

Pyrolysis of *N*-Ureidopyrroles. Preparation of Pyrrolo[2,1-*a*]-
phthalazin-6(5*H*)one Derivatives.

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Received October 2, 1974

In the course of our study of the chemistry of *N*-ureidopyrrole derivatives (1) it was observed by one of us that fusion of 2-ureido-5-phenyl-2-methylpyrrole-3-carboxylic acid affords the 3-methyl-5,6-dihydropyrrolo[2,1-*a*]phthalazin-6(5*H*)one (V).

This fact prompted us to consider that *N*-ureidopyrroles having a phenyl group at the α position might be useful synthetic intermediates in the formation of a new heterocyclic ring fused to the original pyrrole ring. Furthermore, examination of the literature revealed that these products had not been previously described; therefore we have extended our study to 1-ureido-2,5-diphenylpyrrole (1c), 1-ureido-5-phenyl-2-methyl-3-carbaethoxypyrrole (Ia) and 1-ureido-2-phenyl-5-methyl-3-carbaethoxypyrrole (Ib).

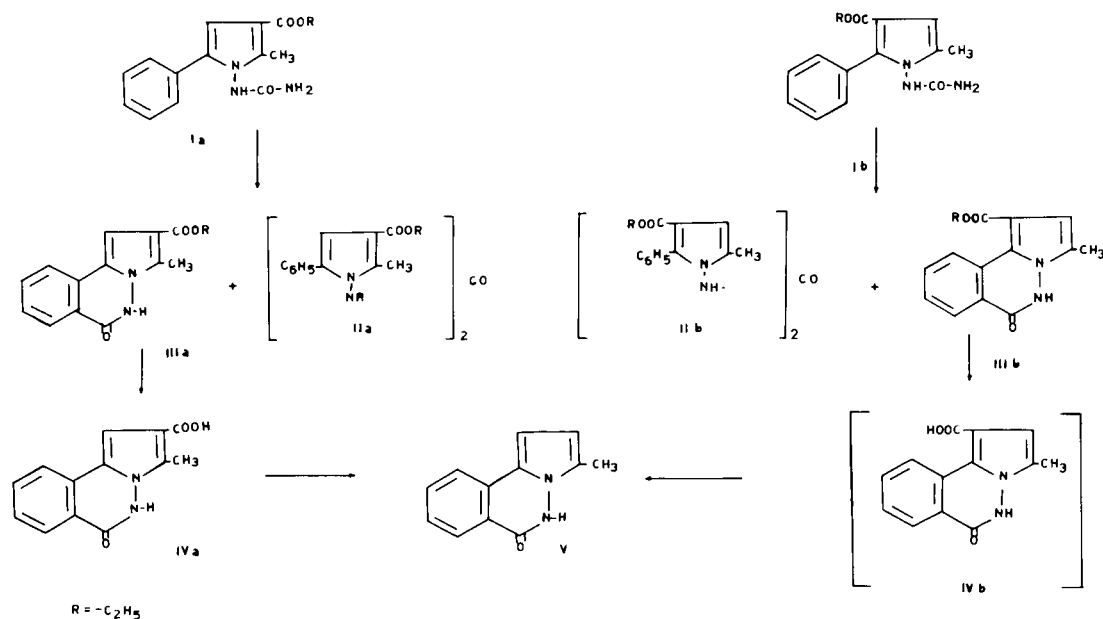
By heating Ia and Ic at 260-280° for 30 minutes on an oil bath, a complex reaction mixture was obtained from which the desired pyrrolophthalazinones were isolated by column chromatography over silica gel. Distillation of Ib under reduced pressure afforded IIIb, which was separated by fractional crystallization (Schemes I and II).

The structural assignments of the products were based on analytical and spectroscopic data (ms, nmr, ir), as well as the fact that IIIa and IIIb could be hydrolyzed to the corresponding acids IVa and IVb, which, after decarboxylation afforded V, which was identical with an authentic sample (1).

