**2-Ethyl-3-(*N,N*-diethylamino)-4,6-dichlorobenzofuran (4a)** had nmr spectrum ($CDCl_3$) $\delta$ 0.95 (t, 6 H, methyl), 1.25 (t, 3 H, methyl), 2.79 (q, 2 H, methylene), 3.08 (q, 4 H, methylene), 7.18 (d, 1 H, aromatic), and 7.28 (d, 1 H, aromatic); picrate (ethanol) mp 148.5–149.5°.

*Anal.* Calcd for $C_{20}H_{20}N_4O_8Cl_2$: C, 46.60; H, 3.88; N, 10.87. Found: C, 46.30; H, 3.81; N, 10.72.

**2-Ethyl-3-(*N,N*-diethylamino)-5,7-dichlorobenzofuran (4b)** had nmr spectrum ($CDCl_3$) $\delta$ 0.91 (t, 6 H, methyl), 1.24 (t, 3 H, methyl), 2.77 (q, 2 H, methylene), 3.03 (q, 4 H, methylene), 7.17 (d, 1 H, aromatic), and 7.40 (d, 1 H, aromatic); picrate (ethanol) mp 172–173°.

*Anal.* Calcd for $C_{20}H_{20}N_4O_8Cl_2$: C, 46.60; H, 3.88; N, 10.87. Found: C, 46.15; H, 3.87; N, 10.68.

**Registry No.**—**1**, 15299-99-7; **2**, 38740-02-2; **2** picrate, 38740-03-3; **3a**, 38740-04-4; **3b**, 38740-05-5; **4a**, 38740-06-6; **4a** picrate, 38740-07-7; **4b**, 38740-08-8; **4b** picrate, 38740-09-9.

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# Reexamination of the Claisen–Schmidt Condensation of Phenylacetone with Aromatic Aldehydes[1]

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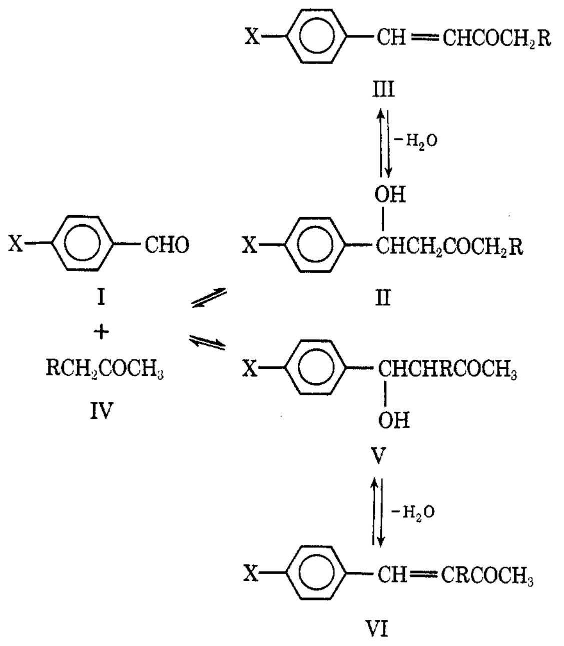
Although the base-catalyzed reaction of aldehydes with ketones of the type $RCH_2COCH_3$ can, in principle, occur with two possible orientations (Scheme I) the condensation of aromatic aldehydes with such ketones usually occurs at the methyl group.[2] It has been shown[3–6] that the rate-determining step in reactions of this type involves the condensation process, namely, attack by an enolate ion of IV at the carbonyl group of I. In basic solution methyl-*n*-alkyl ketones form approximately equal amounts of the two isomeric enolates while branched alkyl groups favor the less highly substituted enolate;[7] hence a mixture of both unsaturated ketones, III and VI, would be expected from the base-catalyzed condensations of the ketones IV with aldehydes. Because this is not the case, the *product*-determining step is believed to involve large rate differences in the competing dehydrations of the intermediate ketols, II and V. For example, the reaction of 2-butanone (IVb) with benzaldehyde affords the unsaturated ketone IIIb exclusively.[4,5] Independent synthesis of ketols IIb and Vb followed by treatment with base revealed that Vb retrogressed to reactants[5] while both dehydration and retrogression occurred with IIb.[4,5] The exclusive formation of methyl condensation products is usually observed only when reaction conditions are vigorous enough to cause dehydration of the intermediate ketols. Under milder conditions ketols II and V can both be isolated in reactions of aromatic aldehydes with 2-butanone.[5,8,9] The preferential cleavage of type V ketols to reactants has been attributed to steric hindrance to dehydration imposed by bulky R groups.[4,5,10,11]

