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Studies on Ketene and Its Derivatives. LXXXII.[1] Reaction of Diketene with *N*-Phenylhydroxylamine Derivatives

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The reaction of diketene with *N*-arylhydroxylamine (Ia—g) gave *N*-hydroxyacetoacetanilide derivative (VI), as a main product, besides the formation of azobenzene derivative (II), azoxybenzene derivative (III), 2-methylindole derivative (IV), and 2-aryl-5-methyl-4-isoxazolin-3-one (V). In the cases of Ia, Ic and Id, the reaction gave 2′-acetonylacetoacetanilide derivative (VIIa, c, d), which on hydrolysis with alkali was transformed to 1,5-dihydro-4-methyl-2*H*-1-benzazepin-2-one derivative (VIIIa, c, d).

In the formation of 2-methylindole derivative from Ic and Ie, reactions proceeded regiospectifically to give 2,6-dimethylindole (IVc) and 6-chloro-2-methylindole (IVe), respectively. Similarly in the formation of compound VII from Ic, the reaction gave a sole product (VIIc).

The reaction mechanisms are also discussed in connection with the structural elucidations.

Matter, *et al.*[3] reported that reaction of *N*-phenylhydroxylamine (Ia) with diketene in the presence of a catalytic amount of pyridine in benzene with cooling gives *N*-hydroxyacetoacetanilide (VIa), which then cyclizes to 5-methyl-2-phenyl-4-isoxazolin-3-one (Va) by treating with boron trifluoride etherate. On the other hand, the reaction of diketene with hydroxylamine and its *N*-alkyl derivatives gives 3-methyl-3-isoxazolin-5-one derivatives *via* *O*-acetoacetyl intermediates.[4] It should also be noted that Hamana and his co-workers obtained 3-ethoxycarbonyl-2-methylindole derivatives in the reaction of *N*-arylhydroxylamine with ethyl acetoacetate.[5] In connection with the above studies, we studied reinvestigation to clarify the probability of *O*-acetoacetylation of *N*-phenylhydroxylamine derivatives and some interesting results thus obtained are shown in the present report.

N-Phenylhydroxylamine derivatives (Ia—g) reacted with diketene in chloroform under ice-cooling to afford their *N*-acetoacetyl derivatives (VIa—g) in 70—85% yields as reported by Matter, *et al.*[3] However, the reaction under reflux gave several kinds of reaction products.

When a solution of *N*-phenylhydroxylamine (Ia) and diketene in chloroform was refluxed, a reddish brown tar was obtained. Separation of the products by silica gel column chromatography followed by recrystallization gave rise to azobenzene (IIa), azoxybenzene (IIIa), 2-methylindole (IVa), 5-methyl-2-phenyl-4-isoxazolin-3-one (Va), *N*-hydroxyacetoacetanilide (VIa), and 2′-acetonylacetoacetanilide (VIIa) in 7%, 13%, 18%, 10%, 40%, and 4% yields, respectively.

Of these products, Ia—VIa are already known, and identified unequivocally by comparison of infrared (IR) and nuclear magnetic resonance (NMR) spectra and mixed fusion with the corresponding authentic samples prepared according to the methods described in literatures.[3,6]

1) Part LXXXI: T. Kato and M. Noda, *Chem. Pharm. Bull.* (Tokyo), **24**, 1408 (1976).
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3) M. Matter, C. Vogel, and R. Bosshard, Ger. Patent, 1146494 [*Chem. Abstr.*, **59**, 10058*g* (1963)].
4) A.R. Katrizky, S. Øksne, and A.J. Boulton, *Tetrahedron*, **18**, 777 (1962); M. Fujimoto and M. Sakai, *Chem. Pharm. Bull.* (Tokyo), **13**, 248 (1965).
5) S. Saeki, M. Hayashida, T. Sukamoto, and M. Hamana, *Heterocycles*, **2**, 445 (1974).
6) *a*) L. Marion and C.W. Oldfield, *Can. J. Research*, **25B**, 1 (1947); *b*) F. Arndt, "Organic Synthesis," Coll. Vol. III, ed. by E.C. Horning, John Wiley & Sons, Inc., New York, 1960, p. 597.

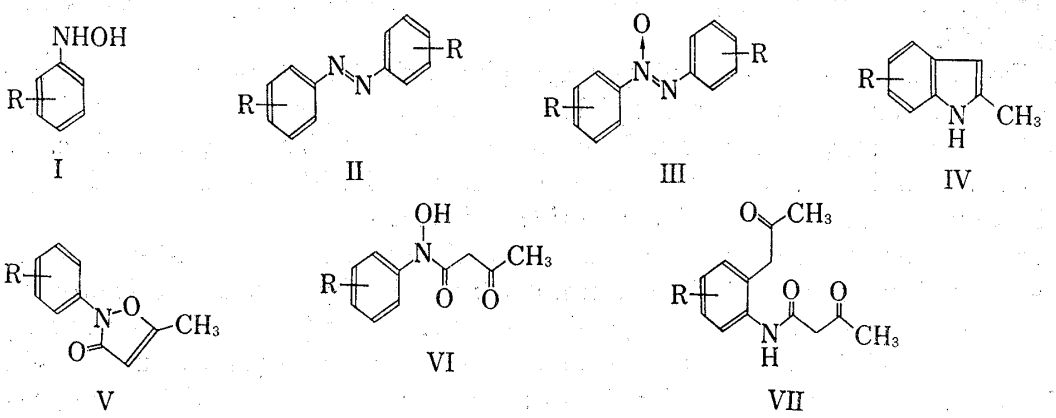
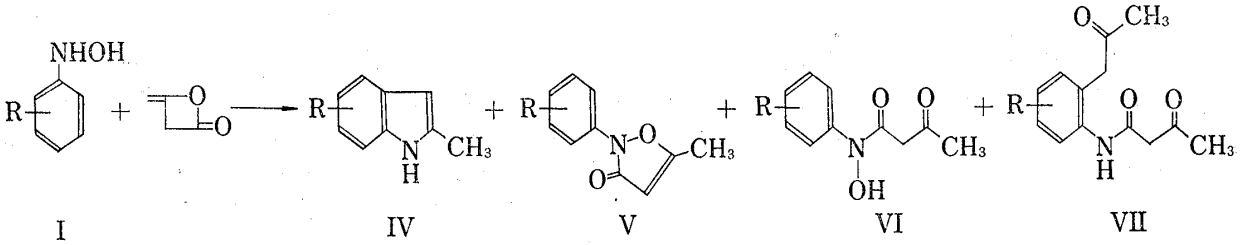