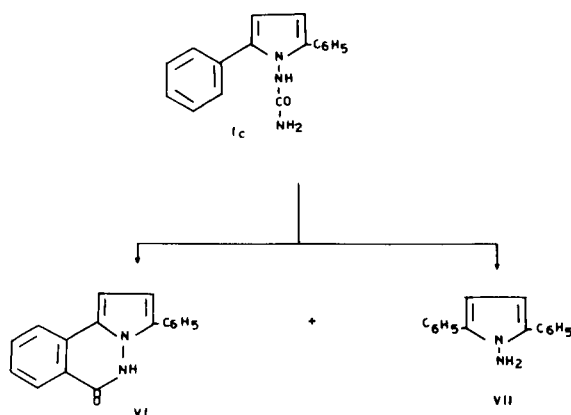
When the product IIIa, taken as an example, was treated with ethereal diazomethane the *N*-methylated derivative was obtained quantitatively. Its ir spectrum showed a strong carbonyl band at 1700 cm^{-1} , whereas the uv spectrum was quite similar to that of the parent unsubstituted compound, indicating that compound IIIa exists predominantly in the keto form.

As shown in Scheme III, the formation of the compounds IIIa,b and VI from *N*-ureidopyrroles may be accounted for by a reaction path in which initial loss of ammonia, resulting in formation of an isocyanate group, is followed by cyclization due to electrophilic attack by the isocyanate group on the benzene ring leading to pyrrolo-

Scheme I



Scheme II



phthalazinones according to an earlier proposed mechanism (2).

In addition, an intermediate such as VIII explains the formation of an *N*-aminopyrrole, through hydrolysis of the isocyanate group. In fact, from a fusion mixture of Ic together with VI, the 1-amino-2,5-diphenylpyrrole (VII) was isolated as was shown with a sample prepared by an independent route (3). Instead of analogous *N*-aminopyrrole derivatives, fusion of Ia and Ib yielded products formulated as the *N,N'*-bis(1-pyrrolyl)urea derivatives IIa and IIb on the basis of elemental analysis and spectral data. Their mass spectra had $M^+ = 514$ and the nmr spectra showed, besides the other signals, a peak downfield (2H) attributable to the two equivalent NH groups and multiplets (10H) for the two phenyl groups. The ir spectra showed a sharp absorption band at 3240 cm^{-1} due to the NH groups and bands for the amide and ester carbonyls at 1660 and 1720 cm^{-1} , respectively.

EXPERIMENTAL

Melting points were determined on Buchi-Tottoli apparatus and are uncorrected. Ultraviolet absorption spectra were measured in ethanol solution on a Beckmann DB recording spectrophotometer; infrared absorption spectra were determined in nujol mulls with a Perkin-Elmer infracord 137 spectrophotometer. The nmr spectra were obtained with a Jeol C-60H spectrometer (TMS as internal reference). A 270 Perkin Elmer mass spectrometer was employed for determination of low resolution 70 ev mass spectra.

Pyrolysis of 1-Ureido-2-phenyl-5-methyl-3-carbomethoxy-pyrrole (Ib).

Compound Ib (4) (1 g.) was heated on a metallic bath to 90° at 0.1 mm Hg in a microdistillation apparatus. A yellow liquid was distilled which solidified on standing. The examination of the crude product revealed the presence of two products IIb and IIIb, which were separated by fractional crystallization from ethanol.

Compound IIb (250 mg.) melted at $328\text{--}330^\circ$; molecular weight by mass spectroscopy m/e 514; ir 3240 cm^{-1} (2 x NH) 1660 and 1720 cm^{-1} (3 x CO); nmr (pyridine- d_5) $1.20\ \delta$ (6H, t, 2 x $\text{CH}_2\text{-CH}_3$, $J = 7.0$ Hz) $2.20\ \delta$ (6H, s, 2 x CH_3) $4.10\ \delta$ (4H, q, 2 x $\text{CH}_2\text{-CH}_3$, $J = 7.0$ Hz) $6.60\ \delta$ (2H, s, 2 x CH) $7.20\text{--}7.80\ \delta$ (10H, m, 2 x C_6H_5) $11.60\ \delta$ (2H, s, 2 x NH).

Anal. Calcd. for $\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_5$: C, 67.69; H, 5.88; N, 10.89. Found: C, 67.98; H, 5.91; N, 11.01.

