Ferrocene Derivatives

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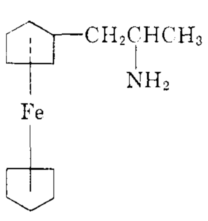
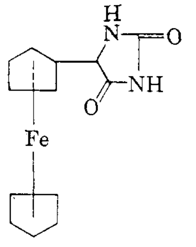
As part of an investigation dealing with the preparation of ferrocene analogues of pharmacologically active substances, we have prepared ferrocene derivatives related to amphetamine and diphenylhydantoin.

The amphetamine analogue was prepared by condensation of ferrocenecarboxyaldehyde[1] with nitroethane, followed by reduction of the crude condensation product with lithium aluminum hydride to give 2-aminopropylferrocene (I). The intermediate nitroolefin was very heat-sensitive, being thereby converted to a tar.


I


II

Ferrocenecarboxyaldehyde was converted to 5-ferrocenylhydantoin (II) on heating with ammonium carbonate and potassium cyanide under pressure. Attempts to convert benzoylferrocene[2] to the corresponding hydantoin (as a more exact analogue of diphenylhydantoin) under the same conditions were unsuccessful.

Compound I showed very weak anorexic and central nervous system stimulant activity; compound II showed virtually no central nervous system depressant activity in mice.

EXPERIMENTAL

2-Amino-1-ferrocenylpropane hydrobromide (I). A solution containing 10.2 g. (0.05 mole) of ferrocenecarboxaldehyde, 11.25 g. (0.15 mole) of nitroethane, and 7 g. of ammonium acetate in 50 ml. of acetic acid was refluxed for 2 hr. The solution was then diluted with ice water and extracted with ether. The ethereal extract was dried and concentrated to give 10.7 g. (79%) of 1-ferrocenyl-2-nitropropene as a dark purple oil. An ethereal solution of 6.8 g. (0.025 mole) of 1-ferrocenyl-2-nitropropene was added to a suspension of 6 g. of lithium aluminum hydride in ether. The resulting yellow mixture was refluxed for 5 hr. and then treated with 30 ml. of water. The suspension was filtered and the filtrate was concentrated to give a dark oil which crystallized to a semisolid on standing. Attempts to purify the free base by recrystallization were unsuccessful. The hydrobromide salt was prepared and recrystallized from methanol–ethyl acetate–ether, m.p. 198–200° dec.

Anal. Calcd. for $C_{13}H_{18}NBrFe$: C, 48.18; H, 5.60. Found: C, 48.21, 48.22; H, 5.78, 6.00.

5-Ferrocenylhydantoin (II). A mixture of 4.28 g. (0.02 mole) of ferrocenylcarboxaldehyde[1], 2.09 g. (0.03 mole) of potassium cyanide, and 5.76 g. (0.06 mole) of ammonium carbonate in 50% ethanol was heated at 110° for 20 hr. in a pressure bottle. At the end of this period more cyanide (0.03 mole) and carbonate (0.06 mole) were added and heating continued for 48 hr. A dark yellow solid separated and was filtered. Recrystallization from ethanol yielded 3.3 g. (58%) of 5-ferrocenylhydantoin, m.p. 250–252°.

Anal. Calcd. for $C_{13}H_{12}N_2O_2Fe$: C, 54.96; H, 4.26; N, 9.85. Found: C, 54.60, 54.68; H, 4.69, 4.68; N, 9.81.

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[1] G. D. Broadhead, J. M. Osgerby, and P. L. Pauson, *J. Chem. Soc.*, 650 (1958).

[2] M. Rausch, M. Vogel, and H. Rosenberg, *J. Org. Chem.*, **22**, 903 (1957).

