The Rearrangement of 1-Methyl-1-acetylimide-2-phenylpyrrolidine

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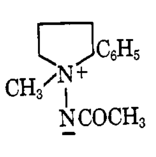
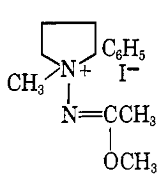
1-Methyl-1-acetylimide-2-phenylpyrrolidine upon pyrolysis formed methyl isocyanate, 1-methyl-2-phenylpyrrolidine, and 1-methyl-2-acetyl-3-phenylhexahydropyridazine. The structure of the last compound was demonstrated by an independent synthesis from 1-methyl-3-phenyl-Δ^2-tetrahydropyridazin-6-one. The formation of methyl isocyanate and 1-methyl-2-phenylpyrrolidine is analogous to the Curtius reaction and also occurs with trimethylaminebenzimide. The phenyl isocyanate expected in the latter was not isolated but was trimerized by the trimethylamine.

The successful rearrangement of 1,1-dimethyl-1-*p*-nitrobenzylamine-2-acetylimide to 1,1-dimethyl-2-*p*-nitrobenzyl-2-acetylhydrazine[2] suggested a study of the rearrangement of a heterocyclic aminimide incorporating a benzyl group in the heterocyclic ring as a possible method for preparing pyridazine derivatives.

In this work the rearrangement of 1-methyl-1-acetylimide-2-phenylpyrrolidine (I) is described. The aminimide was prepared from 2-phenylpyrrolidine[3] by reactions described earlier.[4]



I



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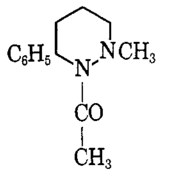
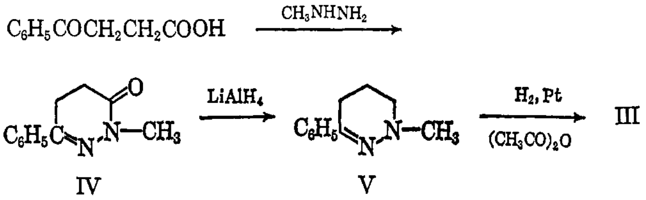


III

The structure of the aminimide I was supported by its infrared spectrum which showed a band at 1550–1600 cm.$^{-1}$ and by the infrared spectrum of the α-methoxyethylidene derivative (II) formed by reaction of the aminimide with methyl iodide.[2] The aminimide (I), when treated with hydriodic acid, gave the methiodide of 1-acetamino-2-phenylpyrrolidine.

Distillation of the aminimide at reduced pressure gave as the major products, 1-methyl-2-phenylpyrrolidine and methyl isocyanate, which were identified by the formation of N,N-dimethyl-2-phenylpyrrolidinium iodide and N-methyl-N′-phenylurea, respectively. The minor product was 1-methyl-2-acetyl-3-phenylhexahydropyridazine (III). This structure was established by an independent synthesis from β-benzoylpropionic acid by the steps indicated.



IV V

The structure of 1-methyl-3-phenyl-Δ^2-tetrahydropyridazin-6-one (IV) was supported by its infrared and n.m.r. spectra. Reduction of this compound (IV) with lithium aluminum hydride gave 1-methyl-3-phenyl-Δ^2-tetrahydropyridazine (V) which showed a weak band at 1583 cm.$^{-1}$ for the carbon–nitrogen double bond in the infrared and the characteristic splitting pattern for the aromatic hydrogens of a benzylidene system in the n.m.r. spectra observed for ketoximes. The reduction of 1-methyl-3-phenyl-Δ^2-tetrahydropyridazine with hydrogen in the presence of platinum and acetic anhydride gave 1-methyl-2-acetyl-3-phenylhexahydropyridazine (III) and other products. Separation of the pure compound III was effected by chromatography on alumina.

The small yield of 1-methyl-2-acetyl-3-phenylhexahydropyridazine (III) obtained from the pyrolysis of 1-methyl-1-acetylimide-2-phenylpyrrolidine when compared to the nearly quantitative yield of rearrangement products formed in the pyrolysis of N-methyl-2-phenylpyrrolidine N-oxide[5] and N-methyl-2-(3-pyridyl)pyrrolidine N-oxide[6] suggests that considerable delocalization of the negative charge occurs in the aminimide I and is responsible for the different results.

