[Chem. Pharm. Bull. 12 (6) 718 ~ 724]

UDC 547.745.07

103. Kentaro Okumura and Ichizo Inoue: Synthetic Studies on 2-Pyrrolidinone Derivatives. I. Synthesis of 1-Phenyl-3-dialkylamino-2-pyrrolidinone and its 5-Methyl Analog.

(*Osaka Research Laboratory, Tanabe Seiyaku Co., Ltd.*[*1])

In 1959 Wright and co-workers[1] reported that N-*tert*-aminoalkylpropionanilides (I), new derivatives of propionanilide, are effective as analgesic agents. The compounds in this series are considered as analogs of Methadone or Isomethadone, in which the quaternary carbon atom and one of the phenyl groups have been replaced by a nitrogen atom. During these few years, we synthesized several derivatives of these type of compounds (II[2], III[3], and V[4]) in order to study correlation between the chemical structure and the pharmacological activity, and found that some of them have a strong analgesic, antiinflammatory, and antipyretic activity.

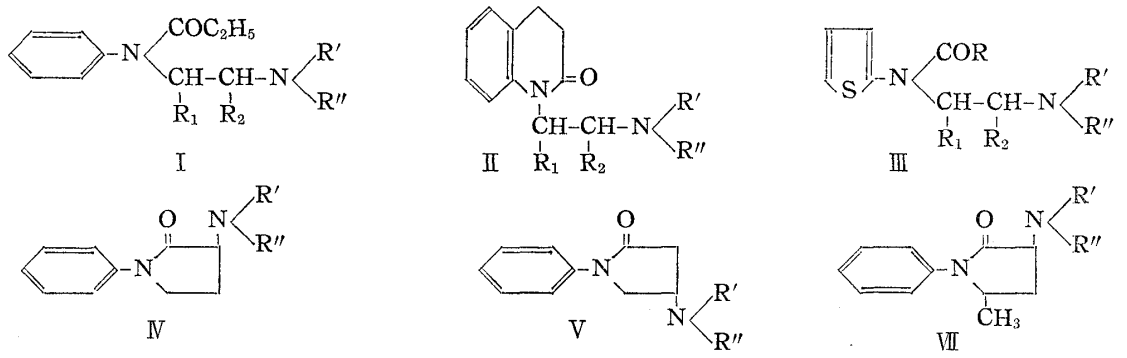

Chart 1.

In the present paper the syntheses of 1-phenyl-3-*tert*-amino-2-pyrrolidinone and its 5-methyl analogs are described. It was initialy attempted to obtain 1-phenyl-3-*tert*-amino-2-pyrrolidinone *via* 1-phenyl-2,3-pyrrolidinedione (VIII), prepared according to the procedure of Southwick[5], but this method was abandoned because of low yield resulted from the instability of the lactam-bond toward aqueous acid (Chart 2). So, an alternative route shown in Chart 3 was pursued, which turned out successful. Thus, according to Berti's[6] or Sheradsky's[6] method, 2-bromo-γ-butyrolactone (IX) was treated with piperidine and morpholine to give Xa and Xb respectively, which furnished XIa and XIb on being treated with aniline.

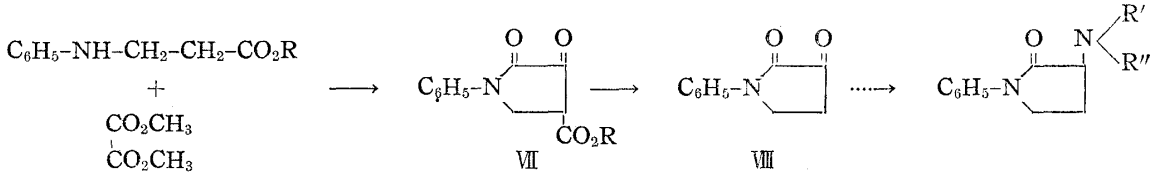

Chart 2.

*1 962 Kashimacho, Higashiyodogawa-ku, Osaka (奥村健太郎, 井上一三).

1) W. B. Wright, Jr., H. J. Brabander, R. A. Hardy, Jr.: J. Am. Chem. Soc., **81**, 1518 (1959).
2) N. Shigematsu: This Bulletin, **9**, 970 (1961); N. Sugimoto, K. Okumura, N. Shigematsu, G. Hayashi: Annual report of Tanabe Seiyaku Co., Ltd., Vol. **6**, 67 (1961).
3) N. Sugimoto, K. Okumura, N. Shigematsu, G. Hayashi: This Bulletin, **10**, 1061 (1962).
4) Presented at the Kinki local meeting of the Pharmaceutical Society of Japan, Nov. 23rd., 1962.
5) P. L. Southwick, R. T. Crouch: J. Am. Chem. Soc., **75**, 3413 (1953).
6) F. A. Berti: Gazz. chim. ital., **84**, 420 (1954); T. Sheradsky, Y. Knobler, M. Frankel; J. Org. Chem., **26**, 1482 (1961).

The synthesis of XVI was attempted in the similar way, but the intermediate (Xc) failed to give any definite product; only resinous material being obtained. This difficulty was, however, circumvented by treating 2-amino-γ-butyrolactone hydrobromide (XII), the amination[7] product of IX, with aniline to form XIII, which was further submitted to reductive alkylation with phenylacetaldehyde furnishing XV, followed by methylation by Eschweiler-Clark's method[8] to yield XVI. Direct methylation of XIII by the same method yielded the corresponding N-dimethylamino derivatives (XIV).