Debrominations with Trialkyl Phosphites

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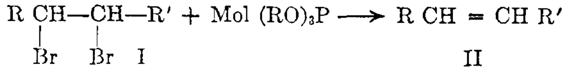
The reaction of vicinal dihalides with trialkyl phosphites has been reported to proceed *via* the normal Arbuzov Reaction to yield the corresponding mono- and diphosphonates.[1,2a,b] The formation of an olefin, as the major product, has been reported only in cases involving polyhalogenated compounds.[3,4]

We have found that a vicinal dihalide, where one or both of the halogens is contiguous to a carbonyl function, is converted smoothly and in good yield, with *one* mole equivalent of trialkyl phosphite, to the olefin.



$$\underset{\text{I}}{\mathrm{R}\,\underset{\text{Br}}{\mathrm{CH}}\text{—}\underset{\text{Br}}{\mathrm{CH}}\text{—}\mathrm{R'}} + \text{Mol } (\mathrm{RO})_3\mathrm{P} \longrightarrow \underset{\text{II}}{\mathrm{R\,CH = CH\,R'}}$$

a. $R = R' = C_6H_5CO$
b. $R = C_6H_5$; $R' = C_6H_5CO$ (1)
c. $R = C_6H_5$; $R' = CO_2H$

Attempts at debromination in the usual manner led to: a) reduction of the double bond when zinc was employed; b) tars when sodium iodide was used.

With two or more moles of trialkyl phosphite, the diphosphonate III is formed

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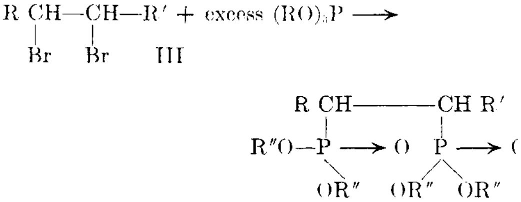
(1) G. M. Kosolapoff, *OrganoPhosphorus Compounds*, Wiley, New York, 1950; pp. 122.

(2)(a) G. Kamai and V. A. Kukhtin, *Trudy Kazan. Khim. Tekhnol. Inst. im. S. M. Kirova*, **21**, 141 (1956); *Chem. Abstr.*, **51**, 11985b (1957). (b) A. N. Pudovik and M. G. Imaev, *Izvest. Akad. Nauk S.S.S.R. Otdel. Khim. Nauk.*, 916 (1952); *Chem. Abstr.*, **47**, 10463e (1953).

(3) G. Kamai, *Izvest. Akad. Nauk S.S.S.R. Otdel Khim Nauk* 923 (1952); *Chem. Abstr.*, **47**, 10461a (1953).

(4) H. R. Davis, U.S. Pat. 2,742,510; *Chem. Abstr.*, **51**, 2847 (1957).



(2)

EXPERIMENTAL

Debromination of trans-dibenzoylethylene dibromide (Ia). A 20-g. sample of *trans*-dibenzoylethylene dibromide and 5.5 ml. of trimethyl phosphite were dissolved in 150 ml. of dry toluene and the solution was refluxed for 20 hr. The solvent was removed and the residue crystallized from ethanol. There was obtained 10.7 g. (92%) of product, m.p. 108–10°, which did not depress the melting point of an authentic sample of *trans*-dibenzoylethylene (IIa).

Debromination of chalcone dibromide (Ib). A 5.0-g. sample of chalcone dibromide and 1.9 ml. of trimethyl phosphite were dissolved in 75 ml. of dry toluene and the solution was refluxed for 2 hr. The solvent was removed and the residue was crystallized from ethanol. There was obtained 2.3 g. (80%) of product, m.p. 55–56°, which did not depress the melting point of an authentic sample of chalcone (IIb).

Debromination of cinnamic acid dibromide (Ic). A 10.0-g. sample of cinnamic acid dibromide and 4.5 ml. of trimethyl phosphite were dissolved in 150 ml. of dry toluene and the solution was refluxed for 20 hr. The reaction mixture was worked up identically to the previous reactions and yielded 4.4 g. (92%) of cinnamic acid IIc.

