SYNTHESIS OF 2-AMINO-8-BENZYLIDENE-4-PHENYL--3,4,5,6,7,8-HEXAHYDRO- AND -5,6,7,8-TETRAHYDROQUINAZOLINE DERIVATIVES

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Received November 19th, 1984

Base-catalyzed reaction of 2,6-dibenzylidenecyclohexanone and alkylguanidines gave 2-alkylamino-8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazolines *IVa–c*, which were oxidized to 2-alkylamino-8-benzylidene-4-phenyl-5,6,7,8-tetrahydroquinazolines *Va–c*. The acylamino (*VIa–c*, *VIIa–d*, *IXa,b*) and diacylamino derivatives (*VIIIa,b*) of the 2-amino-8-benzylidene--4-phenyl-3,4,5,6,7,8-hexahydroquinazoline (*II*), 2-amino-8-benzylidene-4-phenyl-5,6,7,8-tetrahydroquinazoline (*III*) and compounds *Va–c* have also been prepared. These compounds having the *E*-configuration were converted into the *Z* isomers *XIIa–e* by photoisomerization. The structures were confirmed by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR).

There are several methods known for the synthesis of 2-aminoquinazolines. They start usually from ketones and guanidine derivatives. Modest and coworkers synthesized the 2,4-diamino-5,6,7,8-tetrahydroquinazoline from cyclohexanone and dicyandiamide[1]. Wendelin and coworkers prepared several 2-amino-pyrimidines and -quinazolines from α,β-unsaturated ketones (chalcones, cyclohexanones) and guanidine[2–4]. Previously we reported the synthesis of 2-amino-8-benzylidene-4-phenyl--3,4,5,6,7,8-hexahydroquinazoline (*II*) and 2-amino-8-benzylidene-4-phenyl-5,6,7,8--tetrahydroquinazoline[5] (*III*). In the present paper the alkyl and acyl derivatives of these compounds will be discussed.

Base-catalyzed reactions of 2,6-dibenzylidenecyclohexanone (*I*) and alkylguanidines gave 2-alkylamino-8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazolines *IVa–c*. Compound *IVa* ($R^1 = C_2H_5$) turned into the aromatic compound *Va* during the purification. The aminolysis of 8-benzylidene-4-phenyl-2-methylmercapto-3,4,5,6,7,8--hexahydroquinazoline[6,7] (*X*) with appropriate alkylamines in butanol or dimethylformamide did not give the expected 2-alkylamino-8-benzylidene-4-phenyl-3,4,5,6,7,8--hexahydroquinazolines *IVb,c* but the known[7] 8-benzylidene-4-phenyl-3,4,5,6,7,8--hexahydro-2(1*H*)-quinazolinon (*XI*) was isolated. Applying the results of Lempert

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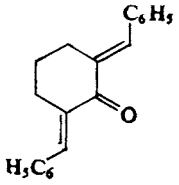

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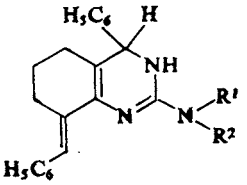
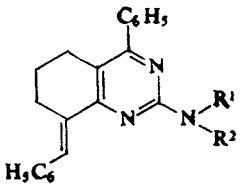
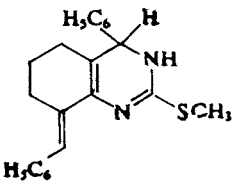


II, $R^1 = R^2 = H$
IVa, $R^1 = C_2H_5$, $R^2 = H$
IVb, $R^1 = C_4H_9$, $R^2 = H$
IVc, $R^1 = C_6H_5CH_2$, $R^2 = H$
VIa, $R^1 = H$, $R^2 = C_6H_5CO$
VIb, $R^1 = H$, $R^2 = 2\text{-}CH_3C_6H_4CO$
VIc, $R^1 = H$, $R^2 = 4\text{-}CH_3C_6H_4CO$

