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Reaction of Pyrazolo[1,5-*a*]pyrimidine Derivatives with Nucleophiles. V.[1] X-Ray Determination of the Molecular Structure of a Reaction Product of 6,7-Diethoxycarbonylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile with *N*-Methylindole

TAKUSHI KURIHARA,* MAYUMI KATSUDA, KEIKO NASU, MASATOSHI INOUE, and MITSUNOBU DOI

Osaka College of Pharmacy, 2–10–65, Kawai, Matsubara, Osaka 580, Japan

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The structure of the reaction product **3a** of 6,7-diethoxycarbonylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1**) with *N*-methylindole in the presence of triethyloxonium fluoroborate was determined as 2-(4-cyano-1-ethyl-3-pyrazolyl)-4-ethoxycarbonyl-6-methyl-1-(1-methyl-3-indolyl)-1,2,5,6-tetrahydropyrido[4,3-*c*]quinolin-5-one by X-ray analysis.

Keywords——pyrazolo[1,5-*a*]pyrimidine; triethyloxonium fluoroborate; indole; pyrido[4,3-*c*]quinoline; X-ray analysis

Reaction of 6,7-diethoxycarbonylpyrazolo[1,5-*a*]pyrimidine-3-carbonitrile (**1**) with two equivalents of *N*-methylindole in the presence of triethyloxonium fluoroborate (Et_3OBF_4) in dichloromethane (CH_2Cl_2) gave a complex mixture from which we previously isolated diethyl 1,4-dihydro-4-methyl-3-(*N*-methyl-3-indolyl)cyclopent[*b*]indole-1,2-dicarboxylate (**2a**) in 69% yield.[2] An X-ray crystal structure determination[2] and some reactions of **2** have also been reported.[1] Recently we isolated a minor product (**3a**) (5.6% yield, mp 293—294 °C as yellow needles), from the reaction mixture of **1** and *N*-methylindole, and its structure was determined by an X-ray analysis, the results of which are described here.

