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While 2-acetyl and 2-benzoyl-3-aminobenzofurans did not react with hydrazine, monomethyl- and *N,N*-dimethylhydrazine to give the related hydrazones, their 3-*N*-(*p*-toluenesulfonyl) derivatives afforded them smoothly in good yields. Depending upon reaction conditions, products arising from hydrazone cyclization to benzofuropyrazoles and/or from furan ring cleavage at the C2-O bond to give 5-(2-hydroxyphenyl)pyrazoles were also formed. The formation of these products depends upon hydrazones configuration and is discussed. Only (*E*)-isomers appear to undergo furan ring opening. In acidic media at room temperature either the hydrazones or the monomethylhydrazones gave the same related α -azines. Microanalyses, ir, uv, ¹H-nmr and ms spectra are in agreement with the proposed structures.

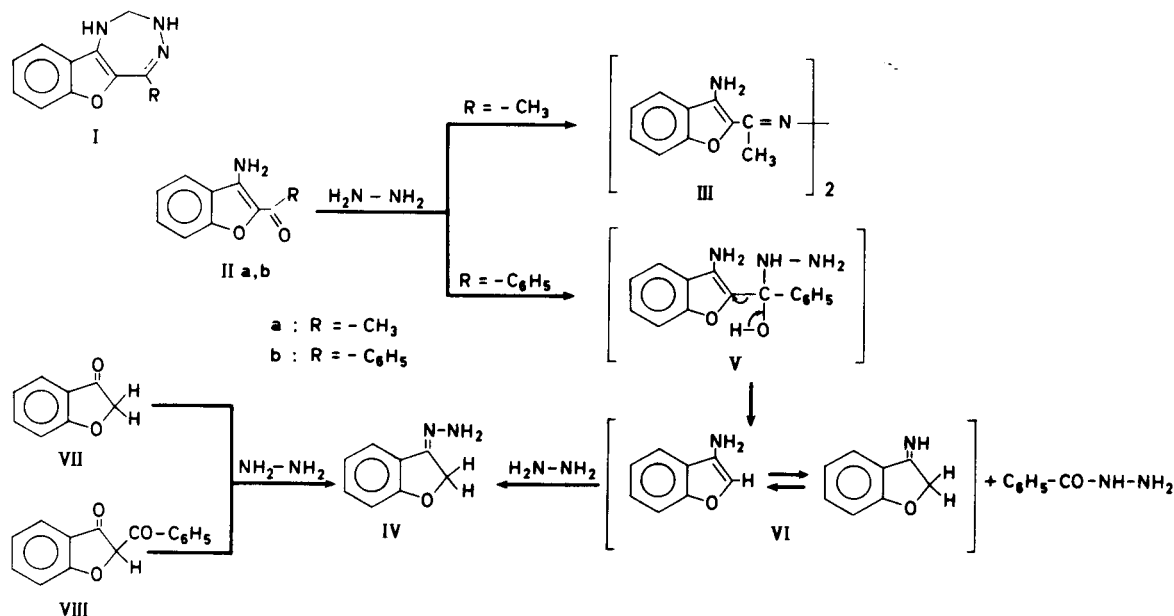
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The reaction of 2-acetyl and 2-benzoyl-3-aminobenzofuran IIa,b [2] with hydrazine, aimed at preparing the related hydrazones as starting materials for the synthesis of derivatives having the still unknown 2,3-dihydro-1*H*-benzofuro[3,2-*e*][1,2,4]triazepine system (I), gave instead only the α -azine of 2-acetyl-3-aminobenzofuran (III), the 3(2*H*)-benzofuranone hydrazone (IV) and benzoylhydrazine when the reaction was carried out in refluxing ethylene glycol monomethyl ether. Under milder conditions (refluxing ethanol), the reaction led to recovery of unreacted IIa (only very poor yields of the azine III were obtained) and IIb.

In boiling ethylene glycol monomethyl ether no reaction of IIa and IIb with *N,N*-dimethylhydrazine was observed (Scheme 1).

The formation of both the hydrazone IV and benzoylhydrazine may be explained by the cleavage of the benzoyl group from the benzofuran C2 carbon atom in the adduct V (not isolated) to yield the 3-aminobenzofuran VI. This compound, still unknown and not isolated, is postulated to exist, like its well-known analogue 3(2*H*)-benzofuranone VII [3], predominantly as the tautomeric imino-dihydrobenzofuran which is quickly hydrolysed to the oxo-compound VII. Attempts to prepare 2- and 3-aminobenzofurans were unsuccessful [4,5].

