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Reaction of Enamino Ketone Bidentate System in N-Substituted 1,2,3,3a,4,5-Hexahydro-6*H*-indol-6-ones toward Some Nucleophilic Species

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The reaction of the N-phenylacetyl and N-phenylpropionyl derivatives of 1,2,3,3a,-4,5-hexahydro-6*H*-indol-6-one (**3** and **10**) toward nucleophilic species are described. Several examples demonstrating intermolecular and intramolecular reactions occurring on the two electrophilic sites of the enamino ketone function and potential utility of these reactions on the synthesis of heterocyclic compounds are presented. A possible mechanism to rationalize these products is also presented.

Keywords——electrophilic reaction of enamino ketone system; N-substituted 1,2,-3,3a,4,5-hexahydro-6*H*-indol-6-ones; iminoenol ether; phosphorus oxychloride; erythrinane-type compound; benzoxazepine

The area of reactivity and versatility of the enamino ketone $\overset{c\ e\ b\ d\ a}{(\rangle N\text{–}C{=}C\text{–}C{=}O)}$ possessing three nucleophilic sites (a, b, and c) and two electrophilic sites (d and e) is of current interest particularly in heterocyclic chemistry, which shows diverse and sometimes complicated reactivity. In contrast to many and increasing examples[2] of the nucleophilic reactions of the enamino ketone group, there are a limited number of reports[2] regarding the electrophilic reactions. In continuation of our work on the synthetic application and reactivity of enamino ketones, we have now studied the behavior of the N-phenylacetyl and N-phenylpropionyl derivatives of 1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (**3** and **10**) toward some nucleophilic species. We describe here some reactions involving nucleophilic attack by phosphorus pentachloride or phosphorus oxychloride on the enamino ketone bidentate system.

The N-phenylacetyl enamino ketone (**3**), conveniently synthesized from 6-methoxyindoline (**1**) in two steps by our general procedure[3] (Chart 1), was treated with phosphorus pentachloride in acetonitrile (or chloroform) at room temperature for 1 hr to give the indoline derivative (**4**) in 72% yield. The formation of **4** can be rationalized in terms of a nucleophilic attack of a chloride ion on the enolized carbon followed by *in situ* oxidative aromatization.

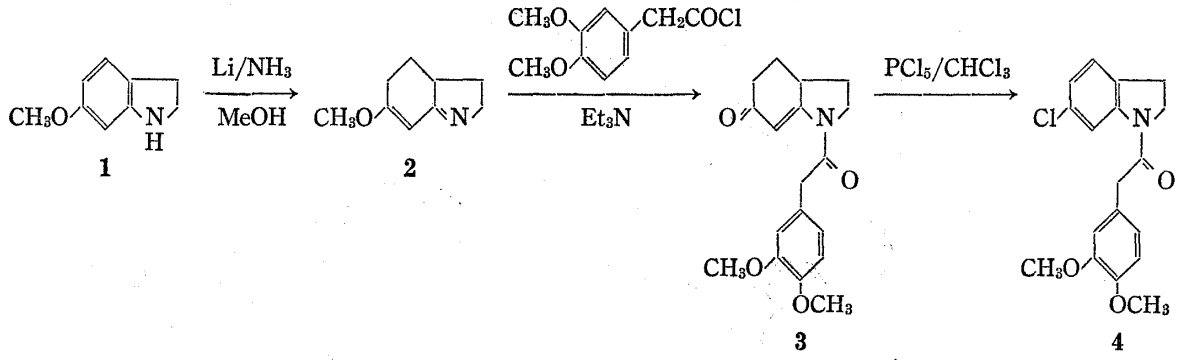

Chart 1

1) Location: *1432-1, Horinouchi, Hachioji-shi, Tokyo, 192-03, Japan.*
2) For reviews see *a*) T. Nishino, C. Kajima, and Y. Omote, *Yuki Gosei Kagaku Kyokai Shi*, 34, 526 (1976); *b*) J.V. Greenhill, *Chem. Soc. Rev.*, **6**, 277 (1977).
3) *a*) H. Iida, S. Aoyagi, and C. Kibayashi, *J. Chem. Soc. Perkin I*, **1975**; 2502; *b*) *Idem, ibid.*, **1977**, 120.

