Reaction of 2-Amino-5-chlorobenzophenone with Alkylnitriles. Preparation of Some Quinoline, Quinazoline and Indole Derivatives.

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While investigating the synthesis of some new quinoline derivatives, it was noticed that 2-amino-5-chlorobenzophenone could be converted to some heterobicyclic systems when reacted with various alkylnitriles. Depending on the structure of the nitrile used, it was possible to prepare quinazolines or quinolines under very similar reaction conditions (Scheme I).

2-Amino-5-chlorobenzophenone furnished quinazoline derivatives I-V when reacted with alkylnitriles possessing no additional electron-withdrawing groups in the α-position to the cyano group. This reaction proceeded in the presence of phosphosphus tribromide, a strong Lewis acid catalyst.

Elimination of water and cyclisation probably takes place in many discreet steps. The first one could be nucleophilic attack of the amino group on the carbon atom of the strongly polarized cyano group followed by rearrangement and elimination of water. The structures of compounds I-V (see Table I) was confirmed by spectroscopic data and elemental analysis.

The ultraviolet spectra of quinazolines I-V exhibited characteristic maxima at 230-235 nm (log ϵ 4-5 x 10^4), 270-275 nm (log ϵ 5-6 x 10^3) and at about 330 nm (log ϵ 3-4 x 10^3), respectively. Weak conjugation with the substituent in position 3 in compounds IV and V, caused the deformation of the band at 270-275 nm to a shoulder

SCHEME I

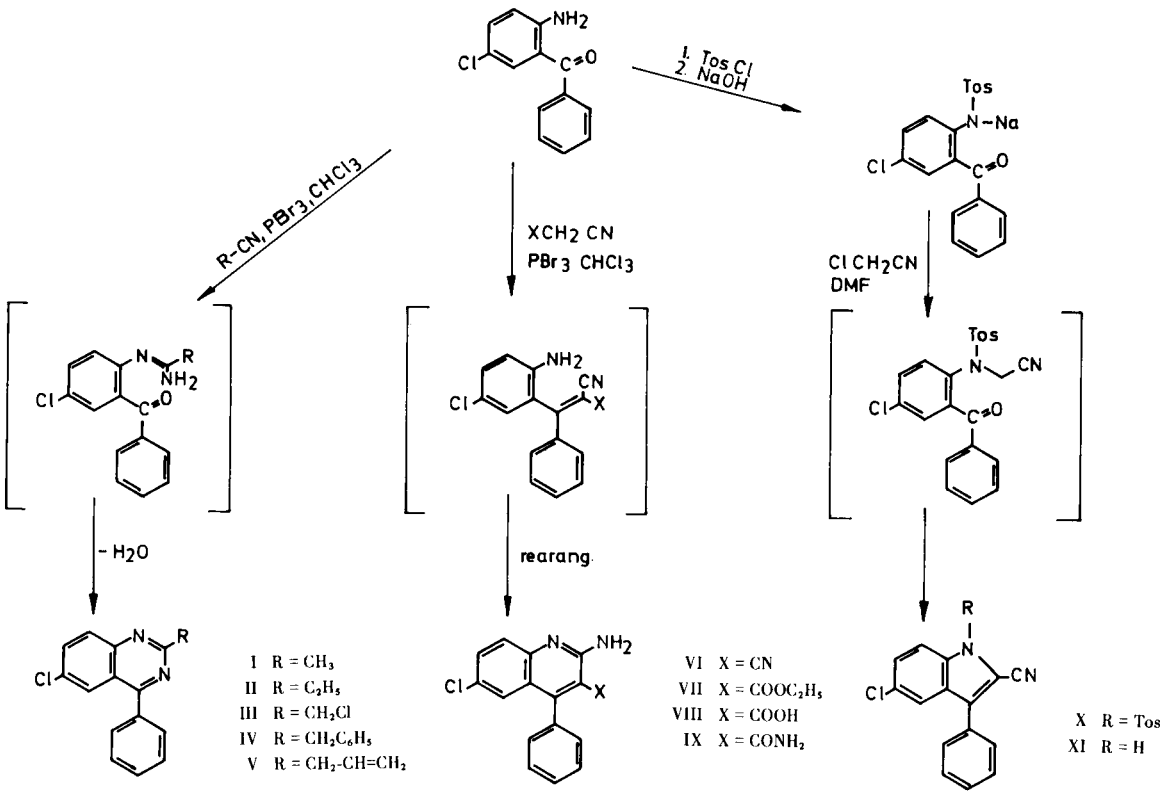
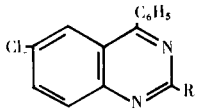


