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Studies of Cycloheximide-Related Compounds. III. A Novel Reaction of Aromatic Nitroketones with Aldehydes and Secondary Amines*[1]

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A novel reaction of aromatic nitroketones with aldehydes in the presence of a secondary amine is described. The products have been shown by degradation and infrared, NMR, and ultraviolet spectral studies to have a 2, 3-dihydro-γ-pyran skeleton. The probable condensation path involves a new reaction of the Mannich type through the interaction of secondary amines with an aromatic nitroketone and a dimeric condensate of an aldehyde with an active methylene group, followed by an intramolecular dehydration to produce a 2, 3-dihydro-γ-pyran ring. Mild hydrolyses of the products afford ketoaldehyde derivatives, which expectedly exhibit ring-chain isomerism, showing a cyclic hemiacetal nature. The scope of the reaction has been further defined.

We previously reported[1] that the acid-catalyzed condensation of glutarimide-β-acetaldehyde (GAA) with a number of aliphatic ketones and dimethylcyclohexanones provided a synthesis for a series of compounds related to cycloheximide, an antibiotic which is used as a fungicide and which possesses anti-tumor and rodent-repellent activities. We were next interested in ascertaining the effects of base catalysts on this condensation. In this connection, Lawes[2] successfully synthesized anhydrocycloheximide by condensing 2, 4-dimethyl-6-formylcyclohexanone with GAA in the presence of potassium carbonate. We have now examined the amine-catalyzed reactions of GAA with some ketones. This paper will report the results of these studies; it has been found that aromatic nitroketones, which failed to react with GAA in the presence of acid catalysts, react with aldehydes and secondary amines to give a novel cyclization product with a dihydropyran ring.

Reactions of nitroketones with GAA and a secondary amine have been generally carried out in a 1 : 2 : 1 molar ratio in absolute ethanol at room temperature. The condensation of *p*-nitroacetophenone with GAA in the presence of piperidine gave the cyclic product I in a 74% yield (Chart 1). A similar reaction of 2-acetyl-5-nitrofuran gave the corresponding cyclic compound, V. The analytical carbon, hydrogen, and nitrogen values obtained for the cyclization products, I and V, were in excellent agreement with the $C_{27}H_{32}N_4O_7$ and $C_{25}H_{30}N_4O_8$, formulas respectively, suggesting that both products consisted of one mole each of nitroketone and piperidine and two moles of GAA. Moreover, it has been found that the above-mentioned reaction is applicable not only to GAA but to a simpler aldehyde such as propionaldehyde. The analogous treatment of *p*-nitroacetophenone with propionaldehyde in the presence of piperidine gave the corresponding cyclic product, VIII, in a 86% yield.

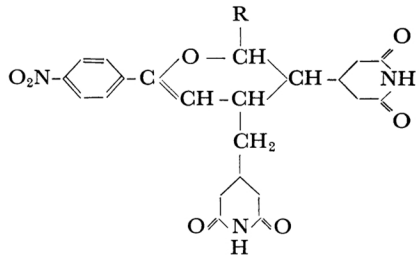
A mild hydrolysis of VIII with dilute hydrochloric acid gave β-ethyl-α-methyl-γ-(*p*-nitrobenzoyl)-butylaldehyde (IX). The spectral data of IX are in agreement with the structure. The infrared spectrum showed the presence of an aromatic ketone group at 1695 cm^{-1} and an aldehyde group at 1725 cm^{-1}. The ultraviolet absorption spectrum showed a maximum at 266 mμ for the *p*-nitrobenzoyl group. The presence of the aldehyde group was further confirmed by its formation of 2, 4-dinitrophenylhydrazone and its positive Tollens reaction. These data made possible an unequivocal structural assignment of IX.

The analogous hydrolysis of I with dilute hydrochloric acid or acetic acid gave the corresponding δ-ketoaldehyde (X-A), from which the corresponding 2, 4-dinitrophenylhydrazone was derived. The infrared and NMR spectra of the ketoaldehyde indicated that they exhibit a ring-chain isomerism and exist in a cyclic hemiacetal form, namely, 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-2-hydroxy-6-(*p*-nitrophenyl)-2, 3-dihydro-γ-pyran (X-B). The presence of the hydroxyl group in X-B was indicated by the absorption band at 3330 cm^{-1} and was confirmed by acetylation. The infrared and NMR spectra of the acetylated product were consistent with the assigned dihydropyran structure.

