ether. The ether extract was dried over potassium carbonate. Distillation through a 9″ centered rod column gave 54.9 g., 91.5%, of recovered oxide, b.p. 100–102° (40 mm.), $n^{25}D$ 1.5313.

Treatment of 2-Iodo-2-phenylethanol with Silver Ion in Methanol.—A solution of 102 g. (0.60 mole) of silver nitrate in 5 l. of methanol was added dropwise with stirring to 125 g. (0.50 mole) of iodohydrin and 50 g. (0.60 mole) of sodium bicarbonate in 1 liter of methanol. The reaction mixture was filtered and the filtrate was concentrated and then added to a liter of water saturated with salt. The mixture was extracted with five 100-ml. portions of ether and the ether extract was dried over magnesium sulfate. Distillation through a 9″ centered rod column yielded 17.55 g., 59.5%, of 2-methoxy-2-phenylethanol, b.p. 120–125° (18 mm.), plus 7.5 g. of polymer which would correspond to 25% of phenylacetaldehyde. The carbinol fraction yielded a 3,5-dinitrobenzoate, m.p. 98.0–98.5°, mixed m.p. with authentic material 98.0–98.5°, mixed m.p. with isomeric material 85–89°.

2-Methoxy-1-phenylethyl Bromide.—To a stirred solution of 40 ml. of dimethylaniline, 30 ml. of dry ether and 76 g. (0.50 mole) of 2-methoxy-1-phenylethanol, 20 ml. (0.21 mole) of phosphorus tribromide was added dropwise while the temperature was kept below 0°. After the addition was complete, the stirring was continued for an hour and the temperature was allowed to rise to 20°. The reaction mixture was then cooled to 0° again and 20 ml. of water was added. The reaction mixture was then added to 400 ml. of water and the oil which separated was taken up with three 100-ml. portions of ether. The ether was dried over magnesium sulfate, then distilled through a 5″ Vigreux column to yield 34.1 g., 32%, of impure product, b.p. 88–92° (1 mm.), $n^{25}D$ 1.5480, d^{25}_4 1.332, MR_D 51.31 (calcd. 49.57).

Treatment of 2-Methoxy-1-phenylethyl Bromide with Silver Ion in Methanol.—A solution of 62.6 g. (0.369 mole) of silver nitrate in 3.2 l. of methanol was added dropwise with stirring over a period of *ca.* half-hour to 62.2 g. (0.74 mole) of sodium bicarbonate and 72.1 g. (0.335 mole) of 2-methoxy-1-phenylethyl bromide in 1 l. of methanol. The reaction mixture was filtered and the methanol was distilled off through a 9″ Vigreux column. When 1 l. of solution remained, it was added to 1 l. of a saturated salt solution and extracted with five 100-ml. portions of ether. The ether was distilled off through a 13″ Vigreux column and the residue was distilled through a 9″ centered rod column yielding 37.5 g., 68%, of product, b.p. 107–115° (20 mm.), $n^{25}D$ 1.5035.

Analysis of the product by the dinitrophenylhydrazine method indicated *ca.* 20 mole per cent. of material, calculated as acetal, which gives phenylacetaldehyde dinitrophenylhydrazone.

A mixture of *ca.* 35 g. of the crude product and 400 ml. of 2 *N* sulfuric acid was steam distilled and the distillate was extracted with ether. The ether extract was dried over potassium carbonate. Distillation at 20 mm. pressure through a centered rod column yielded *ca.* 15 g. of product, b.p. 107–109° (20 mm.), with 10 g., b.p. 108–109° (20 mm.), $n^{25}D$ 1.4943, presumably styrene glycol dimethyl ether.

Anal. Calcd. for $C_{10}H_{14}O_2$: C, 72.26; H, 8.50. Found: C, 72.03; H, 8.39.

The dinitrophenylhydrazine analytical method indicated less than 2% of phenylacetaldehyde-forming compounds.

