Nucleophilic Character of Alkyl Radicals. XIV. Homolytic δ-Aminoalkylation of Protonated Quinoxaline

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A new general reaction of wide synthetic interest, involving homolytic δ-aminoalkylation of quinoxaline in acidic medium, is described. Primary and secondary alkylamines, through the corresponding *N*-chloroamines, and tertiary alkylamines, through the corresponding *N*-oxides, are used. The mechanism of the reaction, involving intramolecular hydrogen abstraction by amino radical cations, and the unusual selectivity are discussed in terms of nucleophilic character of the alkyl radicals and of polar effects in the aromatic substitution.

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The homolytic alkylation of protonated heteroaromatic bases is one of the most interesting substitution reactions in heterocyclic chemistry (1). The great synthetic interest is due to the cheap availability of a very large variety of alkyl radicals, the high yields, the simple experimental conditions, and the very high positional and substrate selectivity. The main causes of these favourable characteristics are considered to be the nucleophilic character of the alkyl radicals and the electron-deficiency of protonated heteroaromatic bases (1). Thus the reaction is much less important in the homocyclic aromatic series and with unprotonated heteroaromatic bases. The selectivity of attack is generally limited to the α and γ positions to the protonated heterocyclic nitrogen in agreement with the prevalent influence of the polar factors.

According to this view the diprotonation of a heteroaromatic base, such as quinoxaline, should provide a strongly electron-deficient substrate and therefore a system highly reactive towards nucleophilic radicals. We will show in this paper that protonated quinoxalines are extraordinarily effective traps for alkyl radicals, which permit a large variety of new syntheses by δ-aminoalkylation by primary, secondary and tertiary alkyl amines. A preliminary report has been given previously (2).

Results and Discussion

Quinoxaline is a weak base. The Hammett acidity function (3) (H_0) for the monoprotonated base is 0.5 and for the diprotonated base is -3.02. Therefore, the diprotonation takes place significantly only in a strongly acidic medium.

In order to obtain alkyl radicals in strongly acidic medium we used intramolecular hydrogen abstraction by amino radical cations ($R_3\overset{+}{\underset{\cdot}{N}}$) from primary and secondary *N*-chloroamines and from *N*-oxides of tertiary alkylamines with at least one C-H bond in the δ-position.

The Hofmann-Loffler reaction (4) of protonated *N*-chloroamines has a wide synthetic interest, providing an elegant synthesis of cyclic amines. It is a free radical chain reaction, characterized by the propagation steps of equations (1) and 2).

(1)

$$R\text{-}\overset{+}{\underset{\cdot}{N}}H\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}CH_3 \rightarrow R\text{-}\overset{+}{N}H_2\text{-}CH_2\text{-}CH_2\text{-}CH_2\text{-}\dot{C}H_2$$

I

(2)

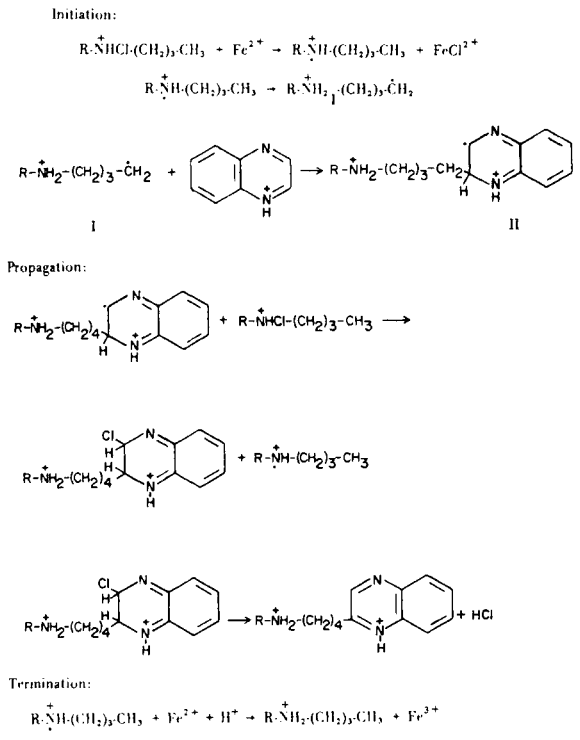
$$R\text{-}\overset{+}{N}H_2\text{-}(CH_2)_3\text{-}\dot{C}H_2 + R\text{-}\overset{+}{N}HCl\text{-}(CH_2)_3\text{-}CH_3 \rightarrow R\text{-}\overset{+}{N}H_2\text{-}(CH_2)_3\text{-}CH_2Cl + R\text{-}\overset{+}{\underset{\cdot}{N}}H\text{-}(CH_2)_3\text{-}CH_3$$

