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Reaction of Tryptamine and Aniline with δ-Valerolactone and Its Dehydro Derivatives. A New Synthesis of 1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-*a*]quinolizine

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The reaction of tryptamine with δ-valerolactone in tetralin gave δ-hydroxyamide (**3**) as the main product and the lactam (**4**) as the minor product. However, the reaction of 5,6-dihydro-2-pyrone with tryptamine or aniline afforded a mixture of the corresponding αβ- and βγ-unsaturated lactams, whereas, 2-pyrone did not react with either tryptamine or aniline to give the corresponding pyridone. Cyclization of **3** or **4** by Bischler-Napieralski reaction and followed $NaBH_4$ reduction provided a convenient synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine (**23**).

In contrast to the extensive studies on the mechanism of γ-butyrolactones with various amines,[2] there appears to be relatively little known about the reaction mechanism of 6-membered lactones with amines.[3] In recent letter, we reported a method for the preparation of 5,6-dihydro-2-pyrone and 2-pyrone.[4] In present work, the reactions of δ-valerolactone (**2**), 5,6-dihydro-2-pyrone (**9**), and 2-pyrone with tryptamine and aniline were investigated and we developed a new and convenient synthesis of 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]-quinolizine (**23**) by cyclization of the lactam (**4**) or the hydroxyamide (**3**).

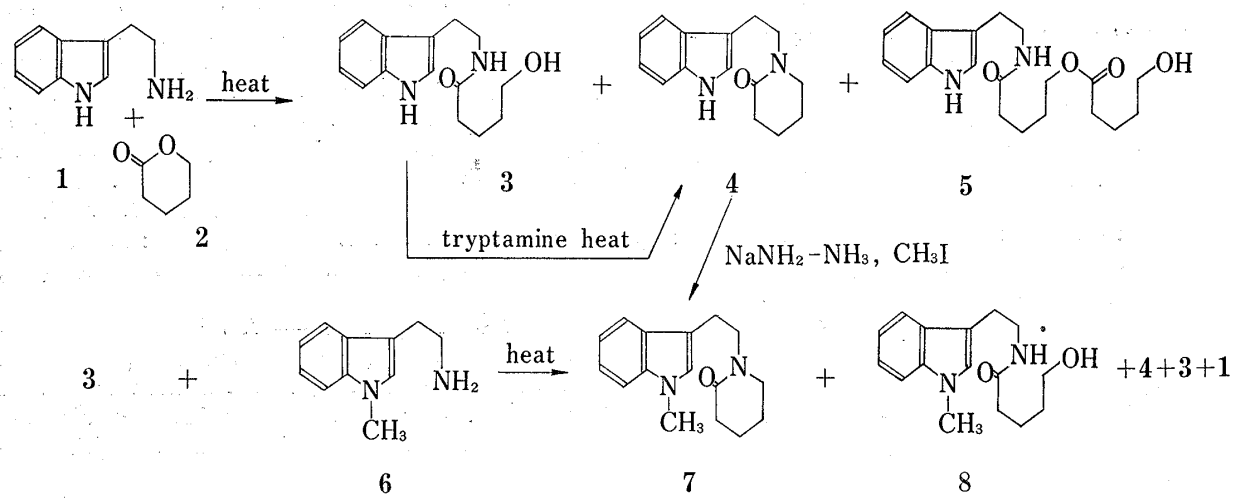

Chart 1

1) Location: *a*) *Yayoi-cho, Chiba-shi, 280, Japan*; *b*): *Sapporo, Hokkaido, 060, Japan.*
2) *a*) Y. Knobler, E. Bonni, and T. Sheradsky, *J. Org. Chem.*, **29**, 1229 (1964); *b*) J.B. Johnes and J.M. Young, *Canad. J. Chem.*, **44**, 1059 (1966).
3) A.L.J. Beckwith, "The Chemistry of Amides," edited by J. Zabicky (Series Editor S. Patai), Interscience Publishers, Inc., New York, 1970, p. 102.
4) M. Nakagawa, M. Tonozuka, M. Obi, M. Kiuchi, T. Hino, and Y. Ban, *Synthesis*, **1974**, 510.

When tryptamine (**1**) and δ-valerolactone (**2**), which is now commercially available, were mixed in equivalent amounts in tetralin and refluxed in presence or absence of anhyd. $MgSO_4$, reaction occurred during 3.5—6 hr to give the hydroxyamide (**3**), the lactam (**4**), and the ester (**5**) in 70%, 4%, and 9.6% yields, respectively. The structures of **3** and **4** were confirmed by their spectral data and correct elemental analysis. In addition, the amide ester (**5**) was characterized by alkaline hydrolysis to **3** and by an alternative synthesis from **3** and **2**. In accord with the observation[3] that the reaction of γ- and δ-lactones with aliphatic amines under mild conditions affords γ- and δ-hydroxyamides, on treating **1** with **2** in boiling EtOH for 12—17 hr, exclussive acyl-O-fission of **2** by **1** occurred, yielding **3**. Similar reactions have been observed in the reaction of N_a-methyltryptamine with isochroman-3-one and its derivatives performed in EtOH.[5] Attempts to convert **3** by heating in tetralin in presence or absence of anhyd. $MgSO_4$, failed to yield the lactam (**4**) and the starting material (**3**) was recovered. Refluxing **3** in tetralin with a small amounts of conc. H_2SO_4 or acetic anhydride showed only a trace of **4** on thin-layer chromatography (TLC) and the reaction mixture became intractable tar. However, heating **2** in tetralin at reflux temperature with 2 moles of **1** gave rise to the increased yield of **4** (23%) besides the main product **3** (76%) and no amide ester (**5**) was detected, suggesting that **4** was not formed by the dehydration of the hydroxyamide (**3**) achieved at highly elevated temperature. However, δ-lactamization of δ-hydroxy-N-alkylamide (**3**) involves reversible δ-lactone formation before irreversible O-alkyl fission as observed in the case of γ-lactamization of γ-hydroxy-N-alkylamide.[2]

In order to demonstrate the existence of this unfavored side of δ-hydroxy-N-alkylamide-δ-valerolactone equilibrium, **3** was refluxed in tetralin with **1** for 7 hr under N_2 and a 41% yield of **4** was obtained. Further indication in favour of this assumption was given by the observation that when N_a-methyltryptamine (**6**) (2 moles) was treated with **3** (1 mole) instead of **1** under similar reaction conditions, **7** was isolated in 19% yield together with **8** (43%), **3** (17%), **4** (6%), and a mixture of **1** and **6**. The drastic conditions in the presence of the aliphatic amine was required to force the thermal shift of the equilibrium back to the δ-lactone. These results provide a good evidence for the lactamization of the δ-hydroxy-N-alkylamide in our reaction conditions. Thus, the formation of the δ-lactam (**7**) proceeds via lactonization of **3** and subsequent O-alkyl fission of **2** by the amine (**6**) to the δ-amino-valeric acid which spontaneously cyclized to give **7** in the reaction condition as depicted in the Chart 2.

