Tetrahedron. Vol. 33, pp. 489 to 495. Pergamon Press 1977. Printed in Great Britain

PHOTOCHEMICAL SYNTHESIS OF 1,2,3,4-TETRAHYDROISOQUINOLIN-3-ONES FROM N-CHLOROACETYLBENZYLAMINES

MASAKI IKEDA, KEN-ICHI HIRAO, YOHMEI OKUNO, NAGANORI NUMAO and OSAMU YONEMITSU*
Faculty of Pharmaceutical Sciences, Hokkaido University, Sapporo 060, Japan

(*Received in Japan* 20 *August* 1976; *Received in UK for publication* 5 *October* 1976)

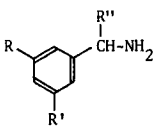
Abstract—When N-chloroacetyl-3-hydroxybenzylamine (**37**) in aqueous acetonitrile was irradiated, both *ortho* and *para* photocyclizations with reference to the OH group occurred to give 7- and 5 - hydroxy - 3 - oxo - 1,2,3,4 - tetrahydroisoquinolines (**52, 53**). Similarly, 1-methylisoquinoline derivatives (**54, 55**) were synthesized. N-Chloroacetyl - 3,5 - dihydroxybenzylamine (**39**) gave a single photoproduct, 5,7 - dihydroxy - 3 - oxo - 1,2,3,4 - tetrahydroisoquinoline (**56**). These photocyclizations were smoothly extended to the synthesis of 1-benzyl, 1-(4'-methoxybenzyl)- and 1 - (3',4',5' - trimethoxybenzyl) - isoquinoline derivatives (**58** ~ **64**).

N-Chloroacetylphenethylamines having electron-donative substituents on their aromatic rings readily undergo photocyclizations to afford many novel heterocyclic compounds.[1] Among these photoreactions, the most typical one is the formation of 1,2,4,5 - tetrahydro - 3H - benzazepin - 2 - ones. N-Chloroacetyl derivatives of homologous amines, phenylpropylamines and phenylbutylamines, also afford the corresponding benzazocine and benzazonine derivatives.[2] As an extension we now report the photochemical synthesis of 1,2,3,4 - tetrahydroisoquinolin - 3 - ones from N - chloroacetylbenzylamines.[3]

The Pomeranz–Fritsch method[4] involving acid-catalyzed cyclization of acetals is quite simple and useful for the preparation of 7- and 8-substituted isoquinolines, which are difficult to prepare by other usual isoquinoline syntheses such as the Bischler–Napieralski and Pictet–Spengler methods. Acetals with substituted hydroxy and alkoxy groups on their aromatic rings, however, usually cyclize in strong acids, but this is sometimes responsible for side reactions. The photocyclizations of N-chloroacetylbenzylamines are expected to proceed regardless of pH of their solutions, and may provide an additional method for the preparation of isoquinolines.

RESULTS AND DISCUSSION

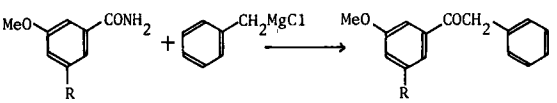
Synthesis of starting amines. Simple benzylamines (**1**, **2**, **3**) were prepared in good yield by the Raney Ni reduction of the corresponding oximes.[5]



1: R=OH, R'=R''=H[6]
2: R=OH, R'=H, R''=Me
3: R=R'=OH, R''=H

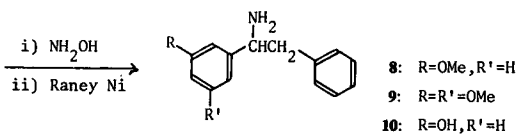
The preparation of α-arylphenethylamines was carried out according to three essentially known procedures. The Grignard reaction was first applied to prepare intermediary ketones. 3-Methoxybenzamide (**4**) was allowed to react with benzylmagnesium chloride in boiling ether for 48 hr[7] to yield a desoxybenzoin (**6**),[8] which was converted to its oxime, and then reduced to an amine (**8**). Compound **8** was demethylated by the treatment with 47% hydrobromic acid to give the starting amine (**10**). Similarly, **11** was synthesized from 3,5-dimethoxybenzamide (**5**) via **9**.

The use of benzonitriles instead of benzamides in the Grignard reactions brought about a considerable reduction in reaction time.[9] Thus 3-benzyloxybenonitrile (**12**) gave **13** in almost quantitative yield by the treatment with benzylmagnesium chloride in boiling ether for 5 hr. The oxime of **13** was reduced easily to **10** in good yield. The reaction of **12** with 4-methoxybenzylmagnesium chloride[10] gave similarly **14**.

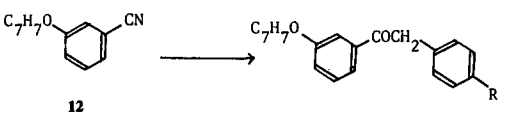


4: R=H
5: R=OMe

6: R=H
7: R=OMe



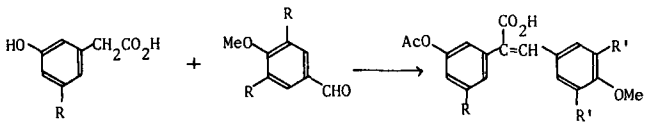
8: R=OMe, R'=H
9: R=R'=OMe
10: R=OH, R'=H
11: R=R'=OH



12

13: R=H
14: R=OMe

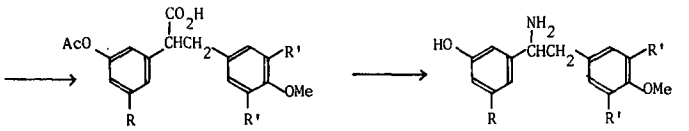
The second method for the preparation of starting amines involves the Perkin reaction.[11] Anisaldehyde (**17**) and 3-hydroxyphenylacetic acid (**15**) in acetic anhydride containing triethylamine was heated for 28 hr to give a condensed cinnamic acid (**19**), which was readily reduced to **22**. The acid (**22**) was converted to an amine (**25**) by the Curtius rearrangement in fair yield. Other two amines (**26**, **27**) were also synthesized in a similar manner.



15: R=H
16: R=OH

17: R=H
18: R=OMe

19: R=R'=H
20: R=H,R'=OMe
21: R=OAc,R'=OMe



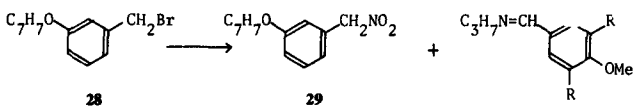
22: R=R'=H
23: R=H,R'=OMe
24: R=OAc,R'=OMe

25: R=R'=H
26: R=H,R'=OMe
27: R=OH,R'=OMe

The third method involves intermediary α-nitrostilbene, which was easily synthesized from phenylnitromethanes[12] and Schiff's bases of aromatic aldehydes according to the Robertson method.[13] An acetic acid solution of 3-benzyloxyphenylnitromethane (**29**) and the Schiff base (**30**) prepared from anisaldehyde (**17**) and n-propylamine was allowed to stand for 12 hr and gave an α-nitrostilbene (**32**) in good yield. Reduction of **32** with LAH gave an amine (**34**), which was easily debenzylated to **25** by catalytic reduction. In a similar manner **26** was also synthesized via **33** and **35**.

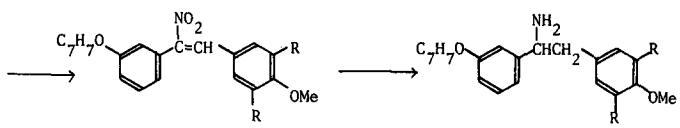
Photocyclizations. Since N - chloroacetyl - 3 - methoxyphenethylamine (**45**) on irradiation gave smoothly the corresponding benzazepinone derivatives (**46**, **47**),[15] N-chloroacetyl - 3 - methoxybenzylamine (**36**) was expected to give isoquinolines (**48**, **49**). Irradiation of an aqueous acetonitrile solution of **36** with a 100 W high pressure mercury lamp, however, gave only negative indications of the formation of photocyclization products. Compounds **50** and **51** were isolable products and identified by their spectral data.

