1,3-*vs*- 1,5-DIPOLAR REACTIVITY OF 1-PHENYLMETHYL-4N-ACETYLIMINO-1*H*-1,2,4-TRIAZOLIUM BETAIN TOWARD AROMATIC ISOTHIOCYANATES

Peter ZÁLUPSKÝ and Augustín MARTVOŇ

Department of Organic Chemistry,
Slovak Institute of Technology 812 37 Bratislava

Received December 23th, 1982

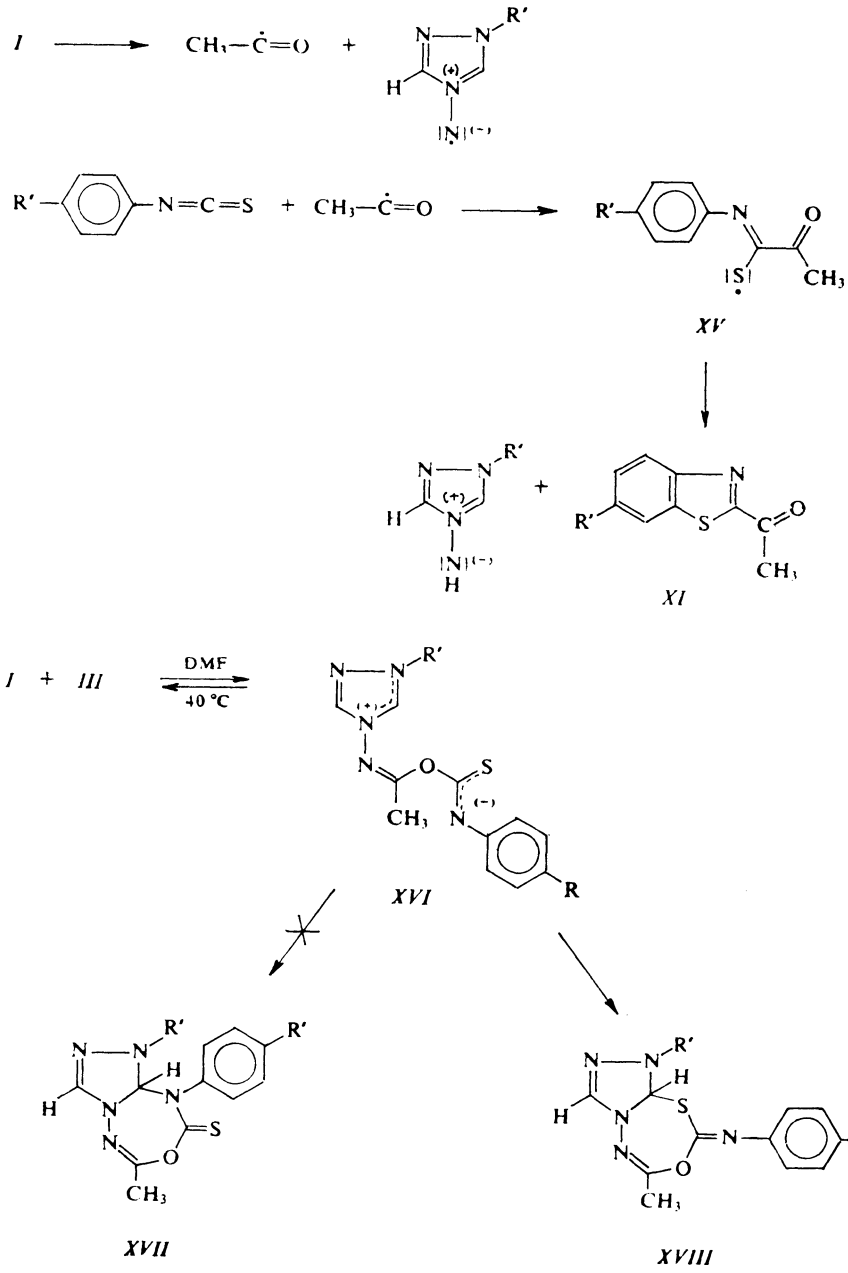
The title betain *I* was found to display both 1,3 and 1,5-dipolar reactivity, depending on reaction conditions. Whereas the reaction with aromatic isothiocyanates in nonpolar solvents produced cycloadducts in concerted manner stepwise addition in dimethylformamide led to a single product, presumably with sevenmembered ring. An open-chain intermediate could be isolated and characterized.

