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Synthesis of Pyrazolone Derivatives. XXII.[1] Synthesis of Benzo-[4,5]cyclohepta[1,2-*c*]pyrazole-diones[2]

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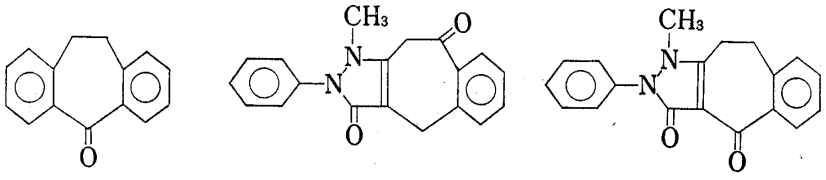
Treatment of methyl 4-benzyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (**7a**) with dimethyl sulfate followed by hydrolysis of the resulting methyl 4-benzyl-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (**9**) afforded 4-benzyl-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-acetic acid (**12**). 1-Methyl-2-phenyl-3,9-dioxo-1,2,3,4,9,10-hexahydrobenzo[4,5]-cyclohepta[1,2-*c*]pyrazole (**2**) was prepared by cyclization of **12** with polyphosphoric acid. The synthesis of 1-methyl-2-phenyl-3,4-dioxo-1,2,3,4,9,10-hexahydrobenzo[4,5]cyclohepta-[1,2-*c*]pyrazole (**3**) which is structurally related to **2** was also carried out starting from 4-bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one (**15**).

In the course of an investigation of compounds containing linear tricyclic ring systems, it was found that certain derivatives of 10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5-one (**1**) exhibited a number of interesting effects on the central nervous system. Of these, 5-substituted-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cycloheptene derivatives (amitriptyline and nortriptyline[4]) have been widely used clinically as an effective antidepressant agent. After consideration of the structural relationships, it appeared that an investigation of similar derivatives of ring systems structurally related to **1** might lead to compounds with useful pharmacological properties. This paper is concerned with the synthesis of 1-methyl-2-phenyl-3,9-dioxo-1,2,3,4,9,10-hexahydrobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (**2**) and 1-methyl-2-phenyl-3,4-dioxo-1,2,3,4,9,10-hexahydrobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (**3**) in which one of the aromatic rings of **1** is replaced by a pyrazole ring.



1 **2** **3**

Chart 1

4-Benzyl-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-acetic acid (**12**), a useful intermediate in the synthesis of **2**, was prepared from the readily available dimethyl 3-oxoglutarate (**4**) as outlined in Chart 2. Reaction of **4** with benzyl bromide in methanol in the presence of sodium methoxide gave 2-benzyl-3-oxoglutarate (**5a**) as a colorless oil in 53% yield and 2,4-dibenzyl-3-oxoglutarate (**6**) as a crystal in 15% yield respectively, while reaction in dimethylformamide gave **6** as the major product. Two glutarates were separated readily in pure form by the repeated fractional distillation. Treatment of **5a** with phenylhydrazine at 100° gave methyl 4-benzyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (**7a**) as a sole product in 68% yield. In

1) Part XXI: I. Ito and T. Ueda, *Tetrahedron*, 30, 1027 (1974).
2) A part of this paper was presented at the 92th Annual Meeting of Pharmaceutical Society of Japan, Osaka, April 1972.
3) Location: *3-1 Tanabe-dori, Mizuho-ku, Nagoya.*
4) R.D. Hoffsommer, D. Taub, and N.L. Wendler, *J. Org. Chem.*, 27, 4134 (1962).

this reaction the formation of methyl 5-oxo-1-phenyl-3-pyrazoline-3-benzylacetate (**8**) was also anticipated, because **5a** has two ester functions in its structure which are condensable with phenylhydrazine. However, the formation of **8** was denied by means of the inspection of nuclear magnetic resonance (NMR) spectrum, namely NMR spectrum of **7a** did not exhibit an olefinic proton signal which might be observed in that of **8**. The structure of **7a** was confirmed by the further experiments as described below. N-methylation of **7a** with dimethyl sulfate or methyl iodide gave methyl 4-benzyl-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (**9**) in good yield. Prolonged heating of **9** with 2% potassium hydroxide afforded easily 4-benzyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one (**10**) which was identical with an authentic sample[1] prepared in two steps *via* 4-benzyl-3-methyl-1-phenyl-3-pyrazolin-5-one (**11**), starting from ethyl benzylacetoacetate.

