Research on Nitrogen Heterocyclic Compounds. XV. Synthesis of 1*H*,4*H*-Pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine Derivatives

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The synthesis of derivatives of 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine, a new tricyclic nitrogen-containing nucleus is reported. Condensation of arylaldehydes with 4-aminomethyl-1-phenyl-5-(1-pyrryl)pyrazole afforded the title compounds. Bischler-Napieralski intramolecular cyclization of 4-acetamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole was also studied. The reaction led to 6-methyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine or alternatively to 4-chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole depending on the solvent used.

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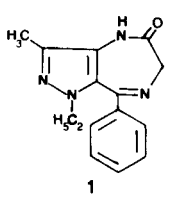
Ripazepam (**1**), zometapine (**2**) and **3**, the thiophene analog of triazolam, provide examples of highly active psychotropic agents. Ripazepam resembled diazepam in anti-anxiety pharmacological profile and has been studied in the clinic [2]. Zometapine was inactive as an antianxiety and anticonvulsant agent but showed promising antidepressant activities [3]; finally, **3** had hypnotic and antianxiety effects similar to that of triazolam [4].

These interesting pharmacological properties encouraged further researches directed to the synthesis of compounds related to benzodiazepines in which the fused benzene ring is replaced by pyrazolo or thieno moieties [5].



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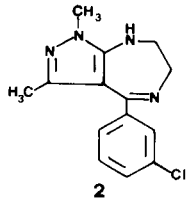

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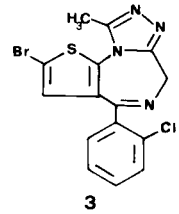

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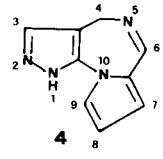
Among tricyclic nitrogen rings with an incorporated 1,4-diazepine nucleus, 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo-[1,2-*a*][1,4]diazepine (**4**) is a novel one with chemical features resembling the skeleton structure of the above reported substances.



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For the synthesis of 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]-[1,4]diazepine derivatives we started from 5-amino-4-cyano-1-phenylpyrazole, prepared as described by Cheng and Robins from the reaction between phenylhydrazine and ethoxymethylenemalononitrile [6].

Reaction of 5-amino-4-cyano-1-phenylpyrazole with 2,5-dimethoxytetrahydrofuran in boiling glacial acetic acid afforded 4-cyano-1-phenyl-5-(1-pyrryl)pyrazole (**5**), which was then reduced by lithium aluminum hydride to give 4-aminomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**6**). Treatment of this compound with 40% aqueous formaldehyde and gaseous hydrochloric acid in ethanol at reflux furnished directly 5,6-dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo-[1,2-*a*][1,4]diazepine (**9**) as the hydrochloride.

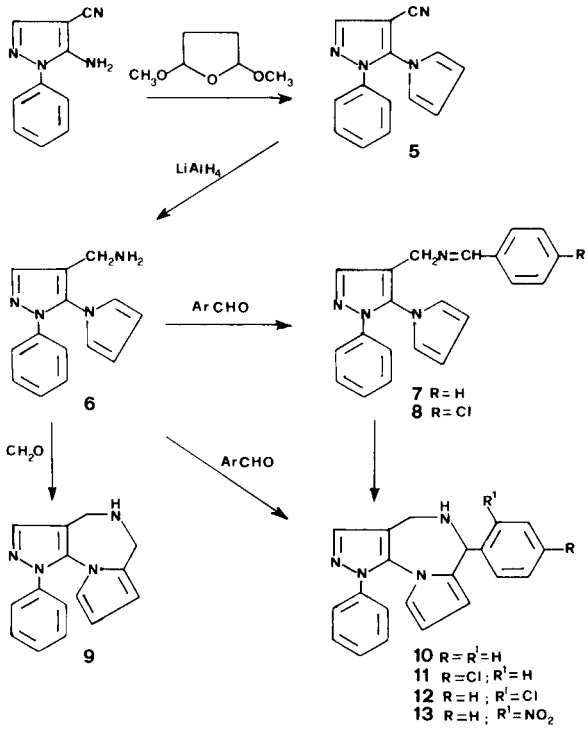
Condensation of benzaldehyde or *p*-chlorobenzaldehyde with **6** in boiling ethanol led to the corresponding Schiff's bases **7** and **8**, which in turn were cyclized in good yield to 5,6-dihydro-1,6-diphenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo-[1,2-*a*][1,4]diazepine (**10**) and 6-*p*-chlorophenyl-5,6-dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**11**) respectively by treatment with gaseous hydrochloric acid in ethanol at the boiling point (Scheme 1).

