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30. Isoo Ito, Taisei Ueda, and Ethuyoshi Kurokawa : Synthesis of Pyrazolone Derivatives. X.*1 Synthesis of 2,4,6-Trioxohexahydro-5-pyrimidinyl Derivatives.*2

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In 1925 Pfeiffer[1] described on pyrabital, which was a molecular compound of 1 mole of barbital and 2 moles of aminopyrine, that in pyrabital, barbital's own hypnotic action and toxicity for heart disappeared and according to Bürgi's law analgesic effect of aminopyrine was increased.

The present report, as a part of studies on synthesis of pyrazolone derivatives, concerns with the synthesis of some new type of compounds which comprize barbital and pyrazolone derivatives.

The scheme of synthesis of 1-phenyl-2-methyl-3-[(3,5-disubstituted-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-4-substituted-3-pyrazolin-5-one (C) is shown in Chart 1.

Starting compounds, 1-phenyl-2-methyl-3-bromomethyl-4-bromo-3-pyrazolin-5-one (I)[2] and 1-phenyl-3-bromomethyl-2,4-dimethyl-3-pyrazolin-5-one (II)[3] were condensed with ethyl ethoxymagnesiumalkylmalonate by the method of Lund, *et al.*[4] to give ethyl 2-substituted-2-(1-phenyl-2-methyl-4-alkyl-5-oxo-3-pyrazolin-3-yl)-methylmalonate (B). These compounds were then condensed with urea to obtain the objective compounds (C).

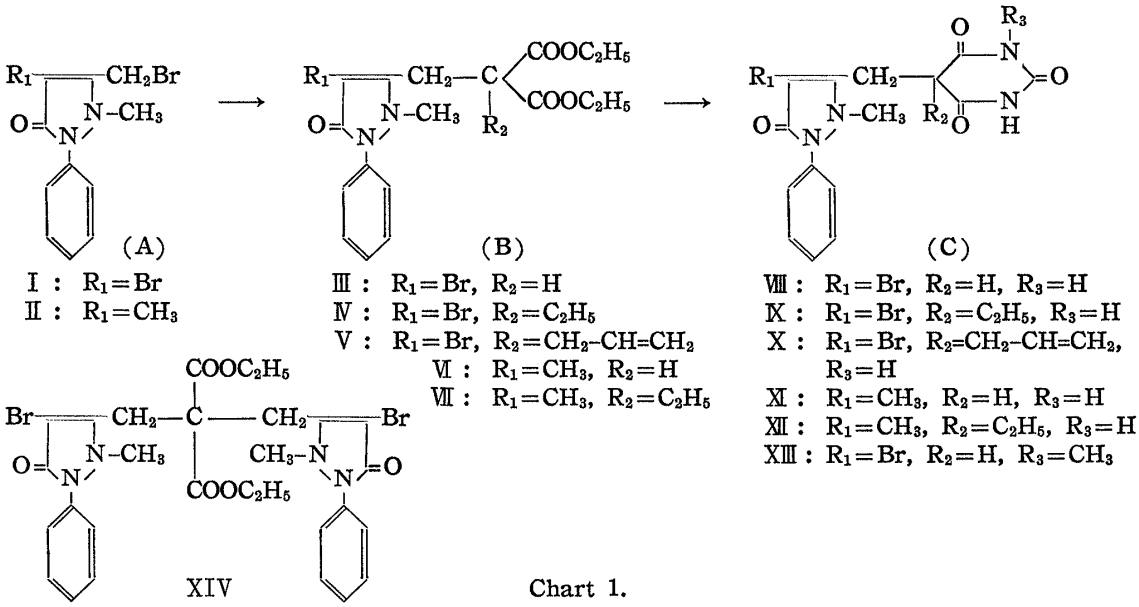


Chart 1.

The compound which was provided by condensation with I and ethyl malonate was already prepared by Ito,[5] one of the present authors. In that case, when sodium ethylate was used as a condensing agent, the yield of objective compound (III) was only

*1 Part IX. I. Ito : Yakugaku Zasshi, **81**, 1739 (1961).
*2 Presented at the Tokai Branch Meeting of Pharmaceutical Society of Japan. June, 12, 1965.
*3 Hagiyama-cho, Mizuho-ku, Nagoya (伊藤磯雄, 植田泰誠, 黒川悦義).

1) Pfeiffer, P. : Z. Physiol. Chem., **146**, 98 (1925).
2) H. Graef, J. Ledrut, G. Combes : Bull. soc. chim. Belges, **61**, 331 (1952)(C. A., **47**, 12363 (1953)).
3) Höchst. Farbwerke : Chem. Zentr., **1909**, I, 806.
4) H. Lund, A. U. Hansen, A. F. Voigt : Chem. Zentr., **I**, 1961 (1934).
5) Part V. I. Ito : Yakugaku Zasshi, **79**, 709 (1959).