SCHEME I



a, X = H; R = H
b, X = H; R = $CH_3$
c, X = $OCH_3$; R = H
d, X = H; R = $C_6H_5$
e, X = $CH_3$; R = $C_6H_5$
f, X = $OCH_3$; R = $C_6H_5$
g, X = Cl; R = $C_6H_5$
h, X = $NO_2$; R = $C_6H_5$

A reaction frequently cited[12,13] as involving exclusive methyl condensation is the hydroxide-catalyzed condensation of phenylacetone (IIId) with benzaldehyde;[14,15] substituted benzaldehydes have also been reported to afford unsaturated ketones corresponding to methyl condensation only.[16] Since the more highly substituted enolate of phenylacetone is strongly favored in basic solution[7] these results have prompted the belief[12,13] that ketol Vd must undergo retrogression in preference to dehydration.

We have examined the base-catalyzed reaction of phenylacetone with several aromatic aldehydes under similar conditions to those reported previously and have quantitatively determined the components of the crude products using glc and nmr analysis. In every reaction but one, unsaturated ketones corresponding to both possible modes of condensation were produced. The results are shown in Table I.[17] The relative mole ratios of III:VI were determined by glc analysis, using pure samples of the unsaturated ketones as standards. Samples of VI were prepared independently by the piperidine-catalyzed condensa-

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[1] The receipt of a Lafayette College Research Fund grant in support of this research is gratefully acknowledged.

[2] A. T. Nielsen and S. J. Houlihan, "Organic Reactions," Vol. 16, Wiley, New York, N. Y., 1968, and references cited therein.

[3] J. D. Gettler and L. P. Hammett, *J. Amer. Chem. Soc.*, **65**, 1824 (1943).

[4] D. S. Noyce and W. L. Reed, *J. Amer. Chem. Soc.*, **81**, 624 (1959).

[5] M. Stiles, D. Wolf, and G. V. Hudson, *J. Amer. Chem. Soc.*, **81**, 628 (1959).

[6] P. L. Nayak and M. K. Rout, *J. Indian Chem. Soc.*, **47**, 807 (1970).

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[9] H. Midorikawa, *Bull. Chem. Soc. Jap.*, **27**, 131 (1954).

[10] M. R. F. Ashworth and J. E. Dubois, *Bull. Soc. Chim. Fr.*, 147 (1955).

[11] C. S. Rondestvedt and M. E. Rowley, *J. Amer. Chem. Soc.*, **78**, 3804 (1956).

[12] Reference 2, p 35.

[13] H. O. House, "Modern Synthetic Reactions," W. A. Benjamin, New York, N. Y., 1965, p 222.

[14] P. L. Southwick, L. A. Pursglove, and P. Numerof, *J. Amer. Chem. Soc.*, **72**, 1604 (1950).

[15] G. Goldschmiedt and H. Krczmar, *Monatsh. Chem.*, **22**, 659 (1901).

[16] G. Goldschmiedt and H. Krczmar, *Monatsh. Chem.*, 749 (1901).

[17] See Experimental Section.

TABLE I

BASE-CATALYZED REACTION OF PHENYLACETONE WITH SUBSTITUTED BENZALDEHYDES, $p$-$XC_6H_4CHO$

| Registry no. | X | Reaction temp, °C | Reaction time, hr | Relative mole ratio III:VI | Total yield[a] of III + VI, % | Yield of isolated III, % |
|---|---|---|---|---|---|---|
| 100-52-7 | H | 65 | 18 | 91:9 | 92 | 44 |
| 104-87-0 | $CH_3$ | 65 | 18 | 92:8 | | 19 |
| | $CH_3$ | 80 | 24 | 90:10 | 88 | 50 |
| 123-11-5 | $OCH_3$ | 65 | 18 | 90:10 | | 24 |
| | $OCH_3$ | 80 | 24 | 90:10 | 88 | 43 |
| 104-88-1 | Cl | 65 | 18 | 87:13 | 68 | 24 |
| 555-16-8 | $NO_2$ | Various[b] | Various[b] | Trace VIh | | 0 |

[a] Determined by glc and nmr analysis, as detailed in Experimental Section. [b] Reference 17.

tion of phenylacetone with the appropriate aromatic aldehyde, a procedure which has previously been found to produce condensation at the methylene group[18-20] and subsequent formation of the cis-diaryl alkene when R is phenyl.[18,21] Work-up of the hydroxide-catalyzed reaction mixtures afforded pure samples of III, invariably the major product of these reactions. The structures of all products were verified *via* nmr and ir, as well as elemental analysis for new compounds.

