sulted in the formation of the amide of 2-N-methylpyrroleacetic acid.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.83; H, 7.29; N, 20.27. Found: C, 61.14; H, 6.85; N, 20.24.

Hydrolysis of 1.5 g. of the nitrile with 20 ml. of 80% ethanol containing 3 g. of sodium hydroxide gave a quantitative yield of 2-N-methylpyrroleacetic acid, m.p. 113° after recrystallization from ligroin. It did not depress the m.p. of an authentic sample.[8]

(B) 2-N-Phenylpyrroleacetonitrile.—Alkylation of 12.5 g. of sodium cyanide with 20 g. of the methiodide of II in 125 ml. of water yielded 6.1 g. (57%) of colorless liquid, b.p. 115° (0.5 mm.), $n^{25}D$ 1.5822, which decomposed slowly at room temperature.

Anal. Calcd. for $C_{12}H_{10}N_2$: C, 79.09; H, 5.53; N, 15.41. Found: C, 79.46; N, 5.22; N, 15.48.

Hydrolysis gave a quantitative yield of 2-N-phenylpyrroleacetic acid. The light tan crystals melted at 113° after three recrystallizations from benzene–ligroin.

Anal. Calcd. for $C_{12}H_{11}NO_2$: C, 71.63; H, 5.24. Found: C, 71.70; H, 5.41.

(C) Diethyl (2-N-Methylpyrrolemethyl)-malonate.—A mixture of 64 g. of malonic ester in which had been dissolved 1.84 g. of sodium and 24 g. of the methiodide of I was heated with stirring at 120° for 14 hours in a nitrogen atmosphere until the evolution of basic gases had ceased completely. Water was added to the dark solution and the mixture extracted with ether. The dried ether extract was distilled *in vacuo*, approximately 10 g. of material being collected at 120–140° (1 mm.). Redistillation yielded 6.8 g. (31%) of ester, b.p. 132–138° (1 mm.), $n^{20}D$ 1.4818. It decomposed slowly at room temperature.

Anal. Calcd. for $C_{13}H_{19}NO_4$: C, 61.64; H, 7.56. Found: C, 61.27; H, 7.14.

The diamide was prepared by allowing 0.5 g. of the ester to stand with 10 ml. of ammonium hydroxide solutions. White needles separated after a few days, m.p. 215° (dec.) from water.

Anal. Calcd. for $C_9H_{13}N_3O_2$: N, 21.53. Found: N, 21.45.

Hydrolysis of the malonate with aqueous alcoholic potassium hydroxide solution gave reddish viscous material from which a small amount of beige needles, m.p. 144° (dec.), could be isolated by extraction with benzene. This compound decomposed before it could be analyzed.

Attempts to alkylate ethyl cyanoacetamidoacetate resulted in highly colored tarry fractions which could not be purified satisfactorily.

(D) Ethyl (2-N-Methylpyrrolemethyl)-cyanoacetate.—From 22.6 g. of ethyl cyanoacetate containing 0.92 g. of sodium and 12 g. of methiodide there was obtained 2.3 g. (26%) of condensation product, b.p. 130–135° (1 mm.), $n^{20}D$ 1.5048.

Anal. Calcd. for $C_{11}H_{14}N_2O_2$: C, 64.06; H, 6.84. Found: C, 64.25; H, 6.80.

(E) Diethyl (2-N-Phenylpyrrolemethyl)-malonate.—Alkylation of 42.5 g. of malonic ester containing 1.2 g. of sodium with 17.1 g. of the methiodide of II in the usual manner gave 10.1 g. (65%) of ester, b.p. 155–156° (0.5 mm.), $n^{20}D$ 1.5271.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.54; H, 6.71. Found: C, 68.34; H, 6.84.

Hydrolysis of the ester with aqueous alcoholic alkali gave a viscous oil which solidified after prolonged rubbing. Recrystallization from ethyl acetate–petroleum ether resulted in a slightly colored amorphous solid which melted at 115–116° with decomposition. Analysis showed this to be (2-N-phenylpyrrolemethyl)-malonic acid.

Anal. Calcd. for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05. Found: C, 65.16; H, 4.98.

TALLAHASSEE, FLORIDA RECEIVED MARCH 15, 1951

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE FLORIDA STATE UNIVERSITY]

Synthesis of 2,4,8-Trimethylazulene

BY WERNER HERZ

2,4,8-Trimethylazulene has been synthesized. It does not appear to be identical with pyrethazulene.

