

TRAPPING AN INTERMEDIATE OF THE POLONOVSKI REACTION

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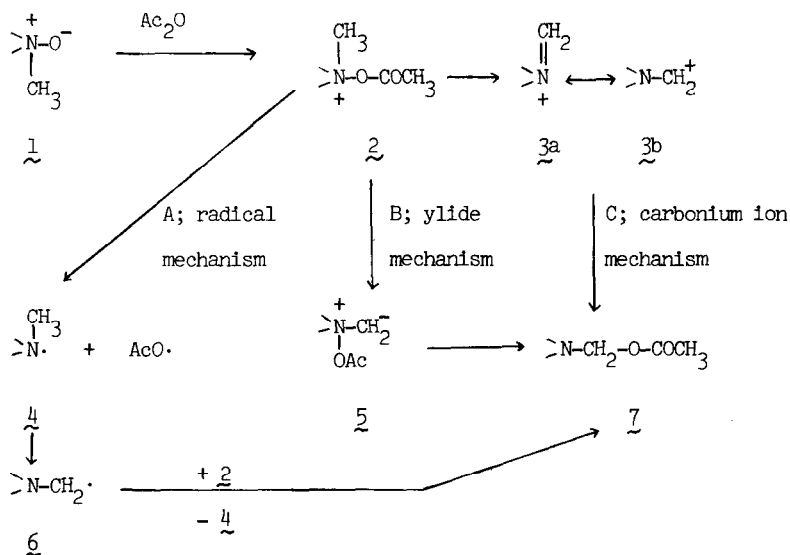
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t-Amine oxides occur widely in both animals and plants and biosynthesis of trimethylamine oxide from trimethylamine has been demonstrated<sup>1)</sup>.

The Polonovski reaction<sup>2)</sup>, whereby t-amine oxides containing at least one N-methyl group are converted by acetic anhydride into N,N-disubstituted acetamides and formaldehyde, suggested that the biological step might be one of oxidative demethylation mediated in the cellular environment<sup>3)</sup>. Several mechanisms of the Polonovski reaction have been proposed as shown in Scheme 1<sup>4,5)</sup>.

Scheme 1



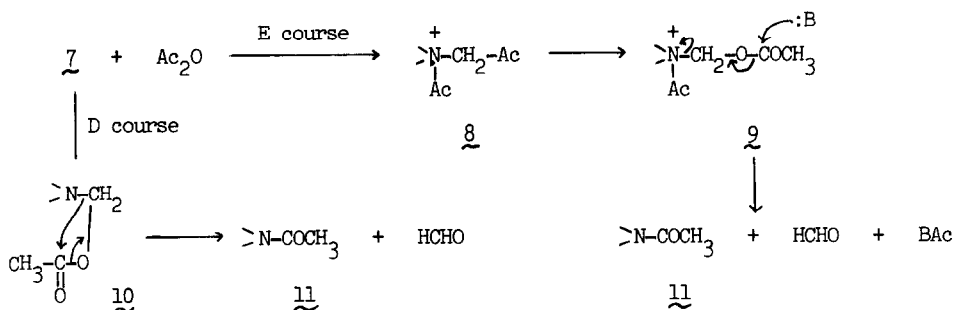
It was pointed out<sup>5)</sup> that the ylide intermediate 5 was unstable and less probable than 3 and that involvement of the free radical intermediate<sup>6)</sup> in the reaction of trimethylamine oxide with acetic anhydride was rejected, although the available evidence does not permit decision

between an ionic and a (solvent-cage or short-lived) free radical mechanism.

$\alpha$ -Aminocarbiniol ester 7 is a hypothetical intermediate and has not been isolated. Plausible mechanisms of the formation of acetamide 11 are shown in Scheme 2<sup>4,5</sup>).

The Polonovski reaction in the presence of alcohols suggested involvement of the intermediate 9<sup>7</sup>).

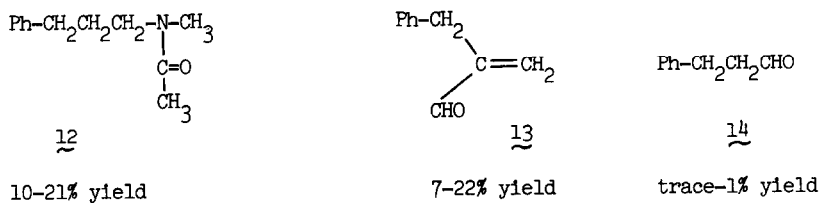
Scheme 2



We felt that pertinent evidence bearing on the mechanism of the Polonovski reaction would be made available by trapping experiment of the proposed intermediates.

