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REDUCTION OF 12-ACETYLAMINOINDOLO[1,2-c]QUINAZOLINES. PREPARATION OF DERIVATIVES OF THE NEW HETEROCYCLIC SYSTEM INDOLO[3,2-d][1,3]BENZODIAZEPINE

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Reduction of derivatives of 12-acetylaminoindolo[1,2-c]quinazoline yielded the corresponding 12-acetylamino-5,6-dihydroindolo[1,2-c]quinazolines, recyclization of which under the influence of dilute hydrochloric acid led to the formation of derivatives of the hitherto unknown system indolo[3,2-d][1,3]benzodiazepine.

It is known that several of the aminoacyl derivatives of 12-aminoindolo[1,2-c]quinazoline possess sedative properties [1]. Extending the search for biologically active compounds into the indolo[1,2-c]quinazolines, we have studied the reduction of 12-acetylaminoindolo-[1,2-c]quinazolines Ia-d [2-4] by sodium borohydride in acetic acid. From the results of [5] one would expect that the amide group would here be reduced to a secondary amino group. However, we found that under these conditions 12-acetylamino-5,6-dihydroindolo[1,2-c]quinazolines (IIa-d) are formed in high yields. In other words, the C=N bond in the 1,2-position of the pyrimidine ring undergoes reduction. Reductive alkylation of the pyrimidine ring

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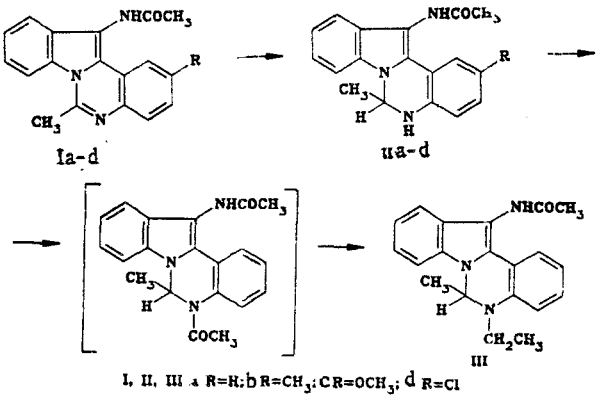
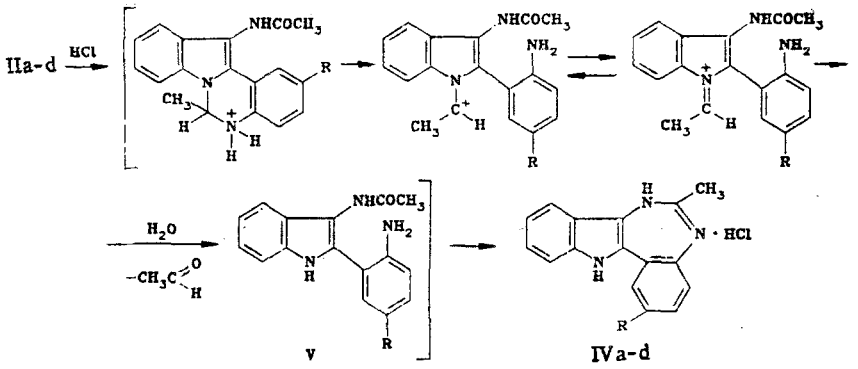
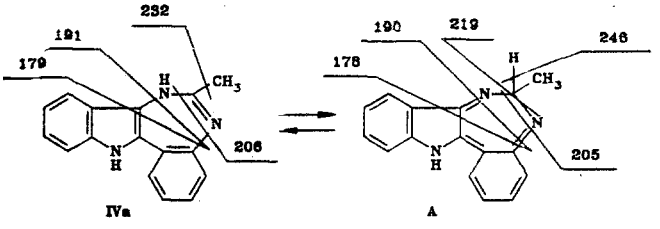
at higher temperature gives, from compound Ia, 5-ethyl-6-methyl-12-acetylamino-5,6-dihydroindolo[1,2-c]quinazoline (III). Compound IIa is formed as an intermediate and this is then acetylated under the reaction conditions with subsequent reduction of the acetyl group. An analogous reductive alkylation of dihydropyrazinocarbazole was reported in [6].