Derivatives **12** and **13** were obtained directly by the reaction of **6** with *o*-chloro- and *o*-nitrobenzaldehyde in the presence of gaseous hydrochloric acid without isolating the corresponding Schiff's bases.

As a further route to prepare derivatives of 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine we explored the Bischler-Napieralski intramolecular cyclization of 4-acetamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**14**), obtained by treatment of **6** with acetic anhydride.

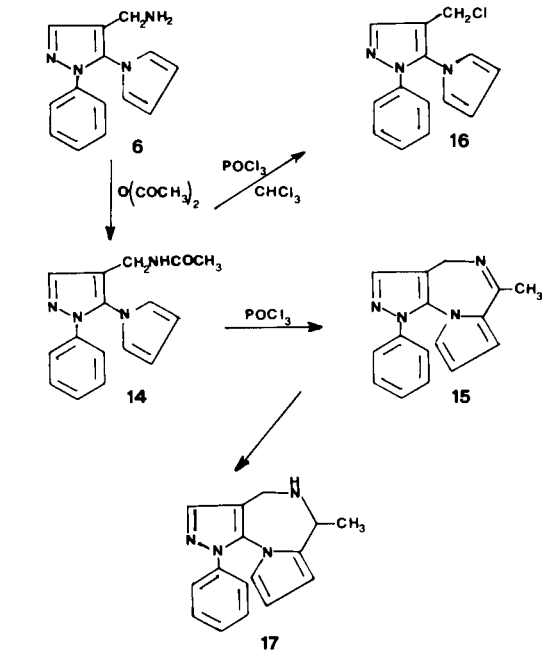
We observed that intramolecular condensation of **14** was greatly affected both by the temperature and the solvent used in the reaction. When **14** was refluxed in toluene in the presence of phosphorus oxychloride 6-methyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**15**) formed in poor yield (21%), whereas the use of chloroform under the same conditions led to 4-chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole (**16**) as the main detectable product (33% yield). Compound **15** was obtained in fair yield (64% of theoretical amount) when the Bischler-Napieralski cyclization was carried out in absence of solvent by treating **14** with phosphorus oxychloride at room temperature for 3 hours.

Scheme 1

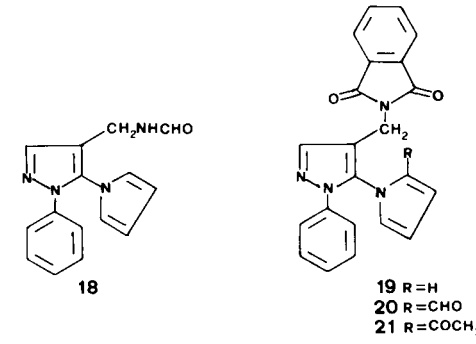


Catalytic reduction of **15** afforded 5,6-dihydro-6-methyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**17**) (Scheme 2).

Scheme 2



Attempts to obtain the desmethyl derivative of **15** by intramolecular cyclization of **18** led only to an unworkable mixture. Similar difficulties were encountered when **20** and **21** were treated with hydrazine hydrate to remove the phthalimido moiety.



Derivatives **18-21** were obtained by conventional methods [7].

Actually the 1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine derivatives here reported are under both biological and pharmacological screening as potential antitumoral and antianxiety agents.

EXPERIMENTAL

All melting points were taken on a Fisher-Johns apparatus and are uncorrected. Infrared spectra (nujol mulls) were run on a Perkin-Elmer model 297 spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian EM-390 instrument (TMS internal standard). The mass spectra were recorded on a Hewlett-Packard 5908-A mass spectrometer with an electron beam energy of 70 eV. Merck according to Brockmann alumina and silica gel 60 were used for chromatographic purifications. Elemental analyses were performed by A. Pietrogrande, Padova, Italy.

4-Cyano-1-phenyl-5-(1-pyrryl)pyrazole (**5**).

