Notes

Chem. Pharm. Bull. 25(6)1443—1446(1977)

UDC 547.774.04 : 547.892.04

Synthesis of Pyrazolone Derivatives. XXX.[1] Synthesis of Pyrazolo[3,4-*b*][1,4]oxazepines[2]

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(Received September 3, 1976)

A novel bicyclic ring, pyrazolo[3,4-*b*][1,4]oxazepine was synthesized. The Mannich reaction of 3-hydroxy-5-methyl-1-phenyl pyrazole (I) with *p*-substituted aniline gave 3-hydroxy-5-methyl-1-phenyl-4-(*p*-substituted anilino)methyl pyrazoles (II, III, IV, V), which were reacted with chloroacetyl chloride to give 3-methyl-2-phenyl-5-(*p*-substituted)-phenyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*][1,4]oxazepin-6-ones (VI, VII, VIII, IX). The reduction of VI, VII, and VIII with lithium aluminum hydride gave 3-methyl-2-phenyl-5-(*p*-substituted)phenyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*][1,4]oxazepines (X, XI, XII) and ring-opened products (XIII, XIV, XV).

Keywords——pyrazolone derivatives; Mannich reaction; pyrazolo[3,4-*b*][1,4]-oxazepines; Reductive fission of amido derivatives; Reduction of amido by $LiAlH_4$

Among pyrazolo[3,4-*b*][1,4]benzoxazepines some pharmacologically interesting compounds[4] have been reported. It is, therefore, of interest to investigate a new bicyclic ring pyrazolo[3,4-*b*][1,4]oxazepine, the synthesis and characterization of which are the basis of this report. This bicyclic ring system is not listed in "Chemical Abstract" or "The Ring Index"[5] and appears to be a novel heterocyclic type.

The synthesis of pyrazolo[3,4-*b*][1,4]oxazepines was carried out as outlined in Chart 1. The Mannich reaction of 3-hydroxy-5-methyl-1-phenylpyrazole[6] (I) with *p*-substituted aniline and 37% formaline gave 3-hydroxy-5-methyl-1-phenyl-4-(*p*-substituted anilino)methylpyrazoles(II,III,IV,V) in 72—93% yield. The reaction of II, III, IV and V with chloroacetylchloride in the presence of potassium carbonate and acetone yielded the objective cyclized products: 3-methyl-2-phenyl-5-(*p*-substituted)phenyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]-[1,4]oxazepin-6-ones (VI, VII, VIII, IX). Their thin-layer and gas chromatography disclosed that this reaction gave a sole cyclized product. The infrared (IR) spectra of VI, VII, VIII and IX showed the absorptions of amido carbonyl groups at 1655—1660 cm^{-1}. Thus the cyclization of A-type was denied. Furthermore, the following experiments confirmed the structures of VI, VII, VIII and IX.

The reduction of VI, VII and VIII with lithium aluminum hydride in tetrahydrofuran (THF) gave 3-methyl-2-phenyl-5-(*p*-substituted)phenyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*]-[1,4]oxazepines (X, XI, XII) and ring-opened products (XIII, XIV, XV) in a ratio of 3:4.

1) Part XXIX: I. Ito, N. Oda, H. Kakishima, T. Kato, K. Asano, and T. Sugawara, *Chem. Pharm. Bull.* (Tokyo), **25**, 1124 (1977).
2) This work was presented at the 96th Annual Meeting of Pharmaceutical Society of Japan, Nagoya, April 1976.
3) Location: *Tanabe-dori, Mizuho-ku, Nagoya.*
4) L.R. Swett, R.G. Stein, and E.T. Kimura, U.S. Patent 3424758 (1969) [*C.A.*, **70**, 106493*y* (1969)]; U.S. Patent 3450694 (1969) [*C.A.*, **71**, 101900*g* (1969)].
5) 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).
6) H.Z. Lecher, R.P. Parker, and R.C. Conn, *J. Am. Chem. Soc.*, **66**, 1959 (1944); K. Mayer, *Chem. Ber.*, **36**, 717 (1903); A. Michaelis, *Ann.*, **338**, 273 (1905).