TABLE I

2-Substituted-4-phenyl-6-chloroquinazolines



Compound	R	Yield (a)	M.p., °C	Formula	Calcd., % C	H	N	Found, % C	H	N
I	$-CH_3$	55	106-107	$C_{15}H_{11}ClN_2$	70.74	4.35	11.00	70.39	4.38	11.04
II	$-C_2H_5$	43	103-104	$C_{16}H_{13}ClN_2$	71.47	4.88	10.42	71.78	5.04	10.78
III	$-CH_2Cl$	59	124-125	$C_{15}H_{10}Cl_2N_2$	62.31	3.46	9.69	62.04	3.80	9.84
IV	$-CH_2C_6H_5$	35	145-146	$C_{21}H_{15}ClN_2$	76.24	4.57	8.46	75.85	4.66	8.85
V	$CH_2-CH=CH_2$	22	145-147	$C_{17}H_{13}ClN_2$	72.73	4.67	9.98	72.63	4.63	9.78

(a) After recrystallization from ethanol.

shifted bathochromically to 285-290 nm.

The infrared spectra of compounds I-V exhibit very characteristic strong bands in the regions 1555-1560, 1450-1550, 1480-1495, 1440-1450 and 1380-1395 cm^{-1}, respectively. The nmr spectra of compounds I, II, and V are cited in the experimental section. Compounds I and III had been synthesized earlier by some different methods (2,3) and their literature data confirm the structures ascribed to I-V.

When the nitrile used in the reaction with 2-amino-5-chlorobenzophenone possessed an active methylene group, as in malononitrile or cyanoacetic ester, the reaction proceeded through another pathway (Scheme I). An aldol type condensation is the most probable first step, followed by ring closure through an interesting rearrangement of the β,γ-unsaturated nitrile derivative. Such rearrangements are, however, well known in the cyclisation of similar heterocyclic systems (4,5). Thus, some 2,3-, as well as 2,4-disubstituted quinolines, were obtained by a similar procedure starting from *o*-aminobenzophenone and polyfunctional carbonyl compounds (6), or simple ketones (7), respectively. The structure of the compounds obtained was confirmed by their spectroscopic characteristics (see Experimental), as well as by the structure of the products of hydrolysis VIII and IX (8).

After this work was finished a paper appeared describing another route to compounds VI and IX. The substantially higher yield of VI by our method indicates the greater efficacy of Lewis acid catalysis (8).

The third reaction, somewhat different from the first two, formed a 3-phenylindole ring *via* the intermediate preparation of sodium *N*-(2-benzoyl-4-chlorophenyl)-*p*-toluenesulfonamide (9) and subsequent cyclisation with chloroacetonitrile (Scheme I). It is of interest that under the reaction conditions used, the tosyl-moiety remained intact on the indole ring, and could be separately hydrolysed (X → XI). The same procedure failed, however, when some benzoyl amides of 2-amino-5-chlorobenzophenone were employed. The scope of this reaction is under further investigation.

