[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, BAR-ILAN UNIVERSITY]

The McFadyen-Stevens Reduction in the Aliphatic Series

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Aliphatic aldehydes possessing a quaternary α-carbon atom have been prepared by the method of McFadyen and Stevens.

The alkaline decomposition of 1-acyl-2-arylsulfonylhydrazines to yield aldehydes was first described by McFadyen and Stevens,[1] and a comprehensive review of this reaction has since been published.[2] The work of McFadyen and Stevens[1,2] established that this method was applicable, in varying yields, to the preparation of aromatic and heterocyclic aldehydes, but that it failed completely in the aliphatic series. This generalization, that the McFadyen-Stevens reduction is not applicable to the preparation of aliphatic aldehydes, has been generally accepted and quoted.[3,4]

To date, the only apparent exception is the preparation by Roberts[4] of cyclopropanecarboxaldehyde (16% yield as the 2,4-dinitrophenylhydrazone) from cyclopropanecarboxylic benzenesulfonhydrazide. However, as Roberts states, this success may be attributed to the well known "unsaturation" properties of the cyclopropane ring.

The apparent complete failure of the McFadyen-Stevens reduction in aliphatic cases has remained unexplained. It has been implied[2,3] that this failure may be due to the occurrence, in aliphatic cases, of an alternate reaction leading to 1,2-diacylhydrazines. This suggestion is based mainly on a questionable analogy to certain findings in the Kalb-Gross reaction[2,3,5] but has no experimental findings to support it in the McFadyen-Stevens reaction in the aliphatic series.[6] We were therefore, led to suspect that this limitation on the McFadyen-Stevens reduction may be only apparent, and that, in fact, aliphatic aldehydes, formed as usual, were destroyed by secondary processes. This suspicion was strengthened when a perusal of the literature showed that in all aliphatic cases tried, the expected aldehyde would have an α-hydrogen and would therefore be subject to self-condensation in the hot alkaline reaction mixture.

$$2\ RCONHNHSO_2Ar + 2\ OH^- \longrightarrow RCONHNHCOR + 2\ ArSO_2^- + N_2 + 2\ H_2O$$

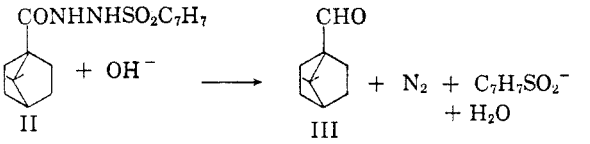
To test this hypothesis, the McFadyen-Stevens reduction of *N'*-*p*-toluenesulfonylpivalhydrazide (I) was attempted. The pivalaldehyde

$$(CH_3)_3CCONHNHSO_2C_7H_7 + OH^- \longrightarrow (CH_3)_3CCHO + N_2 + C_7H_7SO_2^- + H_2O$$

formed, lacking an α-hydrogen, would not undergo aldol-type condensations. Furthermore, the carbonyl group in such "neopentyl"-type systems is sterically hindered and destruction of the aldehyde by a Cannizzaro reaction should also be retarded. To obtain I, the known pivalhydrazide[8] was treated with *p*-toluenesulfonylchloride in pyridine solution.

When I was submitted to the usual McFadyen-Stevens reaction conditions (ethylene glycol solution, solid sodium carbonate, 160° for two minutes) a 15% yield of pivalaldehyde was isolated in the form of its 2,4-dinitrophenylhydrazone. Extending the reaction time to eight minutes did not substantially affect the yield (12%). However, when the reaction time was reduced to *thirty seconds* a 40% yield of pivalaldehyde 2,4-dinitrophenylhydrazone was obtained.

We also studied the reduction of *N'*-*p*-toluenesulfonylapocamphane-1-carbohydrazide (II) to yield apocamphane-1-carboxaldehyde (III).



II III

(1) J. S. McFadyen and T. S. Stevens, *J. Chem. Soc.*, 584 (1936).

(2) E. Mosettig, *Org. Reactions*, VIII, 232 (1954). For additional references, see footnote 4 of ref. 7.

(3) C. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, 65, 482 (1943).

(4) J. D. Roberts, *J. Am. Chem. Soc.*, 73, 2959 (1951).

(5) L. Kalb and O. Gross, *Ber.*, 59, 727 (1926).

