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A STUDY OF THE MANNICH REACTION WITH PROPARGYL ALCOHOL

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Although 1-alkynes are known to partake in the Mannich reaction, the seeming inertness of propargyl alcohol in undergoing this condensation prompted us to investigate the mechanism of this reaction. During this investigation we applied these theoretical aspects to the synthesis of a group of aminobutynols of the type $R_2N—CH_2—C\equiv C—CH_2OH$. The sequence of events in the Mannich reaction has been subject to many debates, two explanations being offered. One possible course is an aldol condensation of the active hydrogen component I with formaldehyde, followed by reaction of the acetylenic alcohol II with a secondary amine to produce the Mannich base III.

$$\underset{\text{I}}{R'—C\equiv C—H} + HCOH \rightarrow \underset{\text{II}}{R'—C\equiv C—CH_2OH} + R_2NH \rightarrow \underset{\text{III}}{R'—C\equiv C—CH_2—NR_2}$$

The alternative is the formation of the methylol derivative of the amine IV, followed by its reaction with the active hydrogen compound (1).

$$HCHO + HNO_2 \rightarrow \underset{\text{IV}}{HO—CH_2—NR_2} + \underset{\text{I}}{R'—C\equiv C—H} \rightarrow \underset{\text{III}}{R'—C\equiv C—CH_2—NR_2}$$

Since the acetylenic compound, in our case, was propargyl alcohol, it seemed probable that the second type of reaction was followed. Formation of the hydroxymethyl derivative of the acetylenic compound would lead to the production of 2-butyne-1,4-diol, with the probability of amination of both ends of the chain. The high yields of the expected products, however, precluded this line of reasoning. Also, attempts to isolate 2-butyne-1,4-diol were unsuccessful. Although the Mannich reaction proceeds well for 3-alkyl- and

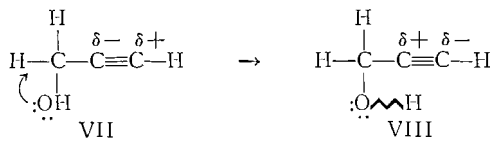
3-aryl-1-alkynes (2) and for some hydroxy-1-alkynes (3), the method is not available if the hydroxy group of the latter is propargylic.

Although McLeod and Robinson (4) and Fernandez *et al.* (5) have shown that ethers of the type $R_2N—CH_2—O—R$ are formed under conditions similar to those of the Mannich reaction, and although it has been shown that propargyl alcohol reacts with amine and formaldehyde preferentially at the hydroxylic group rather than the acetylenic C—H, under the conditions described in this paper we were unable to isolate these ethers from the reaction mixture even without the copper catalyst, the bis-aminomethane $R_2N—CH_2—NR_2$ being the main product isolated. We must therefore conclude that the preferential reaction cited above does not obtain under these conditions. The limitation imposed upon the reaction with propargylic alcohols was overcome by esterifying (3) or etherifying (6) the hydroxyl function.

We have circumvented these steps by the use of cupric sulfate as a catalyst, following, to a limited extent, a German patent (7). The process was greatly modified. The elucidation of this process threw light upon the mechanism of the Mannich reaction. It is well understood that 1-alkynes may be envisioned as possessing two polarization forms V and VI, in which form VI accounts for the "acidity" of the acetylenic hydrogen. A hydroxy group propargylic to the acetylenic function prevents formation of the "acidic" polariza-

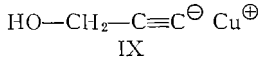
V VI

tion form VI by virtue of an electron shift involving an unbound electron pair on the oxygen atom. This phenomenon probably accounts for the well-known acidity of the hydrogen on a propargylic hydroxyl function. The electron shift would, incidentally, reverse the polarization pattern of the molecule and preclude the existence of an active acetylenic hydrogen (VII to VIII). However, since the Mannich reaction depends