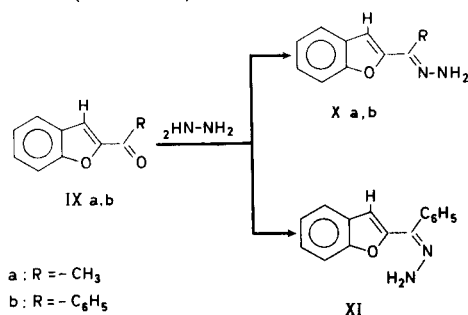
It is not surprising, therefore, that the behaviour of IIa and IIb towards hydrazine is quite similar to that reported for their analogues 2-acetyl- and 2-benzoyl-3(2*H*)-benzofuranones. While the first one gave the related α -azine similar to III, the second (VIII) yielded the same 3(2*H*)-benzo-



Scheme 1

furanone hydrazone IV for which a melting point of 105–106° was reported [6]. In our hands, the same product IV, obtained also by reaction of hydrazine either with the 3(2*H*)-benzofuranone VII or with the mentioned 2-benzoyl-3(2*H*)-benzofuranone VIII, presented an ill-defined melting point ranging from 125° to 165° because of its instability and because of molecular transformations occurring during the heating, although its nmr and ms spectra agreed with the reported ones [6].

By way of contrast, 2-acetyl and 2-benzoylbenzofurans IXa,b with hydrazine in refluxing ethanol afforded smoothly the expected hydrazones. From IXa only the hydrazone Xa [7] was obtained, while from IXb [8] two isomeric hydrazones Xb and XI resulted, whose ms spectra presented the same molecular peak and the same fragmentation pattern (Scheme 2).



Scheme 2

Comparison of ¹H-nmr spectra of Xb and XI allowed the assignment of their configurations. In the spectrum of the former the phenyl ring, "sandwiched" between the benzofuran moiety and the -NH₂ group, is represented by a unique sharp peak at δ 7.47 while the corresponding phenyl ring of the latter gives two main peaks at δ 7.53 and 7.33, thus revealing its conjugation with the carbon-nitrogen double bond (the *ortho* hydrogens are shifted downfield). This finding is in full agreement with a published ¹H-nmr study on isomeric (*E*)- and (*Z*)-*N,N*-dimethylhydrazones of a series of alkyl phenyl ketones [9]. According to this study, the configuration to be assigned should be the (*E*)-configuration to the hydrazone Xb and the (*Z*)-configuration to its isomer XI.

Moreover, the fact that only one hydrazone was obtained from the methyl ketone IXa while two resulted from the phenyl ketone IXb, appears to be a consequence of the bulk difference between the methyl group and the benzofuran moiety, which reasonably should favour the formation of the (*E*)-isomer Xa.

Finally, uv absorption spectra (10⁻²*M* ethanolic solutions) of the (*E*)-isomers Xa and Xb resemble closely, while that of XI shows remarkable differences (see Experimental).

The observed difference of reactivity between ketones II and IX could be explained by the "vinylogue" amidic character of the amino and carbonyl functions, enhanced by conjugation with the benzofuran moiety, which might account for a diminished polarizability of the C=O bond and hence for its failure to react with hydrazine in compounds II. Actually, while for the methyl ketone IIa, acidic conditions led to reaction with hydrazine and to formation of the α-azine III, under the same conditions a very complex reaction mixture resulted from the phenyl ketone IIb.

Two strong sharp ν NH bands at 3490 and 3360 cm⁻¹ and a very strong ν CO band (at 1650 cm⁻¹ for IIa, 1625 cm⁻¹ for IIb) are showed by 2.5 × 10⁻²*M* and 2.5 × 10⁻³*M* carbon tetrachloride solutions, while in their nmr spectra (deuteriochloroform solutions) the peak (2H) of the amino group has a chemical shift of 6.47 (IIa) and 6.12 (IIb) ppm, thus revealing that no intramolecular hydrogen bonded structure such as A or B contributes to the actual one.

