TABLE I

PRODUCTS FROM CONDENSATIONS OF 2,6-CYCLOHEPTADIENONE OR 2,7-CYCLOOCTADIENONE WITH PRIMARY AMINES AND DIMETHYLAMINE HYDROCHLORIDE

Compd	Yield, % (wt, g)[a]	Mp or bp (mm), °C
3a	64 (0.89)	42.5–44 (dist),[b] 97 (12)
3b	59 (3.2)	23–24 (dist), 123–124 (0.18)[c]
3c	56 (1.7)	48 (0.1)[d]
4a	53 (0.65)	62–64 (subl)[e]
4b	62 (1.70)	72–73 (MeOH–H_2O)[f]
5	64 (1.2)	213 dec (MeOH–Et_2O)[g]
6	78 (0.79)	268 dec (MeOH–Et_2O)[h]

[a] Results tabulated here were from the first effort. Purified products were also characterized by means of their ir and nmr spectra. [b] Mmp 42.5–44°. [c] n^{24}_D 1.5540 [lit.[11a] bp 134–137° (0.4 mm), n^{25}_D 1.5526]. Dipiperonylidene derivative, mp 194–195° (C_2H_5OAc) (lit.[11b] mp 194–195°). [d] n^{24}_D 1.4892 [lit.[11c] bp 41–42° (0.08 mm), n^{20}_D 1.4885]. Picrate, mp 190–191° (H_2O) (lit.[11c] mp 189°). [e] Lit.[10b] mp 62–64°. [f] Lit.[11d] mp 70–73° (employing petroleum ether). [g] *Anal.* Calcd for $C_9H_{16}NOCl$: C, 56.98; H, 8.45; N, 7.38. Found: C, 57.00; H, 8.45; N, 7.35. [h] *Anal.* Calcd for $C_{10}H_{18}NOCl$: C, 58.96; H, 8.90; N, 6.87. Found: C, 58.88; H, 8.94; N, 6.61.

primary amine with the appropriate cycloalkadienone appears to be the most attractive alternative[9] to the versatile and well-tested Robinson–Schöpf synthesis.[1,10,11]

Registry No.—**1**, 1192-93-4; **2**, 1073-76-3; **3a**, 532-24-1; **3b**, 28957-72-4; **3c**, 3423-30-1; **4a**, 28861-13-4; **4b**, 28861-14-5; **5**, 28861-15-6; **6**, 28957-73-5.

Acknowledgment.—We wish to thank Professor E. C. Friedrich for a generous sample of **2**.

(9) For other alternatives, see P. Karrer and H. Alagil, *Helv. Chim. Acta*, **30**, 1776 (1947); B. F. Putney and T. O. Soine, *J. Amer. Pharm. Ass.*, **44**, 17 (1955); W. Parker, R. A. Raphael, and D. I. Wilkinson, *J. Chem. Soc.*, 2433 (1959); N. J. Turro and S. S. Edelson, *J. Amer. Chem. Soc.*, **90**, 4499 (1968).

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Geometrical Isomers of Ortho-Substituted Acetophenone N,N-Dimethylhydrazones

GEORGE R. NEWKOME*[1] AND N. S. BHACCA

Department of Chemistry, Louisiana State University, Baton Rouge, Louisiana 70803

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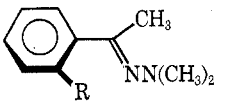
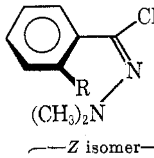
Our previous paper[2] described the preparation of aldehyde and ketone N,N-dimethylhydrazones and their facile conversion to the corresponding azine-free unsubstituted hydrazones. We now wish to report the presence of E and Z ortho-substituted acetophenone N,N-dimethylhydrazones[3] and the isolation of their methiodides. During the course of this work, 16 meta- and para-substituted acetophenone N,N-dimethylhydrazones were prepared[2] and in each case existed as a single stereoisomer, which was presumed to have the E configuration through the analysis of the nmr spectral data. The CCH_3 chemical shifts varied randomly from 2.24 to 2.35 ppm downfield from TMS, whereas the NCH_3 chemical shifts changed from 2.49 to 2.62 ppm correlating rather well to the Hammett $\sigma_{m,p}$ parameters,[4] albeit the chemical shift differences are quite small. Similar preponderance of a single isomer has been reported for ketone N-methyl imines[5] and aldehyde N,N-dimethylhydrazones.[6]