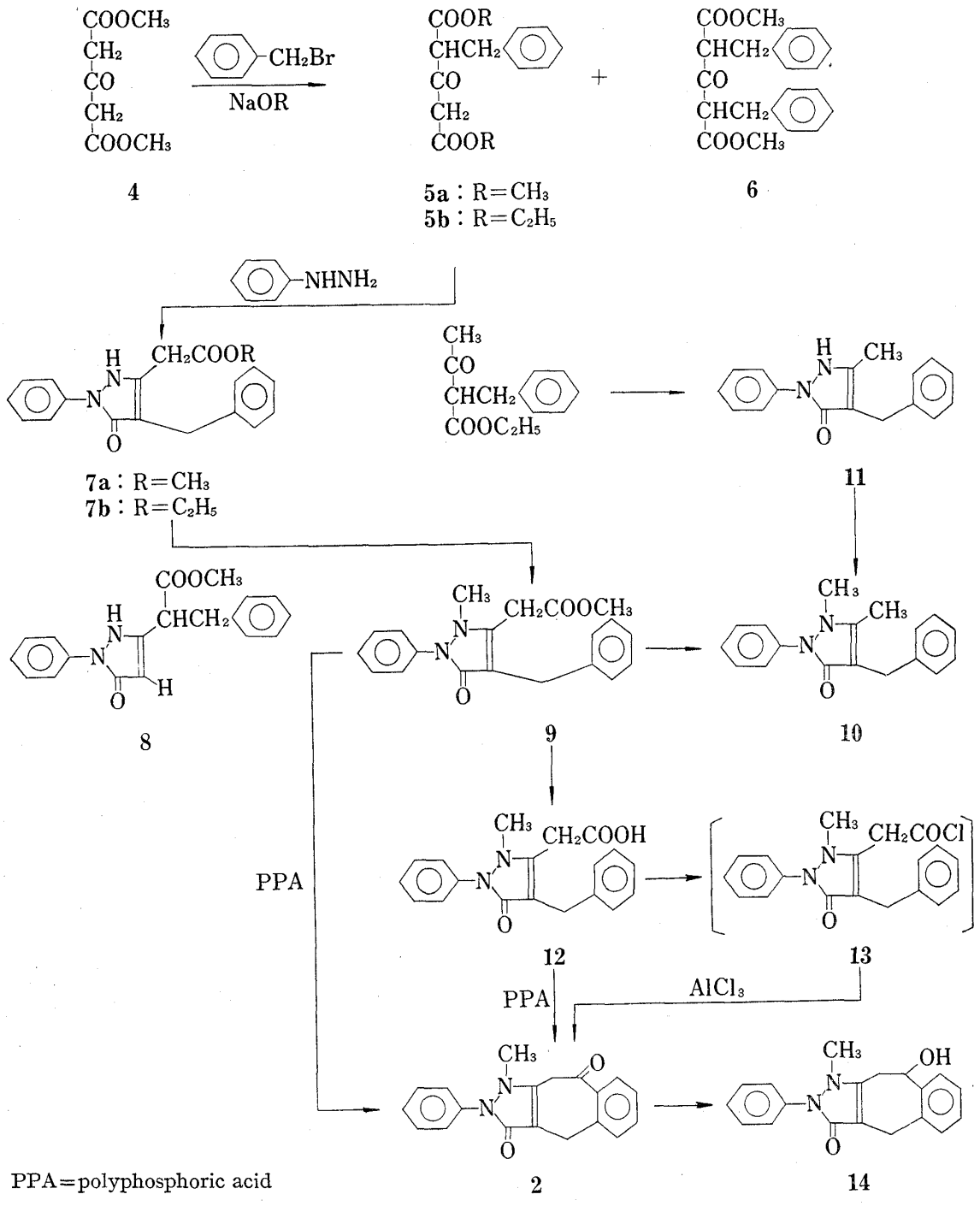
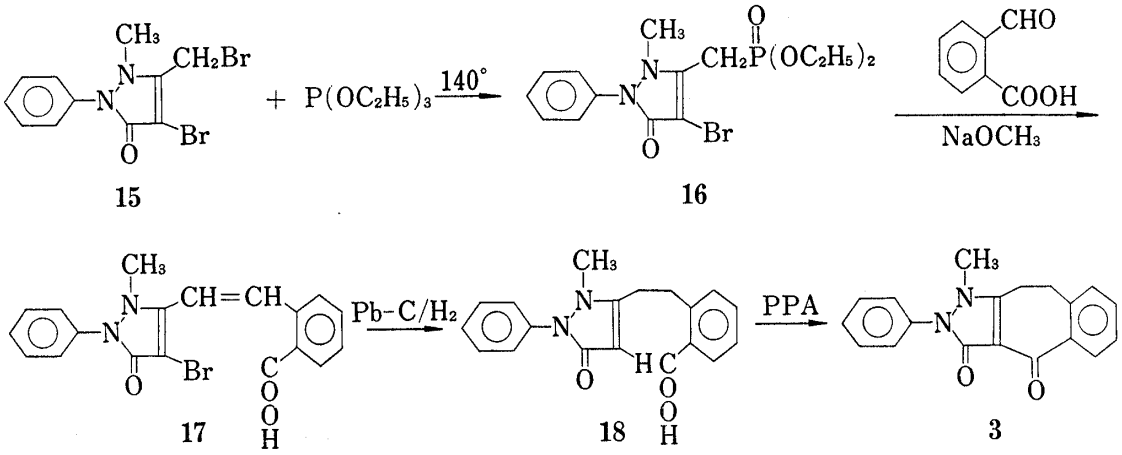


