was recrystallized from a mixture of benzene and pet. benzine to give yellow needles of Vd (1.7 g, 85%), mp 67—68°. *Anal.* Calcd. for $C_7H_7O_4NS$: C, 41.80; H, 3.51; N, 6.96. Found: C, 41.45; H, 3.87; N, 6.59.

Phenyl (Methylthio) methyl Ketone (Va): colorless oil, bp 96—98° (2 mmHg). *Anal.* Calcd. for $C_9H_{10}OS$: C, 65.05; H, 6.07. Found: C, 64.77; H, 6.19.

4-Bromophenyl(methylthio)methyl Ketone(Vb): colorless needles from pet. ether, mp 45—46°. *Anal.* Calcd. for C_9H_9OSBr: C, 44.10; H, 3.70. Found: C, 44.02; H, 3.65.

2-Furyl(methylthio)methyl Ketone (Vc): colorless needles from a mixture of ether and pet. ether, mp 35—36°. *Anal.* Calcd. for $C_7H_8O_2S$: C, 53.84; H, 5.16. Found: C, 53.55; H, 5.00.

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Benzodiazepines. III.[1] A Novel Synthesis of a 1-Cyclopropylmethyl-1,4-benzodiazepine Derivative

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Recently it has been reported[3] that a new benzodiazepine derivative, 7-chloro-1-(cyclopropylmethyl)-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (VI) was a potent drug for the relief of tension and anxiety, which had qualities different from chlordiazepoxide and diazepam.

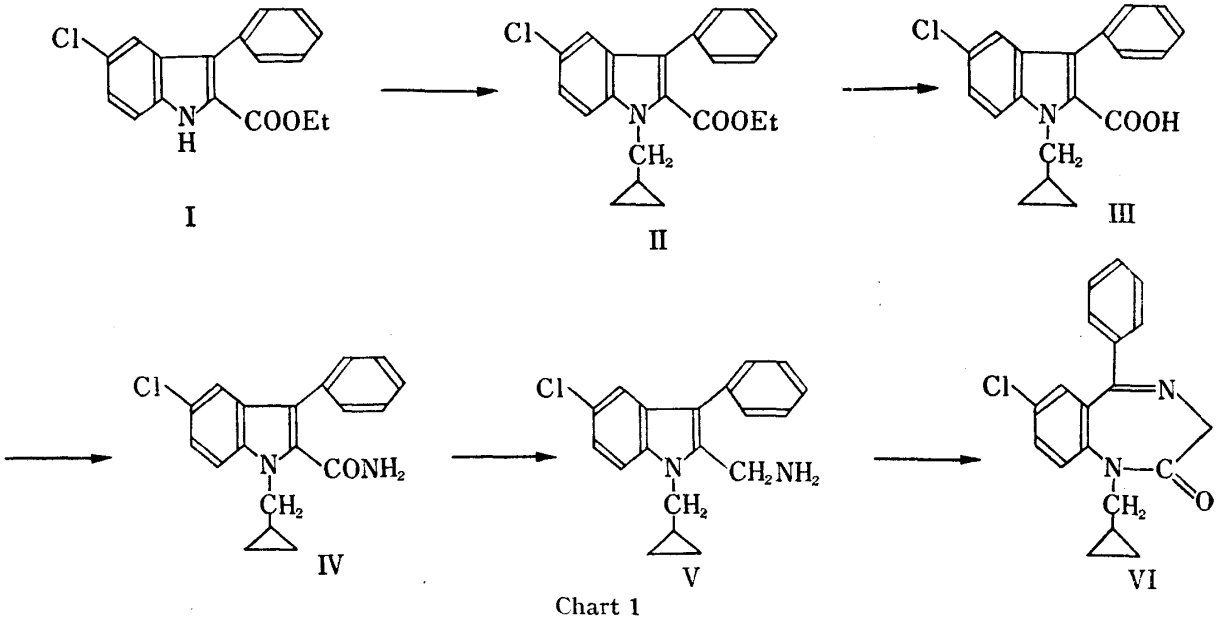

Chart 1

1) Part II: *Chem. Ber.*, **101**, 4245 (1968).
2) Location: *278, Kasugade-cho, Konohana-ku, Osaka.*
3) E. Kingstone, A. Villeneuve and I. Kassay, *Current Therapeutic Reserch*, **8**, 159 (1966).

We have found that diazepam was prepared from the corresponding 2-aminomethylindole derivative in a good yield by a new procedure. This new procedure can be used to synthesize a variety of benzodiazepine, and the present paper deals with the synthesis of VI by this procedure as an example (Chart 1).