45% and ethyl bis(1-phenyl-2-methyl-4-bromo-5-oxo-3-pyrazolin-3-yl)methylmalonate (XIV) was obtained as by-product. However, when metal magnesium was used according to the method of Lund, *et al.*, the objective compound was obtained in 92.5% yield.

In the reaction of ethyl ethylmalonate and II, when sodium ethylate was used as a condensing agent, the objective compound (IV) was obtained in 50% yield, together with a small amount of by-product of m.p. 225° (decomp.). This compound was assigned to be XIV, from determination by the mixed melting point, elemental analyses, and the comparison of the infrared spectrum.

However, by using magnesium instead of sodium, the condensation proceeded smoothly and improved the yield to 90%.

As for synthesis of 1-phenyl-4-[(2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-2,3-dimethyl-3-pyrazolin-5-one (XVIII), the scheme is shown in Chart 2.

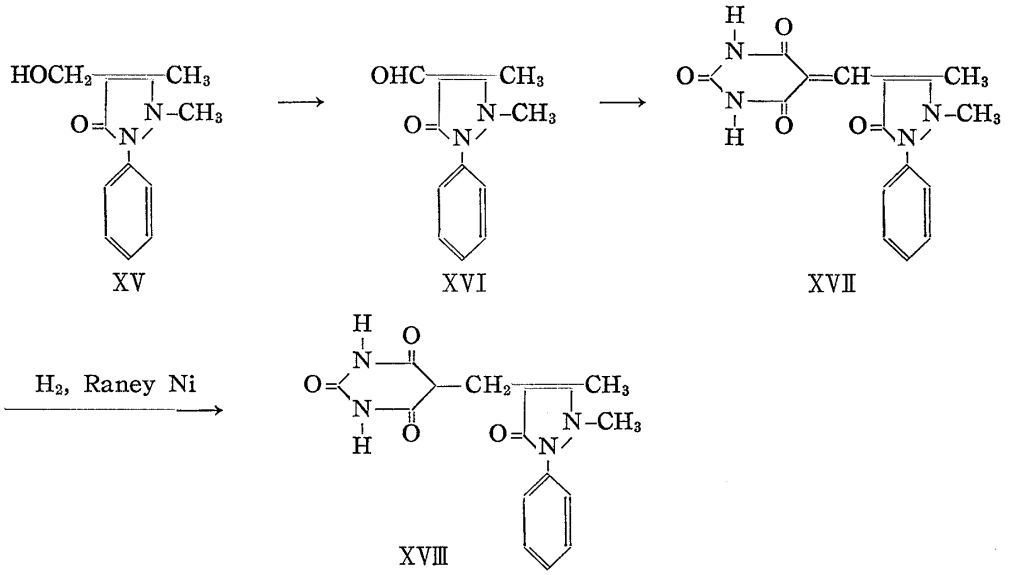


Chart 2.

1-Phenyl-4-formyl-2,3-dimethyl-3-pyrazolin-5-one (XVI)[6] prepared by the reaction with 1-phenyl-4-hydroxymethyl-2,3-dimethyl-3-pyrazolin-5-one (XV)[7] and active manganese dioxide was condensed with barbituric acid to give XVII. This compound was then reduced to XVIII.

On the other hand, an attempt for synthesis of 1-phenyl-4-halogenmethyl-2,3-dimethyl-3-pyrazolin-5-one from XV was made on an object to obtain XVIII. This attempt, however, was unsuccessful.

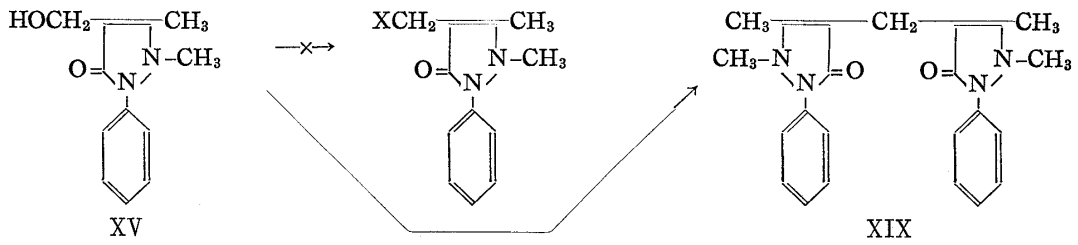


Chart 3.

