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The Aldol Condensation of Aromatic Aldehydes with N-Acetyl-2-pyrrolidinone: Synthesis of 3-Arylidene-2-pyrrolidinones

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The synthesis of several 3-arylidene-2-pyrrolidinones (V) by aldol condensation between aromatic aldehydes and N-acetyl-2-pyrrolidinone is reported. The UV-spectra of structures of type V compounds are discussed and compared with those of the corresponding α-arylidene-γ-butyrolactones.

During the course of the investigation on the isomerizations and cyclizations of 3-(2-amino- and 2-hydroxyarylidene)-γ-butyrolactones (I) (3,4), the preparation of the corresponding nitrogen heterocycles, the substituted 2-pyrrolidinones (II) became desirable to further study this reaction. The synthesis of this class of compounds, the 3-arylidene-2-pyrrolidinones (V) has not been previously reported.

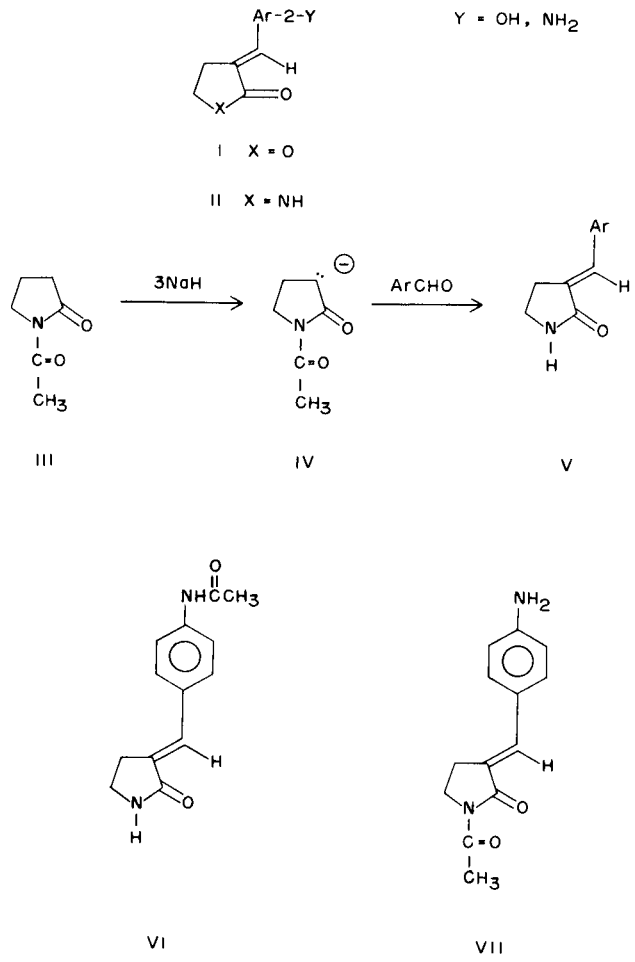
The preparation of these compounds by direct aldol type condensation of 2-pyrrolidinone with aromatic aldehydes seemed less evident for two important reasons. First, the weak acidity of the α-hydrogens has been cited (5,6), particularly, these hydrogens are much less acidic than those of γ-butyrolactone, which readily undergoes base-catalyzed aldol condensation with aromatic aldehydes (7-9). This effect is clearly a result of the decreased electronegativity of nitrogen compared to that of oxygen. Second, reactions of 2-pyrrolidinone with aldehydes by addition of the N-H moiety across the aldehyde carbonyl group have been reported (10,11). Nevertheless, the Claisen condensation (12) of the 2-pyrrolidinone ring was accomplished with N-alkyl-2-pyrrolidinones many years ago (13), and more recently with both N-methyl- and N-acyl-pyrrolidinones (14). The products of these reactions were N-substituted-3-acyl(aroyl)-2-pyrrolidinones. However, the aldol condensation between N-methyl-2-pyrrolidinone and benzaldehyde was unsuccessfully attempted.

In view of these considerations, it was thought that a direct aldol condensation of 2-pyrrolidinone with aromatic aldehydes might be accomplished if the lactam nitrogen function were protected with a sufficiently strong electron-withdrawing group, *e.g.* an acetyl group, which would enhance the acidity of the α-hydrogens and simultaneously protect the N-H moiety from reacting.