The reaction producing methyl isocyanate and 1-methyl-2-phenylpyrrolidine is analogous to the Curtius reaction with the tertiary amine serving as the leaving group. To test the generality of this reaction, trimethylaminebenzimide was prepared by a modification of the method of Hinman[7] and pyrolyzed under similar conditions. Products obtained were trimethylamine, the trimer of phenyl isocyanate and a minor amount of an unknown product. The phenyl isocyanate expected undergoes facile trimerization to 1,3,5-triphenyl-s-triazine-2,4,6(1H,3H,5H)-trione in the presence of tertiary amines.[8]

Experimental[9]

1-Nitroso-2-phenylpyrrolidine.—To a stirred solution of 131 g. of 2-phenylpyrrolidine[3] in 525 ml. of acetic acid, cooled in an ice bath, were added simultaneously from two dropping funnels acetic acid (144 ml.) in 210 ml. of water and 152 g. of 97% sodium nitrite in 315 ml. of water. The time required for the addition was 1.5 hr. and stirring, with cooling, was continued for another 2 hr. A yellow-green oil separated from the aqueous layer when stirring was stopped. The two layers were separated and the aqueous layer was discarded. The oil (164.3 g.) was diluted with ether (400 ml.) and washed with water, sodium bicarbonate solution, and twice more with water. Removal of the ether gave a residue which distilled at 110–116° (0.02 mm.), $n^{21}\text{D}$ 1.5673, yield 118 g.

The infrared spectrum of the nitroso compound had a broad intense band at 1180–1360 cm.$^{-1}$ in carbon tetrachloride.[10]

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[1] Abstracted in part from the Ph.D. Thesis of R. C. Gueldner, Feb. 1964.

[2] S. Wawzonek and E. Yeakey, *J. Am. Chem. Soc.*, **82**, 5718 (1960).

[3] E. B. Knott, *J. Chem. Soc.*, 186 (1948).

[4] S. Wawzonek, J. Chua, E. L. Yeakey, and W. McKillip, *J. Org. Chem.*, **28**, 2376 (1963).

[5] L. D. Quin and G. L. Roof, *ibid.*, **27**, 4451 (1962).

[6] C. H. Rayburn, W. R. Harlan, and H. R. Hamer, *J. Am. Chem. Soc.*, **72**, 1721 (1950).

[7] R. L. Hinman and M. Flores, *J. Org. Chem.*, **24**, 660 (1959).

[8] A. W. Hofmann, *Ber.*, **18**, 765 (1885).

[9] Melting points are corrected and boiling points are not.

[10] R. N. Haszeldine and J. Jander, *J. Chem. Soc.*, 691 (1954).

Maximum absorption in the ultraviolet region occurs at 233 mμ in ethanol (log ε 3.86).

Anal. Calcd. for $C_{10}H_{12}N_2O$: C, 68.16; H, 6.86; N, 15.90. Found: C, 68.20; H, 6.96; N, 15.91.

1-Amino-2-phenylpyrrolidine.—To an ice-cooled solution of 32 g. of lithium aluminum hydride dissolved in dry ether (1100 ml.) by 1 hr. of refluxing, was added 100 g. of 1-nitroso-2-phenylpyrrolidine in 110 ml. of dry ether. Only 5–10 ml. of the solution was added initially. After stirring for 0.5 hr. since no reaction had taken place, the ice bath was removed and the flask was allowed to warm to room temperature; heat was applied until the reaction was initiated. The flask was again cooled in ice and the addition was completed. The resulting mixture was stirred for 6.2 hr. and then refluxed for 1 hr. The flask was again cooled in ice, and the excess hydride and complex were decomposed. The resulting white precipitate was removed by filtration, and the filtrate was dried over potassium carbonate and concentrated. The residue, 82.3 g. (89%), distilled at 73–76° (0.2 mm.) and gave 75.0 g. of a colorless liquid, $n^{28}\mathrm{D}$ 1.5509.

The infrared spectrum showed no nitroso absorption at 1180–1360 cm.$^{-1}$. Titration indicated an equivalent weight of 163 ± 4.