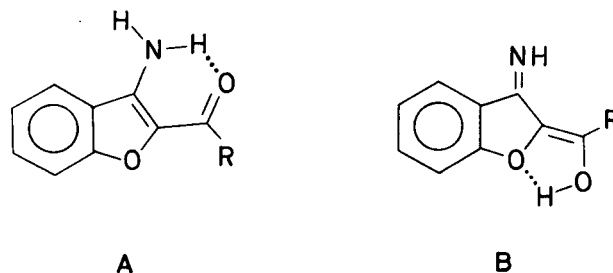
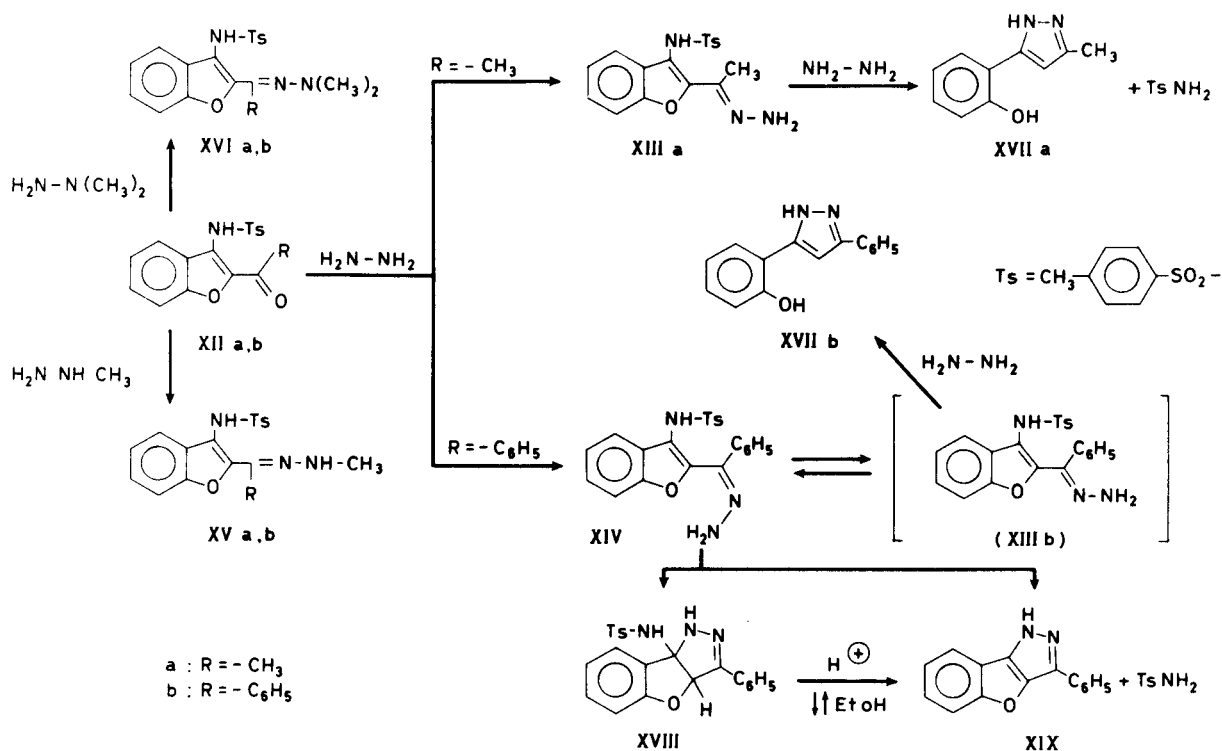


Figure 1

This "vinylogue" amidic character and/or the poor polarizability of the carbonyl group appears to be lost in the *N*-(*p*-toluenesulfonyl) derivatives XII of II, which gave smoothly with hydrazine, *N*-methylhydrazine and *N,N*-dimethylhydrazine under mild conditions (ambient temperature or 1 hour refluxing ethanol) the related hydrazones XIII, XIV, XV and XVI. Prolonged reaction times lowered the yields of the hydrazones XIII and XIV and gave rise to other products which were isolated and identified (Scheme 3).

The fact that from both the methyl ketone XIIa and the phenyl ketone XIIb the corresponding 5-(2-hydroxyphenyl)-3-phenylpyrazole (XVIIb) [11] were obtained, but only from XIIb also the 3-phenyl-8b-*p*-toluenesulfonylamido-3a,8b-dihydro-1*H*-benzofuro[3,2-*c*]pyrazole (XVIII) and the 3-phenyl-1*H*-benzofuro[3,2-*c*]pyrazole (XIX) [6] resulted, suggests the occurrence in the reaction mixture of only one intermediate hydrazone XIIIa in the first case, but of both isomeric hydrazones XIIIb and XIV in the second, although only one hydrazone could be isolated in both cases.

This suggestion, in agreement with the above reported isolation of the hydrazones X and XI (Scheme 2), leads to the reasonable conclusion that the products obtained are



Scheme 3

dependent on the configuration of the hydrazones formed.

Indeed, Ocksay and Vargha [12] prepared a number of (*Z*)-"syn" and (*E*)-"anti"-furan ketoximes and showed that the reactions of benzofuryl-2-methyl- and benzofuryl-2-phenylketoxime *p*-toluenesulfonates with ethanol proceeded according to their configurations: while the (*E*)-derivatives underwent C2-O ring opening and afforded rearrangement products, the (*Z*)-phenylketoxime underwent Beckmann rearrangement yielding benzofuran-2-carbonic acid anilide, whereas the (*Z*)-methylketoxime remained unchanged [13,14]. In no instance with the (*Z*)-isomers was the furan C2-O bond cleavage observed.

The reasons suggested by these authors to explain the stereospecificity of the reaction of the furyl-2-ketoximes [13] appear to fit in also with the here reported benzofuryl hydrazones. In the (*E*)-benzofurylhydrazones XIII both steric and electrostatic factors allow the carbon-nitrogen double bond to lie in the same plane of the benzofuran moiety, thus giving rise to a complete conjugation and hence to electron displacement from the electron-rich hydrazine nitrogen atoms towards the tosylamido group. This mesomeric effect would induce the furan C2-O bond to be electron deficient so that it would undergo nucleophilic attack by hydrazine and hydrogenolytic cleavage under these reaction conditions.

Such coplanarity and conjugation with the benzofuran system appears to be rather difficult to achieve in the (*Z*)-hydrazone XIV because of steric hindrance and/or electrostatic repulsions between the NH_2 group and the furan oxygen atom. In this case, both electron distribution and steric hindrance would protect and make the same C2-O bond stronger, and as a consequence the cyclization to XVIII and XIX is determined.

