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CONDENSED ISOQUINOLINES. 12*. SYNTHESIS OF NOVEL HETEROCYCLIC SYSTEMS CONTAINING A PARTIALLY HYDROGENATED SPIRO[ISOQUINOLINE-4,4'-(2H)-PYRAN] FRAGMENT

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By condensation of 4-(2-bromomethyl)-3,4,5,6-tetrahydro-2H-pyran-4-carbonitrile with anthranilic acid, its derivatives substituted in the benzene ring (esters, nitrile), and with esters of 2-aminothiophene-3-carboxylic acids and 3-amino-5-bromobenzofuran-2-carboxylic acid there have been synthesized novel derivatives which include spiro-linked tetrahydropyran and 5,10-dihydro-3H-pyrimido[1,2-b]isoquinoline fragments. The pyrimidine ring of the latter was annelated by a substituted benzene, thiophene, or 5-bromobenzofuran ring.

Keywords: benzofuropyrimidine, isoquinoline, condensed isoquinolines, spirocyclic compounds, tetrahydropyran, thienopyrimidine, quinazoline.

We have previously shown [2] that the reaction of (2-bromomethylphenyl)tetrahydro-2H-pyran-4-carbonitrile (**1**) with primary amines gives derivatives of the spiro(isoquinoline-4,4'-2H-pyran) system. It was of interest to investigate the potential of the bromo nitrile **1** as an intermediate in the synthesis of other heterocyclic systems. With this in mind we have studied its condensation with vicinally functionalized aromatic and heteroaromatic amines of type **2** (where Z = COOH, COOEt, COOMe, Ac, CN and A is the aryl or hetaryl fragment). We have also proposed that an intramolecular reaction of the Z function in the intermediate of type **3** can lead to the formation of novel, polycyclic systems in which the isoquinoline ring is spiro-linked to a tetrahydropyran.

Heating the bromo nitrile **1** with ethyl anthranilate in dioxane gives 3',4',5',6',7,12-hexahydrospiro-[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran]-5-one (**4a**). The latter is also formed when heating the bromo nitrile **1** with anthranilic acid itself in DMF although the yield is lower in this case. Use of the method indicated proved valuable for carrying out the reaction with anthranilic acids substituted in the benzene ring which are more available than the corresponding esters. In this way we obtained, in satisfactory yields, the compounds **4b-e** which are substituted in the quinazoline fragment.

Heterocyclic ester analogs of anthranilic acid take part in the reaction with bromo nitrile **1** similarly. Thus the 3,4,5,6,6',11'-hexahydrospiro[2H-pyran-4,6'-4H-thieno[3',2':3,4]pyrimido[1,2-*b*]isoquinoline]-4-ones **5a-d** have been prepared from the ethyl esters of the 2-aminothiophene-3-carboxylic acid series. The reaction of the bromonitrile **1** with methyl 3-amino-5-bromobenzofuran-3-carboxylate gave 2-bromo-3',4',5',6',8,13-hexahydrospiro[2H-benzo[*b*]furo[3',2',:3,4]pyrimido[1,2-*b*]isoquinoline-8,4'-2H-pyran]-7-one (**6**).

