Notes

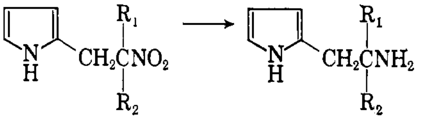
Pyrroles. XV. Some New Alkylations by Means of Pyrrole Mannich Bases[1]

Werner Herz and Ulrich Toggweiler

Department of Chemistry, The Florida State University, Tallahassee, Florida

Received July 22, 1963

In order to extend the methods available for the preparation of pyrrolealkylamines, a study of the alkylation[2] of various nitro compounds by the pyrrole Mannich base[3] was undertaken. Reaction of the sodium salts of nitroethane, 1- and 2-nitropropane, nitrocyclohexane, and ethyl 2-nitropropionate with 2-dimethylaminomethylpyrrole by quaternization *in situ* furnished the 2-pyrrolemethyl-substituted nitro derivatives (I) in yields ranging from 23–51%. Alkylations of nitromethane and ethyl nitroacetate were not successful. Catalytic hydrogenation of the condensation products by a special method (see Experimental) resulted in formation of the desired amines.

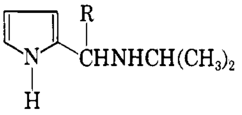


I II

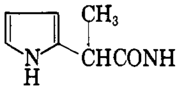
For mechanistic studies of the alkylation reaction we envisaged the synthesis and resolution of Mannich bases carrying a substituent on the carbon atom adjacent to the pyrrole nucleus.[4] Since such bases are not conveniently available from pyrrole by the Mannich reaction,[6] recourse was had to a method involving addition of the substrate to an aldimine.[7,8] In this manner, pyrrole and ethylideneisopropylamine or, more directly, pyrrole, acetaldehyde, and isopropylamine gave the base IIIa in 52% yield. IIIb was formed analogously from pyrrole and benzylideneisopropylamine.

Attempts to quaternize IIIa failed[9] and it was, therefore, necessary to carry out the alkylations with the base itself (elimination–addition conditions), although it has been shown previously[1] that yields in the pyrrole series are much improved when the base is quaternized (substitution conditions). Because of the prolonged time required for completion of the reaction, alkylation of cyanide resulted in formation of the amide (IV, 32%) rather than the nitrile. Similarly, only the lactam V was formed by reaction of IIIa with diethylacetamidomalonate in xylene (*cf.* ref. 3).

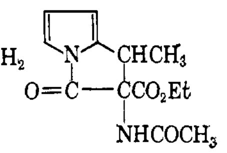
To circumvent this difficulty, the Mannich bases VIa and VIb were prepared from 2,5-dimethylpyrrole and the appropriate aldimine. Reaction of VIa with cyanide ion gave a mixture of the desired nitrile VII (19%) and the corresponding acid (27%). Alkylation of diethyl acetamidomalonate with VIb furnished 60% of the expected product VIII.



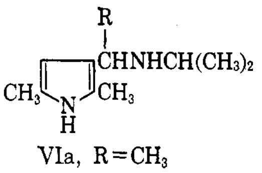
IIIa, R = CH_3
b, R = phenyl



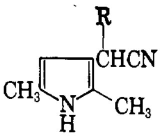
IV



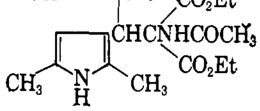
V



VIa, R = CH_3
b, R = phenyl



VII



VIII

Experimental[10]

1-(2-Pyrrole)-2-nitrobutane (Ia, R_1 = Ethyl; R_2 = H).—Sodium (4.9 g., 0.21 g.-atom) was added to 250 ml. of absolute ethanol in a flask fitted with stirrer, condenser, drying tube, dropping funnel, and nitrogen inlet. A mixture of 32.4 g. (0.36 mole) of 1-nitropropane and 22.5 g. (0.18 mole) of dimethylaminomethylpyrrole was added followed by 36.5 g. (0.29 mole) of dimethyl sulfate over a period of 30 min. The temperature was not allowed to rise above 35° and stirring was continued until the evolution of trimethylamine (flushed out by nitrogen) had ceased. The solvent was removed at reduced pressure, the residue poured into ice–water and extracted with ether or methylene chloride. The organic extracts were washed, dried, and distilled to yield 14.5 g. (48%), b.p. 102–103° (0.4 mm.), $n^{22}D$ 1.509. The product and its homologs exhibited a tendency to decompose on standing.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.64. Found: C, 57.81; H, 7.38; N, 16.30.