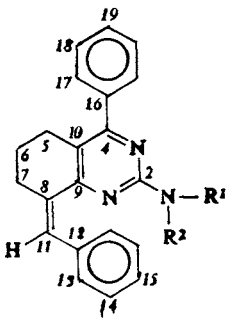


III, $R^1 = R^2 = H$
Va, $R^1 = C_2H_5$, $R^2 = H$
Vb, $R^1 = C_4H_9$, $R^2 = H$
Vc, $R^1 = C_6H_5CH_2$, $R^2 = H$
VIIa, $R^1 = H$, $R^2 = CH_3CO$
VIIb, $R^1 = H$, $R^2 = C_6H_5CH_2CO$
VIIc, $R^1 = H$, $R^2 = C_6H_5CO$
VIId, $R^1 = H$, $R^2 = 4\text{-}CH_3C_6H_4CO$
VIIIa, $R^1 = R^2 = C_6H_5CO$
VIIIb, $R^1 = R^2 = 4\text{-}CH_3C_6H_4CO$
IXa, $R^1 = C_2H_5$, $R^2 = CH_3CO$
IXb, $R^1 = C_2H_5$, $R^2 = C_6H_5CO$



X

XI



XIIa, $R^1 = H$, $R^2 = H$
XIIb, $R^1 = C_2H_5$, $R^2 = H$
XIIc, $R^1 = C_4H_9$, $R^2 = H$
XIId, $R^1 = COCH_3$, $R^2 = H$
XIIe, $R^1 = C_2H_5$, $R^2 = COCH_3$

and Breuer[8], we carried out the reaction in butanol with appropriate alkylamine and acetic acid; alkylamino compounds *IVa–c* were isolated. In the IR spectrum of compound *IVb* the ν(NH) band appeared at 3 250 cm^{-1} and the ν(C=N) band at 1 655 cm^{-1}. In the ^{1}H NMR spectrum the signal of 4-H proton appears at δ 4·74 ppm.

Oxidation of compounds *IVa–c* with $K_3[Fe(CN)_6]$ yielded 2-alkylamino-8-benzylidene-4-phenyl-5,6,7,8-tetrahydroquinazolines *Va–c*. In the IR spectrum of compound *Vb* the ν(NH) band is found at 3 270 cm^{-1}, and a skeletal vibration of the heteroaromatic ring appears as a new band at 1 545 cm^{-1}. In the ^{1}H NMR spectra the absence of the CH proton in position 4 indicates the aromatization. The sole olefine proton in the molecules suffered a paramagnetic shift of 0·5 ppm as compared with the starting base *IVb*; this can probably be attributed to the shielding and conjugation effect of the heteroaromatic ring. This signal exhibits a triplet character (allyl coupling with a methylene group).

The acylation of compound *II* with aromatic acid chlorides yielded 2-acylamino-8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazolines *VIa–c*. The structure of compound *VIa* was supported by its ^{1}H NMR spectrum. The signal of the $C_{(4)}$ methine proton was assigned at δ 4·5 ppm, which value corresponds to that of $C_{(4)}$ methine proton of the compound *II* (4·5 ppm). As the signal of the same proton was shifted paramagnetically (0·6 ppm) in consequence of the 3-acylation of 8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazoline-2(1*H*)-thion owing to the anisotrop shielding effect of the neighbouring C=O group[6], whereas the position of the same signal did not change in the 2-acylamino derivatives of the 2-amino-8-benzylidene-4-phenyl-5,6,7,8-tetrahydro-4*H*-3,1-benzothiazine[9]; thus the 2-acylamino structure seems to be probable.

Acylation of the compound *III* with aliphatic acid chlorides (acetyl chloride, phenylacetyl chloride) gave the 2-acylamino-8-benzylidene-4-phenyl-5,6,7,8-tetrahydroquinazolines *VIIa,b*. In the IR spectrum of *VIIa* the amide-I band appeared at 1 660 cm^{-1} and the ν(NH) band can also be found at 3 200 cm^{-1}. Using aromatic acid chlorides as acylating agents, the following observations were made: *a*) with 1 : 1·5 amine : acid chloride molar ratio and refluxing for 1·5 h, 90% of mono and 10% of diacyl compound was obtained, *b*) with 1 : 4 amine : acid chloride molar ratio and refluxing for 4–5 h, 100% of the diacyl compound was formed. The monoacylamino compounds *VIIc,d* as primary products made with aromatic acid chlorides have IR and ^{1}H NMR spectra similar to those of compounds *VIIa,b*. In the ^{1}H NMR spectra the signal of the =CH proton is shifted paramagnetically by 0·1 ppm and a separate signal of two aromatic protons (δ 7·7–8·0 ppm) also appears, these are the protons located in the neighbourhood of the C=O group. The structures of the N,N-diacylamino compounds *VIIIa,b*, formed in the second step, are confirmed by the following observations: In the IR spectrum of *VIIIa* there is no NH band,

