Chem. Pharm. Bull. 18(10)1994—1999(1970)

UDC 547.891.9.04.07

Synthesis of Pyrazolone Derivatives. XV.[1] Synthesis of 1-Methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]benzothiepin-3,4-dione and Its Derivatives[2]

Isoo Ito and Taisei Ueda

Faculty of Pharmaceutical Sciences, Nagoya City University[3]

(Received March 20, 1970)

As a part of continuing studies on the synthesis of pyrazolone derivatives, synthesis of 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]benzothiepin-3,4-dione (VI) and its derivatives was described.

The title compounds which comprize pyrazolone structures and benzothiepin moieties in their molecules have been prepared as potential psychotropic agents.

The scheme of synthesis of 1-methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]-benzothiepin-3,4-dione (VI), which is a key compound, is outlined in Chart 1.

The preparation of 2-(1-phenyl-2-methyl-5-oxo-3-pyrazolin-3-yl)methylthiobenzoic acid (V), which is an important intermediate material of VI, was carried out first by the route of formation of 1-phenyl-2-methyl-3-chloromethyl-3-pyrazolin-5-one (III). The synthesis of 1-phenyl-2-methyl-3-hydroxymethyl-3-pyrazolin-5-one[4] (II) from 1-phenyl-2-methyl-3-bromomethyl-4-bromo-3-pyrazolin-5-one[5] (I) was reported previously by Ito, one of the present authors.

Halogenation of II was effected by the reaction of phosphorus pentachloride to III, whose structure was confirmed by its elemental analysis, infrared (IR) spectrum, and nuclear magnetic resonance (NMR) spectrum. Condensation of III with thiosalicylic acid in the presence of ethanolic sodium hydroxide gave V in 88% yield.

The above mentioned route to V *via* III, however, was not favourable, since the halogenation of II resulted in a poor yield (22%) and the synthetic route took long steps. Thus, an alternate preparation of V was begun with the reaction between I and thiosalicylic acid to give 2-(1-phenyl-2-methyl-4-bromo-5-oxo-3-pyrazolin-3-yl)methylthiobenzoic acid (IV) in a quantitative yield. Subsequent dehalogenation of IV was examined by the following three methods: (a) controlled potential electrolytic reduction, (b) catalytic reduction in an autoclave in the presence of Raney nickel catalyst, and (c) the reduction by iron powder and hydrochloric acid. Their yields were (a) 95%, (b) 42%, and (c) 37% respectively. The method (a) gave the most excellent yield and its procedure was simple.

The half-wave potential (E 1/2) of IV was recorded at -1.5 V *vs.* S.C.E. in 5% sodium hydroxide, and controlled electrolytic reduction was carried out under mercury cathode and lead anode at 1.5 V. The compound, thus obtained by the above three methods, was identical with the sample prepared from III and thiosalicylic acid by the comparison of the IR spectra and the mixture melting point.

Ring closure of V in the presence of polyphosphoric acid (PPA) provided VI in 79% yield. The IR absorption band of carboxylic acid disappeared in this cyclized compound (VI)

1) Part XIV: I. Ito and T. Ueda, *Chem. Pharm. Bull.* (Tokyo), **17**, 1309 (1969).
2) This work was presented at the 89th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April 1969.
3) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
4) I. Ito, *Yakugaku Zasshi*, **76**, 822 (1956).
5) H. Graef, J. Ledrut, and G. Combes, *Bull. Soc. Chim. Belges*, **61**, 331 (1952) [*C.A.*, **47**, 12363 (1953)].

and that of aromatic carbonyl function was observed at 1690 cm^{-1}. The data of elemental analysis of VI and its molecular ion (M^+), *m/e*: 322 in the mass spectrum agreed with the formula $C_{18}H_{14}O_2N_2S$. Moreover, main fragments ion peaks observed at *m/e*: 290 (M^+-32) and 261 (a meta stable ion peak).

The ultraviolet (UV) absorption maximum of VI was observed at 325 mμ which indicated the formation of a new conjugated system. The NMR spectrum gave data in agreement with the assigned structure.