Anal. Calcd. for $C_{10}H_{14}N_2$: C, 74.03; H, 8.70; N, 17.27. Found: C, 74.16; H, 8.92; N, 17.58.

The picrate of this material, recrystallized from ethanol, formed yellow-orange prisms melting at 138.5–139.5°.

Anal. Calcd. for $C_{16}H_{17}N_5O_7$: C, 49.11; H, 4.38; N, 17.90. Found: C, 49.89; H, 4.39; N, 17.63.

The methiodide was prepared in a quantitative yield by treating the hydrazine with excess methyl iodide in anhydrous ether. Recrystallization from acetonitrile yielded small white plates melting at 144–145°.

Anal. Calcd. for $C_{11}H_{17}IN_2$: C, 43.44; H, 5.63; N, 9.21. Found: C, 43.31; H, 5.71; N, 9.15.

1-Acetamino-2-phenylpyrrolidine.—To an ice-cooled, stirred solution of 75.0 g. of 1-amino-2-phenylpyrrolidine in 300 ml. of benzene, acetic anhydride (47.1 g.) in 150 ml. of benzene was added dropwise. The addition required 2 hr. Stirring was continued for 0.5 hr. and the mixture was allowed to stand overnight. The benzene solution was washed with sodium bicarbonate solution and with water and dried over sodium sulfate. The volume of the benzene solution was reduced to 250 ml. by distillation of the benzene, initially at atmospheric pressure (to remove water) and finally at reduced pressure. To the resulting hot benzene solution was added 200 ml. of hot cyclohexane, and the product was allowed to crystallize slowly. The white needles weighed 86.2 g. and melted at 115.5–117°. A small sample when recrystallized from acetonitrile melted at 116–117.5°.

Anal. Calcd. for $C_{12}H_{16}N_2$: C, 70.56; H, 7.90; N, 13.71. Found: C, 70.41; H, 7.61; N, 13.60.

The infrared spectrum of this material (in chloroform) showed carbonyl absorption at 1665 cm.$^{-1}$.

When the product is refluxed in acetic anhydride, the diacetylhydrazine is obtained, m.p. 70.0–71.5°.

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.36; N, 11.38. Found: C, 68.16; H, 7.36; N, 11.31.

Reaction of Methyl Iodide with 1-Acetamino-2-phenylpyrrolidine.—A mixture of 77.0 g. of 1-acetamino-2-phenylpyrrolidine and 100 g. of methyl iodide in 200 ml. of dry ether and 100 ml. of acetonitrile was refluxed for 4 days. Seeding of the reaction mixture after the first day caused a slow crystallization of product as the reaction proceeded. Decantation of the solvent left 87.5 g. of pure white prisms melting at 137–139°. When the reaction mixture was refluxed for an additional 2 days, concentrated and diluted with dry ether, an additional 11.6 g. (m.p. 137–139°) separated and gave a total yield of 76%. The product was very soluble in water.

Titration to a phenolphthalein end point with base gave an equivalent weight of 345 ± 5 for the salt. An infrared spectrum of the product showed carbonyl absorption at 1710 cm.$^{-1}$ in chloroform. The n.m.r. spectrum showed methyl hydrogen peaks at 2.32 and 3.31 p.p.m. and an acidic proton at 10.72 p.p.m. (with respect to tetramethylsilane as an internal standard).

Anal. Calcd. for $C_{13}H_{19}IN_2O$: C, 45.10; H, 5.53; N, 8.09. Found: C, 45.09; H, 5.25; N, 8.17.

1-Methyl-1-acetylimide-2-phenylpyrrolidine (I).—To 75.4 g. of the methiodide in 50 ml. of water was added sodium hydroxide (9.0 g.) in water (10 ml.). The oil which separated from the aqueous layer was extracted with three 50-ml. portions of chloroform. The combined portions were dried over sodium sulfate, filtered, and concentrated to a colorless, viscous oil weighing 42.6 g. (89.5%). The oil could not be crystallized and is soluble in water, benzene, and carbon tetrachloride and insoluble in ether and saturated hydrocarbons.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.29; H, 8.49; N, 13.10.

An infrared spectrum of a thin film of the oil displayed a broad, intense band at 1550–1600 cm.$^{-1}$. The n.m.r. spectrum had resonance peaks for the methyl hydrogens at 1.67 and 2.85 p.p.m.