6) S. Sugasawa, K. Mizukami: This Bulletin, **3**, 393 (1955).
7) K. Bodendorf, G. Koralewski: Arch. Pharm., **271**, 101 (1933) (C. A., **27**, 2671 (1933)).

As shown in Table I, in comparatively low reaction temperature starting material was recovered, but when heated on a water bath bis(1-phenyl-2,3-dimethyl-5-oxo-3-pyrazolin-4-yl)methane (XIX)[8] was obtained.

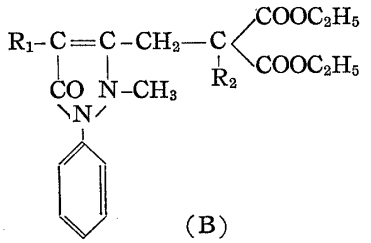
Table I. The Result of Reaction with Reagent and 1-Phenyl-4-hydroxymethyl-2,3-dimethyl-3-pyrazolin-5-one (XV)

No.	Reagent	Solvent	Temp. (°C)	Time (hr.)	Result
1	PBr_3	$CHCl_3$	0～5	10	recovery of starting material
2	〃	pyridine	0～5	24	〃
3	〃	pyridine, $CHCl_3$	80～100	10	bis (1-phenyl -2,3-dimethyl-5-oxo-3-pyrazolin-4-yl)-methane (XIX)
4	HBr, conc. H_2SO_4		80	5	〃
5	$SOCl_2$	$CHCl_3$, ligroin	60	5	〃

Experimental*4

General Procedure for Synthesis of Ethyl 2-Substituted-2-(1-phenyl-2-methyl-4-alkyl-5-oxo-3-pyrazolin-3-yl)methylmalonate (B)——To a solution of 6 ml. of dry. EtOH and 3 drops of dry CCl_4, 0.01 mole of Mg was dissolved with stirring under heating on a water bath After Mg was dissolved completely, 0.01 mole of ethyl alkylmalonate dissolved in 2 ml. of dry ether was added and finally 0.01 mole of 1-phenyl-2-methyl-3-bromomethyl-4-bromo(or methyl)-3-pyrazolin-5-one was added and refluxed on the water bath with stirring for 7 hr. After cooling, solvents were removed under reduced pressure and 15% H_2SO_4 was added into the residue cooling with ice. The resulting precipitates were extracted with $CHCl_3$, and the extracts were washed with water, dried over anhyd. Na_2SO_4 and $CHCl_3$ was removed to obtain white crystals, which were recrystallized from EtOH. Analytical data of the compounds are summarized in Table II.

Table II.



(B)

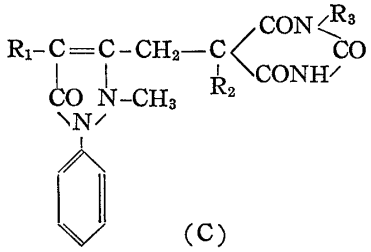
No.	R_1	R_2	m.p. (°C)	Appearance	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1	Br	C_2H_5	128～129	prisms	$C_{20}H_{25}O_5N_2Br$	52.98	5.52	6.18	52.71	5.76	5.77
2	〃	CH_2-CH=CH_2	97～98	〃	$C_{21}H_{25}O_5N_2Br$	54.19	5.38	6.02	54.26	5.54	5.94
3	CH_3	H	72～73	〃	$C_{19}H_{24}O_5N_2$	63.32	6.71	7.77	63.66	6.82	7.28
4	〃	C_2H_5	119～120	〃	$C_{21}H_{28}O_5N_2$	64.93	7.27	7.21	64.57	7.15	7.46

1 Ethyl 2-ethyl-2-(1-phenyl-2-methyl-4-bromo-5-oxo-3-pyrazolin-3-yl)methylmalonate (Ⅳ)
2 Ethyl 2-allyl-2-(1-phenyl-2-methyl-4-bromo-5-oxo-3-pyrazolin-3-yl)methylmalonate (Ⅴ)
3 Ethyl 2-(1-phenyl-2,4-dimethyl-5-oxo-3-pyrazolin-3-yl)methylmalonate (Ⅵ)
4 Ethyl 2-ethyl-2-(1-phenyl-2,4-dimethyl-5-oxo-3-pyrazolin-3-yl)methylmalonate (Ⅶ)

General Procedure for Synthesis of 1-Phenyl-2-methyl-3-[(3,5-disubstituted-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-4-substituted-3-pyrazolin-5-one (C)——0.1 g. of Na was dissolved in 5 ml. of dry EtOH. To this solution was added a solution of 0.01 mole of ethyl 2-substituted-2-(1-phenyl-2-methyl-

*4 All melting points are uncorrected.
8) A. Schuftan : Ber., 28, 1181 (1895).