The use of alkyl radicals of type I for the homolytic alkylation of protonated quinoxaline is connected to the possibility of overcoming the chlorine atom transfer from protonated *N*-chloroamine to the alkyl radical [equation (2)], which is a very fast reaction (5). Actually our results indicate that, carrying out the Hofmann-Löffler reaction in the presence of quinoxaline, the attack of the radical I on the heteroaromatic bases successfully competes with the chlorine transfer of equation (2). That is not surprising because the absolute rate constants for the addition of alkyl radicals to monoprotonated quinoxaline

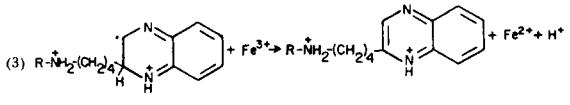
(6) are in the range of 10^6-10^7 M^{-1} sec^{-1} and an even higher rate can be foreseen for diprotonated quinoxaline. The competition of the reaction (2) can be further reduced by working with a low concentration of *N*-chloroamine, which is added slowly as the least component to the reaction mixture containing ferrous salt as initiator.

The results obtained with a variety of amines are given in Table 1. The examples reported clearly indicate the general character of the reaction because primary and secondary, acylic and cyclic amines can be used; the hydrogen abstraction takes place from methyl and methylene C-H bonds giving rise to primary and secondary alkyl radicals. The very clean substitution reaction on quinoxaline is explained, in our opinion, by the chain mechanism shown in Scheme 1.

Scheme 1



The oxidation of the radical adduct II by Fe^{3+} according to equation (3) is considered less important in concentrated sulphuric acid owing to the very low solubility of the ferric salt in the reaction mixture and the very high ionization potential of the protonated radical adduct. The reaction



in fact also takes place in the absence of iron salts, by thermal initiation; in this case the conversions are lower because the kinetic chain appears to be short and the thermal initiation is less effective than the redox initiation.

The results given in Table 1 indicate that the reaction involves interesting synthetic and theoretical aspects. The considerable synthetic interest arises from the high yields, even with high conversion of the base, the large variety of amines, which can be used (practically all the numerous *N*-chloroamines used in the Hofmann-Löffler reaction) (4), the simple experimental conditions, the selectivity and the lack of any simple alternative synthetic route to the same products.

From a mechanistic point of view the most interesting aspect concerns the positional selectivity. This last is very peculiar compared with the results obtained with all the numerous homolytic bases previously investigated (1). The substitution in fact always takes place only in α and γ to the protonated heterocyclic nitrogen. This behaviour is still observed when the reaction is carried out in solution of sulphuric acid at concentrations <40%; only the 2 position of quinoxaline is attacked. At higher concentrations of sulphuric acid the 6 position is also attacked; this is the first case in which the benzene ring

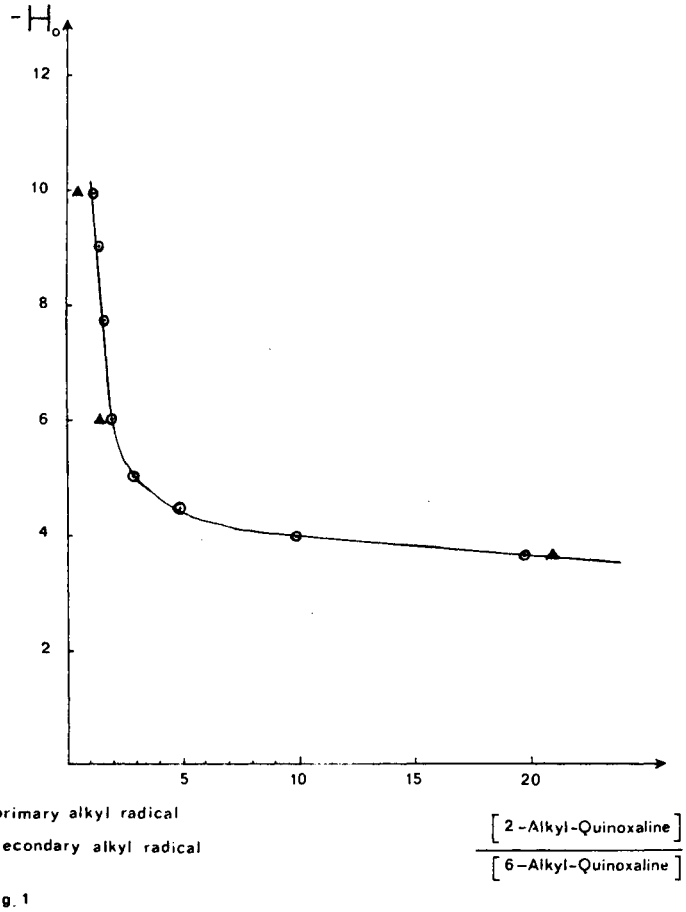
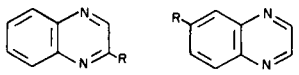


