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Synthesis and Reactions of α-Bromoaroylacetarylamides

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Benzoylacetanilide and fourteen of its substituted derivatives were brominated to give α-bromobenzoylacetanilides (I). The spectral data of I indicate that they exist mainly in the keto form. Reaction of I with phenylhydrazine yielded 4-phenylazo-1,3-diaryl-2-pyrazolin-5-ones (IV). Treatment of I with thiourea and thioacetamide gave 2-amino-4-arylthiazole-5-carboxanilides (XII) and 2-methyl-4-arylthiazole-5-carboxanilides (XIII), respectively. With excess of concentrated sulfuric acid or polyphosphoric acid, α-bromobenzoylacetanilides (I) were converted into 3-bromo-4-aryl-2-quinolones (XVI). Structural assignments were based on the elemental and spectral analyses.

Aroylacetarylamides are readily available,[1] but there have been no reports on the preparation and reactions of α-bromoaroylacetarylamides (I) and their α-iodo analogs (II). Very little is known about α-chloro derivatives (III).[2] Thus, from an interest in the chemistry of aroylacetarylamides,[1,3] we have studied the preparation of two series of the α-halo derivatives (I—II) and some of their reactions.

$$RC_6H_4COCH(X)CONHC_6H_4R'$$

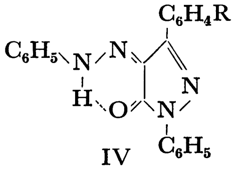
I, X=Br
II, X=I
III, X=Cl

a, R=R'=H
b, R=H; R'=3-CH_3
c, R=H; R'=4-CH_3
d, R=H; R'=4-CH_3O
e, R=H; R'=3-Cl
f, R=H; R'=4-Cl
g, R=H; R'=3-Br
h, R=H; R'=4-Br
i, R=H; R'=3-NO_2
j, R=H; R'=4-NO_2
k, R=H, R'=4-$COOC_2H_5$
l, R=Br; R'=H
m, R=4-NO_2; R'=H
n, R=4-CH_3O; R'=H
o, R=4-Cl; R'=H

When benzoylacetanilide in acetic acid solution was treated with an equimolar amount of bromine in the same solvent, α-bromo derivative (Ia) was obtained in 80% yield. The other α-bromobenzoylacetanilides (Ib—o) were prepared from the corresponding benzoylacetanilides in a similar manner.

The structure assignment of I was based on elemental and spectral analyses. Thus, the NMR spectrum of Ia ($CDCl_3$) showed a multiplet absorption due to ten protons at δ 8.25—7.65 ppm and two one proton singlets at δ 4.90 (-COCHBr-) and 9.43 (-CONH-) ppm. Its IR spectrum (KBr) showed a benzoyl CO band at 1715 cm^{-1} and an anilide CO band at 1665 cm^{-1}. The high frequency position for the benzoyl carbonyl, which ordinarily falls near 1705 cm^{-1}, might be expected in view of the presence of bromine substituent on the α-carbon atom. The identity of the bromination products was also confirmed by treatment of I with acidified potassium iodide[4] to give the parent benzoylacetanilides.

It has been reported[1] that the electronic absorption pattern of benzoylacetanilides in ethanol was in each case characterised by the presence of two maxima in the 305—350 and 240—280 nm regions. These were assigned to the cinnamoyl and benzoyl chromophores of the enol and keto froms, respectively. In the UV spectra of the α-bromoanilides (Ia—o), the cinnamoyl band was absent; each exhibited only one band in the 240—270 nm region. This suggests that the α-bromobenzoylacetanilides (Ia—o), unlike their parent compounds, exist mainly in the keto form in ethanol. This might be ascribed to the instability of the enol form of I which probably results from the large steric interaction between the voluminous bromine atom and the benzene nuclei.[5]



