*Anal.* Calcd. for $C_{17}H_{18}O_5$: C, 67.54; H, 6.00; OMe (5), 30.80. Found: C, 67.43; H, 6.13; OMe, 30.84.

**2′,5,7-Trimethoxyisoflavone (XXVI).**—Cyclization of this ketone (1.5 g.) in methyl formate (50 ml.) with sodium dust (1 g.) in the usual way followed by acidification of the reaction mixture with excess 2 *N* hydrochloric acid gave rise to a crystalline precipitate of 2,3-dihydro-2-hydroxy-2′,5,7-trimethoxyisoflavone (XXIV) (1.3 g.) which separated from a large volume of ethyl acetate in rosettes of colorless needles, m.p. 196° (dec.). This compound was insoluble in cold 2 *N* sodium hydroxide, exhibited a negative ferric reaction in alcohol and decomposed on attempted vacuum sublimation.

*Anal.* Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.48; H, 5.63.

When a solution of this 2,3-dihydroisoflavone (1 g.) in acetic acid (7 ml.) was refluxed for 30 minutes and the product isolated by dilution with water followed by purification from ethyl acetate, 2′,5,7-trimethoxyisoflavone (0.9 g.) separated in colorless, massive rectangular prisms, m.p. 140°, insoluble in cold 2 *N* sodium hydroxide solution, having a negative ferric reaction in alcohol and subliming unchanged at 200° (0.01 mm.).

*Anal.* Calcd. for $C_{18}H_{16}O_5$: C, 69.22; H, 5.16; OMe (3), 29.80. Found: C, 69.43; H, 5.25; OMe, 30.73.

**2,4-Dihydroxy-6-methoxyphenyl 4-Methoxybenzyl Ketone (XXVII).**—Prepared from phloroglucinol monomethyl ether (2.5 g.) and *p*-methoxyphenylacetonitrile (2.5 g.) in the usual manner, the ketone (1.5 g.) separated from aqueous methanol or aqueous acetic acid in slender, colorless needles, m.p. 129–130°, having an intense red-brown ferric reaction in alcohol.

*Anal.* Calcd. for $C_{16}H_{16}O_5$: C, 66.65; H, 5.59. Found: C, 66.58; H, 5.82.

**7-Hydroxy-4′,5-dimethoxyisoflavone (XXVIII). (Genistein 4′,5-Dimethyl Ether).**—The previous ketone (1.4 g.) was cyclized with methyl formate (25 ml.) and sodium dust (0.5 g.) and the product, which could not be induced to crystallize, was isolated with chloroform and refluxed with acetic acid (10 ml.) during 10 minutes. Isolation of the product by dilution with water followed by purification from a large volume of methanol gave rise to 7-hydroxy-4′,5-dimethoxyisoflavone (0.5 g.) in pale fawn-colored prisms m.p. 294–5° (dec.), readily soluble in cold 2 *N* sodium hydroxide solution, having a negative ferric reaction in alcohol and demethylated almost quantitatively during 3 hours refluxing with hydriodic acid (sp. gr. 1.7) to genistein, m.p. 296–298°.

*Anal.* Calcd. for $C_{17}H_{14}O_6$: C, 68.45; H, 4.73. Found: C, 68.01; H, 5.13.

Waltz[14] records the m.p. 290–293° for a specimen of genistein 4′,5-dimethyl ether prepared by the partial demethylation of genistein trimethyl ether.

**4′,5,7-Trihydroxy-6-methylisoflavone (XXXI).**—Genistein was methylated by the method of Baker and Robinson[11] to yield 5-hydroxy-4′,7-dimethoxy-6-methylisoflavone (XXX). When a solution of this isoflavone (1 g.) in hydriodic acid (25 ml., sp. gr. 1.7) was refluxed during 3 hours and the product isolated in the usual way, 4′,5,7-trihydroxy-6-methylisoflavone (0.7 g.) separated from aqueous methanol in very pale yellow needles, m.p. 274°, unchanged by sublimation at 150° (0.01 mm.), and having an intense green ferric reaction in alcohol.

