Mrs. H. Matsuba and Mr. M. Shirōzu for the microanyalyses and to Messrs. H. Yano and H. Matsui for infrared and ultraviolet spectral measurements. This work was supported by the Grant-in-Aid for Scientific Reserch provided by the Ministry of Education, to which they are also grateful.

Summary

By means of paper chromatography, it was fonud that DHA was very reactive with ammonia, ammonium chloride, methylamine, ethanolamine or aniline in aqueous solutions even under a mild condition such as keeping in an incubator (37°), and pyridone derivatives were easily formed via Schiff's base type compounds (the first reaction product). It was also observed that DHA had lost its activity against some bacteria and fungi when it reacted with ammonia or primary amines.

(Received August 11, 1962)

UDC 547.812.5.07:615.778.47-011

71. Sadao Iguchi and Atsuko Inoue: Studies on Pyrone Derivatives. X.*[1] On the Reaction of Dehydroacetic Acid to the Primary Amines and Ammonia. (2).

(*Institute of Pharmaceutical Sciences, Faculty of Medicine, Kyushu University*[*2])

As reported in previous paper,*[1] it seems noteworthy that dehydroacetic acid (DHA) is apt to transform readily into pyridone derivatives even under a mild condition when it coexists with ammonia or primary amines in aqueous solutions.

We continued to investigate the mechanism of the reaction in more detail, and by the success of capturing the intermediate of the reaction to pyridone which had not been able to detect by paper chromatography, it became possible to explain the reaction process of the pyridone transformation under a mild condition. The details of the experiment are described in this paper.

In this experiment, we used benzylamine as the representative of primary amines at first, because of its easiness of treatment.

Though Schiff's base I, m.p. 79~81°, was formed when DHA reacted with the equivalent mole of benzylamine at room temperature, a new compound II, $C_{21}H_{24}ON_2$ (m.p. 118~119°), was obtained in the presence of an excess of benzylamine. II was also obtained by treating I with an excess of benzylamine. The compound II was a relatively labile substance having fluorescent property. It gave blue color with ferric chloride solution, whereas the compound I did not show such an apparent color reaction. The compound II was apt to change into N-benzyllutidone monohydrate (III), m.p. 125~127°, at the presence of mineral acids or organic acids such as acetic acid. However, when DHA reacted with benzylamine in the absence of an acid in a sealed tube, only the compound III was isolated. Thus formed lutidone derivative was very stable and remained unchanged even in solutions.

The validity of the structures of I (the primary reaction product) and III (the final product) shown in Chart 1, was supported by infrared, ultraviolet spectra and an elemental analysis.

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*[1] Part IX. This Bulletin, **11**,385 (1963).
*[2] Katakasu, Fukuoka (井口定男, 井上敦子).

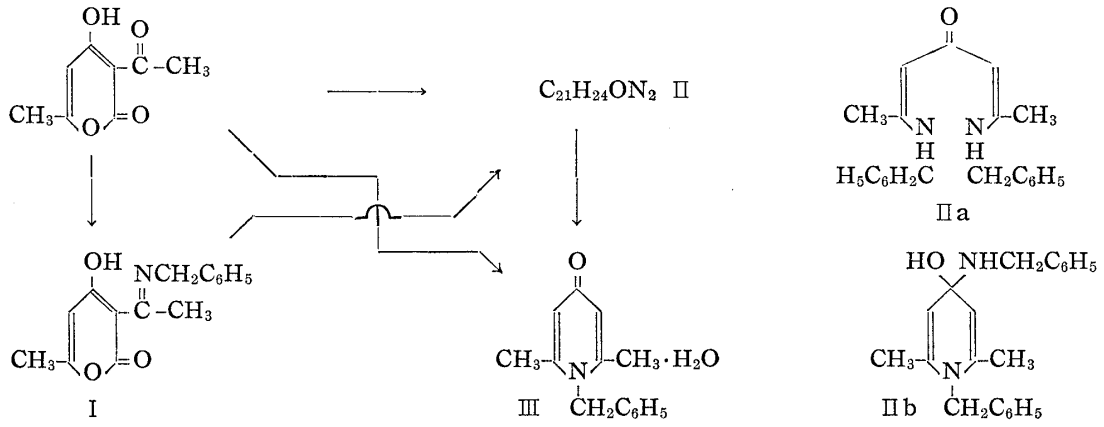


Chart 1.

