Studies on the Synthesis of Heterocyclic Compounds. Part II. Action of Phosphorus Oxychloride on *N*-Methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-acetamidobenzamide

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During attempts to prepare the tricyclic ring system of type III by cyclization of *N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-acetamido benzamide (Ib) under Bischler-Napieralski reaction conditions, the formation of the macro-heterocycle IV was observed, whose structure was determined on the basis of analytical and spectroscopic data as well as on some transformation products.

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We have for some time (1-7) been interested in the synthesis of heterocycles fused to the pyrazole nucleus and we now wish to describe a study directed toward the synthesis of tricyclic compounds of type III. In order to achieve this objective we used Ib as the starting material, which under the reaction conditions described, would eliminate the formation of the quinazolinone II, where R is an alkyl group (Scheme I).

However, upon refluxing Ib under Bischler- Napieralski reaction conditions, we obtained an unexpected macro-heterocycle, to which we assigned structure IV on the basis of analytical and spectroscopic data as well as on the study of some transformation products (Scheme I).

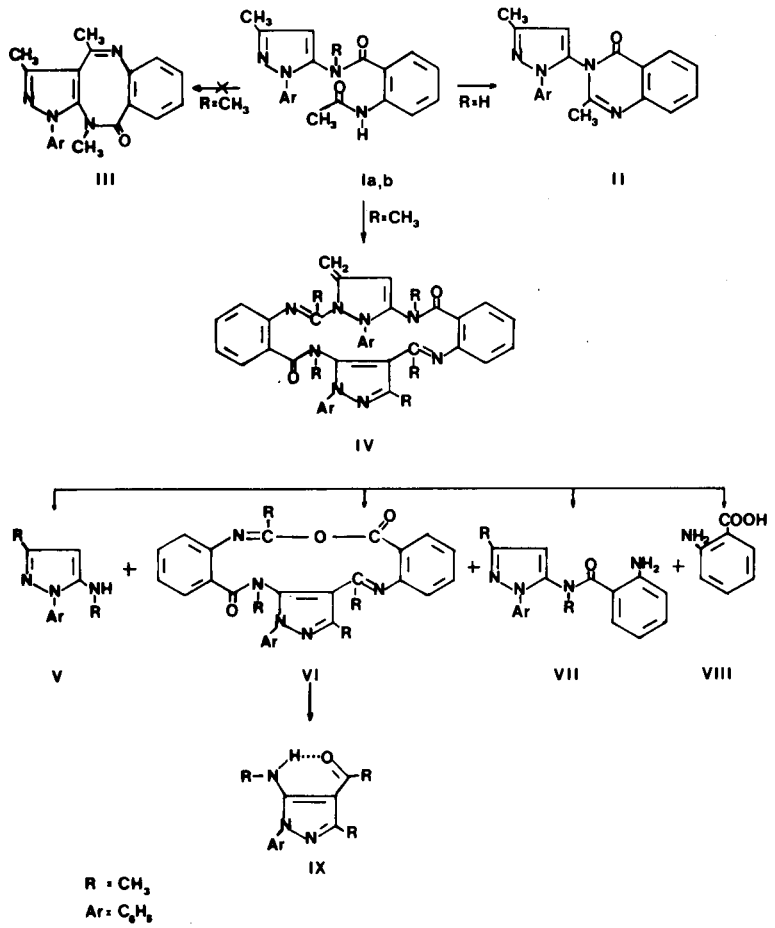
Exact mass measurement of the pure product isolated from the reaction mixture showed a mass ion at m/e 660.294 and suggested an empirical formula of $C_{40}H_{36}N_8O_2$. The nmr spectrum recorded at room temperature (25°) showed some complex and broadened absorptions and a complete analysis by inspection was not possible. However, on heating to 100°, the signals became progressively more sharp and the spectrum was highly informative. In fact, in addition to the aromatic signals (18 H), there appeared five methyl absorptions at δ 1.90, 2.10, 2.27, 3.40 and 3.58, respectively, as sharp singlets, two sharp singlets (2 H) at δ 5.40 and δ 5.48, and a singlet (1 H) at δ 5.90. These last three resonances were attributable to a terminal $CH_2=$ group and a methyne group of a pytazoline nucleus, as was indicated by the hydrolysis data discussed below. On refluxing in acid medium, IV afforded 3-methyl-1-phenyl-5-methylamino-pyrazole (V) and VI of mass ion m/e 491, whose nmr spectrum showed simply four methyl absorptions and aromatic signals (13 H).