The accessibility of 5,6-dihydroindolo[1,2-c]quinazolines opens up the possibility of preparing compounds of a hitherto unknown series — indolo[3,2-d][1,3]benzodiazepine. We have prepared derivatives of 1(3)H-2-methyl-8H-indolo[3,2-d][1,3]benzodiazepine by recyclization of 12-acetylamino-5,6-dihydroindolo[1,2-c]quinazolines by the action of 10% hydrochloric acid in dioxane.



Comparing the IR spectra of the 5,6-dihydroindoloquinazolines IIa-d with those of the starting materials Ia-d, while the acetyl carbonyl stretching vibration band at 1670-1600 cm^{-1} is retained, a second band appears in the 3420-3320 cm^{-1} region, corresponding to the NH group in the 5-position. In the proton NMR spectra of compounds IIa-d a doublet from the protons of the 6-CH_3 group appears at 1.44 ppm, J = 6 Hz, and a quartet from interaction with the 6H-protons at 6.14 ppm. In the mass spectra of the indolo[3,2-d][1,3]benzodiazepines (IVa-d) the molecular ion peak is the maximum. The main route of decomposition of these compounds, shown for compound IVa as an example, is associated with the formation of the following fragments: 247* $[M^{+\cdot}]$, 246 $[M - H]^+$, 232 $[M - CH_3]^+$, 219 $[M - C_2H_4]^{+\cdot}$, 206 $[M - CH_3CN]^{+\cdot}$, 205 $[M - CH_3CHN]^+$, 191 $[M - NHC(CH_3)N]^{+\cdot}$, 190 $[M - NH_2C(CH_3)N]^+$, 179 $[M - CH_3CN - HCN]^{+\cdot}$, 178 $[M - CH_3CHN - HCN]^+$. The presence of the fragments 246 $[M - H]^+$ and 219 $[M - C_2H_4]^{+\cdot}$ is probably explained by the existence of the indolobenzodiazepine in the tautomeric form A under electron bombardment:



We suggest that the recyclization involves protonation, breaking of the pyrimidine ring, hydrolysis with separation of acetaldehyde and cyclization of the intermediate 2-(o-aminoaryl)-3-acetylaminoindole (V) in which the acetyl and amino groups participate.

*Here and below, ion peaks are given m/z values.

TABLE 1. 6-Methyl-12-acetylamino-5,6-dihydroindolo[1,2-c]-quinazolines IIa-d, III

Compound	IR spectra, cm^{-1}		UV spectra, λ_{max}, nm (lg ε)	Proton NMR* spectra, δ, ppm.	Found, %			Formula	Calculated, %		
	NH	C=O			C	H	N (Cl)		C	H	N (Cl)
IIa	3250, 3180	1610	237 (4,69), 305 (4,13), 324 flat (4,01), 352 (4,20)	1,44 (3H, d, J=6 Hz, 6-CH_3); 2,27 (3H, s, $COCH_3$); 6,14 (1H, q, 6-H); 6,66—8,06 (6H, m); 9,58 (1H, s, 12-NH)	74,4	6,0	14,6	$C_{18}H_{17}N_3O$	74,2	5,9	14,4
IIb	3420, 3240	1670	328 (4,65), 307 (4,13), 325 flat (4,00), 355 (4,13)	1,3 (3H, d, J=6 Hz, 6-CH_3); 2,15 (3H, s $COCH_3$); 2,27 (3H, s, 2-CH_3); 5,90 (1H, q, 6-H); 6,60—7,70 (7H, m); 9,38 (1H, s, 12-NH)	74,6	6,4	13,7	$C_{19}H_{19}N_3O$	74,7	6,3	13,8
IIc	3320, 3285	1640		1,35 (3H, d, J=6 Hz, 6-CH_3); 2,35 (3H, s, $COCH_3$); 3,90 (3H, s, 2-OCH_3); 5,86 (1H, q, 6-H); 6,60—7,70 (7H, m); 9,30 (1H, s, 12-NH)	71,4	6,0	12,9	$C_{19}H_{19}N_3O_2$	71,1	6,0	13,1
IId	3360, 3270	1600	239 (4,68), 309 (4,32), 328 flat (4,95), 365 (4,32)	1,28 (3H, d, J=6 Hz, 6-CH_3); 2,2 (3H, s, $COCH_3$); 5,93 (1H, q, 6-H); 6,73—7,87 (7H, m); 9,58 (1H, s, 12-NH)	66,4	4,8	12,6 (10,6)	$C_{18}H_{16}ClN_3O$	66,4	5,0	12,0 (10,9)
III	3280	1630	240 (4,64), 307 (4,13), 325 flat (4,01); 355 (4,13)	1,2 (3H, d, J=6 Hz, 6-CH_3); 1,24 (3H, t, CH_2CH_3); 3,5 (2H, q, CH_2CH_3); 2,14 (3H, s, $COCH_3$); 6,12 (1H, q, 6-H); 6,8—8,0 (8H, m); 9,53 (1H, s, 12-NH)	75,1	6,7	13,0	$C_{20}H_{21}N_3O$	75,2	6,6	13,2

