THE FOUR 6-HALO-7-NITROQUINOXALINES

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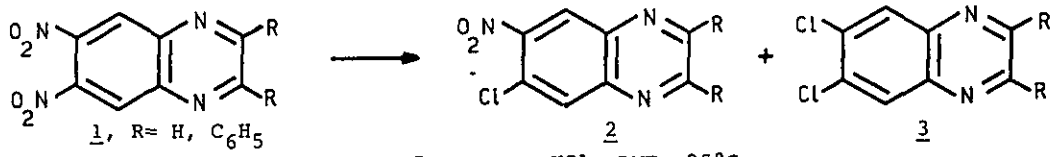
Abstract - The study of relative nucleofugicities of nitro and halogen in quinoxalines required the synthesis of the four 6-halo-7-nitroquinoxalines 2a-d. The fluoro-, chloro- and bromo-derivatives were made from the commercially available or readily accessible 1,2-diamino-4-halobenzenes, using the nitration of the corresponding p-toluenesulfonamides. This scheme failed in the case of the iodo compound because of extensive nitro-deiodination. The synthesis of 6-iodo-7-nitroquinoxaline was finally achieved from m-fluoroiodobenzene by taking advantage of the high reactivity of fluorine, compared to iodine, in 2,4-dinitrohalobenzenes.

The relative nucleofugicities of nitro and halogen[1] in quinoxalines towards various nucleophiles are presently being examined in our laboratory[2,3] ; in a planned extension of this study involving a comparison between the halogens, we needed the title compounds, 6-fluoro-, 6-chloro-, 6-bromo- and 6-iodo-7-nitroquinoxaline (2a-d) respectively.

2,3-Disubstituted 6-chloro-7-nitroquinoxalines were previously reported by Boyer et al.[4] who condensed "impure" 1,2-diamino-4-chloro-5-nitrobenzene with 2,3-butanedione or 9,10-phenanthrenequinone. Our first attempts in this field were based on the finding of Bailey and Wood[5] who observed a facile displacement of a nitro group by a chlorine atom in a quinoline derivative using HCl. Treating 6,7-dinitroquinoxaline 1 with dry hydrogen chloride in DMF at 85°C (Scheme 1) gave, besides unreacted starting material, a mixture of 6-chloro-7-nitroquinoxaline 2b and 6,7-dichloroquinoxaline 3. When it was attempted to force the conditions in order to transform all of the starting material, 3 was the sole product, isolated with a 75% yield. Similar results were obtained with 6,7-dinitro-2,3-diphenyl-quinoxaline.



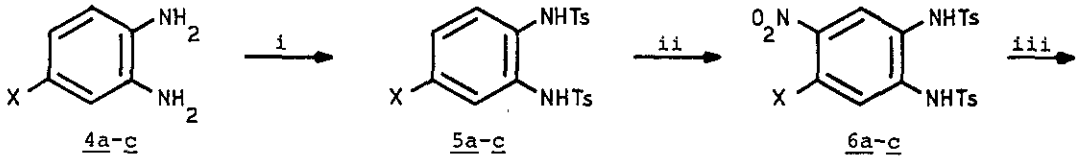
1, R= H, C_6H_5 2 3

Scheme 1. Reagents; HCl, DMF, 85°C

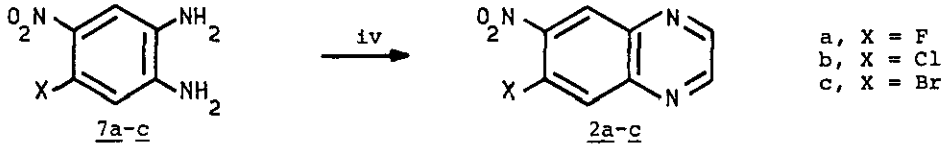
This method suffers several disadvantages, the major one being the need for large scale chromatographic separations. Moreover, this route is precluded for the corresponding methyl derivatives : when 2,3-dimethyl-6,7-dinitroquinoxaline was treated with HCl in DMF, even at room temperature, it gave an insoluble untractable black material.

6-Chloro-7-nitroquinoxaline was recently isolated[6] during our study of the Meisenheimer reaction between phosphoryl chloride and 6-nitroquinoxaline-N_1-oxide; separation of the individual isomers formed in this reaction required careful chromatographic separations which were difficult to scale up preparatively.

