p–p length also. Assuming that the H–O–H angle increases to 118°48′ as in the case when linear H bonds are formed in LFMH, the p–p length increases to 1·67 Å. As this is in fair agreement with our experimental value it is possible that the H bonds which are slightly bent at room temperature become linear as the temperature is raised.

At 370°K the second moment abruptly drops to a very low value. After the experiment, it was noticed that crystals had regrown on the walls of the sample tube from the powder. On heating the sample outside in an open tube we found that the sample first loses its water and then decomposes. But if we heat the sample in a closed tube the sample first gives out water and then dissolves in it becoming a colourless liquid. On slow cooling crystals started growing slowly. An infrared spectrum of the crystal grown in 'melt' showed no change from that grown from solution. In our n.m.r. experiment, since the powder was well packed in the sample tube the sample inside must have 'melted' because of the protective cover of the upper layer, thus accounting for the abrupt transition in the spectrum. This opens up possibilities of growing large crystals of this optically important substance by the melt technique.

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# The Crystal and Molecular Structure of 8-[3-(p-Fluorobenzoyl)propyl]-1-phenyl-1,3,8-triaza-spiro[4,5]decan-4-one, C23H26N3O2F

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Crystals of the title compound, C23H26N3O2F, are monoclinic, space group $P2_1/c$ with $a = 18\cdot571$, $b = 6\cdot072$, $c = 20\cdot681$ Å, $\beta = 118\cdot69°$ and $Z = 4$. The structure was solved by direct methods and refined by block-diagonal least-squares calculations to an $R$ value of 0·09. The results are compared with those obtained previously on butyrophenone derivatives and the observed differences are explained on the basis of conformational energy calculations.

The title compound, usually called spiroperidol, is one of the most potent neuroleptic drugs known to date. It is 3500 times more potent than chlorpromazine in dogs. It seemed interesting to determine this structure and to compare it with the other known compounds in the butyrophenone series (Koch & Germain, 1972).

## Experimental

The single crystals used were obtained as colourless needles by evaporation from a 60:40 mixture of 2-propanol and dimethylformamide. Their quality was rather poor (high mosaicity). The crystal data and

experimental details are given in Table 1. All intensity data were gathered with a Picker card-controlled 4-circle diffractometer. The scattering factors used are those given in *International Tables for X-ray Crystallography* (1962).

### Table 1. *Crystallographic and experimental data*

| $C_{23}H_{26}N_3O_2F$ | M.W. 395·5 |
| Monoclinic $P2_1/c$ | $a = 18·571$ (14) Å |
| | $b = 6·072(4)$ |
| | $c = 20·681$ (15) |
| $F(000) = 840$ | $\beta = 118·69$ (3)° |

Crystal dimensions: $0·30 \times 0·30 \times 0·25$ mm
Source Cu K$\alpha$, Ni filter, $\lambda = 1·5418$ Å, $\omega–2\theta$ scan, $\Delta 2\theta \pm 0·7°$, $\theta_{max} = 57·5°$
Confidence level 2·0
Total number of independent reflexions: 2807
Total observed: 2232

### Structure determination and refinement

The structure was solved by direct methods using the program *LSAM* of Germain, Main & Woolfson (1969). The best *E*-map, according to the figures of merit, showed the whole molecule except for one atom in the phenone group.

Refinement was carried out by the block-diagonal least-squares method with a program written by Ahmed (Ahmed, Hall, Pippy & Huber, 1966). The anisotropic refinement was considered to be complete when all

### Table 2. *Final coordinates and thermal parameters and their standard deviations* ($\times 10^4$)

$$B = \exp (B_{11}h^2 + B_{22}k^2 + B_{33}l^2 + B_{12}hk + B_{13}hl + B_{23}kl) \times 10^{-4}.$$