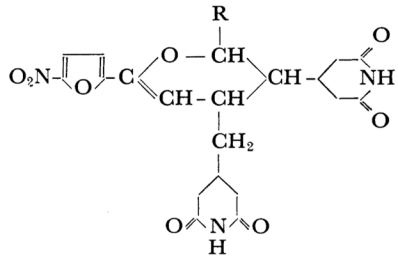
*1 This constitutes Part XXVIII of a series entitled "Studies on Antibiotics and Related Substances," by S. Umezawa *et al.*; a portion of this paper was presented at the Annual Meeting of the Cooperative Cancer Research, Ministry of Education, Tokyo, February 4, 1966.

1) Y. Egawa and S. Umezawa, This Bulletin, **38**, 2169 (1965).

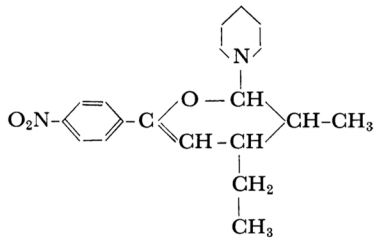
2) B. C. Lawes, *J. Am. Chem. Soc.*, **82**, 6413 (1960).



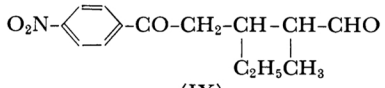
I: R=piperidino
II: R=morpholino
III: R=pyrrolidino
IV: R=diethylamino
Acetate of X-B: R=$OCOCH_3$



V: R=piperidino
VI: R=morpholino
VII: R=pyrrolidino



(VIII)



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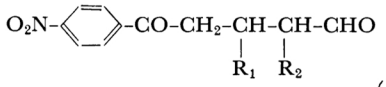
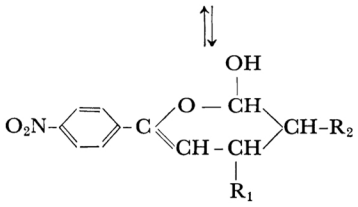


(A)



(B)

X: R_1=3-glutarimidylmethyl
R_2=3-glutarimidyl

Chart 1

It may, accordingly, be assumed that 2, 3-dihydro-γ-pyran rings were formed, for example,

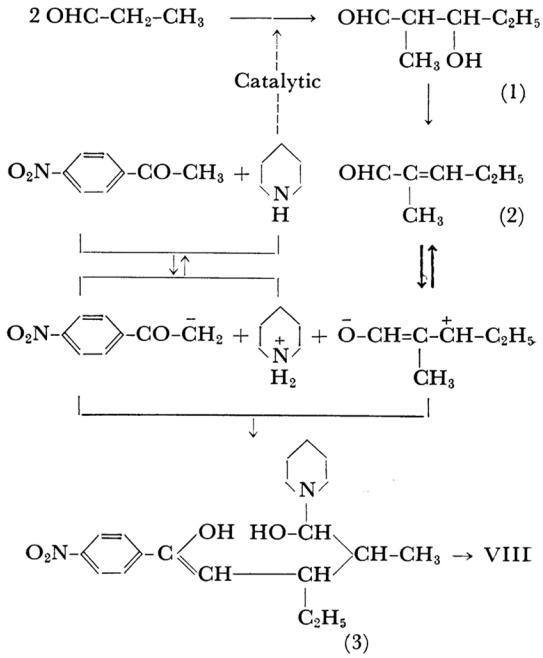


Chart 2

through the interaction of *p*-nitroacetophenone, 2-methyl-2-pentenal (a dimeric condensate of the starting propionaldehyde), and piperidine, or, alternatively, through the interaction of *p*-nitrophenyl butenyl ketone (the condensate of *p*-nitroacetophenone and propionaldehyde), propionaldehyde, and piperidine. In view of the fact that the condensation also took place smoothly when one mole of propionaldol was used (compound 1 in Chart 2) instead of two moles of propionaldehyde, the former pathway seems more likely, as is shown in Chart 2. A Michael addition of *p*-nitroacetophenone with the α, β-unsaturated aldehyde which is produced by the dimeric condensation of an aldehyde may give a δ-ketoaldehyde, to which in turn a secondary amine is added to give a key intermediate, *e. g.*, an aldehyde-amine compound (for example, compound 3 in Chart 2).