*Compounds IIa, b, III, run in DMSO-d_6, IIc, d in mixture of DMSO-d_6 and $CDCl_3$.

TABLE 2. Hydrochlorides of 1(3)H-2-Methyl-8H-indolo[3,2-d][1,3]benzodiazepines IVa-d

Compound	UV spectra, λ_{max}, nm (lg ε)	Proton NMR*, spectra, δ, ppm	Found, %				Formula	Calculated, %				M Mass spec.
			C	H	Cl	N		C	H	Cl	N	
IVa	228 (4,38), 272 (4,45) flat 278 (4,46), 310 (4,08) flat	2,34 (3H, s, 2-CH_3); 7,84 (1H, br.d, J_o=8 Hz, 12-H); 7,40 (1H, q, J_o=8, J_m=2 Hz, 7-H); 7,29 (1H, br.d, J_o=8 Hz, 9-H); 6,95—7,15 (5H, m)	67,6	4,9	12,5	14,7	$C_{16}H_{13}N_3 \cdot HCl$	67,7	5,0	12,5	14,8	247
IVb	228 (4,46), 280 (4,52), 290 (4,50) flat 315 (4,12) flat	2,18 (3H, s, 6-CH_3); 2,31 (3H, s, 2-CH_3); 7,82 (1H, d, 12-H); 7,28 (1H, br.d, 9-H); 7,26 (1H, d, 7-H); 7,11; 7,03 (2H, t, 10-, 11-H); 6,87 (2H, AB-system, 4- and 5-H)	68,8	5,4	11,9	14,0	$C_{17}H_{15}N_3 \cdot HCl$	68,6	5,4	11,9	14,1	261
IVc	228 (4,41), 268 (4,35) flat 298 (4,51), 320 (4,08) flat	2,34 (3H, s, 2-CH_3); 7,82 (1H, br.d, 12-H); 7,29 (1H, br.d, 9-H); 7,11; 7,03 (2H, t, d, 10-and 11-H); 7,05 (1H, d 7-H); 6,93 (1H, d 4-H); 6,63 (1H, q 5-H)	65,3	5,1	11,1	13,3	$C_{17}H_{15}N_3O \cdot HCl$	65,1	5,1	11,3	13,4	277
IVd	231 (4,46), 270 (4,41) flat 291 (4,51), 322 (4,05) flat	2,34 (3H, s 2-CH_3); 7,87 (1H, br.d, 12-H); 7,45 (1H, d, 7-H); 7,28 (1H, br.d, 9-H); 7,01; 7,10 (2H, t, d, 10-and 11-H); 7,13 (1H, q, 5-H); 7,0 (1H, d, 4-H)	60,3	4,2	21,9	13,1	$C_{16}H_{12}ClN_3 \cdot HCl$	60,4	4,1	22,3	13,2	281

*Compounds IVa-d run in DMSO-d_6. NH proton signals in spectra of compounds were observed at 10.44-10.66 and 11.30-11.72 ppm. Splitting of proton signals and spin-spin coupling (J_o = 7-8, J_m = 2-3 Hz) were similar to compound IVa.