In the present paper we first describe a convenient method for the synthesis of 6-fluoro-, 6-chloro- and 6-bromo-7-nitroquinoxaline (2a, 2b and 2c respectively) starting from the corresponding commercially available or readily accessible 1,2-diamino-4-halobenzene. The scheme, involving successively tosylation of the amino groups, nitration, unblocking of the amines and finally condensation with aqueous glyoxal, gave the halo-nitroquinoxalines with an overall yield of almost 50% based on the starting diamines (Scheme 2).



4a-c 5a-c 6a-c



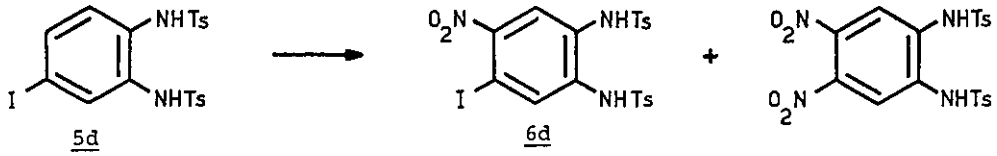
7a-c 2a-c

a, X = F
b, X = Cl
c, X = Br

Scheme 2. Reagents; i: TsCl, C_6H_5N; ii: HNO_3,AcOH; iii: H_2SO_4; iv: OHC-CHO, EtOH

The regioselectivity of the nitration of 4-halo-1,2-di(tosylamino)benzenes, leading almost exclusively to substitution in the 5-position is probably to be related with the size of the tosylamino groups inhibiting ortho attack ; this steric hindrance is apparently large enough to overcome electronic effects as witnessed by the exclusive formation of 4,5-dinitro-1,2-di(tosylamino)benzene on nitration of 1,2-di(tosylamino)benzene[7].

Extrapolation of this scheme to the synthesis of 6-iodo-7-nitroquinoxaline 2d met with unexpected difficulties, as the nitration of 4-iodo-1,2-di(tosylamino)-benzene 5d gave an unseparable 1:3 mixture of the desired iodo-nitro compound 6d besides large amounts of the product originating from a nitro-deiodination. Such a competition between nitro-deprotonation and nitro-deiodination is well documented[8,9], but the experimental conditions are usually quite different from ours.

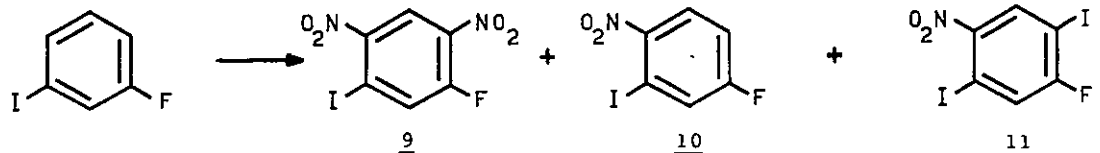


5d 6d

We then tried to react 6-amino-7-nitroquinoxaline[4] with sodium nitrite in mineral acid and to treat the resulting diazonium salt with potassium iodide. In spite of wide variations in experimental conditions[3,10], only trace amounts of the deamination product 6-nitroquinoxaline could be isolated, and no iodinated compound was formed.

Attempts to perform a halogen interchange reaction on 6-fluoro- or on 6-chloro-7-nitroquinoxaline in the presence of potassium iodide, either in refluxing 2-butanone[11] or in hexamethylphosphoric triamide[12], also failed, even in the presence of lithium salts acting as a potential electrophilic catalyst.

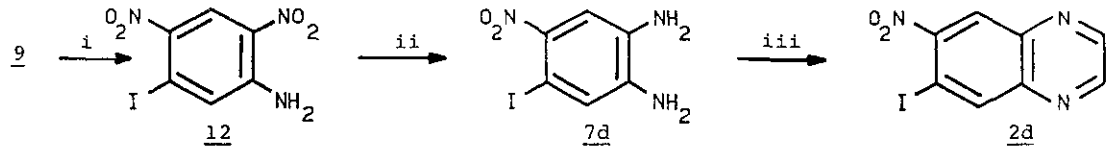
The synthesis of our last target molecule 2d was finally achieved, albeit with a low overall yield (10%), by taking advantage of the large difference in nucleofugicities between fluorine and iodine in S_NAr reactions.