The mass spectrum of the condensation product VIII showed a molecular ion peak at *m/e* 330. The analytical carbon, hydrogen, and nitrogen values for VIII were in excellent agreement with the $C_{19}H_{26}N_2O_3$ formula (mol wt 330). The ultraviolet absorption spectrum of VIII in methanol showed a maximum at 244 mμ, suggesting the presence of a double bond conjugated to the *p*-nitrophenyl group. The infrared spectrum of VIII showed bands at 1645 and 1240,[3] at 1515,

3) The infrared bands of the ether linkage (1241 cm^{-1}) and the double bond (1647 cm^{-1}) of a pure sample of 2, 3-dihydro-γ-pyran were reported by C. D. Hurd, J. Moffat and L. Rosnati, *J. Am. Chem. Soc.*, **77**, 2795 (1955).

TABLE 1. ANALYTICAL VALUES AND MELTING POINTS OF CONDENSATION PRODUCTS AND THEIR DERIVATIVES

Compound	Mp, °C (dec.)	Solvent for recrystallization	Formula	Analyses, % Calcd C	Calcd H	Calcd N	Found C	Found H	Found N	Yield %
I	199—199.5	Acetone	$C_{27}H_{32}N_4O_7$	61.82	6.15	10.68	61.51	6.23	10.43	74
II	203—204	EtOH*1	$C_{26}H_{30}N_4O_8$	59.31	5.74	10.64	58.81	5.71	10.42	46
III	174—175	T. H. F.*1	$C_{26}H_{30}N_4O_7$	61.16	5.92	10.98	60.70	5.95	10.77	64
IV	171.5—172	EtOH*1	$C_{26}H_{32}N_4O_7$	60.92	6.29	10.93	60.56	6.53	10.77	42
V	145—145.5	Acetone	$C_{25}H_{30}N_4O_8$	58.36	5.88	10.89	58.44	6.14	10.56	70
VI	190—190.5	Acetone*1	$C_{24}H_{28}N_4O_9$	55.81	5.46	10.85	55.67	5.64	10.30	60
VII	134—136	THF-EtOH	$C_{24}H_{28}N_4O_8$	57.59	5.64	11.20	57.72	5.33	10.78	64
VIII	154.5—155*2	EtOH	$C_{19}H_{26}N_2O_3$	69.06	7.93	8.43	69.15	7.76	8.24	86
IX	180—182*3	—	$C_{14}H_{17}NO_4$	63.86	6.51	5.32	64.12	6.63	5.16	39
X	229.5—230	AcOH	$C_{22}H_{23}N_3O_8$	57.76	5.07	9.19	57.66	5.17	8.89	77
Acetate of X-B	178—179	isoPrOH	$C_{24}H_{25}N_3O_9$	57.71	5.05	8.41	57.89	5.16	8.28	31

*1 Washed with hot solvent.
*2 Melted without decomposition.
*3 Boiling point under 1 mmHg.