As for the structure of the compound II, either IIa or IIb was assumed to be probable. But the structure IIa seemed more appropriate between the two according to the infrared spectrum. This assumption was further supported by the following fact that the compound II showed no depression in its melting point when mixed with 2,6-bis(benzylamino)-2,5-heptadien-4-one, which was synthesized in another method, i. e., the reaction of 2,6-dimethyl-4-pyrone with an excess of benzylamine.[1] Therefore, the structure of the compound II was assumed to be IIa shown in Charts 1 and 2.

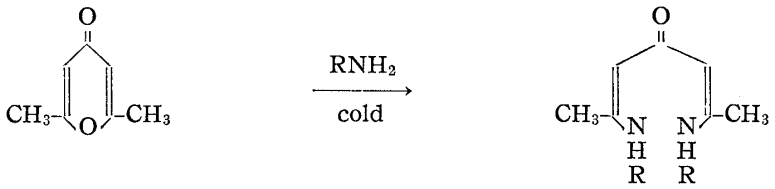


Chart 2.

The similar intermediates could be likewise obtained in the reaction of DHA with methylamine, ethylamine and phenethylamine respectively, and the behavior of these compounds was almost the same as that of benzylamine mentioned above and they finally converted into N-alkyllutidones in all cases.

Thus, the reaction process was assumed as shown in Chart 3. The first reaction product was Schiff's base IV, and secondly decarboxylation occurred in company with opening of lactone ring under the presence of an excess of amines (via the supposed

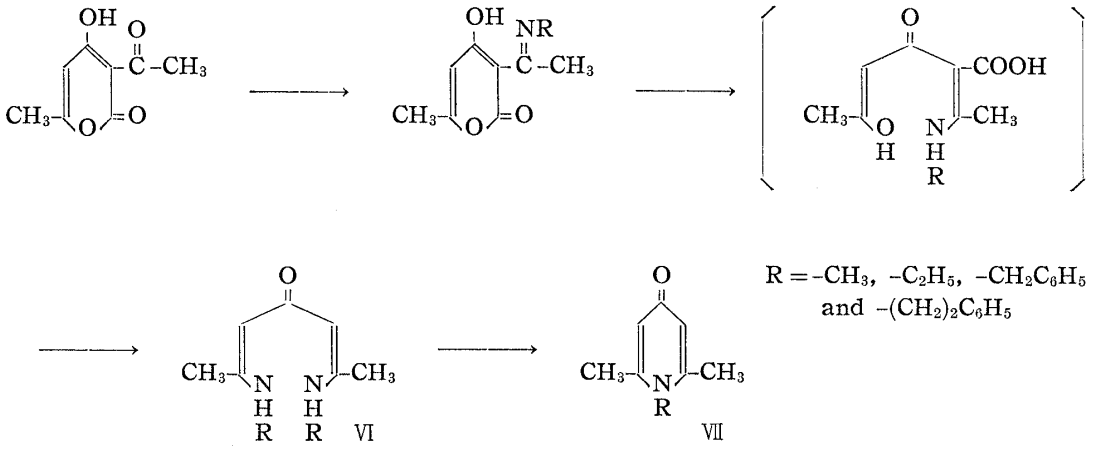


Chart 3.

1) R. T. Conley, *et al.* : Chem. & Ind. (London), **1959**, 1157.

intermediate (V)), followed by the formation of 2,6-bis(alkylamino)-2,5-heptadien-4-one (VI), which was easily apt to change into lutidone derivative (VII) with the release of a mole of amine.

