The Synthesis and Crystal Structure of 2-(3-Methyl-1-oxoisoindoline-2-yl)-butyramide

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The title compound was obtained by N-alkylation of racemic 3-methyl-1-oxoisoindoline with a racemic ethyl-2-bromobutyrate followed by ammonolysis. The two pairs of racemates thus formed could be separated because of their different solubility. The high melting racemate which was obtained in pure form was subsequently recrystallized for the single crystal X-ray study.

$C_{13}H_{16}N_2O_2$, $M_r=232.3$, monoclinic, $P2_1/c$, $a=10.230(2)$, $b=8.017(2)$, $c=16.192(3)$ Å, $\beta=110.31(2)°$, $V=1245(1)$ Å^3, $Z=4$, $D_x=1.24$ Mg m^{-3}, $\mu(MoK\alpha)=0.079$ mm^{-1}, $F(000)=496$. Out of 2910 independent reflexions measured on an automatic diffractometer 1821 had significant intensities. The structure was solved by direct methods and refinement by full-matrix least-squares calculations gave a final $R=0.050$ for 203 parameters. The structure consists of centrosymmetrically related molecules forming infinite chains by N−H···O hydrogen bonds (2.91 and 2.94 Å). The isoindoline group is nearly planar although the benzene part is slightly distorted.

For studies on structure-activity relationships in potentially teratogenic phthalimides and phthalimidines [1,2] we also prepared some amides of 2-(3-methyl-1-oxoisoindoline-2-yl)alkanoic amides.
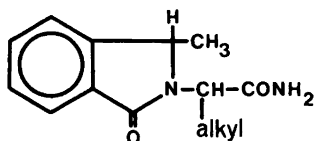
These compounds were obtained by N-alkylation of racemic 3-methyl-1-oxoisoindoline either with a racemic α-bromoalkanoic amide or with a racemic α-bromoalkanoic ester, in this case followed by ammonolysis of the intermediate ester. The amides contain two asymmetric carbon atoms (α and 3) and can accordingly form two pairs of racemates which were obtained as mixtures.

In the case of the butyramide (Alkyl=C_2H_5) differences in solubility permitted easy separation of the mixture into a pure, high melting racemate and a low melting one containing about 10 % of the high melting form. The separation could be monitored by ^{1}H NMR spectroscopy as the 3-methyl groups give distinctly separated doublets (δ 1.57 for high melting, 1.51 for low melting form.) Generally corresponding peaks are shifted to a slightly lower field in the high melting form. This is especially notable for the amide hydrogen atoms, δ 6.05 and ca. 7.5 in the high melting form, 6.0 and 6.8 in the low melting form, suggesting a higher degree of hydrogen bonding in the former. The high melting racemate has now been studied by X-ray crystallography and it is the purpose of the present paper to report this study.

EXPERIMENTAL

Synthesis. 3-Methyl-1-oxoisoindoline[3] (25.5 g; 0.173 mol) in anhydrous dimethylformamide (60 ml) was added below 70 °C as rapidly as foaming

permitted to a suspension of sodium hydride (4.8 g; 0.20 mol) in dimethylformamide (60 ml). After stirring for an additional hour ethyl-2-bromobutyrate (40 g; 0.205 mol) was added dropwise at 70–80 °C during 1 h and the mixture was heated for a further hour on a boiling water bath. Most of the solvent was removed *in vacuo* and the remaining oil was treated with water and extracted into ether, washed and dried (Na_2SO_4). Distillation afforded 38 g of an oil boiling at 205–208 °C/12 mm Hg. The ester (38 g; 0.145 mol) was added to methanol (500 ml) saturated at 0 °C with ammonia. The solution was kept in a sealed, thick-walled bottle for 4 days and then evaporated to dryness. The solid residue was repeatedly crystallized from ethanol to yield 15.6 g of amide, m.p. 164–165 °C, which according to NMR was a pure racemate. Evaporation of the mother liquid from the first crystallization afforded an oil which solidified after several weeks. Repeated recrystallization gave 9.1 g of low melting racemate, m.p. 138–140 °C, which according to NMR contained about 10 % of the high melting isomer.

