SYNTHESIS OF DERIVATIVES OF IMIDAZO[2,1-b]QUINAZOLIN-5(1H)-ONE AND 2,3-DIHYDROIMIDAZO[2,1-b]QUINAZOLIN-5(1H)-ONE

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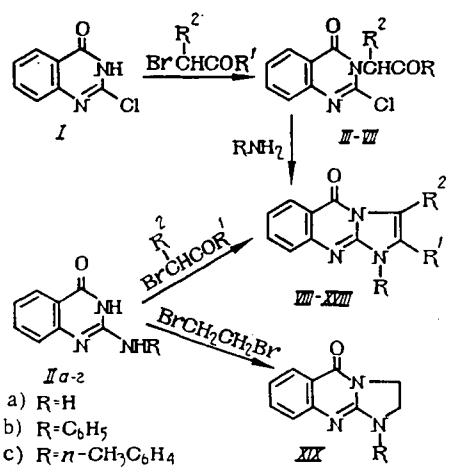
Continuing our research into the synthesis of condensed heterocyclic derivatives of imidazopyrimidines [1, 2] and their benzoanalogs [3-5], we have examined the possibility of using the accessible 2-chloro- and 2-amino(arylamino)quinazolin-4(3H)-ones for the synthesis of the little-studied imidazo[2,1-b]quinazolin-5(1H)-ones and 2,3-dihydroimidazo[2,1-b]quinazolin-5(1H)-ones.

Quinazolin-4(3H)-ones can be alkylated with α-halocarbonyl compounds at N_3 [3, 5, 6]. In our case 2-chloroquinazolin-4(3H)-one (I) easily reacts with α-haloketones in methanol solution in the presence of an equimolecular quantity of sodium methylate forming 3-acylalkyl-2-chloroquinazolin-4(3H)-ones (III-VII, Table 1). As a result of the presence of a labile chlorine atom, these undergo ammonolysis with ammonia and primary amines followed by cyclization to derivatives of imidazo[2,1-b]quinazolin-5(1H)-one (VII-XVIII). This takes place when compounds III-VII are heated with ammonia in dimethylformamide (DMF), dioxane, methanol, ethanol, or in the amine itself. When ammonia or the low-boiling propylamine are used the reaction is carried out in an autoclave at 120-130°C.

We have also developed another, more convenient method for preparing imidazo[2,1-b]-quinazolin-5(1H)-ones, assuming the use as starting materials of 2-amino(arylamino)quinazolin-4(3H)-ones (II). These react with α-haloketones in solution in DMF, dioxane, or methanol in the presence of sodium methylate to form 3-acylalkyl-2-amino(arylamino)quinazolin-4(3H)-ones, which spontaneously rearrange under the reaction conditions to the desired products.

Reaction of 2-(p-chlorophenylamino)quinazolin-4(3H)-one (IId) with 1,2-bromoethane gave the tricyclic compound XIX.



a) R=H
b) R=C_6H_5
c) R=n-$CH_3C_6H_4$
d) R=n-ClC_6H_4

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TABLE 1. 3-Acylalkyl-2-chloroquinazolin-4(3H)-ones (III-VII) and Imidazo[2,1-b]quinazolin-5(1H)-ones (VIII-XVIII)