TABLE 2. IR AND UV SPECTRA OF CONDENSATION PRODUCTS AND THEIR DERIVATIVES

Compound	IR(KBr): cm^{-1} NH	C=O	C=C	Phenyl	Furyl	NO_2	C-O-C	UV absorption*1 mμ (ε)
I	3280, 3200, 3100	1730, 1700	1660	1600	—	1520, 1350	1260	*4
II	3300, 3200, 3100	1730, 1700	1655	1600	—	1520, 1350	1260	*4
III	3260, 3200, 3090	1725, 1690	1650sh	1595	—	1515, 1340	1265	*4
IV	3280, 3200, 3100	1730, 1700	1655	1600	—	1520, 1350	1260	*4
V	3200, 3100	1730sh, 1690	1650sh	—	1575	1525, 1350	1265	230 (11000) 312 (10600)
VI	3220, 3080	1720, 1690	1650	—	1570	1515, 1350	1260	230 (7800) 314 (6100)
VII	3180, 3070	1730, 1700	1650	—	1575	1535, 1350	1265	224 (6500) 310 (6500)
VIII	—	—	1645	1600	—	1515, 1350	1240	235 (14000) 344 (15500)
IX	—	1725, 1695	—	1600	—	1525, 1345	—	266 (17200)
X	3330 (OH), 3220 3110	1730, 1700	1665sh	1610	—	1530, 1350	1260	269 (10300)*2
Acetate of X-B*3	3220, 3100	1730sh, 1700	1665sh	1600	—	1530, 1350	1265	228 (8100) 262 (7400) 325 (6600)

*1 Methanol solution.
*2 10% dioxane-water solution.
*3 1220 cm^{-1} (acetate C-O) was detected.
*4 As these samples were scarcely soluble in ordinary solvents, UV absorptions were not determined.

and at 1350 cm^{-1}, indicating the presence of a double bond, an ether linkage, and a nitro group respectively. The NMR spectrum of VIII in deuterated chloroform was consistent with the assigned structure: τ 4.45 (1H, doublet, J=3 cps) for the olefinic proton, τ 5.65 (1H, doublet, J=9 cps) for the proton adjacent to the oxygen function, τ 7.1 (4 H, multiplet) for protons adjacent to piperidine-nitrogen, τ 8.98 (3H, doublet, J=6 cps) for the 3-methyl proton, and τ 9.05 (3H, triplet, J=6 cps) for the methyl proton of the 4-ethyl group.

Similarly, the *p*-nitroacetophenone and 2-acetyl-5-nitrofuran could be caused to react with GAA and another secondary amine, *e. g.*, morpholine, pyrrolidine or diethylamine, to give the corresponding cyclic products (II, III, IV, VI and VII). Tables 1 and 2 list the melting

points, analyses, yields, ultraviolet absorption maxima, and infrared spectral data.

It has previously been established that Mannich bases resulting from the interaction of a primary base with a ketone and an aldehyde are unstable and undergo cyclization to afford, for example, a tetrahydropyridone or piperidone derivative. However, the above-mentioned reaction is of a new type which has never before, to our knowledge, been described.

Attempts to condense the nitroketones with GAA by other organic amines, such as *N*-methylaniline or triethylamine, were unsuccessful. Acetone, (2R : 4R)-2, 4-dimethylcyclohexanone, and acetophenone failed to react with GAA even when piperidine was used as a secondary amine. It may therefore, be, concluded that the condensation takes place smoothly when an aromatic nitroketone and a secondary amine of pK_a about 9—11 are treated with an aldehyde possessing an active methylene group.

Experimental

The NMR spectra were determined at a frequency of 60 Mc with a Japan Electron Optics JNM-C-60 spectrometer in deuterated chloroform, deuterated dimethylsulfoxide, and trifluoroacetic acid. Tetramethylsilane was used as an internal reference in the sample. Peak positions are given in τ-values.

General Procedure. To a mixture of two moles of GAA[4] (or propionaldehyde) and one mole of *p*-nitroacetophenone (or 2-acetyl-5-nitrofuran) in absolute ethanol (2 m*l* to 1 mmol of the starting material) was added one mole of secondary organic bases, dropwise under stirring at room temperature; the mixture was then allowed to stand for from a few hours to two days. The condensation product usually crystallized out. The solid was washed with a small quantity of ethanol and further purified by recrystallization.