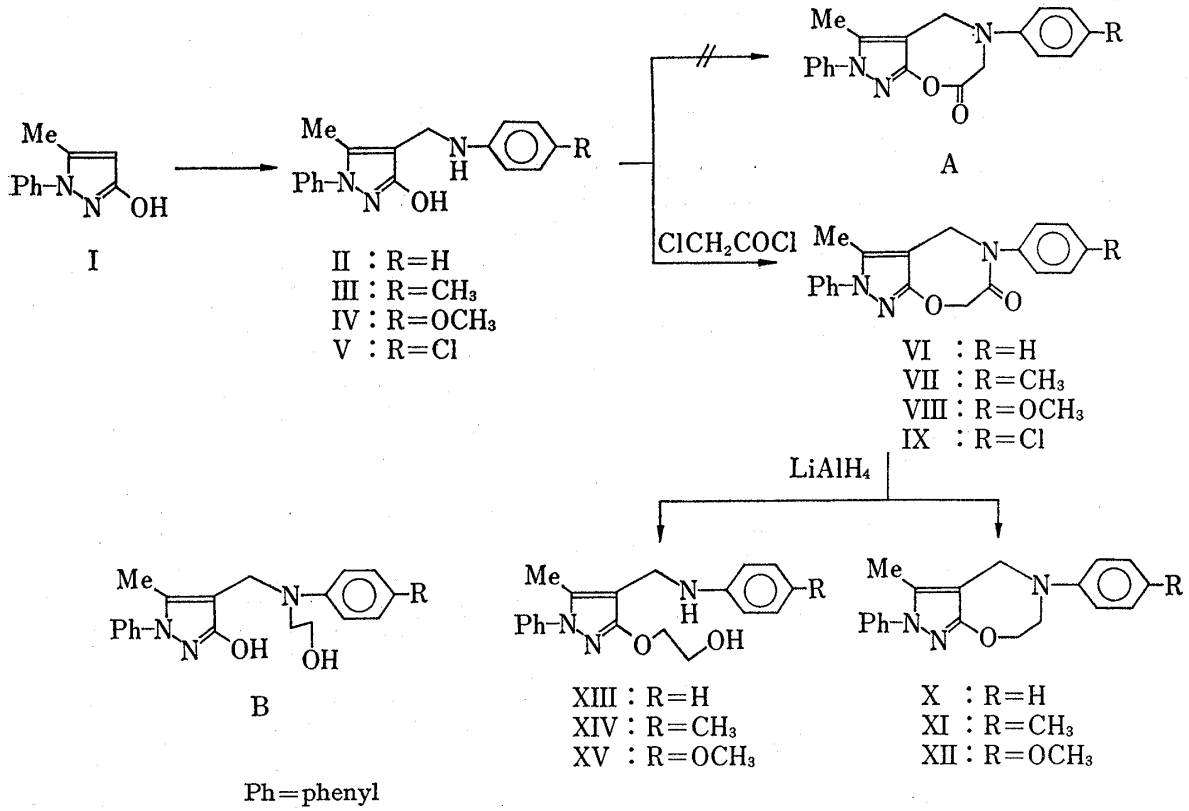


Chart 1

The structures of X, XI and XII were characterized by IR and nuclear magnetic resonance (NMR) spectra. The IR spectra of the ring-opened products (XIII, XIV, XV) disclosed secondary amines at 3380 cm^{-1} as sharp absorptions and alcoholic hydroxy groups at 3480 cm^{-1} as broad absorptions. XIII was identical with the compound obtained by the reduction of methyl (4-anilinomethyl-5-methyl-1-phenylpyrazol-3-yl)oxyacetate (XVI) which was prepared from II and methyl bromoacetate. Furthermore, XIII was acetylated with acetyl chloride to give 3-(2-acetoxy)ethoxy-4-(N-acetylanilino)methyl-5-methyl-1-phenylpyrazole-(XVII), whose IR spectrum revealed new absorptions attributable to an amido carbonyl group at 1650 cm^{-1} and an O-acetylcarbonyl group at 1745 cm^{-1}. Thus the ring-opened products (XIII, XIV, XV) were assigned their structures to 3-(2-hydroxy)ethoxy-5-methyl-1-phenyl-4-(*p*-substituted anilino)methyl-pyrazoles.

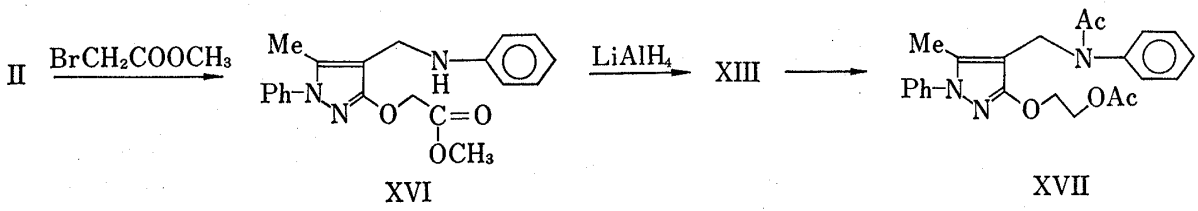


Chart 2

There are some examples[7] of reductive fission of C–N bond of amido derivatives by means of lithium aluminum hydride. It is said that this reductive fission of C–N bond occurrs when a nitrogen atom of an amido group has a bulky group.[8]

