reaction of α,β-epoxy ketone systems under different steric environment in the steroid nucleus was described. A remarkably inert character of the 16α,17-epoxy-20-oxo system in the pregnane series for the ring opening under PPA catalysis with such nucleophile as alkylmercaptans was observed. The efficient catalytic action of PPA for normal ring opening at C-4 of 4β,5:16α,17-diepoxy-5β-pregnane-3,20-dione (Ⅱb) was reported. Ethanethiol reacted with the diepoxide (Ⅱb) in PPA-dioxane affording 16α,17-epoxy-4-ethylthiopregn-4-ene-3,20-dione (Ⅳ) and a further product, 3,4-bis(ethylthio)-16α,17-epoxypregna-3,5-dien-20-one (Ⅴ). Ethanedithiol and 2-mercaptoethanol reacted with Ⅱb, as expected, affording 16α,17-epoxy-20-oxopregna-3,5-dieno[3,4-*b*]dithiane (Ⅵ) and its oxathiane derivative (Ⅶ) respectively.

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142. Shinsaku Minami, Masatsugu Tomita, Hideji Takamatsu,*1 and Shojiro Uyeo*2 : The Schmidt Reaction with Some Tetralone and Indanone Derivatives.*3

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In the previous paper[1] we have reported a synthesis of demethyldeoxylycoramine (Ⅰ), the seven-membered heterocyclic ring of which was elaborated by the use of Bischler-Napieralski reaction. Since, however, the yield of the desired product was not satisfactory and an alternative effective pathway to this ring system still remained to be worked out.*4

Towards the end of this synthetic study, we noted that Ichii[2] had shown that the Schmidt reaction on 1,2-dihydro-3*H*-pyrido[3,2,1-*kl*]phenothiazin-3-one (Ⅱ) afforded, contrary to his initial expectation, compound (Ⅲ) in which the nitrogen atom introduced was not adjacent to a benzene ring. This result led us to believe that the formation of a homodihydroisocarbostyril was possible with a substituted tetralone possessing an electron releasing group (*e.g.* alkoxyl) in the position ortho or para to the carbonyl group, though it had been reported[3] that the Schmidt reaction with tetralone itself gave exclusively homodihydrocarbostyril.

In order to confirm this idea, we undertook several experiments using the tetralone (Ⅸ) and the indanones (XIX and XX). For the synthesis of the tetralone (Ⅸ), 1-(*m*-methoxyphenyl)cyclohexaneacetic acid (Ⅳ)[4,5] was converted into its homologous acid (Ⅷ)

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*3 Presented at the Kinki Branch Meeting of the Pharmaceutical Society of Japan, Kyoto, May, 1963.
*4 Very recently Professor Ban of Hokkaido University reported that the Bischler-Napieralski cyclization to a seven-membered heterocyclic ring could effectively be achieved by using polyphosphoric ester as a condensing agent (19th Annual Meeting of Pharmaceutical Society of Japan (1964)).

1) S. Minami, S. Uyeo : This Bulletin, **12**, 1012 (1964).
2) T. Ichii : Yakugaku Zasshi, **82**, 999 (1962).
3) P. A. S. Smith : J. Am. Chem. Soc., **70**, 320 (1948).
4) T. Takahashi, M. Hori, A. Kanbara : This Bulletin, **7**, 917 (1959).
5) M. Tomita, J. Aritomi, S. Minami : Yakugaku Zasshi, **83**, 1026 (1963).

