TETRAHYDROPYRIMIDINE-5-CARBOXYLIC ACID AMIDES

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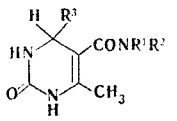
2-Oxo-4-aryl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid amides were obtained by condensation of urea, acetoacetamides, and aromatic aldehydes.

In contrast to tetrahydropyrimidine-5-carboxylic acid esters, which have long been known and have high biological activity [1], insufficient study has been devoted to tetrahydropyrimidine-5-carboxylic acid amides [3], although they do arouse interest inasmuch as they display the properties of coronary dilators [2].

We have obtained I-IV from acetoacetamides, urea, and aromatic aldehydes.



I-IV

I $R^1=R^2=H$, $R^3=Ar$; II $R^1=R^2=C_2H_5$, $R^3=Ar$; III $R^1=H$, $R^2=C_6H_5$, $R^3=Ar$; IV $R^1=H$, $R^2=C_5H_4N$-2, $R^3=Ar$

A maximum in the longwave region at 269-275 nm is observed in the UV spectra of Ia-d, which have an unsubstituted amide group in the 5 position. When one of the amide hydrogen atoms is replaced by a phenyl group (IIIa-g), a bathochromic shift to 275-285 nm is observed, that increases for IVa-f (R^2 = 2-pyridyl), which have a maximum at 287-294 nm. A considerable hypsochromic shift to 265-269 nm is observed when both hydrogen atoms are replaced by ethyl groups (IIa-d). Depending on R^3, a shoulder appears at 211-218 nm in the case of Ia-c, whereas a maximum at 228-232 nm is characteristic for Id, IId, IIId, and IVd (R^3 = p-bromophenyl). A maximum at 264 nm appears when R^3 = p-dimethylaminophenyl (IIIe and IVe).

In contrast to the carbethoxy analogs, in which an anion is formed and the longwave maximum in the UV spectrum undergoes a bathochromic shift, no change is observed in the UV spectra of solutions of the products in alkaline media.

The presence of an ethyl substituent attached to the amide nitrogen atom causes the appearance in the NMR spectrum of IIb of C^{13} signals at 13.2 ppm (CH_3 group) and 40.1 ppm (CH_2), which are absent in the spectrum of Ib, whereas the spectra of both IIb and Ib contain the carbonyl signal of an amide group at 206.7 ppm.

EXPERIMENTAL

The IR spectra of mineral oil and hexachlorobutadiene suspensions of the compounds were recorded with a UR-20 spectrometer. The UV spectra of $5 \cdot 10^{-5}$ M solutions of the compounds in alcohol were recorded with a Specord UV-vis spectrophotometer.

The NMR spectra of dimethyl sulfoxide solutions (39.6 ppm) were recorded with a Bruker spectrospin spectrometer. Acidic [n-butanol—acetic acid—water (4:5:1)] and alkaline [2-propanol—25% ammonia—water (14:1:5)] systems were used for chromatography on FN-11 paper.

2-Oxo-4-phenyl-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxamide (Ia). A 1.1-g (0.02 mole) sample of benzaldehyde, 1.2 g (0.02 mole) of urea, and 15 drops of concentrated HCl

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TABLE 1. 2-Oxo-6-methyl-1,2,3,4-tetrahydropyrimidine-5-carboxylic Acid Amides