1-(2-Pyrrole)-2-nitropropane (Ib, R_1 = CH_3; R_2 = H).—Reaction of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 27 g. (0.36 mole) of nitroethane in the manner described in the preceding paragraph furnished 8.9 g. (32%) of product, b.p. 97–99° (0.5 mm.).

Anal. Calcd. for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.44; H, 6.82; N, 18.40.

2-(2-Pyrrolemethyl)-2-nitropropane (Ic, R_1 = R_2 = CH_3).—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 32.4 g. (0.36 mole) of 2-nitropropane gave 15.2 g. (51%) of product, b.p. 90–92° (0.6 mm.).

---

[1] Previous paper, W. Herz and R. L. Settine, *J. Org. Chem.*, **24**, 201 (1959). Supported in part by the Office of Ordnance Research, U. S. Army, under Contract DA-01-009-ORD-436.

[2] For a review of previously studied alkylations, see H. Hellmann and G. Opitz, "α-Aminoalkylierung," Verlag Chemie, Weinheim, 1960, pp. 285–287.

[3] W. Herz, K. Dittmer, and S. J. Cristol, *J. Am. Chem. Soc.*, **70**, 504 (1948).

[4] This work was begun in 1957 and was interrupted when similar studies using optically active indole derivatives were reported.[5]

[5] J. D. Albright and H. R. Snyder, *J. Am. Chem. Soc.*, **81**, 2239 (1959).

[6] U. Eisner, *J. Chem. Soc.*, 854 (1957).

[7] H. R. Snyder and D. S. Matteson, *J. Am. Chem. Soc.*, **79**, 2217 (1957).

[8] The intramolecular addition of a pyrrolaldimine to the pyrrole nucleus has since been reported: R. B. Woodward, *et al.*, *J. Am. Chem. Soc.*, **82**, 3800 (1960).

[9] For similar observations in the indole series, see ref. 5.

[10] Melting points and boiling points are uncorrected. Analyses by Dr. Weiler and Dr. Strauss, Oxford, England.

Anal. Calcd. for $C_8H_{12}N_2O_2$: C, 57.12; H, 7.19; N, 16.64. Found: C, 56.80; H, 7.48; N, 16.10.

2-(2-Pyrrolemethyl)-1-nitrocyclohexane [Id, $\mathbf{R_1} = \mathbf{R_2} = -(\mathbf{CH_2})_5-$].—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 43.5 g. (0.36 mole) of nitrocyclohexane in the usual manner gave 9.3 g. (25%) of the title compound, b.p. 129–131° (0.4 mm.).

Anal. Calcd. for $C_{11}H_{16}N_2O_2$: C, 63.40; H, 7.74; N, 13.45. Found: C, 62.95; H, 7.78; N, 13.70.

Ethyl 2-Nitro-2-(2-pyrrolemethyl)propionate (Ie, $\mathbf{R_1} = \mathbf{CH_3}$; $\mathbf{R_2}$ = Carbethoxy).—Condensation of 22.5 g. (0.18 mole) of 2-dimethylaminomethylpyrrole with 53 g. (0.36 mole) of ethyl 2-nitropropionate furnished 9.6 g. (23%) of product, b.p. 110–112° (0.3 mm.). This substance decomposed too rapidly for analysis and immediately was reduced to the amine.

1-(2-Pyrrole)-2-aminobutane (IIa).—A solution of 15 g. (0.9 mole) of Ia in 150 ml. of absolute ethanol was refluxed for 0.5 hr. with some Raney nickel, filtered, and reduced in a Parr hydrogenator with 0.2 g. of platinum oxide until hydrogen uptake ceased (when the Raney nickel treatment was omitted, the reduction did not proceed). After removal of solvent, the product was purified through the hydrochloride, regenerated by treatment with base, and distilled to yield 6.8 g. (70%), b.p. 81–82° (0.8 mm.).

Anal. Calcd. for $C_8H_{14}N_2$: C, 69.52; H, 10.21; N, 20.27. Found: C, 69.70; H, 10.10; N, 19.85.

