SYNTHESIS AND ANALGETIC EFFICIENCY OF SOME OXY AND OXO DERIVATIVES OF 4(3*H*)-QUINAZOLINONE

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Dedicated to Dr Miroslav Protiva on the occasion of his 70th birthday.

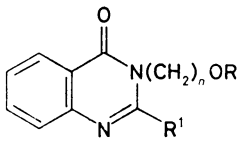
A series of 3-substituted 4(3*H*)-quinazolinone derivatives have been prepared by alkylation of 4(3*H*)-quinazolinone with halogenoethers, halogenoketones, and Mannich bases, and the products have been tested for analgetic effects. The most interesting representatives of the oxy and oxo derivatives are 3-[2-(2′,4′-difluoro-4-biphenylyloxy)ethyl]-4(3*H*)-quinazolinone (*Ib*) and 3-[2-oxo-2-(4-biphenylyl)ethyl]-4(3*H*)-quinazolinone (*IIi*), respectively. Among the group of oxy derivatives also the 2-methylderivative *Ig* has been prepared, viz. by alkylation of 2′,4′-difluoro--4-hydroxybiphenyl with 2-methyl-3-(2-chloroethyl)-4(3*H*)-quinazolinone; the activity of *Ig* is lower than that of *Ib*.

This present work is a part of our project focused on investigation of compounds with anti-inflammatory and analgetic effects. It is known that a quinazoline ring present in a molecule can impart to the substance a number of significant biological effects inclusive the analgetic one[1-3]. We based our study on 4(3*H*)-quinazolinone, being stimulated by some positive results achieved earlier[4,5] with its ester derivatives.

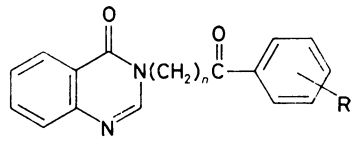
The present paper describes a series of 3-substituted oxy and oxo derivatives of 4(3*H*)-quinazolinone (*I*, *II*) prepared by alkylation with halogenoethers (*Ia*–*If*) and halogenoketones or piperidine Mannich bases (*IIa*–*IIk*). The alkylations with halogenoethers and halogenoketones were carried out in dimethylformamide in the presence of sodium hydride, those with Mannich bases in aqueous methanol. β-Chloroethers were used to prepare the oxy derivatives *Ia*–*Ie*, the respective γ-bromoether being used for *If*. In the synthesis of compound *Ib* other bases also were used instead of sodium hydride, viz. potassium carbonate, potassium hydroxide, and sodium ethoxide, but the yields decreased in the given order. Little satisfactory results were also obtained in the attempts to alkylate 4-hydroxybiphenyl with 3-(2-chloroethyl)-4(3*H*)-quinazolinone[6].

In order to compare the very significant analgetic activity of compound *Ib* with the activity of a derivative with a 2-substituent in the quinazolinone ring, we also

prepared compound *Ig*, i.e. 2-methyl derivative of *Ib*. This comparison was initiated by the known fact that hypnotics of metaqualone type, i.e. 2-methyl-3-(2-methylphenyl)-4(3*H*)-quinazolinone[7], have a substituent at 2-position of quinazolinone ring. Whereas the substituent at 2-position of these compounds has a positive effect on their efficiency, the introduction of methyl group into 2-position of compound *Ib* resulted in a substantial decrease of analgetic activity. Compound *Ig* was prepared by alkylation of 2',4'-difluoro-4-hydroxybiphenyl with 2-methyl-3-(2-chloroethyl)-4(3*H*)-quinazolinone[8] under the same conditions as those used for the other derivatives. The attempts at alkylation of 2-methyl-4(3*H*)-quinazolinone with 2',4'-difluoro-4-(2-chloroethoxy)biphenyl failed.