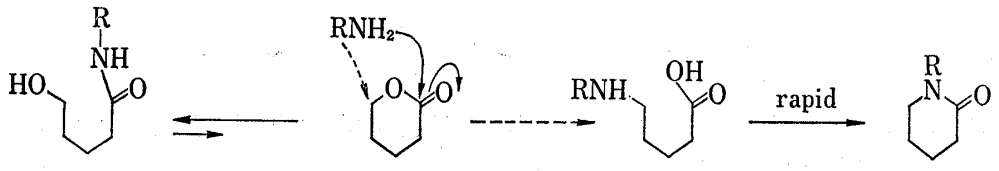

Chart 2

The structure of **7** was identified by correct analysis and by comparison of its spectral data with those of the specimen prepared by methylation of **4** in liquid NH_3 with CH_3I and the structure of **8** was deduced from its spectral data. Additional support for this type of reaction has been obtained by isolation of δ-valerolactone and ammonia on heating δ-hydroxyvaleramide.[6]

On the other hand, the reaction of **1** with 5,6-dihydro-2-pyrone (**9**) proceeded to give a mixture of the unsaturated lactams (**10**) and (**11**) when refluxed in tetralin for 8 hr and the

5) W. Meise and F. Zymalkowski, *Angew. Chem. Internat. Edit.*, **8**, 445 (1969); *idem*, *Tetrahedron Letters*, **1969**, 1475.
6) R.A. Strojny, H.C. White, and E.J. Strojny, *J. Org. Chem.*, **27**, 1241 (1962).

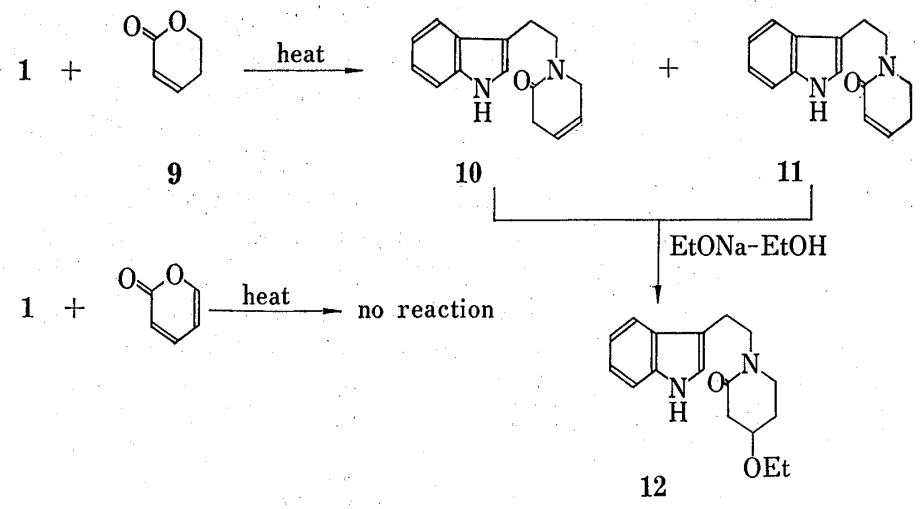

Chart 3

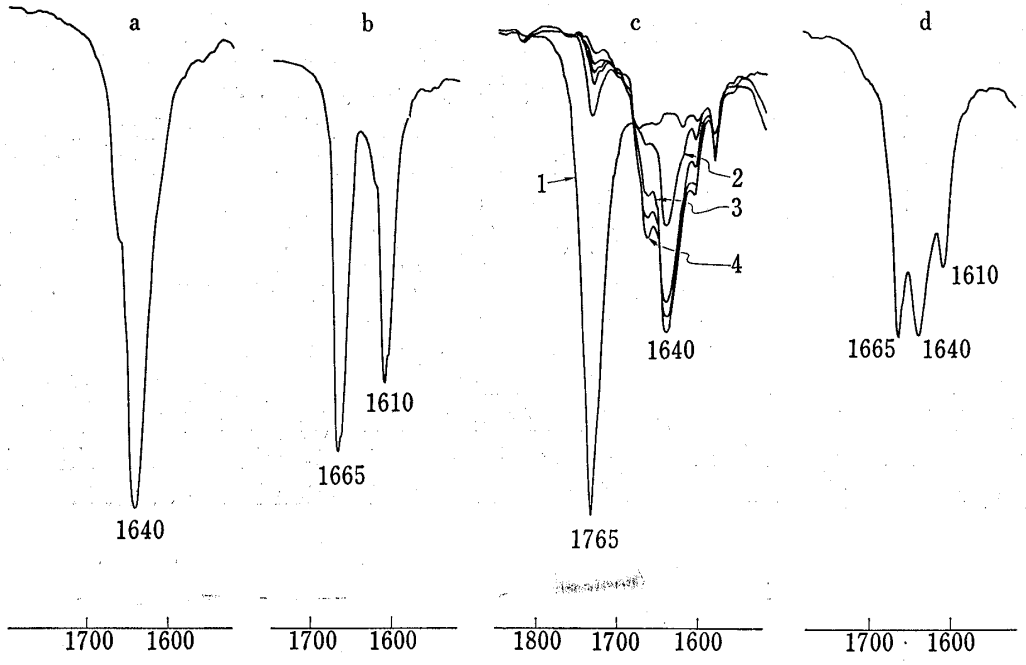

Fig. 1. IR Spectral Change of the Reaction of Tryptamine with 5,6-Dihydropyrone (9)