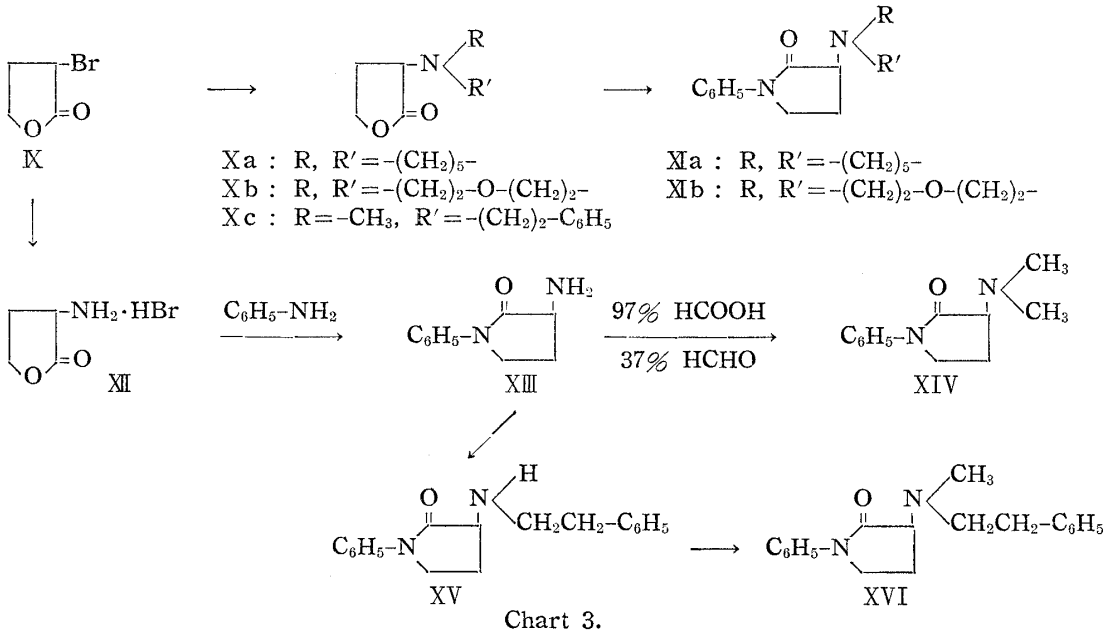

Chart 3.

Expecting a decent increase of analgesic activity, the syntheses of the 5-methyl analogs of 1-phenyl-3-*tert*-amino-2-pyrrolidinone were undertaken. The key intermediate, 1-phenyl-3-amino-5-methyl-2-pyrrolidinone (XVIII) was prepared from XVII, which was derived by the interaction of diethyl 2-allylacetamidomalonate[9] with 47% hydrobromic acid *via* hydrolysis, decarboxylation and lactonization[10] by heating with aniline as shown in Chart 4. 2-Amino-γ-valerolactone hydrobromide (XVII) thus obtained is probably a mixture of diastereoisomers but was used for next step without separation and purification. Condensation of XVII with aniline proceeded at a lower reaction temperature (150~160°) than that of X to yield an oily basic product, which was separated into two diastereoisomers, XVIIIa, m.p. 57~60°, XVIIIb, m.p. 94~96° by the fractional recrystallization of picrates. These were proved to have the same skeletal structure by leading them to one and the same 1-phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone (XIX). The conversion of XVIIIa and XVIIIb to the corresponding *tert*-amines were carried out according to the scheme as shown in Chart 4.

Experimental

2-Morpholino-γ-butyrolactone (Xb)——Twenty grams (0.126 mole) of 2-bromo-γ-butyrolactone (IX) was added to 32.6 g. (0.396 mole) of morpholine with stirring in an ice bath. The reaction mixture was

7) J.E. Livak, E.C. Britton, J.C. Vander Weele, M.F. Murray : J. Am. Chem. Soc., **67**, 2218 (1945); Adolf C.J. Opermann. : Brit. Pat. 734,928 (C.A., **50**, 8717 (1956)).
8) M.L. Moore : Org. Reactions, Vol. **5**, 307 (1949).
9) N.F. Albertson : J. Am. Chem. Soc., **68**, 450 (1946).
10) H.L. Goering, S.J. Cristol, K. Dittmer : *Ibid.*, **70**, 3310 (1948); J. Fillman, N, Albertson : *Ibid.*, **70**, 171 (1948).