VII VIII

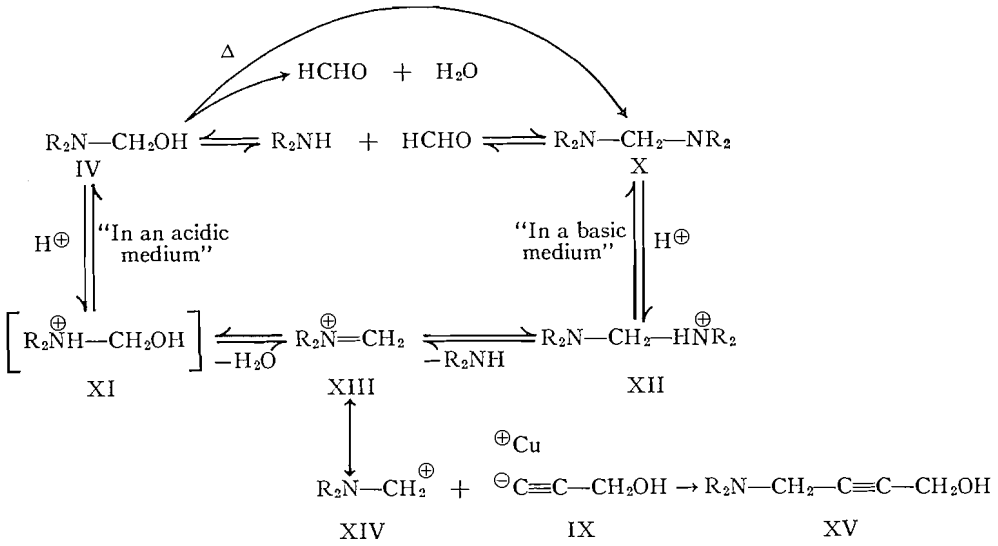
precisely upon the presence of such a labile hydrogen, the condensation does not take place. The sharp and strong band at 2 118 cm^{-1} in the infrared absorption spectrum of propargyl alcohol shows that the acetylenic bond is strongly polarized, but the absence of condensation implies that it exists mainly as form VIII, which can account for both the acidity of the hydroxyl hydrogen and the lack of acidity of the acetylenic hydrogen. The formation of the copper salt IX (8) would produce, however, a labile center, or in essence a carbanion, which would react with the aminomethylol formed between the secondary amine and formaldehyde. The identical copper salt was produced by the reaction of cupric sulfate



IX

and propargyl alcohol alone in a basic medium, even at room temperature. In this case, reduction of the cupric ion is probably effected by the acetylene itself. Since the reaction was carried out in an aqueous medium, insoluble reaction products could be isolated and identified. An oily layer was immediately produced during the preparation of 4-piperidino-2-butyne-1-ol. Upon distillation of this layer, a vigorous evolution of formaldehyde was noted, and the distillate was identified as bis-piperidinomethane (1). The amine and

formaldehyde were not introduced in a 2:1 ratio, however, and the initial product was identified as piperidinomethanol. This product was identified by its infrared spectrum, which was identical with that of the piperidinomethanol produced by the method of Henry (9). Attempts to prepare 4-piperidino-2-butyne-1-ol from piperidinomethanol and propargyl alcohol in the presence of cupric ion in a basic medium resulted in inferior yields, whereas the preparation from the bis-piperidinomethane gave yields similar to those of the whole reaction itself (some yield was obtained even in the cold). It was therefore concluded that the principal species involved in this reaction, when run in a slightly basic medium, is the bis-piperidinomethane formed from the aminomethylol under the influence of heat, and the following mechanism is proposed for the reaction. Although the existence of these intermediates has been postulated by Wagner (10) and reviewed by Helman and Opitz (1), and although the properties of the stable species have been studied in some detail, we have isolated and identified the above-mentioned intermediates from the reaction itself.



It must be understood that the different species IV and X have different stabilities. Whereas IV is unstable in an acidic medium, rapidly reverting to the amine salt and formaldehyde, X will actually form a stable salt. Thus, the pathways of the reaction in acidic and basic media are somewhat different. The reaction in a slightly acid medium contributes to two species at differing rates. The reversible reaction involving IV to regenerate the amine and formaldehyde predominates. However, the formation of the carbenium species XIII by way of the unstable methylol salt XI is also accomplished, but at a much slower rate, as evidenced by the long reaction time in this medium. In a slightly basic medium, X is formed in the reaction, and also by the thermal decomposition of IV. This bis-aminomethane rapidly forms the carbenium species XIII through the intermediate salt XII. It is postulated that the carbenium ion XIV, stabilized by resonance with XIII, is the reactive species in both reactions (1). The carbanion IX formed from cupric sulfate and the 1-alkyne would then enter into reaction with XIV to produce the desired Mannich base XV. A similar series of events was noted during the synthesis of the diisopropyl analogue. By following the changes in the pH values during the preparation of the reaction, it was noted that the introduction of formalin, even when carefully