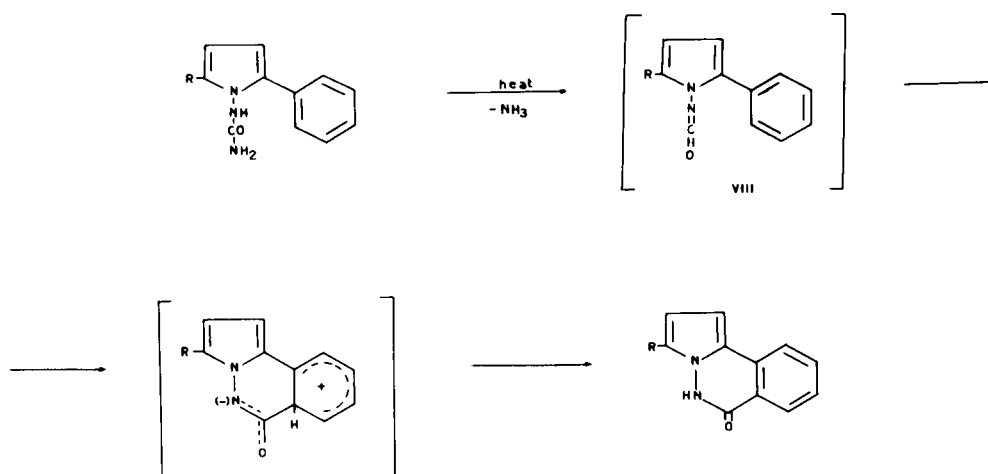
The compound IIIb (450 mg.) as yellow needles melted at $216\text{--}218^\circ$; molecular weight by mass spectroscopy m/e 270; $\text{uv } \lambda_{\text{max}}$ $\log \epsilon$ 330 (3.55) 288 (3.86); ir: 1660 and 1700 cm^{-1} (2 x CO); nmr (dimethylsulfoxide- d_6): $1.30\ \delta$ (3H, t, $\text{CH}_2\text{-CH}_3$, $J = 7.0$ Hz) $2.40\ \delta$ (3H, s, CH_3) $4.24\ \delta$ (2H, q, $\text{CH}_2\text{-CH}_3$, $J = 7.0$ Hz) $6.80\ \delta$ (1H, s, pyrrole CH) $7.50\text{--}8.30\ \delta$ (3H, m, H_7 , H_8 and H_9) $10.64\ \delta$ (1H, m, H_{10}) $13.00\ \delta$ (1H, broad, NH).

Anal. Calcd. for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.47; H, 5.21; N, 10.40.

Pyrolysis of 1-Ureido-5-phenyl-2-methyl-3-carbomethoxy-pyrrole (Ia).

Compound Ia (4) (1 g.) was heated on an oil bath at $260\text{--}280^\circ$ for 30 minutes. The resultant brown mixture was chromatographed on a column (20 x 3 cm) of silica gel (25 g.). Elution with benzene-ethyl acetate (9:1) removed the 2-carbomethoxy-3-methyl-5,6-dihydropyrrolo[2,1-*a*]phthalazin-6-one (IIIa) (ca. 200 mg.) as yellow needles, m.p. $225\text{--}228^\circ$ (ethanol); molecular weight by

Scheme III



mass spectroscopy m/e 270; $uv \lambda$ max nm $\log \epsilon$ 310s (4.09) 288 (4.45) 278 (4.46) 267 (4.54) 242 (4.45); ir: 1660 and 1700 cm^{-1} (2 x CO); nmr (dimethylsulfoxide- d_6): 1.30 δ (3H, t, CH_2-CH_3 , $J = 7.0$ Hz) 2.66 δ (3H, s, CH_3) 4.14 δ (2H, q, CH_2-CH_3 , $J = 7.0$ Hz) 7.14-8.10 δ (5H, m, C_6H_4 and pyrrole CH) 13.50 δ (1H, broad, NH).

Anal. Calcd. for $C_{15}H_{14}N_2O_3$: C, 66.65; H, 5.22; N, 10.37. Found: C, 66.28; H, 5.28; N, 10.28.

Further elution with benzene-ethyl acetate (8:2) removed IIa (420 mg.) m.p. 275-278° (ethanol); molecular weight by mass spectroscopy m/e 514; ir: 3240 cm^{-1} (2 x NH) 1660 and 1720 cm^{-1} (3 x CO); nmr (dimethylsulfoxide- d_6): 1.22 δ (6H, t, 2 x CH_2-CH_3 , $J = 7.0$ Hz) 2.18 δ (6H, s, 2 x CH_3) 4.12 δ (4H, q, 2 x CH_2-CH_3 , $J = 7.0$ Hz) 6.46 δ (2H, s, 2 x CH) 7.10-7.70 δ (10H, m, 2 x C_6H_5) 10.22 δ (2H, s, 2 x NH).