These observations led us to conclude the following: (1) since upon acid hydrolysis, compound IV formed compounds V and VI, which contain two methyl groups and four methyl groups, respectively, a terminal methylene group must have been transformed into a methyl group, justifying the formation of V. (2) The identification of V also clearly indicated that a pyrazole moiety in IV was unsubstituted at position 4. This interpretation was further substantiated by the isolation of small quantities of *N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-amino-benzamide (VII). The near-infrared spectrum of IV showed a typical terminal methylene absorption at 1.615 μ, according to literature reported data (8). Indeed, the presence of a terminal methylene group in IV was strongly supported by oxidation with Lemieux-von Rudloff reagent (9), which caused the formation of formaldehyde, detected and identified as its 2,4-dinitrophenylhydrazone. The isolation of 4-acetyl-3-methyl-1-phenyl-5-methylamino-pyrazole (IX) by alkaline hydrolysis, of VI, indicated that the other pyrazole moiety was completely substituted. The structure of compound IX was determined on the basis of correct elemental analysis and molecular weight by mass spectroscopy, as well as ir and nmr spectra. The low frequency band at 1620 cm^{-1} of the ketonic group at C-4 agrees with a structure intramolecularly hydrogen bonded. This structure also supported by inspection of the nmr spectrum, which showed a broad NH absorption at lower field δ 7.90 than the NH of the parent pyrazole V (10). Moreover, the N-CH_3 resonance appeared as a doublet (3H) at δ 2.50 with J = 5.0 Hz, which was replaced by a single peak upon the addition of deuterium oxide.

It is noteworthy that the hydrolysis products VII, IX and anthranilic acid (VIII), isolated as described in Experimental, accounted well for the sequence of atoms in macrocycle IV. Moreover, the complex nmr spectrum of IV observed at 25° could be attributed to the presence of different isomers, as a consequence of the partial double bond character of the amide groups (11), which on heating, exhibited sharp proton signals for a "single" compound. The apparent minor anomaly was the absence of geminal coupling in the $CH_2=$ signals. However, geminal coupling constants for vinyl derivatives generally have very small positive or negative values and may also be zero (12).

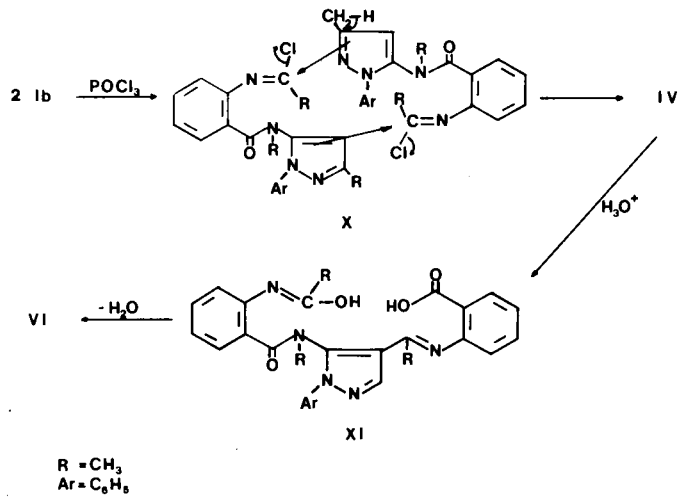
The assigned structure IV can be rationalized by the proposed mechanism shown in scheme II, through the

SCHEME I



formation of the iminochloride intermediate X. The lactone VI could be formed *via* the hypothetical carboxylic acid intermediate XI, followed by cyclodehydration.

SCHEME II



Many attempts to prepare III by carrying out the reaction in a very dilute dry refluxing xylene solution, in order to favour intramolecular cyclization failed. In every case, IV was obtained. Furthermore, upon simple heating Ib in phosphorus oxychloride at different temperatures (room temperature to 100°), only unreacted starting material was obtained in quantitative yield.

EXPERIMENTAL

All melting points were taken on a Buchi-Tottoli capillary melting point apparatus and are uncorrected; ir spectra were determined in a nujol mull (unless otherwise specified) with a Perkin-Elmer infracord 137 spectrophotometer. A Cary model 17 spectrophotometer was used for near-infrared spectrum determination (1 cm quartz cell); nmr spectra were obtained with a Jeol C-60 spectrometer (TMS as internal reference). Mass spectra were run on a Joel JMS-01SG-2 double focusing mass spectrometer operating with an electron beam energy of 75 eV and 10 KW accelerating voltage. Exact mass measurement were performed at 20,000 resolving power and were carred out to an accuracy of ± 10 ppm of the theoretical vaules.