Compound	R^1	R^2	R^3	mp, °C (crystallization solvent)	Empirical formula	Found, %				Calc., %				Yield, %
						C	H	N	Br	C	H	N	Br	
Ia	H	H	C_6H_5	260—262 (2-butanol)	$C_{12}H_{13}N_3O_2$	62,6	5,8	17,9	—	62,3	5,7	18,2	—	41
Ib	H	H	$C_6H_4NO_2$-m	258—260 (butanol)	$C_{12}H_{12}N_4O_4$	51,9	4,6	20,7	—	52,2	4,4	20,3	—	39
Ic	H	H	$C_6H_4NO_2$-p	282—284 (acetic acid)	$C_{12}H_{12}N_4O_4$	52,0	4,3	20,3	—	52,2	4,4	20,3	—	52
Id	H	H	C_6H_4Br-p	242—244 (ethanol)	$C_{12}H_{12}BrN_3O_2$	46,0	3,8	13,3	26,2	46,4	3,9	13,5	25,7	46
IIa	C_2H_5	C_2H_5	C_6H_5	180—182 (ethanol—water)	$C_{16}H_{21}N_3O_2$	67,3	6,2	13,9	—	66,8	6,4	14,2	—	73
IIb	C_2H_5	C_2H_5	$C_6H_4NO_2$-m	215—217 (ethanol)	$C_{16}H_{20}N_4O_4$	57,6	6,4	16,7	—	57,8	6,1	17,0	—	81
IIc	C_2H_5	C_2H_5	$C_6H_4NO_2$-p	225—227 (2-butanol)	$C_{16}H_{20}N_4O_4$	57,7	6,1	16,8	—	57,8	6,1	17,0	—	75
IId	C_2H_5	C_2H_5	C_6H_4Br-p	227—229 (2-butanol)	$C_{16}H_{20}BrN_3O_2$	52,1	5,7	11,1	21,5	52,4	5,6	11,4	21,8	65
IIIa	H	C_6H_5	C_6H_5	252—254 (2-butanol)	$C_{18}H_{17}N_3O_2$	69,8	5,7	13,4	—	70,3	5,6	13,7	—	50
IIIc	H	C_6H_5	$C_6H_4NO_2$-p	276—278 (ethanol)	$C_{18}H_{16}N_4O_4$	60,9	4,9	15,5	—	61,3	4,6	15,9	—	64
IIId	H	C_6H_5	C_6H_4Br-p	292—294 (ethanol)	$C_{18}H_{16}BrN_3O_2$	55,7	4,1	10,7	20,5	56,0	4,2	10,9	20,7	63
IIIe	H	C_6H_5	$C_6H_4N(CH_3)_2$-p	264—266 (ethanol)	$C_{20}H_{24}N_4O_2$	68,7	6,4	15,8	—	68,6	6,3	16,0	—	89
IIIg	H	C_6H_5	C_6H_3OH-m-OCH_3-p	248—250 (2-butanol)	$C_{19}H_{19}N_3O_3$	64,6	5,4	11,9	—	64,1	5,5	11,4	—	61
IVa	H	2-C_5H_4N	C_6H_5	203—205 (butanol)	$C_{17}H_{16}N_4O_2$	66,0	5,5	18,0	—	66,2	5,2	18,1	—	83
IVb	H	2-C_5H_4N	$C_6H_4NO_2$-m	217—219 (2-butanol)	$C_{17}H_{15}N_5O_4$	57,6	4,2	19,4	—	57,8	4,3	19,8	—	49
IVc	H	2-C_5H_4N	$C_6H_4NO_2$-p	240—242 (2-propanol)	$C_{17}H_{15}N_5O_4$	57,6	4,3	19,5	—	57,8	4,3	19,8	—	65
IVd	H	2-C_5H_4N	C_6H_4Br-p	256—257 (2-butanol)	$C_{17}H_{15}BrN_4O_2$	52,5	3,8	14,0	20,3	52,7	3,9	14,4	20,8	57
IVe	H	2-C_5H_4N	$C_6H_4N(CH_3)_2$	229—230 (2-butanol)	$C_{19}H_{21}N_5O_2$	64,8	6,2	19,6	—	64,9	6,5	19,9	—	61
IVf	H	2-C_5H_4N	$C_6H_2(OCH_3)_3$-3,4,5	232—234 (ethanol)	$C_{20}H_{22}N_4O_5$	60,2	5,3	13,7	—	60,3	5,5	14,1	—	66