Anal. Calcd. for $C_{29}H_{30}N_4O_5$: C, 67.69; H, 5.88; N, 10.89. Found: C, 67.99; H, 5.76; N, 10.54.

Pyrolysis of 1-Ureido-2,5-diphenylpyrrole (Ic).

Compound Ic (4) (1 g.) was heated on an oil bath at 260-280° for 30 minutes. The resultant brown mixture was chromatographed on a column (20 x 3 cm) of silica gel (25 g.). Elution with cyclohexane-benzene (4:1) removed the 1-amino-2,5-diphenylpyrrole (VII) (230 mg.) identified by comparison with an authentic sample (3).

Further elution with benzene afforded the 3-phenyl-5,6-dihydropyrrolo[2,1- α]phthalazin-6-one (VI) (350 mg.) as yellow needles m.p. 185-186° (benzene-petroleum ether); molecular weight by mass spectroscopy m/e 260; $uv \lambda$ max nm $\log \epsilon$ 234 (4.35) 294 (3.44); ir: 1660 cm^{-1} (CO); nmr (deuteriochloroform): 6.50 δ (1H, d, H_1 or H_2 pyrrole CH, $J \cong 3.0$ Hz) 6.70 δ (1H, d, H_2 or H_1 pyrrole CH, $J \cong 3.0$ Hz) 7.00-8.20 δ (9H, m, C_6H_5 and C_6H_4) 12.00 δ (1H, broad, NH).

Anal. Calcd. for $C_{17}H_{12}N_2O$: C, 78.44; H, 4.65; N, 10.76. Found: C, 78.76; H, 4.75; N, 10.76.

Hydrolysis of IIIa and IIIb.

Two mmoles of IIIa or IIIb in ethanol (10 ml.) were refluxed for 2 hours with 10% aqueous sodium hydroxide (5 ml.). After

evaporation of ethanol, acidification with 2*N* hydrochloric acid gave the corresponding carboxylic acids (yield 70-75%).

Compound IVa melted at 305-308° (ethanol); ir: 1680 cm^{-1} (broad, 2 x CO); nmr (dimethylsulfoxide- d_6): 2.70 δ (3H, s, CH_3) 7.20 δ (1H, s, pyrrole, CH) 7.24-8.30 δ (4H, m, C_6H_4) 11.80 δ (1H, broad, COOH).

Anal. Calcd. for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.57. Found: C, 64.57; H, 4.24; N, 11.64.

The product IVb was not characterized but directly converted to V (see below).

3-Methyl-5,6-dihydropyrrolo[2,1- α]phthalazin-6-one (V).

The compounds IVa and IVb were maintained in an oil bath at 315-330° until yellow needles sublimed. Further crystallization from ethanol gave V (yield 28-30%) m.p. 234-235°, which was identical with authentic 3-methyl-5,6-dihydropyrrolo[2,1- α]phthalazin-6-one (1).

2-Carbethoxy-3,5-dimethyl-5,6-dihydropyrrolo[2,1- α]phthalazin-6-one.

To 3 mmoles of IIIa in ether a slight excess of ethereal diazomethane was added and, after standing for 24 hours, the *N*-methyl derivative was obtained after evaporation of ether. The product melted at 120-122° (methanol); $uv \lambda$ max nm $\log \epsilon$ 318 (2.60) 304 (3.84) 282 (4.18) 262 (4.29) 240 (4.09); ir: 1700 cm^{-1} (CO); nmr (deuteriochloroform): 1.40 δ (3H, t, CH_2-CH_3 , $J = 6.0$ Hz) 2.70 δ (3H, s, CH_3) 4.00 δ (3H, s, $N-CH_3$) 4.40 δ (2H, q, CH_2-CH_3 , $J = 6.0$ Hz) 7.10 δ (1H, s, pyrrole CH) 7.20-8.00 δ (4H, m, C_6H_4).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: N, 9.85. Found: N, 9.76.

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