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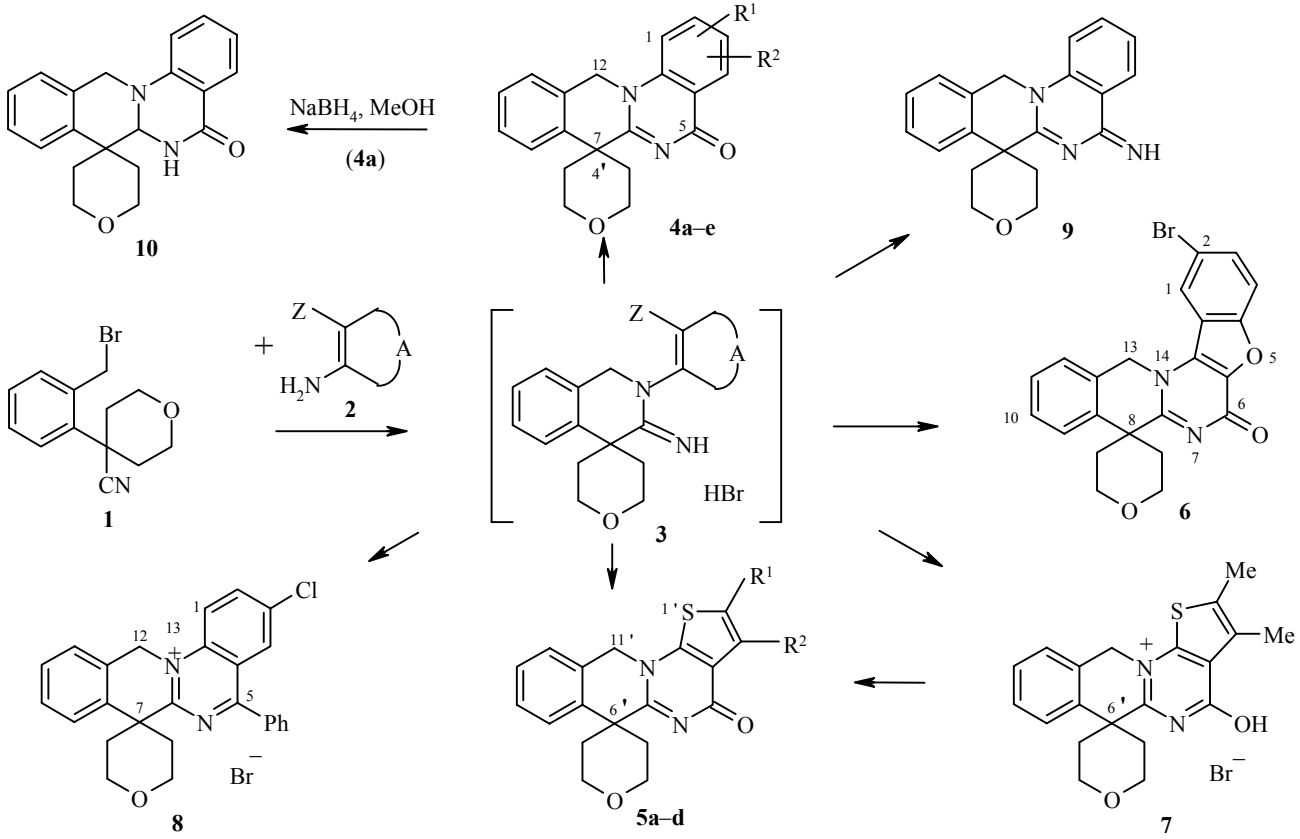

4 a R^1= H; **b** R^1 = 3-Me; **c** R^1 = 2-Cl; **d** R^1 = 3-Br; **e** R^1 = 1-Cl; **a-d** R^2 = H, **e** R^2 = 3-Cl;
5 a R^1 = Me; **b** R^1 = C_2H_5; **c** R^1R^2 = –$(CH_2)_4$–; **d** R^1 = H; **a** R^2= Me, **b** R^2 = H, **d** R^2 = Ph

The IR spectra of compounds **4-6** show absorptions for the stretching of the C=O and C=N groups (see Table 2). The ^{1}H NMR spectra show a singlet for the methylene group of the isoquinoline fragment and complex multiplets for the methylene groups of the tetrahydropyran ring. It should also be mentioned that similar reactions of the structural analog of the starting bromo nitrile **1** (*o*-bromomethylphenylacetonitrile) give a stable hydrobromides of the corresponding condensed isoquinolines in their N-protonated form [3, 4]. In the case of the bromonitrile **1** the crude reaction products are in fact a mixture of the free bases **5** with an admixture of the hydrobromides. Evidently the latter are weak bases due to the steric shielding of the potential nucleophilic center (the pyrimidine nitrogen atom) by the tetrahydropyran ring and readily undergo deprotonation in the conditions of the reaction and/or their purification by recrystallization. Only in the case of the condensation of the bromonitrile **1** with ethyl 2-amino-3,4-dimethylthiophene-3-carboxylate did the crude reaction product appear to be the pure hydrobromide. In contrast to the analog without a spirocyclic structure, this compound exists in the O-protonated form as the 4'-hydroxy-2',3'-dimethyl-3,4,5,6,6',11'-hexahydrospiro[2H-pyran-4,6'-thieno[3',2',:3,4]pyrimido[1,2-*b*]isoquinolin-12-ium] bromide (**7**). This is supported by the IR spectrum in which the C=O absorption band typical of the N-protonated salts is absent. At the same time, the position and appearance of the absorption band at high frequency is more typical of an O–H vibration. The observation of the salt separation should be rationalized not as a peculiarity of the structure as a conjugated base but rather as a case where the poorly soluble protonated salt (in these reaction conditions) falls out of solution before its deprotonation occurs. We particularly draw attention to the poor reproducibility in the synthesis of the salt **7**. In fact, prolonged heating of the reaction mixture or attempts to recrystallize the salt **7** from DMF lead to the free base **5a**.