We therefore assign the isolated hydrazone XIIIa the "anti" benzofuran configuration (*E*). What concerns the other isolated hydrazone XIV, its nmr spectrum shows two main peaks at δ 7.53 and 7.38 for the phenyl $\text{-C}_6\text{H}_5$ ring, thus indicating its "syn" benzofuran configuration (*Z*) [9].

Indeed, when XIIIa was allowed to react with 0.25 moles hydrazine in refluxing ethylene glycol monomethyl ether, only the pyrazole XVIIa could be isolated, while extensive decomposition and formation of tar products was observed. By way of contrast, XIV in refluxing ethanol with 0.25 moles hydrazine afforded smoothly the benzofuropyrazole XVIII and unreacted XIV as the main products. Longer reaction times gave rise also to the pyrazole XVIIb, possibly through isomerization of XIV to XIIIb by an addition-elimination mechanism [15].

The structure of the 3-phenyl-8-*p*-toluenesulfonylam-

ido-3a,8b-dihydro-1*H*-benzofuro[3,2-*c*]pyrazole (XVIII) was established by acid catalyzed elimination of *p*-toluenesulfonamide and formation of the known benzofuropyrazole XIX [6]. The nmr and ms spectra are also in agreement with the proposed structure (see Experimental).

The azines XX and XXII were easily obtained by simple addition of a few drops of hydrogen chloride to an ethanolic solution of the related hydrazones or *N*-methylhydrazones and allowing them to react at room temperature. It is noteworthy that the same azine XXa resulted from either the hydrazones XIIIa or the *N*-methylhydrazone XVa, and the same azine XXIIa could be obtained from both the hydrazone Xa and its *N*-methyl derivative XXI (see Experimental).

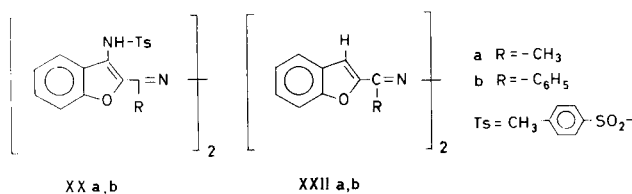


Figure 2

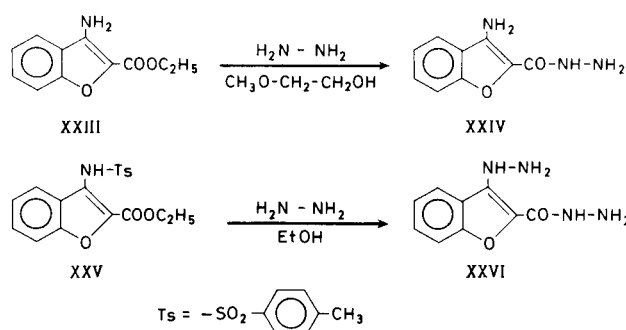
To our knowledge, in the chemical literature, only the isolation of the corresponding azine among the reaction products of 2-ethyl-3-formylbenzofuran with *N*-methylhydrazine has been reported [16].

The only observed differences were reaction times and yields. Starting from the hydrazones, the azines were quickly formed in good to quantitative yields with the liberation of one mole of hydrazine, while longer reaction times were needed and much lower yields resulted when the starting materials were the *N*-methylhydrazones.

In the latter case, *N*-methylhydrazine was identified among the reaction products. It seems therefore reasonable to conclude that the reaction of 2-acetyl-3-aminobenzofuran (IIa) with hydrazine in acidic media to yield the azine III (see Scheme 1) proceeds *via* the related non-soluble hydrazone.

On the contrary, it is not surprising that the same azine XXIb has been obtained from both the (*E*)- and (*Z*)-hydrazones Xb and XI, since isomeric (*Z-E*) equilibria are known to occur in solution or upon addition of a trace of acid [17].

Finally, 3-amino-2-ethoxycarbonylbenzofuran (XXIII), like IIa and Iib, reacted with some difficulty with hydrazine. Only in refluxing ethylene glycol monomethyl ether could the hydrazide XXIV be obtained. By way of contrast, its *N*-tosyl derivative XXV afforded smoothly with hydrazine in refluxing ethanol the 3-hydrazinohydrazide XXVI and *p*-toluenesulfonamide (Scheme 4). Under the same conditions, no reaction of XXIII with *N,N*-dimethylhydrazine occurred.



Scheme 4

EXPERIMENTAL

Melting points were determined on a Kofler hot stage and are uncorrected. The ir spectra were obtained using a Perkin-Elmer 580 spectrophotometer (carbon tetrachloride or deuteriochloroform solutions). The ¹H-nmr spectra were recorded on a Varian T-60 spectrometer, using tetramethylsilane as a reference (ppm are given in δ units). The uv spectra were recorded on a Perkin-Elmer 402 spectrometer. Electron ionization ms were taken with a LKB 2091 equipped with a digital PDP 11 data processing system; samples applied by direct inlet, and probe usually heated from 25-200°, 70 eV. Column chromatography was carried out using silicagel (Merck, 70-250 mesh ASTH) as the adsorbent. Thin layer chromatography was performed on silica gel plates (Merck GF₂₅₄).