The first reported cycloadditions of isothiocyanates with azomethine imines were those using imines derived from 3,4-dihydroisoquinoline[1,2]. Isothiocyanates reacted with their C=N bond forming stable adducts in high yields. This is typical for azomethine imines the double bond of which is not part of the aromatic system. In other cases, the cycloadducts, though still formed in high yields, are unstable due to the loss of resonance energy. In rearomatization process the molecule is either oxidized or the newly formed ring opens up to restore the original aromatic system[3,4].

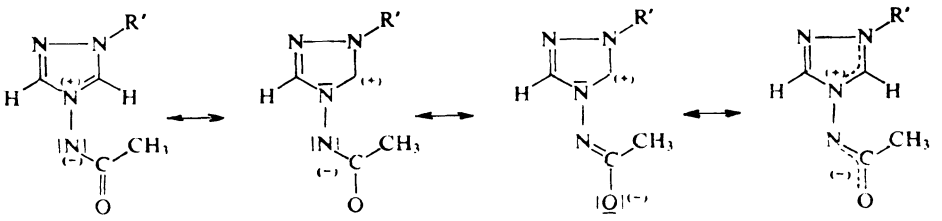
The reactivity in cycloaddition of azomethine imines depends on the charge density at the nitrogen atom. Attachment of an electronwithdrawing substituent reduces the negative charge and the reactivity[5-7]. FMO theory explains this phenomenon in terms of lowering of frontier orbital energy as well as smaller orbital coefficient on terminal nitrogen atom. Though similar consequences can be expected if a conjugative substituent be attached to the nitrogen, the more important aspect of extended dipols is their possibility to react as 1,5-dipoles. Resonance structures of stable and easily available title betain exemplify this. The relative weight of these structures depends, all other things being equal, on reaction conditions, mainly on solvent polarity.

Theoretically, structure having a 1,5-dipole should be less stable than the one with a 1,3-dipole; however charge delocalization on both ends of triazolium betain dipole lessens energy requirements to stabilize 1,5-dipole so that even in such relatively nonpolar solvent as chloroform the triazolium betain reacts with phenyl isocyanate in its extended form[8].

In order to see if the solvent polarity would influence the mode of cycloaddition we carried out the reactions of *I* with substituted aromatic isothiocyanates in benzene and dimethyl sulfoxide at temperatures ranging from 25°–80°C. Due to the poor

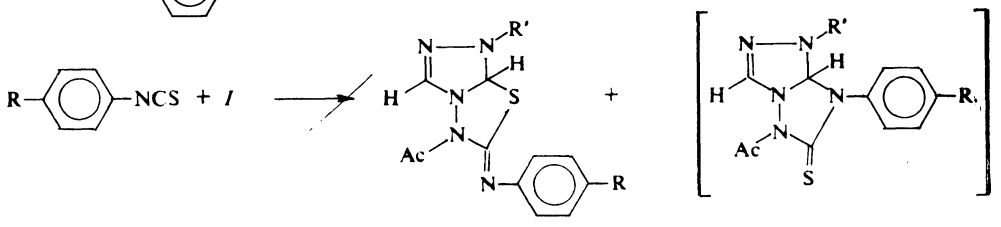


solubility of the betain in benzene, all reactions were conducted at elevated temperatures. The analysis of reaction mixture showed that no products arising from extented form of dipole could be detected. The reaction starts as a concerted 1,3-dipolar cycloaddition across both C=N and C=S bond of the isothiocyanate. This is rather surprising, since cycloadducts on the C=N bond were commonly formed[1,2,9,10].