| | $x/a$ | $y/b$ | $z/c$ | $B_{11}$ | $B_{22}$ | $B_{33}$ | $B_{23}$ | $B_{13}$ | $B_{12}$ |
|---|---|---|---|---|---|---|---|---|---|
| N(1) | 4185 (2) | 2101 (6) | 1254 (2) | 39 (1) | 342 (12) | 23 (1) | −15 (6) | 36 (2) | −85 (6) |
| C(2) | 4765 (3) | 3902 (8) | 1427 (2) | 40 (2) | 354 (15) | 24 (1) | −3 (7) | 35 (2) | −64 (8) |
| N(3) | 4866 (2) | 3992 (6) | 779 (2) | 40 (1) | 332 (11) | 27 (1) | 0 (6) | 38 (2) | −65 (7) |
| C(4) | 4314 (2) | 2869 (6) | 212 (2) | 35 (1) | 248 (12) | 23 (1) | 13 (6) | 37 (2) | −2 (7) |
| C(5) | 3780 (2) | 1550 (7) | 455 (2) | 32 (1) | 262 (12) | 21 (1) | 1 (6) | 33 (2) | −12 (7) |
| C(6) | 3861 (3) | −904 (7) | 314 (2) | 42 (2) | 256 (12) | 30 (1) | 25 (7) | 41 (3) | 15 (8) |
| C(7) | 3391 (3) | −1522( 7) | −487 (2) | 58 (2) | 250 (13) | 33 (1) | −17 (7) | 61 (3) | −18 (8) |
| N(8) | 2522 (2) | −891 (6) | −804 (2) | 52 (2) | 289 (11) | 25 (1) | −29 (6) | 40 (2) | −53 (7) |
| C(9) | 2447 (3) | 1466 (7) | −764 (2) | 43 (2) | 292 (13) | 28 (1) | 18 (7) | 33 (3) | −3 (8) |
| C(10) | 2887 (2) | 2275 (7) | 33 (2) | 3ა (2) | 287 (13) | 28 (1) | −14 (7) | 39 (2) | −3 (8) |
| C(11) | 2071 (4) | −1744 (11) | −1568 (3) | 73 (3) | 602 (24) | 26 (2) | −91 (10) | 51 (4) | −186 (14) |
| C(12) | 1146 (4) | −1577 (11) | −1883 (3) | 72 (3) | 479 (22) | 25 (1) | 15 (9) | 17 ;3) | −112 (13) |
| C(13) | 846 (3) | −3028 (10) | −1461 (3) | 59 (2) | 409 (18) | 33 (2) | 16 (9ა | 28 (3) | −53 (1ა) |
| C(14) | −22 (4) | −2636 (9) | −1662 (3) | 61 (3) | 350 (18) | 39 (2) | 10 (10) | 25 (4) | −4 (11) |
| C(15) | −410 (3) | −4037 (10) | −1336 (3) | 50 (2) | 417 (19) | 36 (2) | −65 (10) | 21 (3) | −31 (11) |
| C(16) | −61 (4) | −5963 (11) | −962 (3) | 62 (3) | 466 (21) | 44 (2) | 30 (11) | 43 (4) | −23 (13) |
| C(17) | −435 (5) | −7315 (17) | −680 (4) | 91 (4) | 859 (41) | 47 (2) | −40 (17) | 62 (5) | −234 (22) |
| C(18) | −1194 (5) | −6583 (18) | −759 (4) | 82 (4) | 1123 (51) | 44 (2) | −184 (19) | 62 (5) | −344 ;4) |
| C(19) | −1554 (5) | −4672 (20) | −1120 (5) | 64 (3) | 1139 (54) | 66 (3) | −214 (23) | 64 (6) | −15ı ι22) |
| C(20) | −1169 (4) | −3402 (15) | −1415 (4) | 48 (2) | 779 (6ა) | 61 (3) | −113 (17) | 34 (5) | 25 (16) |
| C(21) | 3849 (2) | 1786 (7) | 1723 (2) | 34 (1) | 311 (13) | 20 (1) | 9 (6) | 31 (2) | 6 (7ა) |
| C(22) | 4088 (8) | 3203 (8) | 2336 (2) | 38 (2) | 372 (15) | 24 (1) | 8 (7) | 31 (2) | 19 ;18) |
| C(23) | 3790 (3) | 2835 (9) | 2833 (2) | 46 (2) | 430 (17) | 24 (1) | −1 (8) | 38 (3) | 19 (9) |
| C(24) | 3255 (3) | 1176 (10) | 2730 (2) | 44 (2) | 551 (20) | 27 (1) | 33 (9) | 45 (3) | 23 (10) |
| C(25) | 3018 (3) | −216 (10) | 2138 (3) | 45 (2) | 547 (21) | 29 (1) | 2 (9) | 43 (3) | −62 (11) |
| C(26) | 3309 (3) | 72 (8) | 1635 (2) | 44 (2) | 431 (16) | 26 (1) | 4 (8) | 44 (3) | −65 (10) |
| O(1) | 4223 (2) | 2883 (5) | −421 (2) | 51 (1) | 330 (10) | 25 (1) | −8 (5) | 51 (2) | −5ა (6) |
| O(2) | −425 (3) | −1160 (9) | −2097 (3) | 86 (3) | 489 (17) | 88( 3) | 159 (11) | 52 (4) | 129 (12) |
| F(1) | −1577 (3) | −7751 (13) | −483 (3) | 116 (3) | 1548 (43) | 67 (2) | −145 (16) | 102 (4) | −495 (21) |
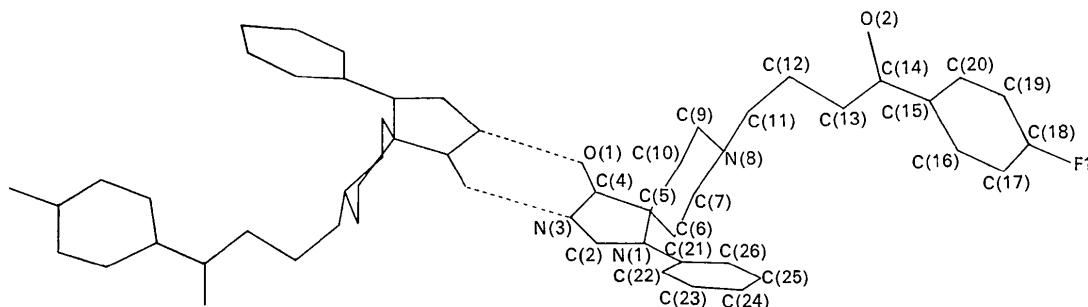