*Anal.* Calcd. for $C_{16}H_{12}O_6$: C, 67.60; H, 4.26. Found: C, 67.24; H, 4.51.

Remethylation of this isoflavone with dimethyl sulfate in boiling acetone gave an almost quantitative yield of 5-hydroxy-4′,7-dimethoxy-6-methylisoflavone.

(14) E. Waltz, *Ann.*, **489**, 118 (1931).

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

# Reactions of Methylcyclopropylcarbinyl Derivatives[1]

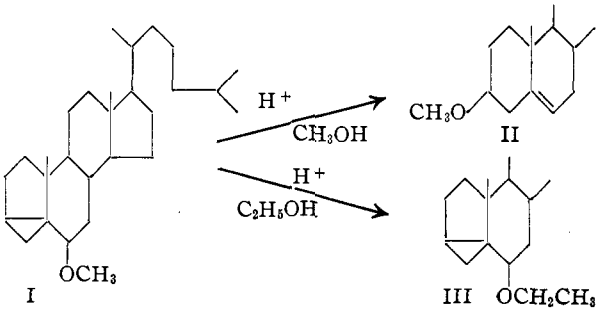
BY RALPH G. PEARSON AND STANLEY H. LANGER

RECEIVED AUGUST 11, 1952

The methylcyclopropylcarbinyl system is treated as an analog of the *i*-cholesteryl system. Methylcyclopropylcarbinol in acidic methanol readily forms methylcyclopropylcarbinyl methyl ether. In acidic ethanol, exchange occurs to the corresponding ethyl ether. Rearrangement to 3-penten-1-yl methyl ether is accomplished only with considerable difficulty.

The unusual reactivity of *i*-cholesterol and *i*-cholesteryl methyl ether (I)[2] prompted us to investigate some of the reactions of methylcyclopropylcarbinyl derivatives. *i*-Cholesteryl methyl ether rearranges rapidly in acidic methanol solution to form the normal cholesteryl methyl ether (II). It has also been shown that in dilute acidic ethanol I exchanges at the 6-position and *i*-cholesteryl ethyl ether (III) may be isolated[2c] before appreciable rearrangement to the normal ether.

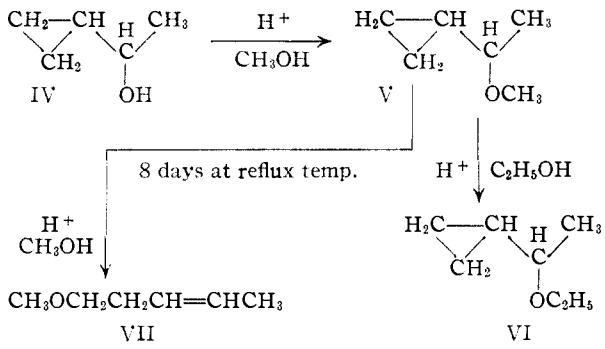
The methylcyclopropylcarbinyl structure would seem to be analogous to the *i*-cholesteryl one, in that it also has a secondary carbon atom adjacent to a cyclopropane ring, and thus might react similarly. We have found that methylcyclopropylcarbinol (IV) reacts with dilute acidic methanol to give methylcyclopropylcarbinyl methyl ether (V). In acidic ethanol, V reacts further with the solvent to give methylcyclopropylcarbinyl ethyl ether (VI). After prolonged reflux with acidic methanol, V will rearrange to give some 3-penten-1-yl methyl ether (VII), analogous to the transformation of I to II.




The extreme tendency of cyclopropylcarbinyl derivatives to rearrange in reactions where intermediate carbonium ions may be postulated to

(1) Taken in part from a thesis presented by Stanley H. Langer in partial fulfillment of the requirements for the degree of Doctor of Philosophy in August, 1951.