Chart 1

Compound (VIIa) was isolated from the last fraction eluted with ethyl acetate during the course of column chromatography, and the structural assignment was made on the bases of spectral data. Namely, the empirical formula, $C_{13}H_{15}NO_3$, indicated that VIIa was derived by decarboxylation from an adduct of one mole of Ia and two moles of diketene. The IR spectrum of VIIa exhibited the characteristic stretching bands at 3500, 3180, 1705, and 1660 cm^{-1} assignable to the hydroxyl, amide-NH, keto, and amide-carbonyl groups. The NMR spectrum in dimethyl sulfoxide (DMSO)-d_6 showed its characteristic signals at 1.20 ppm (3H, singlet), 2.25 ppm (3H, singlet), 2.68 and 2.92 ppm (each 1H, *AB*-quartet, $J=7$ cps), 3.20 ppm (1H, singlet), 5.28 ppm (1H, singlet, disappeared by treatment with D_2O), 7.05—7.42 ppm (4H, multiplet, aromatic protons), and 10.08 ppm (1H, broad, disappeared by treatment with D_2O, NH). The above spectral data were consistent with an enol structure of 2′-acetonyl-

Table I. Reaction of Diketene with N-Phenylhydroxylamine Derivatives



	I R	IV mp (°C)	IV yield (%)	V mp (°C)	V yield (%)	VI mp (°C)	VI yield (%)	VII mp (°C)	VII yield (%)
a	H	60[a]	18	34[b]	20	127[c]	40	130	4
b	2-CH_3	34[d]	20	—	—	—	—	—	—
c	3-CH_3	86[e]	21	56	4	85	37	137[f]	15
d	4-CH_3	116[g]	13	57	2.5	125[h]	40	148	13
e	3-Cl	128[i]	12	—	—	105	40	—	—
f	4-Cl	113[j]	5	102	3	143	47	—	—
g	4-Br	—	—	70	6.5	137	65	—	—

a) lit.[6a] mp 62°,[6b] mp 56—57°
b) lit.[3] mp 33—36°
c) lit.[3] mp 124—125°
d) 2,6-dimethylindole, lit.[6a] mp 35—37°
e) lit.[6a] mp 88.5°
f) 2′-acetonyl-5′-methylacetoacetanilide
g) lit.[6a] mp 114—116°
h) lit.[3] mp 124—125°
i) 6-chloro-2-methylindole, lit.[7b] mp 128°
j) lit.[7c] mp 114—116°

acetoacetanilide. Furthermore, these spectral data were essentially identical with those of VIIc and VIId.

Similarly, six kinds of *N*-phenylhydroxylamine derivatives (Ib—g) were subjected to the reaction with diketene and the mp and yields of the products (IV—VII) are listed in the Table.

Of these products, isomers could be considerable for IVc, IVe, and VIIc. But sole products were obtained, and IVc and IVe were identical with 6-substituted-2-methylindole derivatives by the comparison with authentic specimens.[7]

VIIc was characterized as the acetoacetyl derivative of 2-acetonyl-5-methylaniline but not as 3-methyl isomer by the NMR spectral data; that is, signals of aromatic protons of VIIc appeared at 6.88 ppm (1H, singlet, 6-H) and 6.93 and 7.18 ppm (each 1H, *AB*-quartet, J=8cps, 4-H and 3-H), which is consistent with the 5-methyl derivative (VIIc), but not with the 3-methyl isomer. Further supports for the structure of the compound VIIc were provided by its chemical reactions.

Hydrolysis of 2′-acetonyl-5′-methylacetoacetanilide (VIIc) with 10% sodium hydroxide gave colorless needles of mp 165°, $C_{12}H_{13}ON$ (VIIIc). The IR spectrum exhibited its characteristic band at 1660 cm^{-1} assignable to the amide-carbonyl stretching mode. The NMR spectrum showed signals at 2.05 ppm (3H, singlet, 4-CH_3), 2.35 ppm (3H, singlet, 8-CH_3), 2.80 ppm (2H, singlet, 5-CH_2), 6.40 ppm (1H, broad singlet, 3-H), 6.86 ppm (1H, singlet, 9-H), 6.90 and 7.08 ppm (each 1H, *AB*-quartet, J=7 cps, 7-H and 6-H), 9.45 ppm (1H, broad, NH). Furthermore, these spectral data were essentially identical with those of VIIIa and VIIId.

When VIIIc was hydrogenated over platinum catalyst, one equivalent mole of hydrogen was absorbed giving the compound IX, mp 165°, in which the carbonyl stretching band shifted to the high frequency region (1675 cm^{-1}) and the singlet signal due to 4-methyl group of VIIIc (2.05 ppm) was shifted to high field (1.10 ppm) and at the same time splitted to a doublet signal (J=6 cps). From the above facts, the compound (VIIIc) and (IX) were deduced to be 1,5-dihydro-4,8-dimethyl-2*H*-1-benzazepin-2-one and 4,8-dimethyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one, respectively.

On the other hand, hydrolysis of VIIc with 10% hydrochloric acid gave IVc which was identified by IR and NMR spectral comparison. Hydrogenation of VIIc over platinum catalyst afforded monohydroxy derivative, $C_{14}H_{19}O_3N$ (XII), which was insoluble in 10% sodium hydroxide and negative to the ferric chloride test. The IR spectrum of XII newly exhibited an absorption band due to alcoholic OH stretching mode at 3290 cm^{-1}. The NMR spectrum showed two doublet and a multiplet signals due to methyl, methylene, and methine groups at 1.30 ppm (3H, J=6 cps), 2.50 ppm (2H, J=6 cps), and 4.30 ppm (1H), respectively.

Hydrolysis of XII with alkali or mineral acid gave IVc. From the above chemical and spectral properties, XII can be uniqely assigned to *N*-(2-acetonyl-5-methylphenyl)-3-hydroxybutanamide.