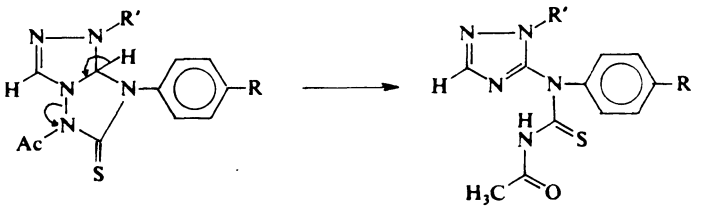
Ia *Ib* *Ic* *Id*

R' = $-CH_2-C_6H_5$



III *IV* *V*

R = CH_3, OCH_3, Br, NO_2, $N(CH_3)_2$, H



V *VI*

NMR and IR data of the adduct *IV* were rather inconclusive as far as structure is involved. More important proved to be mass spectra, containing besides molecular peak at *m/z* 351 a peak at *m/z* 248, corresponding to the substituted 1*H*-1,2,4-triazole-5-thione *X*. The thione is formed after the molecule looses phenyl isonitrile fragment *m/z* 103. In contrast *VI* decomposes in mass spectrometer in different

way, first splitting off its side chain in stepwise process. The formation of *X* was also observed by the acidic hydrolysis of *IV*. Its structure was confirmed by comparison with the authentic sample, prepared from *I* and elemental sulphur[8]. Primary adduct *V* has low stability and have been assumed on account of its isolated rearomatized derivative *VI*. Though both primary cycloadducts have tendency to aromatize, in case of *V* this tendency is assisted by steric congestion on $N_{(1)}$ and $N_{(6)}$. However, since primary adduct could not be isolated, for *V* two more, plausible structures can be put forward, namely *VII* and *VIII*. All three are formally 1 : 1 adducts. Spectral evidence allowed to discriminate among them, the most pertinent being ^{1}H NMR and IR data. The NMR spectra of N-acetyl-N'-5-(1-phenylmethyl-1,2,4-triazolyl)-thiourea displays a singlet at 8·61δ of H_3 on triazole ring, aromatic multiplets and broad band at 8·1δ belonging to NH proton. Further, there are singlets for methylene and methyl group at 5·8 and 1·85δ respectively. Absent is the signal for H_5 proton of the triazole ring suggesting, that this position is occupied. In *I*, H_5 has its distinctive singlet at over 9δ indicating strong deshielding. In spite of its relative acidity, H_5 cannot be exchanged in acidic media for ^{2}H and the position of its signal does not change with temperature. Since both *VII* and *VIII* have unsubstituted positions 3 and 5 they can be excluded. IR data support this conclusion, showing strong absorption at 1 715 cm^{-1}. Structures *VII*, *VIII* would be expected to have absorption bands at 1 680, 1 620 and 1 610 cm^{-1} (ref.[8]). Spectral evidence is supplemented by acid hydrolysis where a secondary amine is formed. Such secondary amines *IX* could in some cases be isolated directly from the reaction mixtures in small yields (Table I).

Besides products having arisen directly or indirectly from cycloaddition, we succeded in isolating an unexpected product, 2-benzothiazolyl methyl ketone *XI*.

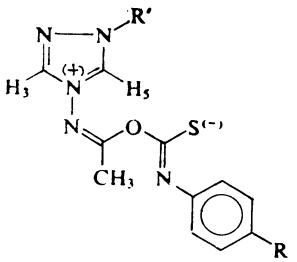
TABLE I

Products distribution in the reaction of *I* with R—C_6H_4—NCS in benzene

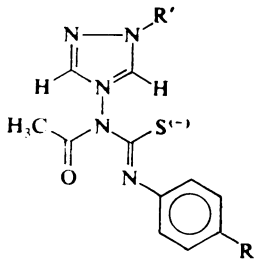
R	Yield, %[a]					Overall yield[b]
	IV	*VI*	*IX*	*X*	*XI*	
a, H	20	68	2	8	6	35
b, CH_3	16	70	—	10	—	32
c, OCH_3	13	69	—	12	—	30
d, Br	18	66	4	9	10	33
e, NO_2	28	54	5	11	14	38
f, $(CH_3)_2N$	10	72	12	4	—	28

[a] Based on reacted betain; [b] based on the whole amount of betain.

