

**237.** *Reaction of Diazoalkanes with Aromatic Aldehydes.*

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Seven substituted benzaldehydes, *o*-phthalaldehyde, the isomeric pyridine-carboxaldehydes and quinoline-2-carboxaldehyde were treated with ethereal diazoethane to give the corresponding ethyl ketones. Three aromatic aldehydes were converted into the *n*-propyl ketones with 1-diazopropane. The average yield was 75%.

DIAZOMETHANE usually<sup>1</sup> reacts with aldehydes to give a mixture of a methyl ketone and a 1,2-epoxide. Diazoethane and 1-diazopropane, by contrast, give only ketones by reaction

<sup>1</sup> Gutsche, *Org. Reactions*, 1954, **8**, 404.

with some aliphatic<sup>2</sup> and aromatic<sup>3</sup> aldehydes. This paper records a more detailed study to determine the limitations for the preparation of alkyl aryl ketones. The results are summarized in the Table. The high yields of ketones obtained in most cases indicate that the reaction may be of importance for the small-scale preparation of ketones where the aldehyde precursor is readily available.

Reactions of aldehydes with electron-withdrawing substituents in the aromatic ring proceeded with brisk evolution of nitrogen and were apparently complete in a very short time. The reactions of *o*-nitrobenzaldehyde and picolinaldehyde were extremely vigorous and difficulty was experienced in controlling them. On the other hand, aldehydes with electron-donating substituents reacted very slowly with the ethereal solutions of the diazoalkanes, and it was necessary to catalyze the reactions of *p*-dimethylaminobenzaldehyde, *p*-tolualdehyde, and *p*-methoxybenzaldehyde with methanol.<sup>4</sup> These qualitative observations seem to be in accord with the suggested<sup>1,4</sup> mechanism for the reaction involving nucleophilic attack of the diazoalkane at the carbonyl carbon.

The poorest yield obtained was 51% of 4-dimethylaminopropiophenone by the reaction of *p*-dimethylaminobenzaldehyde and diazoethane. In this reaction an attempt was made to detect the expected oxide by-product. The crystalline ketone was readily separated from impurities with light petroleum, and a yellow oil was obtained on distillation of the solvent. This oil was not pure oxide, as indicated by two strong bands in the carbonyl region of the infrared spectrum.

Only very poor yields of propiophenone were obtained when the conditions used successfully<sup>6</sup> for the preparation of cycloheptanone from cyclohexanone and diazomethane were applied to the reaction of benzaldehyde and ethylnitrosourea. In two cases, nitrogen was violently evolved after a considerable induction period.

The known ketones were characterized by conversion into derivatives or by elemental analysis; *o*-dipropionylbenzene was characterized by conversion into 1,4-diethylphthalazine.

## EXPERIMENTAL

Boiling points and melting points are uncorrected.

The diazoalkanes were prepared by the general method of Wilds and Meader.<sup>5</sup> The ethereal solutions were assayed by the benzoic acid method and the calculated amount (usually between 0.05 and 0.1 mole) of aldehyde was added. The reaction was allowed to proceed overnight or longer and the products were isolated by distillation through a short column or by recrystallization.

*Reaction of p-Dimethylaminobenzaldehyde with Diazoethane.*—A solution of the aldehyde (13.5 g., 0.090 mole) in ether (50 ml.) and methanol (50 ml.) was added during 5 min. to an equivalent amount of ethereal diazoethane. The reaction proceeded very slowly in the absence of the methanol but quite briskly after its addition. After 24 hr., evaporation of the solvents provided oily crystals. Trituration with a small volume of light petroleum afforded crude ketone (8.25 g., 51%), m. p. 92–95°. Evaporation of the light petroleum provided a dark oil from which a light yellow oil (1.5 g.), b. p. 175–178°/11 mm., was obtained. A centre cut possessed two carbonyl bands in the infrared spectrum at 1680 and 1715 cm.<sup>-1</sup>. The oil was obviously a mixture and was not further investigated.