The reduction of VIIc with sodium borohydride in ethanol gave dihydroxy derivative, $C_{14}H_{21}O_3N$ (XIII), which was also obtained from XII by the reduction with sodium borohydride or by further hydrogenation over platinum catalyst. The compound (XIII) is also insoluble in alkali and negative to the ferric chloride test. The NMR spectrum indicated the presence of two hydroxyl groups at 3.40 ppm and 4.20 ppm except for an NH group (9.30 ppm). At the same time, none of keto-carbonyl bands is appeared in the IR spectrum of XIII. Hydrolysis of XIII with alkali or mineral acid gave 1-(2-amino-4-methylphenyl)-2-propanol (XIV), which was then solidified as diacetyl derivative (XV), 2′-(2-acetoxypropyl)-5′-methylacetanilide. From the above data, the compound XIII was assigned to *N*-[2-(2-hydroxypropyl)-5-methylphenyl]-3-hydroxybutanamide.

7) *a*) M.G. Reinecke, H.W. Johnson, Jr., and J.F. Sebastian, *J. Am. Chem. Soc.*, **91**, 3817 (1969); *b*) J. Robert Piper and F.J. Stevens, *J. Heterocyclic Chem.*, **3**, 95 (1966); *c*) A.R. Bader, R.J. Bridegwater and P.R. Freeman, *J. Am. Chem. Soc.*, **83**, 3319 (1961).

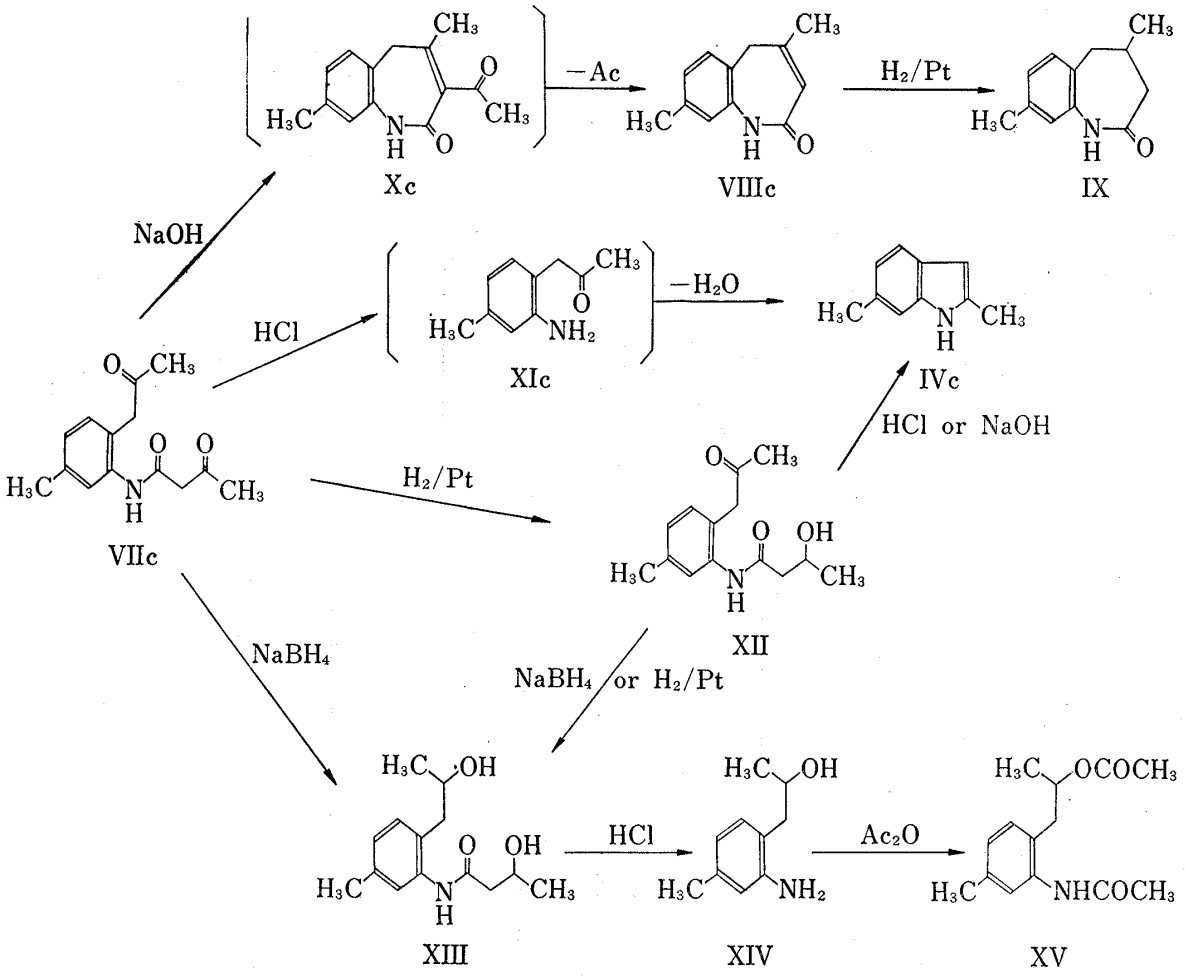


Chart 2

Formation of VIIIc and IVc from VIIc by hydrolysis can be explained as follows; the Claisen type condensation of VIIc with alkali catalyst gives 3-acetyl-4-methyl-2*H*-1-benzazepin-2-one intermediate (Xc), deacetylation of which gave rise to VIIIc. On the other hand, acidic hydrolysis affords *o*-aminophenylacetone intermediate (XIc) which might be unstable and immediately cyclizes into IVc following the Baeyer-Jackson synthesis.[8]

Although several pathways could be taken into the consideration of the formation of these products, a likely mechanism is shown in Chart 3. Namely, *N*-acetoacetylation of *N*-phenylhydroxylamine with diketene gives rise to VI (path a), cyclization of which along path b affords the 4-isoxazolin-3-one derivative (V).

Addition of another mole of diketene to VI along path c would give the *N*,*O*-diacetoacetyl derivative (XV), rearrangement of which followed by decarboxylation affords VII. Actually, the reaction of VII with diketene afforded readily V and VII.

Heating of VII with dilute mineral acid afforded 2-methylindole derivative (IV), however, the reaction did not proceed by using organic acid such as acetic or monochloroacetic acid. Therefore, another pathway should be available for the formation of IV. That is, addition of diketene to I along path d gives the *O*-acetoacetyl-*N*-phenylhydroxylamine intermediate (XVI). Cyclization of XVI affords the 3-isoxazolin-5-one intermediate (XVII), rearrangement of which followed by decarboxylation gives IV (path e).

8) A. Baeyer and O.R. Jackson, *Ber.*, **13**, 187 (1880); R.C. Elderfield, "Heterocyclic Compounds," Vol. III, John Willey & Sons Inc., New York, 1952, p. 38.