a: $\beta\gamma$-unsaturated lactam (**10**)
b: $\alpha\beta$-unsaturated lactam (**11**)
c: 1: 0 time, 2: 30 min reflux, 3: 1 hr, 4: 2 hr
d: after 9 hr reflux

corresponding hydroxyamide was not obtained, irrespective of the solvent (tetralin or EtOH) used. The ratio of the $\beta\gamma$-unsaturated lactam (**10**) to the $\alpha\beta$-unsaturated lactam (**11**) was estimated by the nuclear magnetic resonance (NMR) spectrum to be 5: 8.5. Although the complete separation of **10** and **11** by column chromatography, gas chromatography (GLC), and TLC has not been successful, **11**, mp, 177.5—178° was obtained after fractional recrystallizations from acetone. However, if the reaction mixture was refluxed for only 2 hr in tetralin, the ratio of **10** and **11** was reversed and **10** became predominant and was isolated by column chromatography and subsequent fractional recrystallizations from EtOH, mp 168—169°. The infrared (IR) spectral change of the reaction is given in Fig. 1. After 30 min, the spectrum showed the complete destruction of δ-valerolactone and the appearance of

major band at 1640 cm^{-1} attributed to the $\beta\gamma$-unsaturated lactam (**10**). Absorption bands at 1665 and 1610 cm^{-1} attributed to the $\alpha\beta$-unsaturated lactam (**11**) were increased by prolonged heating and became the major bands. The structures of **10** and **11** were deduced from correct elemental analysis and spectral data. Catalytic hydrogenation of a mixture of **10** and **11** led to the uptake of one mole of hydrogen and gave the saturated lactam (**4**).

The $\beta\gamma$-unsaturated lactam (**10**) failed to isomerize to **11** with excess Et_3N in EtOH, but when a mixture of **10** and **11** was refluxed with NaOEt in EtOH, a new product (**12**), a Michael addition product, was obtained in 33% yield. The conversion of **12** to **11** by an acid such as HCl, BF_3·etherate has not been successful.

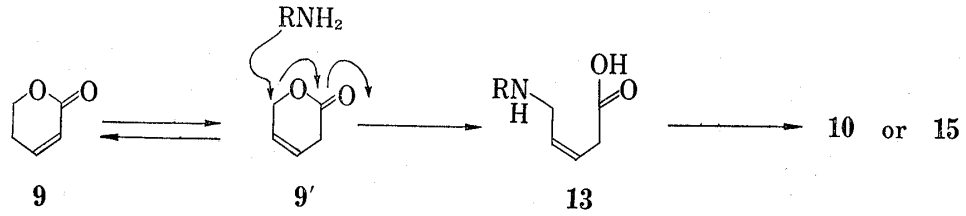

Chart 4

Nucleophilic attack by **1** on the saturated lactone occurred rapidly at the carbonyl group to give kinetically favoured hydroxyamide, whereas, in the course of the reaction of **1** and **9**, there could be assumed to exsist the rapid equilibrium between $\alpha\beta$-unsaturated lactone (**9**) and $\beta\gamma$-unsaturated lactone (**9′**) in the reaction conditions and the irreversible aminolytic

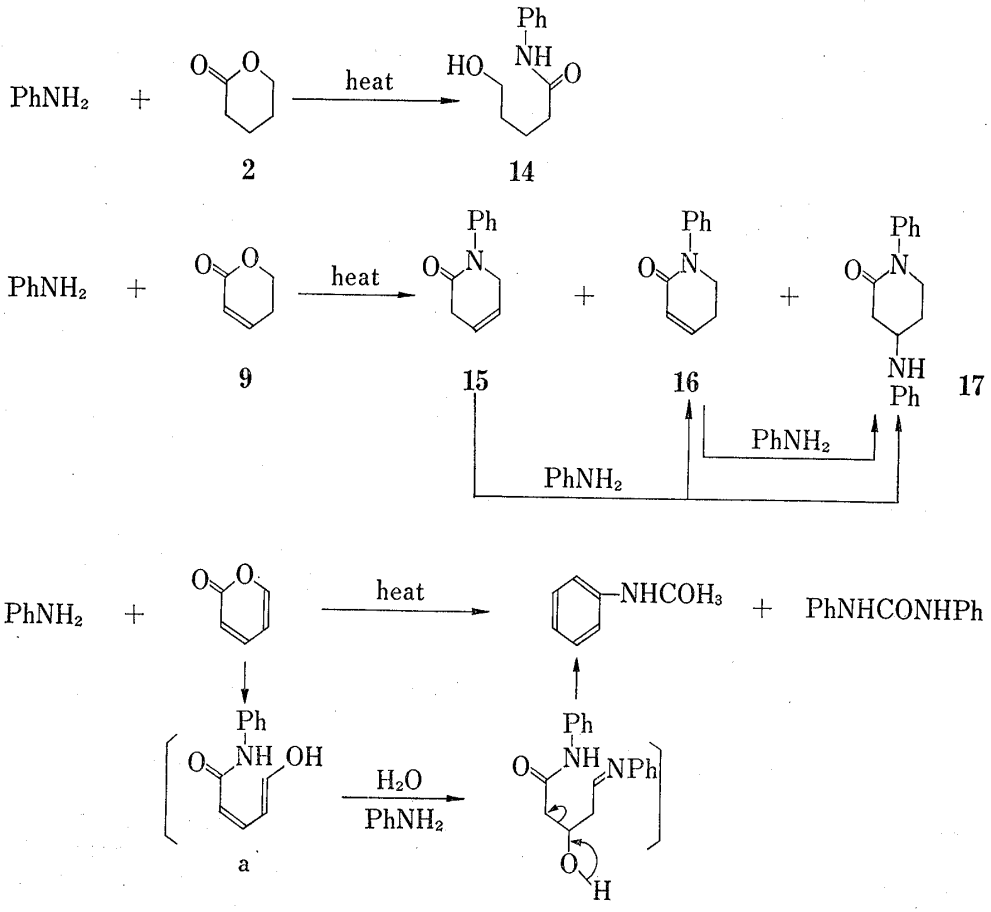

Chart 5

O-alkyl-fission of **9'** was facilitated by the presence of an allylic double bond to give **10**, which then isomerized to **11** in the reaction conditions.