It was found that N-acetyl-2-pyrrolidinone (15,16) reacted smoothly with aromatic aldehydes possessing electron-releasing or neutral substituents in a base-catalyzed aldol-type condensation when the strong base sodium hydride was employed (sodium methoxide was used unsuccessfully) to give the 3-arylidene-2-pyrrolidinones listed in Table I. The reaction scheme is shown (III-V) in Scheme I. Some of these yields may not be the maximum attainable, since most condensations were only attempted once. Initially, benzene was employed as reaction solvent, and the reaction commenced when the benzene was warmed to 50-60° and was completed by reflux. When the more polar solvent tetrahydrofuran was used, probably due to the increased stabilization of carbanion IV an exothermic reaction resulted controllable at 0-10°. An excess of the base effected an *in situ* deacetylation. The more stable *trans*-isomers were obtained (17). The formation of the *trans*-isomer in a very similar system has recently been reported (18). That the *trans*-isomer had been obtained for compounds 1 and 4 (and therefore assumed for the others) was proven by irradiation of approximately 1.0×10^{-4}M. Solutions in 95% ethanol with an Hanovia portable ultraviolet lamp, and the observation after several hours that the long-wave length band in the ultraviolet spectrum had gradually undergone a slight hypsochromic, moderate hypochromic shift (17, 19-21) with the appearance of isobestic points (22). This clearly showed that a photochemical *trans* $\longrightarrow$ *cis* isomerization had occurred and reached photoequilibrium.

Structures for compounds in Table I were proven by elemental analysis and infrared spectra, and corroborated by formation of the N-acetyl derivatives for most of the compounds (see Table II). In addition the structure for the parent compound I was further substantiated by determination of its ultraviolet and n.m.r. spectra. The ultraviolet spectrum of 1 was similar to that for the corresponding lactone, which showed the presence of the same chromophore (see Table III). Compound 1 gave an n.m.r. spectrum in deuterochloroform which exhibited a broad band at 1.8 τ (area 1) for the N-H proton, a complex multiplet of aromatic and vinyl protons centered at 2.4 τ (area 6) and two separate methylene proton multiplets centered at 6.5 τ (area 2) and 6.9 τ (area 2), in complete agreement with the assigned proton skeleton. The infrared spectra of all condensation products were in accordance with the assigned functionalities: namely, N-H $\sim$ 3.20 μ, lactam C = O $\sim$ 5.95 μ, and C = C $\sim$ 6.10 μ. Compound 6 was shown to possess structure VI as assigned rather than the isomeric structure VII, which showed that deacetylation had occurred on the ring nitrogen as usual, rather than on the amino

SCHEME I



nitrogen. The infrared spectrum of 6 did not show an amino doublet at 2.9 μ (VII would have given this), but only revealed broad N-H absorption at 3.10 μ, together with two C = O stretching vibrations and the C = C stretching mode at 6.10 μ. Additional and more conclusive proof for structure VI was obtained from the ultraviolet spectrum of compound 6. The ultraviolet spectrum was similar to that for the corresponding lactone (see Table III) but the long wave length absorption band was shifted to shorter wavelength. This was also observed for compound 1 when compared to the corresponding lactone. This is caused by the greater contribution of resonance structure C (Table III) for the lactam which decreases the contribution of resonance structure B. Resonance structure B is a good representation for the long-wave length electronic transition. If compound 6 would have had alternate structure VII, the presence of the free amino group in the *para*-position would have produced a λ max at considerably longer wave length, as can be seen for the case of the lactone (Table III). This is the result of the greater contribution of resonance structure B, since the Hammett $\sigma_p(NH_2)$ = -0.66 (24), σ_p(NHAc) = 0.00 (24) reflects the increased delocalization of the free amino group. Additionally the λ max for compound 8 was found at 348 mμ, $\sigma_p(NMe_2)$ = -0.83 (24). Also, the presence of the N-acetyl group (in structure VII) would have shifted the λ max to longer wave length than the corresponding lactone (see Table III), reflecting a greater contribution of resonance structure B due to decreased contribution of resonance structure C, which would facilitate the electronic transition. In summary, the fact that the λ max for compound 6 was 309 mμ, at lower wave length than the corresponding lactone, led to the assignment of its structure as VI and not VII.

The N-acetyl derivatives were prepared by warming the appropriate 2-pyrrolidinones with acetic anhydride (see Table II). Their structures were proven by elemental analyses and infrared spectra. The infrared spectra showed the disappearance of the N-H stretching frequency and the appearance of a second C = O stretching frequency ~ 5.8 μ for the acetyl group, with the retention of the lactam C = O ~ 5.9 μ and the C = C ~ 6.10 μ, in accordance with the assigned transformation.

