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Synthesis of Pyrazolone Derivatives. XVII.[1] Synthesis of a Pyrazolo[3,4-*c*]-[1]benzoxepin and Pyrazolo[3,4-*c*][1,5]benzoxazepines

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The synthesis of two new type compounds which having the three ring systems, 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1]benzoxepin-3,4-dione(I), and 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzoxazepin-3-one(II), consisting of the polyphosphoric acid cyclization or the Ullmann reaction of the appropriate pyrazolone derivatives, has been reported.

As a continuation[1] of work underway in this laboratory on the preparation of pyrazolone, derivatives having analgesic or antipyretic effect, it was deemed interesting to synthesize and investigate some new type of condensed ring compounds with hetero atoms as a part of the rings.

This paper deals with the synthesis of two kinds of such compounds, 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1]benzoxepin-3,4-dione(I) and 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzoxazepin-3-one(II).

These three ring systems are not listed in "Chemical Abstract" or "The Ring Index"[3] and appear to be novel heterocyclic types.

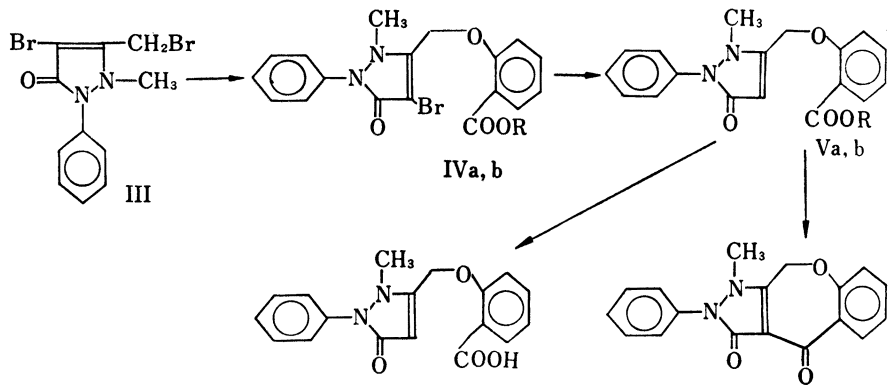

Chart 1

4-Bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (III)[4] was used as the starting material which was reacted with alkyl salicylate in the presence of sodium ethylate to give corresponding alkyl 2-(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methoxyben-

1) Part XVI: I. Ito, T. Ueda and N. Oda, *Chem. Pharm. Bull.* (Tokyo), **18**, 2058 (1970).
2) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
3) A.M. Patterson, L.T. Capell and D.F. Walker, "The Ring Index," 2nd ed., American Chemical Society, Washington, D.C., 1960, and *Supplement* I (1963), II (1964), and III (1965).
4) H. Graef, J. Ledrut and G. Combes, *Bull. Soc. Chem. Belges*, **61**, 331 (1952) (*C.A.*, **47**, 12363 (1953)).

zoates(IVa, b). The benzoates(IVa, b) were dehalogenated by catalytic hydrogenation over Raney nickel. As a by-product in this reaction, a small amount of 2,3-dimethyl-1-phenyl-pyrazolone was obtained showing the occurrence of cleavage at carbon–oxygen bond.

Treatment of the dehalogenated ester(Va) with polyphosphoric acid(PPA)[5] led to a cyclization giving the expected benzoxepin(I). Besides of the cyclized compound a small amount of needles were obtained, which were proved to be 2-(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl) methoxybenzoic acid (VI) by its infrared(IR) and nuclear magnetic resonance(NMR)spectra.