*Preparation of 1,4-Diethylphthalazine.*—A solution containing *o*-dipropionylbenzene (6.64 g.), 85% hydrazine hydrate (2.00 g.), and ethanol (550 ml.) was refluxed for 1 hr. Evaporation of the ethanol afforded a red gum which was dissolved in hot water (800 ml.). The cooled aqueous solution was extracted several times with ether. Evaporation of the ether afforded

<sup>2</sup> R. F. Smith, *J. Org. Chem.*, 1960, **25**, 453.

<sup>3</sup> Adamson and Kenner, *J.*, 1939, 181; Mosettig and Czadek, *Monatsh.*, 1931, **57**, 291.

<sup>4</sup> For a recent discussion of the mechanism and catalysis in the diazoalkane-carbonyl reaction see House, Grubbs, and Cannon, *J. Amer. Chem. Soc.*, 1960, **82**, 4099.

<sup>5</sup> Wilds and Meader, *J. Org. Chem.*, 1948, **13**, 763.

<sup>6</sup> Kohler, Tishler, and Potter, *J. Amer. Chem. Soc.*, 1939, **61**, 1057.

an oily solid (5.14 g., 82%) which yielded yellow crystals, m. p. 82—85° (from ether) (Found: C, 77.6; H, 7.9; N, 15.1.  $C_{12}H_{14}N_2$  requires C, 77.4; H, 7.6; N, 15.0%).

## Reactions with Diazoethane

Aldehyde	Ketone	Yield (%)	B. p./mm., or m. p.		M. p.s of derivatives <sup>a</sup>	
			Found	Reptd.	Found	Reptd.
<i>m</i> -Nitrobenz-	3-Nitropropiofenone	81	97—99°	(101 <sup>b</sup> )	(S) 186—188	(188—189 <sup>c</sup> )
<i>p</i> -Nitrobenz-	4-Nitropropiofenone	78	87—89	(88—89 <sup>d</sup> )	(S) 199—201	(198—200 <sup>d</sup> )
<i>o</i> -Nitrobenz-	2-Nitropropiofenone	61	169—174/20	(175/25 <sup>b</sup> )	(S) 182—183	(183—184 <sup>b</sup> )
Picolin-	Ethyl 2-pyridyl ketone	89	94—98/17	(205/atm. <sup>e</sup> )	(S) 163—164	(165 <sup>f</sup> )
Nicotin-	Ethyl 3-pyridyl ketone	75	115—117/18	(230—232/atm. <sup>e</sup> )	(O) 117—118	(115 <sup>g</sup> )
Isonicotin-	Ethyl 4-pyridyl ketone	79	120—123/22 <sup>h</sup>		(P) 100—103	
2-Quinolinecarbox-	Ethyl 2-quinolyl ketone	52	59—60	(59—60 <sup>j</sup> )		
<i>o</i> -Chlorobenz-	2-Chloropropiofenone	90	122—125/20	(106/12 <sup>c</sup> )	(S) 175—176	(173 <sup>c</sup> )
<i>m</i> -Chlorobenz-	3-Chloropropiofenone	67	43—45	(45—46 <sup>c</sup> )	(S) 181—183	(179—180 <sup>c</sup> )
<i>p</i> -Tolu-	4-Methylpropiofenone <sup>k</sup>	71	121—124/20	(117—119/18 <sup>l</sup> )	(O) 89—90	(87—90 <sup>l</sup> )
<i>p</i> -Dimethylamino-	4-Dimethylaminopropio-	51	101—103 <sup>m</sup>	(103 <sup>n</sup> )		
benz-	phenone					
<i>o</i> -Phthal-	<i>o</i> -Dipropionylbenzene	89	161—167/16°		83—85 <sup>p</sup>	

## Reactions with Diazopropane

<i>p</i> -Methoxybenz-	4-Methoxybutyrophenone	60 <sup>r</sup>	165—167/18	(162—163/20 <sup>r</sup> )	(S) 171—172
Nicotin-	<i>n</i> -Propyl 3-pyridyl ketone	81	133—136/23	(230—232/atm. <sup>s</sup> )	(S) 168—170 (169—170 <sup>t</sup> )
<i>m</i> -Nitrobenz-	3-Nitrobutyrophenone	100	60—61	(61 <sup>u</sup> )	(Ph) 102—103 (103 <sup>v</sup> )