IV

a, R=H; b, R=4-Cl; c, R=4-Br; d, R=4-CH_3O

When Ia was heated with phenylhydrazine in acetic acid for 3 hr, it gave 1,3-diphenyl-4-phenylazo-2-pyrazolin-5-one (IVa). The structure of IVa was established by comparing it with an authentic sample prepared by coupling 1,3-diphenyl-2-pyrazolin-5-one with benzenediazonium chloride.[6] They were found to be identical. In order to explain this, we propose the two mechanisms represented in scheme 1 for the reaction of I with phenylhydrazine. The conversion of V into VI (or X into VIII) is similar to that for the preparation of 2-pyrazolin-5-one derivatives by the reaction of β-keto esters with phenylhydrazine.[7] This was also supported by our finding that the α-bromoanilides, If and Ij yielded IVa only when they were similarly treated with phenylhydrazine. The oxidation of the proposed hydrazine intermediates VII or IX into VIII or X, respectively, is probably effected by

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[2] A. J. Hodgkinson and B. Staskun, *J. Org. Chem.*, **34**, 1709 (1969); T. Van Es and B. Staskun, *Tetrahedron*, **25**, 5941 (1969).

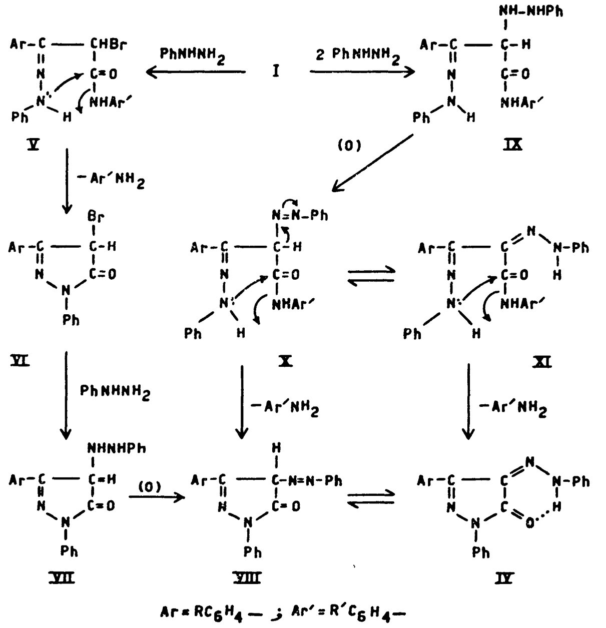
[3] A. S. Shawali, A. Dewidar, and M. M. Naoum, *Indian J. Chem.*, **10**, 464 (1972).

[4] H. G. Garg and M. M. Bokadia, *J. Indian Chem. Soc.*, **34**, 286 (1957) and the references cited therein.

[5] M. I. Kabachnik, S. T. Ioffe, E. M. Papov, and K. Vatsuro, *Tetrahedron*, **12**, 76 (1961).

[6] (a) O. Dimroth and R. Schweizer, *Ber.*, **56**, 1375 (1923); (b) A. Wahl and J. Rolland, *Ann. Chim.* (Paris), **10**, 5 (1928); (c) A. Wahl and C. Silverzweig, *Bull. Soc. Chim. Fr.*, **11**, 61 (1912).

[7] R. H. Wiley and P. Wiley, "Pyrazolones, Pyrazolidionones and Derivatives," Interscience Publishers, John Wiley & Sons, Inc., New York (1964).

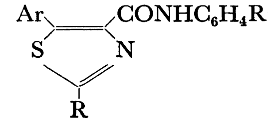


Scheme 1.

atmospheric oxygen during the course of refluxing the reaction mixture. In many cases, atmospheric oxygen suffices for such oxidation of hydrazines.[8]

Treatment of the other α-bromobenzoylacetanilides (Il, In, and Io) with phenylhydrazine in the manner described above afforded the corresponding 4-arylazo-2-pyrazolin-5-ones (IVb, IVc, and IVd), respectively. The structures of the unreported compounds in series IV were derived from their analytical and spectral data. The NMR spectrum of IVc in $CDCl_3$, as an example, exhibited a multiplet at δ 7.33 ppm due to aromatic protons and a singlet due to a highly deshielded proton at δ 13.89 ppm. The low field signal was assigned to hydrogen bonded NH group.[9] Such data indicate that the products IVa—d thus prepared exist in the assigned hydrazone structure IV. The IR spectra of IV are also compatible with this structure. Thus, each of the compounds (IVa—d) exhibited three characteristic bands at 1680 (lactam CO), 1610 (C=N), and 3280 (weak, hydrogen bonded NH) cm^{-1}.