neutralized, brought about an abrupt drop in pH. The resultant solutions were strongly resistant to subsequent change in pH by the addition of excess amine until the amount of amine calculated to produce the bis-aminomethane was introduced. This strongly indicates a parallel course for all the reactions in the series, even those whose bis-aminomethanes are soluble in water.

The effect of pH on the yield in the reaction was studied. The diethyl analogue was prepared several times at varying initial pH values. It was established that at a pH greater than 8, the reaction, as evidenced by the precipitation of metallic copper, was complete after 55 min. At a pH less than 7 the reaction required at least 5½ h, and at pH 3 no reaction occurred. At a pH greater than 9 the yield decreased. It was decided to run all future reactions at pH 8.4.

TABLE I

Effect of pH on the yield of 4-diethylamino-2-butyne-1-ol

Initial pH	Yield (%)	Time of run	Remarks
9.0	62	55 min	Metallic copper precipitates
8.4	80	"	Some precipitation of metallic copper
7.9	80	5½ h	Some copper propargylate remains
6.0	80	"	Some copper propargylate remains
5.0	77	"	Copper propargylate slow to form
4.5	75	"	Copper propargylate slow to form
3.8	65	"	Copper propargylate slow to form
3.0	0	"	Copper propargylate does not form
7.0	0	"	No copper ion present

It should be noted, therefore, that the reaction should be run in a medium which is acidic enough to form and stabilize the postulated carbenium ion but not acidic enough to prevent the formation of the acetylide.

EXPERIMENTAL

The melting points were measured by the capillary method in an electrothermal apparatus and are uncorrected. Carbon–hydrogen analyses were determined by Dr. C. Daesslé, 5757 Decelles Avenue, Montreal. Amine nitrogen was determined by direct titration in acetic acid, using a Radiometer pH meter with a standard glass electrode and a sleeve-type calomel electrode filled with saturated potassium chloride in anhydrous acetic acid. The hydrochloride salt (compound 6, Table II) was determined by the mercuric acetate – acetic acid method of Pifer and Wollish (11) with the same titrating apparatus.

4-Dimethylamino-2-butyne-1-ol

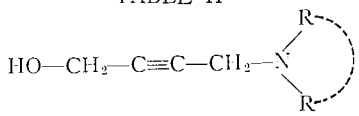
Dimethylamine (1.2 moles) was dissolved in 80 ml of water and the solution was brought to pH 9 by the addition of a solution of 50% sulfuric acid. One and six-tenth moles of 40% formalin solution was added to the mixture followed by 1 mole of propargyl alcohol. A solution of 5 g of anhydrous cupric sulfate in 50 ml of water was admixed with the contents of the reaction vessel, and the pH adjusted to 8.4 by the addition of excess dimethylamine solution.

The reaction mixture was heated at 80° under reflux (dry ice condenser), with stirring, until the greenish precipitate, which gradually turned yellow, showing the formation of copper propargylate, was succeeded by the deposition of metallic copper (55 min). The mixture was cooled and poured into 300 ml of cold concentrated aqueous ammonia. The combined aqueous solutions were then extracted for 9 h with ether in a liquid–liquid extractor. The ether extract was separated and dried over anhydrous magnesium sulfate, and the solvent was evaporated. The residue was distilled *in vacuo* to yield 91.5 g (81%) of the aminobutynol, b.p. 76–78° at 1.5 mm, n_D^{23} 1.4765, $d_4^{22.5}$ 0.941 (reported (12) b.p. 101° at 1.5 mm, $n_D^{27.5}$ 1.4732).

4-Diethylamino-2-butyne-1-ol

This substance was prepared by the general procedure described above, except that the reflux condenser was replaced by a regular Allihn water condenser. A 1 mole run, based on propargyl alcohol, gave 112.8 g (80%) of the desired aminoalcohol, b.p. 92–93° at 2 mm, $n_D^{21.7}$ 1.4784, $d_4^{21.7}$ 0.975 (reported (7) b.p. 105° at 2 mm).

