sample purified by recrystallization from dioxane–petroleum ether (b. p. 60–68°), was obtained as red-brown needles, m. p. 181.5–183°.

Anal. Calcd. for $C_{18}H_{17}O_3N_3$: C, 66.86; H, 5.30. Found: C, 66.73; H, 5.10.

The crude coupling product from 6-methyl-7-hydroxy-2a,3,4,5-tetrahydroacenaphthene obtained at *p*H 8–10 had the m. p. 202–210°; at *p*H 11–13, m. p. 192–197°; in 0.4 *N* sodium hydroxide, m. p. 200–206°. A sample purified by recrystallization from dioxane was obtained as red-brown needles, m. p. 207–209°.

Anal. Calcd. for $C_{19}H_{19}O_3N_3$: C, 67.64; H, 5.68. Found: C, 67.68; H, 5.35.

Summary

2a,3,4,5-Tetrahydroacenaphthene has been prepared both by selective hydrogenation of acenaphthene and by synthesis from 1-tetralone. The properties of the hydrocarbon resemble those of simple polyalkylbenzenes.

7-Hydroxy-, 8-hydroxy-, and 6-methyl-7-hydroxy-2a,3,4,5-tetrahydroacenaphthene were prepared by synthesis from the appropriately substituted tetralones, and their coupling behavior with *p*-nitrobenzenediazonium chloride was observed at various concentrations of alkali. All of the phenols were comparably effective couplers, and it may be concluded that experiments thus far have failed to reveal any marked steric inhibition of resonance in the tetrahydroacenaphthene ring system.

MADISON, WISCONSIN RECEIVED OCTOBER 16, 1948

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF WISCONSIN]

Intramolecular Acylation. II.[1] The Inverse Friedel–Crafts Method

BY WILLIAM S. JOHNSON AND HOWARD J. GLENN[2]

Of the numerous methods available for effecting ring closure of β-arylpropionic or γ-arylbutyric acid derivatives to cyclic ketones, the intramolecular Friedel–Crafts reaction of the acid chloride with aluminum chloride promises to be particularly useful for acids like β-*p*-methoxyphenylpropionic acid, which are resistant to cyclization due to unfavorable reactivity of the aromatic nucleus.[1] Excellent yields have not been generally realized by this method, probably because a large proportion of the cylizations reported in the literature have been conducted under unfavorable conditions. In the present work we are describing a cyclization technique which combines the best features suggested by previous experience.[3] This procedure, which has been tested with nine acids of varying susceptibility to cyclization, apparently differs from others previously reported only in minor respects, some of which nevertheless, have proved to be critical factors and merit emphasis. (1) It has been found important to use acids of good quality, since small amounts of impurities may result in a very impure product. (2) For preparation of the acid chloride, phosphorus pentachloride instead of thionyl chloride was employed because of occasional complications which have been reported to attend the use of the latter.[4] The phosphorus oxychloride produced was always carefully removed, because its presence has been shown to interfere with the cyclization giving lower yields.[5,1] (3) The Friedel–Crafts step was carried out in the inverse manner, *i.e.*, the acid chloride (in benzene solution) was added to a stirred suspension of aluminum chloride in benzene. This technique has the advantage over the conventional method of (*a*) facilitating temperature control through regulation of the rate of addition of the acid chloride and (*b*) maintaining a high concentration of catalyst, a condition that has been shown in *inter*molecular acylation to minimize self-condensation of the resulting ketone,[6] which is a side-reaction that also competes with certain *intra*molecular acylations.[7] The yields for fifteen cases that were found in the literature in which the inverse Friedel–Crafts cyclization was employed apparently without particular regard to other critical factors, were nevertheless generally well above average,[3] thus suggesting a real advantage in this method. (4) Since heating has been shown to have undesirable effects,[7] the temperature of the reaction mixture was never permitted to rise above 25° during the cyclization step. Even with acids that are unusually resistant to cyclization, this treatment afforded excellent yields of ketones. Thus with β-*p*-methoxyphenylpropionic acid, I (R^1 = OCH_3, R^2 = H), which is notoriously resistant to cyclization,[1,8] 6-methoxy-1-hydrindone, II (R^1 = OCH_3, R^2 = H), of fair purity was obtained in practically quantitative yield on a 3-g. scale.

