TABLE II

REACTION CONDITIONS IN ALKYLATIONS OF PYRROLIDINE ENAMINE OF 1-ACETYL-3-OXOPIPERIDINE (1)

Run	Alkylating reagents mg	Alkylating reagents equiv[b]	Ketone 1 mg	Ketone 1 mmol	Enamine 5, mg	Solvent[a]	ml	Temp, °C	Time, hr	Products	mg[c]	%[b]
a	758	2.0	423	3.0	586	D	1.5	100	14	**6a**	301	44
b	532	1.0	424	3.0	584	D	3.0	100	10	**7b**	235	33
										8b	140	20
c	597	1.0	423	3.0	593	D	3.0	100	10	**7c**	230	27
										8c	148	17
d	721	2.0	421	3.0	590	A	2.0	70	12	**6d**	337	62
e	910	1.0	635	4.5	890	D	3.0	100	6	**6e**	120	13
f	735	1.0	517	3.6	717	D	4.2	100	0.6	**6f**	692	76
g	480	1.0	494	3.5	678	D	1.5	100	0.25	**6g**	278	40
h	1001	2.0	425	3.0	588	D	1.5	100	4	**6h**	280	40
i	445	1.1	710	5.0	960	D	5.0	25	8	**6i**	59	6
j	896	3.0	426	3.0	558	D	2.0	100	13	**6j**	334	48
k	1366	4.0	494	3.5	652	D	2.5	100	18	**6k**	352	52

[a] D, dioxane; A, acetonitrile. [b] Based on ketone 1. [c] Weights of isolated products.

Anal. Calcd for $C_7H_{11}NO_2$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.43; H, 7.98; N, 9.75.

The pyrolyzed product remaining on the bottom of the apparatus crystallized on trituration with ethanol. This (240 mg) was recrystallized from ethanol to give an analytical sample of dimer **4**: mp 262–264°; mass spectrum *m/e* 282 (M^+) and 141; ir (Nujol) ν_{max} 1650, 1072, and 986 cm^{-1}. This was scarcely soluble in chloroform, dimethyl sulfoxide, and pyridine.

Anal. Calcd for $C_{14}H_{22}N_2O_4$: C, 59.55; H, 7.85; N, 9.92. Found: C, 59.53; H, 7.77; N, 10.27.

Dimer **5** (500 mg) was suspended in chloroform (20 ml) saturated with dry hydrogen chloride and stirred at room temperature for 4 hr. After addition of sodium carbonate followed by filtration, the mixture was evaporated to leave an oily residue (518 mg). This was separated by preparative tlc and then distilled to give **1** (354 mg), which showed the same ir spectrum and retention time (vpc) as the sample obtained by pyrolysis.

General Procedure.—A solution of 1-acetyl-3-oxopiperidine (**1**) (420–710 mg, 3.5–5.0 mmol) and pyrrolidine (1–2 ml) in benzene (20–60 ml) was refluxed for 2–3 hr, water being removed by azeotropization with a Dean–Stark apparatus. The solution was then evaporated to dryness under reduced pressure to leave the enamine **5**, which showed the ir and nmr spectra superimposable over those of the analytical sample and could be used for further reactions. A part of the enamine was distilled for analysis: bp 125–128° (5 mm) (sublimation apparatus); ir ν_{max} 1640 cm^{-1}; nmr τ 8.17 (6 H, m, $CH_2CH_2CH_2CH_2$ and H at C_5), 7.95 and 7.94 (total 3 H, each s, $NCOCH_3$), 7.76 (2 H, t, J = 6 and 6 Hz, H at C_4), 7.07 (4 H, m, CH_2NCH_2), 6.59 and 6.46 (total 2 H, each t, J = 6 and 6 Hz, H at C_6), and 4.59 and 3.79 (0.6 and 0.4 H, each s, H at C_2).

Anal. Calcd for $C_{11}H_{18}N_2O$: C, 68.00; H, 9.34; N, 14.42. Found: C, 67.76; H, 9.25; N, 14.12.

A solution of the enamine **5** and alkylating reagents (1.0–4.0 equiv) in dioxane or acetonitrile was heated (usually steam-bath temperature) in a sealed tube until the starting material had disappeared or until the product had started to decompose. The reaction mixture was then treated with water (1–4 ml) at *ca.* 100° for 0.5–4.0 hr in a sealed tube and evaporated under diminished pressure. The residue was mixed with water (3–6 ml) and extracted with organic solvents (usually chloroform, 4 × 30 ml). The extracts were dried and submitted to further separation. The detailed reaction conditions were tabulated in Table II.