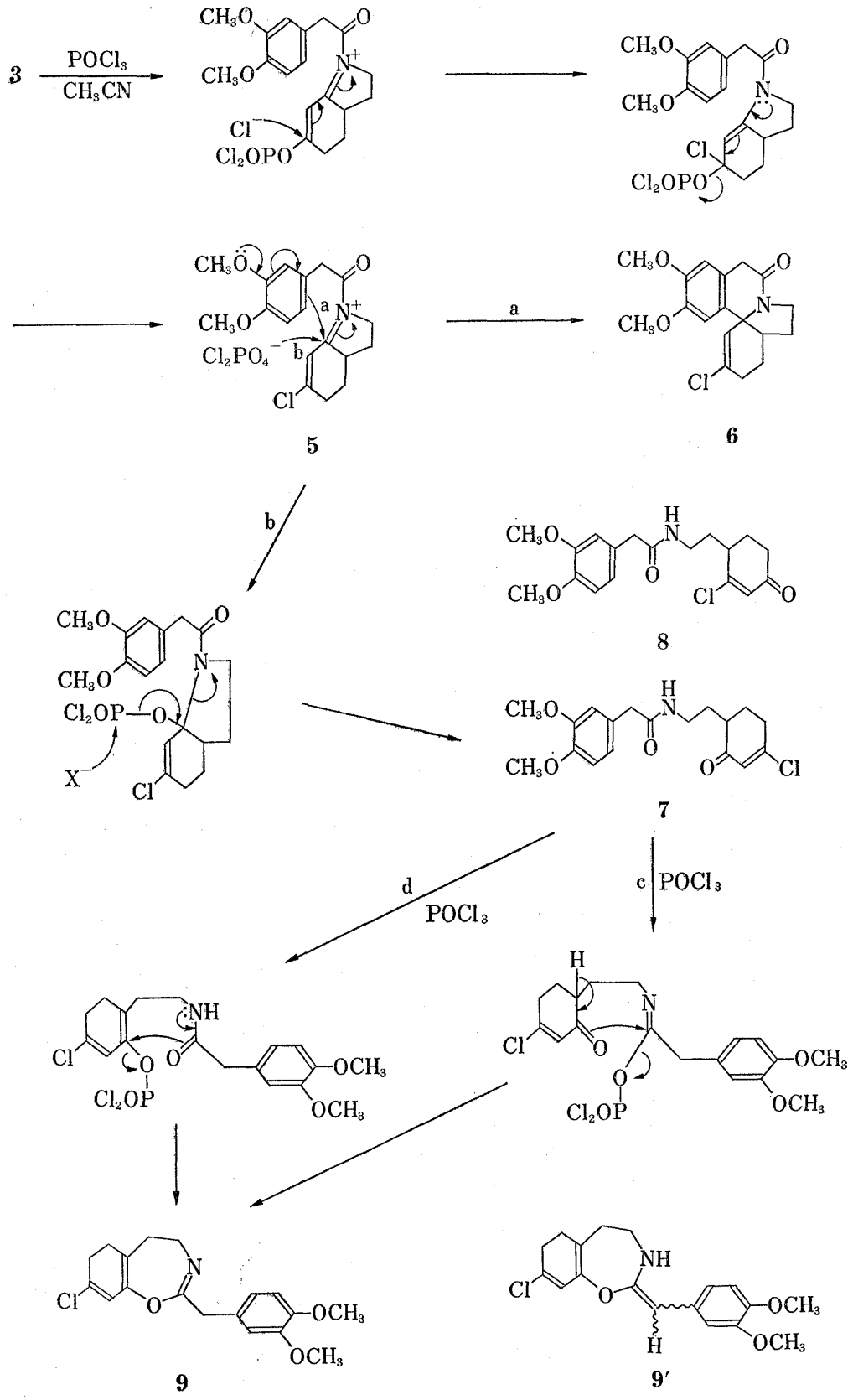

Chart 2

When **3** was heated with phosphorus oxychloride in dry chloroform under reflux for 30 min the ring-opened product (**7**) was obtained in 61% yield. We previously proposed structure (**8**) for this product, whose nuclear magnetic resonance (NMR) spectrum showed a two-proton multiplet at δ 2.68 assigned to the methylene group adjacent to the carbonyl function in the cyclohexenone ring.[4] However one might suspect that this assignment is not fully acceptable since this chemical shift occurred at slightly lower field for assigned methylene group; this signal should be alloted for the methylene group adjacent to the chlorovinyl function rather than the carbonyl function based on the recent article.[5] On the basis of this consideration the former structure (**8**) should be revised as **7**.

When the above reaction using phosphorus oxychloride was carried out in dry acetonitrile, instead of chloroform, three products were isolated and assigned their structures to the erythrinane type spiro compound (**6**), the ring-opened product (**7**), and the oxazepine (**9**). NMR analysis showed that the last product exists in solution as a mixture of imine-enamine tautomers (**9** and **9'**) in a ratio of 45: 55. As shown in Chart 2, the formation of **6** and **7** presumably arises from the common iminium intermediate (**5**) which would generate through initial nucleophilic chlorination of **3** proceeding *via* a similar process to that in the formation of **4**. Subsequent intramolecular nucleophilic