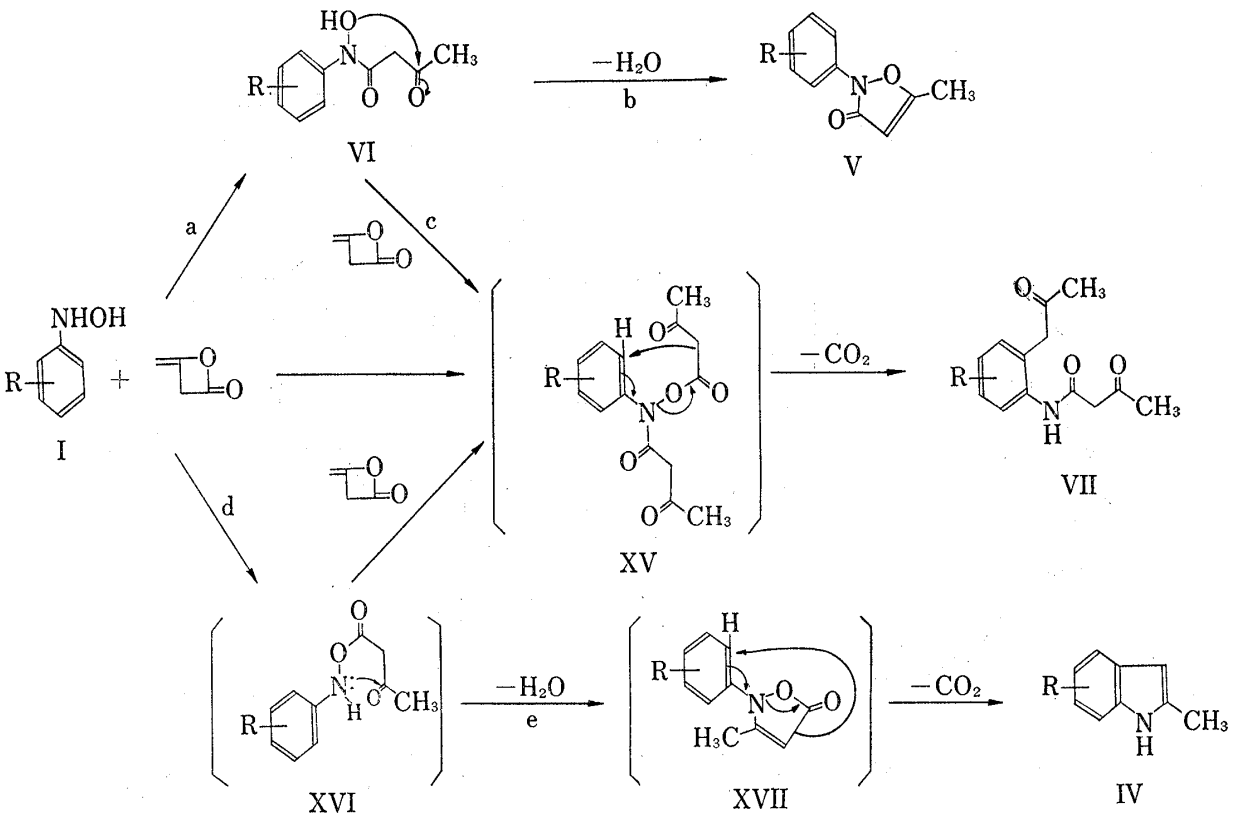


Chart 3

Experimental

All melting points were determined by a calibrated Yanagimoto melting point apparatus. IR spectra were taken on a Hitachi 215 spectrometer. A JNM 4H-100 and a Varian A-60 spectrometers were used for the measurement of NMR spectra, and the chemical shifts showed in ppm from TMS as an internal standard. Abrebiations are as follows: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet. UV spectra were measured by a Hitachi 200-10 spectrometer. Mass Spectra were also taken on a Hitachi RMU-7 mass spectrometer.

Reaction of Diketene with *N*-Phenylhydroxylamine (Ia)——A solution of Ia (2.2 g, 0.02 mole) and diketene (5.1 g, 0.06 mole) in $CHCl_3$ (40 ml) was refluxed for 8 hr. After evaporation of the solvent and excess diketene, the residue was chromatographed on silica gel column using hexane–benzene mixture (1: 1), benzene, $CHCl_3$, and AcOEt as eluants. Elution with hexane–benzene mixture gave orange needles of mp 51°, (IIa) (0.13 g, 7%) and pale yellow crystals of mp 36°, (IIIa) (0.27 g, 13%), undepressed on admixture with authentic samples of azobenzene and azoxybenzene, respectively.

The third fraction eluted with benzene gave a yellow oil, which was distilled under reduced pressure to give a viscous oil of bp 114—116° (2 mmHg). The solidified product was recrystallized from hexane giving pale yellow scales of mp 60°, (IVa) (0.45 g, 18%), undepressed on admixture with a sample of 2-methylindole.

The fourth fraction eluted with benzene gave a yellow oil of bp 96—98° (1 mmHg). Recrystallization of the solidified product from hexane gave yellow crystals of mp 34°, (Va) (0.35 g, 10%), whose spectral data were identical with those of 5-methyl-2-phenyl-4-isoxazolin-3-one prepared according to the literature.[3]

The $CHCl_3$ fraction gave colorless needles of mp 127° (1.6 g, 40%), (VIa), undepressed on admixture with an authentic sample of *N*-hydroxyacetoacetanilide.[3]

The last fraction eluted with AcOEt gave a reddish brown tar which was allowed to stand for two days to give colorless needles (ethanol) of mp 130°, (VIIa) (0.18 g, 4%). *Anal.* Calcd. for $C_{13}H_{15}O_3N$ (2′-acetonylacetoacetanilide): C, 66.93; H, 6.48; N, 6.01. Found: C, 66.63; H, 6.40; N, 5.89. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 3180 (NH), 1705 (C=O), 1660 (C=O). NMR δ (DMSO-d_6): 1.20 (3H, s, acetoacetyl-CH_3), 2.25 (3H, s, acetonyl-CH_3), 2.68 and 2.92 (each 1H, AB_q, J=7 cps, acetonyl-CH_2), 3.20 (1H, s, CO–C<u>H</u>=C(OH)–), 5.28 (1H, s, disappeared by treatment with D_2O, enol–OH), 7.05—7.42 (4H, m, aromatic-H), 10.08 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 232 (7000), 210 (16800). Mass Spectrum *m/e*: 233 (M^+).