α-Azine of 2-Acetyl-3-aminobenzofuran (III).

A mixture of 2-acetyl-3-aminobenzofuran (IIa) [2] (3.5 g, 0.02 mole), 98% hydrazine hydrate (1.5 g, 0.03 mole) and acetic acid (0.1 ml) was refluxed 6 hours in ethanol (30 ml). The azine III separated as a deep red solid on cooling, yield 2.5 g 66%, mp 325-238° dec. The compound is practically insoluble in all commonly used organic solvents; ms: 347 (M+1, 27), 346 (M*, 100), 330 (17), 315 (29), 226 (13), 185 (10), 174 (19), 173 (19), 159 (26), 158 (23), 146 (27), 132 (18), 131 (12), 130 (53), 104 (51), 103 (38), 102 (14), 77 (61), 76 (22), 66 (22), 51 (15), 39 (12).

Anal. Calcd. for C₂₀H₁₈N₄O₂: C, 69.35; H, 5.24; N, 16.18. Found: C, 69.34; H, 5.26; N, 16.39.

3(2*H*)-Benzofuranone Hydrazone (IV).

a) From 3-Amino-2-benzoylbenzofuran (Iib).

Compound Iib (2.4 g, 0.01 mole) and 98% hydrazine hydrate (2 g, 0.04 mole) were refluxed 12 hours in ethylene glycol monomethyl ether (10 ml). The mixture was then evaporated to dryness and the resulting residue crystallized from ethanol and 0.9 g of product (61%), mp 125-165° was obtained. When this residue was chromatographed on an alumina column eluting with chloroform the yield was lower because of light and/or column-induced decomposition of the product. Evaporation of ethanolic crystallization mother liquor gave a residue which was purified by silicagel column chromatography eluting with ethyl acetate and 1.1 g of benzoyl hydrazine (81%), mp 113-115° was thus obtained.

b) From 3(2*H*)-Benzofuranone (VII).

Compound VII [3] (1 g) and 98% hydrazine hydrate (1.5 g) with a few drops acetic acid were refluxed 1 hour in ethanol (20 ml). Crystals separated on cooling, which were collected, rinsed with ethanol and dried, yield 0.7 g (64%).

c) From 2-Benzoyl-3(2*H*)-benzofuranone (VIII).

The compound was prepared as described in the literature [6]; nmr (DMSO-*d*₆): δ 7.40 (m, aromatics, 2H), 7.0 (m, aromatics, 2H), 6.28 (s, -NH₂, 2H), 5.07 (s, CH₂, 2H); ms: 149 (M+1, 11), 148 (M*, 79), 119 (50), 102 (12), 92 (14), 91 (100), 90 (14), 89 (15), 77 (11), 76 (12), 75 (13), 65 (24), 63 (22), 51 (18), 50 (14), 39 (18).

Anal. Calcd. for $C_6H_8N_2O$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.80; H, 5.41; N, 19.11.

Acetyl Derivative of IV.

This compound had mp 190-194° (from ethanol); nmr (DMSO- d_6): δ 10.50 (broad d, -NH-CO, 1H), 7.37 (m, aromatics, 2H), 6.97 (m, aromatics, 2H), 5.03 (s, -CH₂, 2H), 2.20 and 2.00 (two singlets, -CO-CH₃ of (*E*)- and (*Z*)-isomers in about 1:1 molar ratio, 3H all); ms: 190 (M⁺, 46).

Anal. Calcd. for $C_{10}H_{10}N_2O_2$: C, 63.15; H, 5.30; N, 14.73. Found: C, 62.87; H, 5.33; N, 14.91.

Hydrazone of 2-Acetylbenzofuran (Xa).

This compound had mp 144-147° from benzene (lit [7] 146°); nmr (deuteriochloroform): δ 7.33 (m, aromatics, 4H), 6.77 (s, C3-H, 1H), 5.52 (broad, -NH₂, 2H), 2.10 (s, CH₃, 3H); uv (0.005 mmole % in ethanol): λ max 224 (o.d. = 1.15) and 305 nm (o.d. = 1.37), λ min 250 nm.

(*E*)- and (*Z*)-Hydrazones of 2-Benzoylbenzofuran (Xb and XI).

Compound IXb [8] (1.5 g) and 98% hydrazine hydrate (1.5 g) were refluxed 12 hours in ethylene glycol monomethyl ether (10 ml). After solvent removal, the viscous residue obtained was chromatographed on a silicagel column eluting with ethyl acetate-*n*-hexane (1:3) mixture. The (*Z*)-isomer was eluted first (0.5 g, 32%, mp 88-90° from benzene-cyclohexane), followed by the (*E*)-isomer (0.8 g, 51%, mp 60° from chloroform).

(*Z*)-Isomer.

This compound had nmr (deuteriochloroform): δ 7.40 (m, aromatics, 9H, two main peaks at 7.53 and 7.33 for the C₆H₅ group), 6.87 (s, C3-H, 1H), 6.57 (broad, -NH₂, 2H); uv (0.005 mmole % in ethanol): λ max 235 (o.d. = 1.42), 264 (o.d. = 1.47) and 310 nm (o.d. = 1.49), λ min 245 and 285 nm.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.30; H, 5.16; N, 12.00.