	R	R^1	*n*
Ia	4-(C_6H_5)C_6H_4	H	2
Ib	4-(2',4'-$F_2C_6H_3$)C_6H_4	H	2
Ic	2-(C_6H_5)C_6H_4	H	2
Id	2-naphthyl	H	2
Ie	6-Br-2-naphthyl	H	2
If	4-(C_6H_5)C_6H_4	H	3
Ig	4-(2',4'-$F_2C_6H_3$)C_6H_4	CH_3	2



	R	*n*
IIa	4-$CH_2CH(CH_3)_2$	2
IIb	4-$CH(CH_3)_2$	2
IIc	4-OCH_3	2
IId	4-Cl	2
IIe	2,4-Cl_2	2
IIf	3,4-$(OCH_3)_2$	2
IIg	4-(C_6H_5)C_6H_4	2
IIh	4-(2',4'-$F_2C_6H_3$)C_6H_4	2
IIi	4-(C_6H_5)C_6H_4	1
IIj	4-(2',4'-$F_2C_6H_3$)C_6H_4	1
IIk	H	2

In the preparations of compounds *IIa*–*IId* we used β-chloroketones for the alkylation of 4(3*H*)-quinazolinone, α-bromoketones being used in the cases of compounds *IIi* and *IIj*. Compounds *IIe*–*IIh* and *IIk* were obtained by alkylations with the Mannich bases derived from piperidine. The basic member of the group of compounds *II*, i.e. 3-(3-phenyl-3-oxopropyl)-4(3*H*)-quinazolinone (*IIk*) is known[9] but its biological effects have not been described yet.

All the β-chloroethers used for syntheses of compounds *Ia*–*Ie* were prepared from the corresponding hydroxy derivatives by reactions with 2-chloroethyl 4-methylbenzenesulfonate[10]. This way of synthesis proved to be substantially more advantageous than the variant using thionyl chloride. Except 2',4'-difluoro-4-(2-chloroethoxy)biphenyl, all the intermediates derived from β-chloroalkylethers are known. The 3-bromopropylether necessary for synthesis of compound *If* was obtained from 4-hydroxybiphenyl and 1,3-dibromopropane in a known way[11].

The syntheses of the alkylating agents with carbonyl group were selected according to availability of the starting materials. Either we prepared the required β-chloroketones from the corresponding aromatic hydrocarbons by the Friedel–Crafts reaction with 3-chloropropanoyl chloride, or we synthetized the Mannich bases from the corresponding acetophenones by the reaction with paraformaldehyde and piperidine. The α-bromoketones for syntheses of compounds *IIi* and *IIj* were obtained by bromination of 4-acetylbiphenyls by a procedure described[12] for the synthesis of 4-(2-bromoxoethyl)biphenyl. 4-(2-Bromoxoethyl)-2′,4′-difluorobiphenyl and 4-(3-piperidino-1-oxopropyl)-2′,4′-difluorobiphenyl are new alkylating agents.

The compound groups *I* and *II* were submitted to orientation tests for acute toxicity and analgetic activity. The acute toxicity was low with all the substances, the estimated LD50 is higher than 1 000 mg/kg per os. The analgetic activity was preliminarily tested with a dose of 100 mg/kg per os using the test of intraperitoneal irritation[13]. A statistically significant activity, expressed in the percentage of pain inhibition, was found with compounds *Ia* (40%), *Ic* (39%), *If* (45%), and the most distinct analgetic effect lasting more than 16 h after oral application was found with compound *Ib*. Its ED50 value (mg/kg) was 28, the values of reference analgetics being 104 with aminophenazon, 179 with ibuprophen, 190 with acetylsalicylic acid, and 285 with paracetamol. In the compound set *II* statistically significant activities were found with compounds *IIc* (33%), *IIg* (33%), *IIh* (46%), and *IIi* (64%), out of which the best (*IIi*) has ED50 equal to 150 mg/kg.

Among the substances prepared the most interesting is compound *Ib* (VÚFB 15950) which was selected for a detailed investigation of pharmacological properties in the form of methanesulfonate and hydrochloride. Favourable parameters (yield, accessibility, stability) of methanesulfonate prevailed over those of hydrochloride.

EXPERIMENTAL

The melting points were determined by means of a Kofler apparatus and are not corrected The IR spectra were measured in chloroform or in KBr disc and the wavenumbers are given in cm^{-1}. The ^1H NMR spectra were measured with a Tesla BS-567 A (100 MHz) apparatus in chloroform or dimethyl sulfoxide with tetramethylsilane as the internal standard.

General Procedure of Preparation of Compounds *Ia*—*If* by Alkylation of 4(3*H*)-Quinazolinone with Halogenoethers

A solution of 0·02 mol 4(3*H*)-quinazolinone in 40 ml dimethylformamide was treated with 0·022 mol sodium hydride (80%), and the mixture was heated to 100°C with stirring, whereupon this temperature was maintained for another 15 min. Then it was cooled to ca 50°C, and 0·02 mol halogenoether was added at once, whereupon the mixture was stirred at 100°C 3 h. After cooling it was diluted with water, the separated crystalline solid was collected by suction, washed with water, and recrystallized.