The ring closure of α,γ-diphenylbutyric acid, III (R^1 = H, R^2 = C_6H_5), afforded an interesting test since Newman[9] had studied this cyclization

(1) See Johnson and Shelberg, THIS JOURNAL, **67**, 1853 (1945), for the first communication of this series.

(2) Wisconsin Alumni Research Foundation research assistant, 1946–1947; du Pont predoctorate fellow 1947–1948. Present address: Abbott Laboratories, North Chicago, Illinois.

(3) Johnson in Adams, "Organic Reactions," John Wiley and Sons, Inc., New York, N. Y., Vol. II, 1944, Chapter 4.

(4) See ref. 3, p. 137.

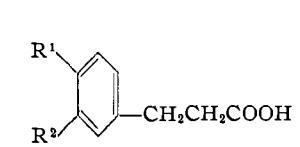
(5) Newman, THIS JOURNAL, **62**, 870 (1940).

(6) Calloway and Green, *ibid.*, **59**, 809 (1937).

(7) See ref. 3, p. 130.

(8) Heinzelmann, Kolloff and Hunter, THIS JOURNAL, **70**, 1386 (1948).

(9) See Procedure III, ref. 3, p. 145.



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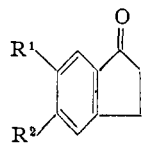

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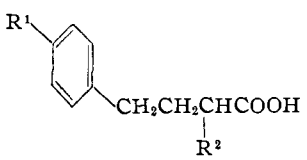

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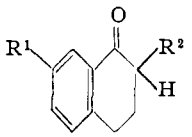

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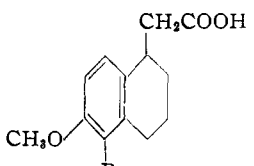

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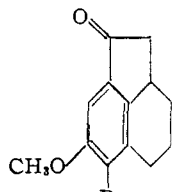


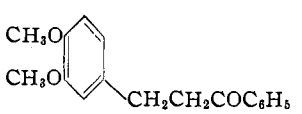
VI

carefully and developed conditions requiring a rather critical heat treatment whereby yields as high as 94% could be realized. When the procedure described in the present work was applied, practically quantitative yields of the ketone, IV (R^1 = H, R^2 = C_6H_5), were produced without heating.

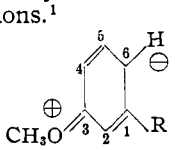
β-Phenylpropionyl chloride was cyclized to 1-hydrindone, II (R^1 = R^2 = H) in nearly quantitative yield, γ-phenylbutyric acid, III (R^1 = R^2 = H), to tetralone-1, IV (R^1 = R^2 = H), in 90% yield on a 50-g. scale,[10] γ-*p*-methoxyphenylbutyric acid, III (R^1 = OCH_3, R^2 = H), to 7-methoxytetralone, IV (R^1 = OCH_3, R^2 = H), in practically quantitative yield on a 20-g. scale, and β-*m*-methoxyphenylpropionic acid, I (R^1 = H, R^2 = OCH_3), to a mixture of 5- and 7-methoxy-1-hydrindone (predominantly the former) in 89% yield. The cyclization of 6-methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic acid, V (R = H), to VI (R = H) proceeded in only 77% yield, although the 5-methyl homolog V (R = CH_3) was cyclized to VI (R = CH_3) in quantitative yield. Both of these cases involve five-membered ring closure meta to a methoxyl group.