The reaction of ethyl 5-chloro-3-phenylindole-2-carboxylate[1] (I) with cyclopropylmethyl bromide in the presence of sodium hydride gives a 1-cyclopropylmethyl-substituted derivative (II), the hydrolysis of which affords 5-chloro-1-cyclopropylmethyl-3-phenylindole-2-carboxylic acid (III). By means of the treatment with thionyl chloride followed by ammonia in ethanol, 5-chloro-1-cyclopropylmethyl-3-phenylindole-2-carboxamide (IV) is prepared from compound III.

The reduction of compound IV by lithium aluminium hydride causes the production of 2-aminomethyl-5-chloro-1-cyclopropylmethyl-3-phenylindole (V), which is treated with chromic acid in glacial acetic acid to yield crystals of compound VI. The infrared absorption spectrum of the crystals is identical with that of an authentic sample prepared by cyclopropylmethylation of 7-chloro-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one.[4] When this compound is admixed with the authentic sample, the melting point undepresses. This ring expansion from compound V to compound VI proceeds smoothly under such mild conditions that the mixture is allowed to stand at room temperature.

Experimental

All melting points were uncorrected. Infrared spectra were recorded on a Perkin Elmer Model 125 Spectrophotometer. Ultraviolet absorption spectra were measured with a Shimadzu Model SV–50A Spectrophotometer.

Ethyl 1-Cyclopropylmethyl-3-phenyl-5-chloroindole-2-carboxylate (II)——To a solution of 18.2 g (0.0605 mole) of ethyl 3-phenyl-5-chloroindole-2-carboxylate (I)[1] in a mixture of 180 ml of toluene and 180 ml of dimethylformamide, was added 3.0 g of a suspension of 55.7% sodium hydride in a mineral oil. After the mixture was stirred at room temperature for 1 hr, 9.0 g (0.0667 mole) of cyclopropylmethyl bromide was added dropwise thereto over 10 min. The mixture was heated under reflux for 3.5 hr with stirring. After cooling, the reaction mixture was poured into 450 ml of ice–water. The organic layer was separated, and further the aqueous layer was extracted with 170 ml of ether. The combined organic layer was washed with saline water, dried over anhydrous sodium sulfate and concentrated under reduced pressure to an oily substance, which was solidified in a short time. The residue was triturated with 50 ml of petroleum ether to yield 18.3 g (85.3%) of compound II, mp 112—114°. From the mother liquor, 1.6 g (7.5%) of the second crop was obtained; the total yield was 19.9 g (93.0%). Recrystallization from 100 ml of EtOH gave 17.4 g of colorless plates, mp 117.5—119.0°. IR ν_{max}^{KBr} cm^{-1}: 1700. UV λ_{max}^{MeOH} $m\mu(\varepsilon)$: 242 (34100), 303 (14300). *Anal.* Calcd. for $C_{21}H_{20}O_2NCl$: C, 71.30; H, 5.69; N, 3.96; Cl, 10.03. Found: C, 71.57; H, 5.62; N, 3.89; Cl, 9.79.

5-Chloro-1-cyclopropylmethyl-3-phenylindole-2-carboxylic Acid (III)——To a solution of 5.3 g (0.047 mole) of KOH in 665 ml of EtOH was added 16.6 g (0.047 mole) of compound II and the mixture was heated under reflux for 2.5 hr. The solvent was evaporated under reduced pressure to a residual substance, to which was added 120 ml of water. The insoluble material was removed by filtration, and the filtrate was acidified with 8 ml of conc. HCl with stirring and cooling. The precipitate was collected by filtration, washed with water and dried to give 15.7 g of compound III, mp 203° (decomp.). Recrystallization from benzene gave colorless powder, mp 205° (decomp.). *Anal.* Calcd. for $C_{19}H_{16}O_2NCl$: C, 70.04; H, 4.95; N, 4.29; Cl, 10.88. Found: C, 70.25; H, 4.79; N, 4.01; Cl, 10.94. IR ν_{max}^{KBr} cm^{-1}: 1672. UV λ_{max}^{MeOH} $m\mu$ (ε): 242 (31900), 303 (11900).

5-Chloro-1-cyclopropylmethyl-3-phenylindole-5-carboxamide (IV)——A mixture of 15.0 g (0.046 mole) of compound III and 16.1 ml of thionyl chloride was refluxed for 2 hr. The mixture was then distilled under reduced pressure to a residue, to which was added 250 ml of ether. After the insoluble material was removed by filtration, gaseous ammonia was passed into the solution for 15 min under cooling. Stirring was continued for additional 30 min at 0°. The precipitate was collected by filtration, washed with water and dried to give 9.7 g of compound IV, mp 186.5—188.5°. Recrystallization from EtOH gave colorless needles, mp 187—189°. An additional 2.5 g of compound IV was obtained from the filtrate, mp 181—185°. UV λ_{max}^{MeOH} $m\mu$ (ε): 239 (29000), 301 (10200). IR ν_{max}^{KBr} cm^{-1}: 3480, 3330, 1678, 1662. *Anal.* Calcd. for $C_{19}H_{17}ON_2Cl$: C, 70.25; H, 5.27; N, 8.62; Cl, 10.91. Found: C, 70.17; H, 5.00; N, 8.19; Cl, 10.83.