Further results which have been obtained on condensation of N-acetyl-2-pyrrolidinone with aromatic aldehydes possessing electron-withdrawing substituents, as well as other aldehydes, and the utilization of these and subsequent compounds for isomerizations and cyclizations as discussed in the introductory paragraph will be the subjects of future publications.

EXPERIMENTAL

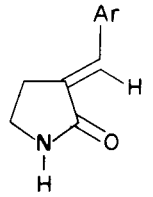
Melting points are uncorrected. Microanalyses by A. Bernhardt, Microanalytisches Laboratorium im Max-Planck Institut, Mülheim/Ruhr, Germany, and Galbraith Laboratories, Knoxville 21, Tennessee. The infrared spectra were taken on KBr discs on a Baird double beam spectrophotometer. The ultraviolet spectra were determined in 95% aqueous ethanol solutions on a Cary Model 11 recording spectrophotometer. The nuclear magnetic resonance spectrum was measured on a Varian A-60 instrument at 60 MC. with TMS used as internal standard.

A. General Condensation Procedure.

A 500 ml. three-necked flask was assembled, equipped with mechanical stirrer, 125 ml. pressure-equalizing dropping funnel with stopper, reflux condenser which has a connecting joint at the top to which was attached a piece of rubber tubing which reached down into a small Erlenmeyer flask filled half-way with tetrahydrofuran (to visually observe the beginning and relative rate of hydrogen evolution), and a thermometer reaching down into the flask. The flask was immersed in an ice-bath and 5.4 g. (0.118 mole) of a 52.5% sodium hydride-mineral oil dispersion (Metal Hydrides, Inc.) was added with 50 ml. of tetrahydrofuran. This heterogeneous mixture was cooled to about 5°. Into the dropping funnel was placed 5.0 g. (0.0394 mole) of N-acetyl-2-pyrrolidinone and 0.0394 mole of the aromatic aldehyde in 50 ml. of tetrahydrofuran. This solution was added dropwise to the flask at a rate which maintained steady hydrogen evolution and a temperature of 5-10° (0.5-1.0 hour). A color (usually yellow) gradually appeared in the reaction mixture. After addition was completed the reaction mixture was stirred for 0.5-1.0 hour at ice-bath temperature. The reaction mixture remained heterogeneous throughout. A small quantity of methanol was then slowly added dropwise from the dropping funnel to destroy the excess sodium hydride, then the reaction mixture was poured into a large beaker half-filled with ice-water (some compounds partially precipitated out), and acidified to congo red test paper with 6 N sulfuric acid. At this point, some compounds had precipitated,

TABLE I

3-Arylidene-2-Pyrrolidinones

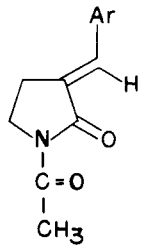


Compound No.	Ar	Formula	Analyses Carbon,% Calcd.	Found	Hydrogen,% Calcd.	Found	Nitrogen,% Calcd.	Found	m.p.,°C	Solvent of recrystallization	Yield % (a)
1	phenyl	$C_{11}H_{11}NO$	76.27	75.70	6.40	6.14	8.09	7.98	174-175	EtOAc	55 (b) 68
2	3,4-methylenedioxyphenyl	$C_{12}H_{11}NO_3$	66.35	66.16	5.10	5.00	6.45	6.52	249-250	*i*-PrOH	66 (b) 100
3	4-methylphenyl	$C_{12}H_{13}NO$	76.97	76.47	7.00	7.37	7.48	7.55	212-213	EtOAc	95
4	2-methoxyphenyl	$C_{12}H_{13}NO_2$	70.91	71.19	6.45	5.99	6.89	6.87	180-181	EtOAc	54
5	4-methoxyphenyl	$C_{12}H_{13}NO_2$	70.91	70.85	6.45	6.48	6.89	6.81	200-201	EtOH-H_2O	30
6	4-acetamidophenyl	$C_{13}H_{14}N_2O_2$	67.81	67.33	6.13	6.01	12.17	12.21	261-263	EtOH	65
7	3,4-dimethoxyphenyl	$C_{13}H_{15}NO_3$	66.93	66.87	6.48	6.70	6.01	6.37	180-181	THF	45 (c)
8	4-dimethylaminophenyl	$C_{13}H_{16}N_2O$	72.19	71.59	7.46	7.37	12.95	12.66	258-260	*p*-dioxane	72 (d)
9	4-isopropylphenyl	$C_{14}H_{17}NO$	78.10	78.44	7.96	8.06	6.51	6.45	183-184	EtOH-H_2O	77
10	2,4,6-trimethylphenyl	$C_{14}H_{17}NO$	78.10	78.00	7.96	7.87	6.51	6.52	185-187	EtOAc	79
11	3-methoxy-4-benzyloxyphenyl	$C_{19}H_{19}NO_3$	73.76	73.59	6.19	6.11	4.53	4.49	172-173	EtOAc	100