Furthermore, unequivocal structural proof was accomplished by catalytic reduction in an autoclave in the presence of Raney nickel catalyst giving 1-phenyl-2,3-dimethyl-4-benzoyl-3-pyrazolin-5-one[6] (VII), a cleavaged compound of VI. VII was identified with the sample prepared from antipyrine (VIII) and benzoylchloride.

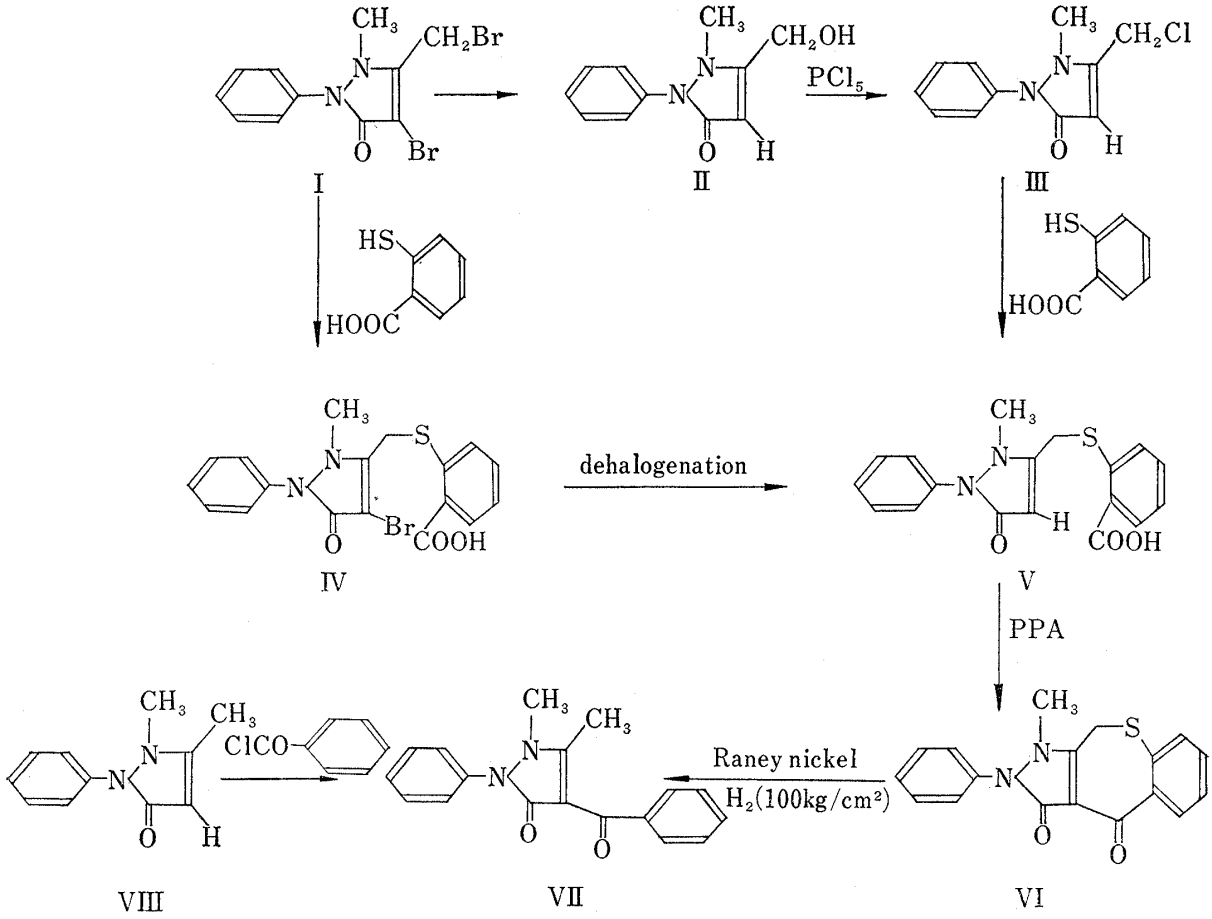
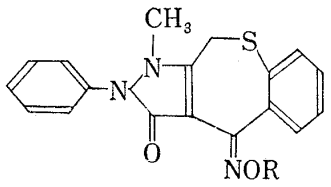