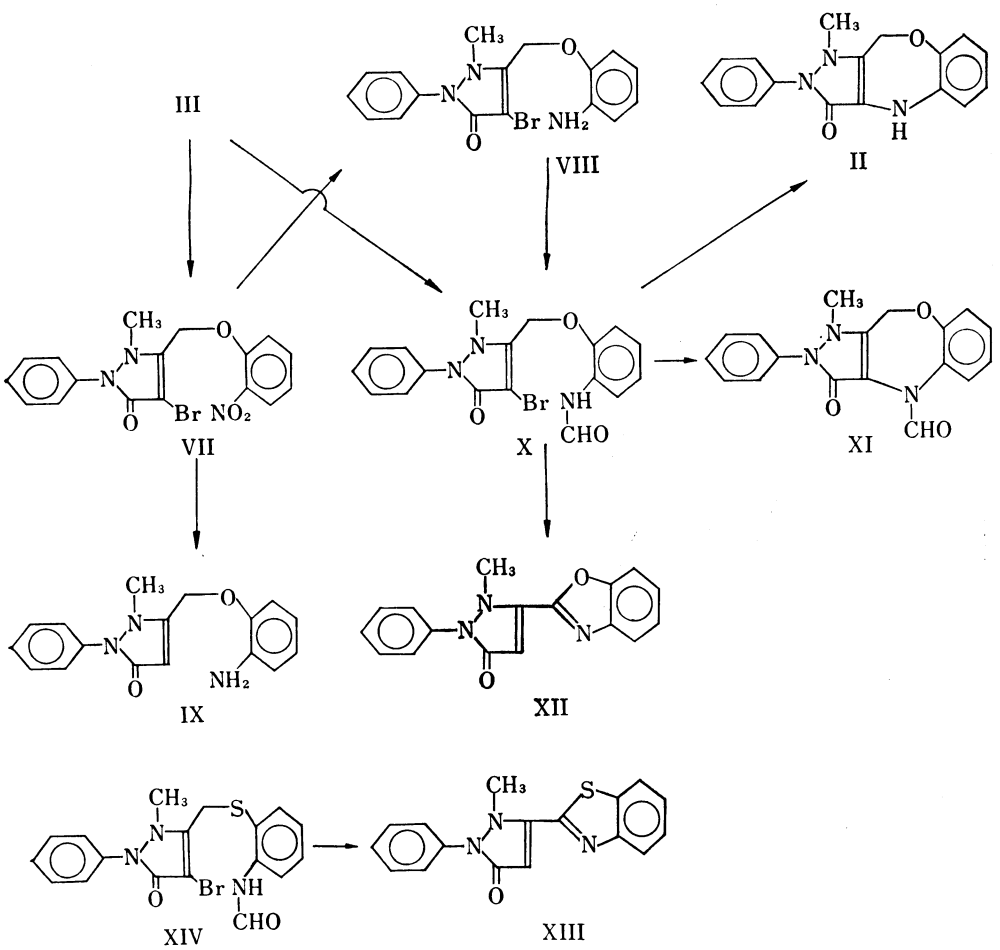

Chart 2

1-Methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzoxazepin-3-one(II) was also synthesized using the dibromide(III) as the starting material. III was reacted with *o*-nitrophenol in the presence of sodium ethylate to give 4-bromo-2-methyl-1-phenyl-3-(2-nitrophenoxy)methyl-3-pyrazolin-5-one(VII) quantitatively. Reduction of VII with stannous chloride gave the corresponding amine(VIII) in a mixture with 3-(2-aminophenoxy)methyl-2-methyl-1-phenyl-3-pyrazolin-5-one(IX). This reduction was achieved more conveniently by catalytically in the presence of Raney nickel catalyst.

5) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, N.Y., 1967, p. 894.

To eliminate the critical nature of following cyclization[6] the amino group of VIII was formylated by refluxing it with formic acid to yield formamido compound(X). A direct condensation of III with *o*-formamidophenol represented an alternative, simple approach to the preparation of the formamido compound (X) in a good yield and was utilized in the current work.

Cyclization of the formamido compound(X) by the Ullmann's method gave the expected benzoxazepine(II) in a mixture with 4-formyl-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzoxazepin-3-one(XI) resulting from the remainding of the formyl group, however, when dimethylformamide (DMF) was used as a solvent 3-(benzoxazol-2-yl)-2-methyl-1-phenyl-3-pyrazolin-5-one(XII) was a sole product.

The structure of II was reliably established by the measurement of IR and NMR spectra. A strong band at 3290 cm^{-1} can be attributed to NH stretching of secondary amine.[7] A formyl carbonyl stretching band at 1696 cm^{-1} which was presented in the starting compound (X) was no longer showed in the spectrum of II. The NMR spectrum of II was characterized by sharp singlets at τ 7.12 and 4.93 corresponding to the methyl and methylene groups respectively, and a broad resonance at approximately τ 3.58 corresponding to the imino group, which was erased on exchange with deuterium oxide.