One of the reactions characteristic of simple 2-pyrone derivatives is their conversion with ammonia, or with amines, to pyridone derivatives[7,8] and 2-pyrone has been reported to react with aqueous ammonia to give 2-pyridone.[9] Thereby, the reaction of **1** with 2-pyrone was carried out in various conditions, *e.g.*, refluxing benzene, xylene, tetralin, or heated to 220° without solvent for 4 hr, but the corresponding pyridone was not obtained and the vigorous conditions result in much decomposition.

As for tryptamine, the reaction of an aromatic amine such as aniline with the lactone (**9**) and 2-pyrone was examined. In contrast to γ-butyrolactone[2] which did not react with aniline, the reaction of δ-valerolactone with aniline at reflux temperature afforded δ-hydroxy-N-phenylamide (**14**) which did not undergo lactamization by long term heating, indicating that δ-lactone-δ-hydroxyamide equilibrium lies in favour of the hydroxyamide even with an aromatic amine. When the reaction of **9** and aniline was carried out for 5.5 hr at 200—210°, the corresponding δ-hydroxyamide was not obtained, but the unsaturated lactams (**15**) (9%), mp 122.5—123.5°, (**16**) (6.5%), mp 101—102°, a Michael addition product (**17**) (10%), mp 134.5—135.5° were formed. The compound (**15**), was stable in tetralin at 200° for 5 hr but readily isomerized to **16**, accompanied with the formation of Michael addition product when heated at 200° in aniline. Likewise, **16** was converted to **17** upon heating at 200° in aniline.

Although the transformation of 2-pyrones to pyridones has been considered general, the reaction of 2-pyrone with aniline, did not afford N-phenylpyridone in our experimental conditions, but unexpectedly, acetanilide and diphenylurea were isolated in 53% and 13% yield, respectively, when heated at boiling point of aniline for 4 hr. The mechanistic pathways for the formation of these two products are not known but the initial Michael type addition of water to (a) and subsequent retroaldol reaction might be involved as shown in the Chart 5.

A number of the possible synthetic route leading to indoloquinolizine (**23**) has been reported in the literature[10] but readily accessibility of **3**, **4**, **10**, **11** through the above reactions prompted us to develope a general procedure for the preparation of **23**.

Bischler-Napieralski reaction of **3** by $POCl_3$ led to the formation of **18** which was, in turn, cyclized sponteneously to **22** on treatment with $NaHCO_3$. The reduction of the salt **22** with $NaBH_4$ yielded **23**, giving over all yield up to 74% yield from **3**. Likewise, cyclization of **4** by $POCl_3$ and followed by $NaBH_4$ reduction gave **23** in 89% yield.

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7) J. Fried, "Heterocyclic Compounds," Vol. 1, edited by R.C. Elderfield, John Wiley and Sons, Inc., New York, 1950, p. 356.

8) J.H. Boyer and W. Schoen, "Organic Syntheses," Coll. Vol. 4, ed. by N. Rabjohn, John Wiley and Sons, Inc., New York, 1963, p. 532.

9) H. von Pechmann and W. Welsh, *Ber.*, **17**, 2391 (1884); N. Campbell, "Chemistry of Carbon Compounds," Vol. IV-B2, ed. by E.H. Rodd, Publishing Company, Amsterdam, 1959, p. 814.

10) *a*) J. Keufer, *Ann. Pharm. France*, **8**, 816 (1950); *b*) L.H. Groves and G.A. Swan, *J. Chem. Soc.*, **1952**, 650; *c*) W.A. Reckhow and D.S. Tarbell, *J. Am. Chem. Soc.*, **74**, 4960 (1952); *d*) S. Sugasawa, M. Terashima, and Y. Kanaoka, *Chem. Pharm. Bull.* (Tokyo), **4**, 16 (1956); *e*) K.B. Prasad and G.A. Swan, *J. Chem. Soc.*, **1958**, 2024; *f*) Y. Ban and M. Seo, *Tetrahedron*, **16**, 5 (1961); *g*) E. Wenkert, R.A. Massy-Westropp, and R.G. Lewis, *J. Am. Chem. Soc.*, **84**, 3732 (1962); *h*) E. Wenkert and B. Wickberg, *ibid.*, **84**, 4914 (1962); *i*) G.C. Morrison, W. Cetenko, and J. Shavel, Jr., *J. Org. Chem.*, **29**, 7771 (1964); *j*) J. Gootjes and W. Th. Nauta, *Rec. Trav. Chim. Pays-Bas*, **84**, 1183, 1427 (1965); *k*) E. Ochiai and M. Takahashi, *Chem. Pharm. Bull.* (Tokyo), **13**, 618 (1965); *l*) R.N. Schut and T.J. Leipzig, *J. Heterocyclic Chem.*, **3**, 101 (1966); *m*) L.J. Dolby and G.W. Gribble, *J. Org. Chem.*, **32**, 1391 (1967); *n*) J. Pospisek, Z. Koblicova, and J. Trojanek, *Chem. & Ind.*, **1969**, 25; *o*) E.M. Fry and J.A. Beisler, *J. Org. Chem.*, **35**, 2809 (1970); *p*) H-P. Husson, L. Chevolot, Y. Langlois, C. Thal, and P. Potier, Abstracts of Papers, 3rd International Congress of Heterocyclic Chemistry B, Sendai, Japan, August, 1971, p. 53; *q*) C.A. Scherer, C.A. Dorschel, J.M. Cook, and P.W. Le Quesne, Abstracts of Papers, 163rd ACS National Meeting, Boston, U.S.A. 1972, p. 68; *r*) G.W. Gribble, *J. Org. Chem.*, **37**, 1833 (1972).

