hours. The pink solid which separated was recrystallized first from ligroin and then from aqueous dimethylformamide to give 0.59 g. (33.4%) of colorless crystals, m.p. 156.5–157.5°.

Anal. Calcd. for $C_{25}H_{20}N_2$: C, 86.2; H, 5.8; N, 8.0. Found: C, 85.9; H, 6.1; N, 8.2.

Phenanthridone.—A mixture of 2 ml. (2.20 g.) of *o*-biphenyl isocyanate and 4.5 ml. of polyphosphoric acid was heated for two hours with constant stirring in an oil-bath held at 140–160°. Addition of the top liquid layer to water yielded 0.02 g. of di-(*o*-biphenylyl)-urea, m.p. 184–185°, while addition of the bottom liquid layer to water and recrystallization of the resulting solid from aqueous dimethylformamide gave 1.92 g. (87.3%) of colorless phenanthridone, m.p. 291–292°.

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A Preparation of Liquid Ammonia Solutions of Sodium Vinylacetylide

BY W. J. CROXALL AND J. O. VAN HOOK

RECEIVED NOVEMBER 30, 1953

Liquid ammonia solutions of sodium vinylacetylide have been used for the introduction of vinylethinyl groups into molecules.[1-3] The solutions were prepared by treating sodium or sodium amide with vinylacetylene in liquid ammonia. Vinylacetylene, however, is difficult to store and handle in the laboratory.[4] We have found that liquid ammonia solutions of sodium vinylacetylide are conveniently prepared in the laboratory by the reaction of sodium amide in liquid ammonia with either 1,4-dichloro-2-butene or 1,2-dichloro-3-butene or a mixture of both. The existence of the sodium vinylacetylide was established by its reaction with (1) ethylene oxide to produce hex-5-en-3-yn-1-ol in 24.5% yield, (2) acetone to produce 1,1-dimethylpent-4-en-2-yn-1-ol in 56% yield and (3) cyclohexanone to produce 1-vinylethinylcyclohexanol in 52% yield.

Experimental

Dichlorobutenes.—A 60–40 mixture of 1,4-dichloro-2-butene and 1,2-dichloro-3-butene was obtained from E. I. du Pont de Nemours and Company, Inc. It was separated into 1,2-dichloro-3-butene (b.p. 47–53° (60 mm.)) and 1,4-dichloro-2-butene (b.p. 78–80° (60 mm.)) by distillation.

Sodium Amide.—This was prepared according to the method of Vaughan, Vogt and Nieuwland.[5]

Sodium Vinylacetylide.—To a stirred solution of sodium amide in 1.5 l. of liquid ammonia, prepared from 33 g. (1.5 moles) of sodium, was added 63 g. (0.5 mole) of 1,4-dichloro-2-butene or 1,2-dichloro-3-butene or a mixture of both over a period of 30 minutes at −35°. The resulting solution was stirred for 3 hours at −30 to −35° to ensure complete reaction.

Hex-5-en-3-yn-1-ol.—Ethylene oxide (114 g., 2.6 moles) was added, over a ten-minute period, under the surface of a stirred solution of 2 moles of sodium vinylacetylide in 3.5 l. of liquid ammonia at −35°. The mixture was stirred at −35° for seven hours and then neutralized by the cautious addition of 107 g. (2.0 moles) of ammonium chloride in small portions, after which the ammonia was allowed to evaporate. To the residue was added slowly 1 l. of water and the mixture was subjected to steam distillation. The 2 l. of distillate was saturated with potassium carbonate and the resulting oil was removed by extraction with ether. The extracts were dried over anhydrous potassium carbonate and distilled to produce 48 g. (24.5%) of hex-5-en-3-yn-1-ol which boiled at 65–70° (10 mm.) and had n^{20}_{D} 1.4958 (lit.[6] b.p. 68–69° (10 mm.), n^{18}_{D} 1.4968).

1,1-Dimethylpent-4-en-2-yn-1-ol.—Redistilled anhydrous acetone (29 g., 0.5 mole) was added to a solution of 0.5 mole of sodium vinylacetylide in 1.5 l. of liquid ammonia over a 15-minute period at −35°. The mixture was stirred for 3 hours at −35° and then neutralized by the cautious addition of 80 g. (1.5 moles) of ammonium chloride, after which the ammonia was allowed to evaporate. To the residue there was added 1 l. of ether and then 300 cc. of water. The ether layer was separated, dried over magnesium sulfate and distilled to give 31 g. (56%) of 1,1-dimethylpent-4-en-2-yn-1-ol, b.p. 65° (24 mm.), n^{21}_{D} 1.4752 (lit.[2] b.p. 67° (24 mm.), n^{20}_{D} 1.4778).

