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ORGANIC REACTIONS WITH POLYPHOSPHORIC ACID—VII*†

WAGNER–MEERWEIN REARRANGEMENT IN THE INTERMOLECULAR ACYLATION OF CYCLOHEPTENE‡

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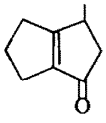
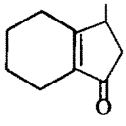
Abstract—Acetylation of cycloheptene in polyphosphoric acid at ~65° is shown to be accompanied by ring-contraction to furnish 2-methyl-Δ^1-acetylcyclohexene as the main product. The same rearrangement§ occurs during the one-step acylation-alkylation of cycloheptene with crotonic acid.

A ONE-STEP synthesis of certain polycyclic systems, involving the action of an αβ-unsaturated acid on a cyclo-olefin, in the presence of polyphosphoric acid (PPA),[1–3] includes bicyclo[0,3,3] octane and bicyclo [0,3,4] nonane derivatives (I, II) which have been prepared by the action of crotonic acid on cyclopentene and cyclohexene respectively. As a logical extension of the reaction, cycloheptene and crotonic acid should give, under similar conditions, the bicyclic ketone III, a useful intermediate



I



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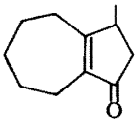

III

for the preparation of 1-methylazulene. However, when the ketone obtained was reduced, dehydrated and dehydrogenated, no azulene was formed. Probably some rearrangement occurred, at the stage of PPA condensation, and this called for an investigation, which is now reported.

Reaction of cycloheptene and acetic acid

The reaction of cyclopentene and cyclohexene with acetic acid and PPA[4] proceeds normally to give the corresponding αβ-unsaturated methyl ketones. The reaction of cycloheptene with acetic acid (1 mol : 1 mole) in PPA, at 65–70°, afforded a product in ~30% yield, which by GLC was found to consist essentially of one component. By comparison of its retention time and IR spectrum, it was shown to be different from an authentic Δ^1-acetylcycloheptene (IV).‖ The compound was readily identified (PMR, IR, GLC) as 2-methyl-Δ^1-acetylcyclohexene (V),[7] an authentic sample of

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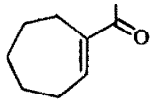
† Communication No. 1074, National Chemical Laboratory, Poona.

‡ Abstracted from the Ph.D thesis of S. B. Kulkarni, Bombay University (1966).

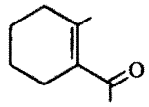
§ The rearrangement which takes place in these reactions was disclosed in an earlier communication.[4]

‖ This was obtained by the action of MeLi on Δ^1-cycloheptone carboxylic acid.[5] The compound has been prepared earlier by other methods.[6]

which was later prepared by the reaction of acetic acid and methylcyclohexene in PPA, for direct comparison. Thus, the reaction of cycloheptene with acetic acid in PPA proceeds with concomitant ring-contraction to furnish essentially V.



IV



V

In another set of experiments the molar ratio of cycloheptene and acetic acid was varied and it was found that with a molar ratio of 1:5 of cycloheptene and acetic acid, a 45% yield of the product was obtained which was shown by GLC to consist of ~85% of V and 10% of IV. With still higher ratios a different reaction resulted and forms the subject of another communication.*

In the earlier stages of this work the condensation of cycloheptene and acetic acid was carried out at ~55°, the product consisted of two components (GLC) in the ratio 35:65 (increasing RT). This product showed in the IR spectrum $\nu^{C=O}$ at 1706 and 1680 cm^{-1} suggesting that in addition to V a non-conjugated ketone is also formed. From the RT of V, it is clear that the non-conjugated ketone corresponds to the component with the lower RT. However, in several later experiments, which were carried out under identical conditions as well as a variety of different conditions (*vide* Experimental) only the conjugated ketone (GLC, IR) was formed. †

During the course of this work it was found that from pure 2-methyl-Δ^1-acetylcyclohexene (V), either a yellow (m.p. 107–108°) or a red (m.p. 125–127°) 2,4-dinitrophenylhydrazone (or a mixture) could be prepared, depending on the method of