Reaction of Diketene with *o*-Tolylhydroxylamine (Ib)——Following the procedure described above, Ib (2.5 g, 0.02 mole) was allowed to react with diketene (5.1 g, 0.06 mole) in $CHCl_3$ (40 ml). Elution with hexane-benzene mixture gave 2,2′-azotoluene (IIb), mp 56° (0.1 g, 5%) and 2,2′-azoxytoluene (IIIb), mp 59° (0.34 g, 15%).

The third fraction eluted with benzene gave a pale yellow oil of bp 90—93° (1 mmHg), which was solidified and recrystallized from hexane to give pale yellow scales of mp 34°, (IVb) (0.43 g, 20%), whose NMR spectrum was identical with that of 2,7-dimethylindole.[7a]

Reaction of Diketene with *m*-Tolylhydroxylamine (Ic)——Following the procedure described above, Ic (2.5 g, 0.02 mole) and diketene (5.1 g, 0.06 mole) were allowed to react in $CHCl_3$ (40 ml).

Elution with hexane–benzene mixture (1: 1) gave 3,3′-azotoluene (IIc), mp 54° (0.11 g, 5%) and 3,3′-azoxytoluene (IIIc), mp 39° (0.23 g, 10%), undepressed on admixture with authentic samples.

The third fraction eluted with benzene gave pale yellow scales (hexane) of mp 86°, (IVc) (0.6 g, 21%), whose NMR spectrum was identical with that of 2,6-dimethylindole.[7a]

The fourth fraction eluted with benzene gave colorless needles (hexane) of mp 56°, (Vc) (0.14 g, 4%). *Anal.* Calcd. for $C_{11}H_{11}O_2N$ (5-methyl-2-(*m*-tolyl)-4-isoxazolin-3-one): C, 69.84; H, 5.82; N, 7.41. Found: C, 69.80; H, 5.82; N, 7.29. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O). NMR δ ($CDCl_3$): 2.28 (3H, s, 5-CH_3), 2.34 (3H, s, tolyl-CH_3), 5.57 (1H, s, 4-H), 6.8—7.6 (4H, m, aromatic-H). Mass Spectrum *m/e*: 189 (M^+, base peak).

The fifth fraction eluted with $CHCl_3$ gave colorless needles ($CHCl_3$–hexane (4: 1)) of mp 85°, (VIc) (1.5 g, 37%). *Anal.* Calcd. for $C_{11}H_{13}O_3N$ (*N*-hydroxy-*m*-acetoacetotoluidide): C, 63.75; H, 6.32; N, 6.76. Found: C, 63.80; H, 6.35; N, 6.50. IR ν_{max}^{KBr} cm^{-1}: 3380 (OH), 1665 (C=O). NMR δ ($CDCl_3$): 1.68 (3H, s, acetoacetyl-CH_3), 2.36 (3H, s, tolyl-CH_3), 2.82 and 3.00 (each 1H, AB_q, J=7 cps, acetoacetyl-CH_2), 4.70 (1H, s, disappeared by D_2O, OH), 6.8—7.5 (4H, m, aromatic-H). Mass Spectrum *m/e*: 207 (M^+).

The last fraction eluted with AcOEt gave colorless needles (ethanol) of mp 137°, (VIIc) (0.65 g, 15%). *Anal.* Calcd. for $C_{14}H_{17}O_3N$ (2′-acetonyl-5′-methylacetoacetanilide): C, 67.99; H, 6.93; N, 5.66. Found: C, 68.05; H, 7.01; N, 5.39. IR ν_{max}^{KBr} cm^{-1}: 3520 (OH), 3200 (NH), 1705 (C=O), 1660 (C=O). NMR δ (DMSO-d_6): 1.18 (3H, s, acetoacetyl-CH_3), 2.21 (3H, s, acetonyl-CH_3), 2.30 (3H, s, tolyl-CH_3), 2.61 and 2.82 (each 1H, AB_q, J=7 cps, acetonyl-CH_2), 3.19 (1H, s, CO–C<u>H</u>=C(OH)–), 5.20 (1H, s, disappeared by D_2O, enol-OH), 6.88 (1H, s, 6-H), 6.93 and 7.18 (each 1H, AB_q, J=8 cps, 4-H and 3-H), 10.0 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 238 (6700), 209 (26000). Mass Spectrum *m/e*: 247 (M^+).

Reaction of Diketene with *p*-Tolylhydroxylamine (Id)——Following the similar procedure described above, Id (2.5 g, 0.02 mole) was allowed to react with diketene (5.1 g, 0.06 mole) in $CHCl_3$ (40 ml). The first and the second fractions eluted with hexane–benzene mixture (1: 1) gave 4,4′-azotoluene (IId), mp 143° (0.12 g, 6%) and 4,4′-azoxytoluene (IIId), mp 71° (0.32 g, 14%).

The third fraction eluted with benzene gave pale yellow scales (hexane) of mp 116°, (IVd) (0.38 g, 13%), whose NMR spectrum was identical with that of 2,5-dimethylindole.[7a]

The fourth fraction eluted with benzene gave colorless needles (hexane) of mp 57°, (Vd) (0.1 g, 2.5%). *Anal.* Calcd. for $C_{11}H_{11}ON$ (5-methyl-2-(*p*-tolyl)-4-isoxazolin-3-one): C, 69.84; H, 5.82; N, 7.41. Found: C, 69.92; H, 5.80; N, 7.22. IR ν_{max}^{KBr} cm^{-1}: 1662 (C=O). NMR δ ($CDCl_3$): 2.28 (3H, s, 5-CH_3), 2.34 (3H, s, tolyl-CH_3), 5.60 (1H, s, 4-H), 7.20 and 7.60 (each 1H, AB_q, J=8 cps, aromatic H). Mass Spectrum *m/e*: 189 (M^+, base peak).

The fifth fraction eluted with $CHCl_3$ gave colorless needles ($CHCl_3$) of mp 125°, (VId) (1.67 g, 40%). *Anal.* Calcd. for $C_{11}H_{13}O_3N$ (*N*-hydroxy-*p*-acetoacetotoluidide): C, 63.75; H, 6.32; N, 6.76. Found: C, 63.68; H, 6.33; N, 6.79. IR ν_{max}^{KBr} cm^{-1}: 3250 (OH), 1660 (C=O). NMR δ ($CDCl_3$): 1.68 (3H, s, acetoacetyl-CH_3), 2.32 (3H, s, tolyl-CH_3), 2.73 and 3.08 (each 1H, AB_q, J=9 cps, acetoacetyl-CH_2), 4.78 (1H, s, OH), 7.08 and 7.45 (each 2H, AB_q, J=8 cps, aromatic-H). Mass Spectrum *m/e*: 189 (M^+).