TABLE I

Analytical data of quinazolines

Compound	Formula (m.w.)	M.p., °C	Yield %	Calculated/Found		
				% C	% H	% N
II.HCl	$C_{21}H_{22}ClN_3$ (351·9)	262—265	67[a]	71·68 71·53	6·30 6·38	11·94 11·68
III	$C_{21}H_{19}N_3$ (313·4)	182—185	17[a]	80·48 80·20	6·11 6·35	13·41 13·45
IVb	$C_{25}H_{29}N_3$ (371·5)	135—137	40[b] 35[c]	80·82 80·87	7·87 7·98	11·31 11·15
IVc	$C_{28}H_{27}N_3$ (405·5)	103—104	51[b] 42[c]	82·93 82·81	6·71 6·87	10·36 10·32
Va	$C_{23}H_{23}N_3$ (341·5)	116—118	39	80·90 80·92	6·79 6·98	12·31 12·10
Vb	$C_{25}H_{27}N_3$ (369·5)	115—117	43	81·26 81·30	7·37 7·52	11·37 11·18
Vc	$C_{28}H_{25}N_3$ (403·5)	137—139	52	83·34 83·49	6·24 6·34	10·42 10·17
VIa	$C_{28}H_{25}N_3O$ (419·5)	172—174	57[d]	80·16 80·02	6·01 6·23	10·02 10·18
VIb	$C_{29}H_{27}N_3O$ (433·6)	141—143	37[d]	80·34 80·17	6·28 6·41	9·69 9·82
VIc	$C_{29}H_{27}N_3O$ (433·6)	163—165	35[d]	80·34 80·28	6·28 6·49	9·69 9·73
VIIa	$C_{23}H_{21}N_3O$ (355·4)	159—160	51[d]	77·72 77·90	5·96 6·09	11·82 11·58
VIIb	$C_{29}H_{25}N_3O$ (431·5)	168—170	41[d]	80·72 80·96	5·84 5·98	9·74 9·60
VIIc	$C_{28}H_{23}N_3O$ (417·5)	88—91	29[e]	80·55 80·43	5·55 5·71	10·06 10·18
VIId	$C_{29}H_{25}N_3O$ (431·5)	99—100	47[e]	80·72 80·87	5·84 5·99	9·74 9·61
VIIIa	$C_{35}H_{27}N_3O_2$ (521·6)	190—192	31[d]	80·59 80·68	5·22 5·31	8·06 8·11
VIIIb	$C_{37}H_{31}N_3O_2$ (549·7)	179—181	42[d]	80·85 80·91	5·68 5·83	7·64 7·52
IXa	$C_{25}H_{25}N_3O$ (383·5)	126—127	53[d]	78·30 78·13	6·57 6·72	10·96 10·69

TABLE I
(*Continued*)

Compound	Formula (m.w.)	M.p., °C	Yield %	Calculated/Found		
				% C	% H	% N
IXb	$C_{30}H_{27}N_3O$ (445·6)	156–157	47[d]	80·87 80·98	6·11 6·27	9·43 9·26
XIIa	$C_{21}H_{19}N_3$ (313·4)	148–149	56	80·48 80·57	6·11 6·28	13·41 13·15
XIIb	$C_{23}H_{23}N_3$ (341·5)	147–149	51	80·90 80·73	6·79 6·91	12·31 12·36
XIIc	$C_{25}H_{27}N_3$ (369·5)	86–88	43	81·26 81·15	7·37 7·53	11·37 11·32
XIId	$C_{23}H_{21}N_3O$ (355·4)	164–167	58	77·72 77·85	5·96 6·08	11·82 11·71
XIIe	$C_{25}H_{25}N_3O$ (383·5)	121–124	39	78·30 78·09	6·57 6·81	10·96 10·72

[a] See in ref.[5]; [b] prepared according to *A*; [c] prepared according to *B*; [d] prepared according to *C*; [e] prepared according to *D*.

the amide-I band appears as a doublet at 1 690 and 1 700 cm^{-1}. The diacyl compound *VIIIa* had the following mass spectrum: molecular ion $M^{\ddagger}$, $m/e = 521$; more intense fragment ions: $M-H^+$ (m/e 520), $M-CO^{\ddagger}$ (m/e 493), $M-HCO^+$ (m/e 492), $M-CO-HCO^+$ (m/e 464), $M-2\,CO^{\ddagger}$ (m/e 465), $M-C_6H_5CO^{\ddagger}$ (m/e 416), $C_6H_5CO^{\ddagger}$ (m/e 105) and $C_6H_5^+$ (m/e 77).