3-(3-Glutarimidyl)-4-(3-glutarimidylmethyl)-6-(4-nitrophenyl)-2-piperidino-2, 3-dihydro-γ-pyran (I), 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-2-morpholino-6-(4-nitrophenyl)-2, 3-dihydro-γ-pyran (II), 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-6-(4-nitrophenyl)-2-pyrrolidino-2, 3-dihydro-γ-pyran (III), 2-diethylamino-3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-6-(4-nitrophenyl)-2, 3-dihydro-γ-pyran (IV), 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-6-(5-nitro-2-furyl)-2-piperidino-2, 3-dihydro-γ-pyran (V), 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-2-morpholino-6-(5-nitro-2-furyl)-2, 3-dihydro-γ-pyran (VI), 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-6-(5-nitro-2-furyl)-2-pyrrolidino-2, 3-dihydro-γ-pyran (VII), and 4-ethyl-3-methyl-6-(4-nitrophenyl)-2-piperidino-2, 3-dihydro-γ-pyran (VIII) were prepared by the general procedure. The melting points, elementary analyses, yields, ultraviolet absorption maxima, and infrared spectral data of the products (I, II, III, IV, V, VI, VII, VIII) are shown in Tables 1 and 2.

4) Y. Egawa, M. Suzuki and T. Okuda, *Chem. Pharm. Bull. (Tokyo)*, **11**, 598 (1963).

Formation of VIII from Propionaldol. *p*-Nitroacetophenone (165 mg, 1 mmol) and propionaldol (120 mg, 1 mmol) were dissolved in absolute ethanol (4 m*l*). Into the solution, piperidine (85 mg, 1 mmol) was then added, drop by drop, under stirring at room temperature, and the mixture was allowed to stand overnight. The condensation product VIII then crystallized out. Recrystallization from ethanol gave light yellow needles, mp 154—155°C, (264 mg, yield 80%). No depression in melting point was observed on admixture with an authentic specimen (mp 154.5—155°C), which had been prepared from *p*-nitroacetophenone, propionaldehyde, and piperidine by the general procedure. NMR spectrum of VIII in deuterated chloroform: τ 1.67 (2H, doublet, J=9 cps) and τ 2.17 (2H, doublet, J=9 cps) for aromatic protons, τ 4.45 (1H, doublet, J=3 cps) for $>C=C\underline{H}-$, τ 5.65 (1H, doublet, J=9 cps) for $-O-C\underline{H}-$, τ 7.1 (4H, multiplet) for $-N\langle^{C\underline{H}_2-}_{C\underline{H}_2-}$, τ 8.0 (4H, multiplet) for $-C\underline{H}_2-C\underline{H}-C\underline{H}-$, τ 8.4 (6H, singlet) for $-N\langle^{-C\underline{H}_2}_{-C\underline{H}_2}\rangle C\underline{H}_2$, τ 8.98 (3H, doublet, J=6 cps) for $C\underline{H}_3-CH-$, and τ 9.05 (3H, triplet, J=6 cps) for $C\underline{H}_3-C\underline{H}_2-$.

Hydrolysis of VIII. To a suspension of 990 mg (3 mmol) of VIII in 25 m*l* of ethanol, 20% hydrochloric acid (2 m*l*) was added at room temperature. After stirring for four hours, the mixture was neutralized with 3 N sodium hydroxide and repeatedly extracted with ethyl acetate. The extract was then washed with water, dried over anhydrous sodium sulfate, filtered, and evaporated. The residue (913 mg) was chromatographed on silica gel (60 g) with *n*-hexane, isopropyl ether-*n*-hexane (1 : 1), and isopropyl ether. Elution with isopropyl ether gave a yellow syrup (313 mg, yield 39%) of β-ethyl-α-methyl-γ-(*p*-nitrobenzoyl)-butylaldehyde (IX). Further purification by distillation under reduced pressure gave a light yellow syrup, bp 180—182°C/1 mmHg.

2, 4-*Dinitrophenylhydrazone of IX.* Yellow prisms, mp 176—176.5°C. IR bands (KBr): 3290, 3100 (NH), 1695 (Ar.C=O), 1615 (C=N), 1590 (phenyl), 1520, 1330 cm^{-1} (NO_2). UV absorption (methanol): 262 mμ (ε 11400), 360 mμ (ε 12600).

Found: C, 53.70; H, 4.52; N, 16.33%. Calcd for $C_{20}H_{21}N_5O_7$ (mol wt, 443): C, 54.17; H, 4.77; N, 15.80%.

