relationship of the acylamino and the sulfamoyl groups is necessary for the elimination to take place was obtained by subjecting IV to

(1) J. G. Topliss, M. H. Sherlock, H. Reimann, L. M. Konzelman, E. P. Shapiro, B. W. Petterson, H. Schneider, and N. Sperber, *J. Med. Chem.*, **6**, 122 (1963); J. G. Topliss, L. M. Konzelman, E. P. Shapiro, and N. Sperber, paper in preparation.

(2) A. Ekbom, *Bihang, K. Svenska Vet. Akad. Handl.*, **27** (II), 3 (1902); *Beilstein*, **27**, 571; J. H. Freeman and E. C. Wagner, *J. Org. Chem.*, **16**, 815 (1951); F. C. Novello, S. C. Bell, E. L. A. Abrams, C. Ziegler, and J. M. Sprague, *ibid.*, **25**, 970 (1960).