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Syntheses of New Pyrazoline Derivatives

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In order to synthesize 1-substituted amino-3,5,5-trimethylpyrazolines, diacetonalcohol was employed as the starting material, from which mesityloxide was prepared by the treatment with a catalytic amount of iodine, followed by the cyclization with hydrazine. The resulting 3,5,5-trimethylpyrazoline was converted to 1-chloroacetyl-3,5,5-trimethylpyrazoline by the reaction with chloroacetylchloride, followed by the reaction with a variety of amine. In this process, the reaction of mesityloxide with hydrazine was deduced to proceed probably through the intermediate of the corresponding hydrazone. Moreover, 1-β-carboethoxyethyl-3,5,5-trimethylpyrazoline was obtained by the reaction of 3,5,5-trimethylpyrazoline with ethyl acrylate.

Although a number of drugs have hitherto been known in a series of pyrazolones, little has been reported relating to other types of the pyrazole ring system. Accordingly, the authors attempted to find new compounds having any pharmacodynamic properties in a series of compounds containing the pyrazoline nucleus.

This paper is concerned with the syntheses of 1-(substituted aminoaceto)-3,5,5-trimethylpyrazoline derivatives.

There are known several methods[2-5] in the synthesis of 3,5,5-trimethylpyrazoline of the preceding intermediate for the preparation of 1-(substituted aminoacetyl)-3,5,5-trimethylpyrazoline derivatives. According to Curtius method,[6] diacetonalcohol was employed as the starting material, from which mesityloxide was prepared by the distillation adding a catalitic amount of iodine, followed by the cyclization reaction with hydrazine to 3,5,5-trimethylpyrazoline. Regarding to this cyclization reaction, Hauser[7] showed the following mechanism in which mesityloxide might react with hydrazine to form the cyclic alcohol and then dehydrate to the corresponding pyrazoline.

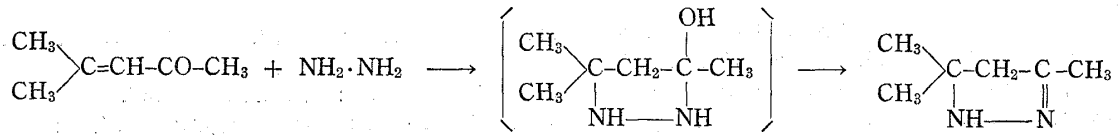


Chart 1

On the other hand, the condensation of mesityloxide with excess hydrazine hydrate was found to afford hygroscopic colorless prisms of the intermediate, which reacted with benzaldehyde in the presence of acetic acid in ethanol to give dibenzylidenehydrazine. This finding apparently seemed to suggest that the reaction between mesityloxide and hydrazine

1) Location: *a) Kuhonji, Oe-machi, Kumamoto; b) Otemachi, Chiyoda-ku, Tokyo.*
2) T. Curtius and H.A. Forstering, *Chem. Ber.*, **27**, 771 (1894).
3) C. Harries and R. Gley, *Ber.*, **32**, 1330 (1899).
4) K.W. Frey and R. Hoffmann, *Monatsch. Chem.*, **22**, 760 (1901).
5) N. Kishner, *Chem. Zentr.*, **1912**, I, 2025.
6) T. Curtius and F. Wirsing, *J. Pr.* 2, **50**, 546 (1894).
7) M. Hauser, *Chem. Rev.*, **63**, 311 (1963).

proceeded through the formation of the corresponding hydrazone as the intermediate, as shown in Chart 2.