(*E*)-Isomer.

This compound had nmr (deuteriochloroform): δ 7.40 (m, aromatics, 9H, one main peak at 7.47 for the C₆H₅ group), 6.33 (s, C3-H, 1H), 5.70 (broad, -NH₂, 2H); uv (0.005 mmole % in ethanol): λ max 224 (o.d. = 1.18) and 310 nm (o.d. = 0.81); λ min 248 nm.

Anal. Calcd. for $C_{15}H_{12}N_2O$: C, 76.25; H, 5.12; N, 11.86. Found: C, 76.27; H, 5.17; N, 11.72.

The ms of the (*E*)- and (*Z*)-isomers is as follows: 236 (M⁺, 100), 219 (19), 207 (63), 179 (28), 178 (44), 133 (28), 131 (19), 118 (35), 115 (19), 114 (16), 106 (20), 104 (17), 103 (22), 102 (20), 91 (25), 89 (31), 78 (18), 77 (34), 76 (20), 65 (15), 63 (27), 51 (29), 39 (20).

2-Acetyl-3-*p*-toluenesulfonylamidobenzofuran (XIIa).

To a solution of 2-acetyl-3-aminobenzofuran [2] (10 g, 0.057 mole) in dry pyridine (50 ml) kept at 0°, a cold solution (0°) of *p*-toluenesulfonylchloride (10.9 g, 0.057 mole) in dry pyridine (30 ml) was added, and the resulting reddish solution kept for 24 hours in a refrigerator. The mixture was poured into ice water and the obtained precipitate collected. The crude product (14.0 g) was chromatographed on a silicagel column eluting with an *n*-hexane-ethyl acetate (3:1) mixture. 2-Acetyl-3-*N,N*-bis(*p*-toluenesulfonyl)aminobenzofuran was first eluted, 6.0 g, (22%) mp 212-214° from ethyl acetate.

Anal. Calcd. for $C_{24}H_{21}NO_6S_2$: C, 59.63; H, 4.38; N, 2.90. Found: C, 59.51; H, 4.44; N, 3.07.

Compound XIIa, eluted after the above compound, was obtained in a yield of 41% (7.6 g) mp 133-134° from cyclohexane.

Anal. Calcd. for $C_{17}H_{15}NO_4S$: C, 62.00; H, 4.59; N, 4.25. Found: C, 61.75; H, 4.64; N, 4.53.

Hydrazone of 2-Acetyl-3-*p*-toluenesulfonylamidobenzofuran (XIIIa).

To a warm solution of XIIa (2 g) in 50% aqueous ethanol (50 ml) 98% hydrazine hydrate (1 ml) was added and the resulting yellow solution allowed to stand 2 hours at room temperature, then kept overnight in a refrigerator. Yellowish needles (1.7 g, 81%) separated, which, after disso-

lution in chloroform and crystallization through addition of three volumes ethanol, melted at 165-168° (at the mp, the formation of red crystals of the azine XXa was observed); nmr (DMSO- d_6): δ 9.58 (broad, -NH-SO₂, 1H), 7.33 (m, aromatics, 8H), 6.87 (s, NH₂, 2H), 2.23 (s, tosyl CH₃, 3H), 1.83 (s, -N=C-CH₃, 3H); ms: 344 (M + 1, 8), 343 (M⁺, 36), 188 (100), 161 (15), 160 (94), 159 (21), 130 (45), 120 (18), 115 (14), 103 (13), 91 (40), 77 (12), 66 (12), 65 (22), 42 (12), 39 (11).

Anal. Calcd. for $C_{17}H_{17}N_3O_3S$: C, 59.47; H, 4.99; N, 12.24. Found: C, 59.21; H, 4.85; N, 12.09.

When XIIa was refluxed 4 hours with hydrazine in ethylene glycol monomethyl ether no hydrazone XIIIa was found in the reaction mixture, but only 5-(2-hydroxyphenyl)-3-methylpyrazole (XVIIa) could be isolated in a 49% yield by silicagel column chromatography eluting with an *n*-hexane-ethyl acetate (5:1) mixture. The product, crystallized from benzene-*n*-hexane, melted at 134-135° (lit [10] 134-135°).

Methylhydrazone of 2-Acetyl-3-*p*-toluenesulfonylamidobenzofuran (XVa).

To a warm solution of XIIa (1 g) in absolute ethanol (5 ml) 98% monomethylhydrazine (1 ml) was added. A white solid immediately separated to give a thick sludge, which was allowed to stand several hours at room temperature. The solid was filtered and rinsed with absolute ethanol-ether (1:1) mixture, to give the crude product (1 g, 90%), which crystallized in leaflets from absolute ethanol, mp 170-171°; nmr (DMSO- d_6): δ 9.47 (s, NH-SO₂, 1H), 7.33 (m, aromatics, 8H), 6.67 (q, -NH-CH₃, 1H), 3.00 (d, -NH-CH₃, 3H), 2.30 (s, tosyl CH₃, 3H), 1.90 (s, -N=C-CH₃, 3H); ms: 357 (M⁺, 10), 203 (16), 202 (100), 174 (66), 159 (35), 158 (27), 146 (10), 130 (42), 103 (12), 91 (33), 77 (13), 65 (18).