The results show no significant variation in the relative yields of the isomeric ketones with changes in aldehyde structure, the relative mole ratio of III to VI being approximately 9:1 for four of the five aldehydes. Increasing the temperature in two of the reactions also caused no significant change in relative product yields. In other reactions of aldehydes with methyl alkyl ketones higher temperatures have been found to favor methyl condensation.[22] Apparently, base-catalyzed dehydration of V relative to II is more favorable when R is phenyl than when R is methyl, a conclusion which suggests that electronic effects play a role in the dehydration step along with steric effects. In particular the transition states in the dehydration of ketols Vd–h are stabilized more when R = phenyl than when R = $CH_3$; no such difference in transition state stabilities is expected in the dehydration of ketols IId–h.[23] As a result, the ratio of rate constants $k_{V \rightarrow VI}/k_{II \rightarrow III}$ should increase with a change in R from methyl to phenyl. Competing with this favorable electronic effect is unfavorable steric interference from the phenyl group in Vd–h, a factor absent in ketols IId–h.[24]

The independence of relative yields of III:VI to the para substituent, X, is probably an indication that any electronic effects caused by variations in X are exerted to the same extent on the dehydration and retrogression steps of both ketols II and V. It is relevant that ketols Va and Vc exhibited nearly identical ratios of dealdolization to dehydration on treatment with dilute NaOH.[4] The rates of both reactions were larger for the $p$-methoxy compound, which was attributed to the fact that both dealdolization and dehydration lead to more effectively resonance-stabilized products when X is $p$-methoxy than when X is hydrogen.

### Experimental Section[25]

**A. Synthesis of 1-($p$-X-Phenyl)-2-phenyl-1-buten-3-ones. 1,2-Diphenyl-1-buten-3-one (VId)** was prepared by the method of Zimmerman, *et al.*:[18] bp 127–132° (0.6 mm); mp 54–55° (lit.[18] mp 55–56°); nmr δ 7.56 (s, 1, –CH=), 7.1 (m, 10, aryl H), 2.22 (s, 3, $CH_3$).

**1-$p$-Tolyl-2-phenyl-1-buten-3-one (VIe).**—A mixture of phenylacetone (15.6 g, 0.116 mol), $p$-tolualdehyde (13.9 g, 0.116 mol), and piperidine (0.24 g) in 80 ml of dry benzene was refluxed for 19 hr using a Dean–Stark trap. Evaporation of solvent under reduced pressure followed by vacuum distillation gave 16.9 g (62%) of light yellow oil, bp 140–145° (0.5 mm), which solidified on standing. Recrystallization from petroleum ether (bp 60–110°) afforded white needles: mp 64–65°; ir 1655 cm$^{-1}$ (C=O); nmr δ 7.62 (s, 1, –CH=), 7.2 (m, 9, aryl H), 2.26 (s, 3, $CH_3$), 2.20 (s, 3, $CH_3$).

*Anal.* Calcd for $C_{17}H_{16}O$: C, 86.40; H, 6.82. Found: C, 86.55; H, 6.94.

**1-$p$-Methoxyphenyl-2-phenyl-1-buten-3-one (VIf)** was prepared by the same method as VIe from $p$-anisaldehyde (15.6 g, 0.116 mol) with a 24-hr reflux period. Vacuum distillation of crude product gave 15.5 g (53%) of viscous yellow oil, bp 159–164° (0.6 mm) [lit.[26] bp 218–220° (8–10 mm)], which gradually crystallized on refrigeration. Recrystallization from petroleum ether (bp 38–50°) afforded white needles: mp 61–63° (lit.[24] mp 63–64°); ir 1658 cm$^{-1}$ (C=O); nmr δ 7.60 (s, 1, –CH=), 7.0 (m, 9, aryl H), 3.66 (s, 3, $OCH_3$), 2.24 (s, 3, $COCH_3$).