Deactivation by Coördination with Catalyst

Application of the cyclization procedure to β-3,4-dimethoxyphenylpropionic acid, I (R^1 = R^2 = OCH_3), gave most unexpected results. Instead of 5,6-dimethoxy-1-hydrindone, II (R^1 = R^2 = OCH_3), we isolated as the preponderant product (70% yield) a crystalline ketone melting after purification at 68–68.5° and having an analysis compatible with the formula $C_{17}H_{18}O_3$. That this was 3,4-dimethoxybenzylacetophenone, VII, arising from intermolecular acylation of the solvent follows from the agreement of its properties with those reported for VII obtained by hydrogenation of 3,4-dimethoxybenzalacetophenone.[11] These observations were all the more surprising in view of the fact that under the same conditions the *p*-methoxy acid I (R^1 = OCH_3, R^2 = H) is cyclized in quantitative yield. It would be expected, however that the latter would be considerably less susceptible to cyclization than the acid I (R^1 = R^2 = OCH_3) which has the additional 3-methoxy group to activate the 6-position into which the ring closes, thus cancelling the de-activating influence of the 4-methoxy group. That I (R^1 = R^2 = OCH_3) does indeed have a greater intrinsic susceptibility to cyclization than I (R^1 = OCH_3, R^2 = H) is suggested by its behavior toward hydrogen fluoride which promoted ring closure to II (R^1 = R^2 = OCH_3) in 88% yield. The acid I (R^1 = OCH_3, R^2 = H) in contrast is cyclized in only 3% yield under the same conditions.[1]



VII



VIII

According to current theories the activating influence of the 3-methoxy group may be rationalized by its participation in the resonance of the benzene nucleus, thus enhancing the contribution of the polarized form VIII (or the corresponding *ortho* quinoid modification) to the electronic state of the molecule. The resultant high electron density at the 6-position favors reaction with the electrophilic carbon of the carbonyl group at the end of the side-chain R thus effecting cyclization. Coördination of the 3-methoxy group with an acid would inhibit the contribution of VIII and, if powerful enough, would tend to render the 6-position sufficiently less nucleophilic (by induction as in the de-activation of the benzene nucleus by the quaternary ammonium ion) than the carbon atom of the solvent benzene, so that reaction could occur more rapidly with the latter. This hypothetical situation was not actually realized with β-*m*-methoxyphenylpropionic acid, I (R^1 = H, R^2 = OCH_3), which underwent only intramolecular acylation (see above), but with the acid I (R^1 = R^2 = OCH_3) the second methoxy group in the 4-position exerts on the 6-position an additional de-activating influence of the type observed with β-*p*-methoxyphenylpropionic acid. The combined effects appear to render the nucleus so unreactive that the competing intermolecular reaction takes precedence. According to this postulate an acid somewhat weaker than aluminum chloride, should favor intramolecular reaction because the inhibition of resonance by coördination would be decreased. The reaction was therefore carried out with stannic instead of aluminum chloride, and indeed a 54% yield of cyclic ketone

(10) This represents an improvement over the procedure of Martin and Fieser, *Org. Syn.*, Coll. Vol. II, 569 (1943), which gives varying yields of 74–91% and involves a laborious steam distillation.

(11) Pfeiffer, Kalckbrenner, Kunze and Levin, *J. prakt. Chem.*, **119**, 109 (1928).

was obtained, none of the product VII of intermolecular acylation being found.

Experimental[12]

General Cyclization Procedure.—To phosphorus pentachloride (in the ratio of 1.1 mole per mole of acid) in a flame-dried distilling flask (protected by a calcium chloride tube) was added 3.00 g. of pure, dried organic acid. In larger runs the acid was added in portions.[13] If the reaction did not start immediately the mixture was warmed gently or a few ml. of benzene added. After copious evolution of hydrogen chloride ceased (usually about fifteen minutes), 15 ml. of dried (over sodium) benzene was added and the flask was fitted with a stopper bearing a small addition funnel and a tube drawn out to a fine capillary extending to the bottom of the flask. The volatile phosphorus compounds were then co-distilled with the benzene at 60–70° (oil-bath temperature) under reduced pressure (water pump), dry air or nitrogen being admitted through the capillary tube. When the volatile materials were largely removed, another 15 ml. of benzene was added from the dropping funnel and the distillation continued. This process was repeated twice again each time with the addition of 15-ml. portions of benzene. The residual acid chloride was then cooled, dissolved in 20 ml. of dry, thiophene-free benzene and transferred with the aid of an additional 15 ml. of solvent through a plug of glass wool into a dropping funnel which was attached to a flame-dried flask bearing a Hershberg mercury-sealed wire stirrer, thermometer and calcium chloride tube. Aluminum chloride[14] (in the ratio of 1.2–1.4 mole per mole of acid) was introduced into the flask with 40 ml. of dry thiophene-free benzene and the suspension stirred with cooling (ice-bath) as the solution of acid chloride was added slowly at such a rate that the temperature of the reaction mixture never rose above 10°. The addition ordinarily required about fifteen minutes during which a highly colored complex formed. The funnel was finally rinsed with an additional 25 ml. of benzene and the stirring continued for two to five hours while the temperature was allowed to rise slowly to 22–24° (not higher).