Herein, we wish to describe our results which clearly implicate ylide intermediate in the Polonovski reaction, although possibility of other mechanisms has still remained since trapping products were isolated in only fair yields.

The Polonovski reaction of trimethylamine oxide<sup>8</sup>) (0.2 mol) with acetic anhydride (0.4 mol) in chloroform in the presence of styrene (0.1 mol) gave a mixture of products (12, 13, 14) derived from styrene besides ordinary Polonovski reaction products with a very small amount of intractable material (recovered styrene; 60-70%).



Identification of 12 (bp. 130-133°/6 torr) was based on elemental analysis, IR, Mass, NMR and comparison with an authentic specimen prepared by treatment of N-methyl-N-3-phenylpropylamine<sup>9</sup>) with acetic anhydride. The NMR spectrum of 12 in CDCl<sub>3</sub> on Varian T-60A shows two single peaks for N-methyl group at  $\delta$ 2.88 and 2.96 with an area ratio of 2:3 and two single

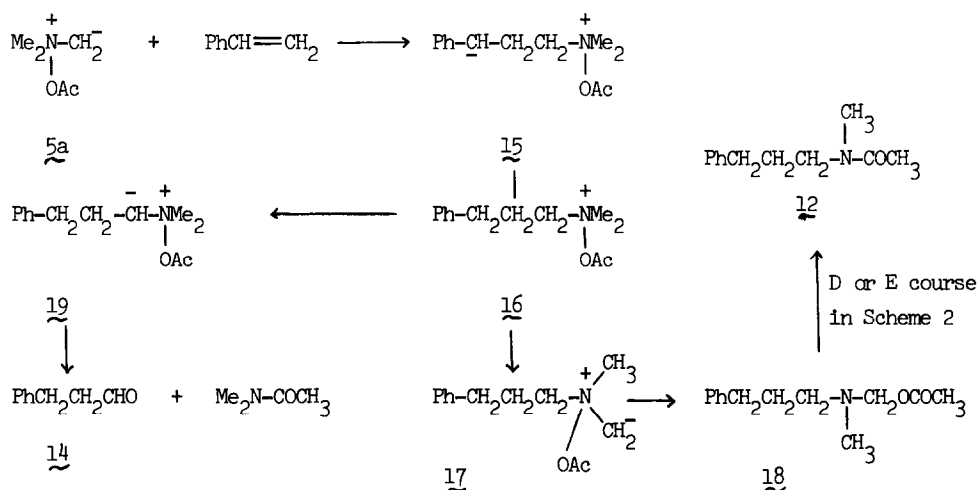
peaks at  $\delta$ 1.92 and 2.00 with an intensity ratio of 2:3 overlapped by a multiplet arising from the central methylene group. We have no conclusive evidence for the assignment of the absorption at  $\delta$ 1.92 while solvent and temperature effects on the spectra of 12 are very large<sup>12)</sup>. The acetamide 12 was further characterized by conversion into N-methyl-N-ethyl-N-3-phenylpropylamine (bp. 68–70°/5 torr) by reduction with  $\text{LiAlH}_4$ .

The structure of 13 (bp. 74–75°/5 torr, semicarbazone mp. 185–187°) was substantiated by elemental analysis, IR, NMR and comparison with an authentic specimen (lit.<sup>10)</sup> bp. 120°/13 torr, semicarbazone mp. 189°).

The Polonovski reaction in the presence of 14 under the same conditions afforded 13 exclusively and thus the simplest mechanism of the formation of 13 would be that aldol condensation of 14 with formaldehyde (or equivalent) followed by dehydration, while no reaction occurred when 14 was treated with formalin, acetic anhydride and triethylamine.

A possible mechanism for the formation of 12 and 14 could be visualized as the reaction of the intermediate 5.

Scheme 3



A radical mechanism of the formation of 18 (thus 12) via an intermediate like 6 (course A in Scheme 1) is also possible one but it is difficult to explain the formation of 14 (thus 13) by the radical mechanism. A carbonium ion mechanism (course C in Scheme 1) is not reasonable one for the formation of 14.

It is known that reaction of methylene ammonium ylides with olefins gave cyclopropanes<sup>11)</sup> but detection of phenylcyclopropane in the reaction mixture was failed.

The Polonovski reaction in the presence of styrene under the same conditions using propionic anhydride instead of acetic anhydride afforded 13 (6% yield) and N-methyl-N-3-phenylpropyl propionamide (bp. 140-143°/7 torr, 18% yield).

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