When treated with anhydrous hydriodic acid in acetonitrile the aminimide I regenerated the methiodide of 1-acetamino-2-phenylpyrrolidine.

1-Methyl-1-α-methoxyethylideneamino-2-phenylpyrrolidinium Iodide (II).—Treatment of the aminimide I with excess methyl iodide for 8 hr. gave a quantitative yield of the α-methoxyethylidene derivative II. Recrystallization from acetonitrile–ethyl acetate–pentane yielded small white needles melting at 122.5–124.5°.

Anal. Calcd. for $C_{14}H_{21}IN_2O$: C, 46.68; H, 5.88; N, 7.78. Found: C, 46.49; H, 5.47; N, 7.62.

The infrared spectrum of this compound shows C=N absorption at 1633 cm.$^{-1}$.

Pyrolysis of 1-Methyl-1-acetylimide-2-phenylpyrrolidine.—Distillation at 180–230°, *in vacuo*, of 49.4 g. of 1-methyl-1-acetylimide-2-phenylpyrrolidine gave methyl isocyanate (5.0 g.), b.p. 40–41°; 1-methyl-2-phenylpyrrolidine (15.8 g.), b.p. 65–67° (1 mm.); and the hexahydropyridazine (III) (8.1 g.), b.p. 135–140° (0.16 mm.). Separation was effected by distillation. The hexahydropyridazine III after two crystallizations from pentane formed white prisms melting at 52.5–53.5°.

The infrared spectrum indicated carbonyl absorption at 1662 cm.$^{-1}$. The n.m.r. spectrum showed methyl hydrogens at 2.10 and 2.19 p.p.m.

Anal. Calcd. for $C_{13}H_{18}N_2O$: C, 71.53; H, 8.31; N, 12.83. Found: C, 71.53; H, 8.06; N, 13.03.

Methyl isocyanate when treated with aniline formed N-methyl-N′-phenylurea, m.p. 150–151.5°, which was identical with an authentic sample.

1-Methyl-2-phenylpyrrolidine was identified by conversion to the methiodide, m.p. 154.5–156° dec., and comparison with an authentic sample.[11]

1-Methyl-3-phenyl-Δ^2-tetrahydropyridazin-6-one (IV).—A mixture of 43.5 g. of β-benzoylpropionic acid and 13 g. of methyl hydrazine in 400 ml. of benzene was stirred for 4 hr. at room temperature and then refluxed on a steam bath for 6 hr. The water formed was collected in a Dean–Stark trap. The benzene solution after washing with water and drying with potassium carbonate gave upon removal of the solvent 46.2 g. of a light brown solid melting at 104–106°. Recrystallization twice from ethyl acetate gave 30 g. of a slightly colored product melting at 106–107.5°.

Anal. Calcd. for $C_{11}H_{12}N_2O$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.21; H, 6.35; N, 14.89.

The infrared spectrum shows a strong band in the carbonyl region at 1667 cm.$^{-1}$, which obscured the C=N absorption. The n.m.r. spectrum shows splitting of the aromatic hydrogen resonance peaks indicating a benzylidene group. The methyl hydrogen resonance peak occurred at 3.41 p.p.m.

1-Methyl-3-phenyl-Δ^2-tetrahydropyridazine (V).—To 8.0 g. of lithium aluminum hydride dissolved in 300 ml. of dry ether by refluxing the mixture for 1 hr. was added, dropwise, 14.6 g. of 1-methyl-3-phenyl-Δ^2-tetrahydropyridazin-6-one (IV) in 100 ml. of warm benzene. The mixture was refluxed for 2 hr., cooled in an ice bath, and the excess hydride and complex were decomposed. The white precipitate was removed by filtration and washed with benzene. The solution was dried over potassium carbonate, filtered, and concentrated. The yield of crude product was 12.5 g. The material boiled at 90–92° (0.55 mm.) and gave 10.5 g. of a pale yellow liquid, $n^{26}\mathrm{D}$ 1.5948.

Anal. Calcd. for $C_{11}H_{14}N_2$: C, 75.82; H, 8.10; N, 16.08. Found: C, 75.93; H, 8.11; N, 15.81.