On the other hand, when N-chloroacetyl - 3 -



28 **29**

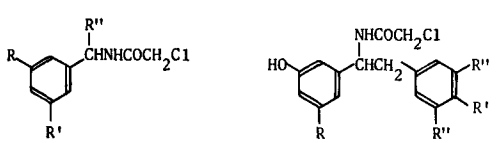
30: R=H
31: R=OMe



32: R=H
33: R=OMe

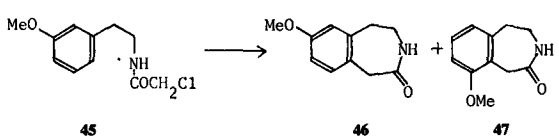
34: R=H
35: R=OMe

Recently, a simple method for the preparation of desoxybenzoins from α-aminonitriles was published[14] and may be applicable for the synthesis of the above amines. The starting amines synthesized above and 3-methoxybenzylamine were allowed to react with chloroacetyl chloride under the usual Schotten–Baumann conditions, and afforded the corresponding N-chloroacetamides (**36** ~ **44**) in good yield.

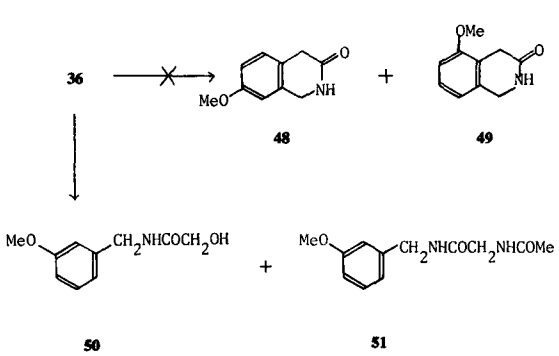


36: R=OMe,R'=R''=H
37: R=OH,R'=R''=H
38: R=OH,R'=H,R''=Me
39: R=R'=OH,R''=H

40: R=R'=R''=H
41: R=R''=H,R'=OMe
42: R=H,R'=R''=OMe
43: R=OH,R'=R''=H
44: R=OH,R'=R''=OMe



45 **46** **47**

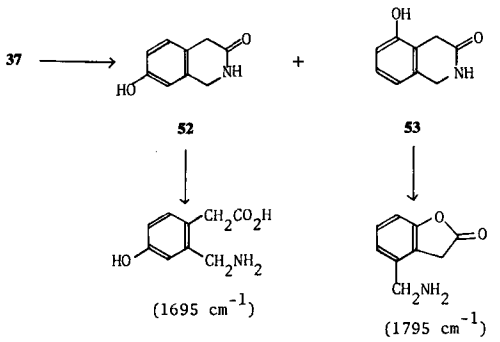


48 **49**

50 **51**

hydroxybenzylamine (**37**) was irradiated under similar conditions, both *ortho* and *para* photocyclizations with reference to the OH group proceeded smoothly to give 5- and 7 - hydroxy - 1,2,3,4 - tetrahydroisoquinolin - 3 - ones, **53** (7%) and **52** (55%).

The structural assignments of **52** and **53**, by analogy to **46** and **47**,[15] depend on the spectral data. On the basis of mass spectra, both **52** and **53** have the composition $C_9H_9NO_2$ (mol wt 163). In the NMR spectrum of **52**, the main product of the photocyclization, the two aromatic protons on 5 and 6 are next to each other and the proton on 8 is separate (*meta* coupling). The three aromatic protons on 6, 7 and 8 in the minor product (**53**) are in a row. An unambiguous chemical proof is based on lactonization of **53** by heating with hydrobromic acid. The structures of the resulting 5-membered lactone was easily recognized by its IR spectrum (1795 cm^{-1}). In contrast **52** was opened to an amino acid (1695 cm^{-1}).



The photocyclization of **38** gave similarly **54** (74%) and **55** (13%), and their structures were established spectroscopically.

The analogous photolysis of N - chloroacetyl - 3,5 - dihydroxybenzylamine (**39**) gave the sole photoproduct (**56**), which was treated with diazomethane and crystallized as the methyl ether (**57**). In its NMR spectrum, the two aromatic protons happen to be in the same position at 6.45 ppm.

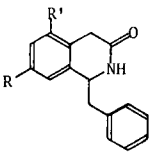
54: R=OH, R'=H
55: R=H, R'=OH

56: R=H
57: R=Me

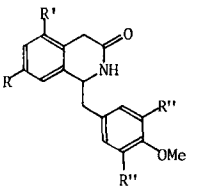
Several 1-benzylisoquinolines were next synthesized from **40** ~ **44** under similar photochemical conditions. Although compound **40** has two aromatic rings capable of photocyclization, on irradiation the photocyclizations occurred only on the phenolic ring to yield isoquinoline derivatives, **58** (69%) and **59** (16%). This result can be accounted for by the low reactivity of N-chloroacetylphenethylamine.[15]

The structures of **58** and **59** were established by spectral data, especially in the mass spectra both **58** and **59** have strong peaks at 162 (base peak) and 134, which indicate clearly that both compounds are isoquinoline derivatives and not benzazepinones. The structural differentiation between **58** and **59** was possible by acid hydrolysis with 6 N HCl or 47% HBr. Compound **59** gave a 5-membered lactone (ν_{max} 1800 cm^{-1}), whereas **58** afforded an amino acid (1695 cm^{-1}), which was recyclized to **58** by heating at 100° *in vacuo*. Similarly, photolysis of **43** resulted in its conversion to one crystalline product (**60**) in good yield.

Compounds, **41**, **42** and **44** have methoxy- and trimethoxybenzene rings, which were reactive under these photochemical conditions, as well as phenolic rings. Actually N-chloroacetyl - 4 - methoxy- and 3,4,5 - trimethoxyphenethylamines gave rise to some photoreactions.[16] Nevertheless the photocyclization of **41**, **42** and **44** occurred also only at the *ortho* and *para* positions with reference to the OH groups in the phenolic rings to afford the corresponding 1 - methoxy- and trimethoxybenzyl - 1,2,3,4 - tetrahydroisoquinolin - 3 - ones, **61** (49%), **62** (36%), **63** (7%) and **64** (59%), respectively.



58: R=OH, R'=H
59: R=H, R'=OH
60: R=R'=OH



61: R=OH, R'=R''=H
62: R=OH, R'=H, R''=OMe
63: R=H, R'=OH, R''=OMe
64: R=R'=OH, R''=OMe

EXPERIMENTAL

1-(3-*Hydroxyphenyl*)*ethylamine* (**2**). To a stirred soln of 2 g of 3 - hydroxyacetophenone oxime in 40 ml EtOH was added 40 ml 2N NaOH and then 3 g Raney Ni. After 30 min, the mixture was filtered through a matting of Celite filter aid. The filtrate was washed with ether, acidified with conc. HCl and washed again with ether. The aqueous layer was neutralized with K_2CO_3 and extracted with EtOAc. Evaporation of the solvent left 1.04 g (55%) of a crystalline powder, which was recrystallized from EtOH to give colorless prisms, m.p. 177–180°; ν_{max} (Nujol) 3320, 3250, 1618 cm^{-1}; *m/e* 137 (M^+), 122 (base peak), 95; δ (DMSO-d_6) 1.18 (3 H, d, J = 7 Hz), 3.7–4.1 (1 H, m), 6.5–7.1 (1 H, m). (Found: C, 70.06; H, 8.07; N, 10.24. $C_8H_{11}NO$ requires: C, 70.04; H, 8.08; N, 10.21%).

3,5-*Dihydroxybenzylamine* (**3**). The Raney Ni reduction of 9.1 g of 3,5 - dimethoxybenzaldoxime (m.p. 113–115°) gave 6.8 g (80%) of 3,5 - dimethoxybenzylamine,[17] which was heated under reflux in 30 ml of 47% HBr for 2.5 hr. After evaporation of the acid, the residue was dried and recrystallized from EtOH to give 5.6 g of 3-hydrobromide; ν (Nujol) 3220, 1610, 1153, 995 cm^{-1}; *m/e* 139 (M^+, base peak), 122. (Found: C, 38.19; H, 4.57; N, 6.59. $C_7H_{10}BrNO_2$ requires: C, 38.19; H, 4.59; N, 6.37%).

3-*Methoxyphenyl benzyl ketone* (**6**). To a stirred soln of benzylmagnesium chloride prepared from 8.0 g Mg, 0.2 g iodine and 22.8 g benzyl chloride in 70 ml anhyd ether was added dropwise 5.4 g of **4** in 60 ml of ether over a 30 min period. The mixture was heated under reflux for 48 hr, then poured onto 200 g of ice-cold 10% H_2SO_4, and extracted with ether. The extract was washed with sat. $NaHCO_3$ aq and NaCl aq and dried over Na_2SO_4. Evaporation of the solvent left **6** as an oil (6.9 g; 85%) $b.p._{.3}$ 169–170° (lit.[8] $b.p._{.16}$ 208–212°); ν_{max} (neat) 1682, 962 cm^{-1}.