Chart 2

Ethyl 4-benzyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (**7b**) was similarly obtained by the reaction of phenylhydrazine with diethyl benzyloxoglutarate (**5b**)[5] which was produced on treatment of **4** with benzyl bromide in ethanol using sodium ethoxide. Hydrolysis of **9** at a low temperature gave **12** in 82% yield.

Attempted cyclization to **2** from ester (**9**) or acid chloride (**13**) was made in the following ways. Polyphosphoric acid cyclization of **9** provided **2** with fairly amounts of tarry products. This cyclization proceeded in poor yield and therefore was considered as an impractical preparation method. The Friedel–Crafts cyclization of **13** was also resulted in poor yield. Cyclization of **12** with polyphosphoric acid, however, improved the yield to 74%. Thus, this procedure was preferable to the ring closure. The structural assignment of **2** was supported by ultraviolet spectrum which showed a marked bathochromic shift compared with the spectrum of **12**. This indicates the formation of a new tricyclic conjugated system. Catalytic reduction of **2** in the presence of Raney nickel catalyst isolated 9-hydroxy-1-methyl-2-phenyl-3-oxo-1,2,3,4,9,10-hexahydrobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (**14**) in 89% yield.

Another benzocycloheptapyrazole (**3**) was synthesized as shown in Chart 3, starting from 4-bromo-3-bromomethyl-2-methyl-1-phenyl-3-pyrazolin-5-one[6] (**15**). Diethyl 4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-methylphosphonate (**16**), obtained as a viscous oil by the reaction of **15** with triethylphosphite, was condensed with *o*-phthalaldehydic acid in dimethylformamide using sodium methoxide to give 2-[β-(4-bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)ethylene]benzoic acid (**17**) in 87% yield. Hydrogenation of **17** over palladium on carbon at 3 kg/cm² resulted in debromination and reduction of vinyl function to yield 2-[β-(2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)ethyl]benzoic acid (**18**). The ring closure to the tricyclic compound (**3**) proceeded smoothly at 130° under reduced pressure. The structural assignment of compounds prepared in Chart 3 was satisfactorily performed with the spectral data.



PPA=polyphosphoric acid

Chart 3

Experimental

Melting points were determined on a Yanagimoto Micro-Melting Point apparatus and are uncorrected. Infrared (IR) spectra were determined with a Nihon Bunko Model IR-G spectrophotometer. NMR spectra were determined on a Japan Electron optics Laboratory Co. JNM-MH-60 spectrometer and all chemical shifts are relative to tetramethylsilane as an internal standard.