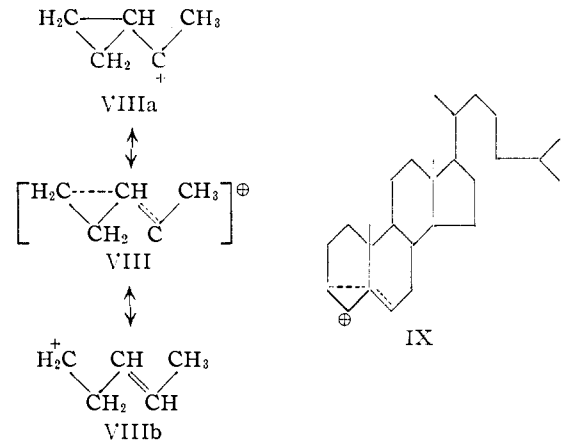
(2) (a) *Cf.* L. F. Fieser and M. Fieser, "Natural Products Related to Phenanthrene," 3rd Ed., Reinhold Publishing Corp., New York, N. Y., 1949, p. 256; (b) L. C. King, R. M. Dodson and L. A. Subluskey, THIS JOURNAL, **70**, 1176 (1948); (c) S. Winstein and A. Schlesinger, *ibid.*, **70**, 3528 (1948).




exist has recently been pointed out.[3-5] Rearrangement of this type might well be facilitated by the fact that the carbonium ion would be a primary one. This might also be a major reason for the ease of interconversion of cyclopropylcarbinyl and cyclobutyl structures.[5] The preparation of V in good yield (*ca.* 60%) from IV is evidence against any pronounced tendency to form a methylcyclobutyl derivative in a reaction which might be expected to involve a carbonium ion intermediate.[6] Further evidence for the failure to rearrange of the methylcyclopropylcarbinyl carbonium ion is the formation of VI from V. The ease of exchange at the carbon atom adjacent to the cyclopropane ring suggests that the methods employed here could easily be adapted for preparation of certain other $\alpha$-substituted cyclopropylcarbinyl ethers. In similar attempts to prepare a conventional aliphatic secondary ether, Norris and Rigby[7] obtained only a 35% yield of *s*-butyl ethyl ether, using far more drastic conditions.

In comparing the tendency toward rearrangement of I to II and V to VII in acidic methanol, it should be noted that the methylcyclopropylcarbinyl structure requires stronger acid solution (*ca.* 0.25 *M*) and a longer period at higher temperature.[8] On the basis of spectra and other physical data, the *trans* form of rearranged product seems to predominate, though the *cis*-pentenyl methyl ether was not synthesized for comparison. From these same data, it appears that even after prolonged refluxing, some unrearranged methylcyclopropylcarbinyl methyl ether remains.

A carbonium ion intermediate (VIII) analogous to the hybrid cholesteryl carbonium ion[9] (IX) could explain the experimental results presented here and several other earlier reports of rearrangements of cyclopropane derivatives.[10,11]




While we had independently considered VIII, it has already been proposed by Roberts, *et al.*[5,12] Though both forms VIIIa and VIIIb contribute to resonance stabilization of VIII, the stringent conditions required for rearrangement of V indicate that form VIIIb contributes even less than the analogous one in the case of IX. This is as expected since in VIIIb, the positive charge is on a primary carbon atom. A comparison of the rates of exchange and rates of rearrangement of I and V is of interest. In acidic ethanol, at reflux temperature, I exchanges about 100 times as fast as V calculated on the basis of recovered products.[13] A rough calculation on the rates of rearrangement in refluxing methanol (extrapolating the *i*-ether data[8] to 64°) gives a factor of about $10^5$ in favor of the *i*-cholesteryl derivative. Thus, exchange without rearrangement is relatively more easy for the methylcyclopropylcarbinyl system.

