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70. Shigehiko Sugasawa and Naoto Yoneda : Synthesis of Pyridopyrazolone Derivatives. I. Synthesis of Pyrido[3, 4-*c*]pyrazolones.

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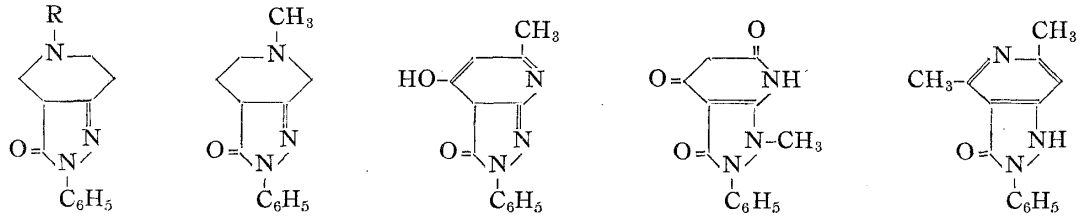
For the purpose of physiological evaluation, synthesis of a series of pyridopyrazolones was undertaken and the present paper is concerned with the synthesis of some 6-substituted 1-phenyl-2-methylpyrido[3, 4-*c*]pyrazol-7-ones.

Several synthetical works have heretofore been recorded in the literature in this field. Englert and McElvain[1] and Dickerman and Lindwall[2] synthesized piperidopyrazolones (A and B) by condensing phenylhydrazine with esters of N-substituted piperidone-carboxylic acids. Lasker and Ghosh[3] and Adams and Fourthroup[4] prepared (C) and (D) by condensing 1-phenyl-3-amino-5-pyrazolone with ethyl acetoacetate and diethyl malonate, respectively. A synthesis of another pyrazolone (E) was recorded by Michaelis[5],[6] as the cyclization product of 4-phenylhydrazinolutidine-3-carboxylic acid.



(A) (B) (C) (D) (E)

In the present synthesis we started from 1-phenyl-3-*β*-methoxycarbonylethyl-5-pyrazolone (II), which Ruggli and Maeder[7] prepared from *β*-oxoadipate and phenylhydrazine. The ester (II), when N-methylated by means of dimethyl sulfate and alkali, followed by esterification, gave 1-phenyl-2-methyl-3-*β*-ethoxycarbonylethylpyrazol-5-one (III), whose hydrazide (IV) was subjected to the modified Curtius degradation according to the method of Sugasawa and Saito,[8] furnishing 3-*β*-aminoethyl derivative (VI). The latter formed a well-defined benzoyl derivative (VIIa) in a good yield.

The cationoid activity of the 4-position of antipyrine is well established. Thus, the above-mentioned benzoyl derivative should cyclize to give the pyridine derivative when subjected to the Bischler-Napieralski type of reaction. As was expected, 1, 6-diphenyl-2-methyl-3, 4-dihydropyrido[3, 4-c]pyrazol-7-one (IXa) was produced in a good yield. The veratramido derivative (VIIb) in a like manner yielded the corresponding 6-veratrylpyridopyrazolone (IXb), which underwent a smooth dehydrogenation to the compound (I), when treated with palladium-carbon in boilling *p*-cymene solution in the presence of a hydrogen acceptor.

Pictet-Spengler type of cyclization was also successfully applied to the amine (VI),