Registry No.—**1**, 34456-78-5; **3**, 34456-79-6; **4**, 34456-80-9; **5**, 34456-81-0; **6a**, 34456-82-1; **6d**, 34456-83-2; **6e**, 34456-84-3; **6f**, 34456-85-4; **6g**, 34456-86-5; **6h**, 34456-87-6; **6i**, 34456-88-7; **6j**, 34456-89-8; **6k**, 34456-90-1; **7b**, 34456-91-2; **7c**, 34456-92-3; **8b**, 34456-93-4; **8c**, 34456-94-5.

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Oxidation of Bis(aroylhydrazones) of α-Dicarbonyl Compounds to 1,2,3-Triazolylisoimides. IV. Substituent Effect

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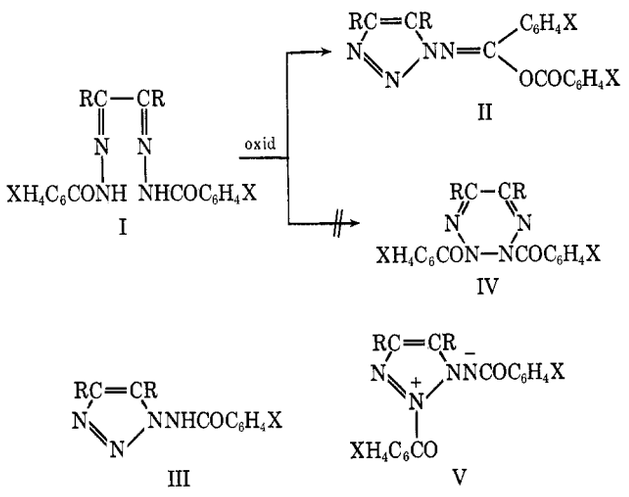
It is known[2,3] that the oxidation of bis(aroylhydrazones) of α-dicarbonyl compounds I gives, instead of the expected 1,2,3,4-tetrazines IV, 1,2,3-triazolylisoimides II.



The structure of the oxidation products was for a long time in doubt, since the zwitterionic formula V had been also proposed[4,5] as an alternative. However,

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(3) N. E. Alexandrou and E. D. Micromastoras, *Tetrahedron Lett.*, 231 (1968).

(4) Personal communication from Professor A. R. Katritzky (1963).

(5) S. Petersen and H. Heitzer, *Angew. Chem., Int. Ed. Engl.*, **9**, 69 (1970).

TABLE I
OXIDATION PRODUCTS OF BIS(AROYLHYDRAZONES)

Bis(aroylhydrazones) I		Isoimides[a] II		
Compd	Mp, °C	Yield, % ($HgO + I_2$)	Mp, °C	Ir, cm^{-1}
Ia, R = C_6H_5; X = *p*-Br	265–267	30	178–179	1755, 1635, 1230
Ib, R = C_6H_5; X = *p*-OCH_3	206–208	15	162–163	1745, 1665, 1250
Ic, R = C_6H_5; X = *p*-NO_2	285–287	25	175–176	1765, 1630, 1235
Id, R = CH_3; R′ = *p*-ClC_6H_4; X = *p*-Cl	282–285	60	187–188	1750, 1635, 1240
Ie, R = C_6H_5; R′ = H; X = *p*-Cl	223–226	30	162–163	1750, 1630, 1250
If, R = CH_3; R′ = *p*-$CH_3C_6H_4$; X = H	227–229	35	168–169	1750, 1630, 1230
Ig, R = CH_3; X = *m*-NO_2	>320	15	161–163	1765, 1650, 1230
Ih, R = C_6H_5; X = *m*-NO_2	226–229	20	166–168	1755, 1670, 1240
Ii, R = C_6H_5; X = *m*-CH_3	176–179	50	143–144	1755, 1655, 1260
Ij, R = CH_3; X = *m*-CH_3	277–279	40	120–122	1750, 1650, 1265
Ik, R = C_6H_5; X = *m*-Cl	216–219	40	157–159	1760, 1655, 1235
Il, R = C_6H_5; X = *m*-Br	245–248	50	156–158	1765, 1660, 1235
Im, R = C_6H_5; X = *o*-CH_3	177–179	5	134–135	1750, 1640, 1220
In, R = C_6H_5; X = *o*-Cl	220–222	7	118–119	1752, 1660, 1240
Io, R = C_6H_5; X = *o*-NO_2	286–288			
Ip, R = CH_3; X = *o*-CH_3	284–287	5	76–78	1750, 1640, 1220
Iq, R = CH_3; X = *o*-Cl	306–307	15	108–109	1755, 1660, 1235
Ir, R = C_6H_5; X = *o*-Br	197–199	17	130–131	1753, 1635, 1230

[a] Satisfactory analyses (±0.4% for C, H, N) were reported for all isoimides except IIo and for triazoles IIIm, IIIn, and IIIσ.[b] [b] Other data on triazoles. IIIm: 15% yield; mp 223–224°; ν 3140, 1675 cm^{-1}. IIIn: 5% yield; mp 231–232°; ν 3150, 1685 cm^{-1}. IIIo: <1%; mp 216–218°; ν 3150, 1705 cm^{-1}; mol wt, calcd 385, found *m/e* 385.

recently Katritzky, *et al.*,[6] have shown by an X-ray analysis that the compounds in question are actually isoimides (II).