TABLE 1. PMR SPECTRAL ASSIGNMENTS OF THE TWO 2,4-DINITROPHENYLHYDRAZONES FROM 2-METHYL-Δ^1-ACETYL CYCLOHEXENE

Assignment	2,4-Dinitrophenylhydrazone from		
	2-Methyl-Δ^1-acetylcyclohexene		Δ^1-Acetyl-cyclohexene
	Yellow	red	
$\underline{CH}_3$			
$>C=C<$	96 (s)	106 (s)	—
$\underline{CH}_3$—C=N—	130 (s)	132 (s)	130 (s)
$>C=\underline{CH}$	—	—	390 (b)
$\underline{NH}$	672	660 (b)	676 (b)
Aromatic protons	484 (2H, m) 538 (1H, d, J = 2 c/s)	484 (2H, m) 538 (1H, d, J = 2 c/s)	490 (2H, m) 554 (1H, b)

*Spectra taken in CCl_4 and values are reported in c/s from TMS; s = singlet, b = broad singlet, d = doublet, m = multiplet.

* Part IX of this series.
† Trace impurities in P_2O_5 and/or phosphoric acid might have been responsible for this divergence.

preparation (*vide* Experimental). Furthermore, when the red derivative was warmed with alcoholic H_2SO_4 aq and left aside for a long time, it slowly underwent complete change over to the yellow product. The PMR spectra[8] of the two preparations show significant differences (Table 1), which ensure that the two products are not merely polymorphs but are stereoisomeric. Several examples of the isolation of stereoisomeric 2,4-dinitrophenylhydrazones have been reported.[8b,8c,9] Though Karabatsos *et al.*[8] have been able to deduce the configuration of several 2,4-dinitrophenylhydrazones by PMR, their results which are based on studies of saturated, aliphatic aldehyde and ketone derivatives, are difficult to extend to the present case of an αβ-unsaturated ketone derivative wherein further complication arises due to the possibility of s-*cis* and s-*trans* isomerism.

Condensation of cycloheptene and crotonic acid

The reaction of cycloheptene and crotonic acid, in equimolar proportions, in presence of PPA at 70 ±2°, furnished a ketonic product in ~40% yield. GLC of this material showed it to consist of seven components in which the last three components (**5**, **6**, **7**, increasing retention time; relative proportions being 1:5:3 respectively) predominated to the extent of over 80%. In view of the results obtained in the condensation of acetic acid and cycloheptene, reaction of crotonic acid with methylcyclohexene was also carried out under the above conditions. The product from this reaction was shown by GLC to consist of essentially (>90%) the same three components (**5**, **6**, **7** in almost the same proportions) of the cycloheptene–crotonic acid condensation. These compounds, from each experiment, were separated by preparative GLC and the IR spectra of the three products from each source were found to be identical with the IR spectra of the corresponding fractions. Thus, it is clear that the products from the cycloheptene–crotonic acid reaction represent ring-contracted ketones.

TABLE 2. PROPERTIES OF THE PRODUCTS FROM THE CONDENSATION OF CYCLOHEPTENE AND CROTONIC ACID

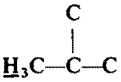
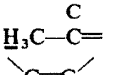
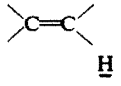
	GLC component No.		
	5	**6**	**7**
b.p./30 mm	137–38°	138–40°	138–40°
n_D^{30}	—	1·5010	1·5045
RRT*	1	1·18	1·32
Semicarbazone, m.p.	—	181–83°	172–74°
2,4-DNP, m.p.	138–40°	150–51°	181–83°
λ_{max}^{EtOH} mμ (ε)	232 (10,400)	235 (10,450)	232 (13,350)
$\nu^{C=O}$ cm^{-1}	1709	1675	1709
$\nu^{C=C}$ cm^{-1}	1626	1650	1626

* Relative retention time with respect to **5**.

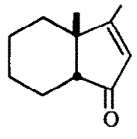
Table 2 summarizes some of the characteristics of these three products. The components **6** and **7** readily furnished semicarbazones and these compounds were, thus, further purified by regeneration from these derivatives; it was ascertained that no isomerization took place during the regeneration step.

All the three compounds analyse for $C_{11}H_{16}O$ and from their UV and IR spectral data are clearly αβ-unsaturated cyclopentenones.[10] Important features of the PMR spectra of these compounds are the presence of one quaternary Me, one vinylic Me and, one vinylic proton in each compound (Table 3). These spectral characteristics, taken along with the mechanistic reasoning,[11] led to the following four possible formulations (VI–IX).