Fig. 1

Table I

δ-Aminoalkylation of Quinoxaline by Alkyl-, Dialkyl-*N*-chloroamines and Trialkylamine *N*-Oxides



1- R = -$(CH_2)_4$-NH-*n*Bu
2- R = -$CH(CH_3)$-CH_2-CH_2-CH_2-NH-*t*-Bu
3- R = $CH(CH_3)$-piperidine
4- R = -$(CH_2)_4$-NH_2
5- R = -$CH(CH_3)$-CH_2-CH_2-CH_2-NH_2
6- R = -CH(Et)-CH_2-CH_2-CH_2-$N(CH_3)_2$

N-Chloroamine	Isomers (a) 2	6	Conversion %	Yield % (b)	Other Isomers	Conditions
Di-*n*-butyl	97	3	10	95	--	(d) RT, 50% H_2SO_4
Di-*n*-butyl	55	45	70	96	5	0°, c. H_2SO_4
Di-*n*-butyl	57	43	28	85	10	(c) 70°, c. H_2SO_4
N-*t*-Butyl-*n*-pentyl	41	59	40	92	3	RT, c. H_2SO_4
N-*t*-Butyl-*n*-pentyl	99	1	35	96	--	RT, 50% H_2SO_4
4-Ethyl-piperidine	38	62	38	82	5	RT, c. H_2SO_4
n-Butyl	58	42	40	90	4	RT, c. H_2SO_4
n-Pentyl	37	63	25	95	2	RT, c. H_2SO_4
N,*N*-Dimethylhexyl *N*-oxide	100	--	48	95	2	RT, 45% H_2SO_4
N,*N*-Dimethylhexyl *N*-oxide	42	58	41	92	9	RT, c. H_2SO_4

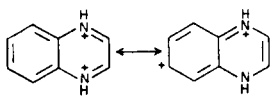
(a) By glc. (b) Based on converted quinoxaline. (c) Without iron salt. (d) RT = room temperature.

Table II

Ratios of the Isomers 2- and 6-Substituted Quinoxaline at Different Acidity

% Sulfuric Acid in Water	Primary Alkyl Radical 2:6	Secondary Alkyl Radical 2:6
96 (concentrated)	1.2	0.5
90	1.4	-
80	1.6	-
70	1.9	1.5
65	2.9	-
60	4.7	-
55	9.6	-
50	19	20
40	>100	>100
30	>100	-

is as reactive as the heterocyclic ring in the homolytic alkylation of protonated polycyclic heteroaromatic bases. The ratio between the 2 and 6 isomers is strongly affected by the acidity of the medium, as the results of Table 2 show. Since the positional selectivity in the substitution of protonated heteroaromatic bases by alkyl radicals is mainly determined by polar factors (1) (nucleophilic character of the radical), we explain this unusual behaviour by diprotonation of quinoxaline and by a large contribution of the resonance form III, characterized by the highest charge separation.