The infrared absorption band for C=N occurred at 1583 cm.$^{-1}$. The n.m.r. spectrum showed splitting of the aromatic hydrogen resonance peaks and methyl hydrogen at 2.88 p.p.m.

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(11) G. C. Jones and C. R. Hauser, *J. Org. Chem.*, **27**, 3572 (1962).

1-Methyl-2-acetyl-3-phenylhexahydropyridazine (III).—Three grams of 1-methyl-3-phenyl-Δ^2-tetrahydropyridazine (V) in acetic acid (4 ml.) and acetic anhydride (20 ml.) was reduced at a hydrogen pressure of 66 p.s.i. in the presence of 400 mg. of platinum oxide. The resulting acetic anhydride solution was refluxed for 3 min. and the excess acetic anhydride was removed *in vacuo*. The residue was neutralized with sodium bicarbonate solution and was extracted with ether. The ether solution was dried over potassium carbonate and the ether was removed. The infrared spectrum of the material showed N–H absorption bands. The residue (1.71 g.) when chromatographed on a alumina using hexane–benzene and benzene–ethyl acetate as eluents gave two fractions which gave 1-methyl-2-acetyl-3-phenylhexahydropyridazine (III) (0.48 g.). Two recrystallizations from pentane gave white prisms melting at 52.5–53.5°, identical in all respects with the product obtained from the pyrolysis of the aminimide.

1,1,1-Trimethyl-2-benzoylhydrazonium *p*-Toluenesulfonate.—A mixture of 1,1-dimethyl-2-benzoylhydrazine (114 g.) and methyl *p*-toluenesulfonate (130 g.) in benzene (1100 ml.) was refluxed for 23 hr. The resulting solid (225 g.) melted at 179–180.5°. Recrystallization from chloroform–ethyl acetate raised the melting point to 179.5–181°.

Anal. Calcd. for $C_{17}H_{22}N_2O_4S$: C, 58.27; H, 6.33; N, 7.99. Found: C, 58.18; H, 6.25; N, 7.79.

Trimethylaminebenzimide.—1,1,1-Trimethyl-2-benzoylhydrazonium methyl-*p*-toluenesulfonate (247 g.) in water (2000 ml.) was treated with 28.2 g. of sodium hydroxide. The resulting solution was extracted with eight 250-ml. portions of chloroform. Removal of the chloroform gave a solid which was recrystallized from chloroform–hexane: m.p. 165.5–167° (lit.[7] m.p. 168–169°); yield, 81g.

Pyrolysis of Trimethylaminebenzimide.[12]—Trimethylaminebenzimide (109 g.) upon heating at 220–230° underwent a vigorous decomposition and gave a gaseous product and a liquid which solidified in the reservoir. The solid (44.2 g.) melted at 289–290° after recrystallization from toluene and did not lower the melting point of 1,3,5-triphenyl-s-triazine-2,4,6(1H,3H,5H)-trione.

The gaseous product (19.1 g.) collected at −78° was converted to a hydrochloride and then to a picrate which melted at 223.5–225° and was identical with trimethylamine picrate.

The tarry residue (21.4 g.) remaining from the distillation gave in addition to the phenyl isocyanate trimer 10 g. of a solid which was insoluble in toluene and melted at 270–281°. The infrared spectrum was complex and showed no carbonyl absorption. Elemental analysis pointed to the presence of only carbon, hydrogen, and nitrogen.

Acknowledgment.—Support of this research by the National Science Foundation is gratefully acknowledged.

[12] Since the submission of the manuscript, similar results for the pyrolysis of trimethylaminebenzimide have been reported: M. S. Gibson and A. W. Murray, *J. Chem. Soc.*, 880 (1965).

2-Aryl-3-acetyl-4(1H)-quinolones[1]

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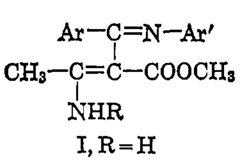
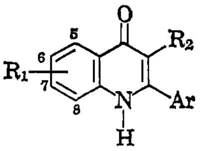
Several compounds claimed to be 2-aryl-3-acetyl-4(1H)-quinolones (III) in the literature have been reformulated as the isomeric VI. The conversion of 2-phenyl-3-acetyl-4-chloroquinoline to 6-phenyl-7-methyldibenzo[*b,h*][1,6]naphthyridine (X) and to 2,4-diphenyl-3-methyl-2H-pyrazolo[4,3-*c*]quinoline (XI) is described. β-Methylamino-α-(N-arylimidoyl)crotonic esters (II, R = CH_3) were thermally cyclized to 2-aryl-3-N-methylacetimidoyl-4(1H)-quinolones (V, R = CH_3).