attack by the aromatic carbon on the iminium function may give **6** (path a). Alternatively, nucleophilic attack by a dichlorophosphate anion may lead to **7** (path b). As for the mechanism of the formation of **9**, either pathway c or d *via* the ring-opened product (**7**) would be conceivable (Chart 2). The intermediacy of **7** in this mechanism was supported by the result that treatment of **7** with phosphorus oxychloride in dry acetonitrile gave **9**.

Our next experiment was conducted on examining the action of phosphorus oxychloride on the N-phenylpropionyl enamino ketone (**10**), which was readily prepared by the reaction of the iminoenol ether (**2**) with 2-(3,4-methylenedioxyphenyl)propionyl chloride in a similar manner to that described for **3**. Upon heating **10** with phosphorus oxychloride in dry acetonitrile for 30 min, a similar result as in **3**, except the formation of the spiro compound, was obtained: The 6-chloroindoline derivative (**11**), the ring-opened product (**12**), and 5,6-methylenedioxy-1-indanone (**13**) were obtained.

In conclusion, it was proved that on treatment with phosphorus oxychloride the enamino ketone system was subject to nucleophilic attack on the site d and e (in the general formula previously cited) providing a new and potential synthetic route to heterocyclic compounds.

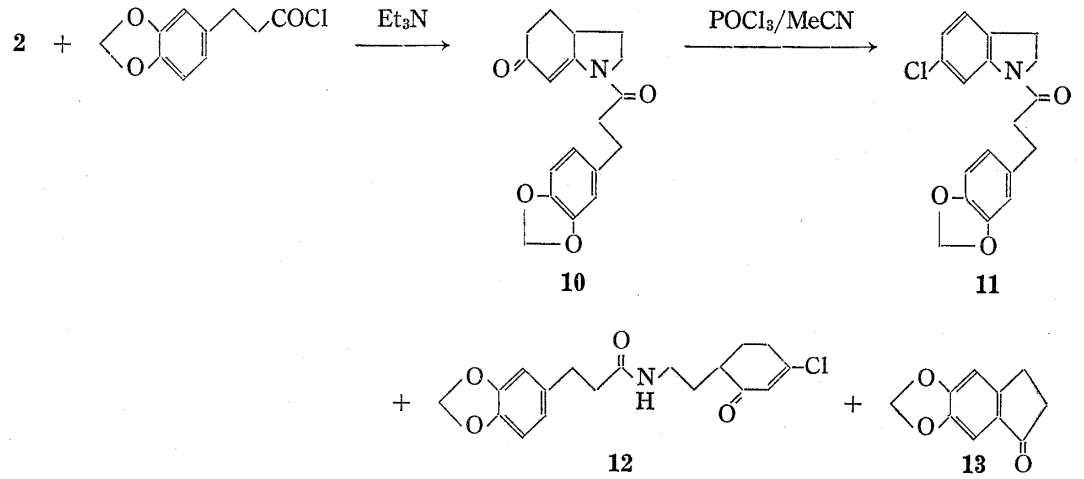

Chart 3

4) H. Iida, S. Aoyagi, K. Kohno, N. Sasaki, and C. Kibayashi, *Heterocycles*, **4**, 1771 (1976).
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Experimental[6]