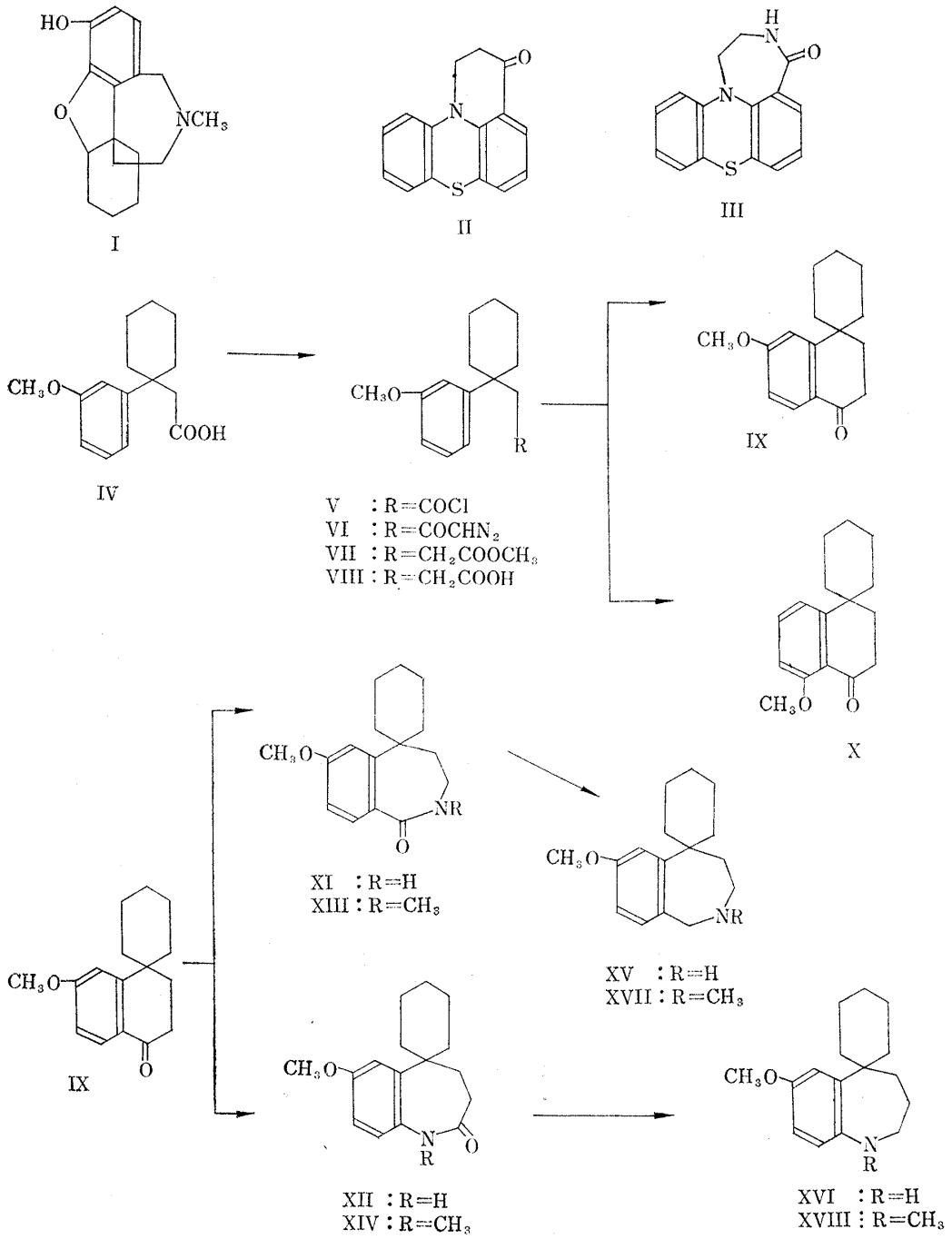

Chart 1.

by the Arndt-Eistert method and then treated with polyphosphoric acid to give 7′-methoxy-2′,3′-dihydrospiro[cyclohexane-1,1′(4′*H*)-naphthalen]-4′-one (Ⅸ), along with a small amount of the 5′-methoxy-isomer (Ⅹ). The Schmidt reaction with the 7′-methoxytetralone (Ⅸ) by treating it with sodium azide in sulfuric acid yielded the homoisocarbostyril (Ⅺ) and homocarbostyril (Ⅻ) in 28% and 38% yield, respectively. We would point out here that positive identification of the desired compound is possible by infrared analysis provided that the isomeric lactam is aiso available. Comparison of the infrared absorption spectra of a pair of lactams (Ⅺ and Ⅻ) and their respective N-methyl derivatives (XIII and XIV) show a small but significant difference (15～20 cm^{-1}) between the homoisocarbostyrils (Ⅺ and XIII) which have the lower frequencies and the

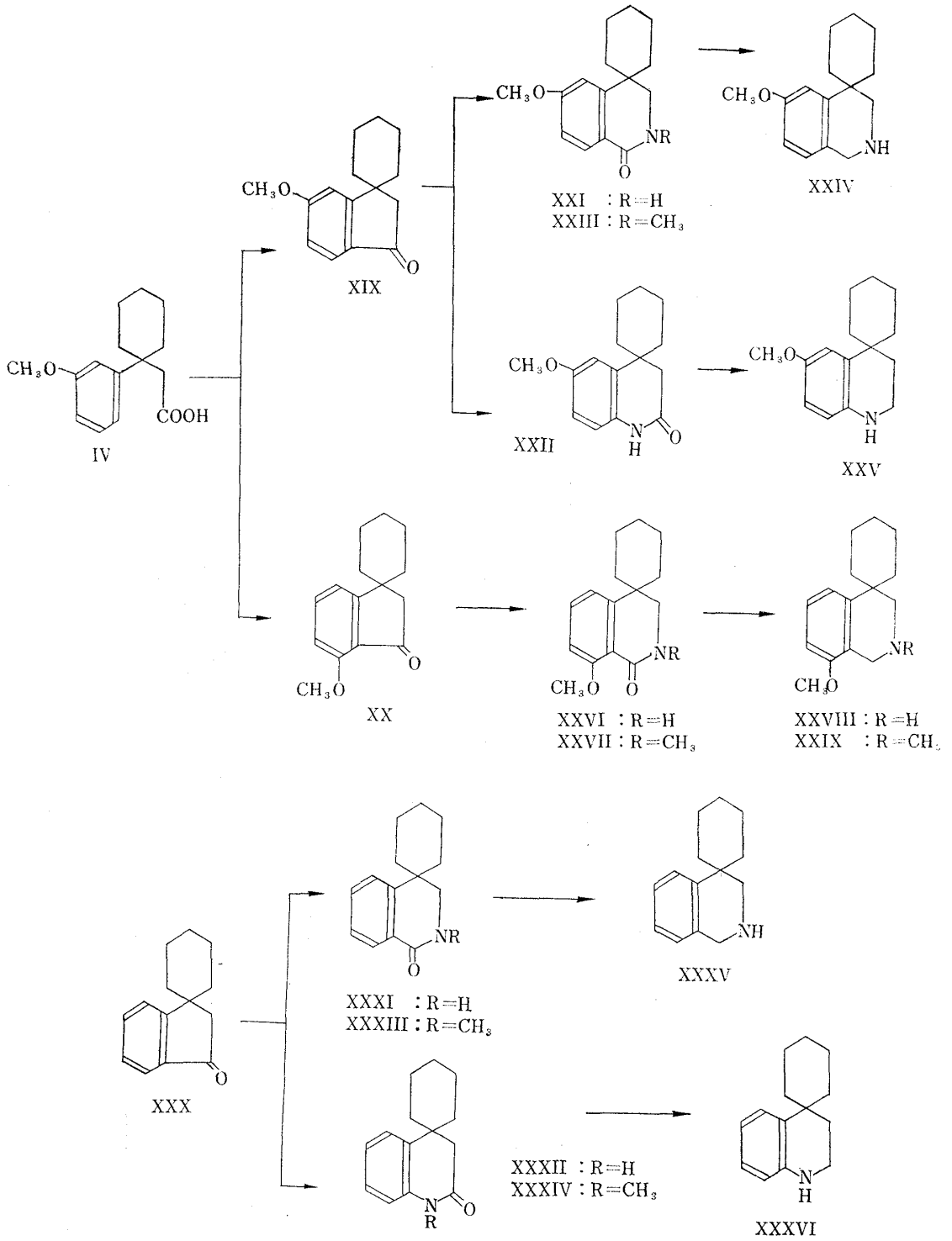

Chart 2.

homocarbostyrils (XII and XIV), respectively (Table I). It would not be safe, however, to assign a structure with certainty to a compound which is either a homoisocarbostyril or a homocarbostyril solely on the basis of its carbonyl band frequency; the isomeric pair must be compared, since the frequency regions for both types of compounds overlap, as shown in Table I.