To an EtOH soln (250 ml) of **6** (5.5 g) was added 15 g of NH_2OH-HCl in 10 ml of water and 60 ml of 10% NaOH, and the mixture was heated under reflux for 30 min. After evaporation of the EtOH, the residue was extracted with ether. The extract was washed with sat. NaCl aq, dried and evaporated to leave a solid. Recrystallization from benzene gave 5.0 g (88%) of the oxime of **6**, m.p. 116–118°; ν_{max} (Nujol) 1606, 1578 cm^{-1}; *m/e* 241 (M^+), 224, 223, 180, 134, 133, 91 (base peak).

1 - (3 -*Methoxyphenyl*) - 2 - *phenylethylamine* (**8**). The above oxime (5.0 g) was reduced with Raney Ni as described above to

give an oil of 3.7 g (79%) of **8**, b.p.$_{.5}$ 165–168°; ν_{max} (neat) 3360, 1600, 1583 cm^{-1}; *m/e* 227 (M$^+$), 211, 136 (base peak).

1 - (3 - *Hydroxyphenyl*) - 2 - *phenylethylamine* (**10**). Compound **8** (3 g) was heated under reflux in 25 ml of 47% HBr and 10 ml of AcOH for 4 hr. After evaporation of the solvent, the residue was dried to give crude **10**, which was used to the next step. For the further purification, see below.

3,5 - *Dimethoxyphenyl benzyl ketone* (**7**). 3,5 - Dimethoxybenzamide (**5**) reacted with benzylmagnesium chloride as described above, and gave crude **7** as an oil, which was chromatographed on a silica-gel column and eluted with benzene to give 3.0 g (78%) of **7** as a solid. Recrystallization from benzene gave colorless needles, m.p. 58–59°; ν_{max} (Nujol) 1682 cm^{-1}; *m/e* 256 (M$^+$), 166 (base peak), 137, 121; δ (CCl_4) 3.72 (6 H, s), 4.08 (2 H, s), 6.45 (1 H, t, J = 2 Hz), 6.98 (2 H, d, J = 2 Hz), 7.19 (5 H, s). (Found: C, 74.97; H, 6.37. $C_{16}H_{16}O_3$ requires: C, 74.98; N, 6.29%).

Compound **7** (2.8 g) was converted to its oxime as described above. Recrystallization from EtOH gave 2.2 g (74%) of pale yellow needles, m.p. 86–89°; ν_{max} (Nujol) 3220, 1640 cm^{-1}; *m/e* 271 (M$^+$), 164 (base peak). (Found: C, 70.67; H, 6.24; N, 5.10. $C_{16}H_{17}NO_3$ requires: C, 70.83: H, 6.32: N, 5.16%).

1 - (3,5 - *Dimethoxyphenyl*) - 2 - *phenylethylamine* (**9**). A soln of 0.9 g of the oxime of **7** in 50 ml of EtOH and 17 ml of 12% KOH was reduced by the treatment with 1.6 g Raney Ni as described above to give 0.9 g of **9** as an oil, which was converted to its hydrochloride by the treatment with HCl in EtOH. Recrystallization from EtOH–ether gave 0.7 g (62%) of colorless prisms, m.p. 194–196°; ν_{max} (Nujol) 1598 cm^{-1}. (Found: C, 65.29; H, 6.80; N, 4.83. $C_{16}H_{20}NO_2Cl$ requires: C, 65.41; H, 6.86; N, 4.77%).

1 - (3,5 - *Dihydroxyphenyl*) - 2 - *phenylethylamine* (**11**). Compound **9** (1.3 g) was hydrolyzed as described above to yield crude **11**, which was used to the next step.

3-*Benzyloxyphenyl benzyl ketone* (**13**). To a stirred soln of benzylmagnesium chloride prepared from 1.5 g (60 mmol) of Mg, 0.1 g iodine and 3.8 g (30 mmol) benzyl chloride in 30 ml anhyd ether was added dropwise 2.1 g (10 mmol) of **12** in 5 ml of ether over a 20 min period. The soln was heated under reflux for 5 hr, cooled and then poured into an ice-cold 10% H_2SO_4. The mixture was heated at 60° for 30 min, then cooled to room temp. and extracted with ether. The extract was washed with sat. $NaHCO_3$ aq and water, and dried over Na_2SO_4. Evaporation of the solvent gave **13** as a crystalline powder in almost quantitative yield. Recrystallization from EtOH gave 2.7 g (90%) of colorless needles, m.p. 70–72°; ν_{max} (Nujol) 1681 cm^{-1}; *m/e* 302 (M$^+$), 211; δ ($CDCl_3$) 4.23 (2 H, s), 5.09 (2 H, s), 7.2–7.6 (9 H). (Found: C 83.62; H, 6.02. $C_{21}H_{18}O_2$ requires: C, 83.42; H, 6.00%).

Compound **13** was converted to its oxime as described above. Recrystallization from EtOH gave 2.0 g (83%) of colorless prisms, m.p. 109–112°; ν_{max} 3238, 1598 cm^{-1}. (Found: C, 79.31; H, 5.96; N, 4.25. $C_{21}H_{19}NO_2$ requires: C, 79.47; H, 6.03; N, 4.41%).

1 - (3 - *Hydroxyphenyl*) - 2 - *phenylethylamine* (**10**). A soln of 1.7 g of the oxime of **13** in 40 ml EtOH and 40 ml 15% KOH was reduced with 5 g Raney Ni to give 735 mg (63%) of **10**. Recrystallization from EtOAc gave colorless prisms, m.p. 168–170°; ν_{max} 3300, 3250 cm^{-1}; δ (DMSO-d_6) 2.78 (2 H, d, J = 6.5 Hz), 3.78 (1 H, t, J = 65 Hz). (Found: C, 78.66; H, 7.10; N, 6.45. $C_{14}H_{15}NO$ requires: C, 78.84; H, 7.09; N, 6.57%).

3 - *Benzyloxyphenyl* 4-*methoxybenzyl ketone* (**14**). Compound **12** reacted with *p*-methoxybenzylmagnesium chloride[10] to give **14**, which was recrystallized from EtOH, m.p. 88–90°; ν_{max} (Nujol) 1685, 1585, 1510, 1250, 1170, 1010 cm^{-1}; *m/e* 332 (*M*$^+$), 211, 121; δ ($CDCl_3$) 3.76 (3 H, s), 4.17 (2 H, s), 5.09 (2 H, s), 6.8–7.6 (13 H, m). (Found: C, 79.75; H, 6.11. $C_{22}H_{20}O_3$ requires: C, 79.49; H, 6.06%).

Compound **14** was converted to its oxime, which was recrystallized from EtOH, m.p. 109–111°; ν_{max} (Nujol) 1595, 1580, 1505, 1230 cm^{-1}; *m/e* 347 (M$^+$), 331, 122, 121.

α - (3 - *Acetoxyphenyl*) - 4 - *methoxycinnamic acid* (**19**). A mixture of 5.5 g of **15**, 10 ml Et_3N and 100 ml Ac_2O was heated at 50° for 1 hr. To the soln was added 5.1 g of **17** and 14 ml of Et_3N, and the mixture was heated under reflux for 28 hr. The mixture was concentrated *in vacuo*, diluted with water, and extracted with EtOAc. The EtOAc layer was extracted with K_2CO_3 aq, and the extract was acidified with HCl and extracted with EtOAc. Evaporation of the solvent left a crystalline powder, which was recrystallized from benzene–hexane and EtOAc–hexane, then sublimed at 135°/15 mm Hg, and finally recrystallized again from benzene to give 2.0 g (17.8%) of colorless needles, m.p. 191–192°; ν_{max} 1760, 1670, 1600 cm^{-1}; *m/e* 312 (M$^+$); δ ($CDCl_3$) 2.24 (3 H, s), 3.73 (3 H, s), 6.6–7.4 (8 H, m), 7.92 (1 H, s), 10.97 (1 H, broad s). (Found: C, 69.37; H, 5.04. $C_{18}H_{16}O_5$ requires: C, 69.22; H, 5.16%).

1 - (3 - *Acetoxyphenyl*) - 2 - (4 - *methoxyphenyl*)*propionic acid* (**22**). Compound **19** (2 g) in 230 ml MeOH in the presence of 0.8 g 10% Pd-C was hydrogenated at room temp. and 1 atm. After 1.5 hr, the catalyst was removed by filtration, and the filtrate was concentrated to dryness to leave 2.1 g of a colorless viscous oil; ν_{max} (neat) 1760, 1740, 1705, 1610, 1585, 1515 cm^{-1}; *m/e* 314 (M$^+$); δ ($CDCl_3$) 2.28 (3 H, s), 2.8–3.5 (3 H, m), 3.74 (3 H, s), 6.6–7.3 (8 H, m).