The nmr spectra of the ortho-substituted acetophenone N,N-dimethylhydrazones (**1a–d**)[2] no longer appeared as two characteristic methyl singlets but rather indicated a mixture of two geometric isomers or conceivably restricted rotational isomers. The observed resonances have been attributed to mixtures of E and Z isomers, since the latter was eliminated by absence of any simplification of the nmr spectra at elevated temperatures.[7] The glc analysis[8] of **1a** showed a 60:40 ratio of the isomeric dimethylhydrazones; attempted preparative glc collection of each isomer in our hands resulted in the isolation of fractions which isomerized to mixtures identical with the starting material as attested to by both nmr and glc analysis. Similar results were obtained with **1** irrespective of the ortho substituent (Table I). The rapid syn–anti isomerization of **1a–d** can occur *via* either the in-the-plane inversion mechanism or out-of-plane rotation mechanism; the inversion mechanism seems to have been conclusively verified in

TABLE I

PMR CHEMICAL SHIFTS[a] FOR METHYL PROTONS





Compd	R	E isomer C–CH_3	E isomer N–CH_3	Isomer ratio, E:Z	Z isomer C–CH_3	Z isomer N–CH_3
1a	OCH_3	2.25	2.51	60:40	2.10	2.28
1b	CH_3	2.31	2.50	53:47	2.08	2.28
1c	Br	2.24	2.52	57:43[b]	2.15	2.31
1d	Cl	2.28	2.51	68:32[b]	2.15	2.25
1e	H	2.26	2.52	100:0		

[a] Chemical shifts are parts per million downfield from internal TMS; CCl_4 solvent, concentration 7%. [b] Estimated by nmr data.

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[1] To whom correspondence should be addressed.

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[5] J. B. Lambert, W. L. Oliver, and J. D. Roberts, *J. Amer. Chem. Soc.*, **87**, 5085 (1965).

[6] (a) G. J. Karabatsos, R. A. Taller, and F. M. Vane, *Tetrahedron Lett.*, 1081 (1964); (b) G. J. Karabatsos and R. S. Taller, *Tetrahedron*, **24**, 3923 (1968).

[7] Samples were subjected to temperatures of as high as 180°; the nmr spectra were essentially unaltered over the range −80 to 180°. The distribution ratio at both 30 and 180° corresponded well to the glc ratio of isomers.

[8] A 0.5 in × 9 ft stainless steel column packed with 20% SE-30 on 60–80 Chromosorb W at 150° was employed in conjunction with a Varian Aerograph Model 90-P. All samples were trapped at −80° and immediately subjected to nmr analysis.

these cases of substituted imines.[9,10] Even though rapid isomerization is operative, the assignment of product distribution by pmr chemical shifts is attainable since the minor isomer must subject the N–CH_3 protons to the strongly shielding effect of the aromatic ring,[11] whereas the chemical shift of the N–CH_3 for the major *E* isomer will closely resemble the unsubstituted case **1e**.

Previously, it has been established *via* ^{13}C carbonyl chemical shifts of substituted acetophenones that ortho substituents induce twisting of the acetyl group from the plane of the aromatic ring by steric inhibition of resonance.[12] Since this deviation from coplanarity exists in the parent ortho-substituted ketones, the corresponding *N*,*N*-dimethylhydrazones (**1a–d**) should also deviate from planarity by a comparable degree, thus minimizing the proximate steric crowding caused by the ortho substituent. Removal of partial resonance stabilization associated with the aryl group allows the ketone derivatives to exist in both *E* and *Z* configurations, as in *N*,*N*-dimethylhydrazones of simple dialkyl ketones.[6b] Such steric interactions are not indicated for the 16 meta- and para-substituted acetophenone *N*,*N*-dimethylhydrazones which exist in the more stable *E* configuration, and in these cases neither heat nor treatment with acid gave evidence for the presence of the *Z* configuration.

The quaternization of **1a** with methyl iodide by standard procedures gave rise to an oil, which upon crystallization from ethanol–ethyl acetate yielded the (*E*)-2′-methoxyacetophenone *N*,*N*,*N*-trimethylhydrazonium iodide. The mother liquor was subsequently concentrated and the residue was recrystallized several times from enthanol at −70° giving the corresponding (*Z*)-methiodide. The nmr spectra are again useful in verifying both the structure and purity; the *Z* and *E* $-N^+(CH_3)_3$ moieties are evidenced by singlets at 3.29 and 3.61 ppm, which can easily be assigned to the *Z* and *E* isomers, respectively. The abnormally high field resonance is assigned to the nearly orthogonal group *Z* to the aromatic ring, while the more downfield absorption is assigned to the (*E*)-trimethylamine moiety. Neither of these methiodides isomerize upon heating at moderate temperatures but do hydrolyze slowly in aqueous media; thus the covalent bonding of the dimethylamino unshared electrons prevented their assistance in the geometrical isomerization.