## Experimental[14]

Methylcyclopropylcarbinol was prepared from redistilled methyl cyclopropyl ketone by reduction with lithium aluminum hydride according to the directions of Nystrom and Brown.[15] Product was treated and recovered by a procedure described by Slabey and Wise.[16] It was noted that incomplete removal of water from the ethereal solution of methylcyclopropylcarbinol resulted in an azeotrope which had b.p. 93–94°. The azeotrope contained about two-thirds alcohol which could be recovered from the water by "salting out" with potassium carbonate. The purified methylcyclopropylcarbinol had b.p. 120.5–121°, $n^{20}D$ 1.4313–1.4316. The phenylurethan derivative had m.p. 69.5–70° (uncor.) in agreement with reported m.p. 69.6–70.5°.[17] The infrared absorption spectrum of the product between 6.8–12 $\mu$ had maxima corresponding to those previously reported.[16]

**Methylcyclopropylcarbinyl Methyl Ether. A.**—To 8.8 g. (0.10 mole) of methylcyclopropylcarbinol in 40 ml. of xylene, 2.3 g. (0.10 mole) of sodium was added in small portions. After standing for one hour, the mixture was heated on the steam-bath for 2.5 hours. To the yellow

(3) L. I. Smith and S. McKenzie, Jr., *J. Org. Chem.*, **15**, 74 (1950).
(4) C. G. Bergstrom and S. Siegel, THIS JOURNAL, **74**, 145 (1952).
(5) J. D. Roberts and R. H. Mazur, *ibid.*, **73**, 2509 (1951); **73**, 3542 (1951).
(6) See, for example, E. R. Alexander, "Ionic Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., 1950, p. 214.
(7) J. F. Norris and G. W. Rigby, THIS JOURNAL, **54**, 2088 (1932).
(8) R. G. Pearson, L. A. Subluskey and L. C. King, *ibid.*, **70**, 3479 (1948). We have also measured the rate constant ($k$ = 1.92 liters/mole-min.) for acid-catalyzed rearrangement of I in a solvent consisting of 10 parts, by volume, of methanol to one part chloroform at 34.85 ± 0.1°. At 24.85 ± 0.1° in the same solvent, $k$ = 0.52 liter/mole-min. The method used for rate measurement was a polarimetric one and details are given in reference 1.
(9) S. Winstein and R. Adams, *ibid.*, **70**, 838 (1948).
(10) N. J. Demjanow and M. Dojarenko, *Ber.*, **55B**, 2718 (1922).
(11) P. Bruylants and A. Dewael, *Bull. classe Sci. Acad. roy. Belg.*, [5] **14**, 140 (1928).
(12) J. D. Roberts, W. Bennett and R. Armstrong, THIS JOURNAL, **72**, 3329 (1950).
(13) In reference 2c, Winstein and Schlesinger report a recovery of 68% of the theoretical cholesteryl ethyl ether, after 1/2 hour of refluxing, from an ethanolic solution (*ca.* 0.027 *M* in $H^+$ ion) initially containing I.
(14) We are indebted to Miss Joyce Sorensen and Mrs. Connie White for microanalyses. Infrared spectra were kindly determined by Miss Rosaland Guy and Mr. George Kincaid.
(15) R. F. Nystrom and W. G. Brown, THIS JOURNAL, **69**, 2648 (1947).
(16) V. A. Slabey and P. H. Wise, *ibid.*, **71**, 3252 (1949).
(17) R. Van Volkenburgh, K. W. Greenlee, J. M. Derfer and C. E. Boord, *ibid.*, **71**, 3595 (1949).

solution, 22 g. (0.15 mole) of methyl iodide was added and the mixture allowed to stand overnight with resultant formation of a yellow precipitate. After refluxing for an additional hour, the liquid layer was distilled through a Vigreux column. The 14.6 g. of material with b.p. 76–121° was dried over sodium sulfate and distilled through a semimicro Stedman column.[18] A total of 2 g. (0.02 mole) of pure product was obtained with b.p. 93.8–94.0° (753 mm.), $n^{25}D$ 1.4020, $n^{20}D$ 1.4040, $d^{20}_4$ 0.819, $d^{25}_4$ 0.814, $MR_D$ 29.90 (calcd. $MR_D$ is 29.96 using 0.61 for exaltation of ring[19]).