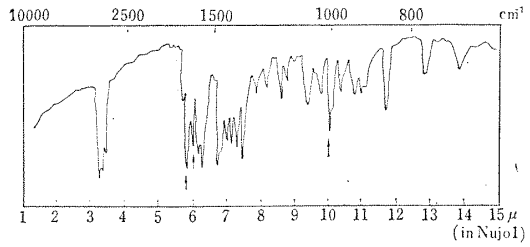


Fig. 1. Infrared Absorption Spectrum of Compound IVa

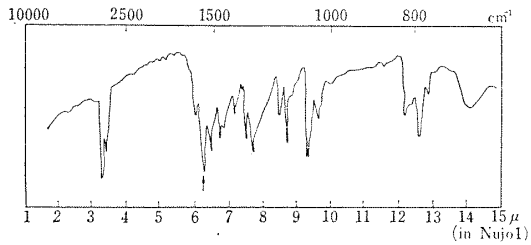


Fig. 2. Infrared Absorption Spectrum of Compound VIa

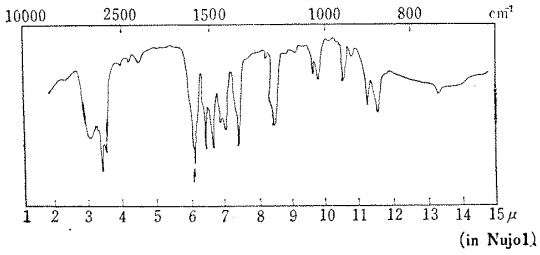


Fig. 3.
Infrared Absorption Spectrum of Compound VIIa

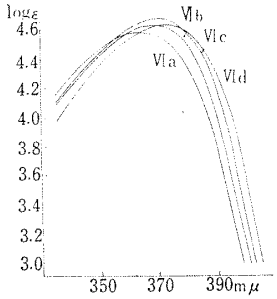


Fig. 4. Ultraviolet Spectra of Compound VI (in EtOH)

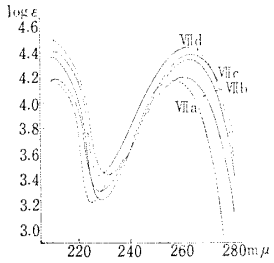


Fig. 5. Ultraviolet Spectra of Compound VII (in EtOH)
------ lutidone

In the papers concerning the reaction between DHA and ammonia which was already published by many investigators,[2~4] only lutidone was reported as the sole reaction product under drastic conditions, for example, by heating at 110° for 8 hours in a sealed tube. The resuls of this transformation has been utilized to support the validity of the structure of DHA admitted now. However, as reported in our previous paper,[*1] we reexamined the reaction of DHA with ammonia especially under a mild condition, and found the new fact that lutidone was also formed not only under the drastic condition but also under a mild condition.

Moreover, the following fact seemed very interesting that in the case of the reaction between DHA and ammonia, the considerable amounts of lutidonecarboxlic acid (XI) was also obtained together with lutidone (XII) at room temperature, while the other amines, i.e., methyl-, ethyl-, benzyl-, and phenethylamine being used, the compound corresponding to this carboxylic acid type (XI) could not be obtained at all. XI was a relatively stable compound and recovered unchanged almost quantitatively even after

2) L. Haitinger: Ber., **18**, 452 (1885).
3) M. Conrad, M. Guthzeit: *Ibid.*, **20**, 154 (1887).
4) A. Michaelis, A. Hölken: Ann., **331**, 245 (1904).

48 hours' refluxing in an alkaline solution. Therefore, it may be considered that lutidonecarboxylic acid (XI) was not the intermediate to lutidone (XII) under these mild conditions adopted in this experiment.

These results indicate that the following processes seem suitable for the reaction of DHA with ammonia under mild conditions: Though the primary reaction product is DHA-imide (VIII), two separate courses may be generated thereafter, one of them leads to the formation of lutidone (XII) as the result of ring closure after opening of lactone ring and decarboxylation (via IX and X, (supporsed intermediates)), while the other produces lutidonecarboxylic acid (XI) by ring closure after opening of lactone ring and intramolecular transformation without decarboxylation (via IX). However, this assumption does not deny the possibility of the reaction process from XI to XII under drastic conditions, since XII was obtained from XI by heating in a sealed tube.[5]

It must be also denoted that 2,6-diamino-2,5-heptadien-4-one (X) could not be isolated in the reaction between DHA and ammonia.