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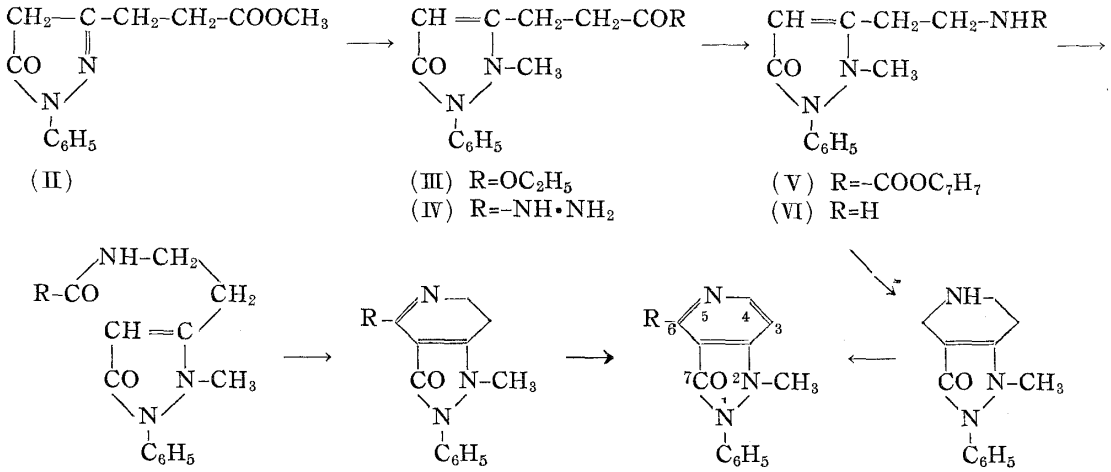
1) S. M. E Englert, S. M. McElvain : J. Am. Chem. Soc., **56**, 700(1934).
2) B. S. Dickerman, H. G. Lindwall : J. Org. Chem., **14**, 530(1949).
3) S. L. Lasker, T. N. Ghosh : Science and Culture, **11**, 506(1946) (C. A. **40**, 4064(1946)).
4) D. A. W. Adams, G. Fourthroup : U. S. Pat. 2, 584, 314 (C. A. **46**, 9618(1952)).
5) A. Michaelis : Ann., **366**, 324(1909).
6) A. Michaelis, K. v. Arend : Ber., **36**, 515(1904).
7) P. Ruggli, A. Maeder : Helv. Chim. Acta, **25**, 936(1942).
8) S. Sugasawa, N. Saito : Proc. Imp. Acad. (Tokyo), **20**, 137(1944); J. Pharm. Soc. Japan, **68**, 65 (1948).

yielding the compound (X) in a fair yield. The dehydrogenation of the latter furnished the corresponding pyrido derivative (I′).

When homoveratroyl derivative of (VI) was subjected to the cyclization under comparable conditions, the reaction mixture became very dirty, from which a colorless crystalline basic substance was isolated, which, however, did not give the correct analysis for the expected compound and its nature is now under investigation.



Ultraviolet absorption spectra of some of the compounds prepared are shown in Fig. 1. Pharmacological testing of (IXb), (I), and (I′) is now under progress.

