[CONTRIBUTION FROM AVERY LABORATORY, THE UNIVERSITY OF NEBRASKA]

Reduction of Methyl Benzoyldiazoacetate. A New Synthesis of Allophenylserine[1]

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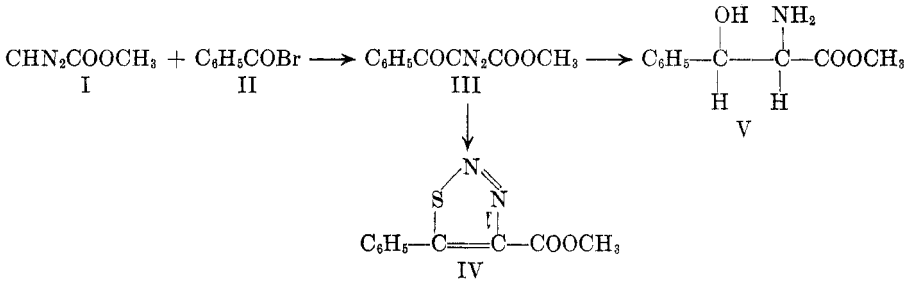
A synthesis of allophenylserine (DL-*erythro*-β-phenylserine) by catalytic reduction of methyl benzoyldiazoacetate is reported. Chemical reduction of methyl benzoyldiazoacetate with aluminum amalgam in moist ether gives a complex mixture of products, including methyl benzoylacetate.

The reaction of methyl diazoacetate (I) with benzoyl bromide (II) to give methyl benzoyldiazoacetate (III) has long been known.[3] The present paper reports the results of an investigation which had as its principal objective the reduction of III to give either a phenylalanine or a β-phenylserine ester.



The attempted reduction of III by a variety of chemical reducing agents led either to recovery of III, or, in the case of aluminum amalgam, to a complex mixture of products (sequel). Conversion of III to the known thiadiazole IV, followed by attempted reduction with either sodium hydrosulfite or Raney nickel (desulfurization) gave only recovered IV. Hence, a catalytic procedure was investigated. Reduction of III in 70% acetic acid over 5% palladium-on-charcoal gave allophenylserine methyl ester (V), isolated in 82% yield as the hydrochloride. The over-all yield of the hydrochloride of V from II was 64%. Conversion of V to allophenylserine (VI) by a known procedure, followed by fractionation of VI by the method of Shaw and Fox[4] did not reveal any of the diastereomeric *threo* form. It is evident that the reduction of III is highly stereospecific, and compares favorably with recently reported syntheses of VI from ethyl benzoylacetate *via* either the oximino[5] or the acetamido[6] derivative. This appears to be the first stereospecific reduction of an acyl- or aroyldiazoacetic ester, although a mixture of the diastereomeric threonines was reported by Birkofer[7] through catalytic reduction of ethyl acetyldiazoacetate. While this investigation was in progress, Fodor and coworkers reported a β-keto-α-amino acid ester from catalytic reduction of ethyl α-bromopalmitoyldiazoacetate,[8] and effected further reduction to the serine derivative with sodium borohydride.

In contrast to the satisfactory yield of V obtained in the catalytic reduction procedure, reaction of III with aluminum amalgam in moist ether gave no yield of the arylserine ester. Two principal fractions, A and B, were isolated from the reaction mixture. The ether-insoluble Fraction A appeared reasonably homogeneous, and after recrystallization from dimethylformamide-water was obtained in a colorless, crystalline condition, m.p. 222–223°. Elemental analysis, combined with Rast molecular weight determination, indicated a molecular formula of $C_{20}H_{22}O_6$ for the pure ester (VII). Alkaline hydrolysis of VII gave the acid, $C_{18}H_{18}O_6$ (VIII),[9] reconverted by ethereal diazomethane to VII. The stability of VIII as the free acid precludes the pos-

(1) The major portion of the present communication is taken from the Ph.D. Thesis of Donald Nixon Thatcher, University of Nebraska, 1954.