Acylation of the compound *Va* yielded 2-acylethylamino-8-benzylidene-4-phenyl-5,6,7,8-tetrahydroquinazolines *IXa,b*. In the IR spectra of these compounds the ν(NH) band cannot be found and the amide-I band appears at 1 660 cm^{-1} and 1 645 cm^{-1}, respectively.

The phenyl ring of the benzylidene group of our heteroaromatic compounds is bound in *E* arrangement (^1H and ^{13}C NMR spectra). The conversion into the *Z* isomers was performed by photoisomerization. In the isomeric mixture the concentration of the *Z* isomer attains the maximum (70–80%) after about 25 h. The separation of isomers was carried out by fractional crystallization. In the ^1H NMR spectrum of *XIIa* the chemical shift of the methylene protons of the cyclohexene ring did not change. The change in the chemical shift of the olefinic proton is re-

markable (*III*: δ 8·1 ppm; *XIIa*: δ 6·7 ppm). In the spectra of the alkyl derivatives *XIIb–e* the signal of the alkyl groups was shifted diamagnetically 0·7 ppm due to the anisotropy effect of the phenyl ring in the benzylidene group. In the ^{13}C NMR spectra of *III* and *XIIa*, which are similar, the high field shift of the $C_{(7)}$ signal in *III* reveals the *Z*-position of the phenyl ring relatively to $C_{(7)}$.

EXPERIMENTAL

The IR spectra were recorded with a SPECORD F5 IR spectrophotometer, the ^{1}H NMR spectra with a Perkin–Elmer R12 A (60 MHz), the ^{13}C NMR spectra with a BRUKER WP-200 instrument (50·327 MHz, ^{1}H noise-decoupling mode, ^{1}H single frequency off resonance decoupling mode, and without decoupling, T = 303 K), and the mass spectra with a JEOL JMS-OlSG-2 spectrometer. For irradiation the UV Analysenlampe, Hanau, λ 366 nm, 125 W was used. The starting 2,6-dibenzylidenecyclohexanone was prepared by aldol condensation[10].

2-Alkylamino-8-benzylidene-4-phenyl-3,4,5,6,7,8-hexahydroquinazolines *IV*

Method *A*) Metallic sodium (0·035 mol) was dissolved in methanol (200 ml) and 2,6-dibenzylidenecyclohexanone (0·020 mol) and the appropriate alkylguanidine hydrochloride (0·025 mol)

TABLE II
Spectroscopic data

Compound	IR (cm^{-1}) (KBr)		^{1}H NMR (δ ppm) (C^2HCl_3)		
	ν(C=N)	ν(NH) amide I	4-H	5,6-CH_2	7-CH_2
II.HCl[a]	1 680 1 655	2 400–3 500[b] –	4·48	1·2–1·9	2·3–2·75
IVb	1 655 1 620	3 250 –	4·74	1·1–2·0[c]	2·4–2·8
IVc	1 655 1 620	3 260 –	4·66	1·3–2·0	2·2–2·7
VIa	1 640 1 620	3 420 1 660	4·53	1·3–2·0	2·3–2·8
VIb	1 645 1 635	3 420 1 655	3·66	1·3–1·9	2·2–2·7
VIc	[d]	3 200 1 650	4·63	1·3–2·0	2·1–2·9

[a] See in ref.[5]; [b] broad band ν(NH), $\nu(=NH_2^+)$; [c] the 5,6-CH_2 signal overlaps the CH_2 signals of the butyl groups; [d] the signal is overlapped by the signal of the C=O group.