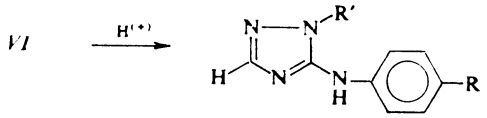
In cases where the ratio of azomethine imine and isothiocyanates was 1 : 1, its yield was of the order of few percent; it raised however to almost 30% when tenfold



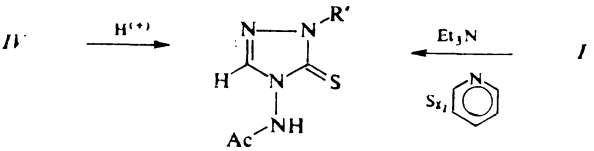
VII



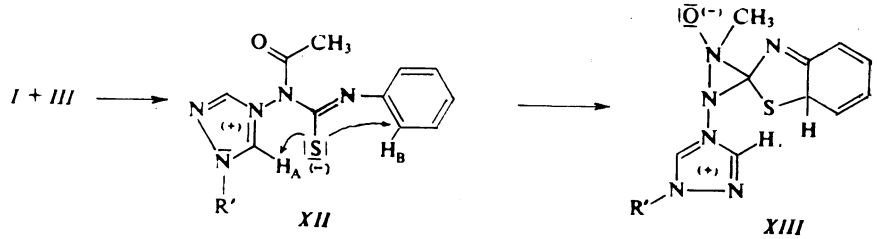
VIII



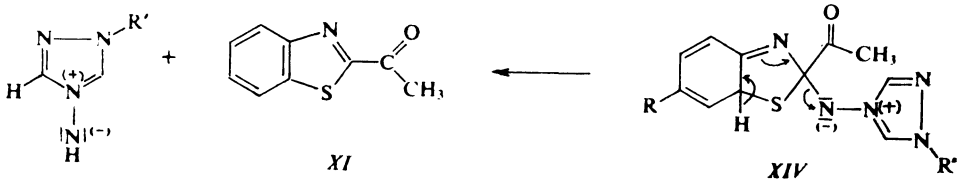
IX



X



XII *XIII*



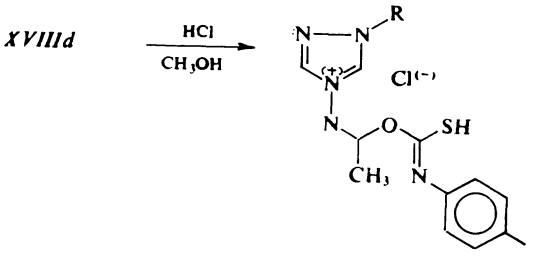
XI *XIV*

excess of isothiocyanate was used. Having no further corroborative evidence, we refrained from suggesting the mechanism of the formation of *XI*.

The outcome of the reaction carried out in dimethylformamide differed from that conducted in hot benzene. No products of 1,3-dipolar cycloaddition were observed, instead a single major product *XIV* was formed. Again it proved to be a 1 : 1 adduct, having in its mass spectrum also a peak at m/z 248, indicating as in case of *IV* sulphur directly attached to the triazole ring. NMR spectrum of *XIV* was very similar to that of *IV*, in IR spectrum however an important difference was the absence of carbonyl absorption band. These data led us to propose for *XIV* the sevenmembered ring structure. As its immediate precursor one have to assume an open-chain adduct *XII*, that is a product of an extended dipole. This is analogous to the adduct found in the reaction of *I* with phenyl isocyanate[8]. More nucleophilic character of the anionic part of *XII* provides enough driving force to promote cyclization to *XIV*.

The absence of 1,3-dipolar cycloaddition products can be explained assuming reversibility of the first step $I + III \rightleftharpoons XII$. In hot benzene 1,3-dipolar cycloaddition is favoured, the concentration of *XII* being very low. In warm dimethylformamide the cycloaddition is too slow to compete, whereas formation of *XII* would be expected to have very small energy requirements. In addition, polar solvent stabilizes the open-chain intermediate, keeping the stationary concentration of *XII* high enough to be isolated or at least to allow for the second, irreversible step, producing *XIV*. Looking at the structure of *XII* with its extensively delocalized charges one wonders if it is not stable enough to be isolated or at least proved spectroscopically. Our efforts in this direction were successful. *XII* could be isolated as red crystalls (λ_{max} = 420 nm, ε = 550), which add methyl iodide under formation of ammonium salt *XVd*.