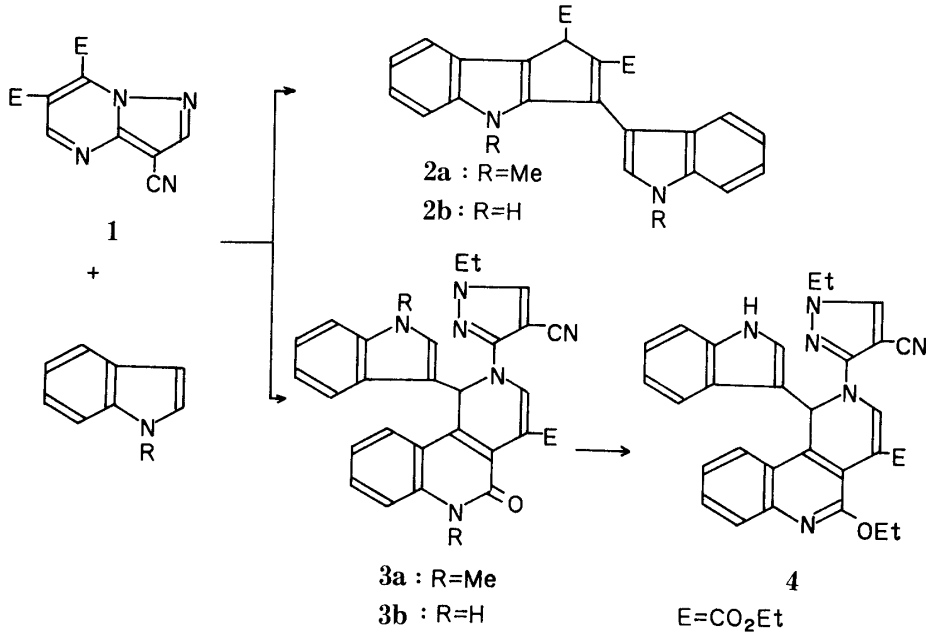

Chart 1

The product **3a**, $C_{31}H_{28}N_6O_3$ [mass spectrum (MS) *m/e*: 532 (M^+)], exhibited two carbonyl absorption bands (1700 and 1640 cm^{-1}) in addition to a band due to a CN group at 2200 cm^{-1} in the infrared (IR) spectrum. The proton nuclear magnetic resonance (^{1}H-NMR) spectrum of **3a** {δ 1.32 and 1.46 (each 3H, each t, $J=7$ Hz, $CO_2CH_2C\underline{H}_3$ and/or $NCH_2C\underline{H}_3$), 3.68 and 3.70 (each 3H, each s, $2\times NCH_3$), 4.19 and 4.27 (each 2H, each q, $J=7$ Hz, $CO_2C\underline{H}_2CH_3$ and/or $NC\underline{H}_2CH_3$), 7.24 [1H, s, C(2)-H on indole ring], 6.98—8.10 [10H, m, $8\times$ Ar-H and C(1)- and C(3)-H], 8.45 [1H, s, C(3)-H on pyrazole ring]} suggested the presence of a $CO_2CH_2CH_3$ group and an NCH_2CH_3 group. Analogously, the reaction or **1** with indole in the presence of an excess of Et_3OBF_4 gave **3b** (31%) as a main product, together with the 1,4-dihydrocyclopent[*b*]indole (**2b**) in 16% yield. The product **3b**, whose IR spectrum showed two carbonyl absorption bands at 1700 and 1650 cm^{-1}, was further treated with Et_3OBF_4 in CH_2Cl_2 at 50 °C for 2 h to give the O-ethyl derivatives (**4**) which exhibited a carbonyl