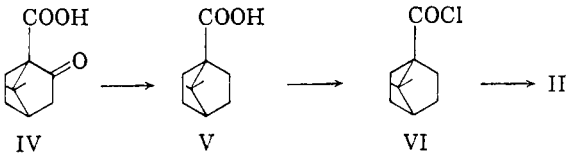
(6) Niemann[3] tries to find further support for the above formulation from the results of the attempted McFadyen-Stevens reduction of benzenesulfonyl-*p*-nitrobenzhydrazide. In place of the expected *p*-nitrobenzaldehyde he isolated *p*-nitrobenzoic acid and an uncharacterized "reaction product of high melting point" assumed to be the *sym*-di-*p*-nitrobenzhydrazide. Alkaline hydrolysis of the latter is assumed to have given rise to the *p*-nitrobenzoic acid. However, the extension from the aromatic to the aliphatic series is not necessarily valid. The *p*-nitrobenzoic acid may have resulted from other reactions, possibly *via* the aldehyde. The *sym*-dihydrazide, if indeed isolated, may have resulted from the reaction of first formed aldehyde with starting material under the alkaline conditions. For an analogous reaction see A. Angeli and V. Castellana, *Chem. Zentr.*, I, 1861 (1909), who obtained 2-benzoyl-1-phenylhydrazine from the reaction of benzaldehyde with 1-phenyl-2-benzenesulfonylhydrazine in alkaline alcoholic solution. Finally, it is mentionable that Newman and Caflisch[7] succeeded in obtaining *p*-nitrobenzaldehyde, though in low yield, by the McFadyen-Stevens procedure.

(7) M. S. Newman and E. G. Caflisch, Jr., *J. Am. Chem. Soc.*, 80, 862 (1958).

(8) H. Wieland, A. Hintermaier, and I. Dennstedt, *Ann.*, 452, 1 (1927).

Here, too, the expected product, III, lacks an α-hydrogen, and the carbonyl group should be even more hindered than in pivalaldehyde.

Apocamphane-1-carboxylic acid (V) was prepared from ketopinic acid (IV) by the Huang-Minlon modification of the Wolff-Kishner reduction,[9] and was converted to its acid chloride, VI. Reaction of VI with *p*-toluenesulfonylhydrazine



in pyridine solution yielded the desired II. Attempts to prepare II by way of apocamphane-1-carbohydrazide and reaction of the latter with *p*-toluenesulfonyl chloride, failed. The reaction of VI with hydrazine hydrate under a variety of conditions always resulted in *N,N'*-bis(apocamphane-1-carboxy)hydrazine as the only isolable product.

When II was submitted to the usual McFadyens-Stevens reaction conditions for thirty seconds a 60% yield of III, isolated as the 2,4-dinitrophenylhydrazone, was obtained. Extending the reaction time to two and one-half minutes resulted in a reduction of the yield to 13%.

Newman and Caflisch[7] have reported that the presence of powdered glass in the reaction mixture results in somewhat improved yields. In reactions reported here the same yields were obtained both in the presence and absence of powdered glass.

In conclusion, it is clear that, contrary to current belief, the McFadyen-Stevens reaction is applicable to the preparation of aliphatic aldehydes, at least in those cases in which the α-carbon is quaternary. The yields obtainable are of the same order of magnitude as those obtained in the aromatic series. Furthermore, it seems indicated that the failure of the McFadyen-Stevens reduction in aliphatic cases reported to date is due to the instability of the product under the reaction conditions, rather than to an inherent difference in the reactivity of the starting hydrazides.

EXPERIMENTAL[10]

General procedure for the McFadyen-Stevens reduction. A solution of 1 g. of 1-acyl-2-arylsulfonylhydrazine in 30 ml. of ethylene glycol was heated to 160° and, in the appropriate cases, 1 g. of ground glass (Pyrex) was added. Three grams of sodium carbonate was added and the reaction mixture was kept at 160–165° with constant stirring for the stated time. After cooling and filtration, the solution was neutralized with dilute hydrochloric acid and treated with 2,4-dinitrophenylhydrazine reagent.[11] The precipitated 2,4-dinitrophenylhydrazone was collected, dried, and recrystallized from ethanol-ethyl acetate.

TABLE I

Compound[a]	Reaction Time[b]	Yield[c], %
I	8	12
I[d]	2	13–16
I[d]	0.5	30–40
II	2.5	13
II	0.5	60

[a] I is N'-*p*-toluenesulfonylpivalhydrazide; II is N'-*p*-toluenesulfonylapocamphane-1-carbohydrazide. [b] In minutes at 160-165°. [c] As pure 2,4-dinitrophenylhydrazone; pivaldehyde 2,4-dinitrophenylhydrazone is known,[12] reported m.p. 210°; found, 208.5-211°. Apocamophane-1-carboxaldehyde 2,4-dinitrophenylhydrazone was prepared as described below. [d] Experiments performed both in presence and in absence of powered glass. No effect on yield of product was observed.