TABLE II



R	Boiling point (°C)	Yield (%)	Melting point (°C)		Formula (benzilate)	Analysis (%)					
			Naphthylurethane*	Benzilate ester		Calculated			Found		
						C	H	N	C	H	N
1. Methyl	76–78 at 1.5 mm	81	101.5–102†	103.5–104	$C_{20}H_{21}O_3N$	74.27	6.54	4.34	74.05	6.65	4.33
2. Ethyl	92–93 at 2 mm	80	76–76.5†	79.5–80	$C_{22}H_{25}O_3N$	75.18	7.17	3.98	75.09	6.99	4.07
3. Pyrrolidino	106–107 at 1.5 mm	84	126–126.5†	124.5–125	$C_{22}H_{23}O_3N$	75.61	6.63	4.01	75.38	6.31	4.17
4. Piperidino	112–113 at 1.5 mm	80	103.5–104†	116–116.5	$C_{23}H_{25}O_3N$	76.01	6.93	3.85	76.37	6.99	3.70
5. Morpholino	104–106 at 0.1 mm§	80	102–103‡	119.5–120	$C_{22}H_{23}O_4N$	72.31	6.34	3.83	72.17	6.53	3.78

R	Boiling point (°C)	Yield (%)	Melting point (°C)		Formula	Analysis (%)			
			Naphthylurethane	Hydrochloride*		Calculated		Found	
						N	Cl	N	Cl
6. Isopropyl	96–98 at 2 mm	87.5	77.5–78	144–144.5	$C_{10}H_{20}ONCl$	6.81	17.23	6.78	17.15

*Recrystallized from 2-propanol.
†Recrystallized from petroleum ether (b.p. 30–60°).
‡Recrystallized from benzene.
§Recrystallized from toluene–heptane, m.p. 51.5–52.5°.

4-Diisopropylamino-2-butyne-1-ol

This aminoalcohol was prepared by the general method described above. Sufficient triethylamine was added to bring the pH to 8 and to aid in the solubilization of the insoluble bis-aminomethane. The reaction was heated at 80° for 72 h. A 1 mole run based on propargyl alcohol gave 147.5 g (87.5%) of the product, $n_D^{21.7}$ 1.4811, $d_4^{21.5}$ 0.931.

4-Pyrrolidino-2-butyne-1-ol

This compound was prepared by the general method described for the dimethyl analogue. A 1 mole run, based on propargyl alcohol, gave 117 g (84%) of the desired aminobutynol, b.p. 106–107° at 1.5 mm, $n_D^{21.7}$ 1.5039, $d_4^{26.5}$ 1.013 (reported (13) b.p. 101–102° at 0.4 mm, n_D^{22} 1.5092).

4-Piperidino-2-butyne-1-ol

This substance was prepared in 50% dioxane–water by the general method described above. A 1 mole run, based on propargyl alcohol, gave 122.4 g (80%) of the product, b.p. 112–113° at 1.5 mm, $n_D^{24.7}$ 1.5095, $d_4^{26.5}$ 1.030 (reported (13) b.p. 112–113° at 0.9 mm).

4-Morpholino-2-butyne-1-ol

This aminoalcohol was prepared by the general method. A 1 mole run, based on propargyl alcohol, gave 124 g (80%) of the desired product, b.p. 104–106° at 0.1 mm, $n_D^{21.7}$ 1.5095 (supercooled liquid), m.p. 51.5–52.5° (reported (14) b.p. 104–106° at 0.1 mm, n_D^{25} 1.5087).

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CONVERSION OF NEOABIETIC ACID INTO MANOOL

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As a consequence of our recent total synthesis of abietoid resin acids (1), various intermediates became available for possible conversion into other diterpenic natural products. Thus, for example, the synthetic ketoester I*a* (2, 3), also a product of the ozonolysis of methyl neoabietate (2–4), appeared to be a likely candidate for transformation into manool (II) and sclareol (III), especially since the more readily accessible sclareol degradation product IV had already been converted into sclareol (5) and the latter had previously