2-Methyl-3-[2-(2′,4′-difluoro-4-biphenylyloxy)ethyl]-4(3*H*)-quinazolinone (*Ig*)

A solution of 2·06 g (0·01 mol) 2′,4′-difluoro-4-hydroxybiphenyl in 40 ml dimethylformamide was treated with 0·26 g (0·011 mol) sodium hydride (80%), and the mixture was heated at 100°C 15 min. After cooling to ca 50°C, 2·2 g (0·01 mol) 2-methyl-3-(2-chloroethyl)-4(3*H*)-quinazolinone[8] was added, and the heating at 100°C was continued for another 3 h. The reaction product was treated in the same way as in the syntheses of compounds *Ia*—*If*.

The yields, solvents used for recrystallizations, and elemental analyses of compounds *Ia*—*Ig* are presented in Table I, the respective spectra are given in Table III.

Synthesis of Compound *Ib* with Application of Potassium Carbonate or Hydroxide

A mixture of 0·10 mol 4(3*H*)-quinazolinone, 2·8 g (0·02 mol) potassium carbonate (or 1·4 g (0·025 mol) potassium hydroxide), and 3·2 g (0·012 mol) 2′,4′-difluoro-4-(2-chloroethoxy)biphenyl in 35 ml dimethylformamide was heated at 100°C with stirring 7 h. The reaction product was isolated in the same way as that described above. The yields were 62 and 50% with application of potassium carbonate and hydroxide, respectively.

Methanesulfonate of compound Ib: A solution of 21 g (0·055 mol) compound *Ib* in 280 ml chloroform was treated with 5·3 g (0·055 mol) methanesulfonic acid, and the mixture was left

TABLE I

Properties of compounds *Ia*—*Ig*

Compound	Yield %	M.p. °C	Solvent	Formula (M.w.)	Calculated/Found		
					% C	% H	% N
Ia	55	185—186	2-propanol	$C_{22}H_{18}N_2O_2$ (342·4)	77·17 76·96	5·30 5·33	8·18 8·03
Ib[a]	67	184—185	ethyl acetate	$C_{22}H_{16}F_2N_2O_2$ (378·4)	69·83 70·12	4·26 4·44	7·40 7·46
Ic	62	162—163	2-propanol	$C_{22}H_{18}N_2O_2$ (342·4)	77·16 77·15	5·31 5·43	8·18 8·12
Id	66	203—204	nitromethane	$C_{20}H_{16}N_2O_2$ (316·3)	75·93 75·88	5·10 5·51	8·86 8·66
Ie[b]	75	242—243	nitromethane	$C_{20}H_{15}BrN_2O_2$ (395·2)	60·77 60·84	3·83 3·74	7·09 7·02
If	50	140—141	2-propanol	$C_{23}H_{20}N_2O_2$ (356·4)	77·50 77·26	5·66 5·65	7·86 7·60
Ig[c]	35	174—175	2-propanol	$C_{23}H_{18}F_2N_2O_2$ (392·4)	70·40 70·53	4·62 4·73	7·14 7·07

[a] % F, calculated: 10·04, found 10·00; [b] % Br, calculated: 20·22, found: 20·28; [c] % F, calculated: 9·68, found: 9·79.

to stand overnight at room temperature. The crystalline salt was collected by suction, washed with chloroform, and dried. Yield 23 g (87%) methanesulfonate, m.p. 188—189°C. For $C_{23}H_{20}F_2N_2O_5S$ (474·5) calculated: 58·22% C, 4·25% H, 8·00% F, 5·90% N, 6·76% S; found: 57·96% C, 4·20% H, 7·98% F, 6·09% N, 6·70% S.