Reaction of 1-(3,4-Dimethoxyphenyl)acetyl-1,2,3,3a,4,5-hexahydro-6*H*-indol-6-one (3) with Phosphorus Pentachloride——A solution of 3[3b] (105 mg) and PCl_5 (200 mg) in dry acetonitrile (5 ml) was stirred at room temperature for 1 hr. The solution was basified with 10% aqueous ammonia and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried ($MgSO_4$), and the solvent was removed by evaporation. Purification by column chromatography of the residue on silica gel using benzene as eluent then recrystallization from benzene gave 6-chloro-1-(3,4-dimethoxyphenyl)acetyl-2,3-dihydroindole (**4**, 80 mg, 72%) as white plates. mp 136—137°. *Anal.* Calcd. for $C_{18}H_{18}ClNO_3$: C, 65.16; H, 5.47; N, 4.22. Found: C, 65.52; H, 5.44; N, 4.19. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1665 (C=O). NMR δ: 3.07 (1H, t, J=8 Hz, 3-H), 3.68 (2H, s, $COCH_2$), 3.82 (6H, s, 2 OCH_3), 4.65 (2H, t, J=8 Hz, 2-H), 6.74 (3H, s, Ar H), 6.86 (1H, dd, J=8 and 2 Hz, 5-H), 6.97 (1H, d, J=8 Hz, 4-H), 8.20 (1H, d, J=2 Hz, 7-H). MS *m/e*: 333 (10%, M^++2), 331 (29, M^+), 178 (53), 151 (100).

When the reaction of **3** with PCl_5 was carried out in dry $CHCl_3$ a similar result as described above was obtained.

Reaction of 3 with Phosphorus Oxychloride in Chloroform——A solution of **3** (600 mg) and $POCl_3$ (500 mg) in dry $CHCl_3$ (50 ml) was gently heated at reflux temperature for 1 hr. The cooled solution was basified with 10% aqueous ammonia and extracted with $CHCl_3$. The $CHCl_3$ extract was washed with water, dried ($MgSO_4$), and the solvent was removed. The residue was purified by column chromatography on silica gel using $CHCl_3$ as eluent to give 3-chloro-6-[2-(3,4-dimethoxyphenylacetamino)ethyl]cyclohex-2-en-1-one (**7**, 410 mg, 61%) as a colorless oil. *Anal.* Calcd. for $C_{18}H_{22}ClNO_4$: C, 61.45; H, 6.30; N, 3.98. Found: C, 61.35; H, 6.43; N, 3.94. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3410 (NH), 1680 sh and 1600 (C=O), 1610 (C=C). NMR δ: 2.68 (2H, m, C(Cl)=C–CH_2), 3.26 (2H, q, J=2 Hz, NCH_2), 3.44 (2H, s, CH_2Ph), 3.84 (6H, s, 2 OCH_3), 5.82 (1H, br s, NH), 6.08 (1H, d, J=1 Hz, vinyl H). MS *m/e*: 353 (10%, M^++2), 351 (30, M^+), 221 (19), 178 (39), 151 (100).

Reaction of 3 with Phosphorus Oxychloride in Acetonitrile——A solution of **3** (3.9 g) and $POCl_3$ (3.0 g) in dry acetonitrile (200 ml) was gently heated at reflux temperature for 30 min. The solvent was removed by evaporation under reduced pressure. After addition of 10% aqueous ammonia (100 ml) to the residue, the resultant oily product was extracted with $CHCl_3$. The $CHCl_3$ solution was washed with water, dried ($MgSO_4$), and evaporated. The residual gum was separated by repeated preparative thin layer chromatography using benzene–MeOH (80: 10) as developer into three major components.