B.—A solution of 8.9 g. (0.10 mole) of methylcyclopropylcarbinol, 1 g. (0.005 mole) of *p*-toluenesulfonic acid monohydrate and 37 ml. of a C.P. grade of methanol was refluxed for 2 hours. After cooling, the solution was neutralized with dilute sodium hydroxide solution. Water (45 ml.) was added and the resultant upper layer washed twice with an equal volume of water. The washed upper layer weighed 1.8 g. The aqueous washings were combined and distilled. The initial 20 ml. of distillate boiled at 65–85° and on addition of 20 ml. of water, 2 layers formed. The upper layer was washed twice with an equal volume of water and the washings returned to the distillation flask. A repetition of the distillation and washing process with collection of successive 10-ml. and 5-ml. portions of distillate brought the total of collected material to 8 g. After drying over sodium sulfate and filtering, the crude product weighed 6.2 g. (60% yield). Distillation through a Stedman column gave a total of 4.8 g. with b.p. 93.5–94.3° (744 mm.). The major portion had b.p. 93.8–94°, $n^{25}D$ 1.4020, $d^{25}_4$ 0.814. The 1 g. residue had $n^{25}D$ 1.4030. The infrared absorption spectrum of this material was identical in every detail with the spectrum of the product from A.

The product did not decolorize dilute permanganate nor decolorize bromine water readily, but tended to give an analysis slightly high for carbon and hydrogen. Therefore, some product was added to a slightly damp vial, allowed to stand over a few crystals of potassium permanganate for two days, dried over Drierite and analyzed.

*Anal.* Calcd. for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.96; H, 12.35.

**Methylcyclopropylcarbinyl Ethyl Ether.**—A solution of 7 g. (0.07 mole) of methylcyclopropylcarbinyl methyl ether, 0.5 g. (0.003 mole) of *p*-toluenesulfonic acid monohydrate and 13 ml. of absolute ethanol was refluxed for 2 hours. After cooling and neutralizing with sodium hydroxide, 20 ml. of water was added. The product was isolated as described in procedure B above. The 6.8 g. of crude product was dried over sodium sulfate and distilled through a Stedman column. A total of 0.8 g. of material boiled at 73–93.8°, 1.4 g. at 93.8–100° ($n^{25}D$ 1.4000–1.4024), and an additional 0.5 g. at 100–109°. The 2.3 g. (29% yield) of desired product had b.p. 109–110.8°, $n^{25}D$ 1.4048–1.4053. The major portion had b.p. 110.5–110.8°, $n^{25}D$ 1.4052, $n^{20}D$ 1.4072, $d^{20}_4$ 0.812, and $MR_D$ 34.62 (calcd. $MR_D$ 34.67[19]). This material did not decolorize bromine water readily.

The sample submitted for analysis was treated with slightly moistened potassium permanganate for two hours before drying with Drierite.

*Anal.* Calcd. for $C_7H_{14}O$: C, 73.72; H, 12.36. Found: C, 73.86; H, 12.80.

*trans*-**3-Penten-1-ol.**—Pure *trans*-3-pentenoic acid was prepared according to the directions of Linstead, Noble and Boorm.[20] The pentenoic acid was reduced to *trans*-3-penten-1-ol with lithium aluminum hydride.[15] The alcohol had b.p. 136–137°, $n^{25}D$ 1.4322–1.4324. Its 1-naphthylurethan had m.p. 92–92.5° (uncor.). Crombie and Harper[21] report b.p. 136–137°, $n^{20}D$ 1.4340 for the alcohol and m.p. 93° for the 1-naphthylurethan.

