

FAILURE TO VERIFY A REPORTED SYNTHESIS OF THE ACONITINE SKELETON

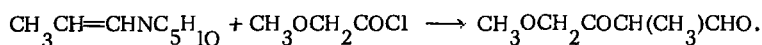
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**Abstract** Attempts to verify the first three stages of a claimed synthesis of the aconitine skeleton (Samir Chatterjee, Tetrahedron Lett. 3249 (1979) have given totally different results. It is concluded that the reported products of these three stages were not in fact obtained

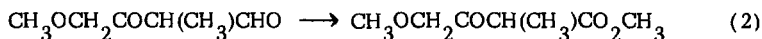
The communication cited above<sup>1</sup> presented evidence of chemical and physical findings so abnormal in so many respects that a caution was issued<sup>2</sup> against accepting the claims before verification. We now report an attempt to verify the first three stages in the claimed synthesis

Stage 1 This is expressible by the transformation



Condensation of equimolar amounts of 1-(1-propenyl)piperidine, methoxyacetyl chloride, and triethylamine in dichloromethane yielded after gentle acid hydrolysis and exhaustive extraction with ether an oil (b. p. 107-110°/7 mm) which was separated into its two components by extraction from ether with ice-cold N NaOH. The neutral product was an oil, 1-methoxyacetyl-piperidine (12.5% yield), b. p. 116°/10 mm,  $\nu_{\text{max}}$  1650  $\text{cm}^{-1}$  (Found C, 61.4, H, 9.6, N, 8.9.  $\text{C}_8\text{H}_{15}\text{O}_2\text{N}$  requires C, 61.1, H, 9.6, N, 8.9%). The acidic product, recovered by acidification and exhaustive extraction with ether, solidified and was crystallized from ether, affording (1.2% yield) 4-methoxy-3-oxobut-1-en-1-ol,  $\text{CH}_3\text{OCH}_2\text{COC}(\text{CH}_3)=\text{CHOH}$  (1), as colourless prisms, m. p. 95-97°,  $\nu_{\text{max}}$  (Nujol) 3240, 1620, 1510  $\text{cm}^{-1}$ ,  $\delta$  ( $\text{CDCl}_3$ ) 1.6 (3H, s), 3.4 (3H, s), 4.1 (2H, s), 7.5 (1H, d), 13.9 (1H, d) (Found C, 55.2, H, 7.8.  $\text{C}_6\text{H}_{10}\text{O}_3$  requires C, 55.4, H 7.7%). The substance was soluble in water and the solution gave a violet colour with  $\text{FeCl}_3$ . S. Chatterjee<sup>1</sup> gave for this substance (formulated as the keto-aldehyde tautomer) b. p. 97-99°/7mm,  $\nu_{\text{max}}$  1730, 1715  $\text{cm}^{-1}$ , and claimed a 78% yield. No substance having these properties was found, and there was no evidence (n. m. r.) of tautomeric change in the substance (1) after prolonged keeping in  $\text{CDCl}_3$  solution.

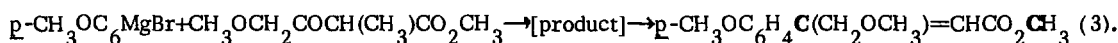
Stage 2 This is expressible by the transformation (Jones oxidation followed by diazomethane)



Addition of Jones reagent (2.665 g  $\text{CrO}_3$  and 4.14 g  $\text{H}_2\text{SO}_4$  with water to 10 ml) dropwise to an ice-cold acetone solution of (1) caused instant oxidation. When 1 atom. equiv. of available oxygen had been added a sample was examined by t.l.c. a large proportion of (1) remained unoxidized (identified by  $\text{R}_F$  and colour with  $\text{FeCl}_3$  spray). Oxidation slowed after addition of 2 atom equivalents of oxygen, after 2.25 equivalents, excess of diazomethane was added directly and the reaction mixture was examined. No product with properties of the keto ester (2) (see below) could be found, and treatment of the crude product, after removal of acetone, with 2,4-dinitrophenylhydrazine HCl gave none of the derivative reported below but, in a slow reaction, a dark red precipitate having the properties of a 2,4-dinitrophenylosazone. S. Chatterjee<sup>1</sup> claimed a 93% yield of (2) a finding that would require almost total oxidation of (1) by 1 atom equivalent of available oxygen.

To prepare authentic (2) we used T. B. Johnson's observation<sup>3</sup> that alkoxyacetic esters undergo the Reformatsky reaction. Methyl methoxyacetate and ethyl 2-bromopropionate in boiling benzene reacted with zinc to yield, after decomposition with sulphuric acid, a fraction (b.p. 95-107°/13 mm) consisting essentially of (2) and the corresponding ethyl ester, it was methanolysed overnight in cold methanolic sodium methoxide to yield (20% overall) the keto ester (2), methyl 4-methoxy-2-methyl-3-oxobutanoate, b.p. 90-92°/10 mm. It gave a deepening blue-violet colour with  $\text{FeCl}_3$ , and seemed to occur largely in the keto form  $\delta$  ( $\text{CDCl}_3$ ) 1.35 (3H, d, J 7Hz), 3.43 (3H, s), 3.75 (4H, s overlapping q, J 7Hz), 4.13 (2H, s) (Found C, 52.5, H, 7.65.  $\text{C}_7\text{H}_{12}\text{O}_4$  requires C, 52.5, H, 7.55%). The 2,4-dinitrophenylhydrazone crystallized from methanol, yellow needles, m.p. 116° (Found N, 16.4.  $\text{C}_{13}\text{H}_{16}\text{N}_4\text{O}_7$  requires N, 16.5%). S. Chatterjee<sup>1</sup> gave 103°/5 mm for (2), our b.p., but not Chatterjee's, is consistent with those of closely analogous keto esters<sup>3</sup>.