TABLE 2. Spectral and Chromatographic Characteristics

Compound	mp, °C (crystallization solvent)	UV spectrum, λ_{max}, nm (log ε)	Chromatography R_f*	Chromatography R_f†
Ia	1700 (83) 1690 (85) 1585 (75) 1420 (79) 1385 (77)	203 (4,14) 218 (3,9) sh 275 (3,76)	0,86	0,67
Ib	1698 (91) 1655 (90) 1590 (80) 1536 (85) 1465 (9) 1381 (94)	207 (4,07) 218 (3,97) sh 269 (3,95)	0,86	0,60
Ic	1690 (85) 1675 (88) 1595 (86) 1485 (85) 1445 (86) 1385 (77)	203 (4,28) 218 (4,10) sh 270 (3,65)	0,84	0,77
Id	1710 (78) 1675 (62) 1602 (61) 1480 (68) 1385 (60)	203 (4,18) 228 (4,15) 275 (3,65)	0,95	0,80
IIa	1710 (84) 1679 (82) 1598 (82) 1465 (66) 1378 (56)	205 (4,40) 218 (4,09) sh 265 (3,38)	0,85	0,85
IIb	1702 (86) 1688 (82) 1600 (87) 1539 (78) 1465 (85) 1380 (75)	202 (4,53) 211 (4,37) sh 266 (4,08)	0,88	0,86
IIc	1712 (56) 1680 (77) 1590 (78) 1530 (66) 1465 (61) 1388 (50)	203 (4,53) 215 (4,32) sh 269 (4,07)	0,96	0,87
IId	1705 (75) 1680 (71) 1598 (73) 1485 (58) 1384 (54)	203 (4,43) 228 (4,19) 269 (3,59)	0,84	0,89
IIIa	1714 (80) 1680 (77) 1600 (56) 1442 (90) 1385 (64)	203 (4,30) 284 (4,10)	0,93	0,93
IIIc	1700 (82) 1672 (86) 1598 (80) 1440 (76) 1390 (54)	204 (4,32) 275 (4,22)	0,93	0,92
IIId	1715 (85) 1685 (72) 1598 (64) 1440 (76) 1390 (72)	204 (4,46) 232 (4,14) 284 (4,01)	0,97	0,91
IIIe	1710 (66) 1670 (21) 1599 (60) 1465 (72) 1390 (52)	208 (4,33) 264 (4,12) 275 (4,01)	0,92	0,81
IIIg	1700 (75) 1679 (80) 1600 (60) 1492 (70) 1389 (56)	204 (4,67) 238 (4,10) 286 (4,20)	0,90	0,87
IVa	1689 (75) 1669 (66) 1599 (50) 1578 (52) 1430 (64) 1435 (75) 1378 (60)	203 (4,20) 242 (3,10) 294 (3,24)	0,87	0,85
IVc	1711 (66) 1675 (72) 1600 (54) 1580 (57) 1526 (82) 1432 (84) 1390 (60)	203 (4,23) 249 (4,15) 287 (4,37)	0,89	0,87
IVd	1705 (80) 1690 (82) 1600 (56) 1580 (66) 1530 (78) 1432 (86) 1390 (52)	203 (4,31) 232 (4,17) 294 (4,13)	0,86	0,85
IVe	1704 (82) 1680 (84) 1592 (56) 1576 (68) 1522 (68) 1435 (84) 1390 (50)	205 (4,31) 264 (4,11) 294 (4,09)	0,79	0,83
IVf	1702 (81) 1682 (85) 1600 (74) 1580 (67) 1520 (78) 1432 (86) 1388 (54)	206 (4,36) 242 (3,90) 290 (3,91)	0,95	0,93
IVb	1705 (84) 1670 (82) 1599 (56) 1579 (76) 1529 (82) 1431 (84) 1378 (60)	205 (4,19) 250 (4,00) 285 (4,26)	0,85	0,82

*System 1 (acidic medium).
†System 2 (alkaline medium).

were added to a solution of 2.02 g (0.02 mole) of acetoacetamide in 50 ml of absolute ethanol, after which the mixture was refluxed on a water bath for 5 h. It was then cooled to give a colorless crystalline precipitate. Compounds Ib-d, IIc,d, and IVa,c-f were similarly obtained.

2-Oxo-4-(m-nitrophenyl)-6-methyl-1,2,3,4-tetrahydropyrimidine-5-(2-pyridyl)carboxamide (IVb). A 1.73-g (0.01 mole) sample of acetoacetic acid 2-pyridylamide and 0.6 g (0.01 mole) of urea were added to a solution of 1.65 g (0.01 mole) of m-nitrobenzaldehyde in 60 ml of glacial acetic acid, after which the mixture was refluxed for 10 h. It was then cooled to give a colorless precipitate. Compounds IIa, IIb, IIIc-e, g, and IVb were similarly obtained.

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