7) K. Banholzer, T.W. Camphell, and H. Schmid, *Helv. Chim. Acta*, **34**, 907 (1952); R.F. Nystrom and W.G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948); F. Galinovsky, A. Wagner, and R. Weiser, *Monatsh.*, **82**, 551 (1951) [*C.A.*, **46**, 4551 (1952)]; G. Wittig and P. Hormberger, *Ann.*, **577**, 11 (1952).

8) S. Kawai and S. Tanaka, "Jikken Kagaku Koza," Vol. 17, I(Ge) ed. by Chemical Society of Japan, Maruzen, Tokyo, 1967, p. 38.

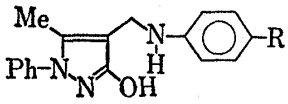
The isolation of XIII, XIV and XV in the above experiment established the structures of VI, VII, VIII and IX, because the reduction of lactum (A) by means of lithium aluminum hydride would give diol[9] (B).

Experimental

All the melting points were determined on a Yanagimoto Micro Melting Point apparatus and are not corrected. The IR spectra were measured with a Nihon Bunko Spectroscopic Co. Ltd. Model IR-A2. The NMR spectra were measured with a Japan Electron Optics Laboratory Co. JNM-MH-100 Spectrometer using tetramethylsilane as internal standard.

3-Hydroxy-5-methyl-1-phenyl-4-(*p*-substituted phenylamino)methylpyrazoles (II, III, IV, V)——A mixture of I (1.74 g), *p*-substituted aniline (0.011 mole), 37% HCHO (0.8 ml), and EtOH (25 ml) was refluxed in an oil-bath (120°) for 10 min. The reaction mixture was cooled and the resulting crystals were recrystallized from benzene.

TABLE I.

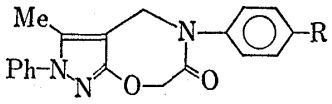


Compd. No.	R	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1} (–NH–)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
II	H	178—182	79	3380	$C_{17}H_{17}ON_3$	73.10	6.13	15.04	73.35	6.35	14.89
III	CH_3	170—172	93	3410	$C_{18}H_{19}ON_3$	73.69	6.53	14.32	73.65	6.62	14.10
IV	OCH_3	168—170	81	3390	$C_{18}H_{19}O_2N_3$	69.88	6.19	13.58	69.92	6.29	13.64
V	Cl	192—193	72	3380	$C_{17}H_{16}ON_3Cl$	65.07	5.14	13.39	65.25	5.37	13.69

3-Methyl-2-phenyl-5-(*p*-substituted)phenyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*][1,4]oxazepin-6-ones(VI, VII, VIII, IX)——A mixture of V (0.001 mole), potassium carbonate (0.6 g), chloroacetyl chloride, and DMF (5 ml) was stirred for 24 hr at room temperature. The reaction mixture was filtered and the filtrate was evaporated to dryness. Addition of a small amount of *n*-hexane gave crystals.

Similarly, VII, VIII and IX were obtained from III, IV and V respectively.

TABLE II.



Compd. No.	R	mp (°C)	Yield (%)	IR ν_{max}^{KBr} cm^{-1} (C=O)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
VI	H	225—226	72	1665	$C_{19}H_{17}O_2N_3$	71.45	5.37	13.16	71.19	5.25	12.95
VII	CH_3	177—179	78	1660	$C_{20}H_{19}O_2N_3$	72.05	5.74	12.60	72.22	5.78	12.64
VIII	OCH_3	102—103	65	1655	$C_{20}H_{19}O_3N_3$	68.75	5.48	12.03	68.59	5.54	11.97
IX	Cl	224—225	43	1655	$C_{19}H_{16}O_2N_3Cl$	64.50	4.56	11.88	64.77	4.56	11.94