Cyclization of β-amino-α-(N-arylimidoyl)crotonates (I) in polyphosphoric acid (PPA)[3] gave the 2-aryl-3-acetyl-4(1H)-quinolones (III) listed in Table I. Also shown in Table I are the melting points of the products alleged by Shah[4,5] and by Usgaonkar[6] to be the title compounds but which are, as shown originally by Singh and Nair,[7] the isomeric 2-methyl-3-aroyl-4-(1H)-quinolones (VI).

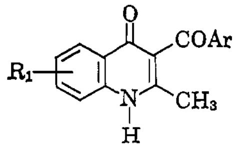


$$\begin{array}{l} \mathrm{Ar{-}\underset{|}{C}{=}N{-}Ar'} \\ \mathrm{CH_3{-}C{=}C{-}COOCH_3} \\ \quad\ \ \mathrm{\overset{|}{N}HR} \end{array}$$

I, R = H
II, R = alkyl



III, R_2 = $COCH_3$
IV, R_2 = H
V, R_2 = C(=NR)CH_3



VI

The structure of 2-*p*-anisyl-3-acetyl-4(1H)-quinolone (III, R_1 = H; Ar = *p*-$CH_3OC_6H_4$) was established unequivocally by oxidation with selenium dioxide and hydrogen peroxide[7] which converted it to a carboxylic acid identical with 2-*p*-anisyl-3-carboxy-4(1H)-quinolone prepared by the Just reaction[8] from N-phenyl-*p*-anisimidoyl chloride and diethyl sodiomalonate. Both acid samples on thermal decarboxylation gave 2-*p*-anisyl-4(1H)-quinolone (IV, R_1 = H; Ar = *p*-$CH_3OC_6H_4$) obtained also by cyclization of crotonate I (Ar = *p*-$CH_3OC_6H_4$; Ar′ = C_6H_5) in liquid paraffin.[9] In concentrated hydrochloric acid 2-*p*-anisyl-3-acetyl-4(1H)-quinolone underwent deacetylation[7] and demethylation to 2-*p*-hydroxyphenyl-4(1H)-quinolone (IV, R_1 = H; Ar = *p*-HOC_6H_4).

The infrared spectra of the 2-aryl-3-acetyl-4(1H)-quinolones (III) showed the carbonyl band at 5.9–6.0 μ[3] (Table I); in 2-methyl-3-benzoyl-4(1H)-quinolone and 2-methyl-3-*p*-anisoyl-4(1H)-quinolone this was at 6.05 and 6.08 μ, respectively. The frequency of CO absorption in the 2-methyl-3-aroyl-4-chloroquinolines IX (6–6.06 μ) was likewise slightly less than in the isomeric 2-aryl-3-acetyl-4-chloroquinolines VII

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[1] The title compounds are named and formulated in terms of the tautomeric form predominating as evidenced by infrared measurements: *cf.* A. R. Katritzky and J. M. Lagowski, *Advan. Heterocyclic Chem.*, **1**, 341 (1963).

[2] To whom inquiries should be addressed.

[3] B. Staskun, *J. Org. Chem.*, **26**, 2791 (1961).

[4] S. A. Kulkarni and R. C. Shah, *J. Indian Chem. Soc.*, **27**, 111 (1950).

[5] T. B. Desai and R. C. Shah, *ibid.*, **26**, 121 (1949).

[6] U. R. Usgaonkar and G. V. Jadhav, *ibid.*, **40**, 75 (1963).

[7] G. Singh and G. V. Nair, *J. Am. Chem. Soc.*, **78**, 6105 (1956).

[8] F. Just, *Ber.*, **19**, 984 (1886).

[9] B. Staskun, *J. S. African Chem. Inst.*, **9**, 89 (1956).