1-Vinylethinylcyclohexanol.—From the reaction of 0.5 mole of sodium vinylacetylide with 0.5 mole of redistilled cyclohexanone and 1.5 l. of liquid ammonia there was obtained 12 g. of recovered cyclohexanone and 31 g. (52% yield, 40% conversion) of 1-vinylethinylcyclohexanol, b.p. 83–87° (3 mm.), n^{20}_{D} 1.5145 (lit.[2] b.p. 84–85° (2 mm.), n^{20}_{D} 1.5169).

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(1) W. H. Carothers and R. A. Jacobson, THIS JOURNAL, **55**, 1097 (1933).

(2) R. A. Jacobson and W. H. Carothers, *ibid.*, **55**, 1622 (1933).

(3) I. M. Heilbron, E. R. H. Jones and B. C. L. Weedon, *J. Chem. Soc.*, 140 (1944).

(4) Vinylacetylene is available from E. I. du Pont de Nemours and Company, Inc., as a 50% solution in xylene, and is shipped in cylinders of approximately one quart. The manufacturer states that the solution in unopened cylinders is relatively stable for approximately one month at ordinary room temperatures but that it is a very dangerous material to handle.

(5) T. H. Vaughan, R. R. Vogt and J. A. Nieuwland, THIS JOURNAL, **56**, 2120 (1934).

(6) I. N. Nazarov and A. N. Elizarova, *Bull. acad. sci. U.R.S.S., Classe sci. chim.*, 189 (1940); *C.A.*, **36**, 742 (1942).

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Dimethoxyindanyl and -indenyl Derivatives[1,2]

BY E. C. HORNING AND G. N. WALKER[3]

RECEIVED JULY 15, 1943

During the course of a study of colchicine and its degradation products we became interested in reactions of methoxyindenes as a class of compounds containing a bicyclic ring system in which the A-ring contained methoxyl groups. A number of products were obtained in reactions designed to introduce various side-chains into the 6,7-dimethoxy-3-indenyl nucleus.

Condensation of ketone I with ethyl cyanoacetate gave an indanylidene cyanoacetate (II). The position of the double bond as illustrated was expected by analogy with 1-indanylidene cyanoacetate, the product of reaction of 1-indanone with ethyl cyanoacetate,[4] and was confirmed by the ultraviolet spectrum of II. Absorption at 343 mμ was in agreement with structure II rather than that of an indenyl derivative. Compound II was methylated in the presence of sodium amide, and the product was hydrolyzed (alkali) and decarboxylated. A nitrile was obtained which had an ultraviolet spectrum consistent with an indene structure IV (maximum of principal peak, 311 mμ).

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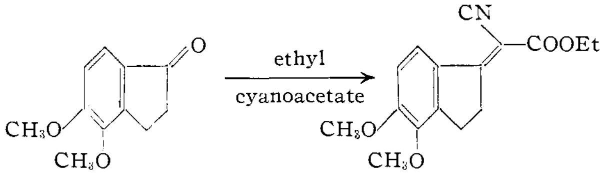
(1) Supported in part by a grant-in-aid from the American Cancer Society, recommended by the Committee on Growth of the National Research Council.

(2) Taken from the Ph.D. thesis of G. N. Walker, University of Pennsylvania, 1951.

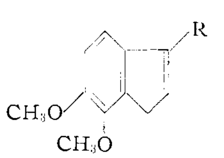
(3) American Cancer Society Predoctoral Assistant, 1949–1950; du Pont Predoctoral Fellow, 1950–1951.

(4) A. C. Cope and L. Field, THIS JOURNAL, **71**, 1589 (1949).

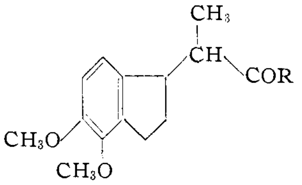
Cope and Field[4] demonstrated rigorously that methylation of 1-indanylidene cyanoacetate is accompanied by a shift of the double bond from the exocyclic position to a position within the five-membered ring. Alkaline hydrolysis and decarboxylation of II also led to a nitrile, formulated as III, which, like IV, resisted further hydrolysis.



