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Bromination of Enamines from Methyl Isopropyl Ketone. III.* Bromination of 2-(1-Pyrrolidinyl)-3-methyl-1-butene

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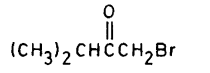
The reaction of 2-(1-pyrrolidinyl)-3-methyl-1-butene with elemental bromine was studied under varying conditions. Reaction in pentane solution followed by hydrolysis afforded high yields of the expected halomethyl ketone, 1-bromo-3-methyl-2-butanone. Reaction in dichloromethane gave several by-products. Mechanisms for the by-product forming reactions are suggested and experimental observations supporting the proposed mechanisms are given.

Previous papers[1] from this laboratory have shown that halomethyl ketones can be prepared in good yields by the halogenation of morpholine enamines from methyl ketones. These enamines were selected for developing the methods, since initial screening experiments for studying the influence of different amino groups on the bromination in dichloromethane of enamines from a model ketone, 3-methyl-2-butanone, *1*, gave the most promising results with the morpholine enamine.[1a] Unfortunately,** the pyrrolidine enamine, *2*, gave very poor yields of the desired bromomethyl ketone, *3*, in these experiments but the side-reactions occurring during bromination of *2* were not identified when the results from the morpholine enamine bromination were communicated.[1a] This paper presents a product distribution study together with some additional observations from the bromination of *2*. The product distributions obtained and the reaction conditions tested are given in Table 1. Yields were determined by GLC. The results can be rationalized by the mechanisms outlined below.

RESULTS

As Table 1 shows, the product distribution is greatly altered by change of solvent. The products before hydrolysis are soluble in dichloromethane whereas they are virtually insoluble in pentane. This may explain why side-reactions are more pronounced in dichloromethane. Reactive species are more likely to encounter each other in homogeneous solution than when precipitated from the reaction medium. The insolubility of the primary products in pentane was demonstrated by GLC analysis of hydrolysed samples of the supernatant liquid.



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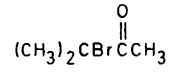

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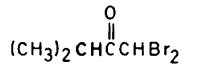

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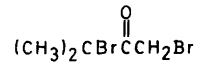

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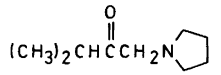

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* Preceding papers, see Ref. 1.

** It is a general observation that the least substituted enamine isomer is strongly favoured in pyrrolidine enamines derived from unsymmetric ketones with different numbers of α and α′ alkyl substituents.[2] 3-Methyl-2-butanone gives only one enamine isomer with pyrrolidine, *viz.*, 2-(1-pyrrolidinyl)-3-methyl-1-butene, whereas morpholine gives an equilibrium mixture of isomeric enamines differing in double bond position. In order to achieve a general method for regiospecific synthesis of halomethyl ketones *via* morpholine enamines, a procedure for transforming isomer mixtures into the terminal double bond isomer was developed.[3]

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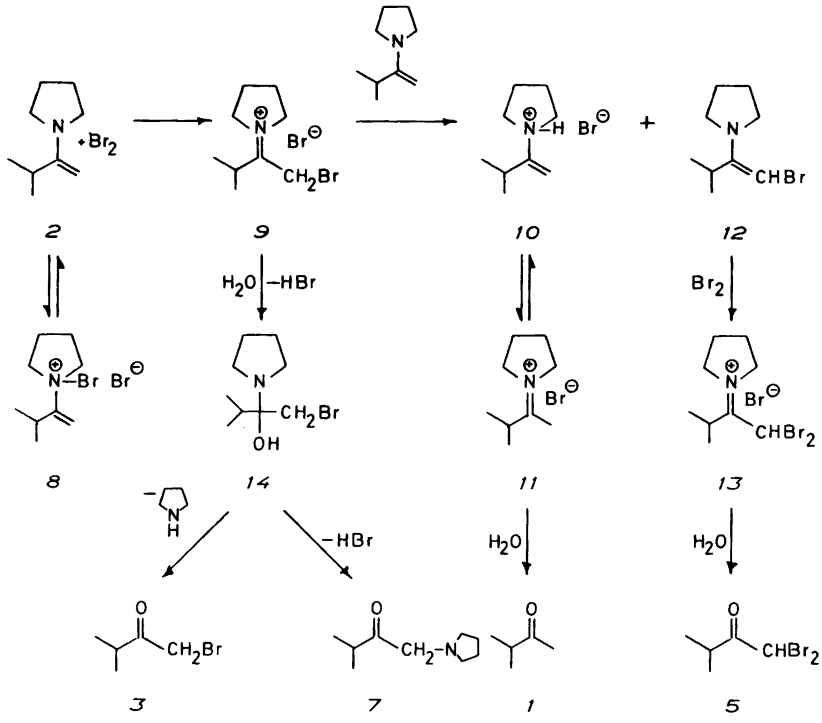
Table 1. Product distribution obtained in bromination of *2*.