1 - (3 - *Hydroxyphenyl*) - 2 - (4 - *methoxyphenyl*)*ethylamine* (**25**). To a soln of **22** (2.1 g) in 30 ml benzene and 0.1 ml pyridine was added 2 ml of $SOCl_2$, and the mixture was allowed to stand at room temp. overnight and then concentrated to leave a pale yellow oil of an acid chloride (ν_{max} 1765 cm^{-1}). A soln of 637 mg of NaN_3 in 2 ml water was added to a chilled soln of the acid chloride in 15 ml acetone with stirring and cooling in an ice-bath. The resulting mixture was stirred at room temp. for 45 min, and then extracted with benzene. The extract was washed with sat. NaCl aq, dried over Na_2SO_4, and concentrated to *ca.* 40 ml. To this azide soln (ν_{max} 2160 cm^{-1}) was added 4 ml of benzyl alcohol, and the mixture was heated at 50° for 15 min, then at 75° for 35 min and evaporated *in vacuo* to leave a urethane (ν_{max} 1760, 1700 cm^{-1}). Saturated HCl (40 ml) in EtOH was added to the urethane, and the mixture was heated under reflux for 3 hr. After evaporation of the solvent, the residue was dissolved in 5% HCl and washed with EtOAc. The aqueous layer was neutralized with $NaHCO_3$ and extracted with EtOAc. The extract was washed with sat. NaCl aq, dried and evaporated to leave 622 mg (33%) of a colorless oil, which was used to the next step without further purification; ν_{max} (Nujol) 3340, 1610 cm^{-1}; *m/e* 122 (base peak); δ (DMSO-d_6) 3.68 (3 H, s), 8.67 (2 H, broad s).

α - (3 - *Acetoxyphenyl*) - 3,4,5 - *trimethoxycinnamic acid* (**20**). A mixture of 4.5 g of **15**, 90 ml Ac_2O and 5 ml Et_3N was heated at 50° for 1 hr. After the addition of 6 g of **18** and 15.4 ml of Et_3N, the soln was heated under reflux for 31 hr, then concentrated, diluted with water and extracted with EtOAc. The EtOAc layer was extracted with K_2CO_3 aq. The K_2CO_3 extract was acidified with HCl and extracted with EtOAc. The extract was washed with sat. NaCl aq, dried and evaporated to leave a brown oil. After decolorization with the aid of active C, the residue was recrystallized from EtOAc–hexane five times to give 4.2 g (38%) of colorless needles, m.p. 148–150°; ν_{max}(Nujol) 1760, 1670 cm^{-1}; *m/e* 372 (M$^+$); δ ($CDCl_3$) 2.26 (3 H, s), 3.58 (6 H, s), 3.81 (3 H, s), 6.35 (2 H, s), 7.0-7.5 (4 H, m), 7.88 (1 H, s), 11.3 (1 H, broad s). (Found: C, 64.51; H, 5.41. $C_{20}H_{20}O_7$ requires: C, 64.54; H, 5.19%).

1 - (3 - *Acetoxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl*)*propionic acid* (**23**). A soln of 5 g of **20** in 240 ml MeOH was hydrogenated with 1.5 g of 10% Pd-C catalyst at 1 atm and room temp. After 2 hr, the catalyst was removed by filtration and the solvent was removed by distillation to leave 5.0 g of a colorless viscous oil: ν_{max} (neat) 1760, 1735, 1590, 1510 cm^{-1}; *m/e* 374 (M$^+$); δ ($CDCl_3$) 2.26 (3 H, s), 2.7–3.5 (3 H, m), 3.70 (6 H, s), 3.78 (3 H, s, 6.25 (2 H, s), 6.9–7.4 (4 H, m).

1 - (3 - *Hydroxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl*)*ethylamine* (**26**). To a soln of 5 g of **23** in 60 ml benzene was added 0.2 ml pyridine and 5 ml of $SOCl_2$, and the mixture was allowed to stand at room temp. overnight. Evaporation of the solvent left an oil [ν_{max} (neat) 1765 cm^{-1}], which was dissolved in 20 ml acetone. After the addition of 1.3 g NaN_3 in 5 ml water with stirring and cooling in an ice-bath, the mixture was stirred at room temp. for 45 min, diluted with water, and extracted with benzene. The extract was washed with water, dried over Na_2SO_4 and concentrated to *ca.* 60 ml. To the azide soln was added 3.5 ml benzyl alcohol, and the mixture was heated at 50° for 10 min, then at 80° for 45 min and finally allowed to stand at room temp. overnight. After evaporation of the solvent, the residue was heated at 160° for 10 min, dissolved in 120 ml sat. HCl in EtOH, and heated again under reflux for 2 hr. Evaporation of the solvent left a pale yellow solid, which was recrystallized from EtOH to

give 2.77g (60%) of colorless prisms, m.p. 237–238°; ν_{max} (Nujol) 3550, 3150 cm^{-1}; *m/e* 182, 181, 122 (base peak); δ (D_2O) 3.0–3.2 (2 H), 3.66 (9 H, s), 4.3–4.6 (1 H), 6.34 (2 H, s), 6.7–7.3 (4 H, m). (Found: C, 59,85; H, 6.79; N, 3.94; Cl, 10.51. $C_{17}H_{22}NO_4Cl$ requires: C, 60.08; H, 6.53; N, 4.12; Cl, 10.43%).

α - (3,5 - *Diacetoxyphenyl*) - 3,4,5 - *trimethoxycinnamic acid* (**21**). A mixture of 2.02 g of **16**, 33 ml Ac_2O and 3.7 ml ether was heated at 50° for 1 hr. To a soln was added 2.35 g of **18** and 2.4 ml Et_3N, and the mixture was heated at 120° for 30 hr. After evaporation of the solvent, 50 ml water was added to the residue, and the mixture was extracted with EtOAc. The EtOAc layer was extracted with sat. $NaHCO_3$ aq, the $NaHCO_3$ extract was acidified with HCl, and extracted again with EtOAc. The extract was washed with sat. NaCl aq, dried and evaporated to leave a solid (2.45 g), which was recrystallized from EtOAc–hexane to give 1.3 g (25%) of colorless needles, m.p. 206–207.5°; ν_{max} (Nujol) 1758, 1670 cm^{-1}; *m/e* 430 (M^+), 388, 346; δ ($CDCl_3$) 2.22 (6 H, s), 3.61 (6 H, s), 3.80 (3 H, s), 6.37 (2 H, s), 6.89 (3 H, s), 7.86 (1 H, s). (Found: C, 61.29; H, 5.02. $C_{22}H_{22}O_9$ requires: C, 61.39; H, 5.15%).

1 - (3,5 - *Diacetoxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl)propionic acid* (**24**). A soln of 1.3 g of **21** in 65 ml MeOH was hydrogenated in the presence of 350 mg 10% Pd-C at 1 atm and room temp. After 1.5 hr, the catalyst was removed and the filtrate was evaporated to leave 1.25 g of a colorless viscous oil; ν_{max} (Nujol) 1762, 1730, 1700, 1585, 1505 cm^{-1}; *m/e* 432 (M^+), 390, 348; δ ($CDCl_3$) 2.23 (6 H, s), 3.10 (2 H, t, J = 7 Hz), 3.6–3.9 (1 H), 3.70 (6 H, s), 3.77 (3 H, s), 6.24 (2 H, s), 6.8–7.3 (3 H), 8.30 (1 H, broad).

1 - (3,5 - *Dihydroxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl)ethylamine* (**27**). To an ice-cold soln of 1.2 g of **24** in 15 ml benzene and 0.03 g pyridine was added 1 ml of $SOCl_2$, and the mixture was allowed to stand at room temp. overnight. After evaporation of the solvent, the residual oil was dissolved in 4 ml acetone. A soln of 273 mg of NaN_3 in 1 ml water was added to the acetone soln with stirring and cooling in an ice-bath, and the mixture was stirred at room temp. for 2 hr. After the addition of water, the mixture was extracted with benzene. The extract was dried and concentrated to *ca.* 20 ml. Benzyl alcohol (1.8 ml) was added to the soln, and the mixture was heated at 100° for 2.5 hr and then concentrated *in vacuo*. The residue was washed with isopropyl ether, dissolved in 16 ml HCl in EtOH and heated under reflux for 3 hr. Evaporation of the solvent left an oil of **27**-hydrochloride, which was solidified by the addition of ether. Recrystallization from EtOH–ether gave 228 mg (18%) of colorless prisms, m.p. 177°; ν_{max} 3450, 3325, 3150 cm^{-1}; δ (D_2O) 3.07 (2 H, d, J = 6 Hz), 3.61 (3 H, s), 3.65 (6 H, s), 4.38 (1 H, t, J = 6 Hz), 6.32 (5 H, s). (Found: C, 56.10; H, 6.21; N, 4.27; Cl, 9.23. $C_{17}H_{22}NO_5Cl \cdot 1/2H_2O$ requires: C, 55.97; H, 6.35; N, 3.84: Cl, 9.72%).