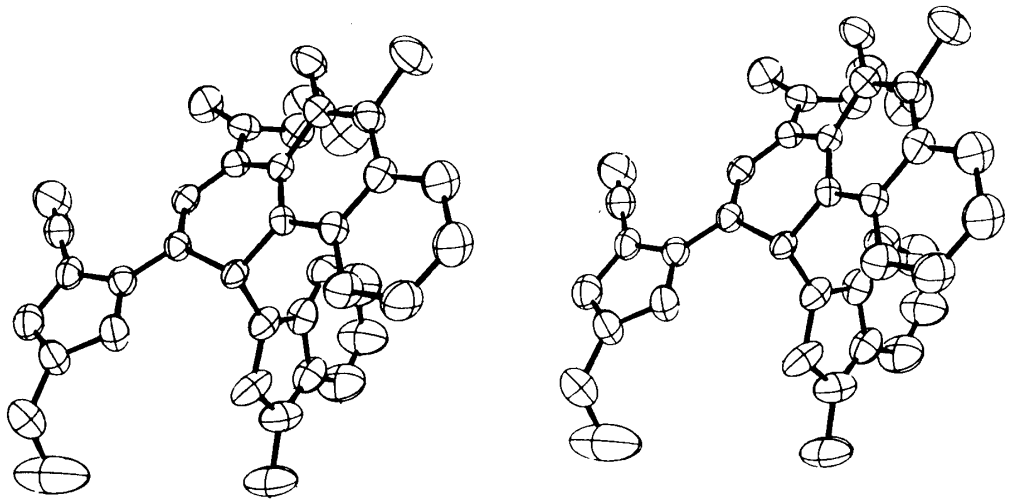

Fig. 1. Stereoscopic View of the Molecule of **3a**

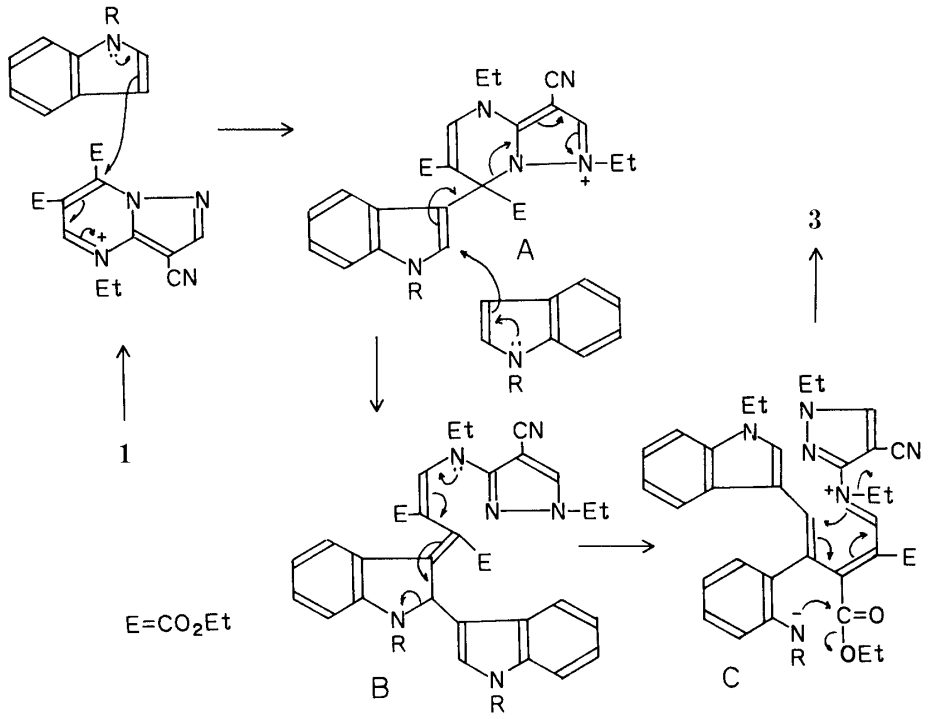

Chart 2

absorption band at 1700 cm^{-1}. Treatment of **3a** with Et_3OBF_4 under the same conditions was ineffective (95% recovery of **3a**). The results indicated the presence of an –NHCO– moiety in **3b**. Thus, in order to obtain definitive evidence for the structures of **3** and **4**, an X-ray crystallographic analysis of **3a** was carried out and its structure was unambiguously established as 2-(4-cyano-1-ethyl-3-pyrazolyl)-4-ethoxycarbonyl-6-methyl-1-(1-methyl-3-indolyl)-1,2,5,6-tetrahydropyrido[4,3-*c*]quinolin-5-one; a stereoscopic view of the molecular is presented in Fig. 1. Hence the structure of **4** was determined to be 2-(4-cyano-1-ethyl-3-pyrazolyl)-5-ethoxy-4-ethoxycarbonyl-1-(3-indolyl)-1,2-dihydropyrido[4,3-*c*]quinoline.

A plausible mechanism for the formation of **3** is shown in Chart 2, *i.e.*, the first stage might involve the nucleophilic attack of an indole at the C_7-position of pyrazolo[1,5-*a*]-pyrimidine to give an indole adduct A. Subsequent attack of the second indole at the C_2-position of the 3-substituted indole of A, followed by fission of the C_7–N bond results in the formation of the biindole B.[3] Electron migration from the 3-aminopyrazole nitrogen to cleave the indoline ring may form the triene C, which cyclizes ultimately to **3** *via* an intramolecular Diels–Alder reaction, followed by deethoxylation as shown in Chart 2.

Thus, this mechanism includes an interesting indole dimerization and intramolecular Diels–Alder cyclization. The reaction of **1** with 2-substituted indoles in the presence of Et_3OBF_4 is now under investigation.

Experimental

All melting points were determined on a Yanagimoto micromelting point apparatus and are uncorrected. IR spectra were recorded on a JASCO IRA-1 spectrometer, ultraviolet (UV) spectra were determined on a JASCO UVIDEC-505 spectrometer in 95% EtOH, and ^{1}H-NMR spectra were recorded with a Hitachi R-24A (90 MHz) spectrometer with tetramethylsilane as an internal standard. MS were recorded with a Hitachi M-80 instrument.