Entry [a]	Product distribution/(%)							Recovery/(%)	
	Organic layer					Aqueous layer			
	1	*3*	*4*	*5*	*6*	*1* [b]	*7* [c]	Ketones	Bromine [d]
A	3	40	0	14	3	23	13	90	82
B	4	18	0	25	4	35	6	91	81
C	4	71	3	5	0	8	<1	91	85
D	15	66	1	5	0	2	<1	89	77

[a] (Temperature, solvent) A (−78 °C, dichloromethane), B (25 °C, dichloromethane) C (−78 °C, pentane), D (25 °C, pentane). [b] Extracted with dichloromethane after neutralization of the aqueous layer and extended hydrolysis time. [c] Extracted from alkaline aqueous layer. [d] On the assumption that *7* is formed *via 14*.

The reactions believed to occur during bromination and hydrolysis are summarized in Scheme 1.

When *2* is added to bromine, a kinetically controlled reversible bromination on nitrogen most probably occurs to yield *8*, which rearranges to the immonium salt *9*. The formation of *8* is supported by the following observation: In pentane, at −78 °C, the initially formed product is an orange-red precipitate, which is stable for several minutes at at this temperature, and which liberates bromine freely to yield 60−80 % of 1,3-dibromopropane (GLC) when propene is bubbled through the reaction mixture. When warmed to room temperature, the orange-red precipitate repidly changes to bright yellow, and does not contain active bromine. A similar but more rapid colour change can also be observed at low temperature in dichloromethane, the mixture initially turning orange-yellow, but the



Scheme 1.

colour fading within *ca.* 30 s and the mixture becoming almost colourless. *N*-Bromination of *secondary* enamines has previously been reported.[4] The bromoimmonium salt *9* may then undergo several further reactions. As Table 1 shows fairly substantial amounts of the parent ketone *1* are found in the *aqueous* layer after the hydrolysis step, especially from the reactions in dichloromethane. The bromomethyl protons in *9* are acidic and can be transferred to unbrominated *2* present in the reaction mixture. The following observation indicates that the large amounts of *1* found in the aqueous layer are due to protonation of *2*: When the aqueous layer (pH *ca.* 0) after hydrolysis from bromination in dichloromethane is separated after 0.5 – 1 h and rapidly made alkaline by the addition of 5 M sodium hydroxide, followed by immediate extraction with deuteriochloroform, the enamine *2* and some *1* can be detected in the extract by ^{1}H NMR and GLC. The yields of *2* by this procedure are in the range 10 – 30 %, poorly reproducible, however, due to difficulties in maintaining the work-up procedure constant. When the aqueous layer is neutralized with dilute sodium hydroxide, the enamine disappears within 15 min. Protonation of enamines is known to occur initially on the nitrogen, to give an enammonium ion followed by a more-or-less slow rearrangement to a more stable immonium ion.[5] Decreased rates of hydrolysis in strongly acidic aqueous solutions have been reported.[6] These findings suggest that *10* is present in the aqueous layer and that the rearrangement to *11* is quite slow under these acidic conditions. The less basic morpholine enamine has not shown this behaviour.

Deprotonation of *9* gives a bromoenamine, *12*, which is further brominated to *13*. Subsequent hydrolysis than gives *5*. Minor amounts of the isomeric dibromoketone *6* are found in the experiments in dichloromethane. There are two explanations for the formation of *6*.

A. *6* is formed by acid-catalysed rearrangement of *5* during the hydrolysis step, dibromomethyl ketones are known to be acid-sensitive and prone to rearrangement.[7]

B. *6* is formed by rearrangement of *13* to an isomeric dibromoimmonium salt.[1a] Rearrangement of *13* is evidence by the following observation: When the reaction mixture from bromination of *2* in dichloromethane is stirred at 25 °C and aliquots are withdrawn at intervals and hydrolysed, the amount of *5* decreases steadily with a concomitant increase of *6*, $t_{\frac{1}{2}}$ *ca.* 75 min. However, as Table 1 shows, comparable amounts of *6* are formed both at −78 and at 25 °C and this would seem to rule out the explanation involving rearrangement of *13*, since the reaction mixture obtained at −78 °C did not show any significant change in the *5*:*6* ratio when stirred at this temperature for 0.5 h.