Fig. 1. View of a dimer of $C_{23}H_{26}N_2O_2F$.

shifts were below 0·3 of their corresponding estimated standard deviations.

The final $R = \sum ||F_o| - |F_c||/\sum |F_o|$ was 0·09 for the 2065 reflexions used in the refinement (167 weak reflexions for which $\Delta F/F_{obs}$ was larger than 0·4 were rejected during the last cycles of refinement).

The final positional parameters and their e.s.d.'s and the corresponding thermal parameters are given in in Table 2. A table of observed and calculated structure factors has been deposited with the National Lending Library, England, as Supplementary Publication No. SUP 30031.*

## Results

The intramolecular bond distances and angles are given in Table 3. The atom numbering scheme is shown

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* Copies of this table may be obtained through the Executive Secretary, International Union of Crystallography, 13 White Friars, Chester CH1 1NZ, England.

in Fig. 1. The poor quality of the crystals can be explained by the intermolecular bonding. Each molecule is bonded to one molecule by two hydrogen bonds $N(3)\cdots O(1)$ 2·867 Å [O(1): $1-x, 1-y, -z$] and $O(1)\cdots N(3)$ [N(3): $1-x, 1-y, -z$]. Hence the crystal is made up of dimers which are held together by packing forces only.

## Discussion

The five-membered ring and the phenyl group are coplanar. As a result of this the phenyl group has the same orientation relative to the piperidine ring as in 4'-fluoro-4-{1-[4-hydroxy-4-(4'-fluoro)phenylpiperidino]}butyrophenone and its hydrochloride (later referred to as $B$ and $C$, $A$ being the title compound). The three derivatives have a different conformation of the side chain. Referring the values of the relevant torsional angles to the atom numbering in $A$ one obtains the values given in Table 4. A calculation for the side chain of $A$ was carried out using a general con-