General Procedure of Preparation of Compounds *IIa*—*IId*, *IIi*, and *IIj* by Alkylation of 4(3*H*)-Quinazolinone with Halogenoketones

The same procedure as that described for syntheses of compounds *Ia*—*If* was also applied to the

TABLE II
Properties of compounds *IIa*—*IIk*

Compound	Yield %	M.p. °C	Solvent	Formula (M.w.)	Calculated/Found		
					% C	% H	% N
IIa	53	105—106	2-propanol	$C_{21}H_{22}N_2O_2$ (334·4)	75·42 75·30	6·63 6·62	8·38 8·56
IIb	54	109—110	2-propanol	$C_{20}H_{20}N_2O_2$ (320·4)	74·97 75·03	6·29 6·31	8·74 8·83
IIc	76	133—134	2-propanol	$C_{18}H_{16}N_2O_3$ (308·3)	70·11 70·17	5·23 5·34	9·09 9·01
IId[a]	78	149—150	2-propanol	$C_{17}H_{13}ClN_2O_2$ (312·7)	65·29 65·56	4·19 4·30	8·95 9·02
IIe[b]	60	114—115	2-propanol	$C_{17}H_{12}Cl_2N_2O_2$ (347·2)	58·81 58·87	3·48 3·40	8·01 8·20
IIf	48	163—164	2-propanol	$C_{19}H_{18}N_2O_4$ (338·4)	67·44 67·30	5·36 5·45	8·28 8·48
IIg	57	187—188	2-propanol	$C_{23}H_{18}N_2O_2$ (354·4)	77·94 77·70	5·12 5·03	7·90 7·96
IIh[c]	50	149—150	ethanol	$C_{23}H_{16}F_2N_2O_2$ (390·4)	70·76 70·55	4·13 4·11	7·18 7·08
IIi	45	186—187	nitromethane	$C_{22}H_{16}N_2O_2$ (340·4)	77·63 77·45	4·74 4·81	8·23 8·15
IIj[d]	80	222—223	nitromethane	$C_{22}H_{14}F_2N_2O_2$ (376·4)	70·20 70·27	3·75 3·82	7·44 7·42
IIk	62	140—141	2-propanol	$C_{17}H_{14}N_2O_2$ (278·3)	73·37 73·40	5·07 5·15	10·07 10·00

[a] % Cl, calculated: 11·33, found: 11·50; [b] % Cl, calculated: 20·42, found: 20·30; [c] % F, calculated: 9·73, found: 9·60; [d] % F, calculated: 10·10, found: 10·17.

alkylations of 4(3*H*)-quinazolinone with β-chloroketones (to prepare compounds *IIa*—*IId*) and with α-bromoketones (to prepare compounds *IIi* and *IIj*).

TABLE III

IR (cm^{-1}) and ^1H NMR (δ, ppm; J, Hz) spectra of compounds *Ia*—*Ig*

Compound	IR[a]	^1H NMR[b]
Ia	1 671 (NC=O); 1 474 (C=C, C=N, quinazolinone); 1 242 (NC=O); 1 219 (C—O); 1 070 (CH_2O)	8·30 (bd, 1 H, J = 8·0, NCOCCH); 8·22 (s, 1 H, NCH=N); 7·20—7·80 (m, 10 H, =CH); 6·92 (d, 2 H, J = 8·5, CH=CCH); 4·36 (m, 4 H, NCH_2CH_2O)
Ib	1 672 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 214 (C—O); 1 178 (CF); 1 053 (CH_2O)	8·30 (bd, 1 H, J = 8·0, NCOCCH); 8·20 (s, 1 H, NCH=N); 7·10—7·80 (m, 7 H, =CH); 7·85 (m, 1 H, FCCH=CF); 6·92 (d, J = 8·5, 2 H, CH=C(O)CH); 4·35 (m, 4 H, NCH_2CH_2O)
Ic	1 670 (NC=O); 1 474 (C=C, C=N, quinazolinone); 1 231 (NC=O); 1 211 (C—O); 1 072 (CH_2O)	8·28 (bd, 1 H, J = 8·0, NCOCCH); 7·79 (s, 1 H, NCH=N); 7·00—7·78 (m, 11 H, =CH); 6·92 (m, 1 H, OC=CH); 4·26 (s, 4 H, NCH_2CH_2O)
Id	1 672 (NC=O); 1 472 (C=C, C=N, quinazolinone); 1 264 (NC=O); 1 218 (C—O); 1 051 (CH_2O)	8·30 (d, 1 H, J = 8·0, NCOCCH); 8·24 (s, 1 H, NCH=N); 7·20—7·80 (m, 8 H, =CH); 7·10 (m, 2 H, CH=C(O)CH); 4·42 (s, 4 H, NCH_2CH_2O)
Ie	1 673 (NC=O); 1 474 (C=C, C=N, quinazolinone); 1 257 (NC=O); 1 224 (C—O); 1 042 (CH_2O)	8·36 (s, 1 H, NCH=N); 8·20 (bd, 1 H, J = 8·0, NCOCCH); 6·90—8·00 (m, 9 H, =CH); 4·45 (s, 4 H, NCH_2CH_2O)
If	1 671 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 243 (NC=O); 1 219 (C—O); 1 053 (CH_2O)	8·32 (bd, 1 H, J = 8·0, NCOCCH); 8·07 (s, 1 H, NCH=N); 7·20—7·80 (m, 10 H, =CH); 6·92 (d, 2 H, J = 8·5, CH=C(O)CH); 4·25 (t, 2 H, J = 7·0, CH_2O); 4·07 (t, 2 H, J = 7·0, NCH_2); 2·32 (m, 2 H, CH_2)
Ig	1 670 (NC=O); 1 474 (C=C, C=N, quinazolinone); 1 445 (CH_3); 1 245 (NC=O); 1 221 (C—O); 1 047 (CH_2O)	8·45 (bd, 1 H, NCOCCH); 6·90 (m, 8 H, =CH); 6·33 (d, 2 H, CH=C(O)CH); 4·46 (m, 4 H, NCH_2CH_2O); 2·94 (s, 3 H, CH_3)