In 1941 Schechter and Haller[1] obtained a blue azulene by zinc dust distillation of pyrethrosin[2] which had the formula $C_{13}H_{14}$ and did not appear to be identical with any azulene then known. Oxidative degradation of its trinitrobenzolate with potassium permanganate yielded only acetic acid, a result which was taken to indicate the presence of three methyl groups on the azulene nucleus. On the basis of the ultraviolet spectrum which resembled that of vetivazulene[3] (2-isopropyl-4,8-dimethylazulene), Schechter and Haller suggested 2,4,8-trimethylazulene as a possible structure for pyrethazulene.

In the light of present-day knowledge concerning the relationship between color and constitution in the azulene series,[4] the presence of a 2-methyl group in a trisubstituted *blue* azulene is not very likely. Like vetivazulene, 2,4,8-trimethylazulene might be expected to show a *violet* coloration. Moreover, the similarity of ultraviolet spectra adduced as an argument for the structural resemblance of vetivazulene and pyrethazulene has recently been shown to be of lesser importance in the identification of azulenes than visual absorption data.[5]

The synthesis of 2,4,8-trimethylazulene and the comparison of its physical properties with pyrethazulene therefore appeared to be of interest.[6] The accompanying flow sheet illustrates the method used for the synthesis of the desired azulene. Reaction of 2,4,7-trimethylindan, prepared by conventional methods, with diazoacetic ester in the manner first employed by Pfau and Plattner[7] for the synthesis of vetivazulene yielded a highly colored ester which after hydrolysis was simultaneously dehydrogenated and decarboxylated with palladium–charcoal. The crude azulene was converted to the trinitrobenzene complex, liberated by chromatographic adsorption and distilled. Thus purified, the *violet* 2,4,8-trimethylazulene boiled at

(1) M. S. Schechter and H. L. Haller, THIS JOURNAL, **63**, 3507 (1941).

(2) W. G. Rose and H. L. Haller, *J. Org. Chem.*, **2**, 484 (1937); M. S. Schechter and H. L. Haller, THIS JOURNAL, **61**, 1607 (1939).

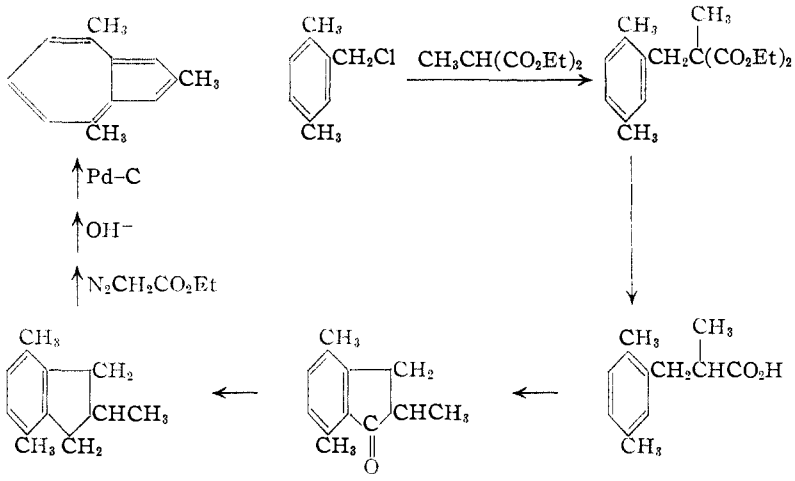
(3) B. Susz, A. St. Pfau and Pl. A. Plattner, *Helv. Chim. Acta*, **20**, 469 (1937).

(4) Pl. A. Plattner, *ibid.*, **24**, 283E (1941); A. J. Haagen-Smit, "Fortschritte der Chemie organischer Naturstoffe," Vol. 5, Springer Verlag, Vienna, 1948, p. 40.

(5) Pl. A. Plattner and E. Heilbronner, *Helv. Chim. Acta*, **31**, 804 (1948).

(6) In the article by Schechter and Haller[1] announcement was made of the contemplated synthesis of 2,4,8-trimethylazulene. However, no work bearing on this problem has been published in the interim.

(7) A. St. Pfau and Pl. A. Plattner, *ibid.*, **22**, 202 (1939).