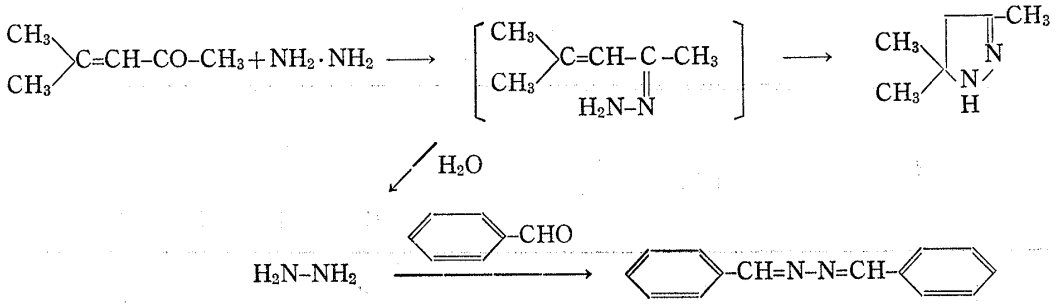


Chart 2

3,5,5–Trimethylpyrazoline was then submitted to react with chloroacetyl chloride.[8] There should be two possible courses of the reaction due to either 3,5,5–trimethylpyrazoline reacts with alkylchloride moiety or acylchloride moiety in chloroacetyl chloride. In consequence, either 1–chloroaceto–3,5,5–trimethylpyrazoline or 3,5,5–trimethylpyrazolinoacetyl chloride may produce through the reaction. Infrared spectrum of the resulting product showed the absorption assigned to the amide carbonyl group at 1680 cm^{-1}, but not the carbonyl group of the acyl chloride. Thus, the product was confirmed to be 1–chloroacetyl–3,5,5–trimethylpyrazoline. Moreover, 3,5,5–trimethylpyrazoline was found to react with ethyl acrylate to give 1–β–carboethoxyethyl–3,5,5–trimethylpyrazoline, in which the structure was confirmed from the infrared spectrum by recognizing the absorption assigned to ester carbonyl group at 1735 cm^{-1}. By treatment of 1–chloroacetyl–3,5,5–trimethylpyrazoline with a variety of amine, such as aliphatic, aromatic, heterocyclic and heteroaromatic amine, in ethanol or benzene, the corresponding amino compounds was obtained in comparative poor yields. When 1–chloroacetyl–3,5,5–trimethylpyrazoline was submitted to react with primary aliphatic and aromatic amines, the reactions were observed to proceed vigorously to give a mixture of the corresponding secondary and tertiary amino compounds, which was difficult to separate by recrystallization except a few examples.

The whole synthetic process are listed in Chart 3.

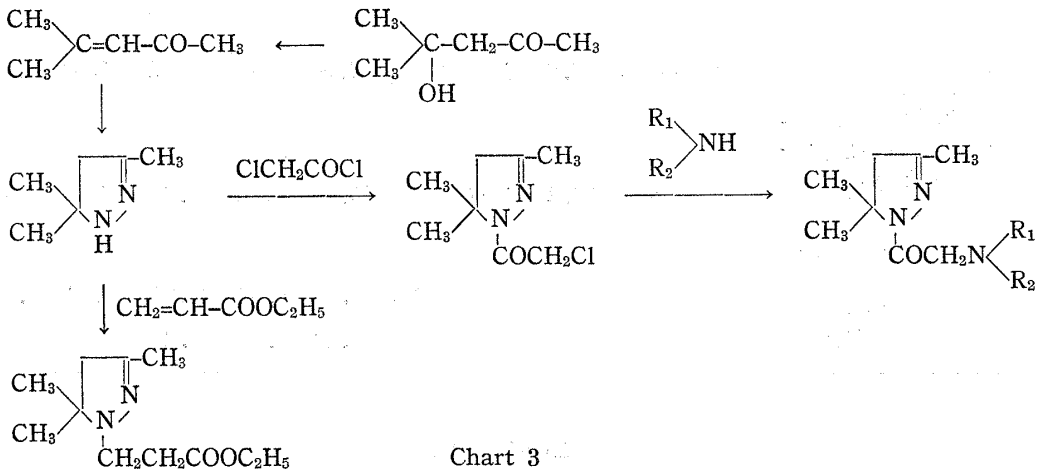
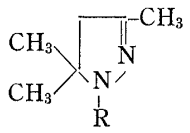


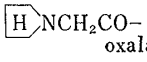
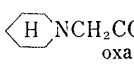
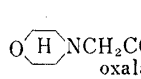
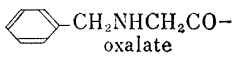
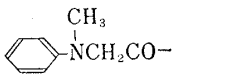
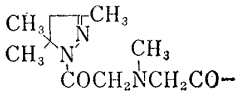
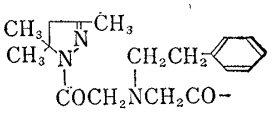
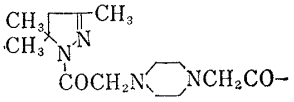
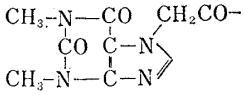
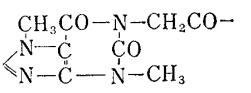
Chart 3

The compounds synthesized are listed in Table I.

8) L. McMaster and F.F. Ahmann, *J. Am. Chem. Soc.*, **50**, 146 (1928).

Pharmaceutical effects of these compounds will be reported in the other paper.

TABLE I. 