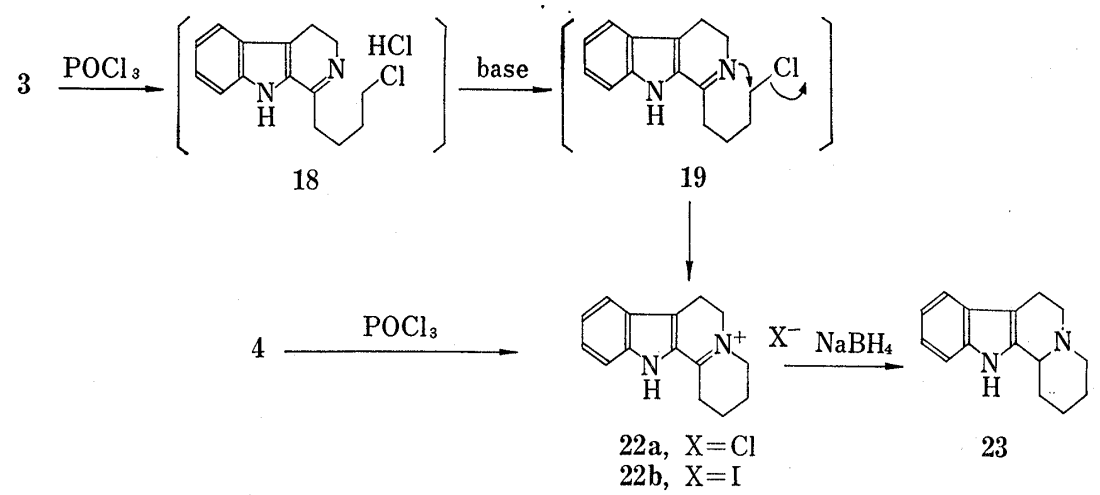

Chart 6

Experimental[11]

Reaction of Tryptamine (1) with δ-Valerolactone (2)——1) A mixture of **1** (16 g, 0.1 mole) and **2** (9.8 g, 0.1 mole) in anhyd. tetralin (50 ml) was refluxed for 3.5 hr under N_2 until **1** had disappeared on TLC (bath temperature 250—256°). Distillation of tetralin *in vacuo* left an oily residue (27.2 g) which was chromatographed on silica gel (280 g). Elution with 3% benzene in CH_2Cl_2 gave 1-[2-(3-indolyl)ethyl]piperidone **4** (900 mg, 3.7%) which was crystallized from benzene to give colorless needles, mp 154.5—155.5°. IR ν_{max}^{KBr} cm^{-1}: 3260 (NH), 1608 (CO). UV λ_{max}^{EtOH} nm (ε): 225 (34940), 276 (4690), 284 (5600), 291.5 (4240). NMR: 1.67 (m, 4H, CH_2CH_2), 2.37 (m, 2H, CH_2CO), 2.90—3.20 (m, 4H), 3.65 (t, 2H), 6.95 (d, 1H, α-H), 7.00—7.70 (m, aromatic H), 8.62 (s, 1H, NH). Mass Spectrum *m/e* (rel. intensity): 242 (8) M^+, 143 (100), 130 (37), 84 (11), 77 (8), 42 (6). *Anal.* Calcd. for $C_{15}H_{18}ON_2$: C, 74.35; H, 7.49; N, 11.56. Found : C, 74.51; H, 7.39; N, 11.47. Elutions with 3% benzene in CH_2Cl_2, CH_2Cl_2, and 2.5% MeOH in CH_2Cl_2 gave **5** (3.44 g, 9.6%) as an oil (bp>200°/0.01 mmHg). IR ν_{max}^{neat} cm^{-1}: 3300 (broad NH, OH), 1720 (ester CO), 1640, 1540 (CONH). Mass Spectrum *m/e*: 360 (M^+). UV: indolic. NMR: 1.62 (m, 8H), 2.00—2.60 (m, 4H), 2.95 (t, 2H), 3.62 (m, 4H), 4.40 (m, 2H), 5.76 (broad s, 1H, NH), 6.99 (d, α-H), 7.00—7.64 (m, 4H, aromatic H), 8.60 (broad s, 1H, NH). Elution with 3—5% CH_3OH in CH_2Cl_2 afforded **3** (18.2 g, 70%), which on crystallizations from acetone–benzene gave colorless needles, mp 82—83°. IR ν_{max}^{KBr} cm^{-1}: 3390, 3250 (NH, OH), 1653 sh, 1635, 1555 (CONH). NMR (d_5-pyridine): 1.60—2.20 (m, 4H), 2.42 (t, 2H, $COCH_2$), 3.19 (t, 2H), 3.80 (m, 4H), 4.88 (broad s, 1H), 7.10—7.90 (m, 4H, aromatic H), 8.30 (s, 1H), 11.65 (s, 1H). Mass Spectrum *m/e* (rel. intensity): 260 (5) M^+, 143 (100), 130 (54), 55 (7). *Anal.* Calcd. for $C_{15}H_{20}O_2N_2$: C, 69.20; H, 7.74; N, 10.76. Found: C, 69.02; H, 7.79; N, 10.58.

2) A soln of **1** (6.4 g, 0.04 mole) and **2** (2.0 g, 0.02 mole) in tetralin (45 ml) was refluxed for 7.5 hr. Work-up as described above gave **4** (1.11 g, 23%), **3** (3.97 g, 76%).

3) A soln of **1** (16 g, 0.1 mole) and **2** (11 g, 0.11 mole) in EtOH (100 ml) was refluxed for 17 hr. The residue, obtained upon evaporation of the solvent, was crystallized from benzene to give **3** (8.5 g), mp 75.5—80°. The mother liquor was concentrated to give a residue (18.5 g) which was chromatographed over silica gel (180 g). Elution with 5% MeOH in CH_2Cl_2 yielded ethyl δ-hydroxyvalerate, bp 92—94°/2 mmHg (lit.[12] 114/14 mmHg). Elution with 20% MeOH in CH_2Cl_2 gave **3** (13.18 g), totaling 21.7 g, 83%. Ethyl δ-hydroxyvalerate: IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1735 (ester CO). NMR: 1.24 (t, 3H, CH_3), 1.40—2.00 (m, 4H, CH_2), 2.31 (m, 2H, CH_2CO), 3.60 (t, 2H, CH_2OH), 3.70 (s, 1H, OH), 4.11 (q, 2H, OCH_2CH_3).

Formation of 3 by Alkaline Hydrolysis of 5——A soln of **5** (100 mg) in EtOH (1 ml) and 2 drops of 10% NaOH was heated at 60—70° for 20 min. The solvent was evaporated and the residue was treated with H_2O and extracted with CH_2Cl_2. The CH_2Cl_2 extract was washed and dried and evaporated to give crude **3** (67 mg, 93%) which on crystallization from acetone–benzene gave colorless needles, identical in comparison (IR, mmp) with **3**.