The mixture was chilled, about 50 ml. of ether introduced to prevent emulsion formation, and then 100 ml. of cold 1:1 hydrochloric acid added with stirring at such a rate that the temperature remained below 15°. The organic layer was separated, washed successively with three portions of 1:1 hydrochloric acid, followed by saturated sodium bicarbonate,[15] 5% potassium hydroxide,[15] water and finally saturated salt solution. Appropriate washing of the aqueous layers in turn with a fresh portion of ether was necessary for effecting clean separations. The combined organic solutions were shaken with a small amount of Norit, dried over anhydrous potassium carbonate, filtered, evaporated and dried to constant weight *in vacuo*.

Any uncyclized acid was recovered by acidification of the bicarbonate solutions, and phenolic material (resulting from demethylation of methoxy derivatives) by acidification of the potassium hydroxide wash solutions.

Cyclization Experiments

β-*p*-Methoxyphenylpropionic Acid, I (R^1 = OCH_3, R^2 = H).—A 3-g. sample of the pure acid,[1] m. p. 103.5–104° was treated by the above procedure with 3.64 g. of phosphorus pentachloride. Cyclization was effected with 3.10 g. of aluminum chloride for five hours. The crude tan ketone, II (R^1 = OCH_3, R^2 = H), amounted to 2.73 g. (quantitative yield), m. p. 103–106°. Distillation in a two-bulb flask at 0.1 mm. was attended by some mechanical hold-up giving 2.20 g. of colorless product, m. p. 108–108.5°. In another experiment with 2.50 g. of acid in which the molecular ratio of catalyst was dropped to 1.25 instead of 1.4, 2.10 g. (93% yield) of product melting at 105–106.2° was obtained. Evaporative distillation under reduced pressure gave a 95% recovery of colorless ketone, m. p. 108–108.5°. Cyclization of a specimen of the acid having approximately the same m. p. as the sample above, but having been submitted to one less recrystallization, gave a quantitative yield of crude ketone which, however, melted at 50–106°. Only 43% of this material could be obtained relatively pure, m. p. 103–105°.

β-Phenylpropionic Acid, I (R^1 = R^2 = H).—Since the acid chloride, b. p. 118–120° (17 mm.), was available, a 3.08-g. sample was treated with 3.04 g. of aluminum chloride for five hours. The yield of almost colorless hydrindone was 2.40 g. (99%), m. p. 39–39.6° with softening at 38.5°. Evaporative distillation at 0.3 mm. gave a 94% recovery of colorless ketone, m. p. 39.8–40.2° (reported,[16] 40–41°). Using the inverse Friedel-Crafts cyclization, Thiele and Wanscheidt,[17] obtained 1-hydrindone in 95% yield. They used petroleum ether as the solvent and warmed the reaction mixture until the complex dissolved.

β-*m*-Methoxyphenylpropionic Acid, I (R^1 = H, R^2 = OCH_3).—The acid was prepared by methylation of β-*m*-hydroxyphenylpropionic acid[18] with dimethyl sulfate followed by crystallization from ether–petroleum ether (40–60°) and recrystallization from dilute methanol; m. p. 44–46.5° (reported,[19] 45°). A 1.50-g. sample was treated with 1.90 g. of phosphorus pentachloride and cyclization was effected with 1.55 g. of aluminum chloride for three and one-half hours at 7–17°. The pale yellow product amounted to 1.20 g. (89% yield), m. p. 63–103°, evidently consisting of a crystalline mixture of 5- and 7-methoxy-1-hydrindone as shown by analysis of material sublimed at 75–90° (0.05 mm.) which melted at 63–100°.

Anal. Calcd. for $C_{10}H_{10}O_2$: C, 74.05; H, 6.22. Found: C, 74.01; H, 6.06.