9 10 11

Scheme 3. Reagents ; KNO_3, H_2SO_4

The nitration of m-fluoro-iodobenzene is reported by Schramm[13] to take place in mixed sulfuric-nitric acid. In our hands, these conditions proved disappointing and only poor yields of the desired dinitro compound 9 were obtained. The use of potassium nitrate in concentrated sulfuric acid reproducibly gave, with a 70% overall yield, a mixture containing (relative amounts) 5-iodo-2,4-dinitrofluorobenzene 9 (77%), the mononitration product 3-iodo-4-nitrofluorobenzene 10 (14%) and a trans-iodination product 2,5-diiodo-4-nitrofluorobenzene (9%). The ammonolysis of 9 was straightforward and the reduction of 12, performed with sodium dithionite, gave a mixture of the ortho- and para-diamine. Reacting the crude mixture with aqueous glyoxal (Scheme 4) afforded 6-iodo-7-nitroquinoxaline 2d with a 29% yield based on 12, which could be very easily separated from the unreacted para-diamine.



Scheme 4. Reagents; i: NH_3, EtOH; ii: $Na_2S_2O_4$; iii: OHC-CHO, EtOH

The reactivities of the four 6-halo-7-nitroquinoxalines are now being examined.

EXPERIMENTAL

^{1}H Nmr spectra were recorded in $CDCl_3$ on a Brüker VM250 spectrometer ; the shifts are relative to internal TMS. Mass spectra were obtained with a VG Micromass 70-70F instrument. HPLC's were performed on a Waters Associates apparatus. Tlc were carried out on (Polygram Sil G or Alox N/UV_{254}) precoated 0.25 mm sheets. Melting points measured on a Reichert hot stage microscope, are uncorrected.

Reaction of 6,7-dinitroquinoxaline with HCl.

A. A solution of 6,7-dinitroquinoxaline[3] (4 g, 18 mmol) in N,N-dimethylformamide (DMF) (40 ml) was heated to 85°C, and a rapid stream of dry HCl was introduced. The temperature rose to 100-110°C. After 7 h, the mixture was cooled and poured onto 200mL of iced water, the solid was filtered, rinsed with water, dried and recrystallised from ethanol in the presence of discolorising carbon,

giving pure 6,7-dichloroquinoxaline (2,47 g, 75%)as white leaflets, mp 210-211°C (lit.[14] 208-210°C); m/z 198.

B. 6,7-Dinitroquinoxaline (5 g, 23 mmol) was dissolved in 50 ml of a 4 M solution of anhydrous HCl in DMF and kept at 80-85°C for 12 h. The same work-up as above gave 4 g of a yellow solid containing (relative molar amounts by HPLC or by ^{1}H nmr in CF_3COOD) starting material (31%), 6-chloro-7-nitroquinoxaline 2b (51%) and 6,7-dichloroquinoxaline (18%). The three components could be separated by chromatography on alumina, eluting with chloroform.

1,2-Diamino-4-bromobenzene 4c

Sodium dithionite (9.4 g, 54 mmol) was added to a well stirred hot solution of 4-bromo-2-nitroaniline[15] (1.95 g, 9 mmol) in a mixture of 36 ml of water and 28 ml of ethanol;discoloration occurred instantaneously. After removal of most of the alcohol, the residue was diluted with water and extracted with dichloromethane. The organic phase was then treated with charcoal, dried ($MgSO_4$) and evaporated, giving 4c (1.46 g, 87%) as pink crystals, mp 62-63°C (lit.[15] 62-63°C).

1,2-Diamino-4-fluorobenzene 4a

4-Fluoro-2-nitroaniline (Aldrich, 5 g, 32 mmol) was introduced in 50 ml of methanol containing 12 ml of 50% aqueous phosphinic acid ; cooling to 0°C was followed by the portionwise and very cautious addition of 1.6 g of 10% Pd/C. The suspension was then heated on a steam bath for 20 min, filtered, brought to pH 8 by addition of ammonium hydroxide and extracted with chloroform. The extract was treated with charcoal, dried ($MgSO_4$) and evaporated to dryness, leaving 4a (3.23 g, 84%) ; mp 92-93°C (lit.[16] 91-93°C) ; it was used without further purification.

The following procedures exemplify the method used to convert the diamines 4a-c into the quinoxalines 2a-c (Scheme 2).