Anal. Calcd. for $C_{18}H_{19}N_3O_3S$: C, 60.49; H, 5.36; N, 11.76. Found: C, 60.28; H, 5.39; N, 12.05.

Dimethylhydrazone of 2-Acetyl-3-*p*-toluenesulfonylamidobenzofuran (XVIa).

Compound XIIa (1.2 g) and *N,N*-dimethylhydrazine (1 ml) were refluxed for 1 hour in ethanol (10 ml) and the solvent evaporated. The obtained residue was chromatographed on a silica gel column eluting with an ethyl acetate-*n*-hexane (1:3) mixture, yield 0.9 g (62%) mp 81-83° (from ethanol); nmr (deuteriochloroform): δ 10.1 (broad, NH-SO₂, 1H), 8.23 (m, aromatics, 1H), 7.57 and 7.07 (two d, tosyl aromatics, 4H all) 7.33 (m, benzofuran aromatics, 8H), 2.58 (s, -N(CH₃)₂, 6H), 2.47 (s, -N=C-CH₃, 3H), 2.38 (s, tosyl CH₃, 3H).

Anal. Calcd. for $C_{19}H_{21}N_3O_3S$: C, 61.44; H, 5.70; N, 11.32. Found: C, 61.42; H, 5.71; N, 11.20.

When the same reaction was carried out in refluxing ethylene glycol monomethyl ether for 3 hours, both the monomethyl hydrazone XVa (45%) and the dimethyl hydrazone XVIa (17%) were obtained.

Reaction of Hydrazone XIIIa With Hydrazine.

When XIIIa was refluxed 5 hours in ethanol with an 0.25 mole ratio 98% hydrazine hydrate, no reaction occurred. The same reaction carried on in refluxing ethylene glycol monomethyl ether for 10 hours, led to 5-(2-hydroxyphenyl)-3-methylpyrazole (XVIIa) (39%), *p*-toluenesulfonylamide and brown decomposition tar products.

2-Benzoyl-3-*p*-toluenesulfonylamidobenzofuran (XIIb).

This compound was prepared in the same manner as XIIa from 3-amino-2-benzoylbenzofuran [2] in a 76% yield, white prisms from ethanol, mp 142-144°.

Anal. Calcd. for $C_{22}H_{17}NO_4S$: C, 67.51; H, 4.38; N, 3.58. Found: C, 67.48; H, 4.45; N, 3.73.

When the same reaction was carried out at 90° for 1 hour, small quantities of 3-*N,N*-bis(*p*-toluenesulfonyl)amino-2-benzoylbenzofuran were also obtained. This product was separated from XIIb by column chromatography on silicagel eluting with a chloroform-*n*-hexane (7:3) mixture, pale yellow leaflets mp 177-179° from ethyl acetate.

Anal. Calcd. for $C_{22}H_{23}NO_6S_2$: C, 63.85; H, 4.25; N, 2.57. Found: C, 63.95; H, 4.28; N, 2.35.

(Z)-Hydrazone of 2-Benzoyl-3-*p*-toluenesulfonylamidobenzofuran (XIV).

To a warm solution of XIIb (1 g) in absolute ethanol (20 ml) 98% hydrazine hydrate (1 ml) was added and the resulting orange solution allowed to stand in the dark for 24 hours. The crystals obtained (0.7 g, 65%) were purified by dissolving them in cold DMF (about 5 ml) and diluting with three volumes absolute ethanol: white glistening leaves mp 214-216° dec; nmr (DMSO- d_6): δ 9.3 (s, $-NH-SO_2$, 1H), 7.5 (m, aromatics, 13H, among them, two main rather sharp peaks at 7.53 and 7.38 ppm of the C_6H_5 phenyl ring), 6.97 (m, $-NH_2$, 2H), 2.37 (s, tosyl $-CH_3$, 3H).

A drop of trifluoroacetic acid promoted immediate isomerization and afforded a 2:1 mixture of (*E*)- and (*Z*)-hydrazones. The (*E*)-isomer showed peaks at 7.28 (main sharp peak for the C_6H_5 phenyl ring) and 2.2 ppm (tosyl CH_3); ms: 406 ($M+1$, 14), 405 (M^+ , 48), 250 (78), 236 (16), 223 (47), 222 (100), 220 (67), 165 (22), 128 (21), 120 (32), 104 (24), 91 (70), 77 (54), 65 (33), 51 (14).

Anal. Calcd. for $C_{22}H_{19}N_3O_3S$: C, 65.18; H, 4.72; N, 10.37. Found: C, 65.27; H, 4.52; N, 10.16.

The diacetyl derivative was prepared in anhydrous pyridine with excess acetic anhydride at 0°. The product was precipitated from the reaction mixture by the addition of anhydrous ethyl ether and purified from DMF-ethanol, yield 73%, mp 228-231°; nmr (DMSO- d_6): δ 14.7 (broad, $NH-COCH_3$, 1H), 7.53 (m, aromatics, 13H), 2.37 (s, tosyl CH_3 , 3H), 2.10 (s, $TS-N-COCH_3$, 3H), 1.67 (broad, $NH-CO-CH_3$, 3H).