Chart 1

The cyclized compound (VI) was converted into 1-methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]benzothiepin-4-one oxime (IX) which was reacted with alkyl halides, such as methyl iodide, ethyl bromide, allyl bromide, and ethyl chloroacetate in the presence of sodium ethoxide to corresponding O-alkyl 1-methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]benzothiepin-4-one oximes (X, XI, XII, XIII). Hydrolysis of XIII provided O-carboxymethyl 1-methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo-[3,4-*c*][1]benzothiepin-4-one oxime (XIV) which was identical with the compound obtained directly by the reaction of IX and monochloroacetic acid in the presence of ethanolic sodium hydroxide.

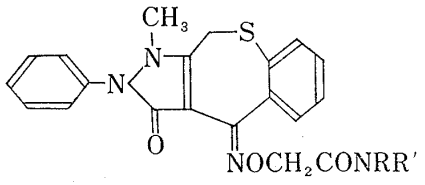
6) H.P. Kaufmann, Ger. Patent 668387 (1938).

TABLE I. O-Alkyl 1-Methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]benzothiepin-4-one Oximes



Compd. No.	Substituent R	mp (°C)	Appearance	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)
X	$-CH_3$	240—242	colorless prisms	85	$C_{19}H_{17}O_2N_3S$	64.94	4.88	11.96	65.03	5.03	12.14	299 (3.98)
XI	$-C_2H_5$	225—226	colorless prisms	81	$C_{20}H_{19}O_2N_3S$	65.73	5.24	11.50	65.64	4.97	11.52	299 (4.07)
XII	$-CH_2-CH=CH_2$	217—218	colorless prisms	79	$C_{21}H_{19}O_2N_3S$	66.82	5.07	11.13	66.59	4.93	11.24	297 (3.95)
XIII	$-CH_2COOC_2H_5$	116—118	colorless prisms	66	$C_{22}H_{21}O_4N_3S$	62.40	5.00	9.92	62.11	4.75	10.20	295 (4.15)

TABLE II. O-(Alkylaminocarbamoyl)methyl 1-Methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]benzothiepin-4-one Oximes



Compd. No.	Substituent NRR′	mp (°C)	Appearance	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N	UV λ_{max}^{EtOH} mμ (log ε)
XV	$-N(C_2H_5)_2$	128—130	colorless prisms	43	$C_{24}H_{26}O_3N_4S$	63.98	5.82	12.44	64.23	5.86	12.18	301 (3.96)
XVI		197—200	colorless prisms	61	$C_{24}H_{24}O_4N_4S$	62.05	5.21	12.06	62.12	5.39	11.90	300 (3.99)
XVII		232—233	colorless needles	57	$C_{25}H_{26}O_3N_4S$	64.91	5.67	12.11	64.68	5.41	12.01	301 (4.06)
XVIII		199—202	colorless prisms	50	$C_{24}H_{24}O_3N_4S$	64.27	5.39	12.49	64.48	5.64	12.51	299 (4.13)