The last fraction eluted with AcOEt gave colorless needles (ethanol) of mp 148°, (VIId) (0.62 g, 13%). *Anal.* Calcd. for $C_{14}H_{17}O_3N$ (2′-acetonyl-4′-methylacetoacetanilide): C, 67.99; H, 6.93; N, 5.66. Found: C, 67.92; H, 7.06; N, 5.39. IR ν_{max}^{KBr} cm^{-1}: 3480 (OH), 3175 (NH), 1705 (C=O), 1660 (C=O). NMR δ (DMSO-d_6): 1.18 (3H, s, acetoacetyl-CH_3), 2.25 (3H, s, acetonyl-CH_3), 2.30 (3H, s, tolyl-CH_3), 2.63 and 2.85 (each 1H, AB_q, J=9 cps, acetonyl-CH_2), 3.18 (1H, s, CO–C<u>H</u>=C(OH)–), 5.22 (1H, s, disappeared by D_2O, enol-OH), 6.93 and 7.10 (each 1H, AB_q, J=8 cps, 5-H and 6-H), 7.08 (1H, s, 3-H), 9.92 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 240 (7200), 210 (28500). Mass Spectrum *m/e*: 247 (M^+).

Reaction of Diketene with *N*-(3-Chlorophenyl)hydroxylamine (Ie)——According to the procedure described above, Ie (2.9 g, 0.02 mole) was allowed to react with diketene (5.1 g, 0.06 mole) in $CHCl_3$ (50 ml). Elution with hexane–benzene mixture (1: 1) gave 3,3′-dichloroazobenzene (IIe), mp 102° (0.13 g, 5%) and 3,3′-dichloroazoxybenzene (IIIe), mp 97° (0.46 g, 17%).

The third fraction eluted with benzene gave pale yellow scales (hexane) of mp 128°, (IVe) (0.39 g, 12%) whose spectral data were identical with those of 6-chloro-2-methylindole.[7b]

The fourth fraction eluted with $CHCl_3$ gave colorless needles ($CHCl_3$) of mp 105°, (VIe) (1.82 g, 40%). *Anal.* Calcd. for $C_{10}H_{10}O_3NCl$ (*N*-hydroxy-3′-chloroacetoacetanilide): C, 52.86; H, 4.40; N, 6.16. Found: C, 52.79; H, 4.32; N, 6.14. IR ν_{max}^{KBr} cm^{-1}: 3350 (OH), 1680 (C=O). NMR δ ($CDCl_3$): 1.69 (3H, s, acetoacetyl-CH_3), 2.78 and 3.19 (each 1H, AB_q, J=14 cps, acetoacetyl-CH_2), 5 04 (1H, s, disappeared by D_2O, OH), 7.05—7.6 (4H, m, aromatic-H). Mass Spectrum *m/e*: 227 (M^+).

Reaction of Diketene with *N*-(4-Chlorophenyl)hydroxylamine (If)——According to the procedure described above, If (2.9 g, 0.02 mole) was allowed to react with diketene (5.1 g, 0.06 mole) in $CHCl_3$ (50 ml). The first and the second fraction eluted with benzene gave 4,4′-dichloroazobenzene (IIf), mp 188° (0.09 g, 3%) and 4,4′-dichloroazoxybenzene (IIIf), mp 159° (0.5 g, 18%).

The third fraction eluted with benzene gave colorless leaflets (hexane) of mp 113°, (IVf) (0.17 g, 5%), whose spectral data were identical with those of 5-chloro-2-methylindole.[7c]

The fourth fraction eluted with $CHCl_3$ gave colorless needles (hexane) of mp 102°, (Vf) (0.11 g, 3%). *Anal.* Calcd. for $C_{10}H_8O_2NCl$ (2-(4-chlorophenyl)-5-methyl-4-isoxazolin-3-one): C, 57.28; H, 3.82; N, 6.70. Found: C, 57.63; H, 3.89; N, 6.43. IR ν_{max}^{KBr} cm^{-1}: 1675 (C=O). NMR δ ($CDCl_3$): 2.34 (3H, s, 5-CH_3), 5.61 (1H. s, 4-H), 7.38 and 7.72 (each 2H, AB_q, J=9 cps, aromatic-H). Mass Spectrum *m/e*: 209 (M^+).

The fifth fraction eluted with $CHCl_3$ gave colorless needles ($CHCl_3$) of mp 143°, (VIf) (2.21 g, 47%). *Anal.* Calcd. for $C_{10}H_{10}O_3NCl$ (*N*-hydroxy-4′-chloroacetoacetanilide): C, 52.86; H, 4.40; N, 6.16. Found: C, 53.05; H, 4.73; N, 6.17 IR ν_{max}^{KBr} cm^{-1}: 3300 (OH), 1680 (C=O). NMR δ ($CDCl_3$): 1.72 (3H, s, acetoacetyl-CH_3). 2.85 and 3.00 (each 1H, AB_q, J=10 cps, acetoacetyl-CH_2), 4.00 (1H, s, disappeared by D_2O, OH), 7.21 and 7.56 (each 2H, AB_q, J=8 cps, aromatic-H). Mass Spectrum *m/e*: 227 (M^+).

Reaction of Diketene with *N*-(4-Bromophenyl)hydroxylamine (Ig)——According to the procedure described above, Ig (3.8 g, 0.02 mole) was allowed to react with diketene (5.1 g, 0.06 mole) in $CHCl_3$ (80 ml). Elution with benzene gave 4,4′-dibromoazoxybenzene (IIIg), mp 173° (0.3 g, 10%). The second fraction eluted with $CHCl_3$ gave colorless needles (hexane) of mp 70°, (Vg) (0.33 g 6.5%). *Anal.* Calcd. for $C_{10}H_8O_2NBr$ (2-(4-bromophenyl)-5-methyl-4-isoxazolin-3-one): C, 47.24; H, 3.15; N, 5.51. Found: C, 47.30; H, 3.02; N, 5.21. IR ν_{max}^{KBr} cm^{-1}: 1690 (C=O). NMR δ ($CDCl_3$): 2.34 (3H, s, 5-CH_3), 5.59 (1H, s, 4-H), 7.40 (4H, m, aromatic-H). Mass Spectrum *m/e*: 253 (M^+, base peak).