TABLE 1. Characteristics for the Condensed Spiro[isoquinoline-4,4'-pyrans] **4-10**

Compound	Empirical formula	Found, % / Calculated, %				mp, °C	Yield, %
		C	H	N	Hal (S)		
4a	$C_{20}H_{18}N_2O_2$	75.60 / 75.45	5.78 / 5.70	8.80 / 8.79		247	73
4b	$C_{21}H_{20}N_2O_2$	75.92 / 75.88	6.12 / 6.06	8.59 / 8.43		248	63
4c	$C_{20}H_{17}ClN_2O_2$	68.15 / 68.09	4.95 / 4.86	8.00 / 7.94	10.15 / 10.05	336	62
4d	$C_{20}H_{17}BrN_2O_2$	60.50 / 60.45	4.40 / 4.31	7.16 / 7.05	20.05 / 20.11	310	58
4e	$C_{20}H_{16}Cl_2N_2O_2$	62.08 / 62.03	4.20 / 4.17	7.30 / 7.23	18.28 / 18.31	286	43
5a	$C_{20}H_{20}N_2O_2S$	68.32 / 68.16	5.93 / 5.72	8.44 / 7.95	(9.18) / (9.10)	260	55
5b	$C_{20}H_{20}N_2O_2S$	68.20 / 68.16	5.80 / 5.72	8.06 / 7.95	(9.20) / (9.10)	170	48
5c	$C_{22}H_{22}N_2O_2S$	69.85 / 69.82	6.00 / 5.86	7.64 / 7.40	(8.52) / (8.47)	249	35
5d	$C_{24}H_{20}N_2O_2S$	72.00 / 71.98	5.10 / 5.03	7.10 / 6.99	(8.14) / (8.01)	265	45
6	$C_{22}H_{17}BrN_2O_3$	60.53 / 60.41	4.07 / 3.92	6.60 / 6.41	18.18 / 18.27	>350	48
7	$C_{20}H_{20}N_2O_2S\cdot HBr$			6.24 / 6.46	18.16 / 18.44	205	56
					(7.29) / (7.40)		
8	$C_{26}H_{22}ClN_2O^+\cdot Br^-$	63.42 / 63.24	4.53 / 4.49	5.12 / 5.67	23.47 / 23.36	173	62
9	$C_{20}H_{19}N_3O$	75.78 / 75.69	6.12 / 6.03	13.70 / 13.24		205	87
9·HBr	$C_{20}H_{19}N_3O\cdot HBr$	60.35 / 60.31	5.15 / 5.06	10.69 / 10.55	20.18 / 20.06	303	53
10	$C_{20}H_{20}N_2O_2$	75.00 / 74.98	6.24 / 6.29	8.65 / 8.74		149	79