4-alkyl-5-oxo-3-pyrazolin-3-yl)methylmalonate and 0.02 mole of urea dissolved in 5 ml. of dry EtOH and refluxed on an oil bath (110~115°) for 7 hr. After cooling the solution was neutralized with HCl and the solvent was removed under reduced pressure. The residue was dissolved into water and made acid (pH 4~5) with dil. HCl. The resulting precipitates were collected by filtration, washed with H_2O and recrystallized from EtOH. Analytical data of the compounds are summarized in Table III.



(C)

TABLE III.

No.	R_1	R_2	R_3	m.p. (decomp.) (°C)	Appearance	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
1	Br	H	H	162	prisms	$C_{15}H_{13}O_4N_4Br$	45.80	3.30	14.21	46.04	3.85	14.21
2	〃	C_2H_5	〃	235	〃	$C_{17}H_{17}O_4N_4Br$	48.45	4.04	13.30	48.61	4.37	12.87
3	〃	CH_2-CH=CH_2	〃	241	〃	$C_{18}H_{17}O_4N_4Br$	49.88	3.93	12.93	50.03	4.19	12.89
4	CH_3	H	〃	288	pillars	$C_{16}H_{16}O_4N_4$	58.53	4.91	17.07	58.86	5.08	16.97
5	〃	C_2H_5	〃	209	〃	$C_{18}H_{20}O_4N_4$	60.66	5.66	15.72	60.42	5.57	16.02
6	Br	H	CH_3	205	prisms	$C_{16}H_{15}O_4N_4Br$	47.17	3.69	13.75	46.75	3.92	13.24

1 1-Phenyl-2-methyl-3-(2,4,6-trioxohexahydro-5-pyrimidinyl)methyl-4-bromo-3-pyrazolin-5-one (VIII)
2 1-Phenyl-2-methyl-3-[(5-ethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-4-bromo-3-pyrazolin-5-one (IX)
3 1-Phenyl-2-methyl-3-[(5-allyl-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-4-bromo-3-pyrazolin-5-one (X)
4 1-Phenyl-3-[(2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-3-2,4-dimethyl-pyrazolin-5-one (XI)
5 1-Phenyl-3-[(5-ethyl-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-2,4-dimethyl-3-pyrazolin-5-one (XII)
6 1-Phenyl-2-methyl-3-(2,4,6-trioxohexahydro-3-methyl-5-pyrimidinyl)methyl]-4-bromo-3-pyrazolin-5-one (XIII)

1-Phenyl-4-[(2,4,6-trioxohexahydro-5-pyrimidinyl)methylene]-2,3-dimethyl-3-pyrazolin-5-one (XVII)——0.005 mole of 1-phenyl-4-formyl-2,3-dimethyl-3-pyhrazolin-5-one (XVI) and 0.005 mole of barbituric acid were dissolved in 20 ml. of acetic anhydride and heated on a water bath for 3 hr. Yellow crystals which appeared were collected by suction, washed with water and then ether, and recrystallized from AcOH. Yield 1.56 g. (96%), m.p. 266°(decomp.), yellow pillars. *Anal.* Calcd. for $C_{16}H_{14}O_4N_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 58.90; H, 4.64; N, 17.08. UV λ_{max}^{EtOH} mμ(log ε): 210(4.17), 260(4.28).

1-Phenyl-4-[(2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-2,3-dimethyl-3-pyrazolin-5-one (XVIII)——Raney Ni prepared from 1.0 g. of Ni-Al alloy was added to a solution of 1.0 g. of XVII dissolved in 100 ml. of EtOH and the mixture was shaken for 5 hr. in an autoclave at 60° under 40 kg./cm² of H_2. The catalyst was filtered off, the filtrate was evaporated and the residue was recrystallized from EtOH. Yield 0.91 g. (91%), m.p. 250°(decomp.). Colorless pillars. *Anal.* Calcd. for $C_{16}H_{16}O_4N_4$: C, 58.53; H, 4.91; N, 17.07. Found: C, 58.37; H, 5.02; N, 17.48. UV λ_{max}^{EtOH} mμ(log ε): 210(4.00).