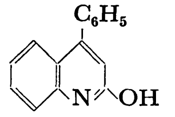
α-Bromobenzoylacetanilides (I), when heated with thiourea, readily gave 2-amino-4-phenylthiazole-5-carboxanilides (XII). α-Bromoanilides (I) also, reacted with thioacetamide to give 2-methyl-4-phenylthiazole-5-carboxanilides (XIII). Both compounds XII and XIII have not yet been reported. Their structures were established by elemental analysis and a study of their spectral data. The UV absorption pattern of XII was in each case characterised by the presence of two maxima: one in the 320—327 ($\log \varepsilon$ 4.15$\pm$0.02) nm region and the other located between 240 and 245 nm ($\log \varepsilon$ 4.33$\pm$0.03). The 2-methyl analogs (XIII) absorb fairly intensively in the regions 306—315 ($\log \varepsilon$ 4.08$\pm$0.1) and 240—280 ($\log \varepsilon$ 4.29$\pm$0.6) nm. All compounds (XII—XIII) showed amide-I band near 1660 cm^{-1} and an absorption band due to the C=N double bond stretching near 1620 cm^{-1} in their IR spectra. Compounds of series XII exhibited also absorption bands in the 3400—3285 cm^{-1} region due to the NH_2 stretching.



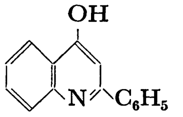
XII, R=NH_2; XIII, R=CH_3

a, Ar=C_6H_5; R′=H
b, Ar=C_6H_5; R′=3-Cl
c, Ar=C_6H_5; R′=3-NO_2
d, Ar=C_6H_5; R′=4-Br
e, Ar=4-ClC_6H_4; R′=H
f, Ar=C_6H_5; R′=4-Cl
g, Ar=4-$CH_3OC_6H_4$; R′=H

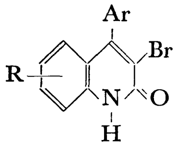
Benzoylacetanilide undergoes cyclization when heated with concentrated sulfuric acid or polyphosphoric acid (PPA) to give XIV or XV depending on the anilide to acid ratio.[10] Utilization of a higher proportion of acid in the reaction favours the formation of XIV. Cyclization of α-bromobenzoylacetanilides (Ia—o) is now being considered. With an anilide–acid (H_2SO_4 or PPA) ratio of 1 : 10, the anilides I were converted into the corresponding 3-bromo-4-aryl-2-quinolones (XVI) in 60—80% yields. Attempts to cyclize α-bromoanilides If and Ij were, however, unsuccessful. This indicates that the ease of cyclization of substituted benzoylacetanilides is influenced by both the position and nature of the substituent present. In line with this finding is the observation that the nitro- and chloro-acetoacetanilides are appreciably decomposed to arylamines even with excess acid reagent.[10]



XIV



XV



XVI

a, R=H; Ar=C_6H_5
b, R=6-CH_3; Ar=C_6H_5
c, R=H; Ar=4-BrC_6H_4
d, R=H; Ar=4-$NO_2C_6H_4$

Staskun[10] has assigned the 2-hydroxy structure XIV for the cyclized product of benzoylacetanilide. However, the spectral data of the compounds XVIa—d prepared revealed that they have the 2-oxo form (XVI). Thus, all compounds exhibited an NH stretching bands at 3312 and 3156 cm^{-1} and a strong CO band at 1650 cm^{-1}. The products XVIa—d gave no colour with alcoholic ferric chloride. The UV absorption maxima of XVIa, as a typical example of the series, in a series of different buffer solutions were not affected by a change in pH, a fact which seems to be compatible with the proposed 2-oxo form (XVI).

Experimental

Melting points are uncorrected. IR spectra were obtained for new compounds and were recorded on a Unicam SP 200G infrared spectrophotometer (1 mg/300 mg KBr). UV

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[8] H. Zollinger, "Azo and Diazo Chemistry, Aliphatic and Aromatic Compounds," Intersciences Publishers, Inc., New York (1961), p. 196.

[9] A. Snavely and C. H. Yoder, *J. Org. Chem.*, **33**, 513 (1968).