3 - *Benzyloxyphenylnitromethane* (**29**). To a chilled soln of 9.2 g of $NaNO_2$ and 10 g urea in 155 ml DMF at −15 ~ −17° was added dropwise 16 g of **28** with stirring over a 1 hr period. The stirring was continued for additional 7 hr at the same temp. After the addition of ice-water, the mixture was extracted with benzene. The extract was washed with water, dried and evaporated to leave pale yellow crystals, which were recrystallized from EtOH to give 6.2 g (44%) of colorless needles, m.p. 53–54°; ν_{max} (Nujol) 1609, 1542, 1375 cm^{-1}; *m/e* 243 (M^+), 197. (Found: C, 69.10; H, 5.37; N, 5.76. $C_{14}H_{13}NO_3$ requires: C, 69.12; H, 5.39; N, 5.76%).

3 - *Benzyloxy* - 4' - *methoxy* - α - *nitrostilbene* (**32**). To a Schiff base (**30**) prepared from 3.1 g of **17** and n-propylamine was added 4 g of **29** in 10 ml of AcOH, and the resulting soln was allowed to stand at room temp. for 12 hr. After evaporation of the solvent, the residue was dissolved in EtOAc, washed with sat. $NaHCO_3$ aq and NaCl aq, and dried over Na_2SO_4. Evaporation of the solvent left a yellow solid, which was chromatographed on a silica-gel column eluting with benzene to give 4.1 g (65%) of yellow crystals. Recrystallization from EtOH gave yellow prisms, m.p. 89–90°; ν_{max} (Nujol) 1640 cm^{-1}; *m/e* 361 (M^+), 315; δ ($CDCl_3$) 3.77 (3 H, s), 5.04 (2 H, s), 6.6–7.3 (8 H, m), 7.35 (5 H, s), 8.17 (1 H, s). (Found: C, 72.95; H, 5.35; N, 3.76. $C_{22}H_{19}NO_4$ requires: C, 73.11; H, 5.30; N, 3.88%).

1 - (3 - *Benzyloxyphenyl*) - 2 - (4 - *methoxyphenyl)ethylamine* (**34**). A soln of 4 g of **32** in 50 ml of THF was added dropwise with cooling in an ice-bath and stirring to a soln of 3 g LAH in 150 ml THF. The mixture was heated under reflux for 12 hr, and the excess hydride was destroyed by the addition of water to the stirred and cooled mixture. A white mass of $Al(OH)_3$ was filtered off and the filtrate was evaporated to leave a yellow oil, which was dissolved in $CHCl_3$, washed with water and dried over K_2CO_3. Evaporation of the solvent left a pale yellow oil, which was converted to its hydrochloride by the addition of HCl in EtOH. Recrystallization from EtOH-ether gave 2.3 g (59%) of **34**-hydrochloride, m.p. 184–185°; ν_{max} (Nujol) 1603 cm^{-1}; δ (DMSO-d_6) 3.1–3.6 (2 H), 3.69 (3 H, s), 4.1–4.4 (1 H), 5.12 (2 H, s), 6.6–7.3 (8 H, m), 7.40 (5 H, s), 8.76 (2 H, broad s). (Found: C, 71.88; H, 6.57; N, 3.60. $C_{22}H_{24}NO_2Cl$ requires: C, 71.43; H, 6.55; N, 3.79%).

1 - (3 - *Hydroxyphenyl*) - 2 - (4 - *methoxyphenyl)ethylamine* (**25**). A soln of 1 g of **34**-hydrochloride in 200 ml MeOH was hydrogenated in the presence of 1 g 5% Pd-C under ordinary pressure at room temp. After 10 hr, the catalyst was filtered off and the filtrate was evaporated to leave 0.7 g of a colorless viscous oil of **25**-hydrochloride, which was used to the next step without further purification (see above).

3 - *Benzyloxy* - 3',4',5' - *trimethoxy* - α - *nitrostilbene* (**33**). To a Schiff base (**31**) prepared from 2.4 g of **18** and n-propylamine was added 2.43 g of **29** in 6 ml AcOH, and the mixture was allowed to stand at room temp. overnight. The precipitated crystals were collected by filtration and dissolved in EtOAc. The soln was washed with sat. $NaHCO_3$ aq and NaCl aq, dried and evaporated to leave yellow crystals, which were recrystallized from EtOAc to give 3.2 g (74%) of yellow prisms, m.p. 113–115°; ν_{max} 1643, 1580 cm^{-1}; *m/e* 421 (M^+); δ (DMSO-d_6) 3.43 (6 H, s), 3.63 (3 H, s), 5.12 (1 H, s) 6.52 (2 H, s), 6.9–7.5 (4 H, m), 7.36 (5 H, s), 8.25 (1 H, s). (Found: C, 68.19; H, 5.54; N, 3.46. $C_{24}H_{23}NO_6$ requires: C, 68.40; H, 5.50; N, 3.32%).

1 - (3 - *Benzyloxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl)ethylamine* (**35**). To a soln of 2 g LAH in 120 ml THF was added dropwise 2.7 g of **33** in 30 ml THF with stirring and cooling in an ice-bath. The mixture was heated under reflux for 12 hr, and the excess hydride was decomposed by the addition of water. A white mass of $Al(OH)_3$ was removed and the filtrate was evaporated to leave an oil, which was dissolved in EtOAc, washed with water and dried. Evaporation of the solvent left an oil, which was converted to its hydrochloride by the addition of HCl in EtOH. Recrystallization from EtOH–ether gave 1.8 g (66%) of colorless prisms, m.p. 160–162°; ν_{max} (Nujol) 3158 cm^{-1}; *m/e* 393, 391, 376, 212, 181; δ (DMSO-d_6) 3.20 (2 H, t, J = 7 Hz), 3.60 (3 H, s), 3.67 (6 H, s), 4.45 (1 H, m), 5.12 (2 H, s), 6.42 (2 H, s), 6.9–7.2 (4 H, m), 7.40 (5 H, s). (Found: C, 66.52; H, 6.58; N, 3.50. $C_{24}H_{28}NO_4Cl$ requires: C, 67.04; H, 6.56; N, 3.25%).

1 - (3 - *Hydroxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl)ethylamine* (**26**). A soln of 1.2 g of **35** in 150 ml MeOH was hydrogenated in the presence of 10% Pd-C to give an oil of **26**, which was dissolved in HCl in EtOH to give its hydrochloride. Recrystallization from EtOH–ether gave 0.9 g (39%) of colorless prisms, m.p. 237–238° (see above).

N-*Chloroacetylation of amines*; *general procedure.* To a stirred soln of 10 mmol of the starting amines synthesized above and 3-methoxybenzylamine in 20 ml of 10% NaOH was added dropwise 15 mmol of chloroacetylchloride over 10 min under ice-cooling. The ice bath was removed, and the mixture was stirred for 0.5–1 hr at room temp. and then acidified with 10% HCl. The acidified soln was extracted with EtOAc, and the extract was washed with water and dried over Na_2SO_4. Evaporation of the solvent left a N-chloroacetylamine (**36** ~ **44**) in 50–95% yield.

N - *Chloroacetyl* - 3 - *methoxybenzylamine* (**36**). Colorless fine needles, m.p. 80–82° (benzene–hexane); ν_{max} 3300, 1652, 1615, 1588, 1555 cm^{-1}; *m/e* 213 (M^+); δ ($CDCl_3$) 3.78 (3 H, s) 4.06 (2 H, s), 4.44 (2 H, d, J = 6 Hz), 6.75–7.4 (5 H, m). (Found: C, 56.17; H, 5.62; N, 6.45. $C_{10}H_{12}NO_2Cl$ requires: C, 56.21; H, 5.66; N, 6.56%).

N - *Chloroacetyl* - 3 - *hydroxybenzylamine* (**37**). Colorless prisms, m.p. 97.5–99° (benzene); ν_{max} (Nujol) 3370, 3165, 1648, 1534 cm^{-1}; *m/e* 199 (M^+), 164 (base peak); δ (DMSO-d_6) 4.09 (2 H, s), 4.22 (2 H, d, J = 6 Hz), 6.55–7.25 (4 H, m), 8.74 (1 H, broad), 9.31 (1 H, s). (Found: C, 54.45; H, 4.99; N, 6.91. $C_9H_{10}NO_2Cl$ requires: C, 54.55; H, 5.05; N, 7.02%).