EXPERIMENTAL

Melting points were determined on a Köfler hot-stage apparatus and are uncorrected. Infrared spectra were run on a Perkin-Elmer Model 137 Spectrophotometer in potassium bromide pellets. Ultraviolet spectra were obtained on a UV-VIS recording Spectrophotometer Opton DMR 21, and nmr spectra were recorded on a Jeol JNM-C-60-HL spectrometer. The solvents used were as indicated in the text; tetramethylsilane (TMS) was used as an internal standard. Mass spectra were recorded at the "Jožef Štefan" Institute, Ljubljana, on a CEC 21-110 C Mass spectrometer at 70 eV. Elemental analyses were performed by the microanalytical laboratory, Department of Organic Chemistry, University of Ljubljana, Yugoslavia.

General Procedure for the Preparation of the Compounds I-V.

To a solution of 3 g. (0.013 mole) of 2-amino-5-chlorobenzophenone and 0.16 mole of the nitrile compound (according to Scheme I) in 30 ml. of chloroform, 2.5 g. (0.009 mole) of phosphorus tribromide were added, dropwise, over a period of 0.5 hour at room temperature and under complete exclusion of moisture from the air. The stirring was prolonged for 3 hours at the same temperature, and thereafter the reaction mixture was gently heated under reflux for 3 hours. The solvent was evaporated *in vacuo*, the oily residue was dissolved in 20 ml. of 96% ethanol, and the solution was neutralized (1*N* sodium hydroxide to *p*H 7. On chilling, the crude product which separated was collected, dried, and recrystallized as indicated in Table I. Nmr spectra of the compounds I, II and V, respectively, exhibited the following peaks (in deuteriochloroform): I δ 2.81 (s, 3H); 7.36-8.00 (m, 8H). II; 1.48 (t, 3H), 3.16 (q, 2H), 7.36-8.00 (m, 8H) V; 2.01 (m, 3H) 7.40-7.95 (m, 8H).

2-Amino-3-cyano-4-phenyl-6-chloroquinoline (VI).

To a solution of 3 g. (0.013 mole) of 2-amino-5-chlorobenzo-

phenone and 2 g. (0.033 mole) of malononitrile in 30 ml. of chloroform, 2.5 g. (0.009 mole) of phosphorus tribromide was added, dropwise, over a period of 0.5 hour at room temperature. After prolonged stirring for 2 hours under the same condition, the crude product began to separate. To complete the reaction, stirring and heating under reflux was continued for an additional 4 hours. After the solvent was evaporated *in vacuo* 2.5 g. (69%) of VI, m.p. 272-273° were obtained on recrystallization from ethanol; ir (strong bands only) 3480, 3200, 2220, 1660, 1580, 1575, 1480, 1415, 830 cm^{-1}; uv (in ethanol) λ max (log ε); 226 (4.58) 254 (4.68) 385 (4.70) $M^+ = 279$.

Anal. Calcd. for $C_{16}H_{10}ClN_3$: C, 68.70; H, 3.65; N, 15.02. Found: C, 69.05; H, 3.81; N, 15.23.

2-Amino-3-carbetoxy-4-phenyl-6-chloroquinoline (VII).

Compound VII was prepared according to the procedure described for VI using 2.5 g. (0.022 mole) of ethyl cyanoacetate. On recrystallization from 96% ethanol, 0.5 g. (12%) of pure VII, m.p. 165-166° was obtained; ir (strong bands only) 3420, 3310, 3150, 1725, 1645, 1520, 1485, 1390, 1295, 1245, 1190, 827 cm^{-1}; uv (in ethanol) λ max (log ε); 228 (4.53), 253 (4.60), 368 (3.33); nmr (in deuteriochloroform) δ 0.73 (t, 3H) 3.86 (q, 2H) 5.99 (s, broad, 2H), 7.1-7.4 (m, unresolved, 8H) $M^+ = 326$.

Anal. Calcd. for $C_{18}H_{15}ClN_2O_2$: C, 66.17; H, 4.62; N, 8.54. Found: C, 66.32; H, 5.00; N, 8.68.