When solved in dimethylformamide and kept at 60°C for several hours *XVd* cyclized to *XIVd*. Using methyl iodide the intermediate *XIIa* could be trapped in the original reaction mixture the NMR spectrum of which shows typical —SCH_3 singlet. Starting betain *I* forms very unstable salt with methyl iodide, releasing CH_3I even at room temperature.



XXd

Cyclization product *XIVd*, when acted upon with diluted methanolic HCl opens the sevenmembered ring to form an ammonium salt *XVId*. This reaction was accomplished in the NMR sample, further decomposition of primarily formed *XVId* was not investigated.

We have observed that given enough nucleophilicity at the negative terminal of the dipole linear adducts could cyclize. That is why, neither the adduct of *I* with phenyl isocyanate, not the azomethine imine itself cyclizes, although such intramolecular cyclization of N-acylated pyridinium betaines are known[11,12]. Betain *I* would not cyclize intramolecularly up to 140°C. An attempted exchange of carbonyl oxygen for sulphur failed since thioacyl derivative formed split off elemental sulphur and cleaved to produce acetonitrile and 1-phenyl-1*H*-1,2,4-triazole.

EXPERIMENTAL

Infrared spectra measurements of solids were carried out in KBr discs, oils as thin films on NaCl or as chloroform solutions. Mass spectra were measured at 70 eV energy, in cases of adducts *XIV* energies of 7–8 eV were tried. UV spectra were taken from methanolic solutions. For separation home-made 20 × 20 cm silica gel plates, 2 mm thick were used, the layer contained inorganic fluorescent indicator.

Cycloaddition of *I* with Isothiocyanates in Benzene

0·05 mol of *I* and 0·15 mol of the isothiocyanate were added to a minimum of benzene and refluxed for 8 h. Shortly after mixing the components the solution turned red. The mixture was diluted with benzene and cooled to precipitate unreacted betain. The filtrate was evaporated, the residue was washed several times with cold n-hexane to remove the isothiocyanate (*p*-nitrophenyl derivative could not be removed by washing). The oily rest was then chromatographed on preparative silica gel layers using chloroform–acetone 95 : 5.

Major products isolated were substituted thioureas *VIa*–*VIe*. The ^{1}H NMR spectrum of *VIa* is discussed in the theoretical part, spectra of substituted thioureas displayed similar features. Mass spectrum: *m/z* $M^{+\cdot}$ 351 (2·7), 298 (8), 261 (8), 217 (14), 201 (14), 182 (8), 171 (6), 135 (100), 91 (77), 77 (69).

1-*Phenylmethyl*-4N-*acetylimino*-1H-1,2,4-*triazol*-5-*thione* (X): M.p. 184–186°C, ^{1}H NMR spectrum: 8·3 δ(1 H, s), 7·42δ (5 H, m) 5·31δ (2 H, s), 2·04δ (3 H, s), taken in C^2HCl_3 with tetramethyl silane as reference. Mass spectrum: *m/z* 249 (12), 248 (56), 190 (15), 188 (9), 178 (7), 179 (12), 148 (29), 106 (30), 104 (15), metastable peaks at *m/z* 145·6 and 46·5. The IR spectrum of *X* was identical with that of authentic sample. *IXa*, m.p. 173–175°C, ^{1}H NMR spectrum $C^2H_3COC^2H_3$, tetramethyl silane: 7·97 (1 H, s), 7·24 (10 H, m), 5·98 (2 H, s), *IXd*, m.p. 199 to 201°C, ^{1}H NMR spectrum: 8·11 (1 H, s), 7·28 (9 H, m), 6·08 (2 H, s). *IXe*, m.p. 218–220°C, ^{1}H NMR spectrum: 8·25 (1 H, s), 7·41–7·25 (9 H, m), 6·18 (2 H, s). *IXf*, m.p. 179–182°C, ^{1}H NMR spectrum: 8·25 (1 H, s), 7·2 (9 H, m), 2·87 (6 H, s), 5·82 (2 H, s).