N-(1-Phenyl-3-methylpyrazol-5-yl)-2-acetamidebenzamide (Ia) and *N*-Methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-acetamidobenzamide (Ib).

A mixture of *N*-R-(1-phenyl-3-methylpyrazol-5-yl)-2-aminobenzamide (10) (6 g.) and acetic anhydride (30 ml.) was stirred at room temperature for 8 hours. The precipitate was collected, dried at 110° and recrystallized (yield 70-75%).

Compound Ia.

The product melted at 148-150° (benzene-petroleum ether); ir (cm^{-1}): 3100-3200 (broad) and 3440 (2 x NH), 1670 and 1690 (2 x CO); molecular weight by mass spectroscopy m/e 334.

Anal. Calcd. for $C_{19}H_{18}N_4O_2$: C, 68.24; H, 5.42; N, 16.76. Found: C, 68.23; H, 5.39; N, 16.74.

Compound Ib.

The product melted at 164-166° (ethanol); ir (cm^{-1}): 3320 (NH) 1670-1680 (CO); nmr (deuteriochloroform): δ 1.93 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.50 (3H, s, CH_3), 6.20 (1H, s, pyrazole CH), 6.50-7.40 and 8.00-8.40 (9H, m, C_6H_5 and C_6H_4), 8.98 (1H, broad, NH); molecular weight by mass spectroscopy m/e 348.

Anal. Calcd. for $C_{20}H_{20}N_4O_2$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.94; H, 5.80; N, 16.05.

2-Methyl-3-(1-phenyl-3-methylpyrazol-5-yl)-4(3*H*)quinazolinone (II).

A mixture of Ia (2 mmoles) and phosphorus oxychloride (7 ml.) was heated at reflux for 1 hour. The cooled reaction mixture was poured into crushed ice mixed with solid sodium bicarbonate and extracted with chloroform (2 x 100 ml). Drying (sodium sulfate) and evaporation left a solid (II) which was crystallized from ethanol, m.p. 162° and was identical (m.p. and mixed m.p. ir, nmr) with 2-methyl-3-(1-phenyl-3-methylpyrazol-5-yl)-4-(3*H*)quinazolinone, prepared by an independent route (13).

Action of Phosphorus Oxychloride on Ib.

A mixture of Ib (14.5 mmoles) and phosphorus oxychloride (50 ml.) was refluxed for 1 hour. Excess phosphorus oxychloride was evaporated under reduced pressure and the reaction mixture was poured into crushed ice mixed with solid sodium bicarbonate and extracted with chloroform (3 x 150 ml.). The organic layers were washed with water, dried (sodium sulfate) and concentrated under reduced pressure to dryness to give a residue, which crystallized from ethanol gave IV (yield 1.75 g.); m.p. 247-249°; ir (cm^{-1}): 1650-1680 (CO); near-infrared (chloroform, 0.67 *M*): 1.615 μ (CH_2=); nmr (DMSO-d_6) (determined at 100°C): δ 1.90 (3H, s, CH_3), 2.10 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.40 (3H, s, CH_3), 3.58 (3H, s, CH_3), 5.40 and 5.48 (2H, 2s, J = 0, CH_2=), 5.90 (1H, s, pyrazole CH), 6.48-8.00 (18 H, m, 2 x C_6H_5 and 2 x C_6H_4); ms: M^+, 660.294 (± 0.003), for $C_{40}H_{36}N_8O_2$ required M^+, 660.296.

The mothers liquor from crystallization of IV were taken to dryness and the residue was chromatographed on a column (3 x 35 cm) of silica gel with 15% water (90 g.). Elution with diethyl ether yielded 80 mg. of VII, identical (m.p. and mixed m.p. ir, nmr) with *N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-aminobenzamide prepared as previously described (10). Further elution with ether gave Ib (70 mg.) unreacted and a product (150 mg.) which was identified as VI (m.p. and mixed m.p. ir, mass, nmr) described below.

Hydrolysis of IV.

A solution of IV (6 g.) in 60 ml. of aqueous 6*N* hydrochloric acid was refluxed for 25 minutes. The precipitated solid (3.2 g.) was crystallized from ethanol-diethyl ether to give VI hydrochloride, m.p. 272-274° dec.; ir (cm^{-1}): 2140 (broad) and 1890 (immonium), 1680 and 1720 (2 x CO).

Anal. Calcd. for $C_{29}H_{26}ClN_5O_3$: C, 65.97; H, 4.97; N, 13.25. Found: C, 65.87; H, 5.12; N, 13.06.