The ultraviolet absorption spectra of the reduction products of the lactams with lithium aluminum hydride gave a confirmative evidence for the assigned structure of

Table I. Infrared Spectra in Chloroform

Compound	XI	XII	XIII	XIV	XXI	XXII	XXXI	XXXII	XXXIII	XXXIV
Carbonyl band (cm^{-1})	1648	1668	1630	1645	1660	1665	1670	1675	1645	1660

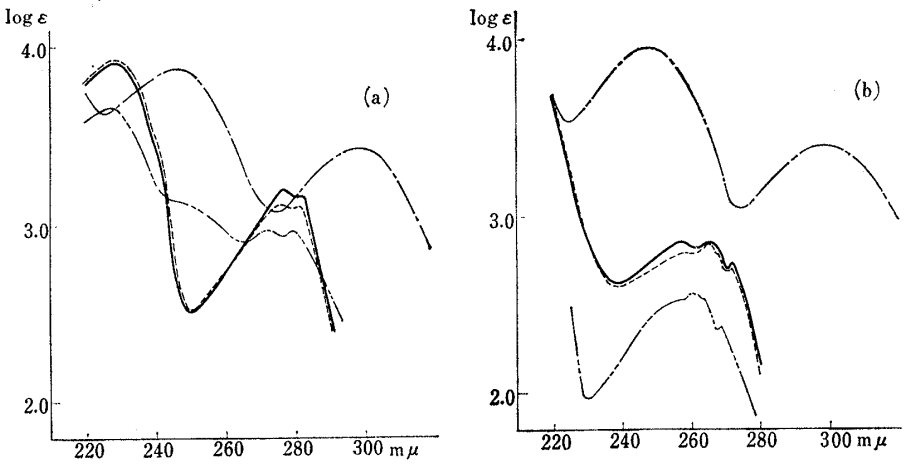

Fig. 1. Ultraviolet Absorption Spectra of Amines in Ethanol

(a): ——— XV – – – – XV hydrochloride —·— XVI
—··— XVI hydrochloride
(b): ——— XXXV – – – – XXXV hydrochloride
—·— XXXVI —··— XXXVI hydrochloride

the lactams. Whereas the ultraviolet spectra of the amines (XV and XVII) derived from the lactams (XI and XIII) remained essentially unaltered in both acid and alkaline media, those of the reduction products (XVI and XVIII) of the lactams (XII and XIV) showed a hypsochromic shift on acidification of their respective alcoholic solutions (Fig. 1a), indicating that the nitrogen atom is linked to the benzene ring in the latter cases.*5

The second way of distinguishing between these isomeric lactams was by the use of the deuterium exchange reaction of NH protons and comparison of their nuclear magnetic resonance spectra. The multiplet at 2.3~2.1 p.p.m. assigned to $-NH-CO-\underline{CH_2}-CH_2-$ in XII did not change to the slightest extent on replacement of the hydrogen attached to nitrogen by deuterium, as shown in Fig. 2b. In contrast, the nuclear magnetic resonance spectrum of the compound (XI) indicated a significant difference in the region (3.4~3.0 p.p.m.) of the methylene adjacent to nitrogen from that resulted from the deuterium exchange reaction (Fig. 2a).

Far more pronounced difference between the yields of isocarbostyrils and carbostyrils was observed in the case of the Schmidt reaction on indanones. Thus the methoxyindanone (XIX) afforded the isocarbostyril (XXI) in 71% yield and the carbostyril (XXII) in only 7% yield. The differentiation between the isomeric pair could be made by the use of infrared, ultraviolet and nuclear magnetic resonance spectra of these compounds and their reduction products (XXIV and XXV) by the procedures discussed above.

The Schmidt reaction with the methoxyindanone (XX) furnished the methoxyisocarbostyril (XXVI) in 66% yield which was characterized as such by the spectroscopic

*5 The hydrochloride of the amine (XV) was identical in all respects with an authentic sample of 7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-2-benzazepine-5,1′-cyclohexane] hydrochloride prepared by using the Bischler-Napieralski reaction.[6]

6) M. Tomita, S. Minami: Yakugaku Zasshi, 83, 1022 (1963).