Dimethyl 2-Benzyl-3-oxoglutarate (5a) and Dimethyl 2,4-Dibenzyl-3-oxoglutarate (6)——To a solution of 0.53 g (0.023 mole) of sodium and 70 ml of absolute methanol was added dropwise 4 g (0.023 mole) of

5) F. Šorm, J. Beránek, J. Smrt, and J. Sicher, *Collection Czech. Chem. Commun.*, **20**, 593 (1955). In this report 5b was prepared from $C_6H_5CH_2CH(COCl)_2$ and $CH_2=CO$.
6) H. Graef, J. Ledrut, and G. Combes, *Bull. Soc. Chim. Belges*, **61**, 331 (1952).

dimethyl 3-oxoglutarate, followed by 3.6 g (0.023 mole) of benzyl bromide. The reaction mixture was refluxed for 24 hr and evaporated *in vacuo*. Water was added to the residue and the solution was extracted with ethyl acetate. Removal of the extracts gave a brown oil which was distilled to afford 2.4 g (53%) of **5a**, bp 139—140° (0.1 mmHg). *Anal.* Calcd. for $C_{14}H_{16}O_5$: C, 63.63; H, 6.10. Found: C, 63.99; H, 5.85. NMR ($CDCl_3$) τ: 2.85 (5H, singlet, aromatic protons), 5.95 (1H, triplet, $J=7.5$ Hz, $C\underline{H}CH_2$), 6.29 (3H, singlet, $COOCH_3$) 6.80 (2H, doublet, $J=7.5$ Hz, $CHC\underline{H}_2$), 6.95 (2H, singlet, $C\underline{H}_2COOCH_3$).

From a fraction, bp 150° (0.1 mmHg) was obtained **6** which solidified on standing. Recrystallization from petroleum ether gave colorless prisms, mp 99—100°. Yield 0.9 g (15%). *Anal.* Calcd. for $C_{21}H_{22}O_5$: C, 71.17; H, 6.26. Found: C, 71.31; H, 6.40. NMR ($CDCl_3$) τ: 2.89 (10H, singlet, aromatic protons), 5.91 (2H, triplet, $J=7.5$ Hz, $2\times C\underline{H}CH_2$), 6.61 (6H, singlet, $2\times COOCH_3$), 6.90 (4H, doublet, $J=7.5$ Hz, $2\times CHC\underline{H}_2$).

Methyl 4-Benzyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (7a)——A mixture of 3.2 g (0.012 mole) of **5a** and 1.3 g (0.012 mole) of phenylhydrazine was heated at 100° for 3 hr. The reaction mixture solidified and was dissolved in ethyl acetate. After dried over magnesium sulfate, the organic solution was evaporated *in vacuo* to afford white powders. Recrystallization from isopropylether gave colorless prisms, mp 120—122°. Yield 2.6 g (68%). *Anal.* Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.86; H, 5.56; N, 8.45. IR ν_{max}^{KBr} cm^{-1}: 1750 ($COOCH_3$). NMR ($CDCl_3$) τ: 6.05 and 6.75 (2H, AB quartet, $J=9$ Hz, $C\underline{H}_2C_6H_5$), 6.30 (3H, singlet, $COOCH_3$), 6.55 (2H, singlet, $C\underline{H}_2COOCH_3$).

Ethyl 4-Benzyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (7b)——A mixture of 1 g (0.003 mole) of **5b** and 0.33 g (0.003 mole) of phenylhydrazine was worked up as described in the preparation of **7a**. After recrystallization from petroleum ether, **7b** was obtained as light yellow prisms, mp 122—124°. Yield 0.69 g (60%). *Anal.* Calcd. for $C_{20}H_{20}O_3N_2$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.36; H, 5.87; N, 8.37.

Methyl 4-Benzyl-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-acetate (9)——a) A suspension of 0.33 g (0.001 mole) of **7a** and 3 g (0.024 mole) of dimethyl sulfate was stirred at 110° for 4 hr. The solution was neutralized with dilute sodium bicarbonate solution and extracted with chloroform. A viscous oil, obtained after removal of extracts was chromatographed on silica gel. Elution with chloroform gave colorless oil which solidified on standing. Recrystallization from ether–methanol gave colorless prisms, mp 148—150°. Yield 0.22 g (65%). *Anal.* Calcd. for $C_{20}H_{20}O_3N_2$: C, 71.41; H, 5.99; N, 8.33. Found: C, 71.67; H, 6.02; N, 8.21. IR ν_{max}^{KBr} cm^{-1}: 1753 ($COOCH_3$). NMR ($CDCl_3$) τ: 6.95 (3H, singlet, N–CH_3).

b) To a suspension of 0.05 g (0.001 mole) of sodium hydride (50% dispersion in paraffin oil) in 10 ml of dry toluene, was added dropwise 0.3 g (0.0009 mole) of **7a**, followed by 0.14 g (0.001 mole) of methyl iodide in 5 ml of dry toluene. The reaction mixture was refluxed for 2 hr. Water was added to the solution and the organic layer was separated. Removal of solvent gave a viscous oil which was triturated with ether. The resulting powders were recrystallized from ether–methanol to give colorless prisms, mp 148—150°; identical with **9** prepared by procedure a). Yield 0.17 g (54%).