Apocamphane-1-carboxaldehyde 2,4-dinitrophenylhydrazone. 1-Hydroxymethylapocamphane was obtained by the lithium aluminum hydride reduction of apocamphane-1-carboxylic acid,[9c] and was oxidized to apocamphane-1-carboxaldehyde essentially by the method of Asahina and Ishidate.[13] The 2,4-dinitrophenylhydrazone was prepared in the usual manner and recrystallized from ethanol–ethyl acetate. M.p. 201–202°.

Anal. Calcd. for $C_{16}H_{20}N_4O_4$: C, 57.84; H, 6.02; N, 16.86. Found: C, 58.01; H, 6.10; N, 17.08.

The apocamphane-1-carboxaldehyde 2,4-dinitrophenylhydrazone obtained from the McFadyen-Stevens reduction was shown to be identical with the authentic material by mixed melting point and identity of infrared spectra.

N'-p-Toluenesulfonylapocamphane-1-carbohydrazide (II). A mixture of 1.5 g. of apocamphane-1-carboxylic acid and 4.5 g. of thionyl chloride was refluxed for 1 hr. The excess thionyl chloride was then removed under vacuum, and the crude acyl chloride was dissolved in dry pyridine. This solution was added dropwise with cooling and stirring, to a solution of 1.48 g. of *p*-toluenesulfonylhydrazide in dry pyridine. After 1 hr. at 0°, the reaction mixture was allowed to stand 1 hr. at room temperature. It was then poured into a mixture of ice and dilute hydrochloric acid. An oil separated and solidified. The solid was washed with dilute hydrochloric acid and water, and recrystallized from 95% ethanol. The *N'-p*-toluenesulfonylapocamphane-1-carbohydrazide forms long needle-like crystals, m.p. 175–177°.

Anal. Calcd. for $C_{17}H_{24}N_2O_3S$: C, 60.70; H, 7.19; N, 8.33; S, 9.51. Found: C, 60.28; H, 7.18; N, 8.70, S, 9.29.

N,N'-Bis(apocamphane-1-carboxy)hydrazine. A mixture of apocamphane-1-carboxylic acid and 12 g. of thionyl chloride were refluxed for 1 hr. The excess thionyl chloride was then removed under vacuum and to the crude acyl chloride was added a mixture of 10 g. of hydrazine hydrate and 10 ml. of dimethylformamide at 0°. After a further hour at 0°, the reaction mixture was poured into ice water and the precipitate was collected and dried. The product, obtained in essentially quantitative yield, was recrystallized from nitromethane. The analytical sample melted at 271.5–276° (decomposition and previous sintering). The melting point is

(9)(a) E. Wedekind, *Ber.*, **57**, 664 (1924); (b) P. D. Bartlett and L. H. Knox, *J. Am. Chem. Soc.*, **61**, 3184 (1939); (c) M. Sprecher, Ph.D. dissertation, Columbia University, New York, 1953.

(10) Melting points were determined on a Köfler hot stage and are uncorrected.

(11) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, 4th Edition, Wiley, New York, 1956, p. 219.

(12) I. Heilbron, *Dictionary of Organic Compounds*, Vol. 4, Eyre and Spottiswoode, London, 1953, p. 224.

(13)(a) Y. Asahina and M. Ishidate, *Ber.*, **67**, 1202 (1934). (b) W. von E. Doering, M. Farber, M. Sprecher, and K. B. Wiberg, *J. Am. Chem. Soc.*, **74**, 3000 (1952).

not a reliable criterion of purity. There were indications of liquid crystal formation, and melting is apparently accompanied by gas evolution.

Anal. Calcd. for $C_{20}H_{32}N_2O_2$: C, 72.24; H, 9.70; N, 8.43. Found: C, 72.05; H, 9.46; N, 8.76.

Another experiment, in which a dimethylformamide solution of apocamphane-1-carbonyl chloride was added dropwise with stirring to a large excess of hydrazine hydrate, yielded the same product.

N'-p-Toluenesulfonylpivalhydrazide. Pivalhydrazide was prepared from methyl pivalate by the procedure of Wieland *et al.*[8] To a cold solution of 1.4 g. of pivalhydrazide in dry pyridine was added 2.55 g. of *p*-toluenesulfonylchloride. After 0.5 hr. at 0°, the reaction mixture was allowed to stand for 3 hr. at room temperature and then poured into a mixture of ice and dilute hydrochloric acid. The precipitate was filtered off and dissolved in ether. The ether solution was extracted three times with dilute hydrochloric acid, washed with saturated sodium chloride solution, dried over magnesium sulfate and evaporated to dryness. The residual *N'-p*-toluenesulfonylpivalhydrazide (1.7 g., m.p. 158–160°) was crystallized from 75% aqueous ethanol, m.p. 159.5–161°.