1-(2-Pyrrole)-2-aminopropane (IIb).—Catalytic reduction of Ib in the same manner gave a 55% yield of IIb, b.p. 80–81° (1 mm.), which decomposed too rapidly for analysis; acetyl derivative, m.p. 93–93.5°; phenylthiourea derivative, m.p. 149–150°. The product was characterized as the acid succinate, m.p. 73–74°.

Anal. Calcd. for $C_{11}H_{18}N_2O_4$: C, 54.52; H, 7.49; N, 11.57. Found: C, 54.11; H, 7.68; N, 11.52.

2-(2-Pyrrolemethyl)-2-aminopropane (IIc).—Prepared from Ic in 73% yield, b.p. 79–79.5°, it decomposed too rapidly to permit analysis. It was characterized as the phenylthiourea derivative, m.p. 125.5–126.5°, and analyzed as the acid succinate, m.p. 145–146°.

Anal. Calcd. for $C_{12}H_{20}N_2O_4$: C, 56.24; H, 7.87; N, 10.93. Found: C, 56.25; H, 7.89; N, 10.90.

Ethyl 2-(2-pyrrolemethyl)-2-aminopropionate (IIe).—This substance, m.p. 72.5–73.5°, was obtained in 58% yield by catalytic reduction of Ie.

Anal. Calcd. for $C_{10}H_{16}N_2O_2$: C, 61.20; H, 8.22; N, 14.28. Found: C, 61.20; H, 8.00; N, 14.56.

2-(Isopropylaminoethylidene)pyrrole (IIIa).—To a solution of 20.2 g. (0.31 mole) of pyrrole in 150 ml. of acetic acid kept below 15° was added, in an atmosphere of nitrogen, 19.5 g. (0.33 mole) of isopropylamine and then over 1 hr. an ice-cold solution of 14 g. (0.32 mole) of acetaldehyde in 60 ml. of benzene. Stirring was continued for 3 hr. and the flask stored in a refrigerator for 3 days. The contents were poured into 500 ml. of ice water and 50 ml. of ether. The ether layer was separated and washed with sodium bisulfate. The combined aqueous layers were washed with ether and brought to pH 7 with 30% sodium hydroxide solution at a temperature not exceeding 20°. The material which precipitated was filtered and the filtrate made basic. The product was extracted with one 100-ml. and two 30-ml. portions of cyclohexane and the extract chilled in a Dry Ice–acetone bath. There precipitated 24 g. (52%) of IIIa, m.p. 49–51°. Sublimation furnished the analytical sample, m.p. 58–58.5°, whose picrate melted at 163–165° dec.

Anal. Calcd. for $C_9H_{16}N_2$: C, 71.00; H, 10.59; N, 18.42. Found: C, 70.85; H, 10.38; N, 18.55.

2-(2-Pyrrole)propionamide (IV).—A solution of 9.0 g. (0.06 mole) of IIIa and 11.7 g. of potassium cyanide in 900 ml. of 80% ethanol was refluxed with stirring for 130 hr. until the evolution of isopropylamine had ceased, concentrated to 70 ml. on the water pump, and extracted thoroughly with methylene chloride. The organic extracts were washed, dried, and evaporated; yield of amide was 2.5 g. (32%), m.p. 120.5–121°, after recrystallization from benzene and vacuum sublimation.

Anal. Calcd. for $C_7H_{10}N_2O$: C, 60.85; H, 7.30; N, 20.28. Found: C, 60.62; H, 7.49; N, 19.88.

The aqueous layer was acidified and extracted with methylene chloride. Purification of the acidic gum, presumably 2-(2-pyrrole)propionic acid, 4 g., by crystallization was unsuccessful; distillation resulted in decomposition.

Preparation of Lactam V.—A solution of 4.5 g. (0.03 mole) of 2-isopropylaminoethylidene pyrrole and 3 g. (0.014 mole) of diethyl acetamidomalonate in 50 ml. of xylene was heated at 90–95° with stirring for 55 hr. About 75% of the theoretical amount of isopropylamine was evolved. Cooling resulted in precipitation of 2.7 g. (51%) of lactam V, which was recrystallized from aqueous ethanol, m.p. 155–155.5°.

Anal. Calcd. for $C_{13}H_{16}N_2O_4$: C, 59.08; H, 6.10, N, 10.60. Found: C, 58.75; H, 6.24; N, 10.35.