Table 3. *Intramolecular bond distances and angles and their e.s.d.'s*

| | | | |
|---|---|---|---|
| N(1)—C(2) | 1·455 (6) Å | C(2)—N(1)—C(5) | 111·1 (3)° |
| N(1)—C(5) | 1·488 (5) | C(2)—N(1)—C(21) | 117·3 (4) |
| N(1)—C(21) | 1·394 (6) | C(5)—N(1)—C(21) | 125·9 (4) |
| C(2)—N(3) | 1·440 (6) | N(1)—C(2)—N(3) | 102·2 (4) |
| N(3)—C(4) | 1·317 (5) | C(2)—N(3)—C(4) | 114·5 (4) |
| C(4)—C(5) | 1·534 (6) | N(3)—C(4)—C(5) | 109·1 (4) |
| C(4)—O(1) | 1·237 (5) | N(3)—C(4)—O(1) | 126·2 (4) |
| C(5)—C(6) | 1·539 (6) | C(5)—C(4)—O(1) | 124·6 (4) |
| C(5)—C(10) | 1·522 (6) | N(1)—C(5)—C(4) | 100·7 (3) |
| C(6)—C(7) | 1·503 (6) | N(1)—C(5)—C(6) | 112·6 (3) |
| C(7)—N(8) | 1·472 (7) | N(1)—C(5)—C(10) | 113·7 (3) |
| N(8)—C(9) | 1·444 (6) | C(4)—C(5)—C(6) | 107·9 (3) |
| N(8)—C(11) | 1·481 (6) | C(4)—C(5)—C(10) | 111·0 (3) |
| C(9)—C(10) | 1·528 (6) | C(6)—C(5)—C(10) | 110·5 (3) |
| C(11)-C(12) | 1·519 (10) | C(5)—C(6)—C(7) | 113·1 (4) |
| C(12)-C(13) | 1·522 (9) | C(6)—C(7)—N(8) | 111·0 (4) |
| C(13)-C(14) | 1·477 (10) | C(7)—N(8)—C(9) | 110·3 (4) |
| C(14)-C(15) | 1·471 (9) | C(7)—N(8)—C(11) | 108·8 (4) |
| C(14)-O(2) | 1·236 (8) | C(9)—N(8)—C(11) | 112·7 (4) |
| C(15)-C(16) | 1·380 (9) | N(8)—C(9)—C(10) | 111·3 (4) |
| C(15)-C(20) | 1·392 (11) | C(5)—C(10)—C(9) | 113·4 (4) |
| C(16)-C(17) | 1·374 (12) | N(8)—C(11)—C(12) | 112·2 (5) |
| C(17)-C(18) | 1·411 (15) | C(11)-C(12)-C(13) | 111·4 (5) |
| C(18)-C(19) | 1·368 (15) | C(12)-C(13)-C(14) | 113·3 (5) |
| C(18)-F(1) | 1·313 (12) | C(13)-C(14)-C(15) | 119·1 (5) |
| C(19)-C(20) | 1·377 (13) | C(13)-C(14)-O(2) | 121·3 (6) |
| C(21)-C(22) | 1·415 (6) | C(15)-C(14)-O(2) | 119·6 (6) |
| C(21)-C(26) | 1·395 (7) | C(14)-C(15)-C(16) | 123·0 (6) |
| C(22)-C(23) | 1·399 (7) | C(14)-C(15)-C(20) | 118·5 (6) |
| C(23)-C(24) | 1·359 (8) | C(16)-C(15)-C(20) | 118·5 (6) |
| C(24)-C(25) | 1·375 (7) | C(15)-C(16)-C(17) | 123·2 (7) |
| C(25)-C(26) | 1·395 (7) | C(16)-C(17)-C(18) | 116·3 (8) |
| | | C(17)-C(18)-C(19) | 122·0 (9) |
| | | C(17)-C(18)-F(1) | 119·9 (8) |
| | | C(19)-C(18)-F(1) | 118·1 (9) |
| | | C(18)-C(19)-C(20) | 119·7 (9) |
| | | C(15)-C(20)-C(19) | 120·3 (8) |
| | | N(1)—C(21)-C(22) | 119·2 (4) |
| | | N(1)—C(21)-C(26) | 123·0 (4) |
| | | C(22)-C(21)-C(26) | 117·8 (4) |
| | | C(21)-C(22)-C(23) | 119·8 (4) |
| | | C(22)-C(23)-C(24) | 121·4 (5) |
| | | C(23)-C(24)-C(25) | 119·5 (5) |
| | | C(24)-C(25)-C(26) | 121·0 (5) |
| | | C(21)-C(26)-C(25) | 120·5 (5) |

formational analysis program (Koch 1971). The re-
sults for $B$ and $C$ would, of course, be expected to be
very similar. For our purpose it was only necessary to
take the torsional and van der Waals energies into
account. The van der Waals energy was computed
with Giglio's function using the values of the param-
eters given in the original paper (Giglio, 1969).