110–115° (1.5 mm.). Its trinitrobenzolate melted at 177–178° and its picrate at 156.5°, whereas the trinitrobenzolate of pyrethazulene reportedly melts at 167–168°. Although the discrepancy in melting points might conceivably be due to impurities contaminating pyrethazulene, the difference in color supports the belief that pyrethazulene and 2,4,8-trimethylazulene are not identical.

The ultraviolet spectrum of 2,4,8-trimethylazulene, reproduced in Fig. 1, shows maxima at 248, 280, 288, 309, 335 and 349 mμ. As expected these values coincide, within the limits of experimental error, with the maxima in the spectrum of vetivazulene[3] (290, 308, 336 and 350 mμ), but neither are they significantly different from the maxima exhibited by pyrethazulene (284, 305, 330 and 347 mμ). In the visible region, bands at 465, 545 and 592 mμ were noted; these values coincide with certain strong bands (544, 587 mμ) in the visible spectrum of vetivazulene.[4]

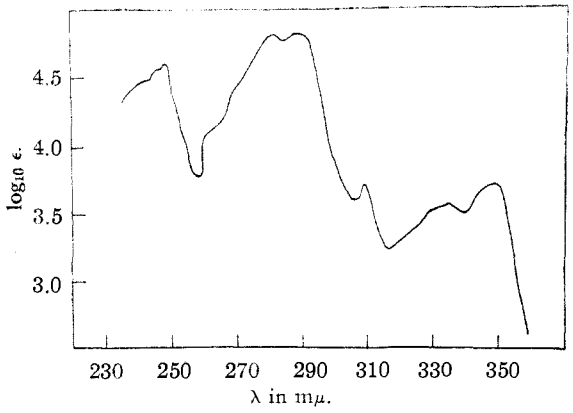


Fig. 1.—Ultraviolet absorption spectrum of 2,4,8-trimethylazulene.

Acknowledgment.—This work was supported in part by a grant from the Research Council of the Florida State University.

Experimental[8]

α-Methyl-β-(2,5-dimethylphenyl)-propionic Acid.—To a dispersion of 24 g. of sodium in 450 ml. of dry xylene was slowly added 184 g. of diethyl methylmalonate. The mixture was refluxed until the sodium had dissolved completely and 160 g. of 2,5-dimethylchloromethylbenzene[9] was added dropwise. After ten hours at reflux the mixture was acidified with acetic acid, diluted with water and extracted with ether. The dried ether layers were distilled at reduced pressure. After a forerun of methylmalonic ester (31 g.), 165 g. (59% based on malonate actually consumed) of crude ester was collected at 105–145° (1.5 mm.). This material was hydrolyzed without further purification by refluxing overnight with 85 g. of potassium hydroxide, 85 g. of water and 270 g. of ethanol. Water was added, the alcohol was removed by distillation, the residue was extracted with ether and acidified. The oil which separated crystallized on cooling. It was filtered, dried and decarboxylated by distillation at reduced pressure. A total of 102 g. of acid (99%) was obtained. Two recrystallizations from petroleum ether gave the analytical sample, m.p. 63°.

Anal.[10] Calcd. for $C_{12}H_{16}O_2$: C, 74.98; H, 8.39. Found: C, 74.71; H, 8.23.

The anilide was prepared from the acid chloride and recrystallized several times from ethanol–water, m.p. 104–104.5°.

Anal. Calcd. for $C_{18}H_{21}NO_2$: N, 4.94. Found: N, 5.21.

2,4,7-Trimethylindanone.—To 100 g. of the acid was added cautiously 110 g. of thionyl chloride. The mixture was heated on the steam-bath for one hour and distilled at reduced pressure, 104 g. of the acid chloride being collected at 100–102° (2 mm.). The acid chloride was cyclized by slow addition to 70 g. of aluminum chloride in 150 ml. of thiophene-free benzene. After five hours at room temperature, the mixture was poured over ice–hydrochloric acid, the organic layer was separated, washed successively with dilute acid, water, dilute base, water and dried. Distillation yielded 75 g. (80%) of trimethylindanone boiling at 92–98° (1.5 mm.). The analytical sample boiled at 90–91° (1 mm.), $n^{20}D$ 1.5510.

Anal. Calcd. for $C_{12}H_{14}O$: C, 82.78; H, 8.10. Found: C, 82.53; H, 7.93.