LOS ANGELES 24, CALIFORNIA

[CONTRIBUTION FROM HALL LABORATORY OF CHEMISTRY, WESLEYAN UNIVERSITY]

Cyanide Ion as a Catalyst for Transesterification. Non-aqueous Buffering

BY QUENTIN R. PETERSEN

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It has been demonstrated that methanolic potassium cyanide, serving as a non-aqueous buffer system, effects the transesterification of several esters. The transesterification reaction has been shown to be an effective alternative to hydrolysis in a system where the hydrolytic reaction is complicated by elimination.

In the course of another investigation it was observed that when a methanolic solution of 7-ketocholesteryl acetate was refluxed with potassium cyanide, 7-ketocholesterol was isolated directly in a pure state (m.p. 170–171.5°, $\alpha^{28}D$ −106°) as the only solid organic product.[1]

Bergstrom and Wintersteiner[2] obtained pure 7-ketocholesterol by the hydrolysis of the acetate with potassium carbonate in 80% methanol, but they did not report the yield. Other workers[3–5] have had considerable difficulty with both yield and purity of the hydrolysis product because of accompanying elimination. Barnett,[3] when using the methanolic potassium carbonate method, obtained material melting 10° low, the impurities being of such a nature that repeated recrystallization did not raise the melting point.

(1) A reaction of zinc cyanide with certain esters, leading to the production of the free alcohol, was described by L. P. McHatton and M. J. Soulal (*Chem. & Ind.*, 1337 (1953)). Inasmuch as neither alcohol nor water was reported present in sufficient quantity to account for the observed result, the mechanism of the reaction carried out by the British workers is not the same as that proposed for the reaction described in this paper.

(2) S. Bergstrom and O. Wintersteiner, *J. Biol. Chem.*, **141**, 602 (1941).

(3) J. Barnett, *J. Chem. Soc.*, 528 (1946).

(4) J. Mauthner and W. Suida, *Monatsh.*, **17**, 579 (1896).

(5) A. Ogota and I. Kawakani, *J. Pharm. Soc. Japan*, **58**, 738 (1938).

In view of the normally troublesome nature of this hydrolysis it was felt that the use of alcoholic cyanide might be a somewhat general answer to the problem of concurrent elimination during hydrolysis. For this reason the reaction was studied further to determine the mechanism, generality and optimum conditions.

For the first part of this study cholesteryl acetate (I) and the base sensitive 7-ketocholesteryl acetate (II) were used. When the original conditions were varied by rendering the reaction anhydrous, no significant change in the course of the reaction was noted. This observation ruled out hydrolysis as a mechanism. The reactions were also found to take place at room temperature, in the presence or absence of water. The results are summarized in Table I.

The only significant difference between I and II was the more rapid rate of reaction of the 7-keto compound, expected on the basis of the electron withdrawing effect of the conjugated carbonyl oxygen. 7-Ketocholesterol was produced from its acetate in approximately one-third of the time necessary to transform cholesteryl acetate into the free alcohol. Additional reflux time did not induce any decomposition of the 7-ketocholesterol.

The effectiveness of a weaker base than cyanide

TABLE I

REACTIONS WITH METHANOLIC POTASSIUM CYANIDE

Ester	Temp., °C.	Water present	Yield, % alcohol
I	Reflux	Yes	94
I	Room	Yes	95
I	Reflux	No	98
I	Room	No	98
II	Reflux	Yes	94
II	Room	Yes	95
II	Reflux	No	100
II	Room	No	93

ion was studied. When acetate ion was used as a catalyst for the reaction, it was found to be ineffective, cholesteryl acetate being recovered in 98% yield after three hours of reflux with methanolic potassium acetate.

Inasmuch as only the alcohol moiety of the reaction products was isolated in the experiments described above, the mechanism of the reaction is not indicated by the experimental results, the alcohol being the expected product of either a hydrolysis or a transesterification. To provide for the facile isolation of the other reaction product (the methyl ester resulting from transesterification or the free acid resulting from hydrolysis), two 3,5-dinitrobenzoates were prepared and treated with methanolic potassium cyanide as described above. In spite of side reactions of the basic solution with the nitro compound, 40–50% of the expected methyl 3,5-dinitrobenzoate was recovered in a pure state from the transesterification of the secondary butyl and cyclohexyl esters of 3,5-dinitrobenzoic acid.