**The 3,5-dinitrobenzoate** of *trans*-3-penten-1-ol was prepared according to standard procedure.[22] Three recrystallizations from ethanol–water mixture gave product with m.p. 53.5–54° (uncor.).

*Anal.* Calcd. for $C_{12}H_{13}O_2N_2$: N, 9.96. Found: N, 10.16.

*trans*-**3-Penten-1-yl methyl ether** was made by a modification of the procedure of Burwell, Elkin and Maury.[23] *trans*-3-Penten-1-ol (4.6 g., 0.054 mole) was added dropwise to 1.4 g. (0.058 mole) of sodium hydride at Dry Ice–acetone temperature. The reaction flask was fitted with a condenser and a drying tube, and allowed to come slowly to room temperature. After 5 hours, 9 g. (0.064 mole) of methyl iodide was added and the mixture allowed to stand overnight. After distillation, all material boiling under 70° was removed and the remainder redistilled through a Stedman column. The 2.5 g. (54% yield) of product had b.p. 100–101.8°, $n^{25}D$ 1.4086–1.4050. The major portion had b.p. 101.5–101.8°, $n^{25}D$ 1.4050–1.4054. The infrared spectrum of this material is discussed later. This material decolorized dilute permanganate and bromine water readily.

*Anal.* Calcd. for $C_6H_{12}O$: C, 71.95; H, 12.08. Found: C, 71.46; H, 12.17.

**Rearrangement of Methylcyclopropylcarbinyl Methyl Ether in Methanol.**—A mixture of 5.6 g. (0.056 mole) of methylcyclopropylcarbinyl ether and 10 g. (0.10 mole) of methylcyclopropylcarbinol was refluxed with 2.5 g. (0.013 mole) of *p*-toluenesulfonic acid monohydrate and 40 ml. of methanol. The reaction was followed periodically by a "bromine uptake" test.[24] After 8 days, when "bromine uptake" had reached 9 drops, the solution was cooled, neutralized with potassium carbonate, and 40 ml. of water was added. The resultant yellow upper layer was washed twice with an equal volume of water. Two successive distillations of combined aqueous layers, followed by separation and washing of resultant ether layers, yielded 13.4 g. of product. This material was dried over magnesium sulfate and carefully fractionated through a Stedman column. The fractions (8.9 g.) with b.p. 90.5–100.8° had $n^{25}D$ 1.4009–1.4040 and "bromine uptake" of 7–29 drops. A total of 3.1 g. (20% yield) of material with b.p. 100.8–101.8°, $n^{25}D$ 1.4044–1.4059 was collected. The latter material readily decolorized dilute permanganate and a center cut had b.p. 101.7–101.8°, $n^{25}D$ 1.4059, $n^{20}D$ 1.4075, $d^{20}_4$ 0.792 and $MR_D$ 31.17 (calcd. for 3-penten-1-yl methyl ether $MR_D$ 31.18).

*Anal.* Calcd. for $C_6H_{12}O$: C, 71.95; H, 12.07. Found: C, 72.08; H, 12.02.

The infrared spectrum of the material with b.p. 101.7–101.8° had absorption maxima corresponding to those of pure *trans*-3-penten-1-yl methyl ether in every detail in the region of 8–14 $\mu$. This is in agreement with evidence that this material is largely *trans*-3-penten-1-yl methyl ether. Minor variations of the order of 0–5% (all low) in absorption intensities might be due to the presence of some *cis*-ether. There were no absorption maxima indicating any remaining methylcyclopropylcarbinyl methyl ether.

Infrared absorption maxima at 11.7 and 12.15 $\mu$ (*ca.* 50% absorption) in fractions (8.0 g.) with b.p. 90.5–99.8° were consistent with the presence of some methylcyclopropylcarbinyl methyl ether in all of these. However, in the fraction (1.2 g.) with b.p. 98–99.8°, absorption at 9.8 $\mu$ had fallen to 65% and absorption at 10.3 $\mu$ had risen to 97%, further suggesting that this cut contained a large amount of *trans*-3-penten-1-yl methyl ether.