Hydrolysis of I with Acetic Acid. A sample (1.05 g) of I was dissolved in acetic acid (20 m*l*), after which the mixture was kept standing overnight at room temperature to deposit a crude solid (660 mg). Recrystallization from acetic acid gave colorless prisms of 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-2-hydroxy-6-(4-nitrophenyl)-2, 3-dihydro-γ-pyran (X-B), mp 229.5—230°C (dec.). NMR spectrum of (X-A) in deuterated dimethylsulfoxide: τ −0.8 (1H, singlet) τ −0.7 (1H, singlet) for the two imide protons, τ 0.2 (1H, singlet) for the aldehyde proton, τ 1.62 (2H, doublet, J=9 cps) and τ 1.82 (2H, doublet, J=9 cps) for the aromatic protons, τ 6.65 (4H, multiplet), τ 7.5—7.8 (10H, multiplet) for the methylene and methine protons of the glutarimide ring, and τ 8.6 (2H, multiplet) for the methylene protons attached to the glutarimide ring.

Hydrolysis of IV with 20% Hydrochloric Acid. To a suspension of IV (40 mg) in dioxane (5 m*l*), 20%

hydrochloric acid (0.8 m*l*) was added at room temperature. After stirring for two hours, the reaction mixture was adjusted to pH 6—7 with a saturated sodium bicarbonate solution and diluted with about 20 m*l* of water. On standing in a refrigerator, a crude solid (11 mg, yield 33%) separated out. Recrystallization from acetic acid gave colorless prisms; the melting point of 227—228°C (dec.), was identical with that of the above-mentioned X-B, undepressed by admixture with an authentic sample. Furthermore, the infrared spectra of the two substances were quite identical.

Acetate of X-B. By the usual procedure, a sample (200 mg) of X-B was acetylated with acetic anhydride (20 m*l*) in pyridine (20 m*l*). The crude acetate (204 mg) was then chromatographed on silica gel (10 g) with isopropyl ether, ethyl acetate - isopropyl ether (3 : 7), and ethyl acetate. The early fractions with ethyl acetate were collected and concentrated to give a solid. Recrystallization from isopropyl alcohol gave colorless prisms (67 mg), mp 178—179°C. NMR spectrum of acetate of X-B in trifluoroacetic acid; τ 0.25 (2H, singlet) for the two imide protons, τ 1.6 (2H, doublet, J=9 cps) and τ 1.8 (2H, doublet, J=9 cps) for the aromatic protons, τ 2.17 (1H, doublet, J=6 cps) for $\rangle$C=C<u>H</u>–, τ 4.15 (1H, multiplet) for –C<u>H</u>(OAc)–, τ 6.6 (4H, multiplet), τ 7.0 (8H, multiplet) for the methylene protons on the two-glutarimide ring, τ 7.7 (3H, singlet) for $-OCOCH_3$, and τ 8.15 (2H, multiplet) for the protons of methylene attached to the glutarimide ring.

2, 4-Dinitrophenylhydrazone of X-A. Yellow prisms, mp 193—195°C. IR bands (KBr): 3300, 3200, 3100 (NH), 1730, 1700 (C=O), 1620 (C=N), 1595 (phenyl), 1525, 1355 cm^{-1} (NO_2). UV absorption (methanol): 262 mμ (ε 20400), 358 mμ (ε 23900).

Found: C, 52.28; H, 4.65; N, 15.25%. Calcd for $C_{28}H_{27}N_7O_{11}$: C, 52.75; H, 4.24; N, 15.38%.

Bioassay. Among the condensation products, 3-(3-glutarimidyl)-4-(3-glutarimidylmethyl)-6-(5-nitro-2-furyl)-2-piperidino-2, 3-dihydro-γ-pyran (V) showed activity against animal tumors (Ehrlich ascites carcinoma and Sarcoma 180 ascites tumor) upon the intraperitoneal injection of 50 mg/kg, while the LD_{50} of V for male dd-mice was found to be 550 mg/kg (i.p.). The derivative, X, which is free from amine inhibited the growth of *T. Vaginalis* at a dilution of 12.5 mcg/m*l* *in vitro*.

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