Reaction of Compound 1 with Indole or *N*-Methylindole——Et_3OBF_4 (5.7 g, 0.03 mol) was added in one portion to a solution of **1** (2.88 g, 0.01 mol) and an indole (0.03 mol) in CH_2Cl_2 (50 ml), and the mixture was vigorously stirred at room temperature overnight. The CH_2Cl_2 solution was washed with cold water (20 ml × 5), and dried over anhyd. Na_2SO_4. After removal of the solvent by evaporation, EtOH (10 ml) was added to the residue. The resulting precipitate was collected by filtration and recrystallized from EtOH to give the cyclopent[*b*]indole [**2a** (69%) or **2b** (16%)], which was identical with an authentic sample.[1] The filtrate yielded a crystalline product, which was recrystallized from CH_3CN to give **3a** (5.6%) or **3b** (31%).

2-(4-Cyano-1-ethyl-3-pyrazolyl)-4-ethoxycarbonyl-6-methyl-1-(1-methyl-3-indolyl)-1,2,5,6-tetrahydropyrido[4,3-*c*]quinolin-5-one (**3a**): mp 292—293 °C (CH_3CN). MS *m/z*: 532 (M^+). IR ν_{max}^{KBr} cm^{-1}: 2210 (CN), 1700, 1640 (CO). ^{1}H-NMR δ: 1.32 and 1.46 (each 3H, each t, J=7 Hz, $CO_2CH_2C\underline{H}_3$ and/or $NCH_2C\underline{H}_3$), 3.68 and 3.70 (each 3H, each s, 2 × NCH_3), 4.19 and 4.27 (each 2H, each q, J=7 Hz, $CO_2C\underline{H}_2CH_3$ and/or $NC\underline{H}_2CH_3$), 7.24 [1H, s, C(2)-H on indole ring], 6.98—8.10 [10H, m, 8 Ar-H, C(1)- and C(3)-H], 8.45 [1H, s, C(3)-H on pyrazole ring]. UV λ_{max}^{EtOH} nm (log ε): 228 (4.22), 370 (3.98). *Anal.* Calcd for $C_{31}H_{28}N_6O_3$: C, 69.91; H, 5.30; N, 15.78. Found: C, 69.65; H, 5.51; N, 15.77.

2-(4-Cyano-1-ethyl-3-pyrazolyl)-4-ethoxycarbonyl-1-(3-indolyl)-1,2,5,6-tetrahydropyrido[4,3-*c*]quinolin-5-one (**3b**): mp 250—251 °C (CH_3CN). MS *m/z*: 504 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3300 (NH), 2210 (CN), 1700 and 1650 (CO). ^{1}H-NMR δ: 1.32 and 1.46 (each 3H, each t, J=7 Hz, $CO_2CH_2C\underline{H}_3$ and/or $NCH_2C\underline{H}_3$), 4.05—4.40 (4H, m, $CO_2C\underline{H}_2CH_3$) and/or $NC\underline{H}_2CH_3$), 6.96—8.10 [10H, m, 8 × Ar-H, C(1)- and C(3)-H], 7.28 [1H, d, J=2 Hz, C(2)-H of indole ring], 8.52 [1H, s, C(3)-H on pyrazole ring], 11.15 (1H, br d, J=2 Hz, NH), 11.85 (1H, s, NH). *Anal.* Calcd for $C_{29}H_{24}N_6O_3 \cdot 1/3\ H_2O$: C, 68.22; H, 4.87; N, 16.46. Found: C, 68.15; H, 4.87; N, 16.37.

2-(4-Cyano-1-ethyl-3-pyrazolyl)-5-ethoxy-4-ethoxycarbonyl-1-(3-indolyl)-1,2-dihydropyrido[4,3-*c*]quinoline (4)——A solution of **3b** (1 g) and Et_3OBF_4 (400 mg) in CH_2Cl_2 (20 ml) was refluxed for 2 h. The CH_2Cl_2 solution was washed with cold water (20 ml × 3), and dried over anhyd. Na_2SO_4. After removal of the solvent by evaporation, the residue was recrystallized from EtOH to give **4** (644 mg, 59%) of mp 258—259 °C. MS *m/z*: 532 (M^+). IR ν_{max}^{KBr} cm^{-1}: 3430 (NH), 2220 (CN), 1700 (CO). ^{1}H-NMR δ: 1.26—1.55 (9H, m, $CO_2CH_2C\underline{H}_3$, $NCH_2C\underline{H}_3$ and $OCH_2C\underline{H}_3$), 4.05—4.66 (6H, m, $CO_2C\underline{H}_2CH_3$, $NC\underline{H}_2CH_3$ and $OC\underline{H}_2CH_3$), 6.95—8.03 [10H, m, 8 × Ar-H, C(1)- and C(3)-H], 7.06 [1H, d, J=2 Hz, C(2)-H on indole ring], 8.54 [1H, s, C(3)-H on pyrazole ring], 11.13 (1H, br d, J=2 Hz, NH). *Anal.* Calcd for $C_{31}H_{28}N_6O_3 \cdot 1/3\ H_2O$: c, 69.12; H, 5.36; N, 15.61. Found: C, 69.24; H, 5.17; N, 15.52.