The fastest moving one was recrystallized from ethyl acetate to give 3-chloro-3,4-dehydro-15,16-dimethoxyerythrinane (**6**, 160 mg, 4%) as white needles. mp 220—222° (sublimed at 199°). MS *m/e*: 335 (17%, M^++2), 333.1121 (46, M^+; Calcd. for $C_{18}H_{20}ClNO_3$: 333.1131), 298 (100). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1658sh, 1632. NMR δ: 3.53 (2H, m, 8-H), 3.43 and 3.67 (2H, AB q, J=19 Hz, 11-H), 3.83 (6H, s, 2 OCH_3), 5.63 (1H, s, 4-H), 6.57 (1H, s, 17-H), 6.81 (1H, s, 14-H).

The second component included **7** (670 mg, 15%) which was identical with the authentic sample obtained in the above experiment. The slowest component was recrystallized from benzene–hexane to give 8-chloro-2-(3,4-dimethoxybenzyl)-4,5,6,7-tetrahydro-1,3-benzoxazepine (**9**, 500 mg, 12%) as white prisms. mp 173—174°. *Anal.* Calcd. for $C_{18}H_{20}ClNO_3$: C, 64.77; H, 6.04; N, 4.20. Found: C, 65.14; H, 5.99; N, 3.88. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: no carbonyl absorptions, 1630 (C=N and C=C). MS *m/e*: 335 (20%, M^++2), 333 (61, M^+), 242 (39), 155 (69), 151 (100). NMR δ: 1.5—3.1 (6H, m, aliphatic H), 3.50 (2H, s, CH_2Ph), 3.84 (6H, s, 2 OCH_3), 6.37 (1H, s, vinyl H), 6.71—6.74 (3H, m, Ar H). These NMR signals due to the imine structure **19** were integrated to 45% of the indicated values while a set of signals integrated to 55% which is consistent with the enamine structure **9′** was observed as bellow: NMR δ: 1.5—3.1 (6H, m, aliphatic H), 3.90 (6H, s, 2 OCH_3), 5.32 (1H, s, N–C=CH), 6.45 (1H, s, vinyl H), 6.83 (1H, d, J=9 Hz, 5′-H), 7.12 (1H, dd, J=9 and 2 Hz, 6′-H), 7.19 (1H, d, J=2 Hz, 2′-H).

Reaction of 3-Chloro-6-[2-(3,4-dimethoxyphenylacetamido)ethyl]cyclohex-2-en-1-one (7) with Phosphorus Oxychloride——A solution of **7** (150 mg) and $POCl_3$ (100 mg) in dry acetonitrile (70 ml) was gently heated at reflux temperature for 20 min. Working-up the reaction mixture in a manner similar to that described for the reaction of **3** with $POCl_3$ in acetonitrile gave **9** (30 mg) which was identical with the above authentic sample.

1,2,3,3a,4,5-Hexahydro-1-[2-(3,4-methylenedioxyphenyl)propionyl]-6*H*-indol-6-one (10)——A solution of 2-(3,4-dimethoxyphenyl)propionyl chloride (1.5 g, 7 mmol) in dry benzene (20 ml) was added dropwise to an ice-cold solution of **2** (1.0 g, 7 mmol) and triethylamine (1.0 g) in dry benzene (20 ml) over a 30-min period. After addition had been completed the reaction mixture was stirred for a further 10 min. The solution was washed with water, dried ($MgSO_4$), and the solvent was removed by evaporation. The residual

6) Melting points were determined with Yanagimoto micro apparatus and are uncorrected. Mass spectra were determined using a Hitachi RMU-7L double-focusing spectrometer at 70 eV. Infrared (IR) spectra were recorded on a Hitachi 215 grating spectrophotometer. ^1H NMR spectra were taken as $CDCl_3$ solution on Varian T-60 and JOEL JMN-PS-100 spectrometers using $(CH_3)_4Si$ as an internal standard.

solid was recrystallized from benzene–hexane to give white plates (1.5 g, 72%). mp 155—156°. *Anal.* Calcd. for $C_{18}H_{19}NO_4$: C, 68.99; H, 6.11; N, 4.47. Found: C, 68.88; H, 6.16; N, 4.50. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1690 (amide C=O), 1640 (conj C=O), 1600 (conj C=C). NMR δ: 5.91 (2H, s, OCH_2O), 6.62—6.77 (4H, m, vinyl H and Ar H).