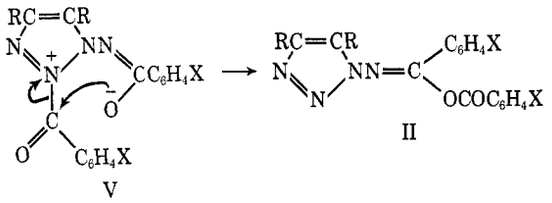
It has been shown[7] previously that the oxidation of bis(aroylhydrazones) to isoimides is sterically influenced and the ortho,ortho′-disubstituted derivatives, especially the bis(mesitoylhydrazones), give instead of II 1-mesitoylamino-1,2,3-triazoles III. In this paper a systematic study of the substituent effect in the oxidation of monosubstituted bis(aroylhydrazones) is made. The aroylhydrazones used as well as their oxidation products are given in Table I.

Oxidation of various meta- or para-monosubstituted bis(aroylhydrazones) Ia–Il with mercuric oxide and iodine[8] gave the expected isoimides II, irrespective of the electronic effect of the substituents X and of the nature of α-diketone used, in yields of 15–60%. In no case were triazole derivatives III formed in isolable amounts.

On the other hand, oxidation of ortho-monosubstituted bis(aroylhydrazones) also gave isoimides, but in yields which, in general, were lower (0–17%) than those from meta or para derivatives, and in some cases 1-aroylaminotriazoles III. The last compounds were obtained from *o*-methyl- and *o*-chlorobis(benzoylhydrazone) of benzil (Im, In), but they were not obtained by oxidation of analogous biacetyl derivatives Ip, Iq, proving thus that the substituents in diketone also influence the oxidation process. The ortho-nitro derivative Io only gave the corresponding benzoylaminotriazole, but in very low yield. Peculiar is the behavior of ortho-bromo derivative Ir, which by oxidation gave isoimide in 17% yield.

In every case of ortho-substituted hydrazones the unoxidized starting material was recovered unchanged.

Although the oxidation of ortho-monosubstituted hydrazones I is actually more complicated than is the oxidation of ortho,ortho′-disubstituted derivatives, it is evident that a steric effect is operating during oxidation, in agreement with the proposed mechanism of isoimide formation (V → II). It is of interest to note that this effect would not be operating if the oxidation products actually had the zwitterionic structure V.



All the isoimides prepared gave in the infrared the characteristic strong ν_{CO} absorption in the region of 1745–1765 cm^{-1}, the absorption position mainly depending[9] on the electronic effect of substituent X. The absorption band is shifted to higher frequencies when the substituent X is an electron-attracting group.

Other characteristic absorptions are found in the regions 1630–1670 ($\nu_{C=N}$, weak) and 1220–1265 cm^{-1} (probably[10] $\nu_{OC=}$, strong). The aroylaminotriazoles showed absorptions at 3140–3150 (ν_{NH}) and 1675–1705 cm^{-1} (ν_{CO}). The nmr spectra of isoimides obtained by oxidation of biacetylbis(aroylhydrazones) always showed two peaks for the C_4 and C_5 methyl protons of the triazole ring at ~τ 7.5 and 7.7.

Although the bis(aroylhydrazones) of unsymmetric α-dicarbonyl compounds (Id, Ie, If) could give by oxidation two isomeric isoimides, in every case only one isomer was isolated and the structure of these products is under further consideration.

The yield of isoimide was increased substantially by using as oxidizing agent, instead of mercuric oxide and iodine, lead tetraacetate in chloroform or in methylene chloride. This oxidizing agent has been

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extensively used for the oxidation of substituted hydrazones and aroylhydrazones.[11-13] The oxidation of bis(aroylhydrazones) Ib, Ie, Ik, Iq, and Ir with lead tetraacetate was carried out by a gentle heating for 2–3 hr. The yields of corresponding isoimides were almost twice those obtained by Stollé's method.[8]

Experimental Section

Melting points are uncorrected and were determined with a Kofler hot-stage apparatus. Ir spectra were measured as Nujol mulls with a Beckman IR-4 or Perkin-Elmer 257 spectrophotometer. Nmr spectra were obtained in $CDCl_3$ with a Varian A-60A spectrometer.

Preparation of Bis(aroylhydrazones) of α Dicarbonyl Compounds.—Those of biacetyl were prepared[14] by heating in ethanol or *n*-propyl alcohol 1 mol of biacetyl with 2.2 mol of the corresponding aroylhydrazines for 6 hr.