11) M. Ps are uncorrected. IR spectra were recorded on Hitachi G-3 model and Hitachi 215-spectrometers. UV spectra were recorded in 95% EtOH on Hitachi EPS-3T spectrophotometer. NMR spectra were determined with JEOL JNM4H-100 and a Varian Associates HA-100 spectrometers in $CDCl_3$ (otherwise stated) with trimethyl silane (TMS) as internal standard. The chemical shift was expressed by the δ-value in ppm. Mass spectra were obtained on a Hitachi RMU-6E mass spectrometer.

12) R. Robinson and L.H. Smith, *J. Chem. Soc.*, **1937**, 371.

Formation of 5 by the Reaction of 3 with 2——A mixture of **3** (750 mg) and **2** (450 mg) in tetralin (10 ml) was refluxed for 13 hr. The solvent was evaporated to give a residue (1.21 g) which was chromatographed on silica gel. Elution with CH_2Cl_2–acetone (2: 2) gave **5** (935 mg, 58%) whose IR spectrum and *Rf*-value on TLC were identical with those of the sample prepared as above 1). Further elution with the same solvent gave **3** (118 mg).

N-[2-(3-Indolyl)ethyl]-2-piperidone (4) from 3——A mixture of **3** (1 g, 3.8 mmole) and **1** (620 mg, 3.8 mmole) in tetralin (5 ml) was heated at 240±10° for 7 hr under N_2 and tetralin was distilled *in vacuo*. The residue was chromatographed over silica gel (17 g). Elution with 3% CH_3OH in CH_2Cl_2 yielded **4** (381 mg, 41%), mp 154.5—156 (from acetone–benzene). Further elution with same solvent with 5% MeOH–CH_2Cl_2 gave unreacted **1** (424 mg, 68%).

N-[2-(1-Methyl-3-indolyl)ethyl]-2-piperidone (7)——A soln of **4** (605 mg, 2.5 mmole) in CH_2Cl_2 (10 ml) was added dropwise to a cold stirred soln of $NaNH_2$ in liq. NH_3, prepared by Na (200 mg, 8.7 mole), $Fe(NO_3)_3 \cdot 9H_2O$ (450 mg) in liq. NH_3 (500 ml) in dry ice–acetone and after 30 min stirring, CH_3I (490 mg, 3.5 mmole) was added. The ammonia was allowed to evaporate, H_2O was added, followed by extraction with CH_2Cl_2. The extracts were washed, dried, and evaporated. The residue (641 mg) was subjected to preparative TLC (silica gel/CH_2Cl_2: acetone=3: 1). The less polar band gave **7** (333 mg, 52%), mp 121—122° (from benzene). IR ν_{max}^{KBr} cm^{-1}: 1640 (lactam CO). NMR: 1.66 (m, 4H), 2.38 (m, 2H, CH_2CO), 2.90—3.22 (m, 4H), 3.61 (t, 2H), 3.70 (s, 3H, N-Me), 6.85 (s, 1H, α-H), 9.90—7.30, 7.50—7.70 (m, 4H, aromatic H). Mass Spectrum *m/e* (rel. intensity): 256 (12) M^+, 159 (15), 158 (100), 144 (40). *Anal.* Calcd. for $C_{16}H_{20}ON_2$: C, 74.96; H, 7.87; N, 10.93. Found: C, 75.03; H, 7.96; N, 10.84.

Reaction of 3 with 1-Methyltryptamine——A mixture of **3** (650 mg, 2.5 mmole) and **6** (870 mg, 5 mmole) in tetralin (5 ml) was refluxed for 15 hr under N_2 and tetralin was distilled *in vacuo*. The residue was chromatographed on silica gel (30 g) by elution with benzene. The first fraction gave a mixture of **3**, **7**, and **8** (371 mg). The second fraction eluted with 2.5% MeOH–benzene gave **8** (112 mg). The third fraction eluted with 20% MeOH–benzene gave a mixture of lactams **7** and **4** (633 mg). The last elution with 50% MeOH–$CHCl_3$ afforded a mixture of **6** and **1** (452 mg). The first and third fractions were further purified by chromatography on silica gel and followed by preparative TLC (3% MeOH–CH_2Cl_2) to give **7** (122 mg, 19%), mp 110—115°, identical (IR, mmp) with an authentic specimen prepared as above, **4** (38 mg, 6.4%), mp 145.5—151.5°, **8** (295 mg, 43%) an oil, and **3** (107 mg, 17%), mp 79—80.5° and a mixture of **6** and **1** (145 mg, totaling 597 mg) were recovered. **8**, IR $\nu_{max}^{CHCl_3}$ cm^{-1}: 3440, 3340 (NH, OH), 1660, 1525 (CONH). Mass Spectrum *m/e* (rel. intensity): 274 (10) M^+, 185 (8), 158 (100), 144 (77), 130 (8). NMR: 1.58 (m, 4H, CH_2), 2.12 (m, 2H, CH_2CO), 2.78 (broad s, OH or NH), 2.90 (t, 2H, CH_2), 3.54 (m, 4H, CH_2O and CH_2N), 3.70 (s, 3H, CH_3N_a), 5.80 (broad s, NH or OH), 6.82 (s, 1H, α-H), 7.00—7.60 (m, 4H, aromatic H).

Reaction of 1 with 9——1) A soln of **1** (1.6 g, 0.01 mole) and **9** (0.98 g, 0.01 mole) in tetralin (10 ml) was heated at 195—205° for 2 hr under N_2. The solvent was distilled and the residue (2.57 g) was chromatographed on silica gel (40 g). Elution with CH_2Cl_2 gave a mixture of **10** and **11** (**10**>**11**). Fractional recrystallizations from EtOH gave **10** (867 mg, 36%) as colorless needles, mp 168—169°. IR $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3218 (NH), 1614 (lactam CO). UV λ_{max}^{EtOH} nm (ε): 222.5 (38000), 275 (5680), 283 (6010), 291 (5370). NMR: 2.90—3.20 (m, 4H), 3.70—3.96 (m, 4H), 5.70 (m, 2H, olefinic H), 7.05 (d, 1H, α-H), 7.10—7.75 (m, 4H, aromatic H), 8.35 (s, 1H, NH). Mass Spectrum *m/e* (rel. intensity): 240 (12) M^+, 144 (15), 143 (100), 130 (34), 81 (6). *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.74; H, 6.68; N, 11.61.