Reaction of 10 with Phosphorus Oxychloride in Acetonitrile——To a stirred solution of **10** (1.5 g) in dry acetonitrile (70 ml) was added $POCl_3$ (3.0 ml) and the mixture was heated under gentle reflux for 35 min. The solution was evaporated to dryness under reduced pressure, leaving a residue which was mixed with 5% aqueous K_2CO_3 (30 ml) and extracted with benzene. The benzene layer was washed with water then 5% HCl and dried ($MgSO_4$). Evaporation of the solvent gave a brown, oily substance which was chromatographed on silica gel. Elution with benzene gave 6-chloro-1-[2-(3,4-methylenedioxyphenyl)propionyl]-2,3-dihydroindole (**11**, 700 mg, 44%) as white needles. mp 129—130°. *Anal.* Calcd. for $C_{18}H_{16}ClNO_3$: C, 65.56; H, 4.89; N, 4.25. Found: C, 65.53; H, 4.79; N, 4.31. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1660 (C=O). NMR δ: 4.05 (2H, t, J=8.5 Hz, NCH_2), 5.93 (2H, s, OCH_2O), 6.73 (3H, s, Ar H), 7.02 (2H, s, 4-H and 5-H), 8.28 (1H, br s, 7-H). MS *m/e*: 331 (11%, M^++2), 329 (30, M^+), 155 (57), 153 (90), 135 (100).

Further elution with benzene gave 5,6-methylenedioxy-1-indanone (**13**, 85 mg, 19%) as white crystals. mp 163—165° (lit.[7] mp 164—165°). IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 1684 (C=O).

Finally eluting with benzene–$CHCl_3$ (50:50) gave 3-chloro-6-[2-[2-(3,4-methylenedioxyphenyl)propionamido]ethyl]cyclohex-2-en-1-one (**12**, 30 mg) as a thick oil. IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440—3340 (NH), 1685 sh, (ketone C=O), 1660 (amide C=O), 1612 (C=C). NMR 1.27—2.27 (9H, m, aliphatic H), 2.42 (2H, t, $COCH_2$), 2.27 (2H, m, C=C(Cl)–CH_2), 2.87 (2H, t, CH_2Ph), 3.28 (2H, m, NCH_2), 5.90 (2H, s, OCH_2O), 5.91 (1H, br s, NH), 6.67 (3H, s, Ar H). MS *m/e*: 351 (36%, M^++2), 349 (100, M^+), 219 (91), 177 (79).

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Synthesis of 3-*tert*-Butylpyridine[1]

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3-*tert*-Butylpyridine (**11**) has been synthesized from neopentyl alcohol in 16% overall yield through a five-step sequence. Among the steps involved are the cycloaddition of α-*tert*-butylacrolein (**9**) to butyl vinyl ether and conversion of the resulting dihydropyran derivative (**10**) into the pyridine base (**11**).

Keywords——3-substituted pyridine; α,β-unsaturated aldehyde; vinyl ether; dihydropyran; bromination; Grignard reaction; Mannich reaction; Diels–Alder reaction

Our recent papers on the mercuric acetate–(ethylenedinitrilo)tetraacetic acid oxidation of 1,3-disubstituted piperidines[3,4] and on the ferricyanide oxidation of 3-substituted 1-ar-

1) Presented in part at the 45th Meeting of Hokuriku Branch, Pharmaceutical Society of Japan, Kanazawa, November 26, 1977.

2) Location: *13-1 Takara-machi, Kanazawa 920, Japan.*

3) T. Fujii, S. Yoshifuji, K. Michishita, M. Mitsukuchi, and K. Yoshida, *Chem. Pharm. Bull.* (Tokyo), **21**, 2695 (1973).

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