[a] In $CHCl_3$, the spectrum of compound *Ie* was measured in KBr; [b] in $CDCl_3$, the spectrum of compound *Ie* was measured in hexadeuteriodimethyl sulfoxide.

TABLE IV

IR (cm^{-1}) and ^1H NMR (δ, ppm; J, Hz) spectra of compounds *IIb*–*IIk*

Compound	IR[a]	^1H NMR[b]
IIb	2 960, 2 874 (CH_3), 1 683 (C=O); 1 672 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 253 (NC=O)	8·38 (s, 1 H, NCH=N); 8·27 (bd, 1 H, J = 8·0; NCOCCH); 7·87 (d, 2 H, J = 8·5, CH=C(CO)CH); 7·40–7·80 (m, 3 H, =CH); 7·27 (d, 2 H, J = 8·5, CH=C(C)CH); 4·42 (t, 2 H, J = 7·0, NCH_2); 3·56 (t, 2 H, J = 7·0, $COCH_2$); 2·92 (m, 1 H, CCH); 1·23 (d, 6 H, J = 7·0, 2 CH_3)
IIc	2 840 (OCH_3); 1 681 (C=O); 1 672 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 251 (NC=O); 1 029 (CH_2O)	8·38 (s, 1 H, NCH=N); 8·30 (bd, 1 H, J = 8·0, NCOCCH); 7·92 (d, 2 H, J = 8·5, CH=C(CO)CH); 7·40–7·80 (m, 3 H, =CH); 6·90 (d, 2 H, J = 8·5, CH=C(C)CH), 4·42 (t, 2 H, J = 7·0, NCH_2); 3·84 (s, 3 H, OCH_3); 3·54 (t, 2 H, J = 7·0, $COCH_2$)
IId	1 682 (C=O); 1 671 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 259 (NC=O); 1 094 (CCl)	8·35 (s, 1 H, NCH=N); 8·28 (bd, 1 H, J = 8·0, NCOCCH); 7·86 (d, 2 H, J = 8·5, CH=C(CO)CH); 7·40–7·80 (m, 3 H, =CH); 7·40 (d, 2 H, J = 8·5, CH=C(Cl)CH); 4·42 (t, 2 H, J = 7·0, NCH_2); 3·56 (t, 2 H, J = 7·0, $COCH_2$)
IIe	1 682 (C=O); 1 672 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 260 (NC=O); 1 071 (CCl)	8·30 (s, 1 H, NCH=N); 8·25 (bd, 1 H, J = 8·0, NCOCCH); 7·72 (d, 1 H, J = 2·0, ClCCH=CCl); 7·5 (d, 1 H, J = 8·0, COCCH=); 7·40–7·80 (m, 3 H, =CH); 7·27 (dd, 1 H, J = 8·0, 2·0, ClCCH=); 4·40 (t, 2 H, J = 7·0, NCH_2); 3·57 (t, 2 H, J = 7·0, $COCH_2$)
IIf	2 840 (OCH_3); 1 683 (C=O); 1 671 (NC=O); 1 472 (C=C, C=N, quinazolinone); 1 263 (NC=O); 1 022 (OCH_3)	8·38 (s, 1 H, NCH=N); 8·39 (bd, 1 H, J = 8·0, NCOCCH); 7·40–7·80 (m, 5 H, =CH); 6·86 (d, 1 H, J = 8·0, CCH=); 4·42 (t, 2 H, J = 7·0, NCH_2); 3·89, 3·90 (s, s, 6 H, 2 OCH_3); 3·54 (t, 2 H, J = 7·0, $COCH_2$)
IIg	1 681 (C=O); 1 673 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 251 (NC=O)	8·39 (s, 1 H, NCH=N); 8·28 (bd, 1 H, J = 8·0, NCOCCH); 8·00 (d, 2 H, J = 8·5, CH=C(CO)CH); 7·30–7·80 (m, 10 H, =CH); 4·44 (t, 2 H, J = 7·0, NCH_2); 3·60 (t, 2 H, J = 7·0, $COCH_2$)
IIh	1 682 (C=O); 1 672 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 250 (NC=O); 1 182 (CF)	8·41 (s, 1 H, NCH=N); 8·32 (bd, 1 H, NCOCCH); 8·04 (d, 2 H, CH=C(CO)CH); 6·80–7·80 m, 8 H, =CH); 4·46 (t, 2 H, NCH_2); 3·64 (t, 2 H, $COCH_2$)