The dinitrophenylhydrazone was recrystallized from benzene and melted at 212.5°.

Anal. Calcd. for $C_{18}H_{18}N_4O_4$: N, 15.85. Found: N, 15.91.

2,4,7-Trimethylindan.—Two hundred grams of freshly cleaned mossy zinc was amalgamated and refluxed for 18 hours with 80 g. of the indanone, 250 g. of concentrated hydrochloric acid and 100 ml. of water. Three 100-ml. portions of hydrochloric acid were added at five-hour intervals. The cold mixture was diluted with water and extracted with ether. The washed and dried ether solution yielded 69 g. of 2,4,7-trimethylindan, b.p. 76–79° (2.5 mm.). The analytical sample boiled in the same range, $n^{20}D$ 1.5228.

Anal. Calcd. for $C_{12}H_{16}$: C, 89.97; H, 10.08. Found: C, 90.16; H, 10.09.

2,4,8-Trimethylazulene.—In a flask fitted with reflux condenser and immersed in an oil-bath 50.5 g. of the indan was heated to 130°. Ten grams of ethyl diazoacetate was added dropwise and the temperature was raised gradually to 165°. After two hours the mixture was fractionated at reduced pressure. The fraction boiling above 120° (3 mm.) was allowed to remain in the distilling flask and the recovered trimethylindan (44.5 g.) was again subjected to the reaction with diazoacetic ester. After five such runs there was obtained 23.5 g. of unreacted indanone and 37 g. of a red viscous liquid boiling in the range 120–160° (2.5 mm.).

The dark red oil was dissolved in 150 ml. of ethanol and 40 ml. of water and saponified with 20 g. of potassium hydroxide. Water was added, the alcohol was removed by distillation, unsaponified material (1.7 g.) was extracted with ether, the aqueous layer was acidified and the green oil

(8) Melting points are uncorrected.

(9) J. V. Braun and J. Nelles, *Ber.*, **67**, 1094 (1934).

(10) Analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

was extracted with ether. Distillation of the dried ether extracts yielded 4 g. of forerun (b.p. up to 165° at 3 mm.) and 15.5 g. of a dark green viscous oil boiling at 165–170° (3 mm.).

The product was transferred to a small distilling flask, mixed with 2 g. of 10% palladium–charcoal and slowly distilled over an open flame. The violet distillate was redistilled using a modified Claisen flask. Fraction 1, wt. 2.8 g., b.p. up to 105° (1.5 mm.), was fairly mobile; fraction 2, wt. 3.1 g., deeply colored and more viscous, boiled in the range 105–140° (1.5 mm.). The higher-boiling material could be used for a second dehydrogenation.

Fraction 2 was dissolved in 20 ml. of ethanol and treated with 4 g. of trinitrobenzene in 125 ml. of warm ethanol. The purple trinitrobenzolate separated immediately and weighed 4.1 g. The derivative was dissolved in a minimum of hexane–benzene (2:1) and decomposed by chromatography over alumina. The violet eluate was concentrated and distilled, the fraction boiling at 110–115° (1.5 mm.) being collected. This material, wt. 1.55 g., was used for absorption spectra and for the preparation of the derivatives described below. On prolonged chilling, it crystallized and remelted at 29°.

The trinitrobenzolate, purplish-black needles from absolute ethanol, melted at 177–178°.

Anal. Calcd. for $C_{19}H_{17}N_3O_8$: C, 59.53; H, 4.47; N, 10.96. Found: C, 59.48; H, 4.43; N, 10.87.

The picrate, reddish-black needles from absolute ethanol, melted at 156.5°.

Anal. Calcd. for $C_{19}H_{17}N_3O_7$: C, 57.15; H, 4.29; N, 10.52. Found: C, 56.75; H, 4.36; N, 10.31.

The ultraviolet spectrum of the redistilled azulene in *n*-pentane solution was determined on a Beckman model DU spectrophotometer and is reproduced in Fig. 1.