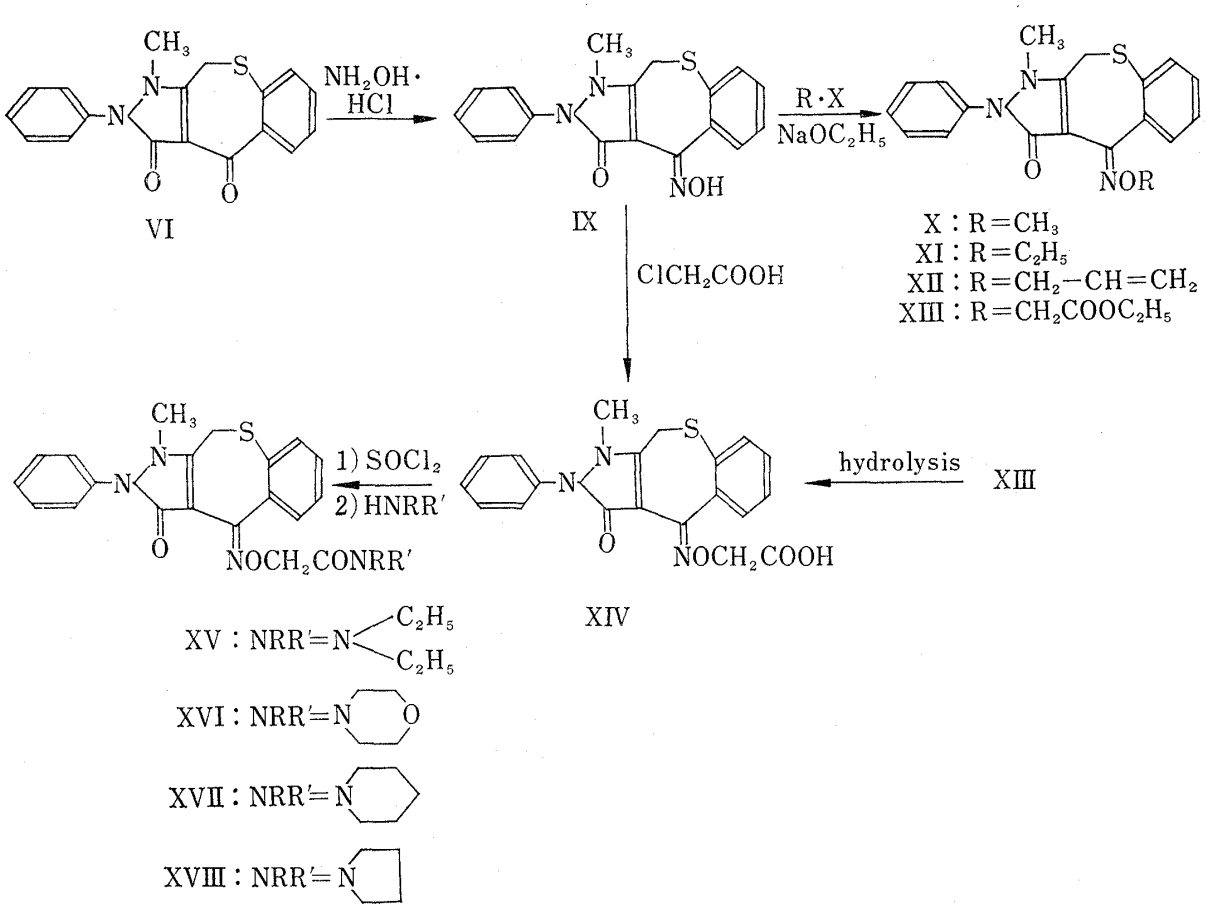


Chart 2

The carboxylic acid (XIV) was introduced to acid chloride, to which alkylamines such as diethylamine, morpholine, piperidine, and pyrrolidine were reacted to obtain corresponding amides (XV, XVI, XVII, XVIII).

Experimental[7]

1-Phenyl-2-methyl-3-chloromethyl-3-pyrazolin-5-one (III)——To a stirred solution of 2 g (0.01 mole) of II in 30 ml of dry chloroform was added 2 g of phosphorus pentachloride in portions. The mixture was allowed to stand at room temperature overnight, heated under reflux for 1 hr, and the solvent was distilled off. The residue was poured into water, saturated with potassium carbonate, and extracted with benzene. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to obtain 0.5 g (22%) of colorless prisms, mp 102—105°. A second crystallization from benzene provided the analytical sample, mp 108—110°. Positive Beilstein test. *Anal.* Calcd. for $C_{11}H_{11}ON_2Cl$: C, 59.33; H, 4.98; N, 12.58. Found: C, 59.62; H, 5.15; N, 12.88. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=O). UV λ_{max}^{EtOH} (log ε): 274 (3.85), 284 (3.88). NMR ($CDCl_3$) ppm: 3.30 (3H, singlet, N–C<u>H</u>$_3$), 4.60 (2H, singlet, –C<u>H</u>$_2$–Cl), 5.82 (1H, singlet, –C<u>H</u>=), 7.62 (5H, singlet, aromatic protons).