TABLE III
Spectroscopic data

Compound	IR (cm^{-1}) (KBr)		^1H NMR (δ ppm) (C^2HCl_3)		
	ν(C=C$_{Ar}$)	ν(NH) amide I	=CH	6-CH_2	5,7-CH_2
III[a]	1 535	3 465, 3 290[b]	8·12	1·4—1·9	2·4—3·0
Va	1 545	3 250	8·15	1·4—1·9	2·3—3·0
Vb	1 545	3 270	8·13	1·2—2·0[c]	2·4—3·1
Vc	1 545	3 235	8·08	1·4—1·9	2·4—3·0
VIIa	1 530	3 200 1 660	8·15	1·4—2·0	2·5—3·1
VIIb	1 535	3 400 1 655	8·0—8·3[d]	1·5—2·0	2·6—3·1
VIIc	1 535	3 300 1 690	8·25	1·5—2·0	2·5—3·0
VIId	1 530	3 440 1 685	8·25	1·5—2·0	2·6—3·1
VIIIa	1 540	1 690, 1 700	7·68	1·4—1·9	2·5—3·0
VIIIb	1 540	1 690, 1 700	7·85	1·4—2·0	2·5—3·0
IXa	1 530	1 660	8·19	1·4—2·0	2·6—3·1
IXb	1 530	1 645	7·1—7·7[e]	1·4—1·9	2·6—3·0
XIIa	1 525	3 420[b]	6·65	1·4—2·1	2·5—2·8
XIIb	1 545	3 290	6·68	1·6—2·1	2·5—3·1[f]
XIIc	1 545	3 265	6·67	1·6—2·1	2·4—2·9[g]
XIId	1 535	3 190 1 665	6·77	1·6—2·1	2·4—2·9
XIIe	1 530	1 655	6·73	1·6—2·1	2·4—3·0

[a] See in ref.[5]; [b] NH_2; [c] the 6-CH_2 signal overlaps the CH_2 signals of butyl group; [d] the =CH signal overlaps the broad NH signal, it became sharp in ^2H_2O; [e] the =CH signal overlaps the Ar signal; [f] The 5,7-CH_2 signal overlaps the CH_2 signal of the ethyl group; [g] The 5,7-CH_2 signal overlaps the CH_2 signal of the butyl group.

TABLE IV

^{13}C NMR chemical shifts (ppm, C^2HCl_3) of quinazolines *III* and *XIIa*

Atom	*III*	*XIIa*	Atom	*III*	*XIIa*
2	167·3	166·9	12	137·3	138·8
4	161·2	161·9	13	129·8	129·2
5	26·7	26·0	14	128·1	128·1
6	23·1	23·7	15	128·7	128·6
7	27·8	34·1	16	138·5	137·7
8	134·5	135·1	17	128·5	128·3
9	160·8	160·8	18	128·1	127·3
10	117·6	118·2	19	127·3	126·7
11	130·0	132·1			

were added. The mixture was refluxed for 5—10 h with the exclusion of atmospheric moisture and poured into water. The precipitate was filtered off, washed with water until neutral and crystallized from methanol.

Method *B*) The synthesis was carried out according to ref.[8].

Aromatization of Hexahydroquinazolines *IV*

Compound *IV* (0·010 mol) was suspended in water (100 ml) and benzene (100 ml); potassium hydroxide (0·020 mol) and $K_3[Fe(CN)_6]$ (0·021 mol) were added to the suspension. The mixture was stirred for 16 h. Then, the benzene phase was separated, the aqueous phase extracted with benzene (2 × 100 ml), and the combined benzene phases were washed with water until neutral. The solution was dried over $MgSO_4$, filtered next day and evaporated. The residue was crystallized from methanol.

Acylation of 2-Amino- and 2-Alkylamino Compounds

Method *D*) The amino compound (0·005 mol) was dissolved in pyridine (50 ml) and the appropriate acid chloride (0·0075 mol) was added. The mixture was refluxed for 1·5 h and poured into water. The precipitate was filtered off, washed with water, dried and the mono- and diacyl products were separated by crystallization from methanol.

Method *C*) The amino compound (0·005 mol) was dissolved in pyridine (50 ml) and the acid chloride (0·020 mol) was added to the solution which was then refluxed for 4—5 h. Further processing was effected as before.

Photoisomerization of (*E*)-2-Aminoquinazolines

Compound of *E*-configuration (0·005 mol) and methylene blue (5 mg) were dissolved in methanol (300 ml), and the solution was externally irradiated in an Erlenmeyer flask (Ergon) at 38°C for 25 h. Samples were withdrawn periodically from the reaction mixture and, after evaporation, the ^1H NMR spectrum of the oil obtained was recorded to determine the isomeric composition

of the mixture. At the end of the reaction the mother liquor was evaporated, and the residue was dissolved in benzene. This solution was washed with 10% HCl and water until colourless and neutral, then dried over $MgSO_4$. After evaporation, the residue was subjected to fractional crystallization from methanol. The purity of the fractions was checked by ^1H NMR technique. The other data for compounds *II* . HCl, *III*—*IX* and *XII* are shown in Tables I—IV.

The authors' thanks are due to R. Ohmacht for recording the IR *spectra and for the analytical results, to L. Prókai for measuring the mass spectra, and to Mrs E. Bleszity and Miss H. Tencz for technical assistance.*

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