On crystallization of the sublimate from dilute methanol three-fourths of the product separated as fairly pure 5-methoxy-1-hydrindone, m. p. 108–110.5°, with previous softening, indicating that this isomer was formed in preponderance. The m. p. after recrystallization was 109–110.5°, and was not depressed on admixture with an authentic specimen of the ketone.[18]

The only previous report of cyclization of this acid is by Ingold and Piggott[19] who used aluminum chloride in petroleum ether on the acid chloride. The conditions involved heating on the steam-bath which effected some demethylation. No yields were reported, but the presence of both possible isomers was demonstrated.

γ-Phenylbutyric Acid, III (R^1 = R^2 = H).—A 50-g. sample of the acid, m. p. 47–49.5°, was converted to the acid chloride with 70 g. of phosphorus pentachloride, five 25-ml. portions of benzene being used for removal of the phosphorus oxychloride. The acid chloride was then dissolved in 100 ml. of benzene and added to 56 g. of aluminum chloride suspended in 150 ml. of solvent. After the addition which required forty-five minutes, 50 ml. of benzene was used for rinsing the funnel. The mixture was stirred for fifteen minutes in the cold and four hours at 22–24°, and then the addition complex was decomposed with 100 ml. of ether and 250 ml. of 1:1 hydrochloric acid. The 1-tetralone, b. p. 165–170° (46–49 mm.) amounted to 40.0–40.4 g. (90–91% yield). Starting acid amounting to 2.4 g., m. p. 45–47.5°, was recovered from the bicarbonate washings.

α,γ-Diphenylbutyric Acid, III (R^1 = H, R^2 = C_6H_5).—A 3.00-g. sample of the acid[20] (m. p. 72.7–73.5° after

(12) All melting points are corrected.

(13) See footnote 116b of ref. 3.

(14) Aluminum chloride supplied by either Merck and Co. (yellow powdered material) or J. T. Baker Chemical Co. (reagent grade) was used with equal success.

(15) Washing was continued with successive portions until no turbidity was produced on acidification.

(16) Kipping, *J. Chem. Soc.*, 480 (1894).

(17) Thiele and Wanscheidt, *Ann.*, **376**, 269 (1910).

(18) Johnson, Anderson and Shelberg, THIS JOURNAL, **66**, 218 (1944).

(19) Ingold and Piggott, *J. Chem. Soc.*, 1469 (1923).

(20) Prepared from α-phenyl-β-benzoylpropionitrile, *Org. Syn.*, Coll. Vol. II, 498 (1943), according to the procedure of Newman THIS JOURNAL, **60**, 2947 (1938).

three recrystallizations from 60–68° petroleum ether) was treated with 2.74 g. of phosphorus pentachloride, and cyclization was effected with 2.32 g. of aluminum chloride for five hours. The yield of crude product was 2.71–2.78 g. (98–100%) with a melting point varying from 75–76 to 73–75°. The acidic material recovered from the alkaline washings was negligible. Recrystallization of the 2.78-g. product from petroleum ether (60–68°) gave 2.38 g. melting at 76–77° and 0.24 g. melting at 74–76°, making the total yield of recrystallized material 94%. The reported m. p. is 76.2–77°.[20]

When a sample of the acid of approximately the same m. p., but having been recrystallized only twice was cyclized, the yield of crude product was good (97%) but the quality inferior (m. p. 69–73°). Recrystallization gave only 81% yield of ketone melting at 73–76°.

γ-*p*-Methoxyphenylbutyric Acid, III ($R^1 = OCH_3$, $R^2 = H$).—A 20.0-g. sample of the acid (m. p. 60.5–62° after recrystallization from petroleum ether (60–68°) containing a small proportion of benzene) was converted to the acid chloride with 24.0 g. of phosphorus pentachloride, four 15-ml. portions of benzene being used for removal of the phosphorus oxychloride. The acid chloride was then dissolved in 50 ml. of benzene and added to 19.3 g. of aluminum chloride suspended in 50 ml. of benzene. After the addition, which required twenty minutes, 25 ml. of benzene was used for rinsing making the total volume 125 ml. The mixture was stirred for fifteen minutes in the cold, then four hours at 22–24°. The yield of crude pale yellow crystalline ketone was 17.90 g. (99%), m. p. about 59–61°. Recrystallization from ether–petroleum ether (60–68°) gave in the first crop 14.33 g. of light tan prisms, m. p. 61–62° (reported,[21] 62–63°). From the bicarbonate wash 0.17 g. of acid was recovered, m. p. 54–57°. The potassium hydroxide washings yielded 0.08 g. of oil having a phenolic odor. This acid has been cyclized in 88% yield by the action of stannic chloride on the acid chloride.[22]