2-(1-Phenyl-2-methyl-4-bromo-5-oxo-3-pyrazolin-3-yl)methylthiobenzoic Acid (IV)——To 100 ml of 4% ethanolic sodium hydroxide were added 7.7 g (0.05 mole) of thiosalicyclic acid and 17.3 g (0.05 mole) of I.

7) All melting points were determined on a Yanagimoto Micro-Melting Point apparatus and were uncorrected. The ultraviolet absorption spectra were taken with a Hitachi Recording Spectrophotometer EPS-3T, and the infrared absorption spectra were measured with a Nihon Bunko Spectroscopic Co. Ltd. Model IR-S. The NMR spectra were measured with a Varian A-60 spectrophotometer in deuteriochloroform and tetramethylsilane was used as an internal reference. Mass spectrum was taken on Hitachi Mass Spectrometer, Model RMU-6E equipped with double forcusing system.

The mixture was heated under reflux for 1 hr and the solvent was distilled to dryness. The residue was dissolved in water and filtered to remove an insoluble substance. The filtrate was neutralized with 10% sulfuric acid, and the resulting white precipitates were collected by filtration, mp 198—202° (decomp.). Yield 20 g (95%). Crystallization from ethanol provided the analytical sample as colorless prisms, mp 205—207° (decomp.). Beilstein test and sulfur test were positive. *Anal.* Calcd. for $C_{18}H_{15}O_3N_2SBr$: C, 51.56; H, 3.61; N, 6.68. Found: C, 51.83; H, 3.78; N, 6.52. IR ν_{max}^{KBr} cm^{-1}: 3200—3500 (OH), 1690 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 255 (4.04), 287 (3.99). NMR (DMSO) ppm: 3.29 (3H, singlet, N–C$\underline{H}_3$), 3.78 (2H, singlet, –C$\underline{H}_2$–), 7.30—7.80 (8H, multiplet, aromatic protons), 8.00—8.10 (1H, multiplet, aromatic proton).

Half-wave potential[8] (E 1/2): −1.5 V*vs.* S.C.E. (in 5% sodium hydroxide).

2-(1-Phenyl-2-methyl-5-oxo-3-pyrazolin-3-yl)methylthiobenzoic Acid (V)——a) A solution of 5 g of IV in 500 ml of 5% sodium hydroxide was submitted to controlled potential electrolytic reduction under the following condition. Catholyte: 5 g of IV in 500 ml of 5% sodium hydroxide. Anolyte: 50 ml of 20% sodium hydroxide. Cathode: mercury (20 cm^2). Anode: lead (100 cm^2). Temperature: 10—15°. Cell voltage: 1.5 V.

After the reaction the solution of catholyte was neutralized with 15% sulfuric acid. The resulting precipitates were collected by filtration, washed with water, and dried. Yield 3.8 g (95%), mp 245—250° (decomp.). Recrystallization from ethanol provided the analytical sample as colorless prisms, mp 255—256° (decomp.). Negative Beilstein test. *Anal.* Calcd. for $C_{18}H_{16}O_3N_2S$: C, 63.51; H, 4.74; N, 8.23. Found: C, 63.29; H, 4.93; N, 8.50. IR ν_{max}^{KBr} cm^{-1}: 3200—2500 (OH), 1690 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 248 (4.33), 280 (4.22). NMR (DMSO) ppm: 3.22 (3H, singlet, N–C$\underline{H}_3$), 3.74 (2H, singlet, –C$\underline{H}_2$–), 5.50 (1H, singlet, =C$\underline{H}$–), 7.22—7.70 (8H, multiplet, aromatic protons), 7.88 (1H, multiplet, aromatic proton).