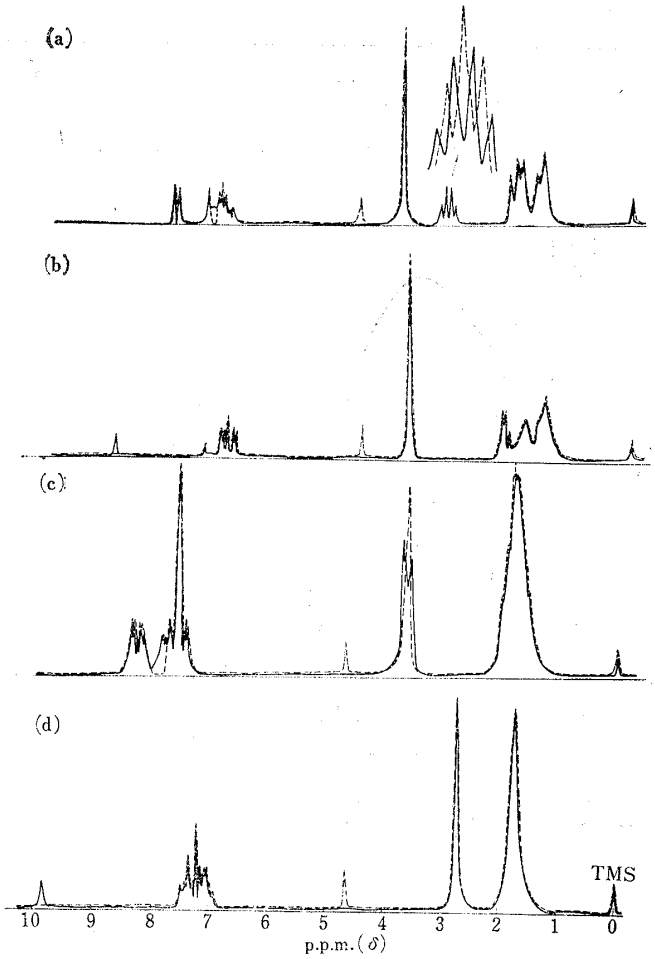

Fig. 2. Nuclear Magnetic Resonace Spectra of Lactams at 60 Mc. in Deuteriochloroform

——— non-deuterated lactams
– – – – deuterated lactams
(a) XI (b) XII (c) XXXI (d) XXXII

properties of it, its N-methyl derivative (XXVII) and the reduction products (XXVIII and XXIX) of the two lactams.

In contrast to the results obtained above for the methoxytetralone and the methoxyindanones, the indanone (XXX),[7] which contains no methoxyl group in the benzene ring, afforded predominantly (77%) the carbostyril (XXXII) and only a trace (6%) of the isocarbostyril (XXXI). The structure of these compounds were established by the methods employed as above (Table I, and Figs. 1b and 2c, d).

From the above experimental results it is clear that the methoxyl group located in the aromatic ring must play an important role in determining the course of the reaction.

As to the mechanism of this reaction, we will discuss in a forthcoming paper.

Experimental*6

1-(*m*-Methoxyphenyl)cyclohexanepropionic Acid (VIII)——The acid chloride (V) was prepared by heating 1-(*m*-methoxyphenyl)cyclohexaneacetic acid (IV,[4,5] 15.0 g.) and excess $SOCl_2$ (29.6 g.) on a water-bath for 0.5 hr. After removal of excess reagent by evaporation under reduced pressure, benzene was added to the residue and again evaporated to dryness. The residue was taken up in dry ether (150 ml.) and the ethereal solution was added dropwise to an ethereal solution of CH_2N_2 prepared from nitrosomethylurea (22 g.). After the solution had been kept overnight at room temperature, it was concentrated to dryness under reduced pressure to give the diazoketone (VI). This was dissolved in MeOH (150 ml.) and a slurry of freshly prepared Ag_2O (1.5 g.) was added to the mixture which was refluxed for 4 hr., filtered and evaporated. Distillation yielded the ester (VII, 11.9 g.) as a pale yellow oil, b.p_6 190°. *Anal.* Calcd. for $C_{17}H_{24}O_3$: C, 73.88; H, 8.75. Found: C, 73.09; H, 8.58. IR cm^{-1}: $\nu_{C=O}$ 1738 (liq.). A mixture of VII (11.2 g.), and NaOH (4.8 g.) in H_2O (44 ml.) was heated in an oil-bath at 130~150° for 1.5 hr., cooled, diluted with H_2O and washed with ether. The aqueous layer was acidified and extracted with ether. The extracts were washed with H_2O, dried ($MgSO_4$), and concentrated to dryness to give a crystalline mass (9.7 g.) which after recrystallization from benzene yielded the acid (VIII) as prisms (3.90 g.), m.p. 127~128°. *Anal.* Calcd. for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 73.03; H, 8.44. IR cm^{-1}: $\nu_{C=O}$ 1698, δ_{C-H} 765, 695 (KBr). UV λ_{max}^{EtOH} mμ (log ε): 277~278 (3.33), 280.5 (3.28).

Cyclization of the Acid (VIII)——The carboxylic acid (VIII, 2.85 g.) and polyphosphoric acid (50 g.) were heated on a water-bath for 1.5 hr., poured onto crushed ice and extracted with ether. The extracts were washed with aqueous $NaHCO_3$, and H_2O, dried ($MgSO_4$) and evaporated. The residue was recrystallized from MeOH to yield 7′-methoxy-2′,3′-dihydrospiro[cyclohexane-1,1′(4′*H*)-naphthalen]-4′-one (IX, 2.03 g.) as prisms, m.p. 86.0~87.0°. *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.74; H,

*6 Nuclear magnetic resonance spectra were taken on a Varian Associate A-60 spectrometer for deuteriochloroform solutions with tetramethylsilane as the internal standard.

7) L. F. Schwartzman: J. Org. Chem., **15**, 517 (1950).

H, 8.29. IR cm^{-1}: $\nu_{C=O}$ 1670, δ_{C-H} 850 (1,2,4-trisubstituted benzene) (KBr.). UV λ_{max}^{EtOH} mμ (log ε): 227 (4.15), 278 (4.19). The semicarbazone: needles (from acetone). m.p. 220~222° (decomp.). *Anal.* Calcd. for $C_{17}H_{23}O_2N_3$: C, 67.75; H, 7.69; N, 13.94. Found: C, 67.94; H, 7.78; N, 13.94.