(2) DuPont Teaching Assistant, 1953–54.

(3) H. Staudinger, J. Becker, and H. Hirzel, *Ber.*, **49**, 1978 (1916).

(4) K. N. F. Shaw and S. W. Fox, *J. Am. Chem. Soc.*, **75**, 3421 (1953).

(5) Y. Chang and W. H. Hartung, *J. Am. Chem. Soc.*, **75**, 89 (1953).

(6) W. A. Bolhofer, *J. Am. Chem. Soc.*, **74**, 5459 (1952).

(7) L. Birkofer, *Ber.*, **80**, 86 (1947).

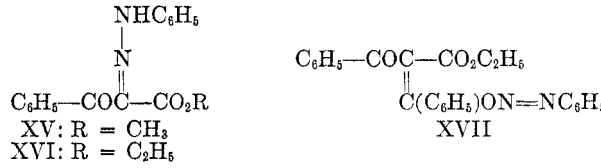
(8) I. Sallay, F. Dutka, and G. Fodor, *Helv. Chim. Acta*, **37**, 778 (1954). *Chem. Abstr.*, **49**, 6098 (1955).

(9) The analytical data are satisfactory also for an acid with formula $C_{15}H_{18}O_5$. However, this interpretation would require that the ester precursor of such a monobasic acid have a molecular formula of $C_{16}H_{18}O_5$. Although the molecular weight determination is in agreement with the latter formula, the carbon value would be seriously in error. The Rast procedure would appear to be subject to greater error than the carbon determination.

sibility that VIII is DL-β,β'-diphenyl-β,β'-dihydroxyadipic acid (IXa), which is known to lactonize spontaneously.[10] Although meso-β,β'-diphenyl-β,β'-dihydroxyadipic acid (IXb) is known in the free state, it loses water to give a lactone so readily that it cannot be purified by crystallization.[11] The acid VIII was recrystallized easily from dilute methanol. A dimethyl ester (X) of either IXa or IXb was considered as a possible reduction product, since it could be formed by pinacol reduction of the intermediate methyl benzoylacetate (XII), previously formed by reductive cleavage of III with loss of nitrogen. Attempts to acetylate VII under a variety of conditions were unsuccessful, even though the infrared spectrum revealed the presence of the hydroxyl function. Repeated attempts to obtain useful products for assigning structure by oxidation procedures gave either recovery of starting material or benzoic acid.

In contrast to Fraction A, the ether-soluble Fraction B was obtained as an oil, which could not be induced to crystallize. Fraction B was reacted with 2,4-dinitrophenylhydrazine(XI) in order to isolate derivatives of any substances containing suitably reactive carbonyl groups. There was obtained a crystalline derivative which gave a nitrogen analysis satisfactory for the known 2,4-dinitrophenylhydrazone of methyl benzoylacetate (XII). However, it was observed concurrently that the readily available ethyl dibenzoylacetate underwent cleavage of a benzoyl group during reaction with XI, to give the same derivative obtained from ethyl benzoylacetate and XI. Accordingly it was apparent that Fraction B could contain either XII or methyl dibenzoylacetate (XIII), or both XII and XIII. It is considered reasonable to assume that XII and XIII would be very similar chemically to ethyl benzoyl- and dibenzoylacetate, respectively.

A partial solution of the problem involving the composition of Fraction B was obtained by reacting it with benzenediazonium chloride (XIV). Although the reaction product was an orange-colored oil which did not crystallize, chromatography of the product on silicic acid–Celite gave, together with other fractions, a crystalline yellow substance, m.p. 74–75°, which was stable on the adsorbent. It was shown concurrently that while XVI (from commercially available ethyl benzoylacetate and XIV) appeared stable on silicic acid–Celite, XVII (from ethyl dibenzoylacetate and XIV) is not. Hence, it is considered reasonably certain that the yellow compound, m.p. 74–75°, is the phenylhydrazone (XV) reported[12] to melt at 76°, formed by tautomerization of the initially formed benzenediazonium coupling product of methyl benzoylacetate, which was present in Fraction B. In addition to XV, chromatography of the reaction product of Fraction B and XIV gave two resinous