6-Methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic Acid, V (R = H).—A 3.00-g. sample of the acid, m. p. 83–84°,[23] was treated with 3.12 g. of phosphorus pentachloride, and cyclization was effected with 2.66 g. of aluminum chloride for four hours. The yield of crude 7-methoxy-2a,3,4,5-tetrahydro-1-acenaphthenone, VI (R = H), m. p. 78.5–82.5°, was 2.12 g. (77%). Only 0.10 g. of acidic product was recovered from the bicarbonate washings. Evaporative distillation at 130–140° (0.2 mm.) gave a 71% recovery of colorless material m. p. 88–89.5°. An additional 10% of less pure material, m. p. 84.5–88°, was recovered by continuing the distillation. An analytical sample was prepared from the first fraction by three recrystallizations from petroleum ether (60–68°) followed by evaporative distillation. The colorless needles melted at 89.6–90.8°.

Anal. Calcd. for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98. Found: C, 77.34; H, 6.86.

5-Methyl-6-methoxy-1,2,3,4-tetrahydronaphthyl-1-acetic Acid, V (R = CH_3).—A 1.00-g. sample of this acid, m. p. 159–159.5°,[23] was treated with 1.00 g. of phosphorus pentachloride, and cyclization was effected with 0.81 g. of aluminum chloride suspended in 20 ml. of benzene. The addition of the acid chloride in 15 ml. of solvent required fifteen minutes, 15 ml. of benzene being used for rinsing. The mixture was then stirred for an additional fifteen minutes in the cold, and for two and one-half hours at 22–24°. The yield of crude 6-methyl-7-methoxy-2a,3,4,-5-tetrahydro-1-acenaphthenone, VI (R = CH_3), m. p. 121–125.5°, was 0.925 g. (100%). A single crystallization of 0.920 g. from ethyl acetate–petroleum ether (60–68°) gave in the first crop 0.717 g., m. p. 123–125.5° and in the second 0.034 g., m. p. 122–124°. Recrystallization gave colorless blades, m. p. 124.4–126.4°.

Anal. Calcd. for $C_{14}H_{16}O_2$: C, 77.75; H, 7.46. Found: C, 77.97; H, 7.16.

(21) Campbell and Todd, THIS JOURNAL, **64**, 928 (1942).

(22) Thomas and Nathan, *ibid.*, **70**, 331 (1948).

(23) Preparation described by Johnson and Glenn, *ibid.*, **71**, 1087 (1949).

β-3,4-Dimethoxyphenylpropionic Acid, I ($R^1 = R_2 = OCH_3$).—3,4-Dimethoxycinnamic acid was prepared by the condensation of veratraldehyde (83 g.) with malonic acid (93 g.) in pyridine (115 ml.) with 1 ml. of piperidine according to the procedure for the preparation of *p*-methoxycinnamic acid.[1] The crude product was dissolved in 5% sodium carbonate, filtered, washed with ether, and acidified. The yield of 3,4-dimethoxycinnamic acid was 100 g. (96%), m. p. 183.4–184.2° with softening at 180° (reported,[24] 180°). Hydrogenation of once recrystallized (from benzene-petroleum ether) material in glacial acetic acid over platinum oxide catalyst gave a 94% yield of crude I ($R^1 = R^2 = OCH_3$), m. p. 95–97°, softening at 92°. Material for the cyclizations was twice recrystallized from benzene to give colorless crystals, m. p. 97.5–98.5° (reported,[25] 97°).

(*a*) *Cyclization with Hydrogen Fluoride.*—A 3.00-g. sample of the acid was treated with hydrogen fluoride overnight at room temperature by the procedure described for β-*p*-methoxyphenylpropionic acid.[1] The cyclization apparently proceeded in only one direction giving 2.42 g. (88% yield) of 5,6-dimethoxy-1-hydrindone, II ($R^1 = R^2 = OCH_3$), m. p. 118.8–119.5° (reported, 115,[25] and 116–117[26]). Recrystallization did not raise the melting point. When the reaction time was reduced to three hours the yield dropped to 73%.