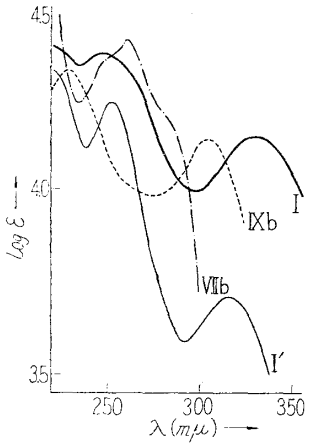
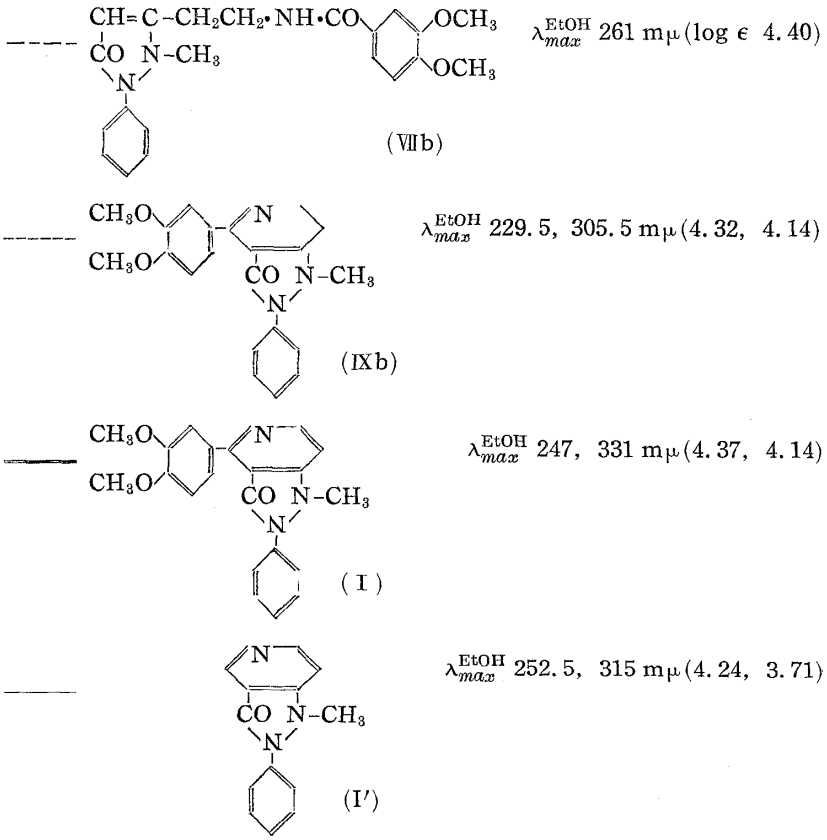


Fig. 1.

Ultraviolet Absorption Spectra (in EtOH)



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Experimental

1-Phenyl-2-methyl-3-β-ethoxycarbonylethyl-5-pyrazolone (III)—A mixture of (II) (33.5 g., 1 mol. equiv.)[7] and Me_2SO_4(20 g., 1.2 mol. equiv.) was heated in an oil bath at 160~170° for 2.5 hrs. On cooling, the reaction mixture was mixed with aq. NaOH soln. (16 g. NaOH in 75 cc. H_2O), the whole was heated on a water bath for 30 mins., decolorized, and filtered. The filtrate was neutralized with HCl with cooling, separating 27 g. of 1-phenyl-2-methyl-3-β-carboxyethyl-5-pyrazolone (free acid of III) in 80.6% yield. Purified from EtOH, forming colorless scales of m.p. 212~213°. *Anal.* Calcd. for $C_{13}H_{14}O_3N_2$: C, 63.4; H, 5.7; N, 11.4. Found: C, 63.55; H, 5.6; N, 11.2.

This acid (20 g.) was esterified by refluxing for 2.5 hrs. with dehyd. EtOH (200 cc.) added with conc. H_2SO_4(40 cc.) and then worked up as usual, yielding faint orange colored crude ester (III) in 89% yield or 19.8 g. Distilled *in vacuo*, giving colorless oil, b.$p_{0.25}$ 182~228°, which solidified on cooling; m.p. 75~76.5°. *Anal.* Calcd. for $C_{15}H_{18}O_3N_2$: C, 65.7; H, 6.6; N, 10.2. Found: C, 65.5; H, 6.6; N, 10.2.

Hydrazide (IV)—From the foregoing ester and anhyd. NH_2NH_2 added with a little EtOH on a steam bath for 10 hrs. Yield nearly theoretical. Purified from EtOH to colorless needles of m.p. 126~127.5°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_4$: C, 60.0; H, 6.2; N, 21.5. Found: C, 59.7; H, 6.05; N, 21.2.

The hydrazide was further characterized through its piperonylidene derivative, prepared as usual, as colorless needles, m.p. 240~241°, from dehyd. EtOH. *Anal.* Calcd. for $C_{21}H_{20}O_4N_4$: C, 64.3; H, 5.1; N, 14.3. Found: C, 63.9; H, 4.85; N, 14.3.