It should be noted that an analogous breaking of a pyrimidine ring has been observed previously in tetrahydropyrimido[3,4-a]indoles under the action of dilute acid [7].

A study of biological activity, carried out by L. M. Polukhina in the chemotherapy of infectious diseases laboratory of the Ordzhonokidze Institute showed that compounds IVa-d possessed an average degree of antitubercular, antibacterial, and fungistatic activity in experiments in vitro. Compound IVa also showed weak antiviral activity.

EXPERIMENTAL

Infrared spectra were run on a Perkin Elmer spectrophotometer in mineral oil, UV spectra on a Perkin Elmer 575 in ethanol. Mass spectra were obtained on a Varian MAT-112 mass spectrometer with direct introduction of the sample into the ion source. Ionization energy was 70 eV and the temperature 180°C. Proton NMR spectra of compounds IIa-d, III were plotted on a JNM-4H-100 instrument, compounds IVa-d on an XL-200, with TMS internal standard. Monitoring of the reactions and of the individual compounds was carried out on Silufol UV-254 plates in 9:2 benzene–methanol.

3-p-Methoxyphenylazoindole was prepared by the method of [2] from 58.5 g (0.5 mole) indole, 500 ml methanol and the diazonium salt prepared in the usual way from 61.5 g (0.5 mole) p-anisidine, 150 ml hydrochloric acid and 34.5 g (0.5 mole) sodium nitrite. Yield 70 g (63%), mp 135-136°C (1:1 hexane–benzene). Found (%): C 71.9, H 5.2, N 17.1. Calculated for $C_{15}H_{13}N_3O$ (%): C 71.7, H 5.2, N 16.7.

N-Acetyl-p-methoxyphenylazoindole was prepared by the method of [3] from 70 g (0.41 mole) 3-p-methoxyphenylazoindole and 200 ml acetic anhydride. Yield 73 g (92%), mp 134-135°C (from MeOH). IR spectrum: 1710 cm^{-1} (C=O). UV spectrum, λ_{max}, nm (log ε): 222 (4.26), 230 (4.25) flat, 345 (4.38) flat, 368 (4.41). Found (%): C 69.6, H 5.3, N 14.3. Calculated for $C_{17}H_{15}N_3O_2$ (%): C 69.6, H 5.2, N 14.3.

2-Methoxy-6-methyl-12-acetylaminoindolo[1,2-c]quinazoline (Ic) was prepared by the method of [3] from 36.1 g (0.1 mole) N-acetyl-3-p-methoxyphenylazoindole, 300 ml glacial acetic acid, 12 g (0.14 mole) fused sodium acetate, 15 ml (0.1 mole) acetic anhydride, and 39 g (0.6 mole) zinc dust. Yield 25.5 g (80%), mp 283-285°C (from DMF), IR spectrum (cm^{-1}): 1650 (C=O), 3250 (NH). UV spectrum, λ_{max}, nm (log ε): 224 (4.40), 246 (4.52), 284 (4.46), 336 (4.98) flat, 350 (4.17), 368 (4.13). Found (%): C 71.6, H 5.4, N 13.2. Calculated for $C_{19}H_{17}N_3O_2$ (%): C 71.5, H 5.4, N 13.2.

6-Methyl-12-acetylamino-5,6-dihydroindolo[1,2-c]quinazoline (IIa). To a suspension of 5.78 g (0.02 mole) indoloquinazoline Ia in 420 ml glacial acetic acid at 15-18°C in a current of nitrogen was added, in portions with stirring, 3.78 g (0.1 mole) sodium borohydride; stirring was continued for 5-10 min at the same temperature and the mixture then poured into 2 liters of water. The precipitated solid was filtered off and washed with water and MeOH. Yield 4.8 g (83%), mp 260-262°C (1:1 DMF–water).