Anal. Calcd. for $C_{12}H_{18}O_3N_2S$: C, 53.32; H, 6.71; N, 10.37; S, 11.87. Found: C, 53.36; H, 6.63; N, 10.69; S, 12.04.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA AT RIVERSIDE]

The Chemistry of β-Bromopropionyl Isocyanate. IV. Elimination Reactions of Some β-Bromopropionic Acid Derivatives[1]

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The rates of dehydrobromination of two β-bromopropionylcarbamates and two β-bromopropionylureas with chloroform were measured in chloroform and compared with the rates of ethyl β-bromopropionate and β-bromopropionanilide. Differences are attributed to the inductive effect.

The reaction of β-bromopropionyl isocyanate with amines and alcohols leads to β-bromopropionylureas and carbamates,[2] and a study of the rates of elimination reactions of such compounds was of interest. The rates of reactions of ethyl β-bromopropionate with amines were studied by McElvain.[3] Tertiary amines were found to be the principal products from piperidine, though they were apparently formed by an elimination-addition mechanism. The hydrolysis reactions of β-bromopropionic acid derivatives have received considerable study.[4–7] The product to be expected from the reaction of bases with ethyl β-bromopropionate or other derivatives of β-bromopropionic acid depends upon the reaction conditions. In some cases[3,8–10] displacement products have been reported; in others[11] the unsaturated products were obtained. The addition of amines and ammonium salts to acrylyl esters and amides[12,13] has been reported.

Chloroform was chosen as the solvent for the present work in spite of its low boiling point and slow reaction with amines. Its solubility properties for the compounds in question were reasonably good, it could be rendered anhydrous easily, and the rates of elimination were found to be measurable for both simple derivatives of propionic acid and derivatives of β-bromopropionyl isocyanate.

EXPERIMENTAL

Ethyl β-bromopropionate was prepared from β-bromopropionic acid and ethanol with sulfuric acid. The product was worked up in a normal manner to yield the ester, b.p. 45° (3 mm.). The material used in the kinetic determinations was redistilled, a center cut being retained.

The samples of β-bromopropionanilide (m.p. 119–120°)[14] and its *p*-nitro derivative (m.p. 144–145°) were prepared by reaction of the amine with β-bromopropionyl chloride in chloroform. The product was precipitated from the chloroform with ether and crystallized from methanol.

The preparation of methyl and phenyl β-bromopropionylcarbamates from β-bromopropionyl isocyanate and the alcohol has been reported.[15] The preparation of *N*-phenyl-*N'*-β-bromopropionylurea and *N*-(β-phenylethyl)-*N'*-β-bromopropionylurea has been reported. The melting points of the four compounds agreed with those reported, and they were crystallized several times from methanol and chloroform prior to the kinetic runs.

The chloroform was extracted with concentrated sulfuric acid, washed with water, dried with calcium chloride, and stored over calcium hydride. Immediately prior to use the chloroform was distilled from calcium hydride.

(1) Supported by a grant from the National Science Foundation.

(2) H. W. Johnson, Jr., and D. E. Bublitz, *J. Am. Chem. Soc.*, **80**, 3150 (1958).

(3) W. V. Drake and S. M. McElvain, *J. Am. Chem. Soc.*, **56**, 697 (1934); **56**, 1810 (1934).

(4) E. Saito, *Bull. soc. chim. France*, **1948**, 404.

(5) J. F. Lane and H. W. Heine, *J. Am. Chem. Soc.*, **73**, 1348 (1951).

(6) E. Saito, and R. Schmitz, *Bull. Soc. chim. France*, **1952**, 513.

(7) J. Eloranta, *Ann. Acad. Sci. Fennicae*, Ser. A., II, No. 70 (1956). *C.A.*, **51**, 9480 (1957).

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(9) N. L. Wendler, *J. Am. Chem. Soc.*, **71**, 375 (1949).

(10) Brit. Patent **653,452**. *C.A.* **46**, 1038 (1952).

(11) Swiss Patent **280,474** (1952); *C.A.*, **47**, 6977 (1953). U. S. Patent **2,640,073**; *C.A.* **48**, 3995 (1954).

(12) Ger. Patent **869,489**. *C.A.*, **48**, 11483 (1954).

(13) R. Dobenko, *J. Org. Chem.*, **25**, 1123 (1960).

(14) E. H. Charlesworth and H. J. Anderson, *Can. J. Research*, **28B**, 1 (1950).

(15) H. W. Johnson, Jr., H. A. Kreyssler, and H. L. Needles, *J. Org. Chem.*, **25**, 279 (1960).