[10] B. Staskun, *ibid.*, **29**, 1153 (1964) and the references cited therein.

spectra were determined from a Beckman DK spectrophotometer. NMR spectra were recorded on a Varian A-60 spectrometer with TMS as internal reference. Benzoylacetanilides were prepared from the appropriate arylamine and ethyl benzoylacetate.[11] Aroylacetanilides were reported by Shawali *et al.*[1]

Preparation of α-Bromoaroylacetarylamides (Ia—o). General Procedure: A solution of bromine (4.8 g, 0.03 mol) in glacial acetic acid (30 ml) was added dropwise over a period of 1 hr to the appropriate aroylacetarylamide (0.03 mol) dissolved in the same solvent (60 ml) with stirring at room temperature. After 2 hr, the mixture was poured into water and the precipitated solid was filtered. In some cases the resulting solid precipitated before dilution. The crude product was washed with water and recrystallized from dilute ethanol. The results are given in Table 1.

TABLE 1. α-BROMOAROYLACETARYLAMIDES

Compound No	Mp, °C	Yield %	Formula	Bromine % Calcd	Bromine % Found
Ia[a]	133—134	80	$C_{15}H_{12}BrNO_2$	25.15	24.98
Ib	116—118	75	$C_{16}H_{14}BrNO_2$	24.10	24.00
Ic	141—142	77	$C_{16}H_{14}BrNO_2$	24.10	23.97
Id	144—145	70	$C_{16}H_{14}BrNO_2$	22.98	23.00
Ie	107—108	70	$C_{15}H_{11}ClBrNO_2$	22.69	22.17
If	125—126	75	$C_{15}H_{11}BrClNO_2$	22.69	22.12
Ig	129—130	75	$C_{15}H_{11}Br_2NO_2$	40.28	39.98
Ih	136—137	76	$C_{15}H_{11}Br_2NO_2$	40.28	40.00
Ii	140—142	70	$C_{15}H_{11}BrN_2O_4$	22.03	21.78
Ij	146—147	65	$C_{15}H_{11}BrN_2O_4$	22.03	21.90
Ik	130—131	60	$C_{18}H_{16}BrNO_4$	20.51	20.29
Il	181—182	70	$C_{15}H_{11}Br_2NO_2$	40.28	40.10
Im	145—147	70	$C_{15}H_{11}BrN_2O_4$	22.30	21.85
In	135—136	75	$C_{16}H_{14}BrNO_3$	22.98	23.10
Io	180—182	70	$C_{15}H_{11}BrClNO_2$	22.69	22.18

a) Calcd: C, 56.60; H, 3.77; N, 4.40%. Found: C, 56.45; H, 3.80; N, 4.38%.

Preparation of 1-Phenyl-3-aryl-4-phenylazo-2-pyrazolin-5-ones, (IVa—d). A mixture of α-bromobenzoylacetanilide (Ia) (1.6 g, 0.005 mol) and phenylhydrazine (2 ml) in acetic acid (10 ml) was refluxed for 3 hr and cooled. The precipitated product was collected and recrystallized from acetic acid. The product obtained was identified as 4-phenylazo-1,3-diphenyl-2-pyrazolin-5-one (IVa), mp 172—173 °C. Mixed mp with an authentic sample (prepared by coupling of benzenediazonium chloride with 1,3-diphenyl-2-pyrazolin-5-one as described before[6]) showed no depression. When each of the α-bromoanilides Il, In, and Io was treated with phenylhydrazine following the same procedure as for Ia, compound IVa was the only product obtained.

The other α-bromoaroylacetanilides If, Ih, and Id reacted with phenylhydrazine and yielded the following derivatives of 5-pyrazolones: IVb, mp 205 °C (55%) (lit,[6b] 203—205 °C); IVd; mp 177 °C (70%) (lit,[6c] mp 176—177 °C) and IVc, mp 201°C (65%). Found: C, 60.19; H, 3.61; Br, 18.98; N, 13.25%. Calcd for $C_{21}H_{15}BrN_4O$: C, 60.13; H, 3.57; Br, 19.09; N, 13.36%.