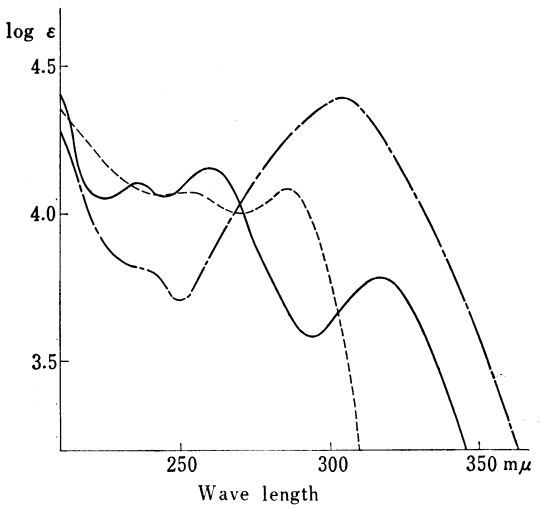

Fig. 1. Ultraviolet Absorption Spectra (in EtOH)

———: 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo-[3,4-*c*][1,5]benzoxazepin-3-one (II)
– – – –: 4-formyl-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzoxazepin-3-one (XI)
– – – – –: 3-(benzoxazol-2-yl)-2-methyl-1-phenyl-3-pyrazolin-5-one (XII)

The compound (XI) was formulated in the light of the following facts. In the IR spectrum of this product there were absorption bands at 1693 and 1660 cm^{-1} showing the formyl and pyrazolone carbonyl groups respectively. And by the absence of any imino absorption band in the 3 μ region. NMR spectrum of XI revealed a sharp singlet at τ 1.16 corresponding to the formyl proton, and no imino proton signal.

The benzoxazolyl compound (XII) was formulated in the light of the following facts. In the IR spectrum XII showed pyrazoline carbonyl band at 1657 cm^{-1} and no formyl carbonyl band at the 6 μ region. The NMR spectrum revealed sharp singlets at τ 6.48 and 3.66 corresponding to the N-methyl protons and the olefin proton respectively, and showed no any other signal except the aromatic proton signals. The higher intensity (log ε 4.39) and the location (306 mμ) of the ultraviolet (UV) spectrum of XII, as shown in Fig. 1, can be taken as indicative of the extension conjugated system.

In addition, the structure was supported by following fact. An analogous side reaction in the Ullmann's reaction has already been reported by the authors.[1] Namely, 3-benzothiazolyl-3-pyrazoline derivatives (XIII) have been obtained from 3-(2-formamidophenyl)thiomethyl-3-pyrazoline derivatives (XIV) by boiling with potassium carbonate and copper bronze in DMF as a solvent.

6) *e.g.*, E.A. Nodiff, S. Lipschutz, P.N. Craig and M. Gordon, *J. Org. Chem.*, **25**, 60 (1960); A. Roe and W.F. Little, *J. Org. Chem.*, **20**, 1577 (1955).
7) L.J. Bellamy, "The Infra Red Spectra of Complex Molecules," 2nd ed., John Wiley and Sons., Inc., New York, N.Y., 1958, p. 203.

Experimental

Melting points were measured by capillary tubes and uncorrected. IR spectra were taken on a Nihon Bunko Model IR-S spectrophotometer and UV spectra on a Hitachi Recording spectrophotometer EPS-3T. NMR spectra were recorded on a Japan Electron optics Laboratory Co. JNM-MH-60 spectrometer using tetramethylsilane as an internal standard.

Methyl 2-(4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methoxybenzoate(IVa)——To a solution of 4.0 g of NaOH in 700 ml of EtOH 22.8 g of methyl salicylate was added, and then 34.6 g of the dibromide (III) was dissolved to the solution. Resulting solution was refluxed for 6 hr on a water bath and left overnight at room temperature. Separating crystals were filtered and recrystallized from EtOH to colorless needles, mp 158°. Yield, 34 g (81.5%). *Anal.* Calcd. for $C_{19}H_{17}O_4Br$: C, 54.69; H, 4.11; N, 6.71. Found: C, 54.69; H, 4.14; N, 6.79. IR ν_{max}^{KBr} cm^{-1}: 2936 (CH), 1718 (C=O ester), 1666 (C=O). NMR (20% solution in $CDCl_3$) τ: 6.70 (3H, singlet, N-CH_3), 6.50 (3H, singlet, $COOCH_3$), 4.82 (2H, singlet, -CH_2-), 2.12—2.96 (9H, multiplet, aromotic protons).