2,6-Dimethyl-12-acetylamino-5,6-dihydroindolo[1,2-c]quinazoline (IIb). Indoloquinazoline Ib (2.8 g, 7.6 mmole) was dissolved in 600 ml glacial acetic acid at 100-110°C. The solution was cooled to 20-25°C and, in a current of nitrogen with stirring, 1.5 g (39.6 mmole) sodium borohydride was added in portions. Stirring was continued for 30 min at the same temperature and the mixture then poured into 2 liters water and made alkaline to pH 8-9 with ammonia. The precipitated solid was filtered off and washed with water and MeOH. Yield 2.8 g (99%), mp 240-242°C (from MeOH).

2-Methoxy-6-methyl-12-acetylamino-5,6-dihydroindolo[1,2-c]quinazoline (IIc) was prepared from 3.2 g (10 mmole) indoloquinazoline Ic, 210 ml glacial acetic acid and 1.9 g (50 mmole) borohydride by a method similar to that for IIa. Yield 2.7 g (84%), mp 235-237°C (from MeOH).

2-Chloro-6-methyl-12-acetylamino-5,6-dihydroindolo[1,2-c]quinazoline (IId). Indoloquinazoline Id (1.1 g, 3.4 mmole) was dissolved in 300 ml glacial acetic acid at 100-110°C. The solution was cooled to 28-30°C and, in a current of nitrogen and with stirring, 0.64 g (17 mmole) sodium borohydride was added in portions. Stirring was continued for 30 min at the same temperature and the mixture then poured into 1.5 liters of water. The precipitate was filtered off and washed with water and methanol. Yield 0.87 g (79%), mp 263-264°C (2:1 DMF–water).

5-Ethyl-6-methyl-12-acetylamino-5,6-dihydroindolo[1,2-c]quinazoline (III). To a suspension of 2.4 g (8.3 mmole) indoloquinazoline Ia in 170 ml glacial acetic acid was added 3.3 g (8.4 mmole) sodium borohydride in portions in a current of hydrogen at 20°C. The mixture was held for 1 h at 50-70°C and poured into water. The precipitated solid was filtered off and washed with water and alcohol. Yield 1.9 g (72%), mp 221-223°C (from MeOH).

Data for compounds IIa-d, III are given in Table 1.

Hydrochloride of 1(3)H-2-methyl-8H-indolo[3,2-d][1,3]benzodiazepine (IVa). To a suspension of 0.6 g (2 mmole) 5,6-dihydroindoloquinazoline IIa in 9 ml dioxane was added 4 ml 10% hydrochloric acid and the mixture heated at bp for 1 h and then evaporated to dryness. Absolute alcohol was added to the residue, stirred and the alcohol evaporated to remove part of the water and excess hydrochloric acid. This operation was repeated 2 or 3 times and the residue then recrystallized from alcohol. Yield 0.2 g (34%), mp 310°C (dec.).

Hydrochloride of 1(3)H-2,6-dimethyl-8H-indolo[3,2-d][1,3]benzodiazepine (IVb) was prepared from 0.6 g (2 mmole) of 5,6-dihydroindoloquinazoline IIb, 9 ml dioxane and 4 ml 10% hydrochloric acid by a method similar to that for IVa. Yield 0.3 g (51%), mp > 330°C (dec.) (from alcohol).

Hydrochloride of 1(3)H-2-methyl-6-methoxy-8H-indolo[3,2-d][1,3]benzodiazepine (IVc). To a suspension of 0.64 g (~2 mmole) 5,6-dihydroindoloquinazoline IIc in 9 ml dioxane was added 4 ml 10% hydrochloric acid and the mixture heated at bp for 1 h. The mixture was then cooled and the solid deposit filtered off and washed with alcohol and ether. Yield 0.25 g (40%), mp > 330°C (dec.).

Hydrochloride of 1(3)H-2-methyl-6-chloro-8H-indolo[3,2-d][1,3]benzodiazepine (IVd) was prepared from 0.8 g (2.5 mmole) 5,6-dihydroindoloquinazoline IId, 12 ml dioxane, and 6 ml 10% hydrochloric acid similarly to compound IVc. Yield 0.58 g (74%), mp > 330°C (dec.).

Data for compounds IVa-d are set out in Table 2.

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