fractions. Also, there was present a compound which moved rapidly down the adsorbent column into the effluent. No crystalline material proved isolable from the effluent, however, and the identity of this substance remains obscure. It is apparent that only one substance, methyl benzoylacetate, has been identified among the aluminum amalgam reduction products of III. However, a sufficiently thorough study has been made to indicate that the reduction is not useful for preparing any one product in satisfactory yield. Further study is not anticipated.

In the course of this work, the infrared spectra of the aroyldiazo ester (III) and the 1,2,3-thiadiazole (IV) were investigated. The spectrum of III in Nujol showed a strong, sharp band at 2165 cm.$^{-1}$ and in carbon tetrachloride solution at 2147 cm.$^{-1}$ This band is attributed to the aliphatic diazo group, on the basis of the presence of similar absorption maxima in the infrared spectra of other aliphatic diazo compounds. Thus diazomethane[13] shows an infrared maximum at 2101 cm.$^{-1}$, diazocyclopentadiene[14] at 2082 cm.$^{-1}$ (carbon tetrachloride), azaserine[15] at 2146 cm.$^{-1}$ (Nujol), and α-diazo-*o*-methoxyacetophenone[16] at 2080 cm.$^{-1}$ (chloroform). A band in the vicinity of 2000–2200 cm.$^{-1}$ in the spectrum of IV is lacking. It is apparent that the —N=N— grouping absorbs completely differently from the true aliphatic diazo grouping.[17] Also, the presence of the diazo band in the spectrum of III affords physical evidence that methyl benzoyldiazoacetate is not a 1,2,3-oxadiazole.

EXPERIMENTAL

Melting points are uncorrected. Nitrogen analyses (Dumas method) were performed by D.N.T. Other microanalyses were carried out by Clark Microanalytical Laboratories or by Micro-Tech Laboratories. The infrared spectra (of Nujol mulls unless otherwise specified) were recorded with a Perkin-Elmer Model 21 spectrophotometer using an

(10) E. Beschke, *Ann.*, **391**, 111 (1912).
(11) E. Beschke, *Ann.*, **384**, 143 (1911).
(12) A. Wahl, *Bull. soc. chim. France*, **3**, 950 (1908).
(13) B. L. Crawford and W. H. Fletcher, *J. Chem. Phys.*, **19**, 406 (1951).
(14) W. von E. Doering and C. H. DePuy, *J. Am. Chem. Soc.*, **75**, 5955 (1953).
(15) S. A. Fusari, R. P. Frohardt, A. Ryder, T. H. Haskell, D. W. Johanessen, C. C. Elder, and Q. R. Bartz, *J. Am. Chem. Soc.*, **76**, 2878 (1954).
(16) A. K. Bose and P. Yates, *J. Am. Chem. Soc.*, **74**, 4703 (1952).
(17) An extensive investigation of the infrared spectra of compounds containing the —N=N— group has been reported by R. J. W. Le Fevre, M. F. O'Dwyer, and R. L. Werner, *Australian J. Chem.*, **6**, 341 (1953).

NaCl prism. Only medium and strong absorption bands are reported herein.

Silicic acid used in chromatographic procedures is Merck reagent grade, approximate formula H_2SiO_3. Celite 535 was employed in all chromatographic work. Chemicals for which preparations are not given are commercially available.

Methyl diazoacetate. This diazo ester was prepared from glycine methyl ester hydrochloride by the method of Womack and Nelson.[18]

Methyl benzoyldiazoacetate. This compound was prepared in 78% yield by the method of Staudinger and coworkers[3]; m.p. 84–85° (lit.[3] m.p., 83–84°).