I II



III, R = CH_2CN
IV, R = $CH(CH_3)CN$
V, R = CH_2COOEt
VI, R = $CH(CH_3)COOEt$



VII, R = OEt
VIII, R = $NHNH_2$

Reformatsky reaction of I with ethyl bromoacetate and with ethyl α-bromopropionate occurred smoothly to give, after dehydration of the initial products, esters to which structures V and VI, respectively, are assigned. Hydrolysis of VI furnished the corresponding acid, in which the ultraviolet spectrum again indicated the presence of an indene ring (λ_{max} 300 mμ). Attempts to prepare derivatives such as acid chlorides and acid hydrazides from V and VI were not successful.

Hydrogenation of the indene, VI, in the presence of a palladium–carbon catalyst, proceeded smoothly. The product, VII, was converted to the acid hydrazide, VIII. Efforts to transform this compound to an amine by the Curtius route were not successful.

Experimental[5]

4,5-Dimethoxyindanone-1 was prepared by the cyclization of the acid chloride from β-(2,3-dimethoxyphenyl)-propionic acid with stannic chloride in benzene. The ketone was distilled (b.p. 160–161° (2 mm.)) and recrystallized from ether (m.p. 74–75°; reported[6] m.p. 82°).

The dark red **2,4-dinitrophenylhydrazone** was recrystallized from benzene; m.p. 256–257°.

Anal. Calcd. for $C_{17}H_{16}O_6N_4$: C, 54.84; H, 4.33. Found: C, 54.74; H, 4.32.

Ethyl 4,5-Dimethoxy-1-indanylidene Cyanoacetate.—The condensation of 4,5-dimethoxy-1-indanone (9.0 g.) with ethyl cyanoacetate (6.4 g.) was carried out according to the general method of Cope[4,7] using 11 ml. of benzene, 0.8 g. of ammonium acetate and 2.5 g. of acetic acid, with a five-hour reflux period. Trituration of the crude product with methanol gave 11.0 g. (81%) of material, m.p. 132–135°. A colorless analytical sample, m.p. 135.5–137°, was obtained from methanol.

Anal. Calcd. for $C_{16}H_{17}O_4N$: C, 66.88; H, 5.97. Found: C, 66.94; H, 5.88.

The ultraviolet absorption spectrum, measured in ethanol, had peaks at 254 mμ (log ε 4.31) and 343 mμ (log ε 4.63) with minima at 230 mμ and 278 mμ.

An attempt to esterify the cyanoester by long refluxing in methanol saturated with hydrogen chloride resulted in recovery of the material.

6,7-Dimethoxy-3-indenylacetonitrile.—A solution of 1.5 g. of 4,5-dimethoxy-1-indanylidenecyanoacetate and 1.0 g. of sodium hydroxide in 5 ml. of water and 20 ml. of ethanol was refluxed for 2 hours. Sulfuric acid was added to the cooled solution, and the mixture was refluxed for a half-hour. Extraction with benzene and isolation of the neutral product gave crystals which were triturated with ether and recrystallized from methanol; pale yellow needles, m.p. 185–186.5°.

Anal. Calcd. for $C_{13}H_{13}O_2N$: C, 72.54; H, 6.09. Found: C, 72.17; H, 6.09.

α-(6,7-Dimethoxy-3-indenyl)-propionitrile. A. Alkylation.—An 11.0-g. sample of ethyl 4,5-dimethoxy-1-indanylidenecyanoacetate was alkylated (sodium amide method) with methyl iodide. From 9.2 g. of crude neutral product there was obtained by distillation 3.6 g. of red oil, b.p. 160–183° (0.07 mm.) with partial decomposition. **B. Hydrolysis.**—The alkylation product was refluxed with 35 ml. of methanol saturated with hydrogen chloride for 2 hours. The neutral product, after isolation, was refluxed with 2.1 g. of sodium hydroxide in 14 ml. of water and 25 ml. of ethanol for 2 hours. The solution was acidified with sulfuric acid and refluxed for another hour. The neutral product was isolated and recrystallized from methanol as pale yellow needles, m.p. 156–158°.

Anal. Calcd. for $C_{14}H_{15}O_2N$: C, 73.34; H, 6.60. Found: C, 73.32; H, 6.71.

The ultraviolet spectrum of this nitrile (ethanol) had peaks at 243 mμ (log ε 4.20) and 311 mμ (log ε 4.25).

Ethyl 6,7-Dimethoxy-3-indenylacetate.—A Reformatsky reaction was carried out with a mixture of 40 g. of activated 30-mesh zinc, 11.7 g. of 4,5-dimethoxyindanone-1, 26 g. of ethyl bromoacetate and 200 ml. of dry benzene. The crude neutral product in ether–benzene was treated with 4.3 g. of phosphorus oxychloride and allowed to stand for 1 hour. It was washed with sodium bicarbonate solution and was dried over magnesium sulfate. The solvents were evaporated, and the residue was distilled *in vacuo*. The product was a pale yellow oil, b.p. 188–193° (4 mm.); yield 10.9 g. (68%).