More useful materials were found in the esters of *p*-iodobenzoic acid. Although a longer time was required for the reaction of these esters (presumably because of both steric and electronic effects), it was possible to isolate the product of transesterification, methyl *p*-iodobenzoate, in 60–85% yield. Free *p*-iodobenzoic acid also was recovered indicating that the alcohol produced was actually a product of both mechanisms, transesterification and hydrolysis. The other possible source of free acid, hydrolysis of the transesterification produced methyl ester, is not possible to rule out on the basis of these experiments.

Cholesteryl *p*-iodobenzoate was prepared to provide an ester from the reaction of which both products could be isolated as easily separable solids. Transesterification of this compound (somewhat complicated by its extreme insolubility in methanol) gave the expected result after eight hours of reflux with dry methanolic potassium cyanide in benzene solution. Cholesterol and methyl *p*-iodobenzoate were isolated in yields approaching theoretical following this procedure.

To determine the effect of an elevated temperature as well as the generality of the reaction with respect to the displacing alkoxide ion, cholesteryl *p*-iodobenzoate was refluxed with a solution of potassium cyanide in cyclohexanol to produce cholesterol and cyclohexyl *p*-iodobenzoate.

That the reaction is not general in preventing the accompanying elimination reaction was shown in an attempt to prepare cholest-4-en-3-one-7β-ol from its benzoate by this reaction. Cholest-4,6-diene-3-one was the only solid recovered from the reaction. The potassium carbonate hydrolysis also gave exclusively the elimination reaction when applied to this benzoate.

It is not inappropriate to point out that the transformations described above have been affected by the maintenance of a low but constant alkoxide concentration by the equilibrium shown below.

$$ROH + CN^- = RO^- + HCN$$

This concept of buffering in non-aqueous alcoholic media has possibilities exceeding those utilized in this work. Solution of ions of differing base strength (such as acetate ion which gives a lower equilibrium concentration of alkoxide ion) coupled with varied concentrations of these ions, could provide the complete spectrum of *constant* alkoxide concentrations optimum for selective action on base-sensitive systems. Variation of the particular alcohol used will permit temperature and solubility selection to meet individual problems.

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Experimental[6]

Reactions of Cholesteryl Acetate and 7-Ketocholesteryl Acetate with Methanolic Potassium Cyanide.—These reactions were run under various conditions with the results shown in Table I. A typical procedure follows:

To 50 ml. of refluxing methanol, previously dried overnight over Drierite, was added a mixture of 0.43 g. of cholesteryl acetate and 0.30 g. of potassium cyanide (dried at 100° under high vacuum for six hours). The solution was protected from atmospheric moisture and refluxed for three hours, after which it was cooled to room temperature. After seven hours the solution was diluted with sufficient water to completely precipitate the steroid fraction and the mixture cooled overnight at 10°. The solid was filtered, washed with water, and dried at 110° for three hours. Ether extraction of the solid residue gave a solution which, upon evaporation, produced 0.38 g. (98%) of cholesterol, m.p. 148°. When non-anhydrous reactions were run, a stoichiometric quantity of water was added. Reactions at room temperature proceeded for three days, and were carried out in sufficient methanol to keep all of the reactants in solution.

Transesterification of *sec*-Butyl 3,5-Dinitrobenzoate.—To a solution of 1.34 g. of *sec*-butyl 3,5-dinitrobenzoate in 70 ml. of absolute methanol was added 0.35 g. of potassium cyanide. An immediate beautiful blue color was produced which turned brown after standing a few minutes at room temperature. The brown solution was protected from atmospheric water and refluxed for four hours. After cooling to room temperature, 30 ml. of water was added to precipitate a solid. The mixture was cooled overnight at 10° and filtered to give 0.52 g. of reddish rosettes. Evaporation of the mother liquor produced 1.09 g. of semi-solid material. The two fractions were combined in benzene solution and chromatographed on Florisil (60–100 mesh, 20 × 2.5 cm.) to yield 0.44 g. (39%) of methyl 3,5-dinitrobenzoate, m.p. 106–107°, undepressed when mixed with an authentic sample.