XIa, m.p. 110–112°C. ^{1}H NMR spectrum, C^2HCl_3: 7·55 (4 H, m) 4·21 (3 H, d). Mass spectrum *m/z* (rel. intensity): 177(100), 149 (27), 134 (43), 122 (24), 107 (14). *XId*, m.p. 188–190°C ^{1}H NMR spectrum δ: 7·6 (4 H, m), 4·28 (3 H, d). *XIe*, m.p. 210–213°C, ^{1}H NMR spectrum δ: 7·75–7·5 (4 H, m), 4·3 (3 H, d). Melting points of *XIa*, 112°C (ref.[10]), and of *XId*, 191°C (ref.[9]).

^{1}H NMR-*Spectral data of* IVa–f (in δ, C^2HCl_3, tetramethylsilane) *IVa*, 8·58 (1 H, s), 8·02 to 7·48 (11 H, m), 5·93 (2 H, s), 2·25 (3 H, s). *IVb*, 8·43 (1 H, s), 7·95–7·38 (10 H, m), 5·88 (2 H, s), 2·31 (3 H, s), 2·2 (3 H, s). *IVc*, 8·45 (1 H, s), 7·9–7·35 (10 H, m), 5·85 (2 H, s), 3·85 and 2·21 (3 H, s). *IVd*, 8·52 (1 H, s), 8·0–7·4 (10 H, m), 5·9 (2 H, s), 2·26 (3 H, s). *IVe*, 8·6 (1 H, s), 8·1–7·5 (10 H, m), 5·96 (2 H, s), 2·28 (3 H, s). *IVf*, 8·4 (1 H, s), 7·8–7·3 (10 H, m), 5·81 (2 H, s), 2·96 (6 H, s) 2·18 (3 H, s) (Table II).

Mass spectra of IVa–IVf, *m/z* (rel. intensity): *IVa*, 248 (36) 190 (9), 179 (6), 148 (22). *IVb*, very weak M^+ 365, 248 (38), 190 (14), 179 (10), 150 (4), 149 (12), 148 (18). *IVc*, 350 (2), 248 (44), 190 (15), 179 (12), 148 (22), 122 (24). *IVd*, 430, 428 very weak, 385, 387 doublet (4), 248 (45), *IVe*, 350 (3), 248 (48). *IVf*, 336 very weak, 248 (52). All peaks relative to *m/z* 91.

1-Phenylmethyl-4N-acetylimino-1*H*-1,2,4-triazole-5-thione (*X*)

2·16 g (0·01 mol) of 1-phenylmethyl-4N-acetylimino-1*H*-1,2,4-triazolium betain and 0·4 g of elemental sulphur were dissolved in pyridine and kept at 80°C for 1 h. The mixture was diluted with water, precipitated product separated by suction, dried and recrystallized from ethanol. Yield 2·1 g (83%), m.p. 191°C (ref.[8]).

Cyclization of *I* with Isothiocyanates in Dimethylformamide

0·02 mol of betain *I* and 0·02 mol of isothiocyanate were dissolved in minimal amount of dimethylformamide and kept at 50°C for 10 h. The solvent was evaporated and resulting oil diluted with small amount of methanol and charcoal was added. The filtrate was slowly precipitated

TABLE II

2-Acetyl-3-(4-X-phenylimino)-6-phenylmethyl-4-thia-1,2,6,7-tetraazabicyclo[3,3,0]-7-octenes *IVa–IVf*