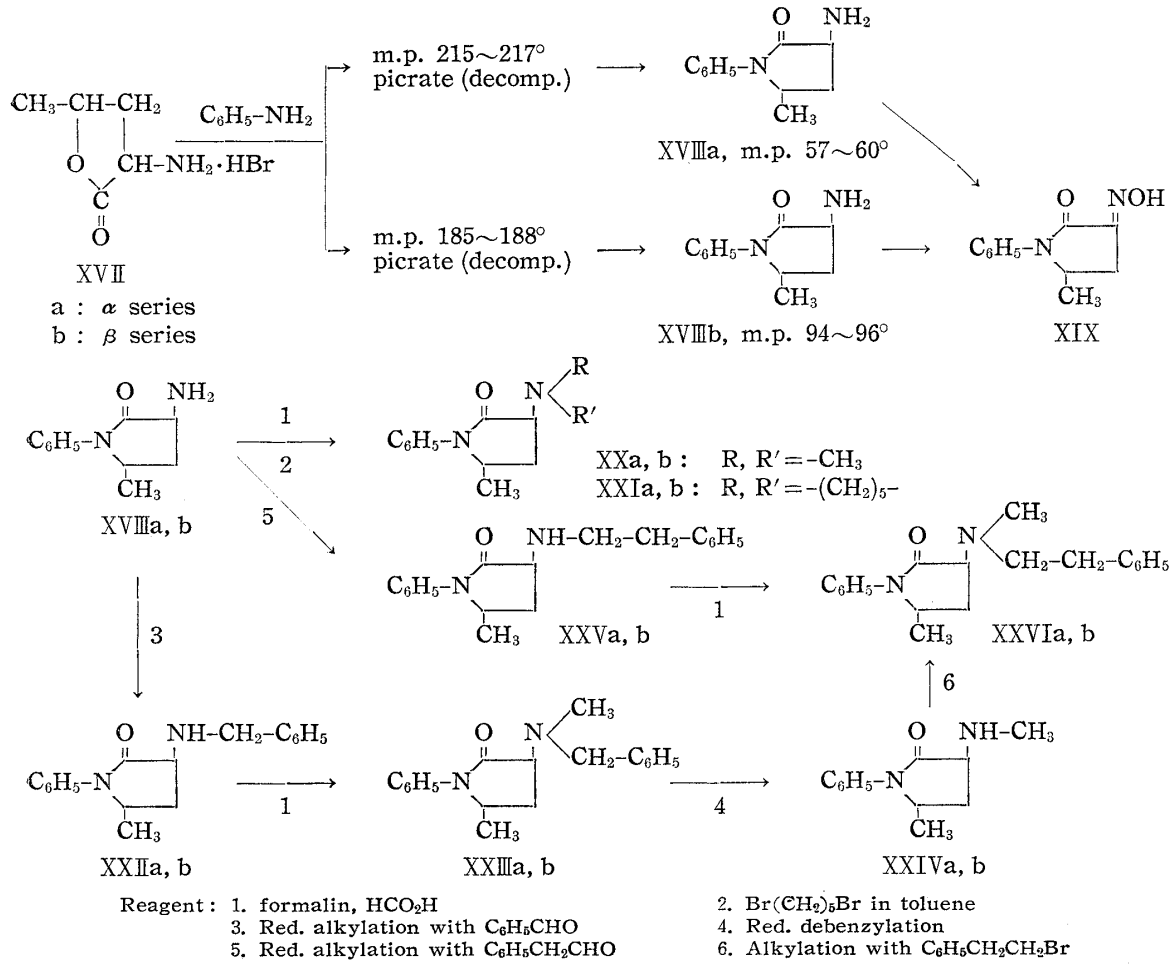

Chart 4.

kept at a room temperature for a week, then poured into Et_2O and the precipitated morpholine·HBr was filtered off. Ethereal layer was evaporated and distillation of the residue afforded 5.0 g. (23% yield) of Xb, b.$p_{0.2}$ 120~125°, picrate in yellow needles from EtOH-H_2O, m.p. 192~194°. *Anal.* Calcd. for $C_6H_{13}O_3N \cdot C_6H_3O_7N_3$: C, 42.00; H, 4.03; N, 14.00. Found : C, 42.33; H, 3.96; N, 14.47.

2-(N-methylphenethylamino)-γ-butyrolactone (Xc)——To well cooled 19 g. (0.14 mole) of N-methylphenethylamine was added 10 g. of 2-bromo-γ-butyrolactone with stirring and the mixture, after being kept at a room temperature for a week, was worked up as in the above experiment to give 7.2 g. (52% yield) of Xc, b.$p_{0.2}$ 143~153°, picrate in yellow needles from EtOH-H_2O, m.p. 144~148°. *Anal.* Calcd. for $C_{13}H_{17}O_2N \cdot C_6H_3O_7N_3$: C, 50.89; H, 4.50; N, 12.50. Found : C, 51.26; H, 4.43; N, 12.31.

1-Phenyl-3-piperidino-2-pyrrolidinone (XIa)——A mixture of 2 g. (0.012 mole) of Xa and 3.5 g. (0.036 mole) of aniline was heated in a sealed tube at 220~250° for 7 hr. Evaporation of the excess aniline *in vacuo* from the reaction mixture left a thick oil, which was taken up in $CHCl_3$ and extracted with 10% HCl. After neutralization of the acidic solution, a basic oil was extracted with $CHCl_3$ and the extract was dried over K_2CO_3, evaporated. Distillation of the residue afforded 1.8 g. of crude XIa, b.$p_{0.6}$ 140~170°, which crystallized on standing and purified by recrystallization from isopropyl ether, giving 0.8 g. (27.6% yield) of XIa, m.p. 80~83°. Melting point of the analytical sample was 84~85°, prisms from isopropyl ether. *Anal.* Calcd. for $C_{15}H_{20}ON_2$: C, 73.73; H, 8.25; N, 11.47. Found : C, 73.37; H, 7.90; N, 11.45. Hydrochloride in colorless prisms from iso-PrOH, m.p. 209~210°. *Anal.* Calcd. for $C_{15}H_{20}ON_2 \cdot HCl$: C, 64.16; H, 7.48; N, 9.97; Cl, 12.53. Found : C, 63.89; H, 7.46; N, 9.70; Cl, 12.54. Picrolonate, in yellow prisms from DMF-Et_2O, m.p. 232~234°. *Anal.* Calcd. for $C_{15}H_{20}ON_2 \cdot C_{10}H_8O_5N_4$: C, 59.05; H, 5.55; N, 16.53. Found : C, 58.98; H, 5.59; N, 16.78.

1-Phenyl-3-morpholino-2-pyrrolidinone (XIb)——A mixture of 5.0 g. (0.0293 mole) of Xb and 8.2 g. (0.087 mole) of aniline was heated in a sealed tube at 220~250° for 4 hr. and the treatment of reaction mixture as in the preceding experiment afforded 2.5 g. of crude XIb, b.$p_{0.09}$ 150~165°, which crystallized on standing, was recrystallized from isopropyl ether to give 1.8 g. (25% yield) of XIb in colorless needles, m.p. 104~105°. *Anal.* Calcd. for $C_{14}H_{18}O_2N_2$: C, 68.27; H, 7.37; N, 11.37. Found : C, 68.29; H, 7.37;

N, 11.12. Hydrochloride in very hygroscopic colorless needles from EtOH, m.p. 177~178°. *Anal.* Calcd. for $C_{14}H_{18}O_2N_2 \cdot HCl$: C, 59.46; H, 6.72; N, 9.91; Cl, 12.54. Found : C, 59.54; H, 6.53; N, 9.70; Cl, 12.09.