^1H NMR (Perkin-Elmer R12, 60 MHz, $CDCl_3$, tetramethylsilane standard). High melting racemate: δ 7.3–7.8 (m, 5H, ArH and NH), 6.05 (broad signal, 1H, NH), 4.65 (quartet, $J=6$ Hz, 1H, CH_3CH 1), 4.27 (t, $J=8$ Hz, 1H, C_2H_5CH), 2.25 (quintet, $J=7$ Hz, 2H, CH_3CH_2), 1.57 (d, $J=6.6$ Hz, 3H, CH_3CH), 0.98 (t, $J=7$ Hz, 3H, CH_3CH_2).

Low melting racemate: δ 7.3–7.9 (m, 4H, ArH), 6.8 and 6.0 (broad signal, 1H, NH), 4.44–4.80 (m, 2H, CH_3CH and C_2H_5CH), 2.10 (quintet, $J=7$ Hz, C_2H_5CH), 1.51 (d, $J=6.6$ Hz, 3H, CH_3CH), 0.95 (t, $J=7$ Hz, CH_3CH_2).

X-Ray study. The high melting form of the title compound was recrystallized from ethanol. The space group and approximate cell dimensions were determined from Weissenberg photographs. One optically perfect crystal trimmed to an almost perfect sphere with a diameter of 0.35 mm was mounted about *b* in a single crystal diffractometer (Philips PAILRED). Graphite monochromatized MoKα radiation was used and accurate cell dimensions (see abstract) were determined. The intensities were collected up to $2\theta=55°$, scan range $\pm1.8–\pm2.4°$, scan speed 2.5° min^{-1}. Fainter reflexions were scanned up to three times and the background was measured for 1 min at each limit of the scan. Out of the 2910 independent reflexions recorded, 1821 were considered observed [$I>3\sigma(I)$]. There was no decrease in intensity as a function of time in periodically measured standard reflexions. For the data reduction including corrections for Lorentz and polarization effects our own data program[4] was used. Absorption corrections were not applied due to the low μ-value.

Structure determination and refinement. The structure was determined with the aid of MULTAN 80.[5] An *E*-map was obtained where all but one of the non-hydrogen atoms could easily be

Table 1. Final positional and thermal parameters for non-hydrogen atoms ($\times10^4$). The e.s.d.'s are given in parentheses. The temperature factors are defined by: $\exp[-2\pi^2(h^2a^{*2}U_{11}+\cdots+2klb^*c^*U_{23}\cdots)]$.

Atom	x/a	y/b	z/c	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
O(1)	5511(1)	1693(2)	4807(1)	275(8)	585(8)	430(10)	−20(7)	190(7)	10(7)
O(2)	265(2)	1724(2)	4336(1)	248(8)	617(8)	575(11)	134(8)	151(7)	76(7)
N(1)	3514(2)	2539(2)	5036(1)	216(9)	455(8)	335(10)	−29(7)	117(8)	−13(7)
N(2)	1636(2)	−548(2)	4780(1)	297(10)	488(8)	512(12)	83(8)	182(9)	23(8)
C(1)	4918(2)	2279(2)	5280(1)	256(11)	381(8)	362(12)	47(8)	108(9)	3(8)
C(2)	5529(2)	2837(2)	6205(1)	296(11)	405(8)	361(12)	20(8)	99(9)	−55(8)
C(3)	6911(2)	2772(3)	6769(2)	328(12)	531(10)	434(14)	36(10)	69(11)	−46(10)
C(4)	7199(3)	3344(3)	7626(2)	427(14)	658(13)	426(16)	59(12)	−1(12)	−126(12)
C(5)	6146(3)	3979(4)	7886(2)	672(19)	780(15)	338(14)	−93(12)	129(13)	−230(15)
C(6)	4775(3)	4046(3)	7322(2)	505(16)	720(14)	417(15)	−142(12)	182(12)	−73(13)
C(7)	4484(2)	3434(3)	6473(1))	360(12)	480(10)	373(13)	−14(9)	138(10)	−70(9)
C(8)	3091(2)	3283(2)	5738(1)	319(11)	482(9)	385(13)	−47(9)	162(10)	−14(9)
C(9)	2315(3)	4932(3)	5475(2)	497(17)	564(11)	665(18)	−85(12)	223(14)	101(11)
C(10)	2546(2)	1816(2)	4217(1)	241(10)	488(9)	293(12)	23(9)	92(9)	−31(9)
C(11)	2023(3)	3057(3)	3466(2)	420(14)	711(13)	450(15)	185(12)	143(12)	22(11)
C(12)	1187(3)	2230(5)	2600(2)	511(17)	1248(23)	377(16)	134(16)	90(13)	81(17)
C(13)	1364(2)	986(2)	4444(1)	215(10)	483(9)	295(11)	15(9)	62(8)	−29(8)