The **semicarbazone** crystallized from alcohol in the form of pale yellow needles, m. p. 234–235° dec. (introduced at 200°).

Anal. Calcd. for $C_{12}H_{15}O_3N_3$: C, 57.82; H, 6.07. Found: C, 57.83; H, 6.52.

(*b*) *Cyclization with Phosphorus Pentoxide.*—Perkin and Robinson[25] obtained an 82% yield of the ketone by cyclization with phosphorus pentoxide. In our hands this procedure gave an 86% yield of quite impure material, m. p. 111–116° from which only a 51% yield of pure II ($R^1 = R^2 = OCH_3$), m. p. 118.4–119.4°, could be isolated by crystallization. The remaining material melted quite low, 93–108°, and may have contained some of the isomeric 6,7-dimethoxy-1-hydrindone.

(*c*) *Cyclization with Stannic Chloride.*—A 0.63-g. sample of the acid was cyclized with 0.700 g. of phosphorus pentachloride and 2.23 g. of stannic chloride according to the procedure of Wilds.[27] A total of 25 ml. of benzene was used, and the reaction mixture was allowed to stand for fifteen hours at room temperature. The total neutral product amounted to 0.311 g. (54% yield) of fairly pure 5,6-dimethoxy-1-hydrindone, m. p. 113.5–117°. Evaporative distillation at 130–135° (0.1 mm.) raised the m. p. to 116–117.5° which was not depressed on admixture with the specimen prepared by hydrogen fluoride cyclization (see above, part *a*).

(*d*) *Attempted Cyclization by the Inverse Aluminum Chloride Method.*—A 3.00-g. sample of the acid, m. p. 96.6–97.8°, was treated (according to the cyclization procedure described at the beginning of the experimental section) with 3.14 g. of phosphorus pentachloride, and then 5.75 g. of aluminum chloride for three hours. The neutral product amounted to 2.72 g., m. p. 59.6–65°. Crystallization of 1.00 g. from petroleum ether gave a total 0.90 g. of colorless plates melting between 63 and 67.8°, the first crop, 0.74 g., melting at 67.4–67.8°. A sample recrystallized four times melted at 67.8–68.4° which is in agreement with the m. p. (67.5–68.5°) reported for 3,4-dimethoxybenzylacetophenone (VII).[11]

Anal. Calcd. for $C_{17}H_{18}O_3$: C, 75.53; H, 6.71. Found: C, 75.52; H, 6.65.

The oxime crystallized from benzene–petroleum ether (60–68°) in the form of almost colorless prisms, m. p. 109–109.8° (reported,[11] 109°).

The **semicarbazone** was unusually low-melting and sol-

(24) Perkin and Schiess, *J. Chem. Soc.*, **85**, 159 (1904).

(25) Perkin and Robinson, *J. Chem. Soc.*, **91** 1073 (1907).

(26) Konek and Szamak, *Ber.*, **55B**, 102 (1922).

(27) Ref. 3, p. 136.

uble in ether. Crystallization from ethyl acetate gave pale yellow needles, m. p. 124.4–125° dec.

Anal. Calcd. for $C_{18}H_{21}O_3N_3$: C, 66.04; H, 6.47. Found: C, 65.63; H, 6.63.

In order to test for the presence of 5,6-dimethoxy-1-hydrindone in the acylation experiment, a sample of the crude product was converted to the semicarbazone. The derivative was formed in 96% yield, and although the m. p. (115–120°) indicated some impurity the product was completely soluble in ether indicating the absence of the ether-insoluble semicarbazone of the dimethoxyhydrindone.

In order to discover if 3,4-dimethoxybenzylacetophenone is convertible to 5,6-dimethoxy-1-hydrindone, 1.00 g. of the former was treated with 1.53 g. of aluminum chloride in benzene for twelve hours at room temperature. The mixture was worked up in the usual way yielding 0.53 g. (53% recovery) of neutral material which was fairly pure starting ketone, m. p. 66–67.5°. The remainder of the material was phenolic and appeared in the potassium hydroxide washings. Methylation with dimethyl sulfate gave 0.46 g. (46%) of tan ketone, m. p. 67–68.5° undepressed on admixture with 3,4-dimethoxybenzylacetophenone.