Ethyl 2-(4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methoxybenzoate(IVb)——This compound was prepared in the same manner as for IVa using ethyl salicylate. Colorless needles, mp 120—121°. *Anal.* Calcd. for $C_{20}H_{19}O_4Br$: C, 55.70; H, 4.44; N, 6.50. Found: C, 55.62; H, 4.52; N, 6.47. IR ν_{max}^{KBr} cm^{-1}: 2926, 2870 (C-H), 1710 (C=O ester), 1663 (C=O). NMR (20% solution in $CDCl_3$) τ: 8.61 (3H, triplet, J= 7 cps, -CH_2-CH_3), 6.62 (3H, singlet, N-CH_3), 5.60 (2H, quartet, J=7 cps, -CH_2-CH_3), 4.74 (2H, singlet, -CH_2-), 2.55—2.95 (9H, multiplet, aromatic protons).

Methyl 2-(2-Methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methoxybenzoate(Va)——A mixture of 5 g of the bromo ester (IVa), 1 g of $NaHCO_3$, 15 ml of water and 250 ml of EtOH was hydrogenated for 7 hr in the presence of Raney nickel prepared from 2 g of the alloy. After removal of the catalyst, the solvent was evaporated to dryness under reduced pressure. The residue was crystallized from EtOH to colorless prisms, mp 124—125°. Yield, 2.6 g (64.1%). *Anal.* Calcd. for $C_{19}H_{18}O_4N_2$: C, 67.45; H, 5.36; N, 8.28. Found: C, 67.31; H, 5.44; N, 8.01. IR ν_{max}^{KBr} cm^{-1}: 1705 (C=O ester), 1650 (C=O). NMR (20% solution in $CDCl_3$) τ: 6.80 (3H, singlet, N-CH_3), 6.16 (3H, singlet, $COOCH_3$), 4.98 (2H, singlet, -CH_2-), 4.35 (1H, singlet, CH), 2.20—3.02 (9H, multiplet, aromatic protons). Concentration of the mother liquor gave 0.2 g of colorless prisms, mp 113° which was proved to be 2,3-dimethyl-1-phenylpyrazolone by its IR spectrum and a mixed melting point determination with an authentic sample.

Ethyl 2-(2-Methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methoxybenzoate(Vb)——This compound was prepared in the same manner as for Va using the corresponding ethyl ester (IVb). Colorless prisms, mp 118°. *Anal.* Calcd. for $C_{20}H_{20}O_4N_2$: C, 68.17; H, 5.72; N, 7.95. Found: C, 68.11; H, 5.71; N, 8.02. IR ν_{max}^{KBr} cm^{-1}: 1708 (C=O ester), 1658 (C=O). NMR (20% solution in $CDCl_3$) τ: 8.65 (3H, triplet, J=7 cps, -CH_2-CH_3), 6.78 (3H, singlet, N-CH_3), 5.66 (2H, quartet, J=7 cps, -CH_2-CH_3), 4.95 (2H, singlet, -CH_2-), 4.30 (1H, singlet, CH), 2.18—3.06 (8H, multiplet, aromatic protons).

1-Methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1]benzoxepin-3,4-dione(I)——A mixture of 5 g of the dehalogenated ester (Va) and 130 g of PPA was stirred on an oil bath at 100—110° for 5 hr. The mixture was diluted with water and adjusted to pH 7.0 with Na_2CO_3. The mixture was extracted with $CHCl_3$ and evaporated to dryness. The residue was crystallized from benzene to colorless prisms, mp 206—207°. Yield, 2.8 g (61.9%). *Anal.* Calcd. for $C_{18}H_{14}O_3N_2$: C, 70.58; H, 4.61; N, 9.15. Found: C, 70.43; H, 4.49; N, 9.07. IR ν_{max}^{KBr} cm^{-1}: 1676 (C=O broad). NMR (20% solution in deutrated DMSO) τ: 6.68 (3H, singlet, N-CH_3), 4.59 (2H, singlet, -CH_2-), 2.02—2.88 (9H, multiplet, aromatic protons). By the concentration of the mother liquor, a small amount of 2-(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)methoxybenzoic acid (VI) was obtained as colorless prisms, mp 193—194°. Yield, 0.03 g. *Anal.* Calcd. for $C_{18}H_{16}O_4N_2$: C, 66.66; H, 4.97; N, 8.64. Found: C, 66.53; H, 4.86; N, 8.48. IR ν_{max}^{KBr} cm^{-1}: 2825—2320 (characteristic peaks of -COOH dimer[8]), 1715 (C=O). NMR (10% solution in deutrated DMSO) τ: 6.78 (3H, singlet, N-CH_3), 4.74 (2H, singlet, -CH_2-), 4.31 (1H, singlet, CH), 4.10 (1H, broad singlet, COOH, erased on exchange with D_2O), 2.22—3.05 (9H, multiplet, aromatic protons).