2-Aminomethyl-5-chloro-1-cyclopropylmethyl-3-phenylindole (V) Hydrochloride——To a suspension of 9.1 g (0.028 mole) of compound IV in 900 ml of dry ether was added 4.8 g of $LiAlH_4$. The mixture was

4) U.S. Patent No. 3, 192200 (1965).

heated under reflux for 4 hr. After the completion of the reaction, 60 ml of water was added dropwise to decompose excess $LiAlH_4$. The ether layer was decanted, dried over anhydrous sodium sulfate and concentrated to dryness under reduced pressure. The oily residue was taken up in ethanolic HCl and the solvent evaporated to a residue, which was recrystallized from 30 ml of ethanol to give 4.7 g of colorless crystals of compound V hydrochloride, mp 224—225°. Recrystallization from EtOH gave colorless crystals, mp 229.5—230°. UV λ_{max}^{MeOH} mμ (ε): 232 (36100), 238 (38100), 267 (9900). IR ν_{max}^{KBr} cm^{-1}: 2617, 1603. *Anal.* Calcd. for $C_{19}H_{19}N_2Cl \cdot HCl$: C, 65.70; H, 5.82; N, 8.06; Cl, 20.41. Found: C, 66.25; H, 5.83; N, 7.93; Cl, 20.57.

An additional 2.49 g of compound V hydrochloride was obtained from the mother liquor; the total yield was 7.19 g (75.0%).

7-Chloro-1-cyclopropylmethyl-1,3-dihydro-5-phenyl-2H-1,4-benzodiazepin-2-one (VI)——A solution of 1.75 g of chromic anhydride in 1.75 ml of water was added dropwise to 2.0 g of compound V in 20 ml of glacial acetic acid on cooling with stirring. The stirring was continued at room temperature for additional 12 hr. The temperature was maintained at 0—10°, while the reaction mixture was added dropwise to 90 ml of 12.4% aqueous ammonia. The mixture was extracted with 20 ml of carbon tetrachloride three times. The carbon tetrachloride layer was washed with 60 ml of water and dried over anhydrous sodium sulfate. The solvent was evaporated to a residue, which was crystallized on the treatment of 2.0 ml of isopropyl alcohol to give 1.27 g (69.9%) of the compound VI, mp 139.5—141.5°. IR ν_{max}^{KBr} cm^{-1}: 3080, 1670. UV λ_{max}^{MeOH} mμ (ε): 229 (30100), 314 (1900). *Anal.* Calcd. for $C_{19}H_{17}ON_2Cl$: C, 70.32; H, 5.28; N, 8.63; Cl, 10.92. Found: C, 70.63; H, 5.13; N, 8.28; Cl, 10.78.

From the mother liquor was given 0.11 g of the 2nd crop, mp 138—140°. The total yield was 1.38 g (76%).

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A Simpler Synthesis of D-Pantothenic Acid 4'-Phosphate[1]

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In the series of studies[3] to propagate Bifidobacterium bifidum (*Lactobacillus bifidus*) in intestines, D-pantothenic acid 4'-phosphate (III) was necessary to examine the nutritional requirement of this microbe of coenzyme A and its precursors. Although several synthetic routes were reported,[4] they were long, and if short, involved production of by-products as indicated in the direct phosphorylation of D-pantothenic acid (I) with diphenyl phosphorochloridate followed by hydrolysis with sodium hydroxide.[4e] A simpler synthesis was attempted as shown in Chart 1 on the basis of the fact that the aliphatic primary hydroxyl group was phosphorylated with dibenzyl phosphorochloridate more readily than the secondary.[5]

1) A part of this work was presented at the 87th Annual Meeting of Pharmaceutical Society of Japan, Kyoto, April 1967.
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4) *a*) T.E. King and F.M. Strong, *Science*, 112, 562 (1960); *b*) J. Baddiley and E.M. Thain, *J. Chem. Soc.*, 1951, 246; *c*) G.D. Novelli, "Methods in Enzymology," vol. 3, Academic Press Inc., New York, N. Y., 1957, pp. 926—928; *d*) F.R. Atherton, U.S. Patent 2870188 (1959); *e*) S. Okada, O. Nagase, and M. Shimizu, *Chem. Pharm. Bull.* (Tokyo), 15, 713 (1967).
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