**1-$p$-Chlorophenyl-2-phenyl-1-buten-3-one (VIg)** was prepared by the same method as VIe from $p$-chlorobenzaldehyde (16.3 g, 0.116 mol). The crude product, a solid, was recrystallized from ethanol, affording light tan needles (16.8 g, 56%): mp 125–126.5°; ir 1660 cm$^{-1}$ (C=O); nmr δ 7.56 (s, 1, –CH=), 7.2 (m, 9, aryl H), 2.27 (s, 3, $CH_3$).

*Anal.* Calcd for $C_{16}H_{13}ClO$: C, 74.86; H, 5.10; Cl, 13.81. Found: C, 74.86; H, 5.25; Cl, 13.65.

**1-$p$-Nitrophenyl-2-phenyl-1-buten-3-one (VIh)** was prepared from $p$-nitrobenzaldehyde (8.76 g, 0.058 mol), phenylacetone (7.78 g, 0.058 mol), piperidine (0.14 ml), and hexanoic acid (0.07 ml) in dry benzene (40 ml). After 18 hr more piperidine (0.18 ml) was added and the solution was refluxed for 20 hr longer. The crude product was vacuum distilled and the fraction with bp 184–195° (0.7 mm) was collected as an orange oil (3.7 g, 24%) which rapidly solidified. Recrystallization from ethanol and then from petroleum ether (bp 60–110°) gave yellow leaflets: mp 110–112°; ir 1668 cm$^{-1}$ (C=O); nmr δ 8.0 and 7.3 (m, ~9, aryl H), 7.61 (s, 1, –CH=), 2.31 (s, 3, $CH_3$).

*Anal.* Calcd for $C_{16}H_{13}NO_3$: C, 71.90; H, 4.90; N, 5.24. Found: C, 72.11; H, 5.06; N, 4.97.

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[18] H. E. Zimmerman, L. Singer, and B. S. Thyagarajan, *J. Amer. Chem. Soc.*, **81**, 108 (1959).

[19] R. Dickinson, *J. Chem. Soc.*, 2234 (1926).

[20] I. M. Heilbron and F. Irving, *J. Chem. Soc.*, 931, 936 (1929).

[21] R. A. Abramovitch and A. Obach, *Can. J. Chem.*, **37**, 502 (1959).

[22] Reference 2, p 77.

[23] This conclusion would be valid for either an E2 or an E1cb transition state.

[24] It is also likely, although the consequences are uncertain, that the location of the phenyl group in V would stabilize the enolate in which dehydration occurs, namely $p$-$XC_6H_5CH(OH)C(C_6H_5){=}COCH_3^-$. In contrast, the favored enolate of II, $p$-$XC_6H_5CH(OH)CH_2CO{=}CHC_6H_5^-$ is not the one in which dehydration can occur.

[25] Melting points were taken on a Fisher-Johns block and are uncorrected. Infrared spectra were determined in $CHCl_3$ on a Beckman IR-10 instrument and were calibrated against the 1601-cm$^{-1}$ peak of polystyrene. Nmr spectra were recorded in $CDCl_3$ on either a Perkin-Elmer R-24 instrument or on a JEOL MH-60 spectrometer. Glc analyses were performed on a Carle Model 8000 gas chromatograph using a 6 ft × 0.125 in. 8% G.E. SF96 on 90–100 mesh Anakrom ABS column. Elemental microanalyses were performed by Dr. G. I. Robertson, Jr., Florham Park, N. J.

[26] T. N. Ghosh, A. Bose, and A. Raychaudhuri, *J. Indian Chem. Soc.*, **37**, 93 (1960).