Ozonolysis of 0.47 g. of the material with b.p. 101.7–101.8° was performed using a procedure similar to one recommended by Henne and Hill.[25] No attempt was made to collect vapor during the ozonolysis. Decomposition of the ozonolysis product, followed by distillation into ethanolic 2,4-dinitrophenylhydrazine solution, gave 70 mg. of 2,4-dinitrophenylhydrazone derivative, m.p. 152–154°. Subsequent recrystallizations from ethanolic solution gave material with m.p. 162–164° which gave no melting point

(18) This column was a 70 cm. jacket-heated one and was used in the rest of this work where a Stedman column is mentioned. The hold-up of this column was about 1–1.5 ml.

(19) G. H. Jeffrey and A. I. Vogel, *J. Chem. Soc.*, 1804 (1948).

(20) L. P. Linstead, E. G. Noble and E. J. Boorm, *ibid.*, 557 (1933).

(21) L. Crombie and S. H. Harper, *ibid.*, **873**, 1715 (1950); see also H. L. Goering, S. J. Cristol and K. Dittmer, THIS JOURNAL, **70**, 3314 (1948).

(22) S. McElvain, "The Characterization of Organic Compounds," The Macmillan Co., New York, N. Y., 1947, p. 193.

(23) R. L. Burwell, Jr., L. M. Elkin and L. G. Maury, THIS JOURNAL, **73**, 2428 (1951).

(24) A crude test consisting of the dropwise addition of saturated aqueous bromine solution, with shaking, to 2 drops of unsaturated material until the bromine color remained for 45–60 seconds. The test was a qualitative one and was always reproducible to within 25%. In such a test, the cyclopropane compounds decolorized 1 or 2 drops of bromine water and *trans*-3-penten-1-ol decolorized 37 drops.

(25) A. L. Henne and P. Hill, THIS JOURNAL, **65**, 752 (1943).

depression on mixing with a sample of acetaldehyde 2,4-dinitrophenylhydrazone.

Infrared spectra were determined on the Beckman IR-2T infrared spectrophotometer at 30° using a 0.03 mm. sodium chloride cell.

Absorption spectra are consistent with assigned structures. Spectra of the methyl and ethyl ethers of methylcyclopropylcarbinol both show absorption maxima in the region of 9 $\mu$ and at *ca.* 9.8 $\mu$ which may be associated, respectively, with the presence of ether linkages[26] and cyclopropane rings.[27] Both ethers show maxima at *ca.* 12.15 $\mu$, in which region absorption has also been noted for cyclopropylmethyl ethyl ether.[4]

Absorption maxima (*ca.* 100%) for *trans*-3-penten-1-yl methyl ether at 8.9 and 10.3 $\mu$ were in accord with the presence of an ether linkage[26] and a *trans* double bond.[21,26a]

**Acknowledgment.**—It is a pleasure to acknowledge helpful discussions with Dr. L. C. King and Dr. A. S. Hussey. One of us (S. H. L.) is indebted to the United States Public Health Service for a fellowship held during the course of this work.

(26) (a) N. B. Colthup, *J. Optical Soc. Am.*, **40**, 397 (1950); (b) M. Josien, N. Fuson and A. S. Cary, THIS JOURNAL, **73**, 4445 (1951).

(27) (a) J. M. Derfer, E. E. Pickett and C. E. Boord, *ibid.*, **71**, 2482. (1949); (b) J. D. Bartleson, R. E. Burk and H. P. Lankelma, *ibid.*, **68**, 2513 (1946).