The mother liquors (0.37 g.) from Ⅸ were chromatographed in benzene on alumina (10 g.). The first benzene eluate (20 ml.) gave mainly Ⅸ and the second fraction (20 ml.) afforded crystals (0.05 g.) which after recrystallization from hexane gave 5′-methoxy-2′,3′-dihydrospiro[cyclohexane-1,1′(4′*H*)-naphthalen]-4′-one (X) as prisms, m.p. 90.0~90.5°. *Anal.* Calcd. for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.24; H, 7.91. IR cm^{-1}: $\nu_{C=O}$ 1676, δ_{C-H} 802, 749 (1,2,3-trisubstituted benzene) (KBr). UV λ_{max}^{EtOH} mμ (log ε): 256~258 (3.93), 312~316 (3.66).

The Schmidt Reaction on the Tetralone (IX)——To a mixture of Ⅸ (2.98 g.) in benzene (20 ml.) and 92.8% H_2SO_4 (6.6 ml.) was added NaN_3 (1.32 g.) in portions with stirring at 56~57° during 8.5 hr. After the evolution of N_2 had ceased, stirring was continued for 0.5 hr. at the same temperature, the mixture was then cooled in an ice-bath and the benzene layer was separated by decantation from the H_2SO_4 layer and discarded. The acidic layer was washed with benzene and diluted with ice-water to separate an oil which was extracted with $CHCl_3$. The $CHCl_3$ extracts were washed with H_2O, dried ($MgSO_4$) and evaporated to dryness to give an oil (2.80 g.) which was chromatographed in benzene on silica gel (30 g.). The benzene eluate gave 7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-1-benzazepine-5,1′-cyclohexan]-2-one (Ⅻ, 1.61 g.) which after recrystallization from EtOH formed prisms (1.20 g.), m.p. 171~172°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40; mol. wt., 259. Found: C, 74.07; H, 8.23; N, 5.29; mol. wt. (Rast), 265. IR cm^{-1}: $\nu_{C=O}$ 1668 ($CHCl_3$); δ_{C-H} 870, 818 (KBr). UV λ_{max}^{EtOH} mμ (log ε): 248 (4.15), ~280 (shoulder, ca. 3.5). NMR: δ p.p.m.: 8.51 (NH, 1H singlet).

Further elution of the column with $CHCl_3$ yielded 7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-2-benzazepine-5,1′-cyclohexan]-1-one (Ⅺ, 1.18 g.) which after recrystallization from ether-$CHCl_3$ formed flakes (0.88 g.), m.p. 143~144°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40; mol. wt., 259. Found: C, 73.84; H, 8.14; N, 5.52; mol. wt. (Rast), 274. IR cm^{-1}: $\nu_{C=O}$ 1648 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε): 252 (4.03). NMR: δ p.p.m.: 7.2 (NH, 1H broad).

2-Methyl-7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-2-benzazepine-5,1′-cyclohexan]-1-one (XIII)——A mixture of Ⅺ (0.26 g.), NaH (0.10 g., content 55% in oil) and dry toluene (6 ml.) was refluxed in an oil-bath at 130° for 2 hr. After cooling, MeI (10 ml.) was added, the whole was heated under reflux for a further 10 hr. and the excess MeI was removed by evaporation. The mixture was diluted with benzene, washed with H_2O, dried ($MgSO_4$) and concentrated under reduced pressure to yield XIII. Crystallization from ether gave prisms (0.21 g.), m.p. 106.5~107.5°. *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.82; H, 8.32; N, 4.79. IR cm^{-1}: $\nu_{C=O}$ 1630 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε): 252 (4.03). NMR δ p.p.m.: 3.17 (N-CH$_3$, 3H singlet).

1-Methyl-7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-1-benzazepine-5,1′-cyclohexan]-2-one (XIV)——In the manner described for methylation of Ⅺ, Ⅻ was methylated to give XIV as prisms in 57% yield (from acetone), m.p. 97.0~97.5°. *Anal.* Calcd. for $C_{17}H_{23}O_2N$: C, 74.69; H, 8.48; N, 5.12. Found: C, 74.82; H, 8.32; N, 5.47. IR cm^{-1}: $\nu_{C=O}$ 1645 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε): 246 (4.12), ~282 (shoulder, ca. 3.4). NMR δ p.p.m.: 3.28 (N-CH$_3$, 3H singlet).

7-Methoxy-1,2,3,4-tetrahydrospiro[5*H*-2-benzazepine-5,1′-cyclohexane] (XV)——Ⅺ (97 mg.) in dry tetrahydrofuran (THF, 10 ml.) was added to a cooled solution of $LiAlH_4$ (0.16 g.) in dry THF (12 ml.). The mixture was refluxed at 80° for 6 hr. and the resulting complex was decomposed by cautious addition of H_2O. The gelatinous precipitate was filtered and washed with THF. The filtrate and the washings were combined and concentrated under reduced pressure, and the residue was taken up in ether and extracted with dil. HCl. The extracts were washed with ether, made alkaline with $NaHCO_3$ and again extracted with ether. The ethereal layer was dried (K_2CO_3) and concentrated to yield the amine (XV, 54 mg.) as an oil, which was identical with the authentic XV[6] by comparison of the IR spectra. UV λ_{max}^{EtOH} mμ (log ε): 230 (3.91), 276 (3.20), 282 (3.17). The hydrochloride: m.p. and mixed m.p.[6] 206~210° (from iso-PrOH). UV λ_{max}^{EtOH} mμ (log ε): 231 (3.99), 275 (3.13), 280 (3.10).

7-Methoxy-1,2,3,4-tetrahydrospiro[5*H*-1-benzazepine-5,1′-cyclohexane] (XVI)——In the manner described above, Ⅻ (90 mg.) was reduced with $LiAlH_4$ (0.16 g.) in dry THF (30 ml.) to give XVI (31 mg.) as a brown oil. IR cm^{-1}: ν_{N-H} 3360 (liq.). UV λ_{max}^{EtOH} mμ (log ε): 246 (3.89), 300 (3.41). The hydrochloride: flakes (from EtOH-acetone-ether), m.p. 166~167°. *Anal.* Calcd. for $C_{16}H_{24}ONCl$: C, 68.20; H, 8.58; Cl, 12.58. Found: C, 67.61; H, 8.44; Cl, 12.47. UV λ_{max}^{EtOH} mμ (log ε): 228 (3.68), 273 (2.98), 280 (2.98).