2-Amino-4-arylthiazole-5-carboxanilides (XII). A mixture of α-bromoaroylacetanilide (0.01 mol) and thiourea (0.8 g, 0.013 mol) in ethanol (30 ml) was refluxed for 3 hr. The reaction mixture was poured into water and made alkaline with ammonium hydroxide. The resulting solid was filtered, washed with water and finally recrystallized from ethanol. The prepared compounds and their physical constants are given in Table 2.

TABLE 2. 2-SUBSTITUTED 4-ARYLTHIAZOLE-5-CARBOXANILIDES

Compound No	Mp, °C	Yield %	Formula	Sulfur % Calcd	Sulfur % Found
XIIa[a]	198—199	80	$C_{16}H_{13}N_3OS$	10.85	10.68
XIIb	193—194	85	$C_{16}H_{12}ClN_3OS$	9.72	9.38
XIIc	225—226	70	$C_{16}H_{12}N_4O_3S$	9.41	9.50
XIId	262—264	77	$C_{16}H_{12}BrN_3OS$	8.55	8.44
XIIe	243—245	80	$C_{16}H_{12}ClN_3OS$	9.72	9.54
XIIIa[b]	119—120	50	$C_{17}H_{14}N_2OS$	10.88	10.75
XIIIb	142—143	55	$C_{17}H_{13}ClN_2OS$	9.75	9.70
XIIIc	139—140	70	$C_{17}H_{13}N_3O_3S$	9.44	9.22
XIIIf	151—152	68	$C_{17}H_{13}ClN_2OS$	9.75	9.69
XIIIg	122—123	64	$C_{18}H_{16}N_2O_2S$	9.88	9.74

a) Found: C, 65.46; H, 4.24; N, 14.02%. Calcd: C, 65.07; H, 4.40; N, 14.23%.

b) Found: C, 69.13; H, 4.70; N, 9.50%. Calcd: C, 69.38; H, 4.76; N, 9.51%.

2-Methyl-4-arylthiazole-5-carboxanilides (XIII). A mixture of α-bromoaroylacetanilide (0.01 mol) and thioacetamide (0.8 g, 0.01 mol) in ethanol (30 ml) was refluxed for 3 hr and then poured into water. The resulting solid was collected, washed with water and recrystallized from ethanol. Characteristics of the compounds prepared are given in Table 2.

TABLE 3. 3-BROMO-4-ARYL-2-QUINOLONES

Compound No	Mp, °C	Yield %	Formula	Bromine % Calcd	Bromine % Found
XVIa[a]	228—230	65	$C_{15}H_{10}BrNO$	26.66	26.42
XVIb	288—290	85	$C_{16}H_{12}BrNO$	25.47	25.23
XVIIIc	310—312	60	$C_{15}H_9Br_2NO$	42.20	42.09
XVId	above 320	65	$C_{15}H_9BrN_2O_3$	23.18	23.00

a) Found: C, 59.89; H, 3.40; N, 4.58%. Calcd: C, 60.01; H, 3.33; N, 4.67%.

Conversion of I to 3-Bromo-2-quinolones (XVI). α-Bromoaroylacetanilide (0.005 mol) was added portionwise over a period of 20—30 min to warm concentrated sulfuric acid (10 g, *d*, 1.84, 98%) at 75—80°C, with manual stirring. Heating was continued for another 30 min at 95°C with stirring; the reaction mixture was then cooled and triturated with water. The resulting solid was collected by filtration and washed with 20 ml of aqueous sodium hydroxide (0.5M). Purification of the alkali insoluble product was effected by recrystallisation from ethanol. The mp and elemental analyses of the 3-bromo-2-quinolones prepared are given in Table 3. The same products XVIa—d were obtained when polyphosphoric acid was used in place of sulfuric acid. Anilides If and Ij could not be cyclized and were recovered unchanged when heated with concentrated sulfuric acid. When α-bromobenzoylacet-*p*-anisidide (Id) was similarly treated with the acid reagent, it gave a water solution product which could not be isolated.

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11) G. H. Brown, J. F. Gueras, R. J. Gledhill, C. J. Kibler, F. C. McCrossen, S. M. Parmerter, P. W. Vittum, and A. Weissberger, *J. Amer. Chem. Soc.*, **79**, 2919 (1957).