2-Amino-3-carboxy-4-phenyl-6-chloroquinoline (VIII).

In 30 ml. of 50% ethanol, 0.4 g. (0.0012 mole) of the compound VII was dissolved and 5 ml. of 1*N* sodium hydroxide was added. The solution was heated for 1 hour on a water-bath and thereafter it was evaporated *in vacuo* to dryness. The residue was dissolved in a minimum of cold water and acidified to *p*H 3. The crude product which separated was suctioned off, and recrystallized from 96% ethanol giving 0.2 g. (55%) of VIII, m.p. 309-310°; ir (strong bands only) 3390, 3200, 2400 and 1950 (braod), 1690, 1545, 1490, 1455, 1370, 1345, 1130, 955, 925, 846, 825 cm^{-1} $M^+ = 298$.

Anal. Calcd. for $C_{16}H_{11}ClN_2O_2$: C, 64.33; H, 3.71; N, 9.38. Found: C, 63.95; H, 3.98; N, 9.01.

2-Amino-3-carboxamido-4-phenyl-6-chloroquinoline (IX).

In 25 ml. of 70% ethanol, 0.50 g. (0.0018 mole) of VI was dissolved, 10 ml. of 20% sodium hydroxide was added and the solution was heated under reflux for 6 hours. The reaction mixture was evaporated to dryness *in vacuo* and the residue recrystallized from 96% ethanol, 0.3 g. (56%) of pure IX, m.p. 254-255° was obtained; ir (strong bands only) 3490, 3350, 3090, 1675, 1630, 1590, 1560, 1480, 1430, 1390, 825 cm^{-1}; uv (in ethanol) λ max (log ε) 217 (4.50), 248 (4.59), 356 (3.71) $M^+ = 297$.

Anal. Calcd. for $C_{16}H_{12}ClN_3O$: C, 64.54; H, 4.05; N, 14.11. Found: C, 64.75; H, 4.35; N, 13.72.

1-Tosyl-2-cyano-3-phenyl-5-chloroindole (X).

Sodium *N*-(2-benzoyl-4-chlorophenyl)-*p*-toluene sulfonamide (19.1 g., 0.0469 mole) was dissolved in 150 ml. of DMF and 9 g. (0.12 mole) of chloroacetonitrile was added dropwise at room temperature. The stirring was prolonged for 1.5 hours at reflux temperature. After cooling, the reaction mixture was poured on ice. The oily product was recrystallized from ethanol giving 13.5 g. (71%) of colorless needles, m.p. 164-165°; ir (strong bands only) 2220, 1600, 1490, 1440, 1380, 1250, 1170, 1090, 1050, 1030, 960, 880, 812, 783, 715, 688 cm^{-1}; uv (in ethanol) λ max (log ε) 225 (4.56), 293 (4.17), 316 (3.96).

Anal. Calcd. for $C_{22}H_{15}ClN_2O_2S$: C, 64.94; H, 3.71; N, 6.88. Found: C, 65.20; H, 3.66; N, 6.94.

2-Cyano-3-phenyl-5-chlorindole (XI).

Five g. (0.0123 mole) of X was dissolved in 40 ml. of 20% sodium hydroxide and the solution was heated under reflux for 0.5 hour. The reaction mixture was cooled, the precipitate was collected by filtration and recrystallized from 96% ethanol giving 2.5 g. (80%) of colorless plates, m.p. 118-119°; ir (strong bands only) 3320, 2210, 1610, 1540, 1280, 1240, 1060, 1010, 955, 880, 795, 768, 740, 695 cm^{-1}; uv (in ethanol) λ max (log ε) 234 (4.61), 298 (3.92).

Anal. Calcd. for $C_{15}H_9ClN_2$: C, 71.27; H, 3.60; N, 11.09. Found: C, 70.88; H, 3.57; N, 11.15.

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