TALLAHASSEE, FLORIDA RECEIVED APRIL 14, 1951

[CONTRIBUTION FROM THE ORGANIC CHEMICAL LABORATORIES, STANFORD UNIVERSITY]

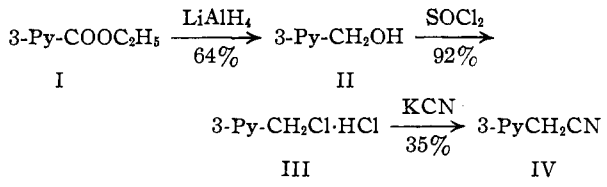
Heterocyclic Basic Compounds. XIV. 4-Phenyl-4-(3-pyridyl)-6-dimethylamino-3-hexanone[1]

BY HARRY S. MOSHER AND JOHN E. TESSIERI[2]

Panizzon[3,4] has condensed 2- and 4-halopyridines with phenylacetonitrile in the presence of sodium amide but did not extend the reaction to the 3-isomer, presumably because of the well-recognized aromatic nature of the 3-position in the pyridine ring. It has been found, however, that 3-bromopyridine is readily converted into α-phenyl-α-(3-pyridyl)-acetonitrile by this reaction. This was converted to 4-phenyl-4-(3-pyridyl)-6-dimethylamino-3-hexanone which is related to the analgesic of the amidone type. In these studies the lithium aluminum hydride reduction of various pyridine esters to the corresponding carbinols was also studied as well as the conversion of 3-pyridylcarbinol to 3-chloromethylpyridine and 3-cyanomethylpyridine.

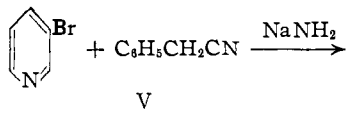
The original plan of this investigation was to prepare pyridine analogs of the analgesic methadone by reactions analogous to those used in its well-known synthesis[5] with the substitution of a cyanomethylpyridine for phenylacetonitrile. None of the three isomeric pyridylacetonitriles has been previously reported.

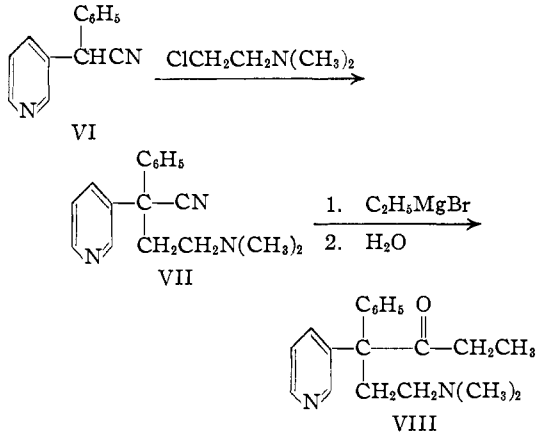
The 3-isomer was made *via* 3-pyridylcarbinol according to the equations



Although the 3-cyanomethyl-pyridine could be brominated successfully, attempted Friedel–Crafts reactions with benzene were uniformly unsuccessful and it was necessary to abandon this approach.

An alternate route, the first step of which has been studied by Panizzon[3,4] for the 2- and 4-isomers, is illustrated by





Apparently this first reaction was not considered feasible for the β-isomer. In spite of the well-recognized aromatic nature of the β-position of the pyridine ring several reactions indicate that 3-bromopyridine is considerably more reactive than bromobenzene.[6] For this reason the reaction of 3-bromopyridine with phenylacetonitrile in the presence of sodium amide was attempted. The reaction was successful and gave the desired product VI in 36% yield. This indicates the activation of the β-position of the pyridine nucleus by the inductive effect of the ring nitrogen atom is greater than generally considered.

The α-phenyl-α-(3-pyridyl)-acetonitrile (VI) was converted to 4-phenyl-4-(3-pyridyl)-6-dimethylamino-3-hexanone (VIII), which is related structurally to the analgesic amidone, by successive

(1) Abstracted from the Ph.D. thesis submitted by J. E. T. to Stanford University in partial fulfillment of the requirements for the Ph.D. degree.

(2) Parke Davis and Co. Research Fellow, 1949.

(3) L. Panizzon, *Helv. Chim. Acta*, **27**, 1748 (1944); **29**, 324 (1946); British Patent 589,625 (June 25, 1947).

(4) M. Hartmann and L. Panizzon, U. S. Patent 2,507,631 (May 26, 1950).

(5) Office of the Publication Board, Report 981 (1945), pp. 94–96.

(6) R. C. Elderfield, "Heterocyclic Compounds," John Wiley and Sons, Inc., New York, N. Y., 1950, Vol. I, p. 517.