4-Fluoro-1,2-di(p-toluenesulfonylamino)benzene 5a

To a stirred solution of 1,2-diamino-4-fluorobenzene 4a (30.6 g, 240 mmol) in 60 ml of dry pyridine was added dropwise a solution of p-toluenesulfonyl chloride (92.7 g, 480 mmol) in 150 ml of dry pyridine, at such a rate that the temperature did not exceed 60°C. The mixture was then heated to 85°C for 18 h, cooled and

poured into 800 ml of iced water containing 200 ml of concentrated aqueous hydrogen chloride. Vigorous stirring was maintained until complete solidification occurred, giving a pink solid which was isolated by filtration, washed with water and pressed dry. Crystallisation from aqueous acetic acid (1:9) gave 5a (100.2 g, 95%) as beige needles; mp 203-204°C ; m/z 434.

5b (yield : 85%) ; mp 206-207°C ; m/z 450

5c (yield : 94%) ; mp 213-214°C ; m/z 494

4-Fluoro-5-nitro-1,2-di(p-toluenesulfonylamino)benzene 6a

About one third of a solution of fuming nitric acid (7 ml) in glacial acetic acid (10 ml) was added under vigorous stirring to a solution of 5a (30 g, 70 mmol) in acetic acid (120 ml) at 60°C. After the initial reaction, addition was completed at such a rate that the temperature remained below 65°C. The thick slurry was maintained at the same temperature for a further 40 min, then cooled and filtered. Crystallisation from ethanol gave the fluoro-nitro compound 6a (23.1 g, 70%) as fine yellow needles, m/z 479. Analytical data for 6a, 6b and 6c are collected in Table 1. 6b : m/z 495 ; 6c : m/z 540.

1,2-Diamino-4-fluoro-5-nitrobenzene 7a

The preceding fluoro-nitro compound 6a (53.8 g, 112 mmol) was heated in concentrated sulfuric acid (120 ml) and water (12 ml) on a steam bath (85°C) for 30 min. The material dissolved progressively while the medium became darker. After cooling, the brown mixture was poured into water (3 l) and gently warmed until the yellow salt had dissolved. After cooling, the red solution was made alkaline (pH 9) with ammonium hydroxide, affording an orange precipitate which was filtered, rinsed with water and dried. Recrystallisation from water or from aqueous ethanol, in the presence of charcoal, gave 7a (17.2 g, 90%) as orange-red needles, mp 195-196°C; m/z 171.

7b (yield : 93%) ; mp 210-212°C ; m/z 187

7c (yield : 90%) ; mp 218-219°C ; m/z 231

6-Fluoro-7 nitroquinoxaline 2a

A 30% aqueous glyoxal solution (18 ml) was added dropwise to a stirred suspension of 7a (10 g, 58 mmol) in hot ethanol (300 ml). The reaction mixture was then refluxed for 1 h. After the starting material had disappeared, as monitored

by tlc (silica gel, hexane-AcOEt, 5:5), the mixture was cooled and the resulting orange precipitate was filtered ; crystallisation from ethanol, in the presence of charcoal, gave 2a (9.1 g, 81%) as yellowish leaflets, mp 166-167°C ; m/z 193. Analytical and ^1H nmr data for 2a, 2b and 2c are collected in Tables 1 and 2, respectively.

Table 1. Analytical data for 1,2-di(tosylamino)-4-halo-6-nitrobenzenes (6a-c) and for 6-halo-7-nitroquinoxalines (2a-d).

	Compound (Formula)	Yield %	Recrystal. Solvent	mp (°C)	Found % (required) C	H	N
6a	$C_{20}H_{18}FN_3O_6S_2$	70	EtOH	226-228	50.0 (50.1	3.8 3.8	8.7 8.8)
6b	$C_{20}H_{18}ClN_3O_6S_2$	75	aq. AcOH	239-240	48.3 (48.45	3.7 3.7	8.4 8.5)
6c	$C_{20}H_{18}BrN_3O_6S_2$	79	AcOH	243-245	44.4 (44.4	3.3 3.4	7.75 7.8)
2a	$C_8H_4FN_3O_2$	81	EtOH	166-167	49.9 (49.75	2.1 2.1	21.9 21.8)
2b	$C_8H_4ClN_3O_2$	83	Toluene	212-214	45.9 (45.8	1.75 1.9	20.2 20.1)
2c	$C_8H_4BrN_3O_2$	74	n PrOH	217-218	37.9 (37.8	1.6 1.6	16.4 16.5)
2d	$C_8H_4IN_3O_2$	29*	n PrOH	235-236	32.0 (31.9	1.35 1.3	14.0 14.0)

*From 5-iodo-2,4-dinitroaniline 12.