Table 2. Final positional parameters for the hydrogen atoms ($\times 10^3$) which all were given $U=0.06$ Å^2. Standard deviations in parentheses.

	x/a	y/b	z/c
HN(2)A	249(3)	−95(3)	489(2)
HN(2)B	104(3)	−96(3)	505(2)
HC(3)	756(3)	228(3)	657(2)
HC(4)	823(3)	324(3)	797(2)
HC(5)	635(3)	440(3)	848(2)
HC(6)	403(3)	462(3)	752(2)
HC(8)	247(3)	249(3)	591(2)
HC(9)A	139(3)	475(3)	499(2)
HC(9)B	216(3)	546(3)	598(2)
HC(9)C	289(3)	561(3)	525(2)
HC(10)	309(3)	96(3)	407(2)
HC(11)A	289(3)	354(3)	340(2)
HC(11)B	146(3)	378(3)	361(2)
HC(12)A	34(3)	167(3)	257(2)
HC(12)B	92(3)	316(3)	214(2)
HC(12)C	172(3)	137(3)	240(2)

located. Switching to the SHELX program system[6] the missing atom was found in a difference map. The positional coordinates of the non-hydrogen atoms were refined with isotropic

thermal parameters to an *R*-value of 0.10. A subsequent difference synthesis gave the positions of all hydrogen atoms. Refinement of positional and anisotropic thermal parameters for the non-hydrogen atoms only and the introduction of a weighting scheme $w=0.80/[\sigma^2(F_o)+0.0005F_o^2]$ brought the *R*-value to 0.052. The three strongest reflexions $|F_o|>65$ were now excluded from further calculations due to indications of extinction. In the final refinement cycle ($R=0.050$) the positional parameters of the hydrogen atoms were refined with fixed isotropic thermal parameters ($U=0.06$ Å^2). A difference map based on the final parameters of all atoms showed no peak higher or lower than 0.2 eÅ^{-3}.

Final positional and thermal parameters for the non-hydrogen atoms are given in Table 1 and the positional parameters for the hydrogen atoms are given in Table 2. Atomic scattering factors were those of International Tables for X-Ray Crystallography.[7] A list of the final structure factors are available on request from the authors.

RESULTS AND DISCUSSION

The atomic numbering is given in the perspective drawing of the molecule (Fig. 1). The bond distances and angles uncorrected for the effects

Table 3. Intramolecular bond distances (Å) and angles (°) with estimated standard deviations in parentheses.

C(1)−O(1)	1.222(2)	C(7)−C(8)	1.509(3)
C(1)−N(1)	1.367(2)	C(8)−C(9)	1.525(3)
C(1)−C(2)	1.472(3)	C(8)−N(1)	1.472(2)
C(2)−C(7)	1.370(2)	N(1)−C(10)	1.467(3)
C(2)−C(3)	1.393(3)	C(10)−C(13)	1.532(2)
C(3)−C(4)	1.387(3)	C(10)−C(11)	1.514(3)
C(4)−C(5)	1.381(3)	C(11)−C(12)	1.516(4)
C(5)−C(6)	1.382(3)	C(13)−O(2)	1.228(2)
C(6)−C(7)	1.388(3)	C(13)−N(2)	1.334(3)
O(1)−C(1)−N(1)	125.3(2)	C(7)−C(8)−C(9)	114.1(2)
O(1)−C(1)−C(2)	128.4(2)	C(7)−C(8)−N(1)	100.8(2)
N(1)−C(1)−C(2)	106.3(2)	C(9)−C(8)−N(1)	113.6(2)
C(1)−C(2)−C(3)	128.9(2)	C(1)−N(1)−C(8)	113.5(2)
C(1)−C(2)−C(7)	108.8(2)	C(1)−N(1)−C(10)	120.8(2)
C(7)−C(2)−C(3)	122.2(2)	C(8)−N(1)−C(10)	124.5(2)
C(2)−C(3)−C(4)	117.1(2)	N(1)−C(10)−C(11)	113.6(2)
C(3)−C(4)−C(5)	120.4(2)	N(1)−C(10)−C(13)	107.3(2)
C(4)−C(5)−C(6)	122.3(3)	C(11)−C(10)−C(13)	112.8(2)
C(5)−C(6)−C(7)	117.2(2)	C(10)−C(11)−C(12)	112.3(2)
C(6)−C(7)−C(2)	120.8(2)	C(10)−C(13)−N(2)	115.3(2)
C(6)−C(7)−C(8)	128.6(2)	C(10)−C(13)−O(2)	121.1(2)
C(2)−C(7)−C(8)	110.6(2)	N(2)−C(13)−O(2)	123.6(2)