The infrared spectrum of methyl benzoyldiazoacetate shows absorption maxima at 2165, 1725, 1618, 1442, 1345, 1268, 1130, and 746 cm.$^{-1}$ In carbon tetrachloride solution, maxima were displayed at 2147, 1728, 1633, and 1120 cm.$^{-1}$

Allophenylserine. To a solution of 10 g. of methyl benzoyldiazoacetate in 70 ml. of glacial acetic acid was added 0.5 g. of 5% palladium on charcoal. A 30-ml. quantity of water was added, and the reaction vessel was attached immediately to the hydrogen line. Hydrogenation was carried out at 40 p.s.i.g. hydrogen, and was permitted to continue until the theoretical quantity was absorbed (*ca.* 5 hr.). After catalyst removal, the reaction mixture was concentrated to 35 ml., cooled to 5°, basified to litmus with concentrated ammonium hydroxide, and extracted with ten 150-ml. portions of ether. Dry hydrogen chloride gas was passed into the dried, combined ether extracts, and the resulting precipitate collected by filtration, washed with dry ether, and dried *in vacuo* over potassium hydroxide; yield, 9.3 g. (82%), m.p. 178–182° (dec.). Recrystallization from methanol-ether gave the colorless allophenylserine methyl ester hydrochloride, m.p. 182° (dec.) [lit. m.p.,[4] 180° (dec.)].

Anal. Calcd. for $C_{10}H_{14}ClNO_3$: N, 6.05. Found: N, 6.12.

The following procedure is essentially that used by Shaw and Fox in preparing allophenylserine from its ethyl ester hydrochloride.[19] Allophenylserine methyl ester hydrochloride (5.7 g.) was hydrolyzed at room temperature by solution in 25 ml. of 2*N* sodium hydroxide containing 1.5 ml. of methanol. After 2 hr., the resulting clear solution was neutralized with concentrated hydrochloric acid and allowed to stand overnight at 5°. Collection of the white needles present, which were then washed with ice water and dried *in vacuo*, yielded 3.38 g. (75%) (from the ester hydrochloride) of allophenylserine, m.p. 189–191° (dec.). This melting point is in agreement with the observation of Shaw and Fox[19] that samples of allophenylserine decompose in the range 189–193°, depending on heating rate and initial bath temperature.

Anal. Calcd. for $C_9H_{11}NO_3$: N, 7.73. Found: N, 7.68.

Application of the fractionation procedure of Shaw and Fox to the isolated acid gave a dioxane complex, characteristic of allophenylserine. No *threo*-β-phenylserine proved isolable.

Allophenylserine methyl ester. Application of the method of Shaw and Fox,[19] for liberating the methyl ester of phenylserine from its hydrochloride, to 2.5 g. of allophenylserine methyl ester hydrochloride gave 1.7 g. of the free methyl ester, which, after recrystallization from ether–petroleum ether (b.p. 30–60°), gave m.p. 108.5° (lit.[4] m.p. 110°).

Anal. Calcd. for $C_{10}H_{13}NO_3$: N, 7.18. Found: N, 7.08.

The methyl ester was obtained also by the general method outlined for preparing the hydrochloride from methyl benzoyldiazoacetate, except that the ether extracts of the basified hydrogenation mixture were evaporated to dryness to give the cream-colored crude ester, m.p. 105–107°. Recrystallization from ether–petroleum ether (b.p. 30–60°) gave 6.6 g. (68%) of white plates of allophenylserine methyl ester, m.p. 108–109°.

Reduction of methyl benzoyldiazoacetate by aluminum amalgam in moist ether. Isolation of fractions. The aluminum amalgam was prepared by permitting 7.5 g. of ether-washed aluminum turnings to stand in a 5% solution of mercuric chloride for 5 min. The amalgamated turnings were washed thoroughly with distilled water and then covered with technical ether.