(a) Unless otherwise stated the yield is for reaction in tetrahydrofuran. (b) Benzene solvent. (c) Toluene solvent. (d) Solution was not acidified.

TABLE II

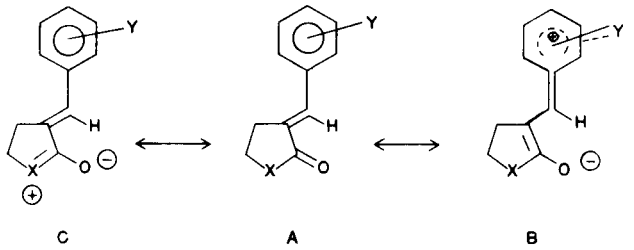
N-Acetyl-3-Arylidene-2-Pyrrolidinones



Compound No.	Ar	Formula	Analyses Carbon, % Calcd.	Found	Hydrogen, % Calcd.	Found	Nitrogen, % Calcd.	Found	m.p.,°C	Solvent of recrystallization
12	phenyl	$C_{13}H_{13}NO_2$	72.54	72.70	6.09	5.98	6.51	6.35	194-195	EtOAc
13	3,4-methylenedioxyphenyl	$C_{14}H_{13}NO_4$	64.86	64.84	5.05	5.25	5.40	5.42	212-213	EtOAc
14	2-methoxyphenyl	$C_{14}H_{15}NO_3$	68.55	68.54	6.16	6.21	5.71	5.71	212-213	EtOAc
15	4-methoxyphenyl	$C_{14}H_{15}NO_3$	68.55	68.58	6.16	6.20	5.71	5.61	180-182	EtOAc
16	3,4-dimethoxyphenyl	$C_{15}H_{17}NO_4$	65.44	65.90	6.22	6.41	5.09	5.18	187-188	EtOAc
17	4-isopropylphenyl	$C_{16}H_{19}NO_2$	74.68	74.10	7.44	7.61	5.44	5.65	177-179	EtOAc
18	2,4,6-trimethylphenyl	$C_{16}H_{19}NO_2$	74.68	75.16	7.44	7.65	5.44	5.34	101-103	MeOH

TABLE III

Ultraviolet Spectral Data



C A B

X=	Y=	Compound (a) (Reference) (b)	λ max(mμ)	ε max
NH	H	1	278	24,000
			224	9,800
			217	12,000
O	H	(7,8)	283	18,000
			225	7,800
			219	8,900
NH	4-NHAc	6	309	52,000
			225	22,000
O	4-NHAc	(9)	317	59,000
			228	22,000
O	4-NH_2	(23)	346	. . .
NH	4-NMe_2	8	348	. . .
O	2-OCH_3	(9)	326	15,000
			280	22,000
			228	15,000
NAc	2-OCH_3	14	333	15,000
			289	18,000
			234	12,000

(a) Numbers refer to Table I. (b) Refers to literature reference.

while others were in solution (and combinations thereof). Depending upon the compound, the aqueous solution was either filtered to collect the product, or extracted with chloroform (or both) and the chloroform solution dried over magnesium sulfate then evaporated to dryness. The precipitate (or residue) was dried and weighed, then recrystallized to constant melting point from an appropriate solvent. The yields reported are those for unrecrystallized compounds.

B. General Acetylation Procedure.

About 1 g. of the appropriate compound was placed in 50 ml. of acetic anhydride, warmed to dissolution and then gently refluxed for about 5 minutes (total time 20-30 minutes). Some compounds precipitated upon cooling the solution and were collected by filtration, while others were obtained when the hot acetic anhydride solution was poured over ice water, stirred to crystallize, and the product filtered off. In either case, the product was washed with water and dried. The yields were always excellent and the compounds were recrystallized to constant melting point from an appropriate solvent (see Table II).

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