TABLE 2. Parameters for the Condensed Spiro[isoquinoline-4,4'-pyrans] **4-10**

Compound	IR spectrum, ν, cm^{-1}		^{1}H NMR spectrum, δ, ppm, spin-spin coupling, *J* (Hz)			
	C=O	C=N	$O(CH_2)_2$, 4H, m	$C(CH_2)_2$, 4H, m	NCH_2, 2H, s	Other signals
4a	1640	1600	3.65-4.10	1.90-2.50	5.51	8.12 (1H, d, *J* = 8, 4-H); 7.90 (2H, m, H_{arom}); 7.15-8.10 (5H, m, H_{arom})
4b	1640	1585	3.75-4.25	2.05-2.60	5.27	8.15 (1H, d, *J* = 2.5, 4-H); 7.20-7.70 (6H, m, H_{arom}); 2.45 (3H, s, CH_3)
4c	1650	1590	3.80-4.25	2.05-2.60	5.24	8.34 (1H, d, *J* = 8, 4-H); 7.25-7.70 (6H, m, H_{arom})
4d	1640	1590	3.80-4.25	2.05-2.55	5.25	8.50 (1H, d, *J* = 2.5, 4-H); 7.86 (1H, dd, *J* = 8, *J* = 2.5, 2-H); 7.15-7.70 (5H, m, H_{arom})
4e	1655	1570	4.20-4.50	2.70-3.05	6.15	8.42 (1H, d, *J* = 2.5, 4-H); 8.26 (1H, d, *J* = 2.5, 2-H); 7.5-7.9 (4H, m, H_{arom})
5a	1625	1580	3.60-4.15	1.85-2.50	5.43	7.10-7.75 (4H, m, H_{arom}); 2.41 (6H, s, 2-CH_3, 3-CH_3)
5b	1620	1570	3.50-4.10	1.90-2.55	5.36	7.30-7.75 (4H, m, H_{arom}); 7.04 (1H, s, 3-H); 1.26 (3H, t, CH_3); 2.85 (2H, m, 2-CH_2)
5c	1625	1570	3.60-4.15	1.90-2.50	5.30	7.30-7.70 (4H, m, H_{arom}); 2.60-3.00 (4H, m, 2-CH_2–, 3-CH_2–); 1.78 [4H, m, –$(CH_2)_2$–]
5d	1630	1560	3.70-4.10	1.95-2.45	5.43	7.30-7.70 (9H, m, H_{arom})
6	1635	1600	3.70-4.15	1.95-2.45	5.83	8.70 (1H, s, 11-H); 7.35-7.90 (6H, m, H_{arom})
7	2540 (O–H)	1580	3.60-4.20	1.90-2.35	5.42	7.30-7.75 (4H, m, H_{arom})
8		1575	3.70-4.10	2.20-2.70	6.41	8.83 (1H, d, J_o = 9, 1-H); 8.65 (1H, dd, J_o = 9, J_m = 2.5, 2-H); 8.39 (1H, d, J_m = 2.5, 4-H); 7.40-8.10 (9H, m, H_{arom})
9		1600	3.65-4.05	1.85-2.45	5.24	8.13 (1H, d, *J* = 8, 4-H); 7.25-7.90 (7H, m, H_{arom})
9·HBr	3200, 3020 (N^+–H)	1650, 1595	3.70-4.10	1.95-2.45	5.82	10.02 (1H, s, NH); 9.91 (1H, s, NH); 8.58 (1H, d, *J* = 8, 4-H); 8.10-8.40 (2H, m, H_{arom}); 7.40-7.95 (5H, m, H_{arom})
10	1645	3160 (N–H)	3.60-3.95	1.60-2.20	4.44; 4.59 (1H, d, J_{gem} = 16)	8.02 (1H, d, *J* = 2, N–H); 7.73 (1H, d, *J* = 8, 4-H); 6.80-7.65 (7H, m, H_{arom}); 5.04 (1H, d, *J* = 2, 7-H_{arom})

The reaction of the bromonitrile **1** with 2-amino-5-chlorobenzophenone occurs with the formation of 3-chloro-5-phenyl-3',4',5',6',7,12-hexahydrospiro[5H-isquino[2,3-*a*]quinazoline-7,4'-2H-pyran-13-ium) bromide (**8**). The IR spectrum of this compound shows the absence of stretching bands for nitrile, secondary amino, iminium salt or a carbonyl group which would have been expected for each of the possible intermediate products. In addition, the spectroscopic parameters for this compound agree well with those obtained earlier [5] for 5-aryl-7,12-dihydroisquino[2,3-*a*]quinazolin-13-ium perchlorates.

The reaction of the bromonitrile **1** with anthranilic acid nitrile gave the 3',4',5',6',7,12-hexahydrospiro[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran]-5-imine hydrobromide (**9**·HBr). The absence of absorption in the region 2200-2250 cm^{-1} and the presence of strong N^+–H and C=N^+ bands point to the formation of this tetracyclic structure. The basicity of the usual organic bases (triethylamine, piperidine) proved insufficient for deprotonation of this salt to the free base. Only by treatment of an alcoholic suspension with aqueous NaOH was it possible to liberate the free imine. Evidently the presence of an amidine fragment in the structure of this compound gives it a high basicity when compared with the oxo derivatives **4-6**.

It was found that the $C_{(6a)}$=$N_{(6)}$ double bond in compound **4a** is readily reduced by sodium borohydride in methanol solution in the presence of DMF (which increases the solubility of the starting compound) to give 5-oxo-3',4',5',6,6',6a,7,12-octahydrospiro[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran] (**10**). The structure of this product was confirmed by IR spectroscopy in which there is absent (when compared with the starting compound **4a**) a C=N band, an N–H band is observed, and the C=O band undergoes the expected shift to higher frequency. The presence of the asymmetric $C_{(6a)}$ atom in the molecule of this compound causes the signals for the protons of the $C_{(12)}$ methylene group to appear in the ^{1}H NMR spectrum as an AB type spin system with a geminal constant of J = 16 Hz. The structural fragment **H**–$C_{(6a)}$–$N_{(6)}$–**H** is characterized by an AX spin system with J_{vic} = 2 Hz. In the presence of D_2O the NH signal is absent and the doublet signal for the $C_{(6a)}$–H proton becomes a singlet.