Anal. Calcd. for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92. Found: C, 68.47; H, 6.90.

α-(6,7-Dimethoxy-3-indenyl)-propionic Acid.—A Reformatsky reaction using 50 g. of zinc, 20.4 g. of 4,5-dimethoxyindanone-1, 30 g. of ethyl α-bromopropionate and 150 ml. of dry benzene, followed by dehydration with 6.5 g. of phosphorus oxychloride, gave 20.6 g. (71%) of ethyl **α-(6,7-dimethoxy-3-indenyl)-propionate**, b.p. 183–194° (2.3 mm.).

Hydrolysis of 10.3 g. of this material was carried out by refluxing it with 17 g. of potassium hydroxide in 70 ml. of ethanol and 30 ml. of water for 2 hours. The cooled solution was diluted, washed with benzene and acidified. The oil which separated was extracted with ether. Evaporation of the washed and dried ether extract and trituration of the residue with methanol gave 6.0 g. of crystalline acid. Further recrystallization (benzene) led to very pale yellow needles, m.p. 218–219° (dec.).

Anal. Calcd. for $C_{14}H_{16}O_4$: C, 67.72; H, 6.50. Found: C, 67.53; H, 6.26.

The ultraviolet absorption spectrum of the acid (ethanol) had peaks at 224 mμ (log ε 4.10), 238 mμ (log ε 4.10) and 300 mμ (log ε 4.35).

α-(4,5-Dimethoxy-1-indanyl)-propiohydrazide. A. Hydrogenation.—A solution of 20.6 g. of distilled ethyl α-(6,7-dimethoxy-3-indenyl)-propionate in 150 ml. of ethyl acetate containing 2.0 g. of 5% palladium–carbon catalyst was shaken under hydrogen (40 lb.) at room temperature. Hydrogen was absorbed very rapidly. The solution was filtered, and the solvent was evaporated. There remained 20.8 g. of colorless oil.

B. Reaction with Hydrazine.—A mixture of 6.5 g. of crude ester from (A) and 25 ml. of hydrazine was kept at 100° for seven days. Upon cooling the mixture, crystallization occurred. The crystals were washed with water and ether and were air-dried (1.3 g.). Recrystallization from methanol or benzene gave colorless flakes, m.p. 154–156°.

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(5) Melting points are corrected.

(6) W. H. Perkin and R. Robinson, *J. Chem. Soc.*, **105**, 2387 (1914).

(7) A. C. Cope, C. M. Hoffman, C. Wyckoff and E. Hardenbergh, This Journal, **63**, 3452 (1941).

Anal. Calcd. for $C_{14}H_{20}O_3N_2$: C, 63.61; H, 7.63. Found: C, 63.46; H, 7.68.

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p-[(2-Amino-4-hydroxy-6-pteridylmethyl)-*p*'-nitrobenzenesulfonylamino]-benzoic Acid and Intermediates

BY BARNEY J. MAGERLEIN AND DAVID I. WEISBLAT

RECEIVED DECEMBER 9, 1953

Recently the synthesis of pteroylglutamic acid was described in which the amino group of the *p*-aminobenzoylglutamic portion was protected by a tosyl group until after the formation of the pteridine nucleus.[1] This note describes the synthesis of crystalline *p*-[(2-amino-4-hydroxy-6-pteridylmethyl)-*p*'-nitrobenzenesulfonylamino]-benzoic acid (VII) and its glutamic acid analog VIIa (Chart I). The *p*-nitrobenzenesulfonyl derivatives are in most cases more readily crystallized than are the tosyl derivatives. This was noted particularly in the preparation of IVa and VII, both of which readily crystallized, although their tosyl counterparts failed to do so. The pteroic acid derivative VII showed 3–8% of folic acid-like activity when assayed with the test organism *S. faecalis* R. Removal of the *p*-nitrobenzenesulfonyl group of VII with 30% hydrogen bromide in acetic acid in the presence of phenol[2] gave a good yield of pteroic acid.