**B. Base-Catalyzed Reactions of Phenylacetone with Para-Substituted Benzaldehydes. Reaction of Phenylacetone with Benzaldehyde.**—Phenylacetone (24.9 g, 0.186 mol) and benzaldehyde (19.7 g, 0.186 mol) were added to a rapidly mechanically stirred solution of NaOH (1.50 g) in water (800 ml) at 65°. After 18 hr the mixture was cooled to room temperature and extracted with five 100-ml portions of $CH_2Cl_2$. The extract was washed with water and dried ($MgSO_4$) and solvent was evaporated under reduced pressure. A small sample of the crude product was set aside for glc and nmr analysis. The remainder of the product was recrystallized from methanol, affording 18.2 g (44%) of *trans*-1,4-diphenyl-3-buten-2-one (IIId): mp 72–75° (lit.[27] mp 73–76°); nmr $\delta$ 7.57 (d, 1, $J$ = 16 Hz) and 6.70 (d, 1, $J$ = 16 Hz) (trans CH=CH), 7.3 (m, 10, aryl H), 3.82 (s, 2, $CH_2$).

Glc analysis of the *crude* product showed a relative yield of 91:9 of IIId:VId; glc and nmr analysis[28] showed a total yield of 92% for IIId + VId.[29]

**Reaction of Phenylacetone with *p*-Tolualdehyde.**—The same procedure as with benzaldehyde was followed. Washing of the crude product with petroleum ether (bp 20–40°) and recrystallization from ethanol afforded 8.2 g (19%) of *trans*-1-phenyl-4-(*p*-tolyl)-3-buten-2-one (IIIe): mp 112.5–114° (lit.[16] mp 115°); nmr $\delta$ 7.57 (d, 1, $J$ = 16 Hz) and 6.66 (d, 1, $J$ = 16 Hz) (trans CH=CH), 7.2 (m, ~9, aryl H), 3.84 (s, 2, $CH_2$), 2.26 (s, 3, $CH_3$). Repetition of the reaction at 80° for 24 hr increased the yield to 21.9 g (50%).

Glc and nmr analysis of the crude products, as above, showed a relative yield of 92:8 for IIIe:VIe for the 65° reaction and 90:10 for the 80° reaction. A total yield (IIIe + VIe) of 88% was found in the latter reaction.

**Reaction of Phenylacetone with *p*-Anisaldehyde.**—The standard procedure was followed. Trituration of the crude product with cold ether and filtration afforded 11.2 g (24%) of *trans*-4-(*p*-anisyl)-1-phenyl-3-buten-2-one (IIIf): mp 98–100° (lit.[16] mp 98–100°); nmr $\delta$ 7.58 (d, 1, $J$ = 16 Hz) and 6.62 (d, 1, $J$ = 16 Hz) (trans CH=CH), 7.25 (m, ~9, aryl H), 3.87 (s, 2, $CH_2$), 3.72 (s, 3, $OCH_3$).

Glc and nmr analysis of the crude products showed relative yields of 90:10 for IIIf:VIf in both reactions. The total yield (IIIf + VIf) was 88% in the 80° reaction.

**Reaction of Phenylacetone with *p*-Chlorobenzaldehyde.**—The standard procedure was used. Two recrystallizations of the crude product from ethanol gave 11.4 g (24%) of *trans*-4-(*p*-chlorophenyl)-1-phenyl-3-buten-2-one (IIIg) as white crystals: mp 102–104°; ir 1655 cm$^{-1}$ (C=O), 970 (trans CH=CH); nmr $\delta$ 7.53 (d, 1, $J$ = 16 Hz) and 6.66 (d, 1, $J$ = 16 Hz) (trans CH=CH), 7.27 (m, 9, aryl H), 3.89 (s, 2, $CH_2$).

*Anal.* Calcd for $C_{16}H_{13}ClO$: C, 74.85; H, 5.10; Cl, 13.81. Found: C, 74.77; H, 5.02; Cl, 13.80.

Glc and nmr analysis of the crude product showed a ratio of IIIg:VIg of 87:13. A total yield (IIIg + VIg) of 68% was found.

**Reaction of phenylacetone with *p*-nitrobenzaldehyde** at temperatures varying from 50 to 75° and times of 6–24 hr afforded either unreacted starting materials and/or a dark red glassy substance which could not be purified. Glc analysis of the crude products showed a trace of VIh but no products other than starting materials could be detected.[30]

**Registry No.**—IIId, 38661-84-6; IIIe, 38661-85-7; IIIf, 38661-86-8; IIIg, 37562-70-2; IVd, 103-79-7; VId, 38661-88-0; VIe, 38661-89-1; VIf, 13938-22-2; VIg, 38661-91-5; VIl, 8661-92-6.