N - *Chloroacetyl* - 1 - (3 - *hydroxyphenyl)ethylamine* (**38**). Colorless prisms, m.p. 64.5–65.5° (benzene); ν_{max} (Nujol) 3320, 3270, 1619, 1582 cm^{-1}; *m/e* 213 (M^+), 178, 136; δ ($CDCl_3$)

1.49 (3 H, d, J = 7 Hz), 4.04 (2 H, s), 5.14 (1 H, q, J = 7 Hz), 6.65–7.1 (4 H, m). (Found: C, 56.24; H, 5.54; N, 6.61. $C_{10}H_{12}NO_2Cl$ requires: C, 56.21; H, 5.66; N, 6.56%).

N - *Chloroacetyl* - 3,5 - *dihydroxybenzylamine* (**39**). Colorless prisms, m.p. 163–165° (EtOAc); λ_{max} (EtOH) (ϵ_{max}) 276 (1910), 282 nm (1880); ν_{max} (Nujol) 3400, 3170, 1657, 1590, 1544 cm^{-1}; *m/e* 215 (M^+), 180 (base peak); δ (DMSO-d_6) 4.09 (2 H, s), 4.11 (2 H, d, J = 6 Hz), 6.12 (3 H, s), 8.59 (1 H, broad), 9.15 (2 H, s). (Found: C, 50.22; H, 4.66; N, 6.55. $C_9H_{10}NO_3Cl$ requires: C, 50.13; H, 4.67; N, 6.52%).

N - *Chloroacetyl* - 1 - (3 - *hydroxyphenyl*) - 2 - *phenylethylamine* (**40**). Colorless prisms, m.p. 111–112° (benzene); ν_{max} (Nujol) 3318, 3196, 1642, 1585, 1525 cm^{-1}; *m/e* 192 (base peak), 122; δ ($CDCl_3$) 3.05 (2 H, d, J = 7 Hz), 3.87 (2 H, s), 5.14 (1 H, q, J = 7 Hz), 6.6–7.2 (9 H, m). (Found: C, 66.29; H, 5.60; N, 4.87. $C_{16}H_{16}NO_2Cl$ requires: C, 66.30; H, 5.56; N, 4.83%).

N - *Chloroacetyl* - 1 - (3 - *hydroxyphenyl*) - 2 - (4 - *methoxyphenyl*)*ethylamine* (**41**). Colorless viscous oil; ν_{max} (Nujol) 3360, 3270, 1656, 1529 cm^{-1}; *m/e* 319 (M^+): λ_{max}(EtOH) (ϵ_{max}) 276 (3760), 282 nm (3160); δ ($CDCl_3$) 3.02 (2 H, d, J = 7 Hz), 3.74 (3 H, s), 3.95 (2 H, s), 5.13 (1 H, m), 6.6–7.15 (8 H, m).

N - *Chloroacetyl* - 1 - (3 - *hydroxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl*)*ethylamine* (**42**). Colorless prisms, m.p. 170–171° (EtOH); ν_{max} (Nujol) 3320, 3270, 1655, 1590, 1555, 1505 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 277 nm (3000); *m/e* 379 (M^+), 286, 198, 181 (base peak); δ (CD_3OD) 3.02 (2 H, d, J = 7 Hz), 3.74 (9 H, s), 3.97 (2 H, s), 5.08 (1 H, t, J = 7 Hz), 6.40 (2 H, s), 6.55–7.2 (4 H, m). (Found: C, 60.00; H, 5.88; N, 3.71. $C_{19}H_{22}NO_5Cl$ requires: C, 60.01; H, 5.85; N, 3.69%).

N - *Chloroacetyl* - 1 - (3,5 - *dihydroxyphenyl*) - 2 - *phenylethylamine* (**43**). Colorless prisms, m.p. 188–190° (EtOAc); ν_{max} (Nujol) 3305, 1665, 1600, 1530 cm^{-1}; λ_{max}(EtOH) (ϵ_{max}) 277 (1880), 283 nm (1870); *m/e* 305 (M^+), 214, 138 (base peak); δ(DMSO-d_6) 2.94 (2 H, d, J = 7 Hz), 3.96 (2 H, s), 4.6–5.0 (1 H, m), 6.10 (1 H, d, J = 2 Hz), 6.20 (2 H, d, J = 2 Hz), 7.20 (5 H, s), 8.55 (1 H broad), 9.12 (2 H, s). (Found: C, 62.92; H, 5.26; N, 4.84. $C_{16}H_{16}NO_3Cl$ requires: C, 62.85; H, 5.27: N, 4.58%).

N - *Chloroacetyl* - 1 - (3,5 - *dihydroxyphenyl*) - 2 - (3,4,5 - *trimethoxyphenyl*)*ethylamine* (**44**). Colorless prisms, m.p. 206.5–208.5° (EtOH); ν_{max} (Nujol) 3410, 3330, 3280, 1650 cm^{-1}; *m/e* 395 (M^+), 302, 181 (base peak), 138; δ (CD_3OD) 2.93 (2 H, d, J = 7 Hz), 3.65 (3 H, s), 3.69 (6 H, s), 3.92 (2 H, s). (Found: C, 57.22; H, 5.77; N, 3.45. $C_{19}H_{22}NO_6Cl$ requires: C, 57.65; H, 5.61; N, 3.55%).

Photolysis of **36**. A soln of 854 mg (4 mmol) of **36** in 400 ml of 50% aqueous MeCN was irradiated with a 100 W high pressure mercury lamp (Eikosha, Osaka) under N_2 for 2.5 hr. The mixture was neutralized by the addition of 0.32 g $NaHCO_3$, concentrated to *ca.* 100 ml and extracted with EtOAc. The extract was washed with sat. NaCl aq, dried and evaporated to leave 0.78 g of an oil, which was chromatographed on a silica-gel column eluting with EtOAc–CH_2Cl_2 (1 : 1) to give three fractions. The first fraction was 134 mg (16%) of the recovered starting material (**36**). The second fraction was 278 mg (36%) of N-*glycoloyl*-3-*methoxybenzylamine* (**50**), which was recrystallized from benzene–hexane to give colorless plates, m.p. 90–92°; ν_{max} 3300, 3200, 1630, 1598, 1555 cm^{-1}; *m/e* 195 (M^+), 121; δ ($CDCl_3$) 3.75 (4 H, s), 4.04 (2 H, s), 4.38 (2 H, d, J = 6 Hz), 6.7–7.3 (5 H, m). (Found: C, 61.55; H, 6.75; N, 7.30. $C_{10}H_{13}NO_3$ requires: C, 61.52; H, 6.71; N, 7.18%). The third fraction was 97 mg (10%) of N-*acetylglycyl*-3-methoxybenzylamine (**51**); ν_{max} 3240, 3130, 1635, 1558 cm^{-1}; *m/e* 236 (M^+), 136; δ ($CDCl_3$) 1.96 (3 H, s), 3.75 (3 H, s), 3.90 (2 H, d, J = 5 Hz), 4.34 (2 H, d, J = 6 Hz), 6.7–7.3 (6 H, m).

Photocyclization of **37**

(a) *In 50% aqueous* MeCN. A soln of 500 mg (2.5 mmol) of **37** in 50% aqueous MeCN was irradiated with a 100 W lamp under N_2 for 1.5 hr. After evaporation of the solvent, the residue was recrystallized from EtOH to give 173 mg of 7 - *hydroxy* - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**52**) as colorless prisms, m.p. 236–238°; ν_{max} (Nujol) 3340, 1645, 860, 840, 813 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 282 nm (2160); *m/e* 163 (M^+); δ (DMSO-d_6) 3.28 (2 H, s), 4.23 (2 H, s), 6.58 (1 H, q, J = 8 and 2 Hz), 6.61 (1 H, d, J = 2 Hz), 6.94 (1 H, d, J = 8 Hz), 7.88 (1 H, broad s), 9.24 (1 H, s). (Found: C, 66.40; H, 5.59; N, 8.88. $C_9H_9NO_2$ requires: C, 66.24; H, 5.56; N, 8.58%). The mother liquor was concentrated and applied on preparative silica-gel TLC developing with CH_2Cl_2–EtOAc–EtOH (20:5:1) gave three zones from top to bottom, 12 mg (3%) of N - *acetyl* - 3 - *hydroxybenzylamine* [colorless prisms, m.p. 95–96.5° (EtOAc-hexane); ν_{max} 3350, 1640, 1550 cm^{-1}; *m/e* 165 (M^+), 122 (base peak); δ (DMSO-d_6) 1.81 (3 H, s), 4.14 (2 H, d, J = 6 Hz), 6.54–7.2 (4 H, m), 8.20 (1 H, broad s), 9.25 (1 H, s)], 30 mg (7%) of 5 - *hydroxy* - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**53**) [colorless needles, m.p. 227–228° (EtOAc); ν_{max} (Nujol) 3288, 1650, 778 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 282 nm (2650); *m/e* 163 (M^+); δ (DMSO-d_6) 3.24 (2 H, s), 4.28 (2 H, s), 6.65 (2 H, d, J = 8 Hz), 7.01 (1 H, t, J = 8 Hz), 7.84 (1 H, broad s), 9.47 (1 H, s). (Found: C, 64.66; H, 5.77; N, 7.93. $C_9H_9NO_2 \cdot 1/4H_2O$ requires: C, 64.08; H, 5.27; N, 8.30%)] and 52 mg of **52** (total yield; 225 mg, 55%).