Table 4. *Torsional angles in the side chain of*
*butyrophenone derivatives*

| | $\varphi_1$ | $\varphi_2$ | $\varphi_3$ | $\varphi_4$ | | |
|---|---|---|---|---|---|---|
| | C(5)–C(6)–C(7)–N(8)–C(11)–C(12)–C(13)–C(14)–C(15) | | | | | |
| $A$ | $-54$ | $-174$ | $168$ | $-64$ | $170$ | $175$ |
| $B$ | $-62$ | $-176$ | $-179$ | $-166$ | $-68$ | $-177$ |
| $C$ | $-59$ | $-173$ | $76$ | $174$ | $-162$ | $173$ |

The torsional energy was evaluated as $U_T = U_o (1 + \cos n\varphi)$. The values of $U_o$ and $n$ were taken from a
study by Allinger, Miller, Van Catledge & Hirsch,
1967) on hydrocarbons and are given in Table 5. We
made the assumption that the rotational barriers for
C–N–C–X are the same as for C–C–C–X when N is a
tetrahedral nitrogen. Calculated positions were used
for the hydrogen atoms.

Table 5. *Values of $U_o$ and $n$ used in the calculations*

| | $U_0$(kcal mole$^{-1}$) | $n$ |
|---|---|---|
| C–C–C–C | 0·65 | 3 |
| H–C–C–C | 1·00 | 3 |
| H–C–C–H | 0·65 | 3 |

The torsional angles $\varphi_1$, $\varphi_2$ and $\varphi_3{}^*$ were allowed to
take all values from 0 to 360° in steps of 60°, all other
parameters being fixed at their experimental value. The
amount of calculation was reduced by taking the sym-
metry of the problem into account. It is obvious from
a model that a combination of angles such as (180, 60,
60) is identical to (60, 300, 300). All combinations
which corresponded to values of the energy less than
19 kcal mole$^{-1}$ above the lowest values (180, 180, 180)
were submitted to a search in which the three angles
were varied from $-30°$ to $+30°$ from their starting
value by steps of 10°.

It turned out that only combinations with a value
of $\varphi_1$ near 60 and 180° have an energy value less than
5 kcal mole$^{-1}$ above the minimum.

A two-dimensional energy map was then computed
where only $\varphi_2$ and $\varphi_3$ were incremented by steps of
10°. Fig. 2 shows the result of this calculation. There
are five nearly equal minima, three of which correspond
to one of the observed conformations of the side chain.
The dark regions of the map correspond to unallowed
conformations (more than 30 kcal mole$^{-1}$ above the

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\* A zero value for the torsional angle along the C(2)–C(3)
bond in C(1)–C(2)–C(3)–C(4) corresponds to the *cis* confor-
mation. A positive angle corresponds to a counterclockwise
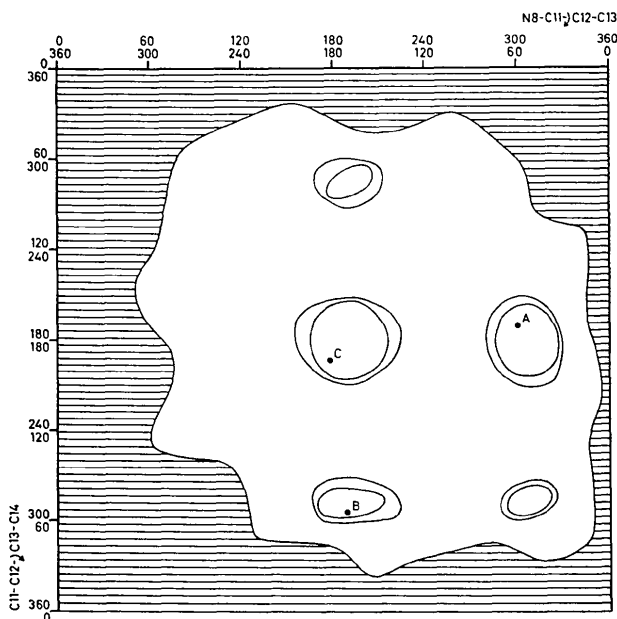rotation of C(4) when looking down from C(3) to C(2).



Fig. 2. Result of the conformational energy calculation for the
side chain of $A$. The upper scale corresponds to $\varphi_1 = 168°$ and
the lower to $\varphi_1 = 72°$. The dots indicate the experimental values
for the $A$, $B$ and $C$ structures respectively. The contours cor-
respond to a difference of 1 kcal mole$^{-1}$.

minimum). The value of $\varphi_4$ was never varied during
the calculations because it is obvious from a model
that the most favourable value will always be close to
180°. It is to be expected that all analogous derivatives
will fall into one of the five minima. The results of our
calculations allow us to explain all the available struc-
tural information. Further study is however required
to determine whether this is relevant to the activity
of these compounds.

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