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# A Reinvestigation of the Condensation of Aliphatic Ketones with Benzil

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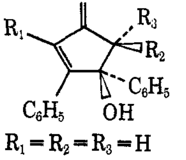
An extensive investigation of the base-catalyzed condensation of acetone and other aliphatic ketones with benzil was carried out many years ago by Japp and his coworkers.[1] The product from the reaction of acetone with benzil was proved to be 4-hydroxy-3,4-diphenyl-2-cyclopenten-1-one (**1**). From the reaction of other aliphatic ketones with benzil, cyclopentenones bearing alkyl groups at C-2 or C-5 were obtained. The structures of these products, however, were not completely established. In the present study some of these products were reinvestigated, and their structures were determined using nmr spectroscopy.

The structure of **1** and that of **2**, which is produced from 3-methyl-2-butanone, are unambiguous, and these compounds serve as models. In addition to signals for aromatic and hydroxylic hydrogens, the spectrum of **1** has a one-proton singlet at $\delta$ 6.66 and an AB pattern [$\delta_A$ 2.98, $\delta_B$ 2.84 ($J_{AB}$ = 19 Hz)]. The spectrum of **2** has a one-proton singlet at $\delta$ 6.74 and three-proton singlets at 1.32 and 0.64. The substituents at C-4 cause these latter to be displaced from $\delta$ 1.03, the reported position for the methyl hydrogen resonance of 5,5-dimethyl-2-cyclopenten-1-one.[2] The methyl group cis to the phenyl group on C-4 lies in the region shielded by the aromatic ring, and this methyl group thus gives rise to the higher field peak.[3]



**1**, $R_1 = R_2 = R_3 = H$
**2**, $R_1 = H$; $R_2 = R_3 = CH_3$
**3**, $R_1 = R_2 = CH_3$; $R_3 = H$
**4**, $R_1 = R_3 = CH_3$; $R_2 = H$
**5**, $R_1 = CH_3$; $R_2 = R_3 = H$
**6**, $R_1 = R_3 = H$; $R_2 = CH_3$
**7**, $R_1 = R_2 = H$; $R_3 = CH_3$

From the reaction of 3-pentanone with benzil Japp and Meldrum obtained two products, one melting at 150° and the other at 128.°[1a] They concluded

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[27] S. A. Fine and R. L. Stern, *J. Org. Chem.*, **32**, 4132 (1967).

[28] Glc analyses were based on comparisons of peak areas of standardized solutions of the pure compounds with peak areas in solutions of the crude product mixtures. Nmr analysis was used as confirmatory evidence. The areas of suitable peaks due to III and VI in the nmr spectrum of the crude product mixtures were compared with the areas of peaks due to unreacted phenylacetone and/or unreacted aldehyde. Total yields obtained by the two methods always differed by less than 4%.

[29] Since the glc retention times of VId–h in the crude product mixtures were precisely the same as the retention times of authentic samples, and since the nmr shifts due to VId–h in the crude product mixtures were identical with those in authentic samples, we conclude that the stereochemistry of VI in our product mixtures is identical with that of the authentic samples, namely cis with respect to the aryl groups. Similar stereochemical results have been observed in a related base-catalyzed condensation: H. E. Zimmerman and L. Ahramjian, *J. Amer. Chem. Soc.*, **81**, 2086 (1959).

[30] The retention times of type VI ketones (d–g) were almost exactly double the retention times of the corresponding type III ketones under the conditions used. The conclusion that IIIh was absent is based on the fact that no peak appeared on the chromatogram even after 15 times the retention time of VIh.

[1] (a) F. R. Japp and A. N. Meldrum, *J. Chem. Soc.*, **79**, 1024 (1901); (b) F. R. Japp and J. Knox, *ibid.*, **87**, 673 (1905); (c) F. R. Japp and A.C. Michie, *ibid.*, **83**, 276 (1903).

[2] T. Matsumato, H. Shirahama, A. Ichihara, H. Shin, S. Kagawa, N. Ito, T. Hisamitsu, T. Kamada, and F. Sakan, *Tetrahedron Lett.*, 4097 (1967).

[3] L. M. Jackman and S. Sternhell, "Applications of Nuclear Magnetic Resonance Spectroscopy in Organic Chemistry," 2nd ed, Pergamon Press, Oxford, 1969, p 234.