In a one-l., wide-mouthed Erlenmeyer flask, 31 g. of methyl benzoyldiazoacetate was dissolved in 750 ml. of technical ether. The aluminum amalgam was introduced into the solution in a perforated glass test tube (3 × 12 cm.), suspended in the solution by a wire to permit the aluminum hydroxide formed to fall away from the active surface of the metal. The reaction commenced immediately, with vigorous evolution of gas. Ether was added to the reaction during the course of the run to maintain the volume of the solution at 750 ml. During the course of the reaction, a piece of moist litmus paper indicated the presence of ammonia in the evolved gases. The reaction was continued until the yellow solution had turned almost colorless; usually this required 4 to 6 hours.

Upon completion of the reduction, any excess aluminum was removed, and then the heterogeneous mixture was poured into a 5.5 × 27.5 cm. chromatographic tube, where the aluminum hydroxide was eluted with two additional liters of ether. From this ether solution there was precipitated, upon standing, a white crystalline solid which was collected by filtration. Evaporation of the ether filtrate yielded a yellow oil and additional solid material. This solid was removed by filtration, washed with dry ether, and added to the first crop. The total yield of solid (Fraction A) was 1.4 g.

The residual yellow oil was suspended in water and extracted continuously with fresh ether to yield a yellow ether solution, which was dried over Drierite. The aqueous layer was still yellow in color and was retained. Distillation of the ether under reduced pressure left a viscous, reddish-orange oil; yield, 11.6 g. (Fraction B).

The yellow aqueous layer was subjected to continuous extraction with *n*-butyl alcohol for 3 days. The butanol then was removed by distillation under reduced pressure to give a residual yellow oil which did not crystallize and was not investigated further.

Characterization of fraction A. Fraction A was a white, crystalline solid, insoluble in most common organic solvents. It was recrystallized from dimethyl formamide–water to give the ester VII with a constant m.p. of 222–223°. A ferric chloride test with VII was negative.

Anal. Calcd. for $C_{20}H_{22}O_6$: C, 67.02; H, 6.19; mol. wt., 358. Found: C, 67.34; H, 6.41; mol. wt. (Rast), 272, 293.

The infrared spectrum of VII showed absorption maxima at 3500, 1737, 1700, 1350, 1207, 1183, 1159, 1068, 1015, 999, 750, and 703 cm.$^{-1}$ The band at 3500 cm.$^{-1}$ is attributed to presence of the hydroxyl function, the band at 1737 cm.$^{-1}$ to the ester function.[20]

The ester VII (0.3 g.) was hydrolyzed with 10 ml. of 5% potassium hydroxide at room temperature. After standing overnight, the clear solution was acidified and the resulting product collected by filtration. Two recrystallizations from methanol-water yielded 0.24 g. of the acid VIII, m.p. 191–192°.

Anal. Calcd. for $C_{18}H_{18}O_6$: C, 65.44; H, 5.49. Found: C, 65.64; H, 5.75.

When the acid VIII was treated with excess ethereal diazomethane, the ester VII was again obtained, m.p. and mixed m.p., 222–223°.

The infrared spectrum of VIII showed absorption maxima at 3515, 1682, 1444, 1355, 1223, 950, and 697 cm.$^{-1}$ The band at 3515 cm.$^{-1}$ is attributed to the hydroxyl function, the band at 1682 cm.$^{-1}$ to the carboxyl carbonyl group.[20]

(18) E. B. Womack and A. B. Nelson, *Org. Syntheses*, **24**, 56 (1944).

(19) K. N. F. Shaw and S. W. Fox, *J. Am. Chem. Soc.*, **75**, 3417 (1953).

(20) F. Miller in *Organic Chemistry*, Vol. III, edited by Gilman, John Wiley and Sons, Inc., New York, 1953, pp. 140–141, 143–150.