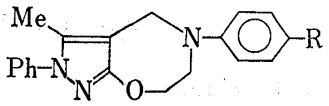
3-Methyl-2-phenyl-5-(*p*-substituted)phenyl-4,5,6,7-tetrahydro-2*H*-pyrazolo[3,4-*b*][1,4]oxazepines (X, XI, XII) and 3-(2-Hydroxy)ethoxy-5-methyl-1-phenyl-4-(*p*-substitutedphenylamino)methyl Pyrazoles (XIII, XIV, XV)——A mixture of VI (0.001 mole), $LiAlH_4$ (57 mg), and dry THF (10 ml) was refluxed for 12 hr. The reaction mixture was poured into 100 ml of saturated aqueous ammonium chloride solution and extracted with AcOEt. The extract was washed with water and dried over anhydrous Na_2SO_4. Solvent was evaporat-

9) R.F. Nystrom and W.G. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

ed and the residue was column chromatographed on silica gel ($CHCl_3$–EtOH (20: 1)). From the first eluate compound (X) was obtained and the second eluate gave the compound (XIII).

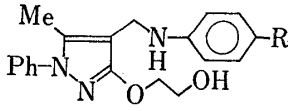
Similarly XI, XII, XIV and XV were obtained from VII and VIII.

Table III.



Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
X	H	152—154	34	$C_{19}H_{19}ON_3$	74.73	6.27	13.76	74.56	6.21	13.50
XI	CH_3	97—98	35	$C_{20}H_{21}ON_3$	75.21	6.63	13.16	75.49	6.63	13.25
XII	OCH_3	133—134	24	$C_{20}H_{21}O_2N_3$	71.62	6.31	12.53	71.52	6.10	12.60

Table IV.



Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
XIII	H	126—127	42	$C_{19}H_{21}O_2N_3$	70.57	6.55	12.99	70.72	6.85	12.78
XIV	CH_3	110—111	45	$C_{20}H_{23}O_2N_3$	71.19	6.87	12.45	71.46	7.05	12.57
XV	OCH_3	101—103	28	$C_{20}H_{23}O_3N_3$	67.97	6.56	11.89	67.70	6.42	11.73

Methyl (4-Anilinomethyl-5-methyl-1-phenylpyrazol-3-yl)oxyacetate (XVI)——A mixture of II (280 mg), potassium carbonate (600 mg), methyl bromoacetate (230 mg), and DMF (5 ml) was stirred for 24 hr at room temperature. The reaction mixture was filtered and the filtrate was evaporated. Addition of a small amount of petroleum ether gave crystals, which were recrystallized from AcOEt–isopropylether to give colorless needles of mp 112—113°, yield 274 mg (78%). *Anal.* Calcd. for $C_{20}H_{21}O_3N_3$: C, 68.36; H, 6.02; N, 11.96. Found: C, 68.38; H, 6.06; N, 11.74. IR ν_{max}^{KBr} cm^{-1}: 3360 (NH), 1762 (ester C=O). NMR $\delta_{ppm}^{CDCl_3}$: 2.27 (3H, singlet, $=\!\!\langle^{CH_3}$), 3.45 (1H, broad, –NH–), 3.76 (3H, singlet, $-OCH_3$), 4.12 (2H, singlet, $=\!\!\langle^{CH_2-N-}$), 4.86 (2H, singlet, $-O-\underline{CH_2}-COOCH_3$), 6.60—7.40 (10H, multiplet, aromatic protons).

Reduction of XVI with Lithium Aluminum Hydride (Synthesis of XIII)——A mixture of XVI (176 mg), dry THF (5 ml), and $LiAlH_4$ (34 mg) was refluxed for 8 hr. The reaction mixture was poured into saturated aqueous ammonium chloride solution and extracted with AcOEt. The extract was washed with water and dried over anhydrous Na_2SO_4. Solvent was evaporated and the residue was recrystallized from isopropyl ether to give colorless prisms of mp 126—127°, yield 285 mg (88%).

This compound was identical with XIII which was obtained from VI by the comparison of IR spectra and the mixture melting point.

3-(2-Acetoxy)ethoxy-4-(N-acetylanilino)methyl-5-methyl-1-phenylpyrazole (XVII)——A mixture of XIII (50 mg) and acetyl chloride (10 ml) was refluxed in an oil bath for 1 hr. Excess acetyl chloride was distilled. The residue was recrystallized from ether–EtOH (1: 1) to give colorless prisms of mp 98—101°, yield 46 mg (63%). IR ν_{max}^{Nujol} cm^{-1}: 1745 (OAc), 1650 (N–Ac). *Anal.* Calcd. for $C_{23}H_{25}O_4N_4$: C, 67.79; H, 6.18; N, 10.31. Found: C, 67.58; H, 6.30; N, 10.53.

Acknowledgement The authors are indebted to the members of the Microanalytical Center of this Faculty for elemental analyses and NMR spectral measurements.