2) A soln of **1** (12 g, 75 mmole) and **9** (7.35 g, 75 mmole) in tetralin (50 ml) was refluxed for 8 hr under N_2 and the solvent was distilled. The residue (24.3 g) was chromatographed on silica gel (200 g). Elution with CH_2Cl_2 gave a mixture of **10** and **11** (**10**: **11**=5: 8.5, estimated by the ratio olefinic protons at δ 5.70 and 6.50 in the NMR spectrum), yield, 14.2 g, 79%. One crystallization from EtOH gave a mixture of **10** and **11** (5.57 g), colorless needles, mp 165—168° as the first crop which was recrystallized from acetone ten times to give analytical pure sample **11** as colorless needles, mp 177.5—178°. A mixture with **10** gave a melting point depression, mp 154—165°. UV λ_{max}^{EtOH} nm (ε) 222 (34210), 275 (5700), 284 (5930), 291.5 (4760). IR ν_{max}^{KBr} cm^{-1}: 3275 (NH), 1656, 1602 (lactam CO). $\nu_{max}^{CH_2Cl_2}$ cm^{-1}: 3460 (NH), 1662, 1602 (lactam CO). NMR: 2.10—2.30 (m, 2H, CH_2), 3.05 (t, 2H, CH_2), 3.28 (t, 2H, CH_2), 3.75 (t, 2H, NCH_2), 5.96 (double triplet, J= 10 Hz, J=2 Hz, 1H, CO–C<u>H</u>=CH–), 6.50 (m, 1H, CO–CH=C<u>H</u>–CH_2), 7.04 (d, 1H, α-H), 7.08—7.74 (m, 4H, aromatic H), 8.44(s , 1H, NH). Mass Spectrum *m/e* (rel. intensity): 240 (16) M^+, 144 (18), 143 (100), 130 (40), 81 (16). *Anal.* Calcd. for $C_{15}H_{16}ON_2$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.01; H, 6.78; N, 11.56.

Catalytic Hydrogenation of 10 and 11——A soln of a mixture of **10** and **11** (480 mg, 2 mmole) in EtOH (50 ml) was hydrogenated over PtO_2 (76 mg) for 70 min until 1 mole of H_2 was absorbed. Work -up in the usual way gave crude **4** (473 mg, 99%), mp 153.5—154.5° (from EtOH), identical in comparison (IR, mmp, TLC) with **4** prepared as above.

4-Ethoxy-[2-(3-indolyl)ethyl]-2-piperidone (12)——A mixture of **10** and **11** (960 mg, 4 mmole) was dissolved in a soln of EtONa in EtOH, prepared from Na (9 mg, 0.4 mmole) and EtOH (50 ml), and refluxed for 7 hr. The solvent was removed. The residue (1.16 g) was extracted with CH_2Cl_2. The extracts were washed, dried, and evaporated to give a residue (1 g) which was subjected to preparative TLC (silica gel/acetone: CH_2Cl_2=1: 10). The less polar band gave unreacted **10** and **11** (182 mg, 19%). The second band afforded

12 as an oil (411 mg, 33%) which was crystallized from benzene–ether to give colorless needles, mp 90.5—92°. IR ν_{max}^{KBr} cm^{-1}: 3240 (NH), 1620 (lactam CO), 1110 (COC). NMR: 1.18 (t, 3H, CH_3), 1.80 (m, 2H, CH_2), 2.53 (m, 2H), 2.90—3.80 (m, 9H), 6.99 (d, 1H, α-H), 7.00—7.70 (m, 4H, aromatic H), 8.38 (s, 1H, NH). Mass Spectrum *m/e* (rel. intensity): 286 (4), 144 (19), 143 (100), 130 (82), 81 (17), 43 (55). *Anal.* Calcd. for $C_{17}H_{22}O_2N_2$: C, 71.30; H, 7.74; N, 9.73. Found: C, 71.34; H, 7.74; N, 9.78.

Reaction of 9 with Aniline——A soln of **9** (2.94 g, 0.03 mmole) in aniline (6 g, 6.5 mole) was refluxed for 5.5 hr and excess of aniline was distilled. The residue (5.96 g) was taken up with CH_2Cl_2 and washed with 3% HCl, saturated NaCl soln. The extracts were dried and evaporated. The residue (5.96 g) was chromatographed on silica gel (66 g) prepared in benzene. Elution with benzene–acetone (10: 1) gave a residue (762 mg) which was separated by column chromatography (silica gel) to give **16** (340 mg, 6.5%) mp 101—102° (benzene–petroleum ether) and **15** (470 mg, 9%), mp 122.5—123.5° (benzene–petroleum ether). **15**: IR ν_{max}^{KBr} cm^{-1}: 1647 (lactam CO), 1595. UV λ_{max}^{EtOH} nm (ε) 228 (3820). Mass Spectrum *m/e* (rel. intensity): 173 (100) M^+, 144 (14), 119 (90), 104 (4), 93 (23), 77 (25), 53 (13). NMR: 3.12 (m, 2H, CH_2CO), 4.23 (m, 2H, CH_2–N), 5.84 (m, 2H, olefinic H), 7.15—7.55 (m, 5H, aromatic H). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.33; H, 6.41; N, 8.04. **16**: IR ν_{max}^{KBr} cm^{-1}: 1662, 1629 (lactam CO), 1595. UV λ_{max}^{EtOH} nm (ε) 268 (3530). Mass Spectrum *m/e* (rel. intensity): 173 (80) M^+, 144 (7), 105 (100), 77 (32), 68 (13), 51 (11). NMR: 2.50 (m, 2H, CH_2), 3.82 (t, 2H, N–CH_2), 6.05 (double triplets, 1H, CH=CHCO, J= 10 Hz, J=2 Hz), 6.68 (m, 1H, CH=CHCO), 7.10—7.50 (m, 5H, aromatic H). *Anal.* Calcd. for $C_{11}H_{11}NO$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.39; H, 6.41; N, 8.05. **17**: IR ν_{max}^{KBr} cm^{-1}: 3400, 3330 (NH), 1650, 1600 (lactam CO). UV λ_{max}^{EtOH} nm: 248, 295. Mass Spectrum *m/e* (rel. intensity): 266 (86) M^+, 173 (19), 146 (13), 132 (100), 119 (46), 106 (33), 93 (30), 87 (31). NMR: 1.90 (m, 1H, C_5–H), 2.20 (m, 1H, C_5–H), 2.41 (q, 1H, C_3–H_A, J_{AB}=17 Hz, J_{AX}=8 Hz), 2.98 (q, 1H, C_3–H_B, J_{AB}=17 Hz, J_{BX}=6 Hz), 3.40 (s, 1H, NH), 3.70 (t, 2H, C_6–H_2), 3.90 (m, 1H, C_4–H_X), 6.60—6.85, 710—7.50 (m, 10H, aromatic H).