b) A mixture of 5 g of IV in 20 ml of 10% sodium bicarbonate and Raney nickel catalyst prepared from 5 g of aluminum–nickel alloy was agitated for 4 hr under 30 kg/cm^2 of hydrogen at 80°. The catalyst was filtered off and the filtrate was neutralized with 10% sulfuric acid. The resulting white precipitate was collected by filtration, washed with water, and dried, mp 245—250° (decomp.). Yield 1.7 g (42%).

c) A mixture of 2 g of IV in 5 ml of concentrated hydrochloric acid and 2 g of iron powder was heated on a steam bath for 3 hr. After cooling the mixture was extracted with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated. The residue was recrystallized from ethanol to colorless prisms, mp 250—253° (decomp.). Yield 0.6 g (37%).

d) To 16 ml of 1% ethanolic sodium hydroxide were added 0.3 g of thiosalicyclic acid and 0.44 g of III. The mixture was heated under reflux for 1 hr and the solvent was distilled to dryness. The residue was dissolved in water and filtered. The filtrate was neutralized with 10% sulfuric acid, and the resulting precipitates were collected by filtration, mp 250—253°. Yield 0.6 g (88%).

The compound (V) obtained here by method b), c) or d) was identical with that obtained by method a) by the comparison of the IR spectra and the mixture melting point.

1-Methyl-2-phenyl-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*][1]benzothiepin-3,4-dion (VI)——To 10 ml of 85% phosphoric acid was added 16 g of phosphorus pentoxide for 5 min under good stirring on an oil bath (110—120°). Then, 2 g of V was added in portions to the mixture. Stirring and heating were continued for 3 hr. The reaction mixture was poured into ice–water, saturated with potassium carbonate, and extrated with chloroform. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated to obtain 1.5 g (79%) of tan prisms, mp 203—205°. Recrystallization from methanol gave colorless prisms, mp 210—211°. *Anal.* Calcd. for $C_{18}H_{14}O_2N_2S$: C, 67.06; H, 4.38; N, 8.69. Found: C, 67.25; H, 4.58; N, 8.49. Mass Spectrum *m/e*: 322 (M^+), 290 (M^+-32), 261 (meta stable ion peak). IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 240 (4.17), 325 (3.99). NMR ($CDCl_3$) ppm: 3.37 (3H, singlet, N–C$\underline{H}_3$), 3.98 (2H, singlet, –C$\underline{H}_2$–), 7.26—7.51 (8H, multiplet, aromatic protons), 7.80—8.10 (1H, multiplet, aromatic proton).

1-Phenyl-2,3-dimethyl-4-benzoyl-3-pyrazolin-5-one (VII)——A mixture of 0.3 g of VI in 50 ml of ethanol and Raney nickel catalyst prepared from 1 g of aluminum–nickel alloy was agitated in an autoclave under 100 kg/cm^2 at 80° for 7 hr. The mixture was filttered and the filtrate was evaporated to brown tar, which was chromatographed on silica gel. Elution with chloroform gave red crystals, mp 140—143°. Yield 80 mg. Recrystallization from ethyl acetate gave colorless prisms, mp 146—147°. Negative sulfur test. *Anal.* Calcd. for $C_{18}H_{16}O_2N_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.66; H, 5.47; N, 9.49. IR ν_{max}^{KBr} cm^{-1}: 1670, 1630 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 241 (4.23), 310 (4.09). NMR ($CDCl_3$) ppm: 2.66 (3H, singlet, $-\underset{\|}{C}-C\underline{H}_3$), 3.38 (3H, singlet, N–C$\underline{H}_3$), 7.50—7.60 (8H, multiplet, aromatic protons), 7.90—8.10 (2H, mutiplet, aromatic protons).

VII was identified with a sample[6] obtained by the reaction of antipyrine and benzoylchloride from the comparison of IR spectra and the mixture melting point.

8) Polarograms were recorded with a Yanagimoto Polarograph, PA-102.