Table 2. ^1H nmr data for the four 6-halo-7-nitroquinoxalines ($CDCl_3$, shifts in ppm downfield from internal TMS)[a].

X	F[b]	Cl[c]	Br[d]	I[e]
H_2 and H_3	8.99 and 8.98	8.98 and 8.97	8.99 and 8.98	8.98 and 8.96
H_5	7.99	8.33	8.55	8.53
H_8	8.85	8.59	8.54	8.84

(a) The shifts for H_2 and H_3 may be inverted ; (b) J_{2-3} 1.9 Hz ; J_{5-F} 10.8 Hz ; J_{8-F} 7.5 Hz ; (c) J_{2-3} 1.8 Hz ; (d) J_{2-3} 1.9 Hz ; (e) J_{2-3} 1.8 Hz.

5-Iodo-2,4-dinitrofluorobenzene 9

m-Fluoro-iodobenzene (Sigma, 10 g, 45 mmol) was added dropwise to a solution of potassium nitrate (10 g, 100 mmol) in 50 ml of concentrated sulfuric acid at 20°C, allowing the autogenous temperature to rise to 65°C. The flask was then placed in a bath thermostated at 145°C (the inner temperature was then 135°C) and kept for 4.5 h. After cooling, the viscous mixture was slowly poured onto ten times its volume of crushed ice. The oily solid which separated was extracted three times with chloroform, the organic phase was washed free of acid, dried and evaporated to dryness, leaving 10 g of a sticky orange-yellow solid containing (relative molar amounts by HPLC) 5-iodo-2,4-dinitrofluorobenzene 9 (77%), 3-iodo-4-nitrofluorobenzene 10 (14%) and 2,5-di-iodo-4-nitrofluorobenzene 11 (9%). Separation was performed by chromatography over alumina with hexane-acetone (8:2). A sample of 5-iodo-2,4-dinitrofluorobenzene, recrystallised from methanol-water (1:1) had mp 98-100°C (lit.[13] 100-101°C) ; δ_H 8.08 (1H, d, 6-H), 8.67 (1H, d, 3-H) ; J_{3-F} 6.8 Hz, J_{6-F} 9.4 Hz ; m/z 312 (base peak).

10 : liquid. δ_H 7.21 (1H, ddd, 6-H), 7.76 (1H, dd, 2-H), 7.96 (1H, dd, 5-H). J_{2-6} 2.6 Hz, J_{5-6} 9.1 Hz, J_{5-F} 5.1 Hz, J_{6-F} 7.2 Hz, J_{2-F} 7.7 Hz. m/z 267 (base peak).

11 : mp 92-94°C. δ_H 7.69 (1H, d, 6-H), 8.29 (1H, d, 3-H). J_{3-F} 5.6 Hz, J_{6-F} 6.8 Hz. m/z 393 (base peak). The ^{13}C nmr spectrum confirms the relative position of the substituents, by assuming the additivity of substituent-induced chemical shifts[17]. Found (δ/ppm) : C-1, 163.2 ; C-2, 80.9 ; C-3, 136.1 ; C-4, 150 (broad, weak) ; C-5, 86.5 ; C-6, 128.4. Calculated for 2,5-diiodo-4-nitrofluorobenzene : C-1, 182.1 ; C-2, 82.3 ; C-3, 136.6 ; C-4, 156.2 ; C-5, 91.4 ; C-6, 128.4. Furthermore, the J_{C-F} splittings are found to be 259.0 Hz, J_{2-F} 27.8 Hz and J_{6-F} 27.8 Hz, and are clearly resolved, showing that the NO_2 group is not ortho to the fluorine atom.

5-Iodo-2,4-dinitroaniline 12

Dry ammonia gas was passed through ethanol (350 ml) for 20 min. The preceding crude nitration mixture (23.7 g) was introduced in one portion under stirring, and bubbling was maintained for 3 h ; the initially yellow solution became progressively orange, and a precipitate formed. Ammonia was then allowed to evaporate, and most of the solvent was removed under vacuo ; the resulting solid was filtered and rinsed with water, giving 19.1 g of impure 12 which, after two recrystallisa-

tions from aqueous ethanol, showed mp 197-198°C. Found : C, 23.4 ; H, 1.3 ; N, 13.5%. $C_6H_4IN_3O_4$ requires C, 23.3 ; H, 1.3 ; N, 13.6%. δ_H $(CD_3)_2SO$ 7.77 (1H, s, 6-H), 8.15 (2H, br s, NH_2), 8.68 (1H, s, 3-H). m/z 308 (base peak).