Compound	R	R^1	R^2	Yield, %	Melting point, deg (dec.)*	Found, %			Brutoformula	Calculated, %		
						C	H	N		C	H	N
III	—	CH_3	H	72	150—2	55,9	3,8	11,8	$C_{11}H_9ClN_2O_2$†	56,1	4,0	11,9
IV	—	C_6H_5	H	64	108—9	64,3	3,8	9,2	$C_{16}H_{11}ClN_2O_2$‡	64,3	3,7	9,4
V	—	4-$CH_3OC_6H_4$	H	63	132—4	62,3	4,3	8,9	$C_{17}H_{13}ClN_2O_3$**	62,1	4,0	8,5
VI	—	4-BrC_6H_4	H	76	175—6	50,6	2,8	7,6	$C_{16}H_{10}ClBrN_2O_2$††	51,0	2,7	7,4
VII	—	C_6H_5	C_6H_5	80	154—6	70,7	4,3	7,9	$C_{22}H_{16}ClN_2O_3$‡‡	70,3	4,3	7,4
VIII	$HOCH_2CH_2$	CH_3	H	94	191—3			17,7	$C_{13}H_{13}N_3O_2$			17,7
IX	$(C_2H_5)_2NC_6H_4$	CH_3	H	70	250—2			15,2	$C_{20}H_{22}N_4O\cdot HCl$			15,1
X	H	C_6H_5	H	58—68	265—7	73,5	4,4	16,3	$C_{16}H_{11}N_3O$	73,5	4,2	16,1
XI	C_6H_5	C_6H_5	H	41—83	272—3	78,7	4,7	12,4	$C_{22}H_{15}N_3O$	78,3	4,5	12,5
XII	4-$CH_3C_6H_4$	C_6H_5	H	91—45	239—241	78,8	5,1	11,8	$C_{23}H_{17}N_3O$	78,6	4,9	11,9
XIII	4-ClC_6H_4	C_6H_5	H	81	290—2	70,5	4,1	11,5	$C_{22}H_{15}ClN_3O$	70,9	4,1	11,3
XIV	4-BrC_6H_4	C_6H_5	H	62	288—290	63,5	3,5	10,0	$C_{22}H_{15}BrN_3O$	63,4	3,5	10,1
XV	C_3H_7	4-BrC_6H_4	H	99	142—4	59,7	4,5	11,3	$C_{19}H_{16}BrN_3O$***	59,7	4,2	11,0
XVI	C_6H_5	4-$CH_3OC_6H_4$	H	50	261—2	75,5	5,1	11,7	$C_{23}H_{18}N_3O_2$	75,0	5,0	11,4
XVII	$HOCH_2CH_2$	C_6H_5	C_6H_5	84	198—200	76,0	5,3	10,9	$C_{24}H_{19}N_3O_2$	75,6	5,0	11,0
XVIII	4-$NH_2SO_2C_6H_4$	C_6H_5	C_6H_2	79	222—4	68,6	3,8	10,9	$C_{28}H_{20}N_4O_3S$	68,3	4,1	11,4

*All compounds melted with decomposition.
†Found, %: Cl 14.6. Calculated, %; Cl 15.0.
‡Found, %: Cl 12.3. Calculated, %: Cl 11.9.
**Found, %: Cl 10.7. Calculated, %: Cl 10.8.
††Found, %: Cl + Br 30.0. Calculated, %: Cl + Br 30.4.
‡‡Found, %:. Cl 9.4. Calculated, %: Cl 9.4.
***Found, %: Br 21.3. Calculated, %: Br 20.9.

The purity of compounds III-XIX was confirmed by thin-layer chromatography, and their structures were verified from the results of elemental analysis and from their IR spectra.

The IR spectra of compounds III-XIX contain the amide carbonyl band in the 1680-1695 cm^{-1} region; in compounds III-VII we also detected the ketone carbonyl band in the 1675-1730 cm^{-1} region. The presence or absence of conjugation with the CO group causes marked differences in the position of the characteristic absorption frequency. For example, in compounds IV-VI conjugation of the carbonyl with the phenyl radical leads to the appearance of absorption bands in the 1675-1690 cm^{-1} region, whereas the acetonyl CO stretching band appears in the 1730 cm^{-1} region.

We established by biological assay that the synthetic compounds show no antimicrobial effect but display activity toward the cardiovascular system, and also produce diuresis. Thus, in female cats intravenous injection of 1-(p-chlorophenyl)-2,3-dihydroimidazo[2,1-b]-quinazolin-5(1H)-one hydrochloride (XX) (dose 100 mg/kg) increased the arterial pressure by 10-30 mm Hg and reduced the rhythm of the cardiac contractions by 15-20%. Compound IX (dose 10-20 mg/kg) increased the arterial pressure by 20-30 mm Hg and increased the frequency of cardiac contractions by 10-15%.

Experiments on white mice established that compound XX (dose 50-100 mg/kg) increased diuresis by 50-68.5% while compound IX reduced it by 25-30%.

EXPERIMENTAL

The IR spectra were recorded as suspensions in vaseline oil with a UR-20 instrument. The properties of the compounds are summarized in Table 1.

3-Acylalkyl-2-chloroquinazolin-4(3H)-ones (III-VII). After addition of 1.8 g (0.01 mole) of 2-chloroquinazolin-4(3H)-one (I) and 0.01 mole of the α-haloketone to a solution of 0.01 mole of sodium methylate or sodium hydroxide in 15-20 ml of methanol, the reaction mixture was refluxed for 5-8 h (to neutral reaction) and then cooled. The precipitate was filtered off and washed with water. Dilution of the mother liquors yielded additional quantities of the same products. Compounds III-VII were colorless crystalline substances, soluble in organic solvents but not in water; for analysis they were purified by crystallization from 1:1 dioxane–water (III) or from 50% methanol (IV-VII).