(b) *In water.* A soln of 790 mg (4 mmol) of **37** in 400 ml water was irradiated as described above for 3 hr. As the reaction proceeded, small amounts of ppt separated out. The mixture was neutralized by the addition of 0.33 g $NaHCO_3$ and evaporated to dryness. The dried residue was extracted with EtOH, and the EtOH was evaporated to leave a solid, which was extracted with EtOAc. From the EtOAc insoluble fraction 288 mg of **52** was isolated. The EtOAc soluble fraction (227 mg) was chromatographed on a silica-gel column (20 g) eluting with CH_2Cl_2–EtOAc (1 : 1) to give 95 mg (12%) of the recovered starting material (**37**), 58 mg (9%) of N - acetyl - 3 - hydroxybenzylamine, 24 mg (4%) of **53** and 32 mg of **52** (total yield; 320 mg, 49%).

Hydrolysis of **52**. 10 mg of **52** was heated under reflux in 47% HBr for 2 hr. After evaporation of the acid, the residual solid was dried and measured its IR spectrum, ν_{max} (Nujol) 1695 cm^{-1}.

Hydrolysis of **53**. 3 mg of **53** was treated as described above, ν_{max} (Nujol) 1795 cm^{-1}.

Photocyclization of **39**. A soln of 320 mg (1.5 mmol) of **39** in 50% aqueous MeCN was irradiated as described above for 3 hr. After the addition of 120 mg of $NaHCO_3$, the mixture was concentrated to dryness and extracted with EtOH. After evaporation of the solvent, the residue was dissolved in MeOH and treated with excess CH_2N_2 in ether. After 2 days, the solvent was evaporated to leave a solid, which was purified with preparative TLC of silica-gel eluting with EtOAc–CH_2Cl_2 (5 : 1) to give 141 mg (45%) of 5,7 - *dimethoxy* - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**56**). Recrystallization from MeOH gave colorless needles, m.p. 191–194°; ν_{max} (Nujol) 3200, 1668 cm^{-1}; *m/e* 207 (M^+), 164 (base peak); δ (DMSO-d_6) 3.20 (2 H, s), 3.74 (3 H, s), 3.77 (3 H, s), 4.30 (2 H, s), 6.45 (2 H, s), 7.93 (1 H, broad s). (Found: C, 63.05; H, 6.17; N, 6.58. $C_{11}H_{13}NO_3$ requires: C, 63.75; H, 6.32; N, 6.75%).

Photocyclization of **38**. A soln of 406 mg (1.9 mmol) of **38** in 190 ml of 50% aqueous MeCN was irradiated for 2.5 hr. After evaporation of the solvent, the dried residue was extracted with EtOH. The EtOH was evaporated to leave a solid, which was recrystallized from EtOH to give 150 mg of 7 - *hydroxy* - 1 - *methyl* - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**54**). Recrystallization again from EtOH gave colorless prisms, m.p. 228–230°; ν_{max} (Nujol) 1648, 839, 863 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 281 nm (2180); *m/e* 177 (M^+), 162 (base peak), 134; δ (DMSO-d_6) 1.35 (3 H, d, J = 7 Hz), 3.32 (2 H, s), 4.42 (1 H, m), 6.60 (1 H,q, J = 8 and 2 Hz), 6.66 (1 H, d, J = 2 Hz), 6.91 (1 H, d, J = 8 Hz), 7.98 (1 H, s). (Found: C, 67.59; H, 6.47; N, 7.69. $C_{10}H_{11}NO_2$ requires: C, 67.78; H, 6.26; N, 7.91%). The above mother liquor was concentrated and applied to silica-gel preparative TLC eluting with EtOH–CH_2Cl_2 (1 : 20) to give 15 mg of the starting material (**38**), 45 mg (13%) of **55** and 100 mg of **54** (total yield; 250 mg, 74%). Recrystallization of crude **55** from EtOAc gave colorless needles of 5 - *hydroxy* - 3 - *oxo* - 1 - *methyl* - 1,2,3,4 - *tetrahydroisoquinoline* (**55**), m.p. 218–220°; ν_{max} (Nujol) 1652, 788 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 273 (2270), 279 nm (2220); *m/e* 177 (M^+), 162 (base peak), 134; δ (DMSO-d_6) 1.30 (3 H, d, J = 6 Hz), 3.21 (2 H, s), 4.45 (1 H, q, J = 6 Hz), 6.69 (2 H, d, J = 7 Hz), 6.98 (1 H, t, J = 7 Hz), 8.07 (1 H, s), 9.62 (1 H, s). (Found: C, 67.65; H, 6.14; N, 7.91. $C_{10}H_{11}NO_2$ requires: C, 67.78; H, 6.26; N, 7.91%).

Photocyclization of **40**. A soln of 150 mg (0.52 mmol) of **40** in 55 ml of 50% aqueous MeCN was irradiated with a 10 W low pressure mercury lamp (Eikosha) for 6 hr. The soln was concentrated and extracted with EtOAc. The extract was washed

with sat. $NaHCO_3$ aq and NaCl aq, dried and evaporated to leave a solid, which was recrystallized from EtOAc to give 64 mg of colorless prisms of 1 - *benzyl* - 7 - *hydroxy* - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**58**). Recrystallization again from EtOAc gave colorless prisms, m.p. 200–201°, ν_{max} (Nujol) 1643 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 282 nm (2380); *m/e* 253 (M^+), 162 (base peak), 134; δ (DMSO-d_6) 2.92 (2 H, d, J = 5 Hz), 3.35 (2 H, s), 4.61 (1 H, m), 6.51–7.22 (8 H, m), 8.91 (1 H, broad), 9.27 (1 H, s). (Found: C, 75.99; H, 5.94; N, 5.50. $C_{16}H_{15}NO_2$ requires: C, 75.87; H, 5.97; N, 5.53%). The above mother liquor of EtOAc was concentrated and applied to preparative TLC of silica-gel eluting with benzene-EtOAc (2:3) to give 9 mg (6%) of the starting material, 21 mg (16%) of **59** and 27 mg of **58** (total yield; 91 mg, 69%). Recrystallization of crude **59** from EtOAc gave colorless prisms of 1 - *benzyl* - 5 - *hydroxy* - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**59**), m.p. 170–171°; ν_{max} (Nujol) 3470, 3155, 1640 cm^{-1}; *m/e* 253 (M^+), 162 (base peak), 134; δ (CD_3OD) 2.9–3.1 (4 H), 4.8 (1 H, m), 6.6–7.4 (8 H, m). (Found: C, 71.42; H, 6.19; N, 5.23. $C_{16}H_{15}NO_2 \cdot H_2O$ requires: C, 70.83; H, 6.32; N, 5.16%).

Hydrolysis of **58**. 5 mg of **58** was heated under reflux in 6 N HCl for 10 hr. After evaporation of the acid, the residue was dried for an IR spectrum, ν_{max} (Nujol) 1695 cm^{-1}. This amino acid was heated *in vacuo* at 100° for 1 hr to recover **58**, whose IR is identical with that of the above sample of **58**.

Hydrolysis of **59**. Compound **59** in 47% HBr was heated under reflux for 4 hr. After evaporation of the acid, the residue was dried for an IR spectrum, ν_{max} (Nujol) 1800 cm^{-1}.