To a well stirred solution of 10.0 g (0.054 mole) of 5-amino-4-cyano-1-phenylpyrazole [6] in 100 ml of glacial acetic acid 7.2 g (0.054 mole) of 2,5-dimethoxytetrahydrofuran were added. The solution was refluxed for 30 minutes while stirring, then evaporated under reduced pressure to remove acetic acid. The residue was treated with ethyl acetate (200 ml), the organic solution was washed with water and then dried over anhydrous sodium sulphate. Evaporation of solvent furnished 4-cyano-1-phenyl-5-(1-pyrryl)pyrazole, mp 84-85° after crystallization from ethanol, yield, 11.8 g (93%); ir: 2230 cm^{-1} (CN).

Anal. Calcd. for $C_{14}H_{10}N_4$: C, 71.78; H, 4.30; N, 23.92. Found: C, 71.83; H, 4.28; N, 23.89.

4-Aminomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**6**).

To a well stirred suspension of 2.0 g (0.05 mole) of lithium aluminum hydride in 100 ml of anhydrous tetrahydrofuran 10.0 g (0.043 mole) of 4-cyano-1-phenyl-5-(1-pyrryl)pyrazole (**5**) were added by small portions, then the mixture was maintained with stirring at room temperature for 18 hours. Addition of aqueous ethanol to destroy the excess lithium aluminum hydride, followed by filtration afforded a solution, which was then evaporated *in vacuo*. The residue was extracted with ethyl ether, the organic layer washed with water and dried over anhydrous sodium sulphate. Removal of the solvent under reduced pressure gave a crude product, which was purified by passing through an alumina column eluting with chloroform to give 8.0 g (80%) of 4-aminomethyl-1-phenyl-5-(1-pyrryl)pyrazole, mp 108-110° (from ethanol); ir: 3350 and 3300 cm^{-1} (NH_2).

Anal. Calcd. for $C_{14}H_{14}N_4$: C, 70.56; H, 5.92; N, 23.51. Found: C, 70.83; H, 5.75; N, 23.42.

4-Benzylideneaminomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**7**).

A solution of 1.4 g (0.0058 mole) of 4-aminomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**6**) and 0.6 g (0.0058 mole) of benzaldehyde in 20 ml of anhydrous ethanol were heated at reflux for 10 minutes. After cooling the precipitate was collected and recrystallized from ethanol to yield 1.4 g (73%) of 4-benzylideneaminomethyl-1-phenyl-5-(1-pyrryl)pyrazole, mp 97-99°.

Anal. Calcd. for $C_{21}H_{18}N_4$: C, 78.24; H, 4.38; N, 17.38. Found: C, 78.31; H, 4.32; N, 17.37.

4-*p*-Chlorobenzylideneaminomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**8**).

This compound was prepared in 83% yield as reported for the above derivative **7** from **6** and *p*-chlorobenzaldehyde, mp 131-132° (from ethanol); nmr (deuteriochloroform): δ 4.6 (s, 2, CH_2), 6.3 (m, 2, pyrrole β-H), 6.8 (m, 2, pyrrole α-H), 7.0-7.9 (superimposed multiplets, 10, benzene and pyrazole protons) and 8.2 ppm (s, 1, CH azomethine).

Anal. Calcd. for $C_{21}H_{17}ClN_4$: C, 69.88; H, 4.76; Cl, 9.82; N, 15.53. Found: C, 69.71; H, 4.82; Cl, 9.79; N, 15.68.

5,6-Dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**9**).

A mixture of 1.4 g (0.006 mole) of 4-aminomethyl-1-phenyl-5-(1-pyrryl)-pyrazole (**6**), 375 mg of 40% aqueous formaldehyde and 30 ml of anhydrous ethanol was heated at reflux for 10 minutes, then a stream of gaseous hydrochloric acid was bubbled into the solution while stirring. After 10 minutes boiling the gas flow was stopped and the cooled mixture was treated with ethyl ether. The hydrochloride which precipitated was filtered off and recrystallized from ethanol-water (2:1 mixture) to give 900 mg (53% yield) of 5,6-dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*]-[1,4]diazepine hydrochloride, mp 286-287° dec; nmr (DMSO-d_6): δ 4.0 (s, 2, CH_2 near pyrrole), 4.32 (s, 2, CH_2 near pyrazole), 6.22 (m, 1, pyrrole β-H), 6.5 (m, 2, pyrrole α-H), 7.53 (m, 5, benzene protons) and 7.9 ppm (s, 1, pyrazole proton).