The bis(aroylhydrazones) of other α diketones were prepared[15,16] by heating in a sealed tube 1 mol of diketone with 2.2 mol of aroylhydrazines for 12 hr at ~150°. The yields in both methods were 70–90%. The analytical data of the prepared compounds were in agreement with their structure and/or their melting points were in agreement with those of the literature.

Oxidation of Bis(aroylhydrazones) of α-Dicarbonyl Compounds. A. With Mercuric Oxide and Iodine.[8]—A mixture of 0.01 mol of bis(benzoylhydrazone), 0.025 mol of mercuric oxide, 0.025 mol of iodine, and 0.5 g of magnesium oxide in 80 ml of dry ether was heated under stirring for 15 hr. After filtration of the mixture the ethereal solution was washed with potassium iodide solution, then with sodium thiosulfate and water, and finally dried with anhydrous sodium sulfate. The oxidation products were obtained after evaporation and crystallization. The aroylaminotriazoles were separated by fractional crystallization or by chromatographic analysis on aluminum oxide. (For the analytical data of the prepared compound see Table I.) The nonoxidized starting material was recovered by treating the precipitate containing the inorganic material with dilute hydrochloric acid and recrystallization.

B. Oxidation with Lead Tetraacetate.—To a mixture of 0.002 mol of bis(aroylhydrazone) in 20 ml of methylene chloride, a solution of 0.004 mol of lead tetraacetate in 20 ml of methylene chloride was added and the mixture was gently heated for 2–3 hr, or it was left at room temperature for 10 hr. The methylene chloride solution was treated with water, and filtered and the organic layer was washed with sodium bisulfite solution, sodium carbonate solution, and water and then dried. The isoimides were obtained after evaporation and recrystallization. They were identical with those obtained by method A.

Registry No.—Ia, 34502-22-2; Ib, 34502-23-3; Ic, 34502-24-4; Id, 34502-25-5; Ie, 34502-26-6; If, 34502-27-7; Ig, 34502-28-8; Ih, 34502-29-9; Ii, 34502-30-2; Ij, 34502-31-3; Ik, 34502-32-4; Il, 34502-33-5; Im, 34502-34-6; In, 34502-35-7; Io, 34502-36-8; Ip, 34502-37-9; Iq, 34502-38-0; Ir, 34502-39-1; IIa, 34566-67-1; IIb, 19226-34-7; IIc, 34502-40-4; IId, 34502-41-5; IIe, 34502-42-6; IIf, 34502-43-7; IIg, 34502-44-8; IIh, 34502-45-9; IIi, 34502-46-0; IIj, 34519-95-4; IIk, 34502-47-1; III, 34519-96-5; IIm, 34502-48-2; IIn, 34502-49-3; IIp, 34599-20-7; IIq, 34502-50-6; IIr, 34519-97-6; IIIm, 34502-51-7; IIIn, 34502-52-8; IIIo, 34502-53-9.

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An Asymmetric Synthesis of Alcohols, Amines, and Amino Acids

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Asymmetric reduction of the ketone moiety has been the subject of much recent investigation.[2] We have reported previously the reduction and reductive amination of aldehydes and ketones using sodium cyanoborohydride ($NaBH_3CN$) as a reducing agent.[3] This new method proved to be especially suitable for the synthesis of isotopically labeled amino acids from the corresponding substituted pyruvic acids. In the hope that we might extend this method to allow preparation of optically active amino acids, we have investigated the use of the structurally similar (*e.g.*, H_3B–X, where X is an electron-withdrawing group) amine–boranes as reducing agents. We were encouraged by a previous report of aldehyde and ketone reduction by the amine–borane system;[4] during the course of our work a detailed study of this reduction appeared.[5] In this report we confirm that both reduction and reductive amination of ketones can be carried out with asymmetric induction to give optically active products, although the optical purities obtained in this synthesis are quite low.

We chose for this study (*R*)(+)- and (*S*)(−)-α-phenethylamine–boranes **2**, which were prepared in 80% yield from the corresponding amine hydrochlorides **1**.[6] The method was initially tested by examining the reduction of acetophenone[7] and 2-heptanone with 1 molar equiv (3 hydride equiv) of amine–borane; the results are summarized in Table I. To ascertain that the rotations were not arising from a trace of α-phenethylamine remaining in the alcohols after work-up, a control experiment was carried out in which alcohol of known optical purity was mixed with (*S*)(−)-α-phenethylamine and subjected to the reaction work-up. The isolated alcohol was free of amine by glpc analysis, and the rotation of the isolated alcohol was identical with that of the starting alcohol. It is apparent that asymmetric reduction did occur, although the optical purities were disappointingly low, presumably owing to the large distance between the asymmetric carbon of the reducing agent and the developing tetrahedral carbon of the product in the transition state. A

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