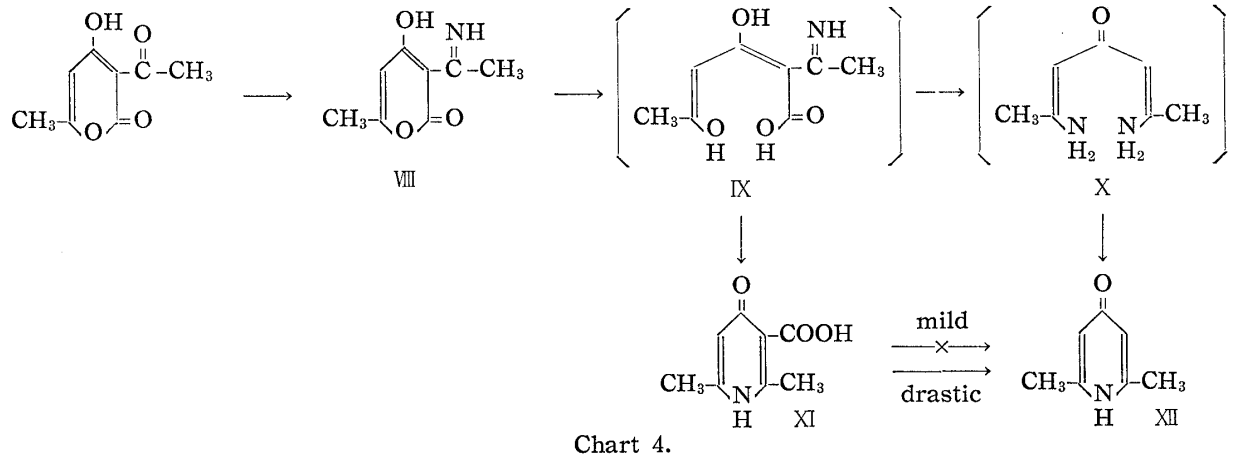
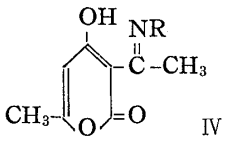


Chart 4.

Experimental

3-(1-Alkyliminoethyl)-4-hydroxy-6-methyl-2-pyrone (IV)——To 5 ml. of EtOH solution containing DHA (3.4 g.) was added an equivalent mole of alkylamime and then kept at room temperature for

Table I.



R	m.p. (°C)	Formula		Analyses (%) C	H	N	Yield (%)	IR $\nu_{C=O}^{Nujol}$ (cm^{-1})
$-CH_3$ (IVa)†	126~129 (EtOH)	$C_9H_{11}O_3N$	Found :	59.54	6.18	7.68	62	1703, 1666
			Calcd. :	59.67	6.08	7.73		
$-C_2H_5$ (IVb)	88~90 (Et_2O-MeOH)	$C_{10}H_{13}O_3N$	Found :	61.72	6.80	7.24	65	1698, 1664
			Calcd. :	61.54	6.67	7.18		
$-CH_2C_6H_5$ (IVc)	79~81 (MeOH)	$C_{15}H_{15}O_3N$	Found :	69.91	5.89	5.50	51	1705, 1666
			Calcd. :	70.04	5.83	5.41		
$-(CH_2)_2C_6H_5$ (IVd)	89~91 (Et_2O)	$C_{16}H_{17}O_3N$	Found :	70.60	6.17	5.13	54	1701, 1666
			Calcd. :	70.84	6.27	5.16		

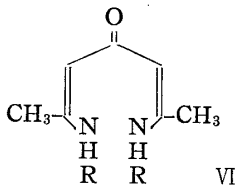
† Here, we must point out the following error that the compound written as 3-(1-methyliminoethyl)-4-hydroxy-6-methyl-2-pyrone in the experimental part of our previous report[6] was not the corresponding substance, but N-metyllutidone was taken up by mistake.