III

In Figure 1 the ratios of the 2 and 6 isomers are plotted against the Hammett acidity function H_0; the large decrease of these ratios with increasing H_0 for values of $H_0 > -5$ and the small variation for $H_0 < -5$ emphasizes the importance of the diprotonation for the activation

Table III

Analytical Data of the Products of δ-Aminoalkylation of Quinoxaline

Compound	Nmr Spectra TMS (internal standard), $CDCl_3$	Mass Spectra m/e	Carbon % Calcd.	Carbon % Found	Hydrogen % Calcd.	Hydrogen % Found	Nitrogen % Calcd.	Nitrogen % Found
1a	8.73 (1H, s), 7.60-8.10 (4H, m, AA'BB') 3.30 (2H, t), 2.60-2.65 (4H, 2t), 2.36 (1H, broad), 1.06-2.05 (8H, m), 0.89 (3H, t)	257 (M^+), 214, 185, 146, 144, 143, 112, 102, 86, 70, 57, 43, 30	74.66	74.76	9.01	8.92	16.33	16.41
1b	8.76 (2H, s), 7.55-8.16 (3H, m?), 2.87 (2 Ht), 2.60-2.66 (4H, 2t), 2.32 (1H, broad), 1.1-2.0 (8H, m), 0.89 (3H, t)	257 (M^+), 214, 172, 158, 144, 143, 112, 86, 30	74.66	74.80	9.01	8.88	16.33	16.34
2a	8.72 (1H, s), 7.6-8.1 (4H, m), 3.14 (1H, sex.), 2.68 (2H, t), 2.35 (1H, br;) 1.4-1.2 (12H, m), 1.4 (3H, d)	271 (M^+), 256, 214, 199, 159, 158, 143, 131, 112, 86, 56, 43, 30	75.23	75.10	9.28	9.35	15.48	15.68
2b	8.76 (2H, s), 7.5-8.2 (3H, m), 2.88 (1H, sex.), 2.68 (2H, t), 2.4 (1H, Br), 1.4-2.0 (13H, m), 1.4 (3H, d).	271, 256, 199, 172, 159, 158, 157, 143, 131, 112, 86, 56, 43, 30	75.23	75.20	9.28	9.37	15.48	15.33
3a	8.73 (1H, s), 7.6-8.1 (4H, m), 3.14 (1H sex.), 2.5-2.8 (5H, m), 2.35 (1H, broad) 1.4-2.0 (4H, m), 1.38 (3H, d)	241 (M^+), 226, 212, 182, 171, 159, 158, 144, 143, 112, 102, 75, 57, 43, 30	74.65	74.81	7.94	8.04	17.41	17.32
3b	8.75 (2H, s), 7.5-8.2 (3H, m), 2.9 (1H, se) 2.5-2.8 (5H, m), 2.4 (1H, broad), 1.4-2.0 (4H, m), 1.38 (3H, s)	241 (M^+), 212, 183, 171, 159, 158, 143, 112, 102, 84, 75, 43, 30	74.65	74.75	7.94	8.01	17.41	17.29
4a	8.75 (1H, s), 7.5-8.2 (4H, m), 4.7 (2H, broad), 3.2 (2H, t), 2.88 (2H, t), 1.5-2.0 (4H, m)	201 (M^+), 183, 182, 171 158, 157, 145, 144, 143, 131, 102, 76, 44, *30*	71.61	71.81	7.51	7.69	20.88	21.02
4b	8.78 (1H, s), 7.6-8.8 (3H, m), 4.8 (2H, broad), 2.96 (2H, t), 2.88 (2H, t), 1.5-2.0 (4H, m)	201 (M^+), 182, 172, 158, 157, 144, 143, 131, 112, 102, 44, 30	71.61	71.60	7.51	7.72	20.88	20.73
5a	8.74 (1H, s), 7.6-8.2 (4H, m), 3.42 (2H broad), 3.16 (1H, sex.), 2.68 (2H, t), 1.4-2.0 (4H, m)	215 (M^+), 198, 197, 172, 159, 158, 157, 144, 129, 85, 56, *30*	72.52	72.68	7.96	7.81	19.52	19.68
5b	8.78 (2H, s), 7.5-8.1 (3H, m), 3.42 (2H broad), 2.86 (1H, sex.), 2.68 (2H, t) 1.4-2.0 (4H, m), 1.4 (3H, d).	215 (M^+), 198, 172, 171, 158, *157*, 144, 131, 103, 77, 44, 30	72.52	72.66	7.96	7.79	19.52	19.41
6a	8.74 (1H, s), 7.6-8.1 (4H, m), 3.0 (1H, q) 2.25 (2H, t), 2.17 (6H, s), 1.1-2.0 (6H, m), 0.9 (3H, t)	257 (M^+), 212, 199, 169, 157, 145, 144, 129, 102, 84, 71, *58*, 44, 30	74.66	74.79	9.01	8.93	16.33	16.52
6b	8.77 (2H, s), 7.5-8.1 (3H, m), 2.7 (1H, q) 2.2 (6H, s), 1.1-2.0 (6H, m), 2.1 (2H, t), 0.8 (3H, t)	257 (M^+), 228, 212, 199, 157, 156, 144, 143, 102, 84, *58*, 30	74.66	74.48	9.01	8.87	16.33	16.47