The acidic mother liquors were extracted with chloroform (3 x 60 ml.) and the combined organic extracts were dried over sodium sulfate. Upon removal of the solvent under reduced pressure, 1.3 g. of crude solid was obtained. Recrystallization from ethanol afforded further quantities (100 mg.) of VI hydrochloride. The mother liquor from crystallization taken to dryness gave an intractable material.

The inorganic layer was basified with aqueous sodium hydroxide and extracted with ether (3 x 60 ml.). The ethereal extracts were dried (sodium sulfate) and evaporated. The resulting residue (1.1g.) was chromatographed on a column (4 x 45 cm.) of silica gel, with 15% water (280 g.), with chloroform. The combined fractions 30-65 (each 20 ml.) were evaporated under reduced pressure and the residue, upon preparative tlc on silica gel (chloroform as eluent) gave 1-phenyl-3-methyl-5-methylaminopyrazole (V) (450 mg.), identical with an authentic sample (10). Further elution with chloroform (fractions 68-74) (each 20 ml.) afforded a product which was recrystallized from ether, m.p. 145-147°. The material was identical in all respects with an authentic sample of *N*-methyl-*N*-(1-phenyl-3-methylpyrazol-5-yl)-2-aminobenzamide (VII) (10).

The remaining aqueous alkaline layer was acidified with concentrated hydrochloric acid, and concentrated to a small volume. The precipitated sodium chloride was filtered off and the solution was adjusted to *p*H 5, and extracted with ether (3 x 50 ml.). The organic phases were dried (sodium sulfate) and evaporated to leave VIII, m.p. 143-146° (benzene), identical with with a sample of anthranilic acid (m.p. and mixed m.p. mass, R_f).

Compound VI.

The hydrochloride salt of VI (3.8 g.) dissolved in chloroform (100 ml.) and triethylamine (5 ml.) was added in one portion. The solution was stirred for 1 hour at room temperature, washed with water (3 x 100 ml.) and dried (sodium sulfate). Removal of the solvent left the free base VI, which was recrystallized from ethanol, m.p. 246-248°; ir (cm^{-1}): 1660-1680 (CO); nmr (deuterochloroform): δ 2.30-2.70 (9H, 3 x CH_3), 3.10 (3H, s, CH_3), 6.50-8.00 (13H, m, C_6H_5 and C_6H_4); molecular weight by mass spectroscopy m/e 491.

Anal. Calcd. for $C_{29}H_{25}N_5O_3$: C, 70.86; H, 5.13; N, 14.25. Found: C, 70.87; H, 5.06; N, 13.93.

4-Acetyl-3-methyl-1-phenyl-5-methylaminopyrazole (IX).

Pure VI (1.5 g.) was introduced into a solution of potassium hydroxide (18 g.) dissolved in ethanol (60 ml.). The resulting suspension was refluxed for 5 hours. The solution was diluted with water (120 ml.) and concentrated under reduced pressure to a volume of 50 ml., the separated solid (0.7 g.) was filtered off and extracted several times with boiling petroleum ether (b.p. 40-60°). The combined ether extracts were evaporated to a small volume when a crystalline material (IX) separated out, m.p. 113-115° (petroleum ether); ir (cm^{-1}): 3250 (NH), 1620 (CO); nmr (deuterochloroform): δ 2.42 (3H, s, CH_3), 2.44 (3H, s, CH_3), 2.50 (3H, d, NH-CH_3, J = 5.0 Hz), 7.40-7.60 (5H, m, C_6H_5), 7.90 (1H, broad, NH); molecular weight by mass spectroscopy m/e 229.

Anal. Calcd. for $C_{13}H_{15}N_3O$: C, 68.10; H, 6.59; N, 18.33. Found: C, 68.05; H, 6.58; N, 18.34.

Oxidation of IV.

A solution of sodium periodate (1.71 g.) and potassium permangante (15 mg.) in water (30 ml.) was adjusted to *p*H 7.6 by adding aqueous sodium hydroxide (10%). Then, a solution of pure IV (500 mg.) in *t*-butyl alcohol (30 ml.) was added. The resultant suspension was shaken for 24 hours. The solid precipitated was filtered off and the solution acidified. Upon distillation, the first

20 ml. were neglected and the successive distilled fractions revealed the presence of formaldehyde, which was isolated by converting it into its 2,4-dinitrophenylhydrazone, purified by preparative tlc on silica gel (benzene as eluent) and identified by comparison with an authentic sample (R_f, m.p. and mixed m.p. mass, ir).

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