Characterization of fraction B. A. Preparation of 2,4-nitrophenylhydrazone. 2,4-Dinitrophenylhydrazine reagent was prepared according to the directions of Shriner and Fuson.[21] A 0.25-ml. quantity of Fraction B in 5 ml. of 95% ethanol was added to the reagent. The solution was allowed to stand 1 hr., and the orange-colored 2,4-dinitrophenylhydrazone present was collected by filtration. One recrystallization from ethanol–ethyl acetate gave orange plates of the 2,4-dinitrophenylhydrazone of methyl benzoylacetate, m.p. 166–167° (dec.) (lit.[22] m.p. 169–170°).

Anal. Calcd. for $C_{16}H_{14}N_4O_6$: N, 15.64. Found: N, 15.44.

Ethyl dibenzoylacetate (prepared by the method of Wright and McEwen[23]) was reacted with the 2,4-dinitrophenylhydrazine reagent. There was obtained, after one recrystallization from ethanol–ethyl acetate, orange plates, m.p. 161–162° (dec.)[24], which gave an analysis satisfactory for the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate.

Anal. Calcd. for $C_{17}H_{16}N_4O_6$: N, 15.05. Found: N, 15.04, 15.01.

The 2,4-dinitrophenylhydrazone of ethyl benzoylacetate was prepared by the same procedure; m.p. and mixed m.p. with the product for which analysis is given immediately above, 161–162°.

B. Chromatographic study of coupling product with benzenediazonium chloride. A 0.5-g. quantity of oily Fraction B was coupled with benzenediazonium chloride according to the procedure of Bülow and Neber[25] as modified by Bolhofer.[6] The quantities of reactants employed were based on the assumption that Fraction B was pure methyl benzoylacetate. Attempts to isolate the coupling product in a crystalline condition direct from the reaction mixture by addition of ice were unsuccessful. There was obtained instead a reddish-orange oil (Residue I), by decanting the aqueous supernatant layer. The decantate slowly deposited additional insoluble oily material, which was not further investigated because of its unpromising, tarry appearance. Residue I resisted all attempts at crystallization from benzene–iso-octane and ethyl acetate–iso-octane, and was dried in a vacuum desiccator over phosphorus pentoxide for several days.

Residue I (145 mg.) in benzene solution was chromatographed on 65 g. of silicic acid–Celite (5:1 wt.), adsorbent column dimensions 33 × 130 mm. The column was developed with benzene-ethanol (500:1 vol.) under a water pump vacuum over a 45-min. period. There was formed during the early stages of development of the chromatogram a pale yellow, fast-moving zone which moved into the column effluent and was retained. Upon completion of development, there was present at the top of the column a stationary zone, which contained resinous material and was discarded

(21) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, John Wiley and Sons, Inc., New York, 1948, p. 171.

(22) W. J. Croxall, J. O. Van Hook, and H. J. Schneider, *J. Am. Chem. Soc.*, **73**, 2713 (1951).

(23) P. E. Wright and W. E. McEwen, *J. Am. Chem. Soc.*, **76**, 4540 (1954).

(24) The melting point of the 2,4-dinitrophenylhydrazone of ethyl benzoylacetate has been reported as 246–247° [G. D. Johnson, *J. Am. Chem. Soc.*, **75**, 2720 (1953)]. Johnson used a different procedure [*J. Am. Chem. Soc.*, **73**, 5888 (1951)] than the one employed in the present work, and purified the derivative by repeated crystallization from different solvents. It is apparent that tautomerization of an initially formed dinitrophenylhydrazone is theoretically possible, as well as the existence of geometric isomers. The exact structure of the 2,4-dinitrophenylhydrazone is not critical in the present study. The major interest in the present work is that the same derivative was obtained from both ethyl benzoyl- and dibenzoylacetate with 2,4-dinitrophenylhydrazine.

(25) C. Bülow and P. Neber, *Ber.*, **45**, 3732 (1912).

There were present two additional bands, an orange-brown one, 2 mm. in width, with trailing edge 13 mm. from the top of the adsorbent column, and a yellow one, 53 mm. in width, with trailing edge 46 mm. from the top of the adsorbent column. The column was extruded and the bands cut out. Elution of the former with acetone gave a resinous material which resisted all attempts at crystallization.