The third fraction eluted with $CHCl_3$ gave colorless needles ($CHCl_3$) of mp 137°, (VIg) (3.5 g, 65%). *Anal.* Calcd. for $C_{10}H_{10}O_3NBr$ (*N*-hydroxy-4′-bromoacetoacetanilide): C, 44.11; H, 3.67; N, 5.14. Found: C, 44.11; H, 3.89; N, 5.11. IR ν_{max}^{KBr} cm^{-1}: 3280 (OH), 1675 (C=O). NMR δ ($CDCl_3$): 1.72 (3H, s, acetoacetyl-CH_3), 2.70 and 3.08 (each 1H, AB_q, J=14 cps, acetoacetyl-CH_2), 4.00 (1H, s, disappeared by D_2O, OH), 7.35 (4H, m, aromatic-H). Mass Spectrum *m/e*: 271 (M^+).

Reaction of VIa with Diketene——A mixture of VIa (3.9 g) and diketene (3.5 g) in $CHCl_3$ (100 ml) was refluxed for 6 hr in the presence of a catalytic amount of Et_3N. Evaporation of the solvent and excess diketene gave a reddish brown tar, which was chromatographed on a silica gel column giving 0.3 g (8%) of Va (mp 33—34°) and 0.1 g (3%) of VIIa (mp 130°).

1,5-Dihydro-4-methyl-2*H*-1-benzazepin-2-one (VIIIa)——A solution of VIIa (0.12 g) in 10% NaOH (30 ml) was refluxed for 3 hr. The reaction mixture was cooled and pale yellow crystals precipitated were collected. Recrystallization from 60% ethanol gave colorless needles of mp 187°, (VIIIa) (0.65 g, 70%). *Anal.* Calcd. for $C_{11}H_{11}ON$: C, 76.27; H, 6.40; N, 8.09. Found: C, 76.35; H, 6.47; N, 8.14. IR ν_{max}^{KBr} cm^{-1}: 3180 (NH), 1655 (C=O). NMR δ ($CDCl_3$): 2.10 (3H, s, 4-CH_3), 2.86 (2H, s, 5-CH_2), 6.53 (1H, s, 3-H), 7.1—7.35 (4H, m, aromatic-H), 9.70 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 290 (1200), 255(s), (8000), 232 (17500). Mass Spectrum *m/e*: 173 (M^+).

1,5-Dihydro-4,8-dimethyl-2*H*-1-benzazepin-2-one (VIIIc)——A solution of VIIc (0.15 g) in 10% NaOH (30 ml) was treated in the same way as above giving VIIIc, mp 165° (colorless needles from 60% ethanol). Yield. 0.07 g (60%). *Anal.* Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 76.92; H, 6.91; N, 7.49. IR ν_{max}^{KBr} cm^{-1}: 3180 (NH), 1660 (C=O). NMR δ ($CDCl_3$): 2.05 (3H, s, 4-CH_3), 2.33 (3H, s, 8-CH_3), 2.80 (2H, s, 5-CH_2), 6.40 (1H, s, 3-H), 6.86 (1H, s, 9-H), 6.90 and 7.08 (each 1H, AB_q, J=7 cps, 7-H and 6-H), 9.45 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 290(s) (1300), 254(s) (8400), 232 (25700). Mass Spectrum *m/e*: 187 (M^+).

1,5-Dihydro-4,7-dimethyl-2*H*-1-benzazepin-2-one (VIIId)——A solution of VIId (0.15 g) in 10% NaOH (30 ml) was treated in the same way as above giving VIIId, mp 167° (colorless needles from 60% ethanol). Yield. 0.08 g (67%). *Anal.* Calcd. for $C_{12}H_{13}ON$: C, 76.97; H, 7.00; N, 7.48. Found: C, 77.01; H, 7.10; N, 7.48. IR ν_{max}^{KBr} cm^{-1}: 3170 (NH), 1660 (C=O). NMR δ ($CDCl_3$): 2.10 (3H, s, 4-CH_3), 2.34 (3H, s, 7-CH_3), 2.80 (2H, s, 5-CH_2), 6.42 (1H, s, 3-H), 7.0 (3H, m, aromatic-H), 8.75 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 295(s) (1300), 255(s) (9000), 235 (29000). Mass Spectrum *m/e*: 187 (M^+, base peak).

Catalytic Hydrogenation of VIIIc——A solution of VIIIc (0.1 g) in a mixture of ethanol and AcOEt (1: 1, 50 ml) was hydrogenated over PtO_2 catalyst at room temperature. After absorption of about 18 ml of H_2, the catalyst was separated by filtration and the filtrate was evaporated to dryness. The residue was recrystallized from 50% ethanol to give colorless needles of mp 163°, (IX) (0.07 g, 70%). *Anal.* Calcd. for $C_{12}H_{15}ON$ (4,8-di-methyl-1,3,4,5-tetrahydro-2*H*-1-benzazepin-2-one): C, 76.15; H, 7.99; N, 7.40. Found: C, 75.99; H, 8.09; N, 7.41. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1675 (C=O). NMR δ ($CDCl_3$): 1.10 (3H, d, J=6 cps, 4-CH_3), 2.08 and 2.92 (each 1H, each q, J=6 and 3 cps, 3-CH_2), 2.35 (3H, s, 8-CH_3), 2.42 (2H, d, J=6 cps, 5-CH_2), 2.60 (1H, m, 4-H), 6.90 (1H, s, 9-H), 6.95 and 7.12 (each 1H, AB_q, J=6 cps, 6-H and 7-H), 8.52 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 285 (1200), 276(s) (1300), 245 (9000), 215 (28500). Mass Spectrum *m/e*: 189 (M^+).