Summary

The behavior of nine acids of varying susceptibility to ring closure has been studied in connection with a cyclization procedure involving an inverse Friedel–Crafts technique in which a solution of the acid chloride in benzene is added to a suspension of aluminum chloride in benzene. The yields of cyclic ketones were generally excellent, except in the case of 3,4-dimethoxyphenylpropionic acid which was shown to effect intermolecular acylation of the solvent giving 3,4-dimethoxybenzylacetophenone. This unusual behavior may be attributed to an inhibition of resonance by coördination of the catalyst with the methoxyl groups. The weaker coördinating agent, stannic chloride, effects intramolecular acylation giving the cyclic ketone.

MADISON, WISCONSIN RECEIVED OCTOBER 16, 1948

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF MERCK & CO., INC.]

The Synthesis of DL-Threonine.* I. From α-Bromo-β-methoxy-*n*-butyric Acid and Derivatives

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Of all the known essential α-amino acids DL-threonine is the most difficult to isolate and to synthesize. The increasing demand for mixtures of the essential amino acids prompted us to evaluate the existing syntheses for DL-threonine with the view of developing a low cost process.

The best-known synthesis of DL-threonine consists in the conversion of crotonic acid into α-bromo-β-methoxy-*n*-butyric acid followed by amination and cleavage of the methoxy group. This sequence of reactions however is complicated by the formation of a mixture of two diastereoisomeric bromo acids, one of which leads to O-methyl-DL-threonine and the other to O-methyl-DL-allothreonine. Of the various reported methods for the preparation of α-bromo-β-methoxy-*n*-butyric acids and their simple derivatives all but one lead to mixtures too poor in the DL-threonine precursor to be useful in the synthesis of this amino acid.

Previous studies of the synthesis of DL-threonine have been handicapped by the facts that no simple separation from DL-allothreonine was known, and no method of analysis of mixtures of the diastereoisomeric amino acids had been developed. The recent description of a microbial assay for L-threonine[2] has greatly simplified the problem. With the aid of this analysis it has become possible to make direct comparisons of the various reported syntheses of DL-threonine and DL-allothreonine and to test the effect of experimental variables and modifications on the relative amounts of the two substances formed in each synthesis. The present paper reports the results of such studies, together with a new practical synthesis of DL-threonine developed in the course of the work.

Until recently the best recorded synthesis of DL-threonine was that of Carter and West.[3] In this method, crotonic acid is treated with mercuric acetate in methanol, and the addition product is brominated. The mixture of bromo acids is aminated, and the reaction products are separated by formylation and isolation of N-formyl-O-methyl-DL-threonine. The latter is converted into pure DL-threonine by boiling hydrobromic acid. The over-all yield of DL-threonine from crotonic acid is about 20%. The yield of DL-threonine from the bromo acid mixture is 30–33% of theory as determined by microbial assay.

Attempts to alter the ratio of diastereoisomeric bromo acids formed by the bromination of α-acetoxymercuri-β-methoxy-*n*-butyric acid were

* This nomenclature is in accord with the rules approved by the American Chemical Society Committee on Nomenclature, Spelling and Pronunciation, as reported by Vickery, *J. Biol. Chem.*, **169**, 237 (1947) and Crane, *Chem. Eng. News*, **25**, 1363 (1947). Throughout this paper the small capital letter prefix will be used in the amino acid sense rather than in the carbohydrate sense. For the sake of brevity however, we have deleted the subscripts which refer to serine, the fundamental substance to which amino acids that bear structural resemblance to the carbohydrates can be formally related.

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(2) Stokes, Gunness, Dwyer and Caswell, *J. Biol. Chem.*, **160**, 35 (1945); Gunness, Dwyer and Stokes, *ibid.*, **163**, 159 (1946).

(3) (a) Carter and West, *Org. Syn.*, **20**, 101 (1940); *cf.* (b) Abderhalden and Heyns, *Ber.*, **67**, 530 (1934).