2-Methyl-7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-2-benzazepine-5,1′-cyclohexane] (XVII)——Reduction of XIII (105 mg.) with $LiAlH_4$ (0.19 g.) in dry THF (16 ml.) gave the base (XVII, 95 mg.) as an oil whose IR spectrum was identical with that of an authentic sample of XVII.[6] The hydrochloride had m.p. 224~226° and was identical with the authentic XVII hydrochloride[6] (mixed melting point and IR).

1-Methyl-7-methoxy-1,2,3,4-tetrahydrospiro[5*H*-1-benzazepine-5,1′-cyclohexane] (XVIII)——Treatment of XIV (90 mg.) with $LiAlH_4$ (0.15 g.) in dry THF (24 ml.) by the usual method gave XVIII as an oil (61 mg.). IR cm^{-1}: N-CH$_3$, ν_{C-H} 2800 (liq.). UV λ_{max}^{EtOH} mμ (log ε): 253~255 (3.87), 298~300 (3.44). The methiodide: needles (from EtOH-ether), m.p. 155~156°. *Anal.* Calcd. for $C_{18}H_{28}ONI \cdot \frac{1}{2} H_2O$ (hemihydrate of XVIII methiodide): C, 52.68; H, 7.12. Found: C, 52.71; H, 6.95.

Cyclization of the Acid (IV)——The carboxylic acid (IV, 35.0 g.) and polyphosphoric acid (338 g.) were heated on a water-bath for 1.5 hr., and treated in the same manner as described for the cyclization of VIII. The neutral product (31.2 g.) was dissolved in hot hexane (350 ml.) and kept at room temperature overnight. The crystals which separated was collected and recrystallized from hexane to give 6′-methoxyspiro [cyclohexane-1,1′-indan]-3′-one (XIX, 8.93 g.) as prisms, m.p. 83.5～85.0°. *Anal.* Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88; OCH_3, 13.47. Found : C, 78.20; H, 7.72; OCH_3, 13.03. IR cm^{-1} : $\nu_{C=O}$ 1698: δ_{C-H} 850 (1,2,4-trisubstituted benzene) (KBr). UV λ_{max}^{EtOH} mμ (log ε) : 224.5 (4.19), 270 (4.17), 288 (4.04),～295 (shoulder, ca. 4.0).

The mother liquors from XIX were concentrated and the residue (22.2 g.) was chromatographed in benzene on silica gel (230 g.). The benzene eluate (1600 ml.) gave an additional crop of XIX (14.7 g.) and the $CHCl_3$ eluate (700 ml.) gave 4′-methoxyspiro[cyclohexane-1,1′-indan]-3′-one (XX, 6.87 g.) which was recrystallized from ether to form prisms (5.54 g.), m.p. 97.5～99.0°. *Anal.* Calcd. for $C_{15}H_{18}O_2$: C, 78.23; H, 7.88; OCH_3, 13.47. Found : C, 77.94; H, 7.64; OCH_3, 13.28. IR cm^{-1} : $\nu_{C=O}$ 1703, δ_{C-H} 800, 785, 745 (1,2,3-trisubstituted benzene) (KBr). UV λ_{max}^{EtOH} mμ (log ε) : 254～256 (4.03), 312～314 (3.68).

The Schmidt Reaction on the Indanone (XIX)——To a mixture of XIX (4.00 g.) in benzene (28 ml.) and 92.8% H_2SO_4 (8.8 ml.) was added NaN_3 (1.83 g.) in portions with stirring at 56～57° during 5.5 hr. After evolution of N_2 had ceased, stirring was continued for 0.5 hr. at the same temperature. Work up in the usual manner gave 6′-methoxyspiro[cyclohexane-1,4′(3′*H*)-isoquinolin]-1′(2′*H*)-one (XXI, 4.15 g.) which on recrystallization from EtOH formed needles (2.34 g.), m.p. 152～153°. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71; OCH_3, 12.65; mol. wt., 245. Found : C, 73.36; H, 7.96; N, 5.61; OCH_3, 12.39; mol. wt. (Rast), 235. IR cm^{-1} : $\nu_{C=O}$ 1660 ($CHCl_3$); δ_{C-H} 865, 838 (KBr). UV λ_{max}^{EtOH} mμ (log ε) : 260～261 (4.12). NMR δ p.p.m. : ～7.2 (NH, 1H broad), 3.49 (-NH-CH_2-, 2H doublet). 2′-Methyl-6′-methoxyspiro [cyclohexane-1,4′(3′*H*)-isoquinolin]-1′(2′*H*)-one (XXIII) : In the manner described for the methylation of XI, XXI was methylated to XXIII in 74% yield. It crystallized as prisms from ether, m.p. 97.0～97.5°. *Anal.*Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40. Found : C, 73.84; H, 8.20; N, 5.13. IR cm^{-1} : $\nu_{C=O}$ 1641 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε) : 262 (4.11). NMR δ p.p.m. : 3.17 (N-CH_3, 3H singlet), 3.49 (-NCH_3-CH_2-, 2H singlet).

The mother liquors (1.80 g.) from XXI were chromatographed in benzene on alumina (40 g.) and the benzene eluate gave an additional crop of XXI (0.69 g.). Elution with $CHCl_3$ gave an oil (0.16 g.) which was combined with the mother liquors from the benzene eluate and rechromatographed in benzene on alumina. The benzene eluate gave a yellow oil which could not be characterized and was discarded. The acetone eluate gave 6′-methoxyspiro[cyclohexane-1,4′(1′*H*)-quinolin]-2′(3′*H*)-one (XXII) as prisms (0.30 g., from EtOH), m.p. 147～148°. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71. Found : C, 73.65; H, 8.03; N, 5.78. IR cm^{-1} : $\nu_{C=O}$ 1665 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε) : 261 (4.12).