5) C.F. Rassweiler, R. Adams: J. Am. Chem. Soc., **46**, 2758 (1924).
6) S. Iguchi, *et al.*: This Bulletin, **7**, 327 (1959).

24 hr. After the solvent was evaporated, the residue was once washed with Et_2O, and recrystallized. Analytical data, melting point and yield of this type of compounds are summarized in Table I.

2,6-Bis(alkylamino)-2,5-heptadien-4-one (VI)——To 5 ml. of EtOH solution of DHA (3.4 g.) was added an excess of alkylamine and kept at room temperature for 24 hr. After the solvent was evaporated, the residue was once washed with Et_2O and then recrystallized. The compound VI gave blue color with $FeCl_3$ solution and was easily changed into VII in the presence of HCl or AcOH. It was proved that the picrate obtained with VI was identical with the picrate of VII. VI was characterized chiefly by infrared absorption spectrum comparing with the authentic sample synthesized in another method.[1] Analytical data, melting point and yield of this type of compounds are summarized in Table II.

Table II.



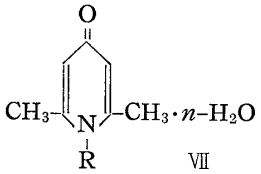
VI

R	m.p. (°C)	Formula		Analyses (%) C	H	N	Yield (%)	IR $\nu_{C=O}^{Nujol}$ (cm^{-1})
$-CH_3$ (VIa)	165～166 (MeOH)	$C_9H_{16}ON_2$	Found :	64.26	9.57	16.70	30	1572
			Calcd. :	64.29	9.52	16.67		
$-C_2H_5$ (VIb)	91～92 (MeOH)	$C_{11}H_{20}ON_2$	Found :	67.22	10.36	14.11	30	1558
			Calcd. :	67.34	10.20	14.28		
$-CH_2C_6H_5$ (VIc)	118～119 (EtOH)	$C_{21}H_{24}ON_2$	Found :	78.57	7.60	8.97	37	1562
			Calcd. :	78.75	7.50	8.75		
$-(CH_2)_2C_6H_5$ (VId)	115～116 (Et_2O)	$C_{23}H_{28}ON_2$	Found :	79.33	7.78	7.77	40	1562
			Calcd. :	79.31	8.04	8.04		

N-Alkyllutidone (VII)——(i) One g. of VI was dissolved into 20 ml. of H_2O, and a few drops of HCl or AcOH were added. After being kept at room temperature for a week or refluxed for 10 hr., the solvent was evaporated. Thus obtained residue was then recrystallized. VII was obtained quantitatively as hydrate.

(ii) The mixture of DHA (6.8 g.) and the equivalent mole of alkylamine (benzylamine or phenethylamine) was heated in a sealed tube for 8 hr. at 110～120°. The reaction mixture was evaporated on a steam bath and then recrystallized. (Yield : 40～50%). The picrate of VII was easily formed by the action of picric acid. Analytical data are summarized in Table III.

Table III.



VII

R	m.p. (°C)	Formula		Analyses (%) C	H	N	Picrate m.p. (°C)	IR $\nu_{C=O}^{Nujol}$ (cm^{-1})
$-CH_3$ (VIIa)	110 (H_2O)	$C_8H_{11}ON \cdot 3H_2O$	Found :	50.30	9.10	7.30	197～199	1640
			Calcd. :	50.21	8.90	7.33		
$-C_2H_5$ (VIIb)	72～73 (H_2O)	$C_9H_{13}ON \cdot 3H_2O$	Found :	52.72	9.55	—	194～195	1655
			Calcd. :	52.68	9.27	6.83		
$-CH_2C_6H_5$ (VIIc)	125～127 (H_2O)	$C_{14}H_{15}ON \cdot H_2O$	Found :	72.67	7.41	6.24	183～185	1639
			Calcd. :	72.72	7.36	6.06		
$-(CH_2)_2C_6H_5$ (VIId)	167～168 (H_2O)	$C_{15}H_{17}ON \cdot H_2O$	Found :	73.42	7.82	5.69	218～220	1650
			Calcd. :	73.47	7.75	5.71		