Elution of the latter B with acetone yielded a yellow oil which was dried thoroughly in a vacuum desiccator. The product then was rubbed repeatedly with iso-octane, with mechanical removal of tar, to give a yellow solid. The latter was dissolved in pure *n*-hexane and the resulting solution permitted to evaporate slowly at room temperature to give the pure coupling product, XV; m.p. 74–75° (lit.[12] m.p. 76°), yield 34 mg. (two crops).

The isolation of crystalline material from the column effluent did not prove feasible. Solvent removal gave an intractable oil.

Chromatography of coupling product (XVII) *from ethyl dibenzoylacetate and benzenediazonium chloride.* The coupling product XVII was prepared by the method outlined by Bülow and Hailer.[26]

A 200-mg. quantity of XVII in benzene solution was chromatographed on 64 g. of silicic acid–Celite (5:1 wt.), adsorbent column dimensions 33 × 132 mm. The chromatogram was developed with benzene-ethanol (500:1 vol.) over a 50–55-min. period under a water-pump vacuum. Initially, a fairly sharp, bright yellow band formed, which then moved down the column quite rapidly, becoming more diffuse as development progressed. After completion of the development period, the trailing edge of the single diffuse zone (28 mm. wide) was 85 mm. from the top of the adsorbent column. The zone was such a faint yellow that it was hardly discernible. The adsorbent column was extruded. The single zone was cut out and eluted with acetone. The faint color was restricted to the outer zone surface, which was exposed to the air. The acetone eluate was poured onto *ca.* 700 ml. of ice-water mixture. A considerable quantity of material solidified during this operation, and was removed mechanically with the aid of a spatula. On standing, the solid mixture melted to give two phases, which were separated in a separatory funnel. The upper phase (apparently containing benzene as solvent) was retained and permitted to evaporate at room temperature overnight. The residual solid, obtained in low yield, was suspended in cyclohexane, and then the colorless product present collected by filtration and air-dried. The material burned completely without leaving an ash, and gave m.p. 108–110°. No other crystalline material proved isolable. The column effluent was colorless.

Methyl 5-phenyl-1,2,3-thiadiazole-4-carboxylate. This substance was prepared from 5 g. of methyl benzoyldiazoacetate dissolved in 50 ml. of methanol by the general method of Staudinger and coworkers. The yield of pure product, m.p. 63–63.5° (lit.[3] m.p. 60°), was 5.2 g. (96%).

The infrared spectrum of the thiadiazole derivative showed absorption maxima at 1727, 1335, 1275, 1228, 1208, 1173, 1010, 832, 749, and 687 cm.$^{-1}$

Saponification of the ester with 10% sodium hydroxide gave 5-phenyl-1,2,3-thiadiazole-4-carboxylic acid, m.p. 156–157° (dec.), [lit.[27] m.p. 157° (dec.)]. The infrared spectrum showed absorption maxima at 3455, 1688, 1601, 1252, 835, 756, and 690 cm.$^{-1}$

5-Phenyl-1,2,3-thiadiazole-4-carboxamide. 5-Phenyl-1,2,3-thiadiazole-4-carboxylic acid (2 g.) was heated under reflux with 10 ml. of thionyl chloride until all of the solid had dissolved and there was no further evolution of hydrogen chloride. The excess thionyl chloride was removed under reduced pressure. The remaining solution was cooled in an ice bath and 10 ml. of concentrated ammonium hydroxide

(26) C. Bülow and E. Hailer, *Ber.*, **35**, 915 (1902).

(27) L. Wolff, *Ann.*, **333**, 1 (1904).

added dropwise. The collected precipitate was recrystallized from absolute ethanol; m.p. 141–142°, yield 1.5 g. (75%).

Anal. Calcd. for $C_9H_7N_3OS$: N, 20.48. Found: N, 20.38.