1-Phenyl-3-amino-2-pyrrolidinone (XIII)——Twenty grams (0.121 mole) of XII and 33.8 g. (0.363 mole) of aniline were heated at 145~165° for 24 hr. Then excess aniline was evaporated *in vacuo* and residue was dissolved in 10% HCl. Insoluble oil was removed by extraction with $CHCl_3$. After neutralization of the acidic aqueous layer, the oily product was extracted with $CHCl_3$ and the extract was dried over anhyd. K_2CO_3, concentrated. Residue was distilled *in vacuo* to give 7.5 g. of crude XIII, $b.p_{0.3}$ 150~157°, which crystallized on standing, was recrystallized from isopropyl ether to give 7.1 g. (33.3%) of XIII, in colorless plates, m.p. 62~65°. Picrate in yellow prisms from DMF-ether, m.p. 226°. *Anal.* Calcd. for $C_{10}H_{12}ON_2 \cdot C_6H_3O_7N_3$: C, 47.41; H, 3.73; N, 17.28. Found : C, 47.90; H, 4.34; N, 17.01. Hydrochloride-hydrate in colorless needles from iso-PrOH, m.p. 214~215°. *Anal.* Calcd. for $C_{10}H_{12}ON_2 \cdot HCl \cdot H_2O$: C, 51.41; H, 6.35; N, 12.14; Cl, 15.37. Found : C, 51.65; H, 6.29; N, 12.80; Cl, 15.39.

1-Phenyl-3-dimethylamino-2-pyrrolidinone (XIV)——A mixture of 1.0 g. (5.7 mmoles) of XIII, 6.5 g. of 97% HCOOH, and 4.6 g. of 37% HCHO was heated on the boiling water bath for 2 hr. Then reaction mixture was concentrated *in vacuo* to dryness and the residue was dissolved in 10% HCl. After removal of non-basic parts by extraction with Et_2O, the aqueous solution was made alkaline with K_2CO_3 and an oily substance was extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3, evaporated. Distillation of the residue at 0.03 mm. (bath temperature, 170~200°) afforded 1.1 g. (93% yield) of XIV. Picrate in yellow needles from DMF-ether, m.p. 154~155°. *Anal.* Calcd. for $C_{12}H_{16}ON_2 \cdot C_6H_3O_7N_3$: C, 49.88; H, 4.42; N, 16.16. Found : C, 50.05; H, 4.43; N, 16.56.

1-Phenyl-3-phenethylamino-2-pyrrolidinone Hydrochloride (XV·HCl)——A suspension of 0.1 g. of $PtO_2 \cdot H_2O$ in 20 ml. of abs. EtOH was shaken with H_2 at an atmospheric pressure for several minutes, until no more H_2 was absorbed, then a solution of 1.53 g. (0.0127 mole) of freshly distilled phenylacetaldehyde and 2.0 g. (0.0113 mole) of XIII in 20 ml. of abs. EtOH was added to the catalyst mixture. The mixture was shaken with H_2, until no more H_2 was absorbed. The catalyst was removed by filtration, and the filtrate was concentrated. The addition of 10% HCl to the residue afforded a crystalline mass, sparingly soluble in H_2O, which was recrystallized from EtOH to give 2.0 g. (71.5%) of XV·HCl in colorless needles, m.p. 235~236°. *Anal.* Calcd. for $C_{18}H_{20}ON_2 \cdot HCl$: C, 68.14; H, 6.62; N, 8.83; Cl,11.19. Found : C, 68.43; H, 6.46; N, 9.05;Cl, 11.22.

1-Phenyl-3-(N-methylphenethylamino)-2-pyrrolidinone (XVI)——A mixture of 0.65 g. (2.3 mmoles) of XV, 2 ml. of 37% HCHO and 2 ml. of 97% HCOOH was heated on a boiling water bath for 9 hr. Reaction mixture was concentrated *in vacuo*. The residue was dissolved in 10% HCl, from which XVI·HCl was extracted with $CHCl_3$. The extract was washed with aq. K_2CO_3 solution, dried over anhyd. K_2CO_3, evaporated, and the distillation of the residue at 0.5 mm. (bath temperature, 220~230°) afforded 0.5 g. (73% yield) of XVI. Hydrochloride-monohydrate in colorless prisms from iso-PrOH-Et_2O, m.p. 109~111°. *Anal.* Calcd. for $C_{19}H_{22}ON_2 \cdot HCl \cdot H_2O$: C, 65.42; H, 6.65; N, 8.03. Found : C, 65.61; H, 6.81; N, 8.12.

2-Amino-γ-valerolactone Hydrobromide (XVII)——A mixture of 25.7 g. (0.1 mole) of diethyl allylacetamidomalonate and 200 ml. of 48% HBr was refluxed for 16 hr. and the solution was concentrated to dryness *in vacuo*. Residual solid was crystallized from 140 ml. of iso-PrOH to give 15.1 g. of a diastereoisomeric mixture of XVII, m.p. 175~182°, which, by benzoylation and a subsequent fractional recrystallization, could be divided into each benzoyl derivative of the diastereoisomers of 2-amino-γ-valerolactone, (a) m.p. 121~123° and (b) m.p. 140~142°, which were identical with the compound reported by Hurd.[11] Analytical sample crystallized from iso-PrOH in colorless prisms, m.p. 185~188°. *Anal.* Calcd. for $C_5H_9O_2N \cdot HBr$: C, 30.61; H, 5.10; N, 7.14. Found : C, 30.47; H, 5.10; N, 6.95.