X-Ray Diffraction of 2-(4-Cyano-1-ethyl-3-pyrazolyl)-4-ethoxycarbonyl-6-methyl-1-(1-methyl-3-indolyl)-1,2,5,6-tetrahydropyrido[4,3-*c*]quinolin-5-one (3a)——Plate-like single crystals were grown from a EtOAc solution by slow evaporation. Preliminary oscillation and Weisenberg photographs were taken to establish the crystal symmetry and

TABLE I. Atomic Parameters ($\times 10^4$) of Nonhydrogen Atoms for **3a** with Isotropic Temperature Factors

Atom	x	y	z	B_{eq}
Molecule A				
C(1)A	6020 (3)	−1291 (2)	6017 (2)	2.9 (1)
N(2)A	5924 (2)	−790 (1)	5371 (2)	3.1 (1)
C(3)A	6668 (3)	−452 (2)	5435 (2)	3.2 (1)
C(4)A	7411 (3)	−389 (2)	6162 (2)	3.1 (1)
C(5)A	7368 (2)	−607 (2)	6905 (2)	2.8 (1)
C(6)A	7956 (3)	−287 (2)	7680 (2)	3.5 (1)
N(7)A	7920 (2)	−533 (2)	8367 (2)	3.7 (1)
C(8)A	7326 (3)	−1032 (2)	8345 (2)	3.7 (1)
C(9)A	7369 (4)	−1290 (2)	9071 (3)	4.7 (2)
C(10)A	6761 (4)	−1766 (3)	9036 (3)	5.0 (2)
C(11)A	6081 (4)	−1982 (2)	8291 (3)	4.9 (2)
C(12)A	6056 (3)	−1744 (2)	7571 (3)	4.2 (2)
C(13)A	6673 (3)	−1268 (2)	7582 (2)	3.1 (1)
C(14)A	6704 (2)	−1037 (2)	6845 (2)	2.7 (1)
C(15)A	6254 (3)	−1972 (2)	5819 (2)	3.7 (1)
C(16)A	7088 (3)	−2255 (2)	5944 (3)	4.5 (2)
C(17)A	7943 (4)	−2044 (3)	6257 (4)	6.2 (2)
C(18)A	8604 (5)	−2489 (4)	6265 (6)	9.5 (4)
C(19)A	8395 (5)	−3106 (3)	5946 (6)	9.3 (4)
C(20)A	7546 (5)	−3346 (3)	5599 (5)	8.1 (3)
C(21)A	6866 (4)	−2912 (2)	5592 (3)	4.8 (2)
N(22)A	5973 (3)	−3021 (2)	5294 (3)	5.8 (2)
C(23)A	5592 (4)	−2466 (2)	5413 (3)	5.0 (2)
C(24)A	5456 (5)	−3605 (3)	4781 (5)	8.2 (3)
C(25)A	5129 (3)	−804 (2)	4647 (2)	3.2 (1)
C(26)A	4923 (3)	−493 (2)	3882 (2)	3.7 (1)
C(27)A	4041 (3)	−687 (2)	3376 (3)	4.3 (2)
N(28)A	3773 (2)	−1066 (2)	3818 (2)	4.4 (1)
N(29)A	4434 (2)	−1150 (2)	4606 (2)	4.0 (1)
C(30)A	5445 (3)	−84 (2)	3626 (2)	4.7 (2)
N(31)A	5880 (4)	234 (2)	3439 (3)	7.1 (2)
C(32)A	2901 (3)	−1381 (3)	3559 (3)	6.0 (2)
C(33)A	2883 (7)	−2057 (5)	3311 (8)	12.5 (6)
C(34)A	8516 (4)	−206 (3)	9156 (3)	5.7 (2)
O(35)A	8432 (2)	188 (1)	7714 (2)	4.6 (1)
C(36)A	8238 (3)	−144 (2)	6142 (2)	3.9 (1)
O(37)A	8253 (2)	289 (2)	5692 (2)	5.6 (1)
O(38)A	8941 (2)	−511 (1)	6617 (2)	5.0 (1)
C(39)A	9779 (4)	−360 (3)	6572 (5)	7.4 (3)
C(40)A	10295 (5)	−926 (5)	6771 (7)	11.6 (6)
Molecule B				
C(1)B	743 (3)	−3503 (2)	805 (2)	3.1 (1)
N(2)B	799 (2)	−4065 (1)	293 (2)	3.3 (1)
C(3)B	1627 (3)	−4316 (2)	471 (2)	3.4 (1)
C(4)B	2327 (3)	−4249 (2)	1227 (2)	3.6 (1)
C(5)B	2122 (3)	−4004 (2)	1881 (2)	3.5 (1)
C(6)B	2702 (3)	−4237 (2)	2720 (3)	4.4 (2)
N(7)B	2464 (2)	−4000 (2)	3317 (2)	4.5 (1)
C(8)B	1715 (3)	−3618 (2)	3145 (2)	4.0 (2)
C(9)B	1531 (4)	−3383 (3)	3784 (3)	5.3 (2)
C(10)B	779 (4)	−2995 (3)	3595 (3)	5.9 (2)
C(11)B	174 (4)	−2844 (3)	2794 (3)	5.5 (2)
C(12)B	365 (3)	−3075 (2)	2168 (3)	4.6 (2)