Catalytic Hydrogenation of VIIc——A solution of VIIc (0.15 g) in ethanol (50 ml) was shaken in H_2 in the presence of PtO_2 catalyst at room temperature. After absorption of about 18 ml of H_2, the catalyst was removed by filtration and the filtrate was evaporated to dryness. The residue was recrystallized from $CHCl_3$–hexane mixture (1: 2) to give colorless needles of mp 115°, (XII) (0.11 g, 73%). *Anal.* Calcd. for $C_{14}H_{19}O_3N$ (*N*-(2-acetonyl-5-methylphenyl)-3-hydroxybutanamide): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.51; H, 7.67; N, 5.50. IR ν_{max}^{KBr} cm^{-1}: 3290 (OH), 3200 (NH), 1710 (C=O), 1660 (C=O). NMR δ ($CDCl_3$):

1.30 (3H, d, J=6 cps, butanoyl-CH_3), 2.22 (3H, s, acetonyl-CH_3), 2.34 (3H, s, tolyl-CH_3), 2.50 (2H, d, J=6 cps, CO-C<u>H</u>$_2$-CH(OH)-), 3.65 (2H, s, acetonyl-CH_2), 3.75 (1H, br s, disappeared by D_2O, OH), 4.30 (1H, m, CH_2-C<u>H</u>(OH)-CH_3), 6.98 and 7.10 (each 1H, AB_q, J=6 cps, 4-H and 3-H), 7.62 (1H, s, 6-H), 8.52 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ(ε): 240(s) (6500), 209 (24000). Mass Spectrum m/e: 249 (M^+).

Reduction of VIIc with Sodium Borohydride——A mixture of VIIc (0.15 g) and $NaBH_4$ (0.02 g) in ethanol (50 ml) was stirred for 30 min at room temperature. After evaporation of the solvent under reduced pressure, the residue was dissolved in water (50 ml). The solution was neutralized with 10% HCl, and extracted with ether. The ether solution was washed with water, dried over $MgSO_4$, and condensed to give colorless needles ($CHCl_3$–hexane mixture (1: 2)) of mp 97°, (XIII) (0.09 g, 60%). *Anal.* Calcd. for $C_{14}H_{21}O_3N$ (*N*-[2-(2-hydroxypropyl)-5-methylphenyl]-3-hydroxybutanamide): C, 66.90; H, 8.42; N, 5.57. Found: C, 66.95; H, 8.50; N, 5.30. IR ν_{max}^{KBr} cm^{-1}: 3500 (OH), 3270 (NH), 1650 (C=O). NMR δ ($CDCl_3$): 1.18—1.35 (6H, overlapped d, J=6 cps, -CH(OH)-C<u>H</u>$_3$×2), 2.31 (3H, s, tolyl-CH_3), 2.42 (2H, d, J=6 cps, Ar-C<u>H</u>$_2$-CH(OH)-), 2.65 (2H, d, J=6 cps, CO-C<u>H</u>$_2$-CH(OH)-), 3.40 (1H, br, disappeared by D_2O, OH), 4.0 (1H, m, CH_2-C<u>H</u>(OH)-CH_3), 4.2 (1H, br, disappeared by D_2O, OH), 4.30 (1H, m, CO-CH_2-C<u>H</u>(OH)-CH_3), 6.85 and 6.98 (each 1H, AB_q, J=9 cps, 3-H and 4-H), 7.58 (1H, s, 6-H). 9.30 (1H, br, NH). UV $\lambda_{max}^{ethanol}$ mμ (ε): 245 (9800), 212 (28000). Mass Spectrum m/e: 251 (M^+).

Hydrolysis of VIIc with Hydrochloric Acid——A mixture of VIIc (0.15 g) and 10% HCl (50 ml) was refluxed for 3 hr. After neutralizing, the mixture was extracted with ether. The ether solution was washed with water and dried over $MgSO_4$. Afer evaporation of ether, the residue was chromatographed on a silica gel column using $CHCl_3$ as an eluant giving IVc (0.03 g, 30%).

Hydrolysis of XII with Sodium Hydroxide——A mixture of XII (0.1 g) and 10% NaOH (30 ml) was refluxed for 3 hr. The reaction mixture was neutralized with 10% HCl and extracted with ether. The ether solution was washed with water and dried over $MgSO_4$. After evaporation of ether, the residue was chromatographed on a silica gel column using $CHCl_3$ as an eluant giving IVc (0.04 g, 70%). Hydrolysis of XII with 10% HCl afforded the same product (IVc).

Hydrolysis of XIII with Hydrochloric Acid——A mixture of XIII (0.2 g) and 10% HCl (50 ml) was refluxed for 3 hr. The reaction mixture was made alkaline with 10% NaOH and extracted with ether. This ether solution was washed with water and dried over $MgSO_4$. After evaporation of ether, the oily residue was chromatographed on a silica gel column using $CHCl_3$–AcOEt mixture (4: 1) as an eluant giving 1-(2-amino-4-methylphenyl)-2-propanol (XIV), as a pale yellow oil. Yield. 0.08 g (60%). IR ν_{max}^{liquid} cm^{-1}: 3200 (OH, NH). NMR δ ($CDCl_3$): 1.22 (3H, d, J=6 cps, -CH(OH)-C<u>H</u>$_3$), 2.32 (3H, s, tolyl-CH_3), 2.60 (2H, d, J=6 cps, -CH(OH)-C<u>H</u>$_2$-Ar), 3.45 (3H, br, OH and NH), 4.03 (1H, m, CH_2-C<u>H</u>(OH)-CH_3), 6.50 (1H, s, 3-H), 6.60 and 6.95 (each 1H, AB_q, J=9 cps, 6-H and 5-H). Mass Spectrum m/e: 165 (M^+).

Heating of the oil (0.08 g) with Ac_2O (1 ml) followed by distillation of excess reagent *in vacuo* gave a crystalline residue. Recrystallization from hexane afforded colorless needles of mp 116°, (XV) (0.07 g, 53%). *Anal.* Calcd. for $C_{14}H_{19}O_3N$ (2′-(2-acetoxypropyl)-5′-methylacetanilide): C, 67.44; H, 7.68; N, 5.62. Found: C, 67.40; H, 7.71; N, 5.60. IR ν_{max}^{KBr} cm^{-1}: 3200 (NH), 1730 (C=O), 1665 (C=O). NMR δ ($CDCl_3$): 1.28 (3H, d, J=7 cps, propyl-CH_3), 2.11 (3H, s, acetyl-CH_3), 2.26 (3H, s, acetyl-CH_3), 2.35 (3H, s, tolyl-CH_3), 2.50 and 3.06 (each 1H, each ABX_q, J=14 cps and J=8 cps, J=14 cps and J=4 cps, propyl-CH_2), 4.74 (1H, m, propyl-CH), 6.88 and 7.02 (each 1H, AB_q, J=8 cps, 6-H and 5-H), 8.05 (1H, s, 3-H), 8.57 (1H, br, NH). Mass Spectrum m/e: 249 (M^+).

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