1-Phenyl-3-amino-5-methyl-2-pyrrolidinone (XVIIIa and XVIIIb)——A mixture of 34 g. (0.174 mole) of the crude XVII and 48 g. (0.52 mole) of aniline was heated at 150~160° for 48 hr. Excess aniline was distilled off *in vacuo*. The residue was taken up in 10% HCl, and, after washing with $CHCl_3$, acidic aqueous solution was made alkaline with K_2CO_3 and the oil was extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3, concentrated. Distillation of the residue afforded 17.6 g. (53%) of colorless oil, $b.p_{0.7}$ 145~150°, which consists of a diastereoisomeric mixture of XVIII. Then, to the distillate in 200 ml. of EtOH was added 21.3 g. of picric acid in 220 ml. of EtOH and resulting yellow crystals were collected by filtration. This picrates were recrystallized from 500 ml. of 60% aq. EtOH to give 17.5 g. of XVIIIa·picrate in yellow needles, m.p. 215~218° (decomp.). The liberation of XVIIIa from XVIIIa·picrate by treatment with aq. LiOH solution and subsequent distillation afforded 5.0 g. (15% yield) of XVIIIa, $b.p_{0.8}$ 140~143° (m.p. 57~60°). Whole mother liquor and the filtrate were combined and concentrated to dryness *in vacuo*. The residue was recrystallized from 200 ml. of EtOH to give 13.6 g. of XVIIIb·picrate in rhombs, m.p. 185~188° (decomp.). The same treatment as in that of XVIIIa gave 4.1 g. (12.4% yield) of XVIIIb, $b.p_{0.2}$ 126~130° (m.p. 94~96° prisms from isopropyl ether). *Anal.* Calcd. for $C_{11}H_{14}ON_2$ (XVIIIa) : C,

11) C. D. Hurd, L. Bauer : J. Org. Chem., 18, 1440 (1953).

69.44; H, 7.42; N, 14.73. Found : C, 69.55; H, 7.12; N, 14.79. *Anal.* Calcd. for XVIIIb : C, 69.44; H, 7.42; N, 14.73. Found : C, 69.88; H, 7.04; N, 14.58. *Anal.* Calcd. for picrate : $C_{11}H_{14}ON_2 \cdot C_6H_3O_7N_3$: C, 48.69; H, 4.09; N, 16.69. Found : for XVIIIa·picrate : C, 48.79; H, 4.16; N, 16.51; for XVIIIb·picrate : C, 48.49; H, 4.16; N, 16.49.

Hydrochloride : XVIIIa·HCl·H_2O in colorless needles from iso-PrOH, m.p. 96~98°. *Anal.* Calcd. for $C_{11}H_{14}ON_2 \cdot HCl \cdot H_2O$: C, 53.98; H, 6.95; N, 11.45. Found : C, 53.88; H, 6.42; N, 11.41.

XVIIIb·HCl in colorless needles from iso-PrOH-Me_2CO, m.p. 215~220°. *Anal.* Calcd. for $C_{11}H_{14}ON_2 \cdot HCl$: C, 58.28; H, 6.18; N, 12.37. Found : C, 57.91; H, 6.43; N, 12.90.

Acetate : XVIIIa·acetate in colorless prisms from benzene, m.p. 131~132°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found : for XVIIIa·acetate : C, 67.69; H, 6.53; N, 12.20.

XVIIIb·acetate in colorless prisms from iso-PrOH, m.p. 180~181.5°. *Anal.* Calcd. for $C_{13}H_{16}O_2N_2$: C, 67.22; H, 6.94; N, 12.06. Found for XVIIIb : C, 67.58; H, 6.98; N, 11.97.

1-Phenyl-3-dimethylamino-5-methyl-2-pyrrolidinone (XXa)——A mixture of 0.87 g. (4.5 mmoles) of XVIIIa, 5 ml. of 97% HCOOH and 3 ml. of 37% HCHO was heated on a boiling water bath for 10 hr. Reaction mixture was concentrated to dryness *in vacuo* and the residue was taken up in 20 ml. of 5% HCl. The aqueous acidic solution was made alkaline with K_2CO_3 and the oil was extracted with $CHCl_3$, and the extract was dried over anhyd. K_2CO_3, evaporated. Distillation of the residue at 0.07 mm. (bath temperature, 140~150°) afforded 0.6 g. (60% yield) of XXa. Hydrochloride in colorless prisms from iso-PrOH, m.p. 206~209°. *Anal.* Calcd. for $C_{13}H_{18}ON_2 \cdot HCl$: C, 61.29; H, 7.46; N, 11.00. Found : C, 61.01; H, 7.26; N, 11.25.

1-Phenyl-3-dimethylamino-5-methyl-2-pyrrolidinone (XXb)——A mixture of 1.0 g. (5.2 mmoles) of XVIIIb, 5 ml. of 97% HCOOH and 4 ml. of 37% HCHO was heated on the boiling water bath for 10 hr. Reaction mixture was treated with a same manner as in the previous experiment and distillation of the residue at 0.08 mm. (bath temperature, 140~150°) afforded 0.93 g. (81% yield) of XXb. Hydrochloride in colorless prisms from iso-PrOH, m.p. 194~197°. *Anal.* Calcd. for $C_{13}H_{18}ON_2 \cdot HCl$: C, 61.29; H, 7.46; N, 11.00. Found : C, 61.08; H, 7.05; N, 10.93.