Hydrolysis of 9——A solution of 0.4 g (0.001 mole) of **9** and 10 ml of 2% potassium hydroxide was heated under reflux for 2 hr and evaporated to dryness. The residue was dissolved in a mixture of water and chloroform. The chloroform layer was separated, dried over magnesium sulfate and evaporated. The resulting oil was triturated with petroleum ether to give crystals. Recrystallization from petroleum ether gave colorless needles, mp 75—77°, identical by IR spectrum and mixture melting point with an authentic 4-benzyl-2,3-dimethyl-1-phenyl-3-pyrazolin-5-one[1] (10). Yield 0.27 g (81%). *Anal.* Calcd. for $C_{18}H_{18}ON_2$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.46; H, 6.62: N, 9.86.

4-Benzyl-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-acetic Acid (12)——A solution of 0.4 g (0.001 mole) of **9** and 10 ml of 2% potassium hydroxide was allowed to stand overnight in a refrigerator and evaporated to dryness. Water was added to the residue and the solution was acidified with 10% hydrochloric acid to yield white precipitates which were collected and dried. Recrystallization from ethanol gave colorless prisms, mp 149—150° (decomp.). Yield 0.31 g (82%). *Anal.* Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.80; H, 5.72; N, 8.56. IR ν_{max}^{KBr} cm^{-1}: 1725 (COOH). NMR ($CDCl_3$–DMSO-d_6) τ: 6.40 (4H, broad singlet, $C\underline{H}_2COOH$ and $C\underline{H}_2C_6H_5$), 7.95 (3H, singlet, N–CH_3).

1-Methyl-2-phenyl-3,9-dioxo-1,2,3,4,9,10-hexahydrobenzo[4,5]cycloheptа[1,2-*c*]pyrazole (2)——a) A solution of 0.3 g (0.0009 mole) of **9** and 10 g of polyphosphoric acid was heated with stirring at 160° for 6 hr. The mixture was treated with cracked ice and the resulting solution was made alkaline with powdered potassium carbonate. The dark green precipitates were extracted with chloroform. Removal of chloroform left tan solids which were recrystallized twice from ethanol using Norite to give pale brown amorphous powders, mp 265—267° (decomp.). Yield 0.054 g (20%). *Anal.* Calcd. for $C_{19}H_{16}O_2N_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 74.62; H, 5.26; N, 9.02. IR ν_{max}^{KBr} cm^{-1}: 1630 (C=O). UV λ_{max}^{EtOH} $m\mu$ (log ε): 302 (4.03). NMR (DMSO-d_6) τ: 6.65 (3H, singlet, N–CH_3), 7.07 (2H, singlet, $C\underline{H}_2CO$), 7.89 (2H, singlet, $C\underline{H}_2C_6H_5$).

b) A solution of 0.3 g (0.0009 mole) of **12** and 3 g of thionyl chloride in 5 ml of dry chloroform was refluxed for 2 hr and evaporated to dryness. The resulting crude acid chloride **13** was dissolved in dry tetrachloroethane containing 0.37 g (0.0027 mole) of aluminum chloride. The mixture was refluxed for 6 hr and extracted with chloroform after treatment of water. Removal of organic extracts gave a dark red oil. Chromatography on aluminum oxide separated brown solids, identical with **2** prepared by procedure a). Yield 0.032 g (12%).

c) A solution of 2 g (0.006 mole) of **12** and 32 g of polyphosphoric acid was worked up as described in a). The reaction product was chromatographed on aluminum oxide to give 1.4 g (74%) of pale brown amorphous powders, identical with **2** prepared by procedure a).

9-Hydroxyl-1-methyl-2-phenyl-3-oxo-1,2,3,4,9,10-hexahydrobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (14)——A mixture of 0.5 g (0.0016 mole) of **2** and 300 ml of absolute ethanol was hydrogenated over 0.5 g of Raney nickel catalyst under a pressure of 5 kg/cm² for 5 hr. The catalyst was removed by suction and the filtrate was evaporated to dryness. The residue was recrystallized from ethanol to give colorless prisms, mp 237—239°. Yield 0.45 g (89%). *Anal.* Calcd. for $C_{19}H_{18}O_2N_2$: C, 74.49; H, 5.92; N, 9.14. Found: C, 74.45; H, 5.93; N, 9.03. IR ν_{max}^{KBr} cm^{-1}: 3336 (OH).