of the 6 position. The nature of the alkyl radical also somewhat affects the positional selectivity in strongly acidic medium; under the same experimental conditions secondary alkyl radicals increase the attack on position 6 compared with primary alkyl radicals. We ascribe this behaviour to the higher nucleophilic character of the secondary alkyl radicals.

We think therefore that the attack on the 6 position of quinoxaline in strongly acidic medium is not an anomalous behaviour, but it is strictly connected with the electron-deficiency of this position and with the consequent nucleophilic reactivity. An important conclusion is that, whereas the nucleophilic reactivity of the 2 position is much higher than that of the benzene ring in unprotonated and monoprotonated quinoxaline, in diprotonated quinoxaline the nucleophilic reactivity is about the same in both the homocyclic and the heterocyclic ring. Owing to the very high acidic character of the diprotonated quinoxaline (H_0 = -3.02), the nucleophilic reactivity cannot be checked by the classical ionic nucleophilic species, which would only show the deprotonation of the base. This incompatibility does not exist with nucleophilic free-radicals, which allow the manifestation of this novel behaviour of quinoxaline.

δ-Aminoalkyl radicals in strongly acidic medium can also be obtained from tertiary alkylamines (7) through the corresponding *N*-oxides according the Scheme 2.

Scheme 2

$$R_2N\text{-}(CH_2)_3\text{-}CH_2R + 2H^+ + Fe^{2+} \rightarrow$$

$$\downarrow$$

$$O$$

$$R_2\overset{+}{\underset{\cdot}{N}}\text{-}(CH_2)_3\text{-}CH_2R + Fe^{3+} + H_2O$$

$$R_2\overset{+}{\underset{\cdot}{N}}\text{-}(CH_2)_3\text{-}CH_2\text{-}R \rightarrow R_2\overset{+}{N}H\text{-}(CH_2)_3\text{-}\dot{C}H\text{-}R$$

IV

The behaviour of radicals of type IV with quinoxaline is substantially identical to that observed with *N*-chloroamines. There is in this case no possibility of thermal initiation, and the presence of ferrous salt is always necessary. Obviously also the rearomatization of the radical adduct of type III is different; it very probably involves an oxidation by Fe^{3+} according to equation (3) and it is somewhat less clean than the process obtained with *N*-chloroamines. The yields on the whole are good; however, in this case the range of synthetic applications of homolylic δ-aminoalkylation reactions were considerably extended.

Moreover, preliminary results indicate that the reaction can be successfully used with a large variety of other protonated heteroaromatic bases (pyridine derivatives, quinoline, phenazine, pyrazine, pyridazine, cinnoline, phthalazine, pyrimidine, quinazoline, purine and pteridine), so that it can be considered an important general synthesis in the heterocyclic series.

EXPERIMENTAL

^1H Nmr spectra were recorded on Varian A60 (or Varian HA-100) spectrometer operating at 60 HMz (or 100 MHz) with TMS as the internal standard in deuteriochloroform solution. Mass spectra were obtained on a Hitachi-Perkin-Elmer RMu 6D spectrometer at 70 eV by use of an all-glass inlet system. For analytical glc a Hewlett-Packard 5750 G instrument, with flame ionization detector using a 6 foot 1/8 inch steel column, packed with 10% UCC-W-982 on Chromosorb W. a.w. DMCS, 80-100 mexh, was used. For preparative glc a Aerograph A 750 with a 5 foot 1/4 inch i.d. column, packed with 10% UCC 60-80 mesh was used (carrier gas nitrogen at flow rate 150 ml./minutes, temperature: isoterm between 200-230°). Column chromatography were carried out on Kieselgel p.F. 254 (Merk).