EVANSTON, ILLINOIS

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DUKE UNIVERSITY]

# Aldol Condensation of Esters with Ketones or Aldehydes to Form β-Hydroxy Esters by Lithium Amide. Comparison with the Reformatsky Reaction[1]

BY CHARLES R. HAUSER AND W. H. PUTERBAUGH[2]

RECEIVED SEPTEMBER 2, 1592

The aldol condensation of *t*-butyl acetate and certain other esters with ketones or aldehydes to form β-hydroxy esters has been effected by means of lithium amide. This new method for preparing β-hydroxy esters is more convenient and, in certain cases (*e.g.*, with nitro ketones), more generally applicable than the Reformatsky reaction. The *t*-butyl β-hydroxy esters produced in our method were, in general, converted to α,β-unsaturated acids by treatment with mineral acids. The *t*-butyl β-hydroxy esters from aromatic nitro ketones were converted to β-hydroxy acids. Certain of the β-hydroxy esters were dehydrated to form the α,β-unsaturated esters.

A recent communication from this Laboratory[3] described the aldol condensation of *t*-butyl acetate with acetophenone to form *t*-butyl β-hydroxy-β-phenylbutyrate (I). This new process was effected in fair yield (31%) by means of sodium amide followed by zinc chloride (simulating the Reformatsky reaction), and in high yield (76%) by means of lithium amide alone. The latter, more promising method involves the metalation of the α-hydrogen of the ester by the lithium amide in liquid ammonia (equation 1), and the condensation of the resulting lithio ester with the carbonyl group of the ketone in ether (equation 2).

$$CH_3COOC(CH_3)_3 + LiNH_2 \xrightarrow{\text{liq. } NH_3} LiCH_2COOC(CH_3)_3 + NH_3 \quad (1)$$

$$LiCH_2COO(CH_3)_3 + C_6H_5COCH_3 \xrightarrow{\text{ether}} C_6H_5C(CH_3)(OLi)CH_2COOC(CH_3)_3 \xrightarrow{HOH} C_6H_5C(CH_3)(OH)CH_2COOC(CH_3)_3 \quad (2)$$

I (76%)

The present paper describes the further development and application of the lithium amide method (Table I). In general, *t*-butyl esters rather than the more common methyl or ethyl esters were employed both to ensure the preferential metalation of the α-hydrogen of the ester by the lithium amide (instead of partial reaction at the carbonyl carbon to form the amide),[4] and to minimize the possible self-condensation of the ester.[5]

The general procedure involves three simple operations followed by a two-hour refluxing period: (a) the ester is added to a molecular equivalent (plus 5%) of lithium amide in liquid ammonia, (b) the ammonia is replaced by ether, and (c) an equivalent of the ketone is added. Since the ester is probably converted almost immediately to its lithio derivative, these three operations should be completed as fast as feasible in order to avoid appreciable self-condensation of the ester. Operations (b) and (c) may be reversed, but, at least with *t*-butyl acetate and acetophenone, this has given a slightly lower yield (70%) than that (76%) obtained by the usual procedure. The general procedure produced only tars with aromatic nitro ketones, but satisfactory results were obtained when the lithio ester was added to the ketone at −70°. This modification is similar to the inverse addition procedure employed by Newman and Smith[6] for the condensation of Grignard reagents with nitro aldehydes.

Although the independent preparation of the lithio ester is recommended with *t*-butyl esters, this procedure has not been very satisfactory with isopropyl acetate because of the occurrence of considerable self-condensation of this ester before

(1) Paper XLVIII on Condensations; paper XLVII, THIS JOURNAL, **73**, 901 (1951).

(2) Carbide and Carbon Chemicals Company Fellow, 1950-1952.

(3) C. R. Hauser and W. H. Puterbaugh, THIS JOURNAL, **73**, 2972 (1951).

(4) *Cf.* M. Hamell and R. Levine, *J. Org. Chem.*, **15**, 162 (1950). See also C. R. Hauser, R. Levine and R. F. Kibler, *ibid.*, **68**, 26 (1946).

(5) See J. C. Shivers, M. L. Dillon and C. R. Hauser, *ibid.*, **69**, 119 (1947).

(6) M. S. Newman and A. S. Smith, *J. Org. Chem.*, **13**, 592 (1948).