TABLE I. (continued)

Atom	x	y	z	B_{eq}
C(13)B	1113 (3)	−3464 (2)	2327 (2)	3.4 (1)
C(14)B	1345 (3)	−3680 (2)	1694 (2)	3.1 (1)
C(15)B	1050 (3)	−2847 (2)	593 (2)	3.3 (1)
C(16)B	540 (3)	−2394 (2)	−62 (3)	3.8 (1)
C(17)B	−353 (3)	−2380 (2)	−672 (3)	4.8 (2)
C(18)B	−617 (4)	−1862 (3)	−1241 (3)	5.7 (2)
C(19)B	−31 (4)	−1366 (3)	−1206 (4)	6.7 (3)
C(20)B	856 (4)	−1357 (3)	−606 (3)	5.7 (2)
C(21)B	1136 (3)	−1884 (2)	−34 (3)	4.2 (2)
N(22)B	1963 (3)	−2006 (2)	606 (2)	5.2 (2)
C(23)B	1911 (3)	−2582 (2)	981 (3)	4.2 (2)
C(24)B	2754 (5)	−1603 (4)	821 (5)	8.7 (4)
C(25)B	34 (3)	−4199 (2)	−449 (2)	3.2 (1)
C(26)B	−40 (3)	−4566 (2)	−1138 (2)	3.5 (1)
C(27)B	−944 (3)	−4522 (2)	−1678 (3)	4.2 (2)
N(28)B	−1339 (2)	−4164 (2)	−1327 (2)	4.4 (1)
N(29)B	−748 (2)	−3956 (2)	−559 (2)	4.0 (1)
C(30)B	600 (3)	−4930 (2)	−1297 (3)	4.6 (2)
N(31)B	1090 (3)	−5225 (2)	−1447 (3)	6.3 (2)
C(32)B	−2291 (4)	−3953 (3)	−1676 (3)	6.2 (2)
C(33)B	−2440 (5)	−3319 (4)	−2084 (8)	13.3 (6)
C(34)B	3033 (4)	−4248 (4)	4165 (3)	7.5 (3)
O(35)B	3330 (2)	−4627 (2)	2890 (2)	5.8 (1)
C(36)B	3233 (3)	−4403 (2)	1315 (2)	4.0 (1)
O(37)B	3411 (2)	−4848 (2)	978 (2)	5.5 (1)
O(38)B	3835 (2)	−3948 (2)	1773 (2)	5.1 (1)
C(39)B	4756 (3)	−4016 (3)	1896 (4)	6.3 (3)
C(40)B	4908 (4)	−3647 (3)	1267 (4)	6.6 (3)