Photocyclization of **43**. A soln of 187 mg (0.61 mmol) of **43** in 60 ml of 50% aqueous MeCN was irradiated with the 10 W low pressure lamp for 5 hr. After the addition of 50 mg $NaHCO_3$, the mixture was concentrated and extracted with EtOAc. The extract was washed with sat. NaCl aq, dried and evaporated to leave a pale brown solid, which was chromatographed on a silica-gel column eluting with CH_2Cl_2–EtOAc (1:1) to give 106 mg (64%) of 1 - *benzyl* - 5,7 - *dihydroxy* - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**60**). Recrystallization from EtOAc-hexane gave colorless prisms, m.p. 220–223°; ν_{max} (Nujol) 3470, 3290, 1640 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 286 nm (2180); *m/e* 269 (M^+), 178 (base peak), 150; δ (CD_3OD) 2.9–3.1 (4 H), 4.60 (1 H, m), 6.23 (2 H, s), 6.8–7.3 (5 H, m). (Found: C, 71.06; H, 5.73; N, 5.00. $C_{16}H_{15}NO_3$ requires: C, 71.36; H, 5.61; N, 5.20%).

Photocyclization of **41**. A soln of 220 mg of **41** in 80 ml of 50% aqueous MeCN was irradiated with the 100 W lamp for 4 hr. The mixture was concentrated and extracted with EtOAc. The extract was washed with sat. $NaHCO_3$ aq and NaCl aq, and dried over Na_2SO_4. Evaporation of the solvent left a solid, which was applied to silica-gel preparative TLC developing with CH_2Cl_2–EtOAc (2:1) to give 17 mg (8%) of the starting material and 95 mg (49%) of 7 - *hydroxy* - 1 - (4 - *methoxybenzyl*) - 3 - *oxo* - 1,2,3,4 - *tetrahydroisoquinoline* (**61**). Recrystallization from EtOAc gave colorless prisms, m.p. 174–175°; ν_{max} (Nujol) 1643 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 276 (3440), 282 nm (3700); *m/e* 383 (M^+), 162 (base peak), 134, 121; δ (DMSO-d_6) 2.90 (2 H, d, J = 5 Hz), 3.40 (2 H, s), 3.75 (3 H, s), 4.61 (1 H, m), 6.65 (1 H, q, J = 2 and 7 Hz), 6.66 (1 H, d, J = 2 Hz), 6.82 (4 H, s), 6.86 (1 H, d, J = 7 Hz), 7.94 (1 H, broad), 9.30 (1 H, s). (Found: C, 71.86; H, 6.05; N, 4.80. $C_{17}H_{17}NO_3$ requires: C, 72.06; 6.05; N, 4.94%).

Photocyclization of **42**. A soln of 379 mg of **42** in 100 ml of 50% aqueous MeCN containing 0.1 g $NaHCO_3$ was irradiated with the 10 W lamp for 10 hr. After evaporation of the solvent, the dried residue was extracted with EtOH. The extract was applied to silica-gel preparative TLC developing with CH_2Cl_2–EtOH (20:1) to give two fractions. The upper fraction was 23 mg (7%) of 5 - *hydroxy* - 3 - *oxo* - 1 - (3,4,5 - *trimethoxybenzyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**63**). Recrystallization from EtOAc gave colorless needles, m.p. 169–171°; ν_{max} (Nujol) 1657 cm^{-1}; *m/e* 343 (M^+), 181, 162 (base peak); δ (DMSO-d_6) 2.89 (2 H, d, J = 4 Hz), 3.3 (2 H, s), 358 (6 H, s), 3.60 (3 H, s), 6.08 (2 H, s), 6.70 (2 H, d, J = 7 Hz), 6.98 (1 H, d, J = 7 Hz), 7.9 (1 H, broad), 9.40 (1 H, s). The lower fraction was 123 mg (36%) of 7 - *hydroxy* - 3 - *oxo* - 1 - (3,4,5 - *trimethoxybenzyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**62**). Recrystallization from EtOAc gave colorless prisms, m.p. 229–231°; ν_{max} 3290, 1640 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 280 nm (2670); *m/e* 343 (M^+), 181, 162 (base peak), 134; δ (DMSO-d_6) 2.90 (2 H, d, J = 4 Hz), 3.41 (2 H, s), 3.60 (9 H, s), 4.65 (1 H, m), 6.15 (2 H, s), 6.60 (1 H, q, J = 8 and 2 Hz), 6.67 (1 H, d, J = 2 Hz), 6.81 (1 H, d, J = 8 Hz), 7.90 (1 H, broad), 9.29 (1 H, s). (Found: C, 66.06; H, 6.21; N, 4.31. $C_{19}H_{21}NO_5$ requires: C, 66.46; H, 6.16; N, 4.08%).

Photocyclization of **44**. A soln of 130 mg of **44** in 50 ml of 50% aqueous MeCN was irradiated with the 100 W lamp for 5 hr. After evaporation of the solvent, the dried residue was purified on silica-gel preparative TLC developing with CH_2Cl_2–EtOH (20:1) to give 70 mg (60%) of 5,7 - *dihydroxy* - 3 - *oxo* - 1 - (3,4,5 - *trimethoxybenzyl*) - 1,2,3,4 - *tetrahydroisoquinoline* (**64**). Recrystallization from EtOH–EtOAc gave colorless prisms, m.p. 260–263°; ν_{max} (Nujol) 3240, 1652 cm^{-1}; λ_{max} (EtOH) (ϵ_{max}) 279 (2840), 285 nm (2450); *m/e* 359 (M^+), 181, 178 (base peak), δ (DMSO-d_6) 2.82 (2 H, d, J = 4 Hz), 3.30 (2 H, s), 3.59 (9 H, s), 6.13 (2 H, s), 6.28 (2 H, s), 7.79 (1 H, broad), 9.07 (1 H, s), 9.24 (1 H, s). (Found: C, 63.21; H, 5.83; N, 3.73. $C_{19}H_{21}NO_6$ requires: C, 63.50; H, 5.89; N, 3.90%).

Acknowledgement—We are grateful to Dr. S. Saito, Tanabe Seiyaku, for his valuable advice.

REFERENCES

[1]Y. Okuno, M. Kawamori, K. Hirao and O. Yonemitsu, *Chem. Pharm. Bull.* Tokyo **23**, 2584 (1975); and refs cited.
[2]Y. Okuno, K. Hemmi and O. Yonemitsu, *Chem. Commun.* 745 (1971).
[3]M. Ikeda, K. Hirao, Y. Okuno and O. Yonemitsu, *Tetrahedron Letters* 1181 (1974).
[4]For a review, see J. M. Bobbitt, *Adv. Heterocycl. Chem.* **15**, 99 (1973).
[5]*cf.* B. Staskun and T. van Es, *J. Chem. Soc.* (C) 531 (1966).
[6]J. Epstein, R. E. Plapinger, H. O. Michel, J. R. Cable, R. A. Stephani, R. J. Hester, C. Billington, Jr. and G. R. List, *J. Am. Chem. Soc.* **86**, 3075 (1964).
[7]*cf.* S. S. Jenkins, *Ibid.* **55**, 703 (1933).
[8]J. Levy and R. Pernot, *Bull. Soc. Chim. Fr.* **49**, 1730 (1931).
[9]*cf.* P. L. Pickard and T. L. Tolbert, *J. Org. Chem.* **26**, 4886 (1961); T. Cuvigny and H. Normant, *Bull. Soc. Chim. Fr.* 4990 (1968).
[10]M. G. Van Campen, D. F. Meisner and S. M. Paramerter, *J. Am. Chem. Soc.* **70**, 2296 (1948); R. C. Elderfield and V. B. Meyer, *Ibid.* **76**, 1883 (1954).
[11]S. Yamamura, M. Ohashi, S. Saito, Y. Iwasawa and A. Kiyomoto, *Japan Kokai* 49135955, 27, Dec. (1974).
[12]N. Kornblum, H. O. Larson, R. K. Blackwood, D. D. Moobery, E. P. Oliveto and G. E. Graham, *J. Am. Chem. Soc.* **78**, 1497 (1956).
[13]D. N. Robertson, *J. Org. Chem.* **25**, 47 (1960); S. M. Kupchan and H. C. Wormser, *Ibid.* **30**, 3792 (1965).
[14]S. F. Dyke, E. P. Tiley, A. W. C. White and D. P. Gale, *Tetrahedron* **31**, 1219 (1975).
[15]Y. Okuno, K. Hemmi and O. Yonemitsu, *Chem. Pharm. Bull. Tokyo* **20**, 1164 (1972).
[16]O. Yonemitsu, T. Tokuyama, M. Chaykovsky and B. Witkop, *J. Am. Chem. Soc.* **90**, 776 (1968); O. Yonemitsu, H. Nakai, Y. Kanaoka, I. L. Karle and B. Witkop, *Ibid.* **91**, 4591 (1969); H. Nakai, K. Hemmi, T. Iwakuma and O. Yonemitsu, *Chem. Pharm. Bull. Tokyo* **20**, 998 (1972).
[17]E. Bach and A. Kjaer, *Acta Chem. Scand.* **25**, 2629 (1971).