1-Phenyl-2-methyl-3-β-benzoxycarbonylaminoethyl-5-pyrazolone (V)—The above-mentioned hydrazide (IV) (14.5 g., 1 mol. equiv.) was dissolved in HCl (prepared from 12.5 cc. of conc. HCl and 30 cc. H_2O), this solution was cooled in ice, and added dropwise with an aq. soln. of $NaNO_2$(3.8 g., 1 mol. equiv., any excess is to be avoided, in 10 cc. H_2O) with vigorous stirring. The reaction mixture was then basified with Na_2CO_3 solution and repeatedly extracted with benzene, which was washed with H_2O and dried over anhyd. Na_2SO_4. The benzene solution was now mixed with pure benzyl alcohol (6 cc., 1 mol. equiv) and the whole was refluxed on a steam bath for 2 hrs. The solvent was now removed and the residue was triturated with ether, giving solid benzylurethane in ca. 50% yield or 9.7 g. Purified from benzene forming colorless plates of m.p. 99~100°. *Anal.* Calcd. for $C_{20}H_{21}O_3N_3$: N, 12.0. Found: N, 11.95.

1-Phenyl-2-methyl-3-β-aminoethyl-5-pyrazolone (VI)—The foregoing urethane (9.5 g.) was dissolved in a mixture of 100 cc. glacial AcOH and 100 cc. of 20% HCl and the mixture was refluxed in an oil bath until the evolution of gas ceased (ca. 1 hr.). Benzyl alcohol and AcOH were now removed in a current of steam and the residual solution was evaporated *in vacuo*, furnishing dihydrochloride of (VI) as a solid; yield, 7.4 g. or 94.2%. Purified from dehyd. EtOH, forming colorless pillars of m.p. 245~246°(decomp.). *Anal.* Calcd. for $C_{12}H_{17}ON_3Cl_2$: C, 49.7; H, 5.9; N, 14.5. Found: C, 49.55; H, 6.2; N, 14.4.

The base forms a monopicrate, which separates from MeOH as orange yellow pillars of m.p. 216~217.5°(decomp.). *Anal.* Calcd. for $C_{12}H_{15}ON_3 \cdot C_6H_3O_7N_3$: C, 48.4; H, 4.1; N, 18.8. Found: C, 48.0; H, 4.1; N, 18.8.

1-Phenyl-2-methyl-3-β-benzamidoethyl-5-pyrazolone (VIIa)—The foregoing amine hydrochloride was dissolved in H_2O and benzoylated after Schotten-Baumann in the presence of Na_2CO_3; yield, 89%. Purified from hydrous EtOH, forming colorless rhombic pillars of m.p. 190~191°. *Anal.* Calcd. for $C_{19}H_{19}O_2N_3$: C, 71.0; H, 6.0; N, 13.1. Found: C, 71.3; H, 5.9; N, 13.1.

1-Phenyl-2-methyl-3-β-veratramidoethyl-5-pyrazolone (VIIb)—The amine was acylated by adding $CHCl_3$ solution of veratroyl chloride in the presence of K_2CO_3 with stirring; yield 96%. Purified from AcOEt, forming colorless plates of m.p. 181~182°. *Anal.* Calcd. for $C_{21}H_{23}O_4N_3$: C, 66.1; H, 6.1; N, 11.0. Found: C, 65.9; H, 6.2; N, 10.7.

The corresponding homoveratramido derivative was prepared in a like manner, forming colorless rhombic pillars of m.p. 153~154.5° from AcOEt. *Anal.* Calcd. for $C_{22}H_{25}O_4N_3$: C, 66.8; H, 6.4; N, 10.6. Found: C, 67.0; H, 6.75; N, 11.1

1,6-Diphenyl-2-methyl-3,4-dihydro[3,4-c]pyrazol-7-one (IXa)—The amide (VIIa, 0.5 g.) in pure benzene (10 cc.) was added with $POCl_3$ (1.5 cc.) and the mixture was refluxed on a steam bath for 1 hr., separating yellowish solid on the bottom, which was collected on a filter after being cooled. This was dissolved in water and basified with NaOH solution, separating the free base; yield, 0.38 g. or 70%. Purified from EtOH, forming colorless rhombic pillars of m.p. 206~207°. *Anal.* Calcd. for $C_{19}H_{17}ON_3$: C, 75.2; H, 5.65; N, 13.85. Found: C, 75.0; H, 5.6; N, 13.8.