<sup>a</sup> S = semicarbazone, O = oxime, P = picrate, Ph = phenylhydrazone. <sup>b</sup> Leonard and Boyd, *J. Org. Chem.*, 1946, **11**, 416. <sup>c</sup> Zenitz and Hartung, *ibid.*, p. 444. <sup>d</sup> Chaudhuri and Ghosh, *J. Indian Chem. Soc.*, 1951, **28**, 563. <sup>e</sup> Engler and Bauer, *Ber.*, 1891, **24**, 2530. <sup>f</sup> Bertucat, *Compt. rend.*, 1951, **232**, 1758. <sup>g</sup> Engler, *Ber.*, 1891, **24**, 2539. <sup>h</sup> Found: C, 70.9; H, 7.0; N, 10.3.  $C_8H_9NO$  requires C, 71.1; H, 6.7; N, 10.4%. <sup>i</sup> Recrystallized from ethanol. Found, N<sub>sp</sub>, 4.0.  $C_{14}H_{13}N_4O_3$  requires N<sub>sp</sub>, 3.9%. N<sub>sp</sub> denotes determination of basic nitrogen by titration with perchloric acid in acetic acid. <sup>j</sup> Kaufmann, Dandliker, and Burkhard, *Ber.*, 1913, **46**, 2929. <sup>k</sup> Reaction catalyzed by the addition of 10 ml. of methanol. <sup>l</sup> Rogers, *J.*, 1956, 2784. <sup>m</sup> Recrystallized from methanol. Found: N, 8.1.  $C_{11}H_{12}NO$  requires N, 8.0%. <sup>n</sup> Nineham, *J.*, 1952, 635. <sup>o</sup> Found: C, 76.0; H, 7.4.  $C_{12}H_{14}O_2$  requires C, 75.8; H, 7.4%. <sup>p</sup> 1,4-Diethylphthalazine. See Experimental. <sup>q</sup> Catalyzed by addition of 20 ml. of methanol. <sup>r</sup> Skraup and Nieten, *Ber.*, 1924, **57**, 1300. <sup>s</sup> Recrystallized from ethanol. Found: C, 61.6; H, 7.3.  $C_{12}H_{11}N_3O_2$  requires C, 61.3; H, 7.3%. LaForge, *J. Amer. Chem. Soc.*, 1928, **50**, 2477. <sup>t</sup> Morgan and Hickinbottom, *J.*, 1921, **119**, 1883.

*Preparation of Propiofenone.*—Ethyl nitrosourethane (29.2 g., 0.2 mole) was added during 45 min. to a stirred solution of benzaldehyde (21.2 g., 0.2 mole) in anhydrous methanol (100 ml.) containing suspended anhydrous sodium carbonate (0.5 g.). The mixture was cooled to keep the temperature below 30°. In this run, nitrogen evolution started immediately. In two other runs the reaction was very slow to start and in one instance started violently after half of the urethane had been added. After the evolution of nitrogen had stopped, the solution was filtered and the solvents evaporated. The residue was stirred with saturated sodium hydrogen sulphite solution (100 ml.) and extracted several times with ether. The ether layer was dried and after two fractional distillations through a short Vigreux column propiofenone (6.2 g., 22%), b. p. 214—216°, was obtained. It was characterized as the 2,4-dinitrophenylhydrazone, m. p. 190—191°.

The bisulphite solution was made strongly basic with sodium carbonate and extracted with ether. After the dried solvent had evaporated benzaldehyde (3.0 g.) was isolated by distillation and identified as the 2,4-dinitrophenylhydrazone.

This work was supported by a generous Grant-in-Aid and Summer Fellowship (to R. F. S.) from the Research Foundation of the State University of New York. Thanks are also due to the Sterling-Winthrop Research Institute for library facilities, and for the microanalyses by Mr. Kenneth Fleisher and his staff.