4-Bromo-2-methyl-1-phenyl-3-(2-nitrophenoxy)methyl-3-pyrazolin-5-one(VII)——To a solution of 13.9 g of *o*-nitrophenol in 250 ml of anhydrous EtOH containing 2.3 g of sodium was added 34.6 g of the dibromide (III) in 500 ml of anhydrous EtOH. The solution was warmed on a water bath at 50—60° for 5 hr. After cooling, separating crystals were filtered and recrystallized from EtOH to colorless needles, mp 210°. Yield, 38.6 g (95.5%). *Anal.* Calcd. for $C_{17}H_{14}O_4N_3Br$: C, 50.51; H, 3.49; N, 10.40. Found: C, 50.58; H, 3.71; N, 10.55. IR ν_{max}^{KBr} cm^{-1}: 1660 (C=O), 1522, 1345 (NO_2). NMR (10% solution in $CDCl_3$) τ: 6.66 (3H, singlet, N-CH_3), 4.68 (2H, singlet, -CH_2-), 2.58—2.85 (9H, multiplet aromatic protons).

3-(2-Aminophenoxy)methyl-4-bromo-2-methyl-1-phenyl-3-pyrazolin-5-one(VIII)——a) A solution of 2 g the nitro compound (VII) in 150 ml of EtOH was hydrogenated for 5 hr in the presence of Raney nickel prepared from 0.8 g of the alloy. During the period the required hydrogen (333 ml) was absorbed. After removal of the catalyst, the solvent was evaporated to dryness. The residue was crystallized from EtOH

8) K. Nakanishi, "IR Absorption Spectroscopy -Practical-," Nankodo, Tokyo, 1960, p. 49.

to colorless prisms, mp 192—193° (decomp.). Yield, 1.2 g (64.8%). *Anal.* Calcd. for $C_{17}H_{16}O_2N_3Br$: C, 54.56; H, 4.31; N, 11.23. Found: C, 54.43; H, 4.50; N, 11.40. IR ν_{max}^{KBr} cm^{-1}: 3420, 3306 (NH_2), 1660 (C=O). NMR (20% solution in $CDCl_3$) τ: 6.77 (3H, singlet, N-CH_3), 6.42 (2H, singlet, NH_2, erased on exchange with D_2O), 4.90 (2H, singlet, -CH_2-), 2.63—3.20 (9H, multiplet, aromatic protons).

b) To a stirred solution of 4 g of the nitro compound (VII) in 100 ml of EtOH, a solution of 6.8 g of stannous chloride in 7 ml of conc. HCl was gradually added. The mixture was heated on a water bath at 60—70° for 2 hr. The mixture was made alkaline with 10% NaOH and extracted with AcOEt. The extract was evaporated to dryness and crystallized from EtOH to colorless prisms, mp 192—193° (decomp.). Yield, 1.8 g (48.6%). This product was identical with the product obtained above method a). From the mother liquor a small amount of 3-(2-aminophenoxy)methyl-2-methyl-1-phenyl-3-pyrazolin-5-one(IX) was obtained as colorless prisms, mp 162°. Yield, 0.1 g. *Anal.* Calcd. for $C_{17}H_{17}O_2N_3$: C, 69.14; H, 5.80; N, 14.23. Found: C, 69.35; H, 5.77; N, 14.35. IR ν_{max}^{KBr} cm^{-1}: 3380, 3330 (NH_2), 1640 (C=O). NMR (20% solution in $CDCl_3$) τ: 6.85 (3H, singlet, N-CH_3), 6.16 (2H, singlet, NH_2, erased on exchange with D_2O), 5.05 (2H, singlet, -CH_2-), 4.32 (1H, singlet, CH), 2.66—3.26 (9H, multiplet, aromatic protons).