The Reaction of XI in Alkaline Medium——(i) The mixture of XI (2.0 g.) and 28% NH_3 (30 ml.) was refluxed for 48 hr. In the course of this reaction, each 10 ml. of aq. NH_3 was added every 3 hr. But XI was recovered unchanged almost quantitatively.

(ii) The mixture of XI (0.4 g.) and 28% NH_3 (10 ml.) was heated in a sealed tube for 8 hr. at 110～120°. The mixture was evaporated on a steam bath and extracted with EtOH. After the solvent was evaporated, a small amount of lutidone (XII) could be isolated, which was identified as a picrate (m.p. 219°), and gave the Rf value of 0.68. (Filter paper; Toyo Roshi No. 50; developing solvent; BuOH-AcOH-H_2O (4 : 1 : 5); spraying agent; Dragendorff; developing time; 16 hr. at 15～20°).

The authors are grateful to Prof. H. Matsumura of this university for his encouragement throughout this work. Thanks are also due to Mrs. S. Matsuba and Mr. M. Shirōzu for the elemental analyses and to Messrs. H. Yano, H. Matsui and K. Hikita for the spectral measurements. This work was supported by the Grant-in-aid for Scientific Research provided by the Ministry of Education, to which they are also grataful.

Summary

The reaction process of DHA, when it reacted with an excess of methyl-, ethyl-, benzyl- or phenethylamine under a mild condition, was clarified as follows: The primary reaction product is Schiff's base, the secondly product 2,6-bis(alkylamino)-2,5-heptadien-4-one, and the final product lutidone derivative. In the case of the reaction of DHA with an excess of ammonia, two compounds, lutidone and lutidonecarboxylic acid, were obtained as final products. But lutidonecarboxylic acid seems not to be the intermediate to lutidone under these mild conditions.

(Received August 11, 1962)

UDC 612.386[615.778.25]-084

72. Hisashi Nogami, Manabu Hanano,[*1] and Hideo Yamada[*2]: Studies on Absorption and Excretion of Drugs. IV.[*3] Absorption of Various Sulfonamides from the Rat Small Intestine by the Perfusion Method *in vivo*.

(*Faculty of Pharmaceutical Sciences, Univesity of Tokyo*[*1] *and Research Laboratory, Shionogi Co., Ltd.*[*2])

A large number of studies on gastrointestinal absorption of sulfonamides have been published. But there have been few kinetic studies on relationship between the absorption rate of sulfonamide and its concentration in the intestine.

The penetration of various sulfonamides across the intestinal barrier *in vitro* was reported in the preceding paper of this series.[1)]

The present paper describes the observations with disappearance rate of sulfonamides from the perfusion solution through the rat small intestine *in vivo* and with the effects of pH of the solution on the disappearance rate, together with discussion of these results.

When the various forms of a given drug in the solution ini the ntestinal lumen (*e.g.* ionic, nonionic, etc.) are in equilibrium under the fixed conditions, the concentration of one form (*e.g.* i-th form) to the total drug must be constant,

$$\frac{C_i}{C}=K_i \qquad (1)$$

where C_i is the concentration of i-th form, C is the total drug concentration and K_i is constant. If the amount of the drug molecules in the i-th form passing across the unit

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*1 Hongo, Tokyo (野上 寿, 花野 学).
*2 Fukushima-ku, Osaka (山田秀雄).
*3 Presented before the Kanto Local Meeting of the Pharmaceutical Society of Japan, Tokyo, January, 1961.
1) H. Nogami, M. Hanano, J. Watanabe: This Bulletin, **10**, 1161 (1962).