Compd. No.	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	$(CH_3)_2NCH_2CO-$ oxalate	216	53.3	$C_{12}H_{21}O_5N_3$	50.16	7.37	14.62	50.20	7.50	14.63
II	$(C_2H_5)_2NCH_2CO-$ oxalate	145—146	44.6	$C_{14}H_{25}O_5N_3$	53.33	7.99	13.32	53.68	8.05	12.82
III	 oxalate	197	45.4	$C_{14}H_{23}O_5N_3$	53.68	7.41	13.42	53.86	7.41	13.12
IV	 oxalate	208—209	33.9	$C_{15}H_{25}O_5N_3$	55.04	7.70	12.84	55.37	7.83	12.81
V	 oxalate	203	35.5	$C_{14}H_{23}O_6N_3$	51.05	7.04	12.76	51.41	7.26	12.64
VI	$(HOCH_2CH_2)_2NCH_2CO-$ oxalate	145	17.2	$C_{14}H_{25}O_7N_3$	48.42	7.26	12.10	48.59	7.27	11.95
VII	 oxalate	157	32.3	$C_{17}H_{23}O_5N_3$	58.27	6.91	11.99	58.79	6.68	12.10
VIII		100—101	27.7	$C_{15}H_{21}ON_3$	69.44	8.16	16.20	69.32	8.09	15.93
IX		114	6.0	$C_{17}H_{29}O_2N_5$	60.87	8.71	20.88	60.78	8.67	20.44
X		89—90	36.7	$C_{24}H_{35}O_2N_5$	67.82	8.30	16.48	67.65	8.39	16.46
XI		202—203	39.0	$C_{20}H_{34}O_2N_6$	61.50	8.78	21.52	61.64	8.80	21.51
XII		248—249	83.3	$C_{15}H_{20}O_3N_6$	54.26	6.06	25.27	54.13	6.19	25.13
XIII		273—274	40.1	$C_{15}H_{20}O_3N_6$	54.26	6.06	25.27	53.91	5.91	25.00
XIV	$H_5C_2OOCCH_2CH_2-$	bp 90/6	24.0	$C_{11}H_{20}O_2N_2$	62.23	9.50	13.20	62.00	9.62	12.90

Experimental

1-Chloroacetyl-3,5,5-trimethylpyrazoline——To a solution of 53 g (0.5 mole) of chloroacetyl chloride in 300 ml of anhyd. ether was added dropwise with stirring and cooling 120 g (1 mole) of 3,5,5-trimethylpyrazoline. After the completion of the addition, stirring was continued for 1 hr under warming. The etheral layer was then separated on cooling, dried over Na_2SO_4 and evaporated to remove ether. The

distillation of the residue gave 51 g (54.2%) of the yellow viscous liquid boiling at 148—158°/25 mm. It was immediately solidified under cooling, mp 43—44°.

General Procedure for the Synthesis of 1-Substituted aminoacetyl-3,5,5-trimethylpyrazoline——1) A mixture of 0.065 mole of amine, 0.025 mole of 1-chloroacetyl-3,5,5-trimethylpyrazoline and 30 ml of EtOH was stirred for 12 hr at room temperature. After removal of EtOH by evaporation, the resulting residue was neutralized with 40% aqueous K_2CO_3 solution and repeatedly extracted with 50 ml of ether. The extracts combined were dried over Na_2SO_4 and the solvent was distilled off. The resulting oily residue was purified by recrystallization or by distillation under reduced pressure. The objective compounds were converted into the corresponding oxalate by the treatment with an equimolar amount of oxalic acid and recrystallized from EtOH.

2) A mixture of 0.065 mole of amine and 0.025 mole of 1-chloroacetyl-3,5,5-trimethylpyrazoline in a small amount of benzene was stirred for 12 hr at room temperature. After removal of amine hydrochloride deposited by filtration, the filtrate was distilled to remove benzene. Recrystallization or distillation of the resulting oily residue gave colorless objective compounds. They were converted into the corresponding oxalates.

3) A solution of 0.065 mole of amine in 100 ml of water containing 0.065 mole of NaOH was heated for 1 hr under reflux. To this solution was added 0.025 mole of 1-chloroacetyl-3,5,5-trimethylpyrazoline and the solution was continued to heat for further 2 to 3 hr. Crystals deposited gradually were collected by suction on cooling and recrystallized from dil. EtOH.

Of compounds listed in Table I, I, II and VI were prepared by procedure (1), III, IV, V, VII, VIII, X, XI and XII, XIII, by procedure (2) and (3) respectively.

1,1'-[Methylamino-N,N-(2,2'-diacetyl)]bis(3,5,5-trimethylpyrazoline) (IX)——A mixture of 6.1 g (0.065 mole) of 30% aqueous methylamine solution, 5 g (0.025 mole) of 1-chloroacetyl-3,5,5-trimethylpyrazoline and 30 ml of EtOH was stirred for 12 hr at room temperature. After removal of EtOH by evaporation, the resulting residue was repeatedly extracted with 50 ml of hot ligroine to give 0.5 g (6%) of needles melting at 114°.

Ethyl β-(3,5,5-trimethylpyrazolino)propionate (XIV)——A solution of 33.6 g (0.3 mole) of 3,5,5-trimethylpyrazoline and 30 g (0.3 mole) of ethyl acrylate in anhyd. EtOH was heated for 2 hr under reflux. The solvent was then removed by evaporation and the residue was distilled under reduced presure to give 15 g of yellow liquid boiling at 80—90°/6 mm.

The Reaction of Intermediate obtained from Mesityloxide and Hydrazine with Benzaldehyde——One mole of mesityloxide was added with stirring into two mole of hydrazine hydrate below 0°. The resulting colorless prisms was rapidly collected by suction and added into a solution of benzaldehyde in EtOH containing a small amount of acetic acid. Recrystallization of the resulting precipitates from EtOH gave yellow needles melting at 93°, which were identified by a mixed melting point determination and the comparison of the IR spectra with an authentic sample prepared from benzaldehyde and hydrazine as dibenzylidenehydrazine.