Diethyl 4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazoline-3-methylphosphonate (16)——Two grams (0.006 mole) of **15** was melted at 130°. To the resulting solution was added 1 g (0.006 mole) of triethylphosphite within 10 min. The mixture was heated at 130° for 3 hr and chromatographed on silica gel. Elution with chloroform afforded a viscous oil which was a sole product by gas chromatography analysis on a 1 m × 3 mm vpc column packed with 1.5% Silicon OV-17 on chromosorb AW. Yield 1.5 g (68%). NMR ($CDCl_3$) τ: 5.72 (4H, quartet, J=7.5 Hz, 2×$OC\underline{H}_2CH_3$), 6.47 (2H, singlet, CH_2), 8.63 (6H, triplet, J=7.5 Hz, 2×$OCH_2C\underline{H}_3$).

2-[β-(4-Bromo-2-methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)ethylene]benzoic Acid (17)——To a suspension of 0.94 g (0.017 mole) sodium methoxide, 3.5 g (0.009 mole) of **16** and 20 ml of dry dimethylformamide was added dropwise 1.3 g (0.009 mole) of *o*-phthalaldehydic acid in 10 ml of dry dimethylformamide. The reaction mixture was heated at 70° for 2 hr, poured onto ice water and acidified with 10% hydrochloric acid. The resulting white precipitates were extracted with chloroform and dried over magnesium sulfate. Removal of extracts gave crystals which were recrystallized from methanol to provide colorless prisms, mp 225—226°. Yield 3 g (87%). *Anal.* Calcd. for $C_{19}H_{15}O_3N_2Br$: C, 57.16; H, 3.79; N, 7.02. Found: C, 57.07; H, 3.55; N, 6.83. IR ν_{max}^{KBr} cm^{-1}: 1690 (COOH). NMR ($CDCl_3$–DMSO-d_6) τ: 1.84 and 3.34 (2H, AB quartet, J= 15 Hz, olefinic protons), 6.70 (3H, singlet, N–CH_3).

2-[β-(2-Methyl-5-oxo-1-phenyl-3-pyrazolin-3-yl)ethyl]benzoic Acid (18)——A solution of 0.4 g (0.001 mole) of **17** and 80 ml of absolute ethanol was hydrogenated over 0.4 g of 20% palladium on carbon under a pressure of 3 kg/cm². The catalyst was removed by suction and the filtrate was evaporated *in vacuo*. The resulting viscous oil was dissolved in saturated sodium bicarbonate solution. After treated with Norite, the solution was acidified with 10% hydrochloric acid. The solids separated were filtered, washed with water and dried. Recrystallization from ethyl acetate–methanol gave colorless plates, mp 242—244°. Yield 0.23 g (72%). *Anal.* Calcd. for $C_{19}H_{18}O_3N_2$: C, 70.79; H, 5.63; N, 8.69. Found: C, 70.56, H, 5.53; N, 8.63. NMR (CD_3-COOD) τ: 1.98—2.80 (10H, multiplet, 4-position proton and aromatic protons), 6.55—7.15 (4H, multiplet, CH_2CH_2), 6.78 (3H, singlet, N-CH_3). Mass Spectrum *m/e*: 322 (M^+).

1-Methyl-2-phenyl-3,4-dioxo-1,2,3,4,9,10-hexahydrobenzo[4,5]cyclohepta[1,2-*c*]pyrazole (3)——A solution of 1 g (0.003 mole) of **18** and 30 g of polyphosphoric acid was heated with stirring at 130° under reduced pressure. After 2 hr, the mixture was poured onto cracked ice and the resulting solution was made strongly alkaline with potassium carbonate. The precipitates were extracted with chloroform. Removal of chloroform gave a viscous oil which solidified on standing. Chromatography on aluminum oxide, followed by recrystallization from isopropyl ether–acetone afforded colorless prisms, mp 223—224°. Yield 0.5 g (53%). *Anal.* Calcd. for $C_{19}H_{16}O_2N_2$: C, 74.98; H, 5.30; N, 9.20. Found: C, 75.11; H, 5.55; N, 9.20. IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 312 (3.91). NMR ($CDCl_3$) τ: 6.45 (4H, singlet, CH_2CH_2), 6.72 (3H, singlet, N–CH_3).

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