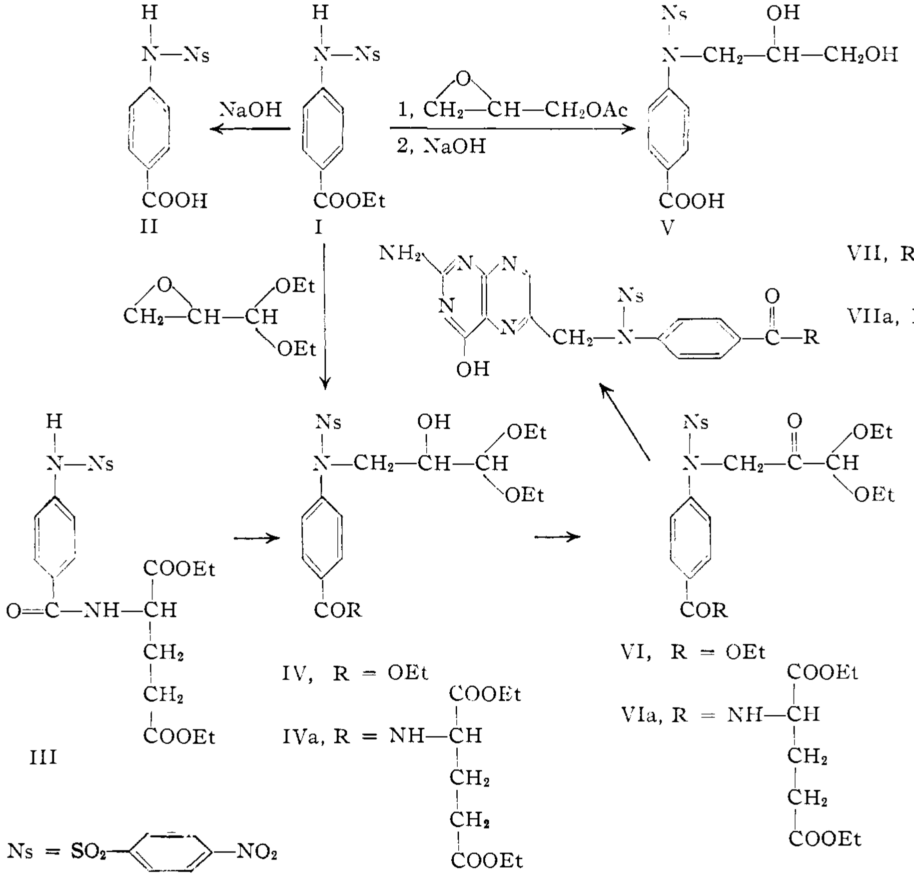

CHART I

Acknowledgment.—The authors are indebted to Mr. L. Stubberfield and Mr. E. Stapert for the microbiological assays; to Dr. G. Pish and Mr. L. Scholten for the ultraviolet absorption data; to Mr. W. A. Struck and associates for the microanalyses; and to G. Staffen for technical assistance.

Experimental

Ethyl N-*p*'-Nitrobenzenesulfonyl-*p*-aminobenzoate (I).—One hundred grams of *p*-nitrobenzenesulfonyl chloride was added to 71 g. of ethyl *p*-aminobenzoate dissolved in 202 ml. of 2,4-lutidine at such a rate that the temperature did not exceed 80°. The solution was heated at 80° for 45 minutes and poured with stirring onto 600 ml. of ice and water. The crude product was collected by filtration, washed, and dried. It weighed 155 g. Recrystallization from 500 ml. of Cellosolve gave 103 g. (68.2% yield), m.p. 187–189°. After several more recrystallizations from Cellosolve and from ethanol it melted at 194–195°.

Anal. Calcd. for $C_{15}H_{14}N_2O_6S$: C, 51.42; H, 4.03; N, 8.00; S, 9.15. Found: C, 51.60, 51.72; H, 4.27, 4.35; N, 8.21, 8.20; S, 9.28, 9.52.

N-*p*'-Nitrobenzenesulfonyl-*p*-aminobenzoic Acid (II).—A solution of 3.5 g. of ethyl N-*p*'-nitrobenzenesulfonyl-*p*-aminobenzoate (I) in 30 ml. of 95% ethanol and 10 ml. of 10% sodium hydroxide was heated under reflux for 0.5 hour. The alcohol was distilled under vacuum. The residue was diluted with 50 ml. of water, acidified and filtered to give 2.84 g. (92.5% yield) of II, m.p. 249–256° dec. Two re-

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[1] D. I. Weisblat, B. J. Magerlein, D. R. Myers, A. R. Hanze, E. I. Fairburn and S. T. Rolfson, THIS JOURNAL, **75**, 5893 (1953).

[2] D. I. Weisblat, B. J. Magerlein and D. R. Myers, *ibid.*, **75**, 3630 (1953).