Anal. Calcd. for $C_{15}H_{15}ClN_4$: C, 62.81; H, 5.28; Cl, 12.36; N, 19.51. Found: C, 62.73; H, 5.30; Cl, 12.25; N, 19.82.

Synthesis of 6-Aryl-5,6-dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo-[1,2-*a*][1,4]diazepine **10-13**. From Schiff Bases **7** and **8**.

Gaseous hydrogen chloride was bubbled into a boiling solution of 0.003 mole of **7** or **8** in 30 ml of absolute ethanol during 30 minutes. The precipitate formed on cooling was collected by suction and recrystallized from a suitable solvent. 5,6-Dihydro-1,6-diphenyl-1*H*,4*H*-pyrazolo[4,3-*f*]-pyrrolo[1,2-*a*][1,4]diazepine hydrochloride (**10**) had mp 266-269° dec after crystallization from ethanol (81% yield).

Anal. Calcd. for $C_{21}H_{19}ClN_4$: C, 69.44; H, 4.96; Cl, 9.78; N, 15.82. Found: C, 69.53; H, 5.07; Cl, 9.61; N, 15.79.

6-*p*-Chloro-5,6-dihydro-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]-diazepine Hydrochloride (**11**).

This compound melted at 264-266° after recrystallization from ethanol-water 2:1 mixture, yield, 77% of the calculated value.

Anal. Calcd. for $C_{21}H_{18}Cl_2N_4$: C, 63.48; H, 4.58; Cl, 17.85; N, 14.10. Found: C, 63.59; H, 4.42; Cl, 17.68; N, 14.31.

The free base **11** had mp 153-154° (from ethanol); nmr (deuteriochloroform): δ 2.02 (s, 1, NH disappeared after treatment with deuterium oxide), 4.1 (s, 2H, CH_2), 5.12 (s, 1, C_6 proton), 5.6 (m, 1, C_8 proton), 6.0 (m, 1, C_7 proton), 6.35 (m, 1, C_9 proton), 7.3-7.6 (superimposed multiplets, 9H, benzene protons) and 7.7 ppm (s, 1, pyrazole proton); ms: m/e 361 (M^+).

From Compound **6** and Arylaldehydes.

A mixture of 0.005 mole of **6** and 0.005 mole of *o*-chloro- or *o*-nitrobenzaldehyde in 20 ml of absolute ethanol was refluxed for 15 minutes, then gaseous hydrogen chloride was bubbled into the solution until saturation and heating was maintained for 30 minutes more. The hydrochloride which precipitated on cooling was collected and recrystallized from 80% ethanol. 6-*o*-Chlorophenyl-5,6-dihydro-1-phenyl-1*H*,4*H*-pyrazolo-[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**12**) melted at 221-223°, yield, 46%.

Anal. Calcd. for $C_{21}H_{18}Cl_2N_4$: C, 63.48; H, 4.58; Cl, 17.85; N, 14.10. Found: C, 63.59; H, 4.45; Cl, 17.89; N, 14.18.

5,6-Dihydro-6-*o*-nitrophenyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo-[1,2-*a*][1,4]diazepine (**13**).

This compound had mp 207-209°, yield, 54%.

Anal. Calcd. for $C_{21}H_{18}ClN_5O_2$: C, 61.84; H, 4.45; Cl, 8.69; N, 17.17. Found: C, 61.96; H, 4.39; Cl, 8.60; N, 17.21.

4-Acetamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**14**).

To a cooled well stirred solution of 5.5 g (0.023 mole) of 4-aminomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**6**) in glacial acetic acid (30 ml) 4 ml of acetic anhydride were added. The mixture was maintained with stirring at room temperature for 1 hour, then poured onto crushed ice and treated with solid sodium carbonate until becoming alkaline. The precipitate was filtered off and recrystallized from ethanol to afford 4.2 g (65%) of 4-acetamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole, mp 128-130°; ir: 3300 cm^{-1} (NH) and 1640 cm^{-1} (CO); nmr (deuteriochloroform): δ 1.85 (s, 3, $COCH_3$), 4.18 (d, 2, CH_2), 6.25 (m, 2, pyrrole β-H), 6.62 (m, 2, pyrrole α-H), 6.9-7.4 (superimposed multiplets, 6, benzene and NH protons) and 7.70 ppm (s, 1, pyrazole proton).