Transesterification of Cyclohexyl 3,5-Dinitrobenzoate.—A procedure, identical with that followed for the *sec*-butyl ester was carried out on 1.47 g. of cyclohexyl 3,5-dinitrobenzoate. The initial reddish precipitate was dissolved in benzene and passed through a Florisil column (60–100 mesh, 9 × 2.5 cm.), to produce 0.57 g. (50%) of methyl 3,5-dinitrobenzoate, m.p. 106–107°.

(6) Melting points were taken on the hot-stage of a polarizing microscope and are corrected. Rotations taken in chloroform. Unless otherwise stated, the term methanol refers to commercial synthetic 99.85% methanol.

Cyclohexyl *p*-Iodobenzoate.—Two grams of cyclohexanol and 6.00 g. of *p*-iodobenzoyl chloride were combined in 38 ml. of pyridine. After two hours at 0°, work up produced an oil which was dissolved in Skellysolve B and chromatographed on a Florisil column (60–100 mesh, 20 × 2.5 cm.). Eluates totalling 70 ml. produced 4.08 g. (62%) of a colorless oil which crystallized, after seeding, into beautiful fern-like crystals, m.p. 42–43°; recrystallized from methanol–water, m.p. 42–43°.

Anal. Calcd. for $C_{13}H_{15}O_2I$: C, 47.29; H, 4.58. Found: C, 47.38; H, 4.21.

Transesterification of Cyclocohexyl *p*-Iodobenzoate.—An anhydrous solution of 0.83 g. of cyclohexyl *p*-iodobenzoate and 0.08 g. of potassium cyanide in 25 ml. of methanol was refluxed for eight hours. Work up and subsequent crystallization from acetone–water gave 0.46 g. (70%) of the methyl ester,[7] m.p. 112–114°, undepressed upon mixture with an authentic sample of the ester. From the mother liquor was isolated 0.05 g. (8%) of *p*-iodobenzoic acid.

In another run the transesterification reaction was refluxed for only two hours, in which case the material originally isolated had m.p. 90–112° indicating that the transesterification was not complete after this time.

Cholesteryl *p*-Iodobenzoate.—A solution of 5.80 g. of cholesterol in 50 ml. of anhydrous pyridine was treated with 4.00 g. of *p*-iodobenzoyl chloride and 20 ml. of pyridine added to effect complete solution. The solution was heated to boiling and then permitted to cool to room temperature. Work up, followed by crystallization from benzene–methanol gave 6.72 g. (73%) of the ester as plates, m.p. 183–184° to a blue fluorescent, refractive melt which cleared at 205–225°, $\alpha^{28}D$ +2.4° (*c* 2.17).

(7) This methyl ester is easily recognizable, even in low concentrations, by its powerful anisole-like odor.

Anal. Calcd. for $C_{34}H_{49}O_2I$: C, 66.21; H, 8.01. Found: C, 66.36; H, 8.01.

Transesterification of Cholesteryl *p*-Iodobenzoate in Methanol.—A sample of 2.82 g. of cholesteryl *p*-iodobenzoate was dissolved in 200 ml. of hot benzene. To this solution was added 1.5 g. of potassium cyanide in 200 ml. of methanol. After 7.5 hours of reflux, 200 ml. of liquid was distilled from the reaction mixture. This distillate, upon evaporation, left 0.82 g. of unchanged starting material. The 200 ml. of solution remaining was evaporated to a solid residue which was extracted with ether. The ether extract was evaporated and the resulting solid chromatographed in benzene on a Florisil column (60–100 mesh, 20 × 2.5 cm.). From the first two 150-ml. fractions there was recovered 0.55 g. (65% based on all cholesteryl *p*-iodobenzoate not actually recovered) of methyl *p*-iodobenzoate, m.p. 109–112°. After an additional 250 ml. of benzene had passed, a solid, m.p. 146–148°, was recovered from the eluate and the column was flushed with acetone; 0.95 g. (68% calculated as above) of cholesterol, m.p. 146°, was thus produced.