Materials.

Quinoxaline, *n*-butylamine, *n*-pentylamine and di-*n*-butylamine were commercial products. 4-Ethylpiperidine (b.p. 156-158°) was prepared in 80% yield by reduction of 4-ethylpyridine with hydrogen over platinium oxide in acetic acid. *N-t*-Butyl-*n*-pentylamine (b.p. 58°/20 mm Hg) was prepared in 79% yield by refluxing *n*-pentyl bromide and *t*-butylamine in DMF (8). *N,N*-Dimethyl-*n*-hexylamine (b.p. 146°) was obtained by refluxing *n*-hexylamine, formic acid and formaldehyde.

All the *N*-chloroamines were prepared as described elsewhere (10,11). The secondary *N*-chloroamines were purified by distillation di-*n*-butyl (b.p. 80°/20 mm Hg), *N-t*-butyl-*n*-pentyl (b.p. 59°/15 mm Hg), 4-ethylpiperidine (b.p. 58°/10 mm Hg); and dissolved in concentrated sulfuric acid. The secondary *N*-chloroamines were used without further purification; the pentane solution of *N*-chloroamine was extracted with concentrated sulfuric acid the acidic layer separated and used after iodometric titration.

N,N-dimethylhexylamine *N*-oxide (m.p. 142°) was prepared starting from the amine and hydrogen peroxide (30% w) (12).

General Procedure for the Alkylation of Quinoxaline.

A solution of *N*-chloroamine (0.05-0.075 mole) in concentrated sulfuric acid (30 ml.) was added dropwise (2-3 hours) at room temperature to a mixture of quinoxaline (0.05 mole), finely powdered ferrous sulfate heptahydrate (0.005 mole) in concentrated sulfuric acid (70 ml.) under vigorous stirring. Stirring was continued for an additional 1-24 hours depending on the chloroamine, to ensure completion. The solution was poured over ice (600 g.) and extracted with chloroform (2 x 150 ml.); most of the unreacted quinoxaline was removed. After alkalinization with 12*N* sodium hydroxide, the solution was extracted with chloroform (2 x 150 ml.). The residue was analyzed by glc or by column chromatography on silica gel, eluent ethyl acetate/methanol 70/30. The results are given in Table 1.

Products.

The analytical data of all compounds isolated are listed in Table III. The 2-substituted derivatives were prepared as pure samples in reactions in 50% sulfuric acid. The 6-substituted derivatives were sometimes separated by column chromatography

but mostly preparative glc was used to isolate pure samples of 2 and 6-derivatives.

Thermal Reaction of Quinoxaline and Di-*n*-butyl-*N*-chloroamine.

A solution of quinoxaline (0.01 mole) and di-*n*-butyl-*N*-chloroamine (0.02 mole) in concentrated sulfuric acid (100 ml.) was heated at 70° for 1 hour. The solution darkened during the reaction and gave some tar; 10% after examination by column chromatography of the chloroform extract. The yield and the conversion are lower than in catalytic reaction (Table I).

Reaction at Different Acidity.

The reactions were carried out under nitrogen at 25° adding to 10 ml. of a solution of quinoxaline (0.1 *M*) and *N*-chloroamine (0.02 *M*) in different mixture of sulfuric acid/water (w/w). finely powdered ferrous sulfate heptahydrate (0.005 *M*) as initiator. The reaction was tested after 1, 3 and 24 hours. The ratio of the products of attack in the 2 and 6 position was unchanged. The results are given in Table II. Glc analysis of the reaction products revealed in all cases the presence of 2-5% of two other compounds arising from the intermolecular hydrogen abstraction by aminium radical of *N*-chloroamine. These products were also obtained by reaction of dimethyl-*N*-chloroamine and di-*n*-butylamine in concentrated sulfuric acid with quinoxaline, and identified as 2- and 6-(3-butylamino)butylquinoxaline, (2:35%, 6:65%).

Reactions of Quinoxaline and *N*,*N*-Dimethylhexylamine *N*-Oxide.

The reaction in 50% sulfuric acid was carried out as described elsewhere for quinoline (7). The reaction in concentrated sulfuric acid was carried out at 70° for 3 hours with the same concentration of the reagents. The results are given in Table I.

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