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.43; H, 5.69; N, 20.03.

4-Formamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**18**).

A mixture of 3.6 g (0.015 mole) of 4-aminomethyl-1-phenyl-5-(1-pyrryl)-pyrazole (**6**) and 10 ml of freshly distilled ethyl formate was refluxed while stirring for 3 hours. The excess of ethyl formate was distilled off under reduced pressure and the solid residue was crystallized from ethanol to give in almost quantitative yield, 4-formamido-1-phenyl-5-(1-pyrryl)pyrazole, mp 115-116°; ir: 3300 cm^{-1} (NH), 1680 and 1645 cm^{-1} (CHO); nmr (deuteriochloroform): δ 4.2 (d, 2, CH_2), 6.26 (m, 2, pyrrole β-H), 6.6 (m, 2, pyrrole α-H), 6.75 (broad, 1, NH), 7.23 (m, 5, benzene protons), 7.70 (s, 1, pyrazole proton) and 8.08 ppm (d, 1, CHO); ms: m/e (relative intensity) 266 (M^+, 100), 237 ($C_{14}H_{13}N_4^+$, 73.8), 222 ($C_{14}H_{12}N_3^+$, 41.2), 200 ($C_{11}H_{10}N_4O^+$, 34.7), and 77 ($C_6H_5^+$,30.5).

Anal. Calcd. for $C_{15}H_{14}N_4O$: C, 67.65; H, 5.30; N, 21.04. Found: C, 67.53; H, 5.28; N, 20.91.

6-Methyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**15**). Method A.

A mixture of 1.0 g (0.0035 mole) of 4-acetamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**14**) and 5 ml of phosphorus oxychloride in 30 ml of toluene was heated at reflux for 2 hours, then evaporated under reduced pressure to remove the solvent. The residue was treated with crushed ice and made alkaline by adding 20% aqueous sodium hydroxide. After extraction with chloroform (2 × 100 ml) and evaporation of the solvent *in vacuo*, the residual oil was passed through a silica gel column (chloroform as eluent). The eluates were then evaporated to afford 6-methyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine, mp 105-106° (from cyclohexane), yield, 21%; nmr (deuteriochloroform): δ 2.38 (s, 3, CH_3), 4.4 (s, 2, CH_2), 6.2 (m, 1, C_6 proton), 6.42 (m, 1, C_7 proton), 6.7 (m, 1, C_9 proton), 7.2-7.6 (m, 5, benzene protons) and 7.65 ppm (s, 1, pyrazole proton); ms: m/e 262 (M^+).

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 73.26; H, 5.38; N, 21.36. Found: C, 73.31; H, 5.40; N, 21.29.

Method B.

Powdered **15** (1.5 g, 0.0053 mole) was added to 5 ml of phosphorus oxychloride previously cooled to 0-5°. The mixture was kept at room temperature for 4 hours with stirring, then poured onto crushed ice (50 g) and made alkaline with concentrated ammonium hydroxide. Extraction with chloroform and evaporation of solvent led to 1.1 g of crude 6-methyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]diazepine (**15**) which was then crystallized from cyclohexane to give 800 mg (64%) of pure product, mp 105-106°.

4-Chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole (**16**).

A mixture of 2.0 g (0.007 mole) of 4-acetamidomethyl-1-phenyl-5-(1-pyrryl)pyrazole (**14**) and 4 ml of phosphorus oxychloride in 30 ml of anhydrous chloroform was heated at reflux for 3 hours, then evaporated *in vacuo*. The residue was treated with crushed ice and basified by adding solid sodium carbonate with stirring. After extraction with chloroform (2 × 100 ml) and evaporation of the solvent under reduced pressure, the residue was chromatographed on silica gel column eluting with chloroform. The first eluates were collected and evaporated *in vacuo* to give 600 mg (33% yield) of 4-chloromethyl-1-phenyl-5-(1-pyrryl)pyrazole, mp 67-68°; nmr (deuteriochloroform): δ 4.40 (s, 2, CH_2Cl), 6.3 (m, 2, pyrrole β-H), 6.7 (m, 2, pyrrole α-H), 7.0-7.4 (m, 5, benzene protons) and 7.82 ppm (s, 1, pyrazole proton); ms: m/e 256.9 (M^+).