Hydrolysis of enamines is believed to proceed *via* a carbinolamine,[5] and *3* is formed by a straightforward hydrolysis of *9 via* the carbinolamine *14*. The aminoketone *7* is probably also formed *via 14*. The formation of *7* can be rationalized by a nucleophilic attack of the nitrogen lone pair to displace bromine, followed by an oxygen-assisted eleavage of the carbinolamine C – N bond, either by a synchronous or by a stepwise process. Similar rearrangements have been described for aminals obtained from α-haloaldehydes.[8] *7* is not formed in significant amounts when *3* is treated with pyrrolidinium bromide in a two-phase dichloromethane – water system and the formation of *7* by a direct substitution of bromine in *3* against pyrrolidine liberated during hydrolysis is therefore less likely. Only low yields of *7* are obtained with pentane as solvent in spite of a high conversion of *2* to *9*. A possible explanation for this difference is that the partition of *14* between the organic and the aqueous layers differs very much between dichloromethane and pentane. It is reasonable to assume that the rather polar *14* is more soluble in dichloromethane than in pentane, and that the higher yields of *7* with dichloromethane are due to the formation of *7* and possibly also *14 in the organic layer*. In the aqueous layer *14* is solvated and the nucleophilic reactivity of the pyrrolidine nitrogen is strongly reduced by protonation and hydrogen bond interactions with the solvent cage.

EXPERIMENTAL

A PYE M 64 Gas Chromatograph with FID was used for GLC analysis. Integrated peak areas were used for quantitations. 4-Methylacetophenone was used as internal standard for determination of *1*, *3*, *4*, *5*, *6* and phenylcyclohexane was used as internal standard for *2* and *7*. Accuracies in the analysis can be estimated to ±3 %. The identities of the compounds obtained in the brominations were confirmed by GLC-MS using an LKB 9000 Mass Spectrometer and with authentic samples as references.

Bromination of 2, *General procedure.* To a well-stirred solution of 10 mmol of bromine in 20 ml of solvent at the temperature given was added in one

amount 1.39 g (10 mmol) of *2* in 20 ml of solvent. After 2 min the mixture was warmed to room temperature (water-bath) and 20 ml of water was introduced and the mixture stirred for 1 h at this temperature. The layers were separated and the aqueous layer was extracted once with 5 ml of dichloromethane. To the combined layers was added a known amount of internal standard and the mixture was analysed by GLC. (Column: 10 % QF-1 on Chromosorb W-AW 100–110 mesh; 2.7 m, 2 mm i.d.).

The aqueous layer was adjusted to pH 7–9 with dilute NaOH and stirred for another 1 h. It was then saturated with NaCl, acidified with concentrated HCl (to prevent extraction of *7*), and extracted four times with 5 ml portions of dichloromethane. The combined organic layers were analysed as above. The aqueous layer was then made alkaline by the addition of 5 M NaOH and extracted four times with 5 ml portions of dichloromethane and the amount of *7* in the combined organic layers determined by GLC after the addition of a known amount of internal standard. (Column: 5 % PEG 20 M + 0.5 % KOH on Chromosorb W 60–80 mesh; 1.5 m, 4 mm i.d.).

Preparation of 7. To a magnetically stirred solution of 8.6 g (0.10 mol) of *1* in 200 ml of dry methanol at 0–5 °C was rapidly added 5.1 ml of bromine.[9] When the bromine colour had disappeared, 8.4 g of powdered $NaHCO_3$ was added in portions, followed by a dropwise addition of 16.6 ml of pyrrolidine in 50 ml of methanol. The mixture was stirred overnight and then treated with 100 ml of 6 M HCl for 1.5 h. Unreacted *3* was removed by extraction with ether. The methanolic layer was made alkaline (pH ~14) and extracted with several portions of ether. Drying (Na_2SO_4) of the combined ether layers and removal of the solvent under reduced pressure afforded a yellow oil, which upon distillation yielded 10.6 g (68 %) of pure *7*, b.p. 182–184 °C/754 mmHg. The molecular formula $C_9H_{17}NO$ was confirmed[10] by mass spectral determination of accurate molecular weight (peak matching using quinoline as reference).[11]

IR (neat film) (cm^{-1}) 1715. ^1H NMR (60 MHz, $CDCl_3$) 1.23 (d, 6 H) $J = 7$ Hz, 1.70–1.93 (m, 4 H), 2.53–2.73 (m, 4 H), 2.63 (spt, 1 H) $J = 7$ Hz (partially obscured) and 3.48 (s, 2 H). ^{13}C NMR (neat) 18.4, 24.0, 37.7, 54.1, 63.4 and 210.6.

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