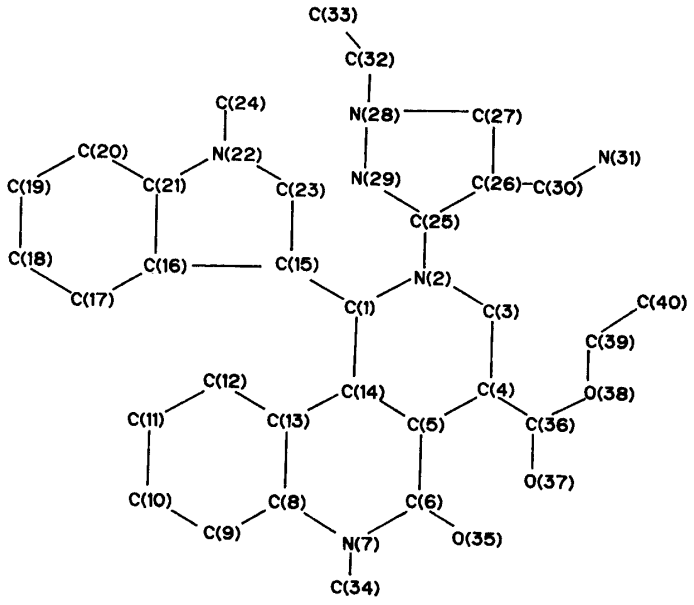

Fig. 2. Atomic Numbering of **3a**

space group. The cell dimensions were obtained by the least-squares method using 24 high-angle reflections measured on a Rigaku AFC-5 diffractometer with a graphite monochromate. The crystal data are as follows: monoclinic, $P2_1/a$, $a=16.606$ (2), $b=20.096$ (3), $c=18.268$ (5) Å, $\beta=116.84$ (2)°, $V=5440$ (2) Å^3 and $Z=8$. Intensity data within $\sin\theta/\lambda$ less than 0.588 Å^{-1} were collected using the $\theta-2\theta$ scan mode at a speed of 8°/min. Four control reflections were measured in order to monitor the crystal and electronic stabilities; no significant change in the intensities was

observed during data collection. Lorentz and polarization corrections were applied, but no absorption corrction was made because of the small crystal size.

The structure was solved by the direct method, using MULTAN.[4] The E-map of the set of phases with the best combined figure of merit synthesized from 644 reflections with $E>1.80$ revealed the position of 60 non-hydrogen atoms. The remaining 20 non-hydrogen atoms were located by subsequent weighted Fourier and difference Fourier synthesis. The crystal structure of **3a**, which contained two molecules in an asymmetric unit (molecules A and B), was refined by a block-diagonal least squares procedure, minimizing the quantity $\sum w(|F_o|-|F_c|)^2$ with weight w equal to $1/(\sigma(F_o)^2+F_{max}\cdot F_o+F_{min}\cdot F_o^2)$. The weighting scheme at the final refinement stage was as follows; $w=0.08773$ for $F_o=0.0$ and w calculated with $F_{max}=0.09524$ and $F_{min}=0.00266$ for $F_o>0.0$. All heavy atoms were refined with anisotropic temperature factors, while isotropic temperature factors were used for the hydrogen atoms, calculated in their stereochemically expected positions. A final R of 0.126 was obtained for nonzero 7975 reflections. The final positional parameters of molecules A and B with their estimated standard deviations are listed in Table I and the atomic numbering is given in Fig. 2. All numerical calculations were carried out on an ACOS-805 computer at the Crystallographic Research Centre, Institute for Protein Research, Osaka University.

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