Derivatives of Imidazo[2,1-b]quinazolin-5(1H)-one (VIII-XVIII). a) After addition of 0.02 mole of the primary amine to a solution of 0.01 mole of the compound (III-VII) in 15 ml of dioxane, the reaction mixture was refluxed for 3-5 h, cooled, and diluted with 30-40 ml of water. The precipitate was filtered off and washed with water and then ether. We obtained VIII, IX, XI–XIV, XVI–XVIII. The hydrochloride of IX was prepared by treating an ethanolic solution of the base with alcoholic hydrogen chloride.

Compound XII was prepared in 45% yield by heating compound IV with p-toluidine in ethanol or methanol.

b) After addition of 0.02 mole of aniline to a solution of 0.01 mole of IV in 10 ml of DMF, the reaction mixture was refluxed for 2 h and was then treated as in experiment a. The yield of XI was 60%.

c) After addition of 5 ml of aniline to 2.00 g (0.01 mole) of IV, the reaction mixture was heated on an oil bath (120-130°C) for 2 h, cooled, and diluted with acetone (40-50 ml); the precipitate was filtered off and washed with water followed by acetone. The yield of XI was 1.4 g (41%).

d) A suspension of 5.98 g (0.02 mole)of IV (VI) in 25 ml of 25% aqueous ammonium hydroxide or n-propylamine was heated at 110-120°C in an autoclave for 6 h. After cooling, the precipitate of X (XV) was filtered off and washed with water.

e) After addition of 0.01 mole of bromoacetophenone to a solution of 0.01 mole of IIb in 15 ml of DMF or dioxane, the reaction mixture was heated on a boiling water bath for 2 h and then treated as in experiment a. The yield of XI (XII) was 83% (91%).

f) After addition of 1.6 g (0.01 mole) of IIa and 2.99 g (0.01 mole) of bromoacetophenone to a solution prepared from 0.01 mole of metallic sodium and 15 ml of methanol, the reaction mixture was refluxed for 4 h and then treated as in experiment a. The yield of X was 2.3 g (68%).

Compounds VIII-XVIII (all were colorless except X and XV, which were yellowish) were crystalline substances, insoluble in water, except for the hydrochloride of IX, which was soluble in organic solvents. For analysis they were purified by crystallization from 1:1 dioxane—water (VIII, XII, XV, XVII), propanol (IX), 50% isopropanol (X), butanol (XI), DMF (XIII, XIV), dioxane (XVI), or 1:1 DMF—water (XVIII).

1-(p-Chlorophenyl)-2,3-dihydroimidazo[2,1-b]quinazolin-5(1H)-one (XIX). A mixture of 2.72 g (0.01 mole) or 2-(p-chlorophenylamino)quinazolin-4(3H)-one (IId) and 3.72 g (0.02 mole) of 1,2-dibromoethane in 25 ml of DMF was refluxed for 8 h, whereupon 2.1 g (0.025 mole) of sodium bicarbonate was carefully added and heating was continued for a further hour, After cooling, the precipitate was filtered off and washed with water. The yield was 2.65 g (98%) of colorless crystals, mp 192-194°C (from 1:1 DMF—water). Found, %: C 64.3, H 3.9, Cl 11.8, N 14.3. $C_{16}H_{11}ClN_3O$. Calculated, %: C 64.8; H 3.8; Cl 11.9; N 14.2. The hydrochloride of XX was obtained as colorless crystals, mp 160-162°C (from 2:1 acetone—methanol). Found, %: Cl 20.8. $C_{16}H_{12}Cl_2N_3O$. Calculated, %: Cl 21.3.

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SYNTHESIS OF 16-ALKYL(ARYL)PSEUDOSOLASODINES

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As part of our search for new methods of cleaving solasodine we have studied the oxidation of solasodine diacetate (I) with sodium dichromate in acetic acid. In the reaction the tetrahydrofuran and piperidine rings were opened and 3β-acetoxy-26-acetylamino-5-cholestene-16,22-dione (IIa) was formed as the principal product. A by-product of the reaction was the previously described 3β-acetoxy-5-bisnorcholene-22,16-lactone (III). Similar oxidation in the sapogenin series [1] gives the sapogenoic acids, which also contain the 1,4-dicarbonyl system. The carbonyl groups in sapogenoic acids [2] are known to differ in reactivity. The carbonyl group at position 16 is more reactive, suggesting that several reactions, particularly the Grignard reaction, may be selective.

The Grignard reaction with IIa has been proposed for the introduction of alkyl and aryl substituents into position 16 of the steroid molecule.

Reaction of IIa with methylmagnesium iodide gave after treatment of the reaction product with ethyl alcohol 16-methyl-22-ethoxy-26-acetylamino-5-furosten-3β-ol (IV). Its PMR spectrum showed a singlet signal from the C_{16} methyl group (1.15 ppm) and signals from the ethyl

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