Stage 3 The composite process is represented thus



The so-called "dehydration of the crude Grignard product" was with  $\text{POCl}_3$ - $\text{C}_5\text{H}_5\text{N}$ .<sup>1</sup> An overall yield of 75% of (3), as a mixture of cis and trans isomers, was claimed. Attention has already been drawn<sup>2</sup> to the absence of a C-methyl group from (3). It was also pointed out that the normal course of the Grignard reaction pictured above would be formation of a magnesium enolate of the keto ester (2), this would be accompanied by an equivalent amount of anisole. Since a similar finding would result from the presence of water or alcohols in the reagents or solvents we used rigorously dried solvents and glass-ware and took the additional precaution of adsorbing the keto ester (2) on Molecular Sieve 4A and extracting it with dried ether in the apparatus used for the reaction. To this solution was added one mole equivalent (by titration) of 4-methoxyphenylmagnesium bromide in ether plus enough dried tetra-

hydrofuran to dissolve the organometallic complex. Reaction was immediate, with formation of a white precipitate. In order to show that anisole was already present the mixture was filtered without access of moisture and the filtrate was evaporated and examined for anisole. The solid was then decomposed with a slight excess of  $\text{NHCl}$  and the products worked up by distillation. In this way 80% of the original keto ester (b.p.  $92^\circ/10$  mm) was recovered and identified by g.l.c. and n.m.r., along with a 60% isolated yield of anisole (some lost through volatility, identified by i.r.). Chatterjee's claim to have obtained a 75% yield of (3) (or of anything else) by  $\text{POCl}_3\text{-C}_5\text{H}_5\text{N}$  treatment of the "crude Grignard product" could therefore be true only if this product was formed from anisole and the keto ester (2). Equimolar amounts of these substances were therefore boiled with  $\text{POCl}_3\text{-C}_5\text{H}_5\text{N}$  for 30 min. Decomposition of the keto ester (2) then appeared complete. Dilute acid was added and the black mixture was distilled until anisole ceased to come over. It was recovered by means of pentane (93% recovery of starting material) and identified (i.r.). The aqueous distillate contained 1-methoxy-2-butanone, identified as the 2,4-dinitrophenylhydrazone, m.p.  $196\text{-}197^\circ$  after crystallization from ethanol ethyl acetate (lit.<sup>4</sup> m.p.  $197\text{-}198^\circ$ ), the n.m.r. spectrum agreed with this assignment. The aqueous acid residue from distillation contained no water-insoluble material therefore, no appreciable amount of (3) was present.

The small amount of residue from distillation of anisole and the keto ester (2) from the Grignard product showed i.r. absorption indicating the presence of an ester. The total residue was saponified with aqueous-methanolic  $\text{NaOH}$  and a crude acidic fraction was obtained. This showed n.m.r. signals attributable to aromatic protons, ( $\delta$  6.7-7.4), aromatic methoxyl ( $\delta$  3.7), aliphatic methoxyl ( $\delta$  3.27) and methyl (two doublets, J 7 Hz, at  $\delta$  0.97 and  $\delta$  1.20) but was clearly a mixture. If it had all been the acid  $\text{CH}_3\text{OC}_6\text{H}_4\text{C}(\text{OH})(\text{CH}_2\text{OCH}_3)\text{CH}(\text{CH}_3)\text{CO}_2\text{H}$ , the yield would be 7%. It was esterified with diazomethane and the ester (0.35 g) was heated in pyridine (5 ml) with  $\text{POCl}_3$  (0.5 ml) (reflux, 30 min). The neutral product (0.142 g) was recovered as usual by means of ether. U.v. examination (in methanol) showed no trace of selective absorption around 290-310 nm where the cinnamic ester (3) would absorb very strongly (S Chatterjee gave 293 nm). There was, however, a considerable peak at 262 nm ( $\epsilon$  6000 based on M 250) and this indicated an alternative mode of dehydration to  $\text{CH}_3\text{OC}_6\text{H}_4\text{C}(=\text{CHOCH}_3)\text{CH}(\text{CH}_3)\text{CO}_2\text{CH}_3$ . In support of this view (i) the product reacted quite slowly with aqueous-alcoholic 2,4-dinitrophenylhydrazine  $\text{HCl}$  to yield a yellow precipitate, (ii) the n.m.r. spectrum showed a new singlet at  $\delta$  6.13 ( $=\text{CHOCH}_3$ ) and the methyl region showed a new doublet (J 7 Hz) at  $\delta$  1.27. Jackman and Lown<sup>5</sup> found that most dehydrating agents with the analogous  $\text{C}_6\text{H}_5\text{C}(\text{OH})(\text{CH}_3)\text{CH}(\text{CH}_3)\text{CO}_2\text{CH}_3$  gave exclusively the  $\beta\gamma$ -unsaturated ester  $\text{C}_6\text{H}_5\text{C}(=\text{CH}_2)\text{CH}(\text{CH}_3)\text{CO}_2\text{CH}_3$ . Since no trace of (3) had been found, the examination ceased at this stage.

Conclusion We have been unable to reproduce S. Chatterjee's reports in any single particular, whether of yield, chemical nature of products, or physical properties of the substances claimed. We conclude that S. Chatterjee did not in fact obtain any of the products mentioned in the first three stages of his synthesis. In that case, he did not prepare the reported product of any later stage, since none of these products is known to be available in nature or by any other synthesis.

## REFERENCES

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