The rapid geometric isomerization of these hydrazones adequately explains the fact that the *o*-haloacetophenone *N*,*N*-dimethylhydrazones give quantitatively 1,3-dimethyl-1*H*-indazole[2,13] after standing for several days at room temperature or heating in a sealed tube at 120° for several hours. The irreversible internal nucleophilic displacement possible only through the *Z* orientation would easily deplete the *E* isomer in this equilibrium mixture by converting it to the cyclized product, followed then by the elimination of methyl halide.[14]

Experimental Section[15]

The ortho-substituted acetophenone *N*,*N*-dimethylhydrazones were prepared according to the procedure described previously.[2] All spectral properties and microanalyses of the compounds were consistent with the assigned structures.[2]

(*Z*)- and (*E*)-2′-Methoxyacetophenone *N*,*N*,*N*-Trimethylhydrazonium Iodide.—A solution of 2′-methoxyacetophenone *N*,*N*-dimethylhydrazone [10 g, 52 mmol, bp 65–66° (0.1 mm)] and methyl iodide (20 g) in absolute ethanol (100 ml) was stirred under nitrogen for 2 days. The solvent was removed *in vacuo* affording a pale yellow semisolid which when washed with anhydrous ether gave the crude crystalline methiodide (14.2 g, 42.5 mmol) in 82% yield, mp 120–146°.

The crude methiodide was recrystallized twice from ethanol–ethyl acetate (2:1) yielding predominately the *E* isomer (4.2 g) as white needles: mp 158–159° dec; ir (KBr) 1628, 723 cm^{-1} (C═N); nmr (D_2O) δ 2.72 (s, CCH_3, 3 H), 3.61 (s, $N^+(CH_3)_3$, 9 H), 3.89 (s, C_{arom} OCH_3, 3 H), *ca.* 7.2 ppm (C_{arom} H, complex, 4 H).

Anal. Calcd for $C_{12}H_{19}N_2OI$: C, 43.12; H, 5.73; N, 8.38. Found: C, 43.06; H, 5.71; N, 8.18.

The mother liquor was concentrated *in vacuo* and recrystallized four times from absolute ethanol at −70° giving analytically pure the *Z* isomer: mp 140–141° dec; ir (KBr) 1640, 750 cm^{-1} (C═N); nmr (D_2O) δ 2.32 (s, CCH_3, 3 H), 3.29 (s, $N^+(CH_3)_3$, 9 H), 3.89 (s, C_{arom} OCH_3, 3 H), *ca.* 7.3 (C_{arom} H, 4 H).

Anal. Calcd for $C_{12}H_{19}N_2OI$: C, 43.12; H, 5.73; N, 8.38. Found: C, 43.10; H, 5.68; N, 8.43.

Registry No.—(*E*)-**1a**, 28541-35-7; (*Z*)-**1a**, 28541-36-8; (*E*)-**1b**, 28541-37-9; (*Z*)-**1b**, 28541-38-0; (*E*)-**1c**, 28541-39-1; (*Z*)-**1c**, 28541-40-4; (*E*)-**1d**, 28541-41-5; (*Z*)-**1d**, 28541-42-6; (*E*)-**1e**, 28541-43-7; (*Z*)-**1e**, 28541-44-8; (*Z*)-2′-methoxyacetophenone *N*,*N*,*N*-trimethylhydrazonium iodide, 28541-45-9; (*E*)-2′-methoxyacetophenone *N*,*N*,*N*-trimethoxyhydrazonium iodide, 28541-46-0.

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[9] A. Mannschreck and U. Koelle [*Tetrahedron Lett.*, 963 (1967)] have recently suggested that the dipolar resonance structure a contributes to the ground state of dimethylhydrazones.

$$>C{=}NN(CH_3)_2 \longleftrightarrow >\bar{C}N{=}\overset{+}{N}(CH_3)_2$$

a

[10] The lateral-shift (inversion) mechanism *vs.* the rotational mechanism has been recently reviewed by Kessler [*Angew. Chem., Int. Ed. Engl.*, **9**, 219 (1970)].

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[14] Other examples of similar geometrical isomerizations are known. See W. Borsche and W. Schriba, *Justus Liegibs Ann. Chem.*, **541**, 283 (1939), and W. Borsche and A. Herbert, *ibid.*, **546**, 293 (1941).

[15] Melting points were determined in sealed capillary tubes on a Thomas-Hoover melting point apparatus and are uncorrected. Nmr spectra were measured in carbon tetrachloride solution with tetramethylsilane as the internal standard on a Varian A-60 instrument. Microanalyses were performed by Spang Microanalytic Laboratory, Ann Arbor, Mich.

Naphthyridine Chemistry. XIII. The Meisenheimer Reaction of the 1,5- and 1,6-Naphthyridine 1-Oxides

William W. Paudler* and David J. Pokorny

Clippinger Laboratories, Department of Chemistry, Ohio University, Athens, Ohio 45701

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The Meisenheimer reaction of the 1,5-naphthyridine mono- and di-*N*-oxides has been reported[1,2] to afford

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[2] E. P. Hart, *J. Chem. Soc.*, 1879 (1954).