1-Methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*] [1] benzothiepin-4-one Oxime (IX)——A mixture of 1 g of IV, 2 g of hydroxylamine hydrochloride, 6 ml of dry pyridine, and 6 ml of absolute ethanol was refluxed on an oil bath for 2 hr. The mixture became transparent solution. The solvents were distilled off and water was added to the residue to obtain white powder, which was collected by filtration, washed with water, and dried. Yield 1 g (95%), mp 214—217° (decomp.). This compound was used to the next procedure without further purification. One part of this compound was recrystallized from ethanol to provide the analytical sample, mp 219—220° (decomp.). *Anal.* Calcd. for $C_{18}H_{15}O_2N_3S$: C, 64.08; H, 4.48; N, 12.45. Found: C, 63.96; H, 4.54; N, 12.23. IR ν_{max}^{KBr} cm^{-1}: 3200 (OH), 1660 (C=O), 1630 (C=N), 980 (N–O). UV λ_{max}^{EtOH} mμ (log ε): 297 (4.02).

O-Methyl 1-methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*] [1] benzothiepin-4-one Oxime (X) (Table I)——To an ethanolic sodium ethoxide (23 mg of sodium in 10 ml of absolute ethanol) was added 0.34 g of IX. The mixture was refluxed for 1 hr. After cooling 2 ml of methyl iodide was added to the mixture and refluxing was continued for additional 2 hr. The solvent was evaporated and water was added to the residue to give white powder. Recrystallization from ethanol gave 0.3 g (85%) of colorless prisms, mp 225—226°.

XI, XII, and XIII were similary prepared from IX and ethyl bromide, allyl bromide or ethyl chloroacetate. Their analytical data are summarized in Table I.

O-Carboxymethyl 1-Methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*] [1] benzothiepin-4-one Oxime (XIV)——a) To 20 ml of 2% ethanolic sodium hydroxide were added 1.7 g (0.005 mole) of IX and 0.95 g (0.005 mole) of monochloroacetic acid. The mixture was heated on a steam bath for 1 hr, and evaporated to dryness. Water was added to the residue and the solution was filtered. The filtrate was neutralized with 10% sulfuric acid to obtain white precipitates, which were collected by filtration and dried. Yield 1.8 g (91%), mp 240—245°. Recrystallization from ethanol provided the analytical sample, mp 250—252° (decomp.). *Anal.* Calcd. for $C_{20}H_{17}O_4N_3S$: C, 60.75; H, 4.33; N, 10.63. Found : C, 60.71; H, 4.45; N, 10.41. IR ν_{max}^{KBr} cm^{-1}: 3200—3500 (OH), 1740 (C=O). UV λ_{max}^{EtOH} mμ (log ε): 295 (4.12).

b) A solution of 0.5 g of XIII in 10 ml of 10% ethanolic potassium hydroxide was heated on a steam bath for 1 hr. The solvent was evaporated to dryness, water was added to the residue and filtered. The filtrate was neutralized with 15% sulfuric acid. The resulting precipitates were collected by filtration. Yield 0.4 g (85%), mp 248—252° (decomp.). IR spectrum of this compound was identical with that prepared by method a), and the mixture melting point did not show any depression.

O-(N,N′-Diethylcarbamoyl)methyl 1-Methyl-2-phenyl-3-oxo-1,2,3,10-tetrahydro-4*H*-pyrazolo[3,4-*c*] [1] benzothiepin-4-one Oxime (XV) (Table II)——To 1 g of XIV in 20 ml of dry chloroform was added 2 g of thionyl chloride. The mixture was refluxed on a steam bath for 30 min. Distillation of chloroform and excess thionyl chloride left a crude acid chloride, to which was added 2 g of diethylamine in 10 ml of dry benzene and the mixture was allowed to stand overnight. The solvent was evaporated and the residue was washed with water to brown powder, which was recrystallized from ethanol to obtain colorless needles, mp 128—130°. Yield 0.48 g (43%).

XVI, XVII, and XVIII were similarly prepared from acid chloride of XIV and morpholine, piperadine, and pyrrolidine. Their analytical data are summarized in Table II.

Acknowledgement The authors express their deep gratitude to the members of Microanalytical center of this Faculty for elemental analysis.