Reaction of 2-Pyrone with Aniline——To a boiling aniline (4 g, 0.43 mole) was added 2-pyrone (1 g, 0.1 mole) dropwise and the reaction mixture was refluxed for 4 hr. The residue (2.5 g) obtained upon distillation of excess aniline was chromatographed on silica gel (4 g). Elution with benzene–$CH_3CO_2C_2H_5$ (1: 1) gave an oil (950 mg) which was subjected to preparative TLC (silica gel/benzene–acetone (1: 1) to give acetanilide (720 mg, 53%), mp 115—115.5° (from CH_2Cl_2). The second eluted product (270 mg, 13%) was crystallized from MeOH to give pale yellow needles, mp 237—238.5°, identical in comparison (IR, mmp) with diphenyl urea.

1-(4-Chlorobutyl)-3,4-dihydro-β-carboline Hydrochloride (18)——A soln of **3** (3 g, 0.011 mole) in $POCl_3$ (28 ml) was refluxed for 3 hr and excess $POCl_3$ was evaporated *in vacuo*. The residue was crystallized from EtOH to give **18** as yellow crystals (2.08 g, 46%), mp 182—186°. The second crop gave 211 mg. The mother liquor was concentrated and subjected to ion exchange column chromatography (Amberlite CG-400, 60 g) prepared in 0.2N HCl in 50% EtOH. Evaporation of the elution and crystallization of the residue from EtOH–$(C_2H_5)_2O$ produced **18** (484 mg), totaling 2.8 g, 62% yield, which was recrystallized for analysis from EtOH–$(C_2H_5)_2O$ to give mp 192.5—193.5°. UV λ_{max}^{EtOH} nm (ε) 244 (11000), 353 (19000). λ_{min}^{EtOH} nm (ε) 230 (10500), 273 (700). $\lambda_{max}^{EtOH\text{-}NaOH}$ nm (ε) 235 (18300), 310 sh (16600), 318 (17200). $\lambda_{min}^{EtOH\text{-}NaOH}$ nm (ε) 226 (22100), 269 (3900). *Anal.* Calcd. for $C_{15}H_{18}N_2Cl_2$: C, 60.61; H, 6.10; N, 9.42; Cl, 23.86. Found: C, 60.54; H, 5.93; N, 9.15; Cl, 24.35.

1,2,3,4,6,7-Hexahydro-12H-indolo[2,3-a]quinolizinium Iodide (22b)——To **4** (4.89 g, 0.02 mole) was added $POCl_3$ (20 ml) and the mixture was refluxed for 60 min. After addition of dry benzene (40 ml), the reaction mixture was left overnight and the precipitates were collected, 4.38 g, mp 185—190°, which was converted to **22b** by addition of KI in EtOH. **22b**, mp 224—226° (MeOH–ether) (lit.[10m] mp 228—229°). IR ν_{max}^{KBr} cm^{-1} 1630 ($C=\overset{+}{N}$). UV λ_{max}^{EtOH} nm (ε) 246 sh (16300), 308 sh (11000), 321 (14500), 352 (22600). λ_{min}^{EtOH} nm (ε) 272 (2900), 326 (14300). $\lambda_{max}^{EtOH\text{-}NaOH}$ nm (ε) 259 sh (6400), 295 sh (12200), 306 (15200), 318 (13900). $\lambda_{min}^{EtOH\text{-}NaOH}$ nm (ε) 268 (4700), 313 (13100).

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine (23)——1) A soln of **3** (10 g, 0.038 mole) in $POCl_3$ (140 ml) was refluxed for 3 hr under N_2. The excess $POCl_3$ was removed *in vacuo* and the residue was dissolved in CH_2Cl_2, and the CH_2Cl_2 extract was washed with $NaHCO_3$ soln, with H_2O, and dried with anhyd. Na_2SO_4 only for a few minutes and evaporated. The residue (**22a**, 7.67 g) was dissolved in MeOH containing a few drops of 10% HCl and $NaBH_4$ (2 g, 53 mmole) was added with stirring. After 30 min stirring, the MeOH was removed *in vacuo* and the residue was extracted with CH_2Cl_2 after addition of a few drops of 5% NaOH to ajust the pH of the soln to 8—9. The CH_2Cl_2 extract was evaporated to give a residue (7.6 g) which was crystallized from benzene–hexane to yield **23** (2.90 g, mp 140—148°). The mother liquor was concentrated and was subjected to column chromatography (Al_2O_3, 100 g). Elution with CH_2Cl_2 gave **23** (3.54 g), totaling 6.44 g (74%). Recrystallization from benzene–hexane gave **23** (4 g, 46%), mp 148—151,5° (lit.[10r] mp 153—154°), which is identical in comparison (IR, UV, TLC, mmp) with a sample prepared by the procedure 2).

2) A soln of **4** (605 mg, 25 mmole) in $POCl_3$ (3 ml) was refluxed for 15 min under N_2 and benzene (20 ml) was added. The reaction mixture was refluxed for another 1 hr and filtered to give a yellow powder (850 mg), mp 180—193°, which was dissolved in MeOH (15 ml) and $NaBH_4$ (380 mg) was added with stirring. After

1 hr stirring, the solvent was evaporated and extracted with CH_2Cl_2. The CH_2Cl_2 was washed, dried, and evaporated to give **23** (504 mg, over all yield, 89%), mp 146—150°.

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