4-Bromo-3-(2-formamidophenoxy)methyl-2-methyl-1-phenyl-3-pyrazolin-5-one(X)——a) A solution of 3 g of the amino compound (VIII) in 10 ml of 99% formic acid was refluxed for 1 hr. The reaction mixture was poured onto 100 ml of ice water. The resulting precipitate was crystallized from MeOH to colorless prisms, mp 225—226° (decomp.). Yield, 2.6 g (80.6%). *Anal.* Calcd. for $C_{18}H_{16}O_3N_3Br$: C, 53.75; H, 4.01; N, 10.45. Found: C, 53.96; H, 4.15; N, 10.67. IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1696 (CHO), 1663 (C=O). NMR (10% solution in deutrated DMSO) τ: 6.70 (3H, singlet, N-CH_3), 4.75 (2H, singlet, -CH_2-), 2.98 (2H, broad singlet, NH), 1.72—2.90 (9H, multiplet, aromatic protons), 0.53 (1H, broad singlet, CHO).

b) A solution of 17.3 g of the dibromide (III) in 500 ml of anhydrous EtOH was added to a solution of 6.9 g of *o*-formamidophenol in 100 ml of anhydrous EtOH containing 1.15 g of sodium. The mixture was stirred for 1 hr and was allowed to stand overnight. Separating crystals were filtered and recrystallized from EtOH to colorless prisms, mp 225—226° (decomp.). Yield, 17.3 g (86.0%). This product was identical with the product obtained above method a).

Cylization of 4-Bromo-3-(2-formamidophenoxy)methyl-2-methyl-1-phenyl-3-pyrazolin-5-one(X)——A mixture of 6 g of the formamido compound (X), 4.1 g of K_2CO_3, and 4.8 g of copper bronze[9] in 480 ml of dry xylene was refluxed for 22 hr with stirring. The hot reaction mixture was filtered and evaporated to dryness. The residue was crystallized from benzene to give 4-formyl-1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzoxazepin-3-one(XI) as colorless prisms, mp 243°. Yield, 1.8 g (37.6%). *Anal.* Calcd. for $C_{18}H_{15}O_3N_3$: C, 67.28; H, 4.71; N, 13.08. Found: C, 67.23; H, 4.79; N, 12.78. UV $\lambda_{max}^{ethanol}$ mμ (log ε): 251 (4.07), 284 (4.08). IR ν_{max}^{KBr} cm^{-1}: 1693 (CHO), 1660 (C=O). NMR (10% solution in $CDCl_3$) τ: 6.99 (3H, singlet, N-CH_3), 4.87 (2H, singlet, -CH_2-), 2.50—2.70 (9H, multiplet, aromatic protons), 1.16 (1H, singlet, CHO).

The mother liquor was evaporated to dryness. The residue was dissolved in benzene, and the solution was passed through a column of alumina. The effluent was evaporated to dryness and crystallized from EtOH to give 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4H-pyrazolo[3,4-*c*][1,5]benzoxazepin-3-one(II) as colorless prisms, mp 225—227°. Yield, 0.5 g (11.4%). *Anal.* Calcd. for $C_{17}H_{15}O_2N_3$: C, 69.61; H, 5.15; N, 14.33. Found: C, 69.42; H, 5.19; N, 14.01. UV $\lambda_{max}^{ethanol}$ mμ (log ε): 236 (4.09), 259 (4.14), 318 (3.78). IR ν_{max}^{KBr} cm^{-1}: 3290 (NH), 1655 (C=O). NMR (10% solution in $CDCl_3$) τ: 7.12 (3H, singlet, N-CH_3), 4.93 (2H, singlet, -CH_2-), 3.58 (1H, broad singlet, NH, erased on exchange with D_2O), 2.46—3.01 (9H, multiplet, aromatic protons).

3-(Benzoxazol-2-yl)-2-methyl-1-phenyl-3-pyrazolin-5-one(XII)——A mixture of 2 g of the formamido compound (X), 0.69 g of K_2CO_3, 0.8 g of copper bronze, and 30 ml of DMF was heated at 150—160° for 20 min with stirring. The mixture was filtered, diluted with 60 ml of water and extracted with benzene. The extract was evaporated to an oil and crystallized from benzene to colorless needles, mp 225—227°. Yield, 0.4 g (27.6%). *Anal.* Calcd. for $C_{17}H_{13}O_2N_3$: C, 70.09; H, 4.50; N, 14.42. Found: C, 70.05; H, 4.48; N, 14.74. UV $\lambda_{max}^{ethanol}$ mμ (log ε): 240 (3.81 shoulder), 306 (4.39). IR ν_{max}^{KBr} cm^{-1}: 1657 (C=O). NMR (10% solution in $CDCl_3$) τ: 6.48 (3H, singlet, N-CH_3), 3.66 (1H, singlet, CH), 2.55—2.86 (9H, multiplet, aromatic protons).

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9) L.F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York, N.Y., 1967, p. 155.