1-Phenyl-3-piperidino-5-methyl-2-pyrrolidinone (XXIa)——A solution of 2.7 g. (0.0142 mole) of XVIIIa and 3.3 g. (0.0142 mole) of 1,5-dibromopentane in 60 ml. of abs. toluene was stirred for 3 hr. under refluxing. To the mixture was added 2.4 g. (0.0284 mole) of $NaHCO_3$ and further stirring under refluxing was continued for 12 hr. After cooling, basic portion was extracted with 10% HCl and the acidic solution was made alkaline with K_2CO_3, extracted with $CHCl_3$. The extract was dried over anhyd. K_2CO_3 and evaporated under reduced pressure. Distillation of the residue afforded 1.7 g. of crude XXIa as a colorless oil, $b.p_{0.09}$ 155~160°, which crystallized on standing. Recrystallization of the crude product from petr. ether gave 1.0 g. (27.4% yield) of XXIa, m.p. 66~75°.

Analytical sample in colorless needles from isopropyl ether, m.p. 79~81°. *Anal.* Calcd. for $C_{16}H_{12}ON_2$: C, 74.38; H, 8.58; N, 10.84. Found : C, 74.36; H, 8.22; N, 10.96.

Hydrochloride in colorless prisms from iso-PrOH, m.p. 208~210°. *Anal.* Calcd. for $C_{16}H_{22}ON_2 \cdot HCl$: C, 65.19; H, 7.81; N, 9.50. Found : C, 65.34; H, 7.97; N, 9.51.

1-Phenyl-3-piperidino-5-methyl-2-pyrrolidinone (XXIb)——A solution of 2.3 g. (0.012 mole) of XVIIIb and 2.7 g. (0.012 mole) of 1,5-dibromopentane, in 45 ml. of abs. toluene was stirred under refluxing for 3 hr. Then to the mixture was added 2.05 g. of $NaHCO_3$ and further stirring under refluxing was continued for 12 hr. The reaction mixture was worked up as described above to give 1.7 g. of crude XXIb, $b.p_{0.4}$ 155~157°, which crystallized on standing. Recrystallization of the crude product from petr. ether afforded 0.9 g. (29% yield) of XXIb, m.p. 70~75°. Analytical sample in colorless needles from petr. ether, m.p. 75~77°. *Anal.* Calcd. for $C_{16}H_{22}ON_2$: C, 74.38; H, 8.58; N, 10.84. Found : C, 74.48; H, 8.69; N, 10.73.

Hydrochloride in colorless prisms from iso-PrOH-Me_2CO, m.p. 222~225°. *Anal.* Calcd. for $C_{16}H_{22}ON_2 \cdot HCl$: C, 65.19; H, 7.81; N, 9.50. Found : C, 64.99; H, 7.26; N, 9.61.

1-Phenyl-3-benzylamino-5-methyl-2-pyrrolidinone (XXIIa)——A solution of 1.9 g. (0.01 mole) of XVIIIa and 1.25 g. (0.012 mole) of benzaldehyde in 50 ml. of abs. EtOH was shaken in an atmosphere of H_2 with 5 ml. of Raney Ni suspended in abs. EtOH. After absorption of theoretical amount of H_2, catalyst was filtered off and the filtrate was concentrated. The residue was taken up in 10% HCl and the desired product, XXIIa, was able to be extracted with $CHCl_3$ as hydrochloride, leaving starting material, XVIIIa, in aqueous layer. The $CHCl_3$ layer was washed with aq. K_2CO_3 solution, dried over anhyd. K_2CO_3, evaporated, and distillation of the residue afforded 1.5 g. (53% yield) of XXIIa, $b.p_{0.3}$ 190~195°.

Picrate in yellow prisms from EtOH-H_2O, m.p. 214~215°. *Anal.* Calcd. for $C_{18}H_{20}ON_2 \cdot C_6H_3O_7N_3$: C, 56.58; H, 4.55; N, 13.75. Found : C, 56.26; H, 4.39; N, 13.85.

1-Phenyl-3-benzylamino-5-methyl-2-pyrrolidinone (XXIIb)——A solution of 4.0 g. (0.021 mole) of XVIIIb and 2.65 g. (0.025 mole) of benzaldehyde in 40 ml. of abs. EtOH was shaken in an atmosphere of H_2 with 8 ml. of Raney Ni suspended in abs. EtOH. The mixture was worked up as described above to give 2.7 g. (45.7%) of XXIIb in colorless needles from isopropyl ether, m.p. 107~109°. *Anal.* Calcd. for $C_{18}H_{20}ON_2$: C, 77.11; H, 7.19; N, 9.99. Found : C, 77.44; H, 7.05; N, 10.05.

1-Phenyl-3-(N-methylbenzylamino)-5-methyl-2-pyrrolidinone (XXIIIa)——A mixture of 1.0 g. (3.6 mmoles) of XXIIa, 3 ml. of 97% HCOOH and 3 ml. of 37% HCHO was heated on a boiling water bath for 8 hr. After the evaporation of the solvent, the residue was taken up in 10% HCl, and XXIIIa·HCl was extracted with $CHCl_3$. The extract was washed with aq. K_2CO_3 solution, dried over anhyd. K_2CO_3. Distillation of the residue afforded 0.92 g. (87% yield) of XXIIIa as pale yellow oil, $b.p_{0.07}$ 180~185°. Picrate in yellow needles from EtOH, m.p. 128~130°. *Anal.* Calcd. for $C_{19}H_{22}ON_2 \cdot C_6H_3O_7N_3$: C, 57.36; H, 4.81; N, 13.38. Found : C, 57.68; H, 4.77; N, 13.61.