In another run all reagents and solvents were carefully dried before use and the reflux continued for 18 hours. Chromatography on alumina produced a quantitative yield of cholesterol and an 85% yield of methyl *p*-iodobenzoate.

Transesterification of Cholesteryl *p*-Iodobenzoate in Cyclohexanol.—One gram of cholesteryl *p*-iodobenzoate was dissolved in 200 ml. of refluxing cyclohexanol and 0.5 g. of potassium cyanide was added. After six hours of reflux the mixture was evaporated to dryness. The residue, when chromatographed in benzene on a 20 cm. × 2.5 cm., 60–100 mesh Florisil column gave 0.29 g. (54%) of cyclohexyl *p*-iodobenzoate, m.p. 40–41°, in the first 140 ml. of eluate. Acetone removed 0.52 g. (80%) of cholesterol, m.p. 145–147°, from the column.

MIDDLETOWN, CONNECTICUT

[CONTRIBUTION FROM THE BAKER CHEMISTRY LABORATORY OF CORNELL UNIVERSITY AND FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF SOUTH CAROLINA]

The Mechanisms of Diazonium Salt Reactions. I. The Products of the Reactions of Benzenediazonium Salts with Methanol

BY DELOS F. DETAR[1] AND MELVIN N. TURETZKY[2]

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Quantitative product studies of the thermal decomposition of benzenediazonium chloride or fluoborate in methanol have shown that anisole (93%) is the principal organic product under acidic conditions; this result points to a heterolytic cleavage of the diazonium C–N bond in the presence of acid. With acetate buffers the reaction is much more complex. Some anisole is produced, but the main product is benzene; smaller amounts of biphenyl and traces of azobenzene also are formed. Oxygen has a most pronounced effect on the reaction; in the presence of oxygen the product mixture is dark brown, and the above products account for only 30–75% of the diazonium salt used. In the absence of oxygen (vacuum train techniques) the reaction is much faster, the product mixture is almost colorless, and 98% or more of the diazonium salt can be accounted for. The reaction in the presence of acetate buffers is almost certainly a free radical chain process, and a new type of electron transfer reaction $\cdot CH_2OH + C_6H_5N_2^+ \rightarrow CH_2OH^{\oplus} + C_6H_5\cdot + N_2$ has been proposed as an essential step. It has been possible to exclude the radical addition step $C_6H_5\cdot + C_6H_6 \rightarrow C_6H_5C_6H_5 + H\cdot$ as a source of biphenyl in these reactions since the yield of biphenyl is not increased by addition of benzene to the reaction mixture. A tentative over-all mechanism is summarized in eq. 1–8. In an incidental investigation it was found that solutions of azobenzene in methanol on exposure to daylight or to a tungsten light in glass flasks give an equilibrium mixture of *cis*-azobenzene and *trans*-azobenzene containing 27–28% of the *cis* isomer.

One of the serious difficulties in interpreting the reactions of free radical intermediates is the lack of information about important details of the mechanisms of these complex reactions. These difficulties have been emphasized by Bartlett and Nozaki[3] and by Edwards and Mayo[4] for the reactions of diacyl peroxides. Under certain conditions as, for example, in the Gomberg–Bachmann reaction[5] diazonium salts constitute useful sources of free radical intermediates. We have undertaken a study of the mechanisms of the cleavage of the C–N bond of diazonium salts with the hope that such studies will lead to a greater understanding of a number of free radical reactions and also to a better understanding of the reactions of the versatile diazonium salts themselves.[6]

It has been known for some time that the C–N bond of diazonium salts can undergo cleavage by at least two distinct processes,[6d] a heterolytic process

(1) Department of Chemistry, University of South Carolina, Columbia, S. C.

(2) Rohm and Haas Research Assistant 1950–1951; U. S. Rubber Research Fellow 1952–1953 at Cornell University.

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