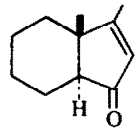
TABLE 3. PMR SPECTRAL ASSIGNMENTS FOR THE PRODUCTS FROM THE CYCLOHEPTENE–CROTONIC ACID CONDENSATION*

Assignment	GLC component No.		
	5	6	7
	62 (s)	67 (s)	74 (s)
	123 (d, J = 1·5 c/s)	115 (s)	122 (d, J = 2 c/s)
	342 (m)	343 (b)	344 (b)

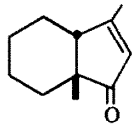
* See footnote to Table 1 for remarks.



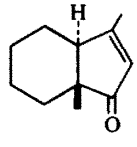
VI



VII



VIII



IX

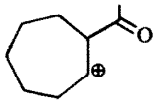
A synthetic sequence, involving intramolecular acylation of suitably constituted lactones with PPA, forms the subject matter of another communication.[12] This work was carried out with the twin purpose of effecting an unequivocal synthesis of 3,8-dimethylhydrind-2-ene-1-one (VIII/IX) and for investigating certain mechanistic aspects of intramolecular acylations with lactones. This synthesis led to the formation of only one of the two isomers (VIII or IX) and this has been found to be indistinguishable (UV, IR, PMR) from the component 5. Its stereochemistry is discussed later.

The remaining two components **6**, **7** were found to be an epimeric pair by partial transformation of **6** into **7** by a short base treatment and hence, must be represented by the pair VI–VII. A synthesis of 3,9-dimethylhydrind-2-ene-1-one (VI/VII) has been reported.[13] From the reported m.ps of its semicarbazone (m.p. 176–177°) and 2,4-dinitrophenylhydrazone (m.p. 184–185°), component **7** must be identical with this. These authors do not define its stereochemistry. The final stage in their synthesis is a cyclization step involving heating with PPA at 60–65° for 6 hr; the product was found to be stable to refluxing methanolic NaOMe and hence must be the thermodynamically more stable *cis*-ketone VI.* The *trans* structure VII can now be assigned to the component **6**.†‡

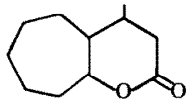
Close similarity in the $\nu^{C=O}$ and $\nu^{C=C}$ values of components **5** and **7** suggests that the former also has the *cis*-configuration VIII.

DISCUSSION

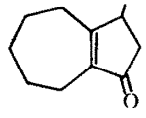
Although Wagner–Meerwein rearrangements with PPA have been observed,[16] the present work is the first example of a ring-contraction during an acylation–alkylation reaction with PPA. The results are readily rationalised in terms of the solvated carbonium ion X. However, it must be mentioned that when the lactone XI is treated with PPA, no ring-contraction occurs and only the expected bicyclo[0,3,5]



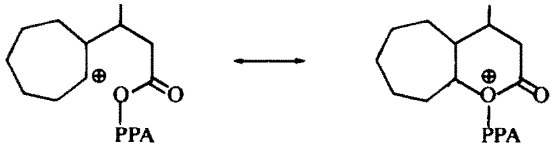
X



XI



XII



XIII

decane derivative XII results,[17] the formation of which must have involved at one stage the species XIII. The difference in the fate of X and XIII must be due to the higher stability of the latter ion.

The alternative possibility that cycloheptene undergoes ring contraction before acylation could not be ascertained as in a single experiment, when cycloheptene

* There is considerable evidence[14] to show that in simple α-hydrindones *cis*-junction is thermodynamically more stable and the presence of an angular Me group only further accentuates the equilibrium in favour of the *cis*-isomer. An olefinic linkage at C_2–C_3 is not expected to alter the picture.

† Normally one would expect that in a PPA reaction the thermodynamically more stable product would predominate because of strongly equilibrating conditions. However, in the present work, condensation of cycloheptene and crotonic acid at 65° was carried out for just 15 min as otherwise, undue polymerization occurred. Hence, though component **6** is formed in larger quantities, the product is not expected to represent the equilibrium stage.

‡ Data has been presented[15] to show that in some hydrindanones, the less stable epimer shows its C=O absorption at higher frequencies; this is not the case in the present instance.

was treated with PPA for 10 min under the conditions of the acylation experiments with a view to isolate any 1-methylcyclohexene, only a dimer and a polymer resulted which were not studied.