2-Isopropylaminobenzylidene Pyrrole (IIIb).—To a solution of 7 g. (0.115 mole) of pyrrole in 75 ml. of benzene was added in a nitrogen atmosphere, with cooling and stirring, 25 ml. of acetic acid followed by 15 g. (0.105 mole) of benzylideneisopropylamine in 75 ml. of benzene. The reaction vessel was stored in the refrigerator overnight and the product worked up in the usual manner. It solidified on cooling, yielding 11.5 g. (58%), m.p. 50.5–51.5°, after crystallization from cycloheptane and vacuum sublimation.

Anal. Calcd. for $C_{14}H_{18}N_2$: C, 78.46; H, 8.46; N, 13.06. Found: C, 78.61; H, 8.50; N, 13.10.

When 10 g. (0.105 mole) of 2,5-dimethylpyrrole was substituted in the above preparation, Mannich base VIb was obtained in 60% yield, m.p. 91–92°, after crystallization from cycloheptane and sublimation.

Anal. Calcd. for $C_{16}H_{22}N_2$: C, 79.29; H, 9.14; N, 11.55. Found: C, 79.03; H, 9.14; N, 11.85.

Diethyl Phenyl-3-(2,5-dimethylpyrrole)methyl-α-acetamidomalonate (VIII).—Reaction of 2.2 g. of VIb with 2.1 g. (0.01 mole) of diethyl acetamidomalonate in boiling toluene for 18 hr. followed by removal of toluene furnished 2.0 g. (60%) of crude VIII, m.p. 179–182°. Two recrystallizations from ethanol raised the melting point to 191.5–192.5°.

Anal. Calcd. for $C_{22}H_{28}N_2O_5$: C, 65.98; H, 7.05; N, 7.00. Found: C, 65.66; H, 6.96; N, 7.35.

3-(Isopropylaminoethylidene)-2,5-dimethylpyrrole (VIa).—To a solution of 47.5 g. (0.5 mole) of 2,5-dimethylpyrrole in 60 ml. of acetic acid and 100 ml. of toluene–hexane (2:1) kept at 0–10° was added dropwise with stirring 43 g. (0.5 mole) of ethylideneisopropylamine. The temperature was then lowered to −10° which caused precipitation of the acetate of the Mannich base. This was filtered, washed with toluene, dissolved in water, and made basic. There was precipitated 45 g. (50%) of VIa which was sublimed *in vacuo*, m.p. 98–99°. The picrate melted at 138–140°.

Anal. Calcd. for $C_{11}H_{20}N_2$: C, 73.28; H, 11.18; N, 15.54. Found: C, 73.17; H, 11.18; N, 15.41.

2-[3-(2,5-Dimethylpyrrole)]propionitrile.—Reaction of 6.4 g. of VIa with 5 g. of potassium cyanide in aqueous ethanol, until the theoretical volume of isopropylamine had evolved, yielded in the neutral fraction 1 g. of the nitrile, b.p. 112–113° (0.6 mm.), nitrile band at 2250 mm.$^{-1}$.

Anal. Calcd. for $C_9H_{12}N_2$: C, 72.94; H, 8.16; N, 18.90. Found: C, 72.80; H, 8.01; N, 18.58.

The acid fraction furnished 1.5 g. of the corresponding acid, m.p. 96–98°. Sublimation raised the melting point to 99.5–100.5°. The substance exhibited the usual air sensitivity of pyrrole acetic acids.

Anal. Calcd. for $C_9H_{13}NO_2$: C, 64.65; H, 7.84; N, 8.38. Found: C, 65.04; H, 7.98; N, 8.22.

The Synthesis of C-15 β-Substituted Estra-1,3,5(10)-trienes. II[1]

E. W. Cantrall, Ruddy Littell, and Seymour Bernstein

Organic Chemical Research Section, Lederle Laboratories,
A Division of American Cyanamid Company,
Pearl River, New York

Received July 1, 1963

In part I of the titled paper[1] certain chemical properties of the Δ^{15}-17-one moiety of 3-methoxyestra-

---

[1] Part I, E. W. Cantrall, R. Littell, and S. Bernstein, *J. Org. Chem.*, **29**, 64 (1964).