1-Phenyl-2-methyl-6-veratryl-3,4-dihydropyrido[3,4-c]pyrazol-7-one (IXb)—Prepared from the amide (VIIb) in a like manner. Crude yield, 83%. Purified from benzene, forming colorless pillars of m.p. 159~160°. *Anal.* Calcd. for $C_{21}H_{21}O_3N_3$: C, 69.4; C, 5.8; N, 11.6. Found: C, 69.1; H, 5.8; N, 11.7.

1-Phenyl-2-methylpiperido[3, 4-c]pyrazol-7-one (X)—A mixture of the amine (VI) dihydrochloride (2 g.), conc. HCl (6 cc.), HCHO solution (6 cc. of 30%), and water (6 cc.) was heated on a steam bath for 2 hrs. and the resultant solution was evaporated *in vacuo*. The residue was purified from dehyd. EtOH, forming colorless plates of m.p. 194~195°(decomp.); yield, 1.68 g. or 80.8%. *Anal.* Calcd. for $C_{13}H_{15}ON_3 \cdot 2HCl$: C, 51.7; H, 5.7; N, 13.9. Found: C, 52.0; H, 5.9; N, 13.6.

1-Phenyl-2-methyl-6-veratrylpyrido[3, 4-c]pyrazol-7-one (I)—The dihydro base (IXb, 0.4 g.) and ethyl cinnamate (0.4 g.) were dissolved in dry *p*-cymene (12 cc.) and to the solution was added 20% Pd-C (0.4 g.). The whole was now refluxed with stirring, in an oil bath at ca. 180° for 2.5 hrs. and filtered from the catalyst while hot. From the filtrate, (I) separated on cooling; yield, 0.26 g. or 65.4%. Some more was recovered by extracting the catalyst with hot benzene. Purified from benzene-hexane, forming colorless pillars of m.p. 167~168°. *Anal.* Calcd. for $C_{21}H_{19}O_3N_3$: C, 69.8; H, 5.3; N, 11.6. Found C, 70.1; H, 5.2; N, 11.5.

1-Phenyl-2-methylpyrido[3, 4-c]pyrazol-7-one (I′)—The dehydrogenation of the dihydro base (X) was carried out in a like manner. The catalyst was filtered off while hot, the catalyst was repeatedly extracted with hot benzene, and both the benzene and *p*-cymene solutions were extracted with dil. HCl. The combined HCl solution was evaporated to a small volume and basified with NaOH with cooling. The separated (I′) was collected and purified from benzene-hexane, forming colorless pillars of m.p. 154~155°. From the filtrate of (I′), some more was recovered by extracting with $CHCl_3$. Crude yield, ca. 40%. *Anal.* Calcd. for $C_{13}H_{11}ON_3$: C, 69.3; H, 4.9; N, 18.7. Found: C, 69.4; H, 5.0; N, 18.6.

Summary

1-Phenyl-2-methyl-3-β-aminoethyl-5-pyrazolone (VI) was prepared, which underwent Pictet-Spengler type of condensation, yielding 1-phenyl-2-methylpiperido[3, 4-c]-pyrazol-7-one (X). Veratroyl compound of (VI) was cyclized after Bischler-Napieralski-Perkin, giving 1-phenyl-2-methyl-3, 4-dihydropyrido[3, 4-c]pyrazol-7-one (IXb). Both (IXb) and (X) were dehydrogenated over palladium-carbon in boiling *p*-cymene, furnishing the corresponding pyrido derivatives (I) and (I′), respectively. Their pharmacological properties are now being examined.

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