EXPERIMENTAL

All m.ps and b.ps are uncorrected. Pet. ether refers to the fraction b.p. 40–60°. All solvent extracts were dried over Na_2SO_4. IR spectra were taken on a Perkin–Elmer Infracord model 137E, either as smears (liquids) or in Nujol (solids). UV spectra were taken on a Perkin–Elmer Spectrophotometer, model 350, in 95% EtOH, unless stated to the contrary. All PMR spectra were taken in 10–20% soln in CCl_4 with TMS as the internal standard, on a Varian Associates A-60 spectrometer; peaks are reported in c/s from TMS.

Analytical GLC was done on Perkin–Elmer Vapour Fractometer, model 154D, using H_2 as the carrier gas and a 2-meter column (external diam 6 mm) packed with 20% diethylene glycol succinate on Chromosorb W. For preparative GLC, a 2·5 cm × 3 meter column, packed with the same material, was used.

Reaction of cycloheptene with acetic acid

(i) *Equimolar ratios of reactants.* To PPA, prepared from P_2O_5 (70 g) and H_3PO_4 (d = 1·75; 30 ml)[18] at 65–70°, a mixture of cycloheptene[19] (9·6 g, 0·1 M) and gl. AcOH (6 g, 0·1 M) was added dropwise with stirring during 5 min. After stirring at 65–70° for 1 hr, the vermillion-red reaction mixture was poured onto ice-water (400 ml) and the product extracted with pet. ether (50 ml × 4). The extract was washed with water, $NaHCO_3$aq (10 ml × 3), brine and dried. The solvent was flashed off and the residue distilled: colorless liquid, b.p. 130–132°/80 mm, yield 3·5–4·0 g. GLC (temp 160°; gas press: 15 psi) revealed essentially one component. IR spectrum: C=O 1685; C=C 1613 cm^{-1}. *Semicarbazone* (pyridine method) was crystallized from EtOH, white crystals m.p. 225–227° (Lit.[7]: m.p. 225–227°).

(ii) *Reaction of cycloheptene with excess of acetic acid.* Cycloheptene (9·6 g, 0·1 M) and gl.AcOH (30 g, 0·5 M) were reacted in PPA (70 g P_2O_5 and 30 ml H_3PO_4) at 55–60°, as above and then worked up in the same manner to give, after distillation, a colourless liquid: b.p. 134–140°/80 mm, yield 5·2 g. GLC (as above) showed the presence of 85% 2-methyl-Δ^1-acetylcyclohexene and 10% acetylcycloheptene in the product, RRT of these components being 1 and 1·33 respectively.

Reaction of methylcyclohexene with acetic acid

1-Methylcyclohexene (9·6 g) and AcOH (6 g) on interaction in PPA (55–60°), by following the procedure and quantities given above under (i), gave a product (4 g), b.p. 120–122°/40 mm, n_D^{24} 1·4950, identical in all respects with the product obtained by the procedure (i).

2,4-Dintrophenylhydrazones of 2-methyl-Δ^1-acetylcyclohexene

(i) *HCl method.* 2-Methyl-Δ^1-acetylcyclohexene (0·6 g) and 2,4-dinitrophenylhydrazine (0·51 g) were added to EtOH (30 ml). After the addition of 1 drop of conc. HClaq the mixture was warmed on a water bath till clear. Red crystals started separating immediately, followed later by yellow crystals. The product (0·5 g, m.p. 97–100°) was dissolved in a little benzene and the soln chromatographed on alumina (neutral/II, 15 cm × 1·5 cm). Benzene–pet. ether (1:3; 25 ml × 5) eluted the yellow compound, while the red zone was later eluted with benzene (25 ml × 2).

The yellow derivative was obtained as leaflets from EtOH, m.p. 107–108°; λ_{max} 365 mμ (ε, 19,300). (Found: C, 56·6; H, 5·6; N, 17·2. $C_{15}H_{18}O_4N_4$ requires: C, 56·6; H, 5·7; N, 17·6%.)

Red derivative crystallized from EtOH as deep red leaflets m.p. 125–127° (Lit.[8b] m.p. 125°); λ_{max} 370 mμ (ε 18,400). (Found: C, 56·2; H, 5·5; N, 17·2. $C_{15}H_{18}O_4N_4$ requires: C, 56·6; H, 5·7; N, 17·6%.)