Reaction of trans-dibenzoylethylene dibromide with excess phosphate (IIIa). A 10.0-g. sample of *trans*-dibenzoylethylene dibromide and 7.0 ml. (2 mole equiv.) of trimethyl phosphite were dissolved in 75 ml. of dry toluene and the solution was refluxed for 20 hr. The solvent was removed and the residue was crystallized from benzene-hexane. There was obtained 7.5 g. (65%) of product, m.p. 131–134°. Three recrystallizations from benzene-hexane afforded the analytical sample, m.p. 134–135°.

Anal. Calcd. for $C_{20}H_{24}O_8P_2$: C, 52.9; H, 5.3; P, 13.6. Found: C, 53.2; H, 5.6; P, 13.9.

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Reaction of Benzyl Methyl Ether with Sodium Metal

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Shorigin[1] has demonstrated the rearrangement of benzyl ethers upon attempted sodium cleavage whereby reaction of benzyl ethyl ether with sodium at 170–210° for four and one-half hours led to 1-phenylpropanol in 30% yield. In the case of the corresponding benzyl methyl ether, no studies with sodium metal have been reported, although it has been shown that benzyl methyl ether (a) rearranges to 1-phenyl ethanol in 35% yield upon treatment with lithium phenyl,[2] (b) forms an uncharacterized product, b.p. 185–190° (12 mm.), in 30% yield when treated with potassium amide[3] in refluxing ether for nineteen hours, and (c) undergoes cleavage to lithium benzyl in 75–83%[4] yield (see however ref. 5 in which a yield of only 11% was obtained) with lithium wire in tetrahydrofuran at ±5°.

We have now found that, unlike the results with lithium which apparently cleaves the ether without rearrangement, the action of sodium on benzyl methyl ether leads consistently to 1-phenylethanol, the product of rearrangement.

In a typical experiment, benzyl methyl ether was heated under nitrogen at 115° for two hours with sodium which under the reaction conditions was a finely dispersed liquid. The purple-black reaction mixture led to a product shown by gas chromatographic analysis to consist of three components: toluene (23%), benzyl methyl ether (61%), and 1-phenylethanol (15%), identified by comparison of their retention times with authentic samples and by gas chromatographic analysis of samples to which authentic material was added. Further confirmation of the presence of 1-phenylethanol was obtained in a similar experiment by fractionation of the crude product and comparison of the infrared spectrum of the appropriate fraction with that of authentic 1-phenylethanol. The amount of 1-phenylethanol (5.5 g.) present in the crude product corresponds to 35% rearrangement.[6]

An experiment performed at 55° with the same reactants was interrupted after partial completion (two and one-half hours) by destroying unchanged sodium with water and isopropanol. Analysis by gas chromatography of the isolated organic layer indicated the presence of toluene (12%) and 1-phenylethanol (3%).

A single attempt to demonstrate the presence of sodium benzyl prior to the hydrolysis of a reaction conducted at 115° was unsuccessful. After completion of the two-hour heating period, a solution of benzophenone in benzyl methyl ether was added as a scavenger for sodium benzyl. However, analysis of the product showed a 63% recovery of benzophenone and no 1,1,2-triphenylethanol could be isolated from the reaction mixture.

In an effort to carry out the cleavage reaction under milder conditions, sodium dispersed in xylene was added to benzyl methyl ether chilled to

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[1] P. Shorigin, *Ber.*, **56**, 176 (1923); **57**, 1627, 1634 (1924).

[2] G. Wittig and L. Lohman, *Ann.*, **550**, 260 (1942).

[3] C. R. Hauser and S. K. Kantor, *J. Am. Chem. Soc.*, **73**, 1437 (1951).

[4] H. Gilman, H. A. NcNinch, and D. Wittenberg, *J. Org. Chem.*, **23**, 2044 (1958).

[5] J. F. Eastham and D. Y. Cannon, *J. Org. Chem.*, **25**, 1504 (1960).

[6] This is a minimum figure. The actual amount of rearrangement is undoubtedly higher, as in the work-up 1-phenylethanol was not recovered from the washes—see Experimental.