Anal. Calcd. for $C_{14}H_{12}ClN_3$: C, 65.16; H, 4.70; Cl, 13.75; N, 16.31. Found: C, 65.23; H, 4.75; Cl, 13.68; N, 16.34.

5,6-Dihydro-6-methyl-1-phenyl-1*H*,4*H*-pyrazolo[4,3-*f*]pyrrolo[1,2-*a*][1,4]-diazepine (**17**).

A solution of 500 mg (0.0019 mole) of **15** in 50 ml of ethanol-ethyl acetate mixture (1:1) was treated with 200 mg of 10% Pd/C and hydrogenated in a Parr apparatus for 4 hours. Filtration and evaporation of solvent afforded an oil (400 mg), which was dissolved in anhydrous ethyl ether (10 ml) and treated with 2 ml of absolute ethanol saturated with gaseous hydrogen chloride. The precipitated hydrochloride of **17** was filtered and recrystallized from 80% ethanol, mp 291-292°, yield, 190 mg (35%).

Anal. Calcd. for $C_{16}H_{17}ClN_4$: C, 63.89; H, 5.69; Cl, 11.80; N, 18.62. Found: C, 64.12; H, 5.55; Cl, 11.96; N, 18.59.

1-Phenyl-4-phthalimidomethyl-5-(1-pyrryl)pyrazole (**19**).

A mixture of **6** (6 g, 0.025 mole) and phthalic anhydride (3.7 g, 0.025 mole) were heated for 15 minutes at 150°. After cooling the solid obtained was recrystallized from ethanol to give **19** (8 g, 87%), mp 146-148°.

Anal. Calcd. for $C_{22}H_{16}N_4O_2$: C, 71.72; H, 4.38; N, 15.21. Found: C, 71.65; H, 4.41; N, 15.32.

5-(2-Formyl-1-pyrryl)-1-phenyl-4-phthalimidomethylpyrazole (**20**).

This compound was prepared in 81% yield from **19** by Vilsmeier-Haack formylation as previously reported [7]. This compound melted at 153-157° after recrystallization from ethanol.

Anal. Calcd. for $C_{23}H_{16}N_4O_3$: C, 69.69; H, 4.07; N, 14.14. Found: C, 69.75; H, 4.03; N, 14.01.

5-(2-Acetyl-1-pyrryl)-1-phenyl-4-phthalimidomethylpyrazole (**21**).

This compound was prepared in 54% yield from **19** by the method previously reported [7]. This compound had mp 168-170° from ethanol.

Anal. Calcd. for $C_{24}H_{18}N_4O_3$: C, 70.23; H, 4.42; N, 13.65. Found: C, 70.38; H, 4.36; N, 13.72.

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REFERENCES AND NOTES

[1] To whom inquiries should be addressed.

[2] H. A. DeWald, I. C. Nordin, Y. J. L'Italien and R. F. Parcell, *J. Med. Chem.*, **16**, 1346 (1973).

[3] H. A. DeWald, S. Lobbestael and B. P. Poschel, *J. Med. Chem.*, **24**, 982 (1981).

[4] K. H. Weber, A. Bauer and A. Langbein, to C. H. Boehringer, Sohn, German Patent 2,533,924, 17 Feb 1977; *Chem. Abstr.*, **86**, 171518e (1977).

[5] I. Ito, T. Ueda and F. Kato, *Chem. Pharm. Bull.*, **25**, 1443 (1977); H. A. DeWald, S. Lobbestael and D. E. Butler, *J. Med. Chem.*, **20**, 1562 (1977).

[6] C. C. Cheng and R. K. Robins, *J. Org. Chem.*, **21**, 1240 (1956).

[7] G. De Martino, M. Scalzo, S. Massa, R. Giuliano and M. Artico, *Farmaco, Ed. Sci.*, **27**, 980 (1972).