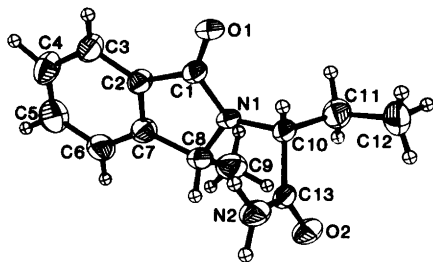772   Carlström, Hacksell, Jönsson and Söderholm

Fig. 1. ORTEP[11] drawing of the molecule showing atomic numbering and vibrational ellipsoids for the non-hydrogen atoms drawn at the 50 % probability level.

of thermal motion are given in Table 3. The C−H distances lie in the range of 0.90−1.02 Å and the two N−H distances are 0.87 Å and 0.97 Å. The bond lengths and angles are much as expected but a few angles deviate from the standard values. Thus, in the benzene ring fused to the five-membered heterocycle two opposite angles, C(2)−C(3)−C(4) and C(5)−C(6)−C(7) show a decrease from 120° by 2.9° (13σ). This seems to be a common feature for indole rings where these two angles always are found to be less than 120° (mean value for 9 structures=117.9°). The same situation is true for isoindoles where one finds a mean value of 118.1° in the three structures reported (Gieren *et al.*,[8] Brisse and Sygusch[9] and Fukuyama *et al.*[10]).

The isoindoline nucleus is essentially planar with a maximum deviation for a ring atom of

0.028(3) Å. Looking at the two fused rings individually the planarity is more pronounced. The maximum deviation of the pyrroline ring is 0.006 (2) Å and that of the benzene ring is 0.012 (3) Å. The angle between these two planes is 2.1 (4)°. As could be expected the atoms of the amide group C(10), C(13), O(2) and N(2) are likewise nearly coplanar, the maximum deviation of an atom being 0.008 (2) Å.

The carbon chain C(10)−C(12) attached to N(1) is approximately perpendicular to the plane of the rings and almost maximally extended, the torsion angles C(8)−N(1)−C(10)−C(11) and N(1)−C(10)−C(11)−C(12) being 90.4(3)° and 172.2(3)°, respectively.

A view of the packing along the *b* axis is presented in Fig. 2. The crystal structure consists of infinite hydrogen bonded chains of molecules related by centres of symmetry. The hydrogen bonds run essentially in the *a* direction. Each molecule is linked to two others by the following hydrogen bonds: N(2)−H(N2)A···O(1)[I] and N(2)−H(N2)B···O(2)[II] where the symmetry codes are (i) 1–*x*, –*y*, 1–*z* and (ii) –*x*, –*y*, 1–*z*. The geometry of these bonds are characterized by N···O distances of 2.907(2) and 2.937(2) Å, respectively. Corresponding N−H···O angles are 176(4) and 176(4)°.
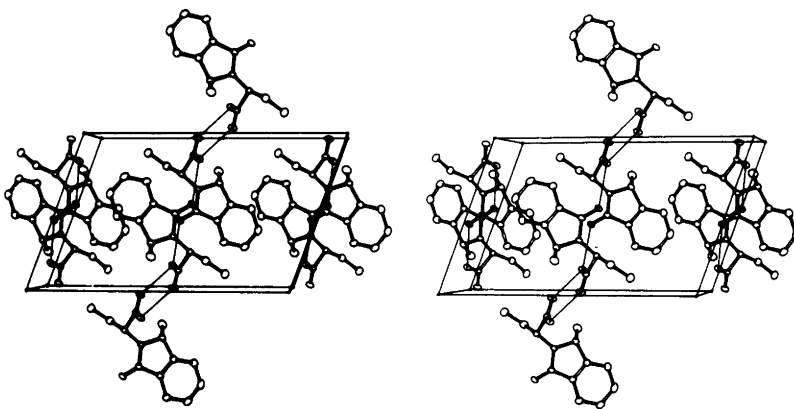
Fig. 2. Stereoview (ORTEP[11]) of the crystal structure. The drawing is essentially seen along *b*. Hydrogen atoms are omitted for clarity. The hydrogen bonds are represented by thin lines.

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