(ii) H_2SO_4 *method.* When the ketone was added to the reagent (50 mg) dissolved in conc H_2SO_4 (0·2 ml) water (0·2 ml) and EtOH (2 ml), only a yellow deriv, m.p. 107–108° (EtOH) was obtained.

(iii) The red deriv (m.p. 125–127°) was suspended in a small volume of aq. alcohol containing a few drops of conc H_2SO_4 and heated on a waterbath for 5 min and left. After 2 hr a mixture of red and yellow crystals (m.p. 86–91°) had separated, which on being allowed to stand for a long time (one week) had completely changed to yellow crystals, m.p. 107–108°.

Δ^1-Acetylcycloheptene. Δ^1-Cycloheptene carboxylic acid[5] (0·5 g, 0·004 M) dissolved in 25 ml dry ether was introduced (0·5 hr) with stirring to an ethereal soln of MeLi (prepared from 60 mg Li and 1·2 g MeI

in 20 ml ether) at ~0° and the reaction allowed to proceed at that temp for 1 hr. After stirring for another hr at room temp, the reaction mixture was worked up (with 5% H_2SO_4aq) to yield, after distillation a colourless liquid (0·35 g, 71%): b.p. 125–127°/50 mm, n_D^{30} 1·4730.

Semicarbazone (pyridine method) was obtained as a white powder from EtOH, m.p. 192–193° (Lit.,[6a] m.p. 195–197°). (Found: N, 21·3. $C_{10}H_{17}ON_3$ requires: N, 21·5%.) After regeneration (oxalic acid–heptane method[20]) from the semicarbazone, the ketone had: b.p. 126°/50 mm; λ_{max} 235 mμ (ε 11,000); IR spectrum: C=O 1681; C=C 1639 cm^{-1}.

Reaction of cycloheptene and methylcyclohexene with crotonic acid

(i) *Condensation of cycloheptene and crotonic acid.* To PPA (from 70 g P_2O_5 and 30 ml H_3PO_4 of d 1·75) maintained at 70 ± 2°, crotonic acid (8·6 g, 0·1 M) was added in one lot with stirring. Cycloheptene (9·6 g, 0·1 M) was next introduced (5 min) and the reaction mixture stirred at that temp for another 15 min and then worked up as described earlier. After distillation, the product was obtained as a liquid, b.p. 137–140°/30 mm, n_D^{24} 1·5051, yield 5·3 g.

(ii) *Methylcyclohexene and crotonic acid.* The condensation was carried out as described above, using 1-methylcyclohexene instead of cycloheptene. The product had: b.p. 138–140°/30 mm, n_D^{22} 1·5010, yield 5·6 g.

GLC of both the products was carried out at 180° and 15 psi press.

Separation of components. Details are given for the separation of the product obtained from cycloheptene–crotonic acid condensation. The same procedure was followed for the product obtained under (ii).

A total of 2 g (0·5 g × 4) of the product was injected on a preparative column at 200° and 15 psi press using N_2 as the carrier gas. The first 4 minor peaks were collected together (0·3 g) and were found to be non-ketonic in nature and were rejected. The remaining three components (**5**, **6** and **7**) were collected separately in yields of 0·2, 0·7 and 0·3 g respectively.

Component **5** (VIII). This did not give a crystalline semi-carbazone. (Found: C, 80·1; H, 9·6. $C_{11}H_{16}O$ requires: C, 80·4; H, 9·7%.) Its 2,4-*dinitrophenylhydrazone* crystallized from alcohol as a red powder, m.p. 138–140°. (Found: N, 16·02. $C_{17}H_{20}O_4N_4$ requires: N, 16·27%.)

Component **6** (VII). The *semicarbazone* (pyridine method) crystallized from alcohol, m.p. 181–183°. (Found: N, 18·8. $C_{12}H_{19}ON_3$ requires: N, 19·0%.) After regeneration from the semicarbazone, the ketone displayed properties listed in Table 2. (Found: C, 80·1; H, 9·6. $C_{11}H_{16}O$ requires: C, 80·4; H, 9·7%.) Its 2,4-*dinitrophenylhydrazone* separated from alcohol in bright red leaflets, m.p. 152–153°. (Found: N, 15·74. $C_{17}H_{20}O_4N_4$ requires: N, 16·27%.)