Compound	Formula (mol.weight)	Calculated/Found				M.p., °C
		% C	% H	% N	% S	
IVa	$C_{18}H_{17}N_5OS$	61·52	4·87	19·93	9·12	143–144
	(351·4)	61·48	4·93	19·97	9·10	
IVb	$C_{19}H_{19}N_5OS$	62·45	5·24	19·16	8·77	138–140
	(365·4)	62·37	5·27	19·41	8·92	
IVc	$C_{19}H_{19}N_5O_2S$	59·83	5·02	18·36	8·40	147–150
	(381·4)	59·76	5·11	18·21	8·28	
IVd	$C_{18}H_{16}BrN_5OS$	50·12	3·74	16·24	7·43	161–163
	(431·3)	50·08	3·79	16·20	7·53	
IVe	$C_{18}H_{16}N_6O_3S$	54·53	4·07	21·20	8·09	186–189
	(396·4)	54·59	4·03	21·28	8·18	
IVf	$C_{20}H_{22}N_6OS$	60·89	6·08	21·70	8·13	142–146
	(394·5)	60·91	6·01	21·19	8·22	

with ether. Separated *XIVa—XIVf* were filtered off, mother liquor concentrated to yield *XIId* in the case of the bromo substituted isothiocyanate. Otherwise the mother liquor contained only rests of starting material and traces of several other substances.

XIId: m.p. 153—157°C. ^{1}H NMR spectrum ($C^2H_3COC^2H_3$, tetramethylsilane, δ): 10·1 (1 H, s), 7·97 (1 H, s), 7·32—7·72 (9 H, m), 6·31 (2 H, s,), 2·97 (3 H, s), 2·76 (3 H, s). Mass spectrum, *m/z* (rel. intensity): 270, 272 (doublet (1), 256, 258 (4), 223, 225 (10), 181, 183 (28), 91 (14), 73 (100). IR spectrum of *XIId* corresponds to that of compound *II*, (ref.[8]). UV maximum λ_{max} = = 310 nm, log ε = 2·96. From elemental analysis data the molecular formula $C_{18}H_{16}BrN_5OS$ was calculated. Spectral data of *XIVa* are representative of the whole series. *XIVa*, m.p. 146 to 148°C. ^{1}H NMR spectrum, C^2HCl_3, tetramethyl silane, 50°C: 9·24 (1 H, s), 7·85—7·36 (11 H, m), 5·76 (2 H, s), 2·04 (3 H, s). Mass spectrum, *m/z* (rel. intensity): 308 very weak, 250 (2), 248 (12), 137 (2), 135 (18), 149 (12), 148 (33), 43 (100). *XIVc*, m.p. 172—174°C, *XIVf* m.p. 141—144°C. The acid hydrolysis of *IVa* and *XIVd* was carried out in refluxing methanolic 1M-HCl for 1 h. The structure of ammonium salt *XVId* was confirmed by elemental analysis, ^{1}H NMR and IR data m.p. 136—138°C from dioxane.

REFERENCES

1. Grashey R., Adelsberger K.: Angew. Chem. *74*, 292 (1962).
2. Huisgen R., Grashey R., Laur P., Leitermann H.: Angew. Chem. *72*, 416 (1960).
3. Huisgen R., Grashey R., Krischke H.: Tetrahedron Lett. *1962*, 387.
4. Beyer H., Leverenz K., Schilling H.: Angew. Chem. *73*, 272 (1961).
5. Okamoto T., Hirobe M., Tamai Y.: Chem. Pharm. Bull. Jap. *11*, 1089 (1963).
6. Okamoto T., Hirobe M., Mizushima C., Ohsawa A.: Chem. Pharm. Bull. Jap. *11*, 781 (1963).
7. Houk K. N., Sims J., Duke R. E. jr, Strozier R. W., George J. K.: J. Amer. Chem. Soc. *95*, 7287 (1973).
8. Becker H. G. O., Sauder N., Timpe H.-J.: J. Prakt. Chem. *311*, 897 (1969).
9. Zubarovskii V. M.: Zh. Obsch. Khim. *24*, 1664 (1954).
10. Zubarovskii V. M.: Zh. Obsch. Khim. *21*, 2199 (1951).
11. Tamura Y., Tsujimoto N., Ikeda M.: Chem. Commun. *1971*, 310.
12. Michalska M.: Tetrahedron Lett. *1971*, 2667.