TABLE IV
(*Continued*)

Compound	IR[a]	^{1}H NMR[b]
IIi	1 686 (C=O); 1 675 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 231 (NC=O)	8·30 (bd, 1 H, J = 8·0, NCOCCH); 8·15 (s, 1 H, NCH=N); 8·04 (d, 2 H, J = 8·5, CH=C(CO)CH); 7·40–7·80 (m, 10 H, =CH); 5·46 (s, 2 H, NCH_2)
IIj	1 680 (C=O); 1 664 (NC=O); 1 476 (C=C, C=N, quinazolinone); 1 263, 1 187 (CF); 1 232 (NC=O)	8·38 (s, 1 H, NCH=N); 8·20 (d, 2 H, J = 8·5, CH=C(CO)CH); 8·20 (bd, 1 H, J = 8·0, NCOCCH); 7·10–8·00 (m, 8 H, =CH); 5·68 (s, 2 H, NCH_2)
IIk	1 686 (C=O); 1 674 (NC=O); 1 473 (C=C, C=N, quinazolinone); 1 252 (NC=O)	8·34 (s, 1 H, NCH=N); 8·26 (bd, 1 H, NCOCCH); 7·92 (m, 2 H, CH=C(CO)CH); 7·20–7·80 (m, 6 H, =CH); 4·40 (t, 2 H, J = 5·0, NCH_2); 3·56 (t, 2 H, J = 5·0, $COCH_2$)

[a] In $CHCl_3$, the spectrum of compound *IIj* was measured in KBr; [b] in $CDCl_3$, the spectrum of compound *IIj* was measured in hexadeuteriodimethyl sulfoxide.

General Procedure of Preparation of Compounds *IIe*–*IIh* and *IIk* by Alkylation of 4(3*H*)-Quinazolinone with Mannich Bases

A mixture of 0·02 mol hydrochloride of Mannich base (derived from piperidine), 0·022 mol 4(3*H*)-quinazolinone, 18 ml methanol, and 26 ml water was refluxed 2 h. After cooling, the precipitated crystalline solid was collected by suction and recrystallized. The melting point found with compound *IIk* (140–141°C) was different from that given in literature[9] (125°C).

The yields, solvents used for recrystallizations, and elemental analyses of compounds *IIa*–*IIk* are given in Table II, the respective spectra (except those of *IIa*) are given in Table IV.

2′,4′-Difluoro-4-(2-chloroethoxy)biphenyl

A solution of 1·2 g (0·03 mol) sodium hydroxide in 2·4 ml water was stirred and 5·47 g (0·026 mol) 2′,4′-difluoro-4-hydroxybiphenyl[14] and 8·5 g (0·036 mol) 2-chloroethyl 4-methylbenzenesulfonate[10] was added thereto. The mixture was heated at 100°C, and the solution formed was stirred at the same temperature 5 h. After cooling, the mixture was diluted with dichloromethane, the solution was washed with water, the solvent was evaporated, and the residue was recrystallized from 2-propanol to give 5·3 g (74%) chloroether, m.p. 72–74°C. For $C_{14}H_{11}ClF_2O$ (268·7) calculated: 62·58% C, 4·12% H, 13·19% Cl, 14·14% F; found: 62·48% C, 4·17% H, 13·20% Cl, 14·12% F. IR spectrum: 1 608 (C=C arom); 1 245 (CF); 1 218 (C–O); 1 180 (CF). ^{1}H NMR spectrum: 7·44 (m, 2 H, CH=CCH); 6·80–7·40 (m, 5 H, =CH); 4·27 (t, 2 H, J = 7·0 Hz, CH_2O); 3·83 (t, 2 H, J = 7·0 Hz, CH_2Cl).