Component **7** (VI). The semicarbazone/pyridine method) crystallized from alcohol as a white powder, m.p. 172–174°. The ketone was regenerated from this to give the pure compound having properties listed in Table 2. (Found: C, 80·2; H, 9·4. $C_{11}H_{16}O$ requires: C, 80·4; H, 9·7%.) Its 2,4-*dinitrophenylhydrazone* crystallized from alcohol as a deep red powder, m.p. 181–183°. (Found: N, 16·04. $C_{17}H_{20}O_4N_4$ requires: N, 16·27%.)

Epimerization of components **6** *and* **7**

Component **6** was refluxed with KOBu^t in t-BuOH (from 0·2 g K and 5 ml t-BuOH) for 3 hr (N_2) and worked up in the usual manner to give a product (20 mg), containing some 20% component **7**, besides **6** (GLC).

Under the above conditions, **7** was recovered unchanged.

REFERENCES

[1] Sukh Dev, *Chem. & Ind.* 1071 (1954).

[2] Sukh Dev, *J. Indian Chem. Soc.* **34**, 169 (1957).

[3] F. D. Popp and W. E. McEwen, *Chem. Rev.* **58**, 321 (1958).

[4] Sukh Dev, *J. Indian Chem. Soc.* **33**, 703 (1956).

[5] Sukh Dev, *J. Indian Chem. Soc.* **33**, 769 (1956).

[6] [a] I. Heilbron, E. R. H. Jones, J. B. Toogood and B. C. L. Weedon, *J. Chem. Soc.* 1827 (1949); [b] N. Jones, H. T. Taylor and E. Rudd, *Ibid.* 1342 (1961).

[7] [a] R. B. Turner and D. M. Voitle, *J. Am. Chem. Soc.* **73**, 1403 (1951); [b] E. A. Braude, E. R. H. Jones, H. P. Coch, R. W. Richardson, F. Sondheimer and J. B. Toogood, *J. Chem. Soc.* 1897 (1949).

[8] For a study of the PMR spectra of 2,4-dinitrophenylhydrazones see: [a] D. Y. Curtis, J. A. Goarse, W. H. Richardson and K. L. Rinehart, *J. Org. Chem.* **24**, 93 (1959); [b] G. J. Karabatsos, J. D. Grahm and F. M. Vane, *J. Am. Chem. Soc.* **84**, 753 (1962); [c] G. J. Karabatsos, F. M. Vane, R. A. Taller and N. Hsi, *Ibid.* **86**, 3351 (1964).

[9] B. E. Gordon, F. Wopat, H. D. Burnham and L. C. Jones, *Analyt. Chem.* **23**, 1754 (1951).

[10] e.g. cf.: H. S. French, *J. Am. Chem. Soc.* **76**, 514 (1952); R. L. Frank, R. Armstrong, J. Kwiatek and H. A. Price, *Ibid.* **70**, 1379 (1948); D. H. R. Barton and P. de Mayo, *J. Chem. Soc.* 142 (1956).

[11] C. Rai and Sukh Dev, *J. Indian Chem. Soc.* **34**, 169 (1957).

[12] Part VIII of this series.

[13] I. N. Nazarov and L. N. Pinkina, *Zh. obshch. Khim.* **20**, 2009 (1950).

[14] e.g. see: E. L. Eliel, *Stereochemistry of Carbon Compounds* pp. 275–278 McGraw-Hill, New York (1962); N. L. Allinger, R. B. Hermann and C. Djerassi, *J. Org. Chem.* **25**, 922 (1960).

[15] G. V. Baddely, T. G. Halsall and E. R. H. Jones, *J. Chem. Soc.* 3891 (1961); T. Norin, *Acta. Chem. Scand.* **15**, 1676 (1961).

[16] F. A. L. Anet and P. M. G. Bavin, *Canad. J. Chem.* **35**, 1084 (1957); **36**, 763 (1958). S. Isoes and M. Nakazaki, *Chem. & Ind.* 1574 (1959).

[17] T. M. Jacob, P. A. Vatakencherry and Sukh Dev, *Tetrahedron* **20**, 2815 (1964).

[18] Sukh Dev, *J. Indian Chem. Soc.* **32**, 262 (1955).

[19] Sukh Dev, *Ibid.* **33**, 769 (1956). The product obtained by this method was GLC pure.

[20] Ref. 2, p. 176.