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Chloroacetates and Dichloroacetates of Flavonol, 7-Hydroxyflavone, and Chrysin[1]

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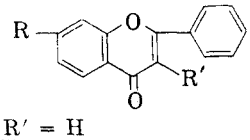
An improved synthesis of 7-chloroacetoxyflavone is reported. The procedure developed has been applied in the preparation of 7-dichloroacetoxyflavone, 3-chloroacetoxyflavone and 7-dichloroacetylchrysin. The attempted solubilization of 7-chloroacetoxyflavone by conversion to the pyridinium salt is reported.

A broad range of biological activity has been demonstrated by flavonoid materials. The present paper describes a series of chloroacetyl and dichloroacetyl derivatives of flavonol, 7-hydroxyflavone and chrysin, which were prepared for evaluation of possible biological activity. The possibility of solubilizing 7-hydroxyflavone as a pyridinium salt of the chloroacetate has been investigated.



I: R = OH; R′ = H
II: R = CH_2ClCOO; R′ = H
III: R = H; R′ = OH
IV: R = H; R′ = CH_2ClCOO
V: R = $CHCl_2COO$; R′ = H

7-Hydroxyflavone (I) was prepared by the method of Robinson and Venkataraman,[2] as well as by fusion of resacetophenone dibenzoate in the presence of benzoic acid and sodium benzoate. The latter procedure is somewhat similar to the modification introduced by Wheeler and coworkers,[3] but utilizes benzoic acid as the reaction medium instead of glycerol, which is quite hygroscopic. 7-Hydroxyflavone is described[2] as forming long colorless needles, m.p. 240°. The product obtained by the benzoic acid fusion method crystallized in long brilliant yellow needles (Form A), m.p. 244–244.5°. Upon hydrolysis of 7-chloroacetoxyflavone (sequel), colorless 7-hydroxyflavone was obtained. After recrystallization from ethanol, very pale yellow needles (Form B), m.p. 244–245° were obtained. Infrared absorption spectra of the two forms, A and B, showed them to be identical on a molecular basis to each other and to the flavone derivative prepared by the method of Robinson and Venkataraman.[2]

7-Chloroacetoxyflavone (II) has been prepared by Row and Seshadri[4] by heating 7-hydroxyflavone with an excess of chloroacetyl chloride. No yield for this reaction was reported, but it was noted that it was very difficult to remove a green color from the product. This procedure, upon being repeated by the authors, led to a greenish black tar, from which only a small amount of starting material proved isolable in pure form. Although an exhaustive study of the reaction mixture was not made, it appeared likely that recrystallization from methanol caused decomposition of any ester present to give 7-hydroxyflavone (sequel). Further experiments using xylene solutions showed the green color to be due to contact of the warm reactants with air. Accordingly, all succeeding reactions were carried out in xylene in an atmosphere of nitrogen with exclusion of air until all of the excess chloroacetyl chloride had been removed by distillation *in vacuo*. Under these conditions, the green color did not appear and colorless needles of 7-chloroacetoxyflavone were obtained in yields up to 77%.

Under anhydrous conditions, 7-chloroacetoxyflavone reacts with pyridine to give a solid product. Extraction of this product with ether removed unreacted starting material and left a light yellow residual solid with a wide melting range. The product, presumably the crude pyridinium salt, was tested for water solubility. Although the

(1) Abstracted from the M.S. Thesis of Walter Wm. Hanneman, University of Nebraska, 1956.

(2) R. Robinson and K. Venkataraman, *J. Chem. Soc.*, 2344 (1926).

(3) A. T. M. Dunne, J. E. Gowan, J. Keane, B. M. O'Kelly, D. O'Sullivan, M. M. Roche, P. M. Ryan, and T. S. Wheeler, *J. Chem. Soc.*, 1252 (1950).

(4) R. Row and T. R. Seshadri, *Proc. Indian Acad. Sci.*, 11A, 206 (1940).