1-Phenyl-3-(N-methylbenzylamino)-5-methyl-2-pyrrolidinone (XXIIIb)——A mixture of 2.7 g. (9.6 mmoles) of XXIIb, 8 ml. of 97% HCOOH and 8 ml. of 37% HCHO was heated on the boiling water bath for 10 hr. and the mixture was worked up as described above to give 2.15 g. (76% yield) of XXIIIb as a pale yellow oil, $b.p_{0.08}$ 183~185°. Picrolonate in yellow needles from EtOH-H_2O, m.p. 187~189° *Anal.* Calcd. for $C_{19}H_{22}ON_2 \cdot C_{10}H_8O_5N_4$: C, 62.35; H, 5.41; N, 15.05. Found : C, 62.46; H, 5.12; N, 15.06.

1-Phenyl-3-methylamino-5-methyl-2-pyrrolidinone (XXIVa)——A mixture of 1.0 g. (3.4 mmoles) of XXIIIa, 3.0 g. of carbon in 30 ml. of EtOH, and 0.64 g. of $PdCl_2 \cdot 2H_2O$ dissolved in 1.5 ml. of conc. HCl and 13 ml. of H_2O was skaken in an atmosphere of H_2. After the absorption of theoretical amount of H_2, catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was taken up in H_2O, and aqueous layer was washed with $CHCl_3$, salted out with K_2CO_3. The separated oil was extracted with $CHCl_3$, and the extract was dried over anhyd. K_2CO_3, evaporated. Distillation of the residue at 0.09 mm. (bath temperature, 155~160°) afforded 0.45 g. (65% yield) of XXIVa, which crystallized on standing, m.p. 68~76°. Analytical sample in colorless leaflets from isopropyl ether, m.p. 72~73.5°. *Anal.* Calcd. for $C_{12}H_{16}ON_2$: C, 70.56; H, 7.90; N, 13.72. Found : C, 70.69; H, 7.68; N, 13.05. Hydrochloride in colorless prisms from iso-PrOH, m.p. 216~217°. *Anal.* Calcd. for $C_{12}H_{16}ON_2 \cdot HCl$: C, 59.82; H, 7.06; N, 11.63. Found : C, 60.16; H, 6.91; N, 11.62.
Picrate in yellow cubes from EtOH, m.p. 167~169°. *Anal.* Calcd. for $C_{12}H_{16}ON_2 \cdot C_6H_3O_7N_3$: C, 49.88; H, 4.42; N, 16.16. Found : C, 50.04; H, 4.37; N, 16.14.

1-Phenyl-3-methylamino-5-methyl-2-pyrrolidinone (XXIVb)——A mixture of 1.5 g. (5.1 mmoles) of XXIIIb, 4.5 g. of carbon in 45 ml. of EtOH, and 1.1 g. of $PdCl_2 \cdot 2H_2O$ dissolved in 2.6 ml. of conc. HCl and 21 ml. of H_2O was shaken in an atmosphere of H_2. The reaction mixture was worked up as described above to give 0.8 g. (78% yield) of XXIVb as colorless oil, $b.p_{0.05}$ 150~160°.
Picrate in yellow needles from EtOH, m.p. 210~215°. *Anal.* Calcd. for $C_{12}H_{16}ON_2 \cdot C_6H_3O_7N_3$: C, 49.88; H, 4.42; N, 16.16. Found : C, 49.98; H, 4.35; N, 15.96.
Hydrochloride in colorless prisms from iso-PrOH, m.p. 228~230°. *Anal.* Calcd. for $C_{12}H_{16}ON_2 \cdot HCl$: C, 59.82; H, 7.06; N, 11.63. Found : C, 59.98; H, 6.90; N, 11.84.

1-Phenyl-3-phenethylamino-5-methyl-2-pyrrolidinone (XXVa)——To a suspension of 0.2 g. of pre-reduced $PtO_2 \cdot H_2O$ in 30 ml. of abs. EtOH was added a solution of 1.9 g. (0.01 mole) of XVIIIa and 1.45 g. (0.012 mole) of phenylacetaldehyde in 20 ml. of abs. EtOH. The mixture was shaken in an atmosphere of H_2, until the absorption of H_2 stopped. The catalyst was filtered off and the solvent was removed under reduced pressure. The residue was taken up in 10% HCl and the product was extracted with $CHCl_3$ as the hydrochloride. The extract was washed with aq. K_2CO_3, dried over anhyd. K_2CO_3, evaporated. Distillation of the residue gave 1.3 g. (44% yield) of XXVa as a pale yellow oil, $b.p_{0.09}$ 198~202°. Picrolonate in yellow leaflets from EtOH-H_2O, m.p. 234~236° (decomp.). *Anal.* Calcd. for $C_{19}H_{22}ON_2 \cdot C_{10}H_8O_5N_4$: C, 62.35; H, 5.41; N, 15.05. Found : C, 62.48; H, 5.19; N, 14.75.
Hydrochloride in colorless prisms from EtOH, m.p. 216~218°. *Anal.* Calcd. for $C_{19}H_{22}ON_2 \cdot HCl$: C, 68.98; H, 7.00; N, 8.47. Found : C, 68.86; H, 6.80; N, 8.52.