6′-Methoxy-2′,3′-dihydrospiro[cyclohexane-1,4′(1′*H*)-isoquinoline] (XXIV)——XXI (2.37 g.) was reduced with $LiAlH_4$ (2.50 g.) in dry THF (70 ml.) and the base (XXIV, 2.17 g.) was isolated as an oil. UV λ_{max}^{EtOH} mμ (log ε) : 279.5 (3.48), ～286 (shoulder, ca. 3.4). The hydrochloride had m.p. 244～245° (from EtOH). UV λ_{max}^{EtOH} mμ (log ε) : 224 (3.96), 278 (3.37), 286 (3.34). This was identical with an authentic sample of XXIV hydrochloride[5] as shown by mixed melting point and comparison of the IR spectra. The picrate could not be induced to crystallize.

6′-Methoxy-2′,3′-dihydrospiro[cyclohexane-1,4′(1′*H*)-quinoline] (XXV)——This was obtained as an oil on treatment of XXII with $LiAlH_4$ in the manner as described above. The picrate formed orange needles (from EtOH), m.p. 145～146°. *Anal.* Calcd. for $C_{21}H_{24}O_8N_4$: C, 54.78; H, 5.25. Found : C, 54.32; H, 4.93.

The Schmidt Reaction on the Indanone (XX)——A mixture of XX (4.00 g.), benzene (28 ml.) and 92.8% H_2SO_4 (8.8 ml.) was submitted to the Schmidt reaction using NaN_3 (1.83 g.) in the manner as described for the tetralone (IX). A dark red oil (4.03 g.) which was obtained was chromatographed in $CHCl_3$ on alumina (40 g.) and the $CHCl_3$ eluate recrystallized from acetone to give 8′-methoxyspiro [cyclohexane 1,4′ (3′*H*)-isoquinolin]-1′ (2′*H*)-one (XXVI, 2.82 g.) as needles, m.p. 180.0～180.5°. *Anal.* Calcd. for $C_{15}H_{19}O_2N$: C, 73.44; H, 7.81; N, 5.71; mol. wt. 245. Found: C, 73.06; H, 7.92; N, 5.60; mol. wt. (Rast), 249. IR cm^{-1} : $\nu_{C=O}$ 1660 ($CHCl_3$); δ_{C-H} 813, 775 (KBr). UV λ_{max}^{EtOH} mμ (log ε) : 240～242 (3.81), 300～301 (3.65). NMR δ p.p.m. : ～7.2 (NH, 1H broad), 3.38 (-NH-CH_2-, 2H doublet). 2′-Methyl-8′-methoxyspiro-[cyclohexane-1,4′(3′*H*)-isoquinolin]-1′(2′*H*)-one (XXVII) was obtained by methylation of XXVI in 49% yield by the method used for the preparation of XIII. It formed prisms (from acetone), m.p. 147.5～148.5°. *Anal.* Calcd. for $C_{16}H_{21}O_2N$: C, 74.10; H, 8.16; N, 5.40; mol. wt., 259. Found : C, 74.05; H, 8.07; N, 5.13; mol. wt. (Rast), 234. IR cm^{-1} : $\nu_{C=O}$ 1642 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε) : 241 (3.78), 300 (3.67). NMR δ p.p.m. : 3.17 (N-CH_3, 3H singlet), 3.42 (-NCH_3-CH_2-, 2H singlet).

8′-Methoxy-2′,3′-dihydrospiro[cyclohexane-1,4′(1′*H*)-isoquinoline] (XXVIII)——A mixture of XXVI (0.50 g.), $LiAlH_4$ (0.45 g.) and dry THF (70 ml.) was refluxed at 80° for 7 hr. and worked up in the usual manner to give the base (XXVIII) as prisms (0.41 g.), m.p. 102～103° (from hexane). *Anal.* Calcd. for $C_{15}H_{21}ON$: C, 77.88; H, 9.15; N, 6.05. Found : C, 77.92; H, 9.15; N, 6.02. IR cm^{-1} : ν_{N-H} ～3400 (KBr). UV λ_{max}^{EtOH} mμ (log ε) : 271～272 (3.23), 279 (3.24). The hydrochloride formed needles (from EtOH), m.p. 241～242°. *Anal.* Calcd. for $C_{15}H_{22}ONCl$: C, 67.27; H, 8.28; N, 5.23; Cl, 13.24. Found : C, 66.94; H,

8.25; N, 5.47; Cl, 13.25. UV λ_{max}^{EtOH} mμ (log ε): 218 (3.88), 273 (3.27), 280 (3.27). The picrate: yellow needles (from EtOH), m.p. 165~168°.

2'-Methyl-8'-methoxy-2',3'-dihydrospiro[cyclohexane-1,4'(1'*H*)-isoquinoline] (XXIX)——A mixture of XXVII (0.11 g.), $LiAlH_4$ (0.10 g.) and dry THF (23 ml.) was refluxed at 80° for 6.5 hr. and gave, after working up, the base (XXIX, 92 mg.) as flakes (from hexane), m.p. 85.0~86.0°. *Anal.* Calcd. for $C_{16}H_{23}ON$: C, 78.32; H, 9.45; N, 5.71. Found: C, 78.30; H, 9.35; N, 5.85. IR cm^{-1}: N-CH_3, ν_{C-H} 2750 (KBr). UV λ_{max}^{EtOH} mμ (log ε): 272 (3.22), 279.5 (3.24). The hydrochloride: needles (from EtOH), m.p. 212~213°. *Anal.* Calcd. for $C_{16}H_{24}ONCl$: C, 68.19; H, 8.59; N, 4.97. Found: C, 68.76; H, 8.75; N, 5.09. UV λ_{max}^{EtOH} mμ (log ε): 218~219 (3.80), 274 (3.32), 280.5 (3.33). The picrate: yellow needles (from EtOH), m.p. 186~188°. *Anal.* Calcd. for $C_{22}H_{26}O_8N_4$: C, 55.69; H, 5.52; N, 11.81. Found: C, 55.79; H, 5.50; N, 11.81.