Bis(1-phenyl-2,3-dimethyl-5-oxo-3-pyrazolin-4-yl)methane (XIX). Method A. Reaction of 1-Phenyl-4-hydroxymethyl-2,3-dimethyl-3-pyrazolin-5-one (XV) with Phosphorus Tribromide——To a solution of 20 ml. of $CHCl_3$ and 5 ml. of pyridine, 2.18 g. of XV was dissolved. To this solution was added dropwise 1.2 g. of PBr_3, cooling with ice under stirring for 30 min. Then the mixture was warmed on a water bath for 10 hr. After cooling, solvents were removed under reduced pressure and ether was added to obtain white solid, which was recrystallized from EtOH. m.p. 176~178°. Yield 1.95 g. This compound was confirmed to be identical with a sample obtained by the method of Schuftan,[8] by the mixed melting point determination.

Method B. Reaction of XV with Hydrogen Bromide-Sulfuric Acid——Into a mixture of 3.4 g. of HBr (S. Gr.: 1.48, 47%) and 2 ml. of H_2SO_4(98%), 2.18 g. of XV was added and heated on a water bath for 5 hr. After cooling, the above reaction mixture was poured into ice water and extracted with $CHCl_3$. The extracts were washed with 10% Na_2CO_3 and then with water, dried over anhyd. Na_2SO_4. $CHCl_3$ was evaporated to obtain white solid, which was recrystallized from EtOH. Yield 1.80 g. m.p. 177~178°. This compound was confirmed to be identical with a sample obtained by the method of Schuftan, by the mixed melting point determination.

Method C. Reaction of XV with Thionyl Chloride——Into a solution of 5 ml. of ligroin and 5 ml. of $CHCl_3$, 0.5 g. of XV was suspended. To this mixture 0.3 g. of $SOCl_2$ was added and stirred on a water bath (60°) for 5 hr. Water was added and extracted with $CHCl_3$, the extracts were washed with 10% Na_2CO_3 and then with water, dried over anhyd. Na_2SO_4, and $CHCl_3$ was evaporated to obtain brown solid, which was recrystallized from EtOH. m.p. 175~177°. Yield 0.31 g. This compound was confirmed to be identical with a sample obtained by the method of Schuftan, by the mixed melting point determination.

The authors express their deep gratitude to Mrs. M. Kataoka and Miss T. Yamagishi for carring out elemental analyses.

Summary

As a part of studies on syntheses of pyrazolone derivatives, syntheses of 1-phenyl-2-methyl-3(or 4)-[(5-substituted-2,4,6-trioxohexahydro-5-pyrimidinyl)methyl]-4(or 3)-substituted-3-pyrazolin-5-one were described.

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31. Kenji Suzuki, Mariko Asaka, and Takashi Abiko: Synthesis of 6-L-Leucine, 6-O-Acetyl-L-threonine, and 6-L-Threonine-bradykinin.*1

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A number of reports have appeared on the synthesis of bradykinin homologs substituted with the other amino acids in place of L-serine. The present writers synthesized 6-L-leucine, 6-O-acetyl-L-threonine, and 6-L-threonine-bradykinin, and their biological activity was examined.

During the progress of the present work, de Wald[1] and Stewart[2] reported the synthesis of 6-L-threonine but their method was different from that used in the present work which enables concurrent synthesis of 6-O-acetyl-L-threonine-bradykinin and it becomes possible to examine the biological activity of the O-acetyl compound as well.

The synthetic route for 6-L-leucine-bradykinin is illustrated in Chart 1. N-Benzyloxycarbonyl-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine *p*-nitrobenzyl ester[3] is debenzyloxycarbonylated with hydrogen bromide-acetic acid solution and L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine *p*-nitrobenzyl ester thereby formed was reacted with N-benzyloxycarbonyl-L-leucine *p*-nitrophenyl ester[4] to form N-benzyloxycarbonyl-L-leucyl-L-prolyl-L-phenylalanyl-N^{ω}-nitro-L-arginine *p*-nitrophenyl ester (I). The tetrapeptide ester obtained by the liberation of benzyloxycarbonyl group from I was

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*1 Nomenclature of bradykinin homologs and abbreviation of amino acids followed those given in Proc. 2nd Intl. Pharmacol. Meeting, Vol. 10. Oxytocin, Vasopressin, and their Structual Analogues. Ed. J. Rudinger, xi (1964). Czechoslovak Medical Press, Praha.

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1) H. A. de Wald, M. K. Craft, E. D. Nicolaides: J. Med. Chem., **6**, 741 (1963).
2) J. M. Stewart, D. W. Woolley: Biochemistry, **3**, 700 (1964).
3) K. Suzuki, T. Abiko, M. Asaka: This Bulletin, **14**, 217 (1966).
4) M. Bodanszky, V. Du Vigneaud: J. Am. Chem. Soc., **81**, 5688 (1959).