1-Phenyl-3-phenethylamino-5-methyl-2-pyrrolidinone Hydrochloride (XXVb·HCl)——To a suspension of 0.05 g. of pre-reduced $PtO_2 \cdot H_2O$ in 20 ml. of abs. EtOH was added a solution of 0.95 g. (5.0 mmoles) of XVIIIb and 0.72 g. (6.0 mmoles) of phenylacetaldehyde in 10 ml. of abs. EtOH. The mixture was shaken in an atmosphere of H_2, until the absorption of H_2 stopped. The catalyst was filtered off and the filtrate was evaporated. The product was extracted with $CHCl_3$ as the hydrochloride and the extract was dried over anhyd. Na_2SO_4, evaporated to give 0.65 g. (39% yield) of XXVb·HCl in colorless crystals. Analytical sample recrystallized from iso-PrOH in colorless prisms, m.p. 232~234°. *Anal.* Calcd. for $C_{19}H_{22}ON_2 \cdot HCl$: C, 68.97; H, 7.01; N, 8.47. Found : C, 68.65; H, 6.80; N, 8.44.

1-Phenyl-3-(N-methylphenethylamino)-5-methyl-2-pyrrolidinone (XXVIa)——1) Method A : by methylation of XXVa : A mixture of 0.5 g. (1.7 mmoles) of XXVa, 2 ml. of 97% HCOOH and 2 ml. of 37% HCHO was heated on a boiling water bath for 8 hr. The reaction mixture was concentrated to dryness *in vacuo*, and the residue was taken up in 10% HCl. The product was extracted with $CHCl_3$ as the hydrochloride and the extract was washed with aq. K_2CO_3, dried over anhyd. K_2CO_3, evaporated. Distillation of the residue at 0.07 mm. (bath temperature 210~215°) afforded 0.47 g. (89% yield) of XXVIa as a pale yellow oil. Picrolonate in yellow needles from EtOH-H_2O, which was identified by the comparison of its IR spectrum with that of the sample prepared by Method B.
2) Method B : by phenethylation of XXIVa : A mixture of 0.4 g. (1.96 mmoles) of XXIVa and 0.185 g. (0.98 mmole) of phenethyl bromide was heated at 130~140° for 5 hr. Then, after cooling, the mixture was taken up in $CHCl_3$, and the unreacted material was removed by extraction with 5% HCl. The $CHCl_3$

layer was washed with aq. K_2CO_3 solution, dried over anhyd. K_2CO_3, evaporated. Distillation of the residue at 0.04 mm. (bath temperature, 200~210°) afforded 0.17 g. (56.5% yield) of XXVIa as yellow oil. Picrolonate in yellow needles from EtOH-H_2O, m.p. 204~205°. *Anal.* Calcd. for $C_{20}H_{24}ON_2 \cdot C_{10}H_8O_5N_4$: C, 62.92; H, 5.63; N, 14.68. Found : C, 62.77; H, 5.66; N, 14.25.

1-Phenyl-3-(N-methylphenethylamino)-5-methyl-2-pyrrolidinone (XXVIb)——1) Method A : by methylation of XXVb : A mixture of 0.28 g. (0.95 mmole) of XXVb, 1 ml. of 97% HCOOH, and 1 ml. of 37% HCHO was heated on a boiling water bath for 9 hr. and the reaction mixture was worked up as described above. 0.25 g. (85% yield) of XXVIb was obtained as a yellow oil, distilled at 0.2 mm. (bath temperature, 210~220°). Picrolonate in yellow cubes from EtOH-H_2O, m.p. 217~218°, which was identified by the comparison of its IR spectrum with that of the sample prepared by Method B.

2) Method B : by phenethylation of XXIVb : A mixture of 0.8 g. (3.92 mmoles) of XXIVb, and 0.37 g. (1.96 mmoles) of phenethyl bromide was heated at 130~140° for 5 hr. Then the reaction mixture was worked up as described in previous experiment. 0.45 g. (74% yield) of XXVIb was obtained as a pale yellow oil, distilled at 0.07 mm. (bath temperature, 210~220°). Picrolonate in yellow cubes from EtOH-H_2O, m.p. 215~217°. *Anal.* Calcd. for $C_{20}H_{24}ON_2 \cdot C_{10}H_8O_5N_4$: C, 62.92; H, 5.63; N, 14.68. Found : C, 62.99; H, 5.40; N, 15.00.

1-Phenyl-3-hydroxyimino-5-methyl-2-pyrrolidinone (XIX)——1) From XVIIIa : To a solution of 1.0 g. (5.2 mmoles) of XVIIIa, 0.1 g. of $Na_2WO_4 \cdot 2H_2O$ and 1 ml. of MeOH in 8 ml. of H_2O was added dropwise 2.7 ml. of 10% H_2O_2 at 15° during 25 min. with stirring and stirring was further continued for 2 hr. at a room temperature. The white crystals which set out, were collected by filtration, giving 0.63 g. (61% yield) of XIX, m.p. 160~165°. Analytical sample in colorless needles from benzene, m.p. 164~165.5°. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found : C, 64.86; H, 5.81; N, 13.79.

2) From XVIIIb : The reaction was carried out as described above and the product was obtained as colorless needles from benzene, m.p. 164~165.5°, in a yield of 39%. Its IR spectrum was identical with that of the sample from XVIIIa, and mixed melting point test showed no depression. *Anal.* Calcd. for $C_{11}H_{12}O_2N_2$: C, 64.69; H, 5.92; N, 13.72. Found : C, 64.37; H, 5.69, N, 13.41.

The authors are grateful to Prof. Emeritus S. Sugasawa of the University of Tokyo and the Director Dr. N. Sugimoto for their kind and helpful advice.

They are also indebted to Dr. K. Kotera for infrared spectral measurements, and to the members of Analysis Room of Tokyo Research Laboratory for elemental microanalyses. Thanks are also due to Mr. M. Ikezaki and Mr. T. Nishihara for their kind technical assistance.

Summary

As a part of studies on antipyretic-analgesic, the 1-phenyl-3-dialkylamino-2-pyrrolidinones and their 5-methyl analogs, including each diastereoisomeres, were synthesized.

(Received February 14, 1964)