EXPERIMENTAL

IR spectra for these compounds were recorded on a Pye Unicam SP3-300 instrument for KBr tablets. ^{1}H NMR spectra for compounds **3b-d** in $CDCl_3$, **3e** in CF_3CO_2D, and the remainder in DMSO-d_6 were obtained on a Bruker WP-100 SY (100 MHz) instrument using TMS as internal standard. Compounds **8** and **10** were recrystallized from methanol, compound **9** from toluene, and the remainder from DMF. The parameters for the compounds synthesized are given in Tables 1 and 2.

3',4',5',6',7,12-Hexahydrospiro[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran]-5-one (4a). A solution of the bromonitrile **1** (0.84 g, 3 mmol) and ethyl anthranilate (0.45 g, 3 mmol) was refluxed in 2-propanol (10 ml) for 8 h. The precipitate from the cooled reaction mixture was filtered, washed with 2-propanol, and then suspended with heating in 2-propanol (10 ml). An excess of morpholine or piperidine was added and the mixture was refluxed for 15 min, cooled, and twice the volume of water added with stirring. The precipitated, colorless product **4a** was filtered off and carefully washed with water.

3,4,5,6,6',11'-Hexahydrospiro[2-pyran-4,6'-thieno[3',2',3:4]pyrimido[1,2-*b*]isoquinoline]-4'-ones (5a-d) and 2-Bromo-3',4,4',5',6',8,13-hexahydrospiro[2H-benzo[*b*]furo[3',2':3,4]pyrimido[1,2-*b*]-isoquinoline-8,4'-2H-pyran]-7-one (6) were prepared similarly from the ethyl esters of the substituted 2-aminothiophene-3-carboxylic acids (**2f-i**) and 3-amino-5-bromobenzofuran-2-carboxylic acid (**2j**) respectively.

3-Methyl-3',4',5',6',7,12-hexahydrospiro[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran]-5-one (4b). A mixture of the bromonitrile **1** (0.84 g, 3 mmol) and 5-methylanthranilic acid (**2b**) (0.45 g, 3 mmol) in DMF (7 ml) was refluxed for 10 h. The precipitate of **4b** from the cooled reaction mixture was filtered and washed on the filter with 2-propanol, water, and then 2-propanol.

Compounds **4c-a** were prepared similarly from the corresponding anthranilic acids **2c-e**.

3-Chloro-5-phenyl-3',4',5',6',7,12-hexahydrospiro[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran-13-ium] bromide (8). A solution of the bromo nitrile **1** (0.84 g, 3 mmol) and 2-amino-5-chlorobenzophenone (0.69 g, 3 mmol) in 2-propanol (10 ml) was refluxed for 8 h. The precipitate from the cooled reaction mixture was filtered and washed with 2-propanol.

4'-Hydroxy-2',3'-dimethyl-3,4,5,6,6',11'-hexahydrospiro[2H-pyran-4,6'-thieno[3',2',:3,4]pyrimido-[1,2-*b*]isoquinolin-12-ium] Bromide (7) was prepared similarly from the bromo nitrile **1** and ethyl 2-amino-3,4-dimethylthiophene-3-carboxylate. The precipitate from the refluxing reaction mixture after 2 h was the pure salt **7**. Since an attempt to carry out an additional purification of this salt by recrystallization led to its deprotonation, an analytical sample was obtained indirectly from the reaction mixture using the starting materials and solvent of high purity.

3',4',5',6',7,12-Hexahydrospiro[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran]-5-iminium Hydrobromide (9·HBr) was prepared similarly to the compound **4a** starting from anthranilic acid nitrile. The free base was obtained by the addition of an excess of 5% NaOH solution to a vigorously stirred, hot suspension of the salt in ethanol followed by stirring for 20 min, cooling, and reprecipitation of the free base using water.

3',4',5',6,6',7,12-Octahydrospiro[5H-isoquino[2,3-*a*]quinazoline-7,4'-2H-pyran]-5-one (10). $NaBH_4$ (0.41 g, 12 mmol) in DMF (2 ml) was added to a suspension of compound **4a** (0.45 g, 2 mmol) in methanol (10 ml). The reaction mixture was refluxed for 2.5 h, cooled, diluted with water, and the precipitate was filtered off and washed with water and alcohol.

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