The Schmidt Reaction on Spiro[cyclohexane-1,1'-indan]-3'-one (XXX)——A mixture of XXX[7] (3.27 g.), benzene (26 ml.) and 92.8% H_2SO_4 (8.3 ml.) was submitted to the Schmidt reaction using NaN_3 (1.74 g.) as described for the tetralone (IX). Working up in the usual manner gave a crystalline mass (3.49 g.) which was recrystallized from EtOH to afford spiro[cyclohexane-1,4'(1'*H*)-quinolin]-2'(3'*H*)-one (XXXII, 1.89 g.) as prisms, m.p. 183~185° (lit.[7] m.p. 185~185.5°). IR cm^{-1}: $\nu_{C=O}$ 1675 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε): 250~252 (4.07). NMR δ p.p.m.: 10.24 (NH, 1H singlet), 2.70 (-CO-CH_2-, 2H singlet). 1'-Methylspiro[cyclohexane-1,4'(1'*H*)-quinolin]-2'(3'*H*)-one (XXXIV): XXXIV was obtained from XXXII (71%) by the method described above as prisms (from hexane), m.p. 80.5~81.0°. *Anal.* Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.34; H, 8.20; N, 5.98. IR cm^{-1}: $\nu_{C=O}$ 1660 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε): 254 (4.06). NMR δ p.p.m.: 3.34 (N-CH_3, 3H singlet), 2.70 (-CO-CH_2-, 2H singlet).

The mother liquors (1.60 g.) from XXXII were chromatographed in benzene on alumina (46 g.). The benzene eluate afforded an additional crop of XXXII (0.82 g.) and the $CHCl_3$ eluate gave spiro[cyclohexane-1,4'(3'*H*)-isoquinolin]-1'(2'*H*)-one (XXXI, 0.20 g.) after recrystallization from acetone as prisms, m.p. 146~148°. *Anal.* Calcd. for $C_{14}H_{17}ON$: C, 78.10; H, 7.96; N, 6.51. Found: C, 78.46; H, 8.12; N, 6.28. IR cm^{-1}: $\nu_{C=O}$ 1670 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε): 230 (4.01), ~275 (shoulder, ca. 3.1). NMR δ p.p.m.: ~7.4 (NH, 1H broad), 3.52 (-NH-CH_2-, 2H doublet). A mixed melting point with XXXII showed a remarkable depression. 2'-Methylspiro[cyclohexane-1,4'(3'*H*)-isoquinolin]-1'(2'*H*)-one (XXXIII): Methylation of XXXI, by the procedure described above for XIII, gave XXXIII in 94% yield as flakes (from hexane), m.p. 89.0~89.5°. *Anal.* Calcd. for $C_{15}H_{19}ON$: C, 78.56; H, 8.35; N, 6.11. Found: C, 78.17; H, 8.14; N, 6.30. IR cm^{-1}: $\nu_{C=O}$ 1645 ($CHCl_3$). UV λ_{max}^{EtOH} mμ (log ε): 229 (3.95), ~250 (shoulder, ca. 3.74), ~262 (shoulder, ca. 3.6). NMR δ p.p.m.: 3.24 (N-CH_3, 3H singlet), 3.55 (-NCH_3-CH_2-, 2H singlet).

2',3'-Dihydrospiro[cyclohexane-1,4'(1'*H*)-isoquinoline] (XXXV)——Reduction of XXXI (0.30 g.) with $LiAlH_4$ (0.50 g.) in dry THF (80 ml.) gave the base (XXXV) as an oil (0.23 g.). UV λ_{max}^{EtOH} mμ (log ε): 259~260 (2.65), 266 (2.69), 273 (2.62). The hydrochloride: needles (from EtOH), m.p. 187~190°. UV λ_{max}^{EtOH} mμ (log ε): 264 (2.53), 269 (2.48), 272 (2.50). This was shown to be identical with an authentic sample of XXXV hydrochloride[5] by mixed melting point and comparison of IR spectra.

2',3'-Dihydrospiro[cyclohexane-1,4'(1'*H*)-quinoline] (XXXVI)——Treatment of XXXII (1.25 g.) with $LiAlH_4$ (2.23 g.) in dry THF (50 ml.) gave the base (XXXVI) as an oil (1.02 g.). UV λ_{max}^{EtOH} mμ (log ε): 248 (3.95), 300 (3.39). The hydrochloride: flakes (from dil. HCl), m.p. 219~222°. *Anal.* Calcd. for $C_{14}H_{20}NCl$: C, 70.72; H, 8.48; N, 5.89; Cl, 14.91. Found: C, 70.98; H, 8.59; N, 5.92; Cl, 14.80. UV λ_{max}^{EtOH} mμ (log ε): 255~258 (shoulder, ca. 2.5), 261 (2.55), 269 (2.37). The benzoyl derivative: m.p. 130.5~131.5° (lit.[7] m.p. 131~132°).

Summary

While the Schmidt reaction on indanones or tetralones containing no substituents on the benzene moiety of the respective molecules are reported to yield carbostyrils or homocarbostyrils as the sole isolable product, it has been shown that when these compounds contain an electron releasing substituent (*e.g.* methoxyl group) in the benzene ring, the Schmidt reaction gives both isocarbostyrils and carbostyrils or homoisocarbosyrils and homocarbostyrils in a variable ratio depending upon the structure of the starting materials.

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