1,2-Diamino-4-iodo-5-nitrobenzene 7d

A fine suspension of 12 (10 g, 32 mmol) in ethanol (500 ml) and water (100 ml) was heated to 75-80°C, and sodium dithionite (22.5 g, 130 mmol) was introduced under vigorous stirring. The mixture rapidly turned from yellow to red and gave rise to a gas evolution. After 45 min, a new portion of dithionite (8.4 g, 48 mmol) in water (50 ml) was added, and the reaction was monitored by tlc (alumina, ethyl acetate). After 2 h, most of the alcohol was evaporated ; the resulting brown-red solid was filtered and washed thoroughly with water, giving a crude mixture of the isomeric ortho- and para-diamines (5.3 g, 19 mM) which was used as such in the next step. A pure sample of 7d was obtained after recrystallisations from methanol ; mp 206-207°C ; DMSO-d_6, δ_H 5.18 (2H, br s, NH_2), 5.96 (2H, br s, NH_2), 7.11 (1H, s, 3-H), 7.41 (1H, s, 6-H) ; m/z 279 (base peak).

6-Iodo-7-nitroquinoxaline 2d

Glyoxal (4.5 ml of a 30% aqueous solution) was added dropwise to a stirred solution of 5.1 g of the impure diamine 7d in 250 ml of ethanol. The disappearance of the diamine was followed by tlc (alumina, $CHCl_3$) ; after 45 min, the mixture was cooled and the resulting precipitate collected by filtration. Crystallisation from n-propanol in the presence of charcoal gave 6-iodo-7-nitroquinoxaline 2d (2.8 g, 9.3 mmol) as bright yellow needles. The yield, based on 12, was 29%. Mp 235-236°C ; m/z 301 (base peak). Analytical and ^1H nmr data are collected in Tables 1 and 2, respectively.

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REFERENCES

1) J.R. Beck, Tetrahedron, 1978, 34, 2057.

2) R. Nasielski-Hinkens, D. Pauwels, and J. Nasielski, Tetrahedron Lett., 1978, 2125.

3) R. Nasielski-Hinkens, M. Benedek-Vamos, and D. Maetens, J.Heterocyclic Chem., 1980, 17, 873.

4) J.H. Boyer, R.S. Buriks, and U. Toggweiler, J. Am. Chem. Soc., 1960, 82, 2213.

5) D.M. Bailey and D. Wood, J.Heterocyclic Chem., 1974, 11, 229.

6) R. Nasielski-Hinkens, E. Vandevijver, and J. Nasielski, Bull. Soc. Chim. Belg., 1986, 95, 663.

7) G.W.H. Cheeseman, J. Chem. Soc., 1962, 1170.

8) R.B. Moodie and K. Schofield, Acc. Chem. Res., 1976, 9, 287.

9) J. Johansson, Acta Chem. Scand., Ser. B, 1981, 35, 723.

10) A.J. de Koning, Recl. Trav. Chim. Pays-Bas, 1981, 100, 421.

11) P.J. Lont and H.C. van der Plas, Recl. Trav. Chim. Pays-Bas, 1972, 91, 850.

12) P.I. Svirskaya, V. Yededia, C.C. Leznoff, and J.M. Miller, J.Heterocyclic Chem., 1985, 22, 149.

13) H.J. Schramm, Hoppe-Seyler's Z. Physiol. Chem., 1972, 353, 874.

14) Y. Ahmad, M.S. Habib, M. Ikram Qureshi, and A. Farooqi, J. Org. Chem., 1973, 38, 2176.

15) W. Czuba and H. Poradowska, Rocz. Chem., 1974, 48, 1233.

16) K. Takatori, Y. Yamada, T. Arai, and R. Nakasawa, Yakugaku Zasshi, 1958, 78, 108 ; Chem. Abstr., 1958, 52, 11013^{e}.

17) E. Pretsch, T. Clerc, J. Seibl, W. Simon, Tables of Spectral Data for Structure Determination of Organic Compounds, Springer Verlag, 1983, C120.

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