4-(2-Bromoxoethyl)-2′,4′-difluorobiphenyl

At room temperature, 15·9 g (0·1 mol) bromine was added dropwise to a solution of 23·2 g (0·1 mol) 2′,4′-difluoro-4-acetylbiphenyl[14] in 109 ml acetic acid with stirring, the mixture was stirred for another 2 h, and then it was diluted with water. The product was collected by suction and recrystallized from hexane to give 18·5 g (60%) bromoketone, m.p. 82–84°C. For $C_{14}H_9BrF_2O$ (311·5) calculated: 53·98% C, 2·91% H, 25·65% Br, 12·20% F; found: 54·20% C, 2·97% H, 25·31% Br, 12·15% F. ^{1}H NMR spectrum: 8·05 (d, 2 H, J = 8·5 Hz, CH=C(CO)CH); 7·64 (m, 2 H, J = 8·5 Hz, CH=CCH); 6·80–7·50 (m, 3 H, =CH); 4·46 (s, 2 H, CH_2Br).

4-(3-Piperidino-1-oxopropyl)-2′,4′-difluorobiphenyl

A mixture of 24·4 g (0·2 mol) piperidine hydrochloride, 9 g (0·3 mol) paraformaldehyde, 60 ml ethanol, 0·5 ml concentrated hydrochloric acid, and 46·5 g (0·2 mol) 2′,4′-difluoro-4-acetylbiphenyl[14] was refluxed 1h, whereupon another 6 g (0·2 mol) paraformaldehyde was added, and refluxing was continued for another 2 h. After the reaction was finished, the warm reaction mixture was diluted with 500 ml acetone, cooled to room temperature, the precipitated product was collected by suction and recrystallized from a mixture ethanol–acetone (1 : 2) to give 38·8 g (53%) hydrochloride of Mannich base, m.p. 215–217°C. For $C_{20}H_{22}ClF_2NO$ (365·9) calculated: 65·48% C, 6·32% H, 9·66% Cl, 10·36% F, 3·82% N; found: 65·60% C, 6·29% H, 9·54% Cl, 10·27% F, 3·68% N.

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REFERENCES

1. Johne S.: Prog. Drug. Res. *26*, 259 (1982).
2. Reisner D. B., Ludwig B. J., Simon E., Dejneka T., Sofia R. D.: Arzneim.-Forsch. *27* I, 767 (1977).
3. Verma M., Sinha J. N., Gujrati V. R., Bhalla T. N., Bhargova K. P., Shauker K.: Pharmacol. Res. Commun. *13*, 967 (1981).
4. Fišnerová L., Grimová J., Roubal Z., Maturová E., Brůnová B.: Cesk. Farm. *35*, 447 (1986).
5. Fišnerová L., Brůnová B., Maturová E., Grimová J.: Cesk. Farm. *39*, 275 (1990).
6. Sen A. B., Singh S. B.: J. Indian Chem. Soc. *42*, 409 (1965).
7. Jackman G. B., Petrow V., Stephenson O.: J. Pharm. Pharmacol. *12*, 529 (1960); Klosa J.: J. Pract. Chem. *14*, 84 (1961).
8. Botros S., Khalifa M.: Pharmazie *31*, 155 (1976).
9. Bal M. S., Deep K., Singh H.: Indian J. Chem. *21* B, 805 (1982).
10. Clemo G. R., Perkin W. H.: J. Chem. Soc. *1922*, 642.
11. Morishita S., Saito T., Hirai Y., Shoji M., Mishima Y., Kawakami M.: J. Med. Chem. *31*, 1205 (1988).
12. Drake N. L., Bronitsky J.: J. Am. Chem. Soc. *52*, 3715 (1930),
13. Amanuma F.: Folia Pharmacol. Jpn. *84*, 543 (1984).
14. Jones H.: Ger. Offen. 2 532 559 (1974); Chem. Abstr. *84*, 164456 (1976).

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