Anal. Calcd. for $C_{26}H_{23}N_3O_5S$: C, 63.80; H, 4.74; N, 8.59. Found: C, 63.69; H, 4.51; N, 8.70.

3-Phenyl-8b-*p*-toluenesulfonylamido-3a,8b-dihydro-1*H*-benzofuro[3,2-*c*]pyrazole (XVIII).

To a warm solution of XIIb (2 g) in absolute ethanol (30 ml) 98% hydrazine hydrate (2 ml) was added and the mixture refluxed for a period of 2-5 hours in an oil bath kept at 100°. In a typical experiment, after 5 hours refluxing crystals of XIV separated after cooling (0.9 g, 43%, mp 208-212°), which were collected and the filtered mother liquor kept in a refrigerator. White, silky needles were thus obtained (0.35 g, 17%, mp 189-191°), which, after crystallization from absolute ethanol, melted at 193-195°; nmr (DMSO- d_6): δ 8.97 (s, $-NH-SO_2$, 1H), 8.40 (apparent s, $-NH-N$, 1H), 7.5 (m, aromatics, 13H, among them, the two doublets at 7.78 and 7.37 of *p*-toluenesulfonyl group were distinguishable), 6.53 (apparent s, 3a-*H*, 1H), 2.38 (s, tosyl- CH_3 , 3H); ms: 407 ($M+2$, 9), 405 (M^+ , 30), 250 (48), 234 (19), 223 (31), 222 (100), 220 (25), 139 (11), 132 (17), 119 (35), 104 (19), 103 (17), 102 (17), 91 (72), 77 (32), 65 (29), 51 (12).

Anal. Calcd. for $C_{22}H_{19}N_3O_3S$: C, 65.18; H, 4.72; N, 10.37. Found: C, 65.17; H, 4.68; N, 10.36.

Longer refluxing times (up to 10 hours) led to poor yields of the hydrazone XIV and, besides XVIII, to formation of variable quantities of 3-phenyl-1*H*-benzofuro[3,2-*c*]pyrazole (XIX) [6] and of 5-(2-hydroxyphenyl)pyrazole (XVIIb) [11], which were isolated by silicagel column chromatography and elution with an *n*-hexane-ethyl acetate (3:1) mixture. The compounds were crystallized respectively from 70% aqueous ethanol (mp 224-225°, lit [6] 217-219°) and from benzene (mp 144-146°, lit [11] 142-143°).

When XIIb was allowed to react with hydrazine in refluxing ethylene glycol monomethyl ether for 1 hour, neither the hydrazone XIV nor the benzofuropyrazole XVIII could be found in the reaction products. Only the pyrazoles XVIIb (67%) and XIX (11%) were isolated. An attempted acetylation of XVIII in dry pyridine with excess acetic anhydride at room temperature led to the recovery of unreacted starting material.

3-Phenyl-1*H*-benzofuro[3,2-*c*]pyrazole (XIX) From the Benzofuropyrazole XVIII.

A solution of XVIII (0.35 g) in a mixture of concentrated hydrochloric acid (15 ml) and 95% ethanol (15 ml) was refluxed for two hours. The colorless solution obtained was then evaporated to dryness and the residue suspended in warm water, 0.2 g of XIX, 99%, mp 223-225° were thus obtained. *p*-Toluenesulfonamide (0.12 g, 81%) resulted from water evaporation.

Reaction of Hydrazone XIV With Hydrazine.

When XIV was refluxed 5 hours in ethanol with 0.25 mole ratio 98% hydrazine, unreacted starting material XIV (60%) and the benzofuropyrazole XVIII (30%) were the main reaction products.

Methylhydrazone of 2-Benzoyl-3-*p*-toluenesulfonylamidobenzofuran (XVb).

Compound XIIb (1 g) and 98% monomethylhydrazine (1 ml) were refluxed for 1 hour in ethanol (15 ml). After cooling, the separated crystals were collected and dried, yield 0.85 g, 80%, mp 192-194° (from ethanol); nmr (DMSO- d_6): δ 8.70 (broad, $-NH-SO_2$, 1H), 7.33 (m, aromatics, 13H), 6.40 (q, $-NH-CH_3$, 1H), 3.0 (d, $-NH-CH_3$, 3H), 2.33 and 2.18 (two s, tosyl- CH_3 , 3H all, respectively for the (*Z*)- and (*E*)-isomers in a ratio of about 3:2). A drop of trifluoroacetic acid led to a 1:1 mixture of the two isomers, while a main sharp peak for the C_6H_5 -phenyl ring of the (*E*)-isomer could be distinguished at 7.25 ppm.

Anal. Calcd. for $C_{23}H_{21}O_3N_3S$: C, 65.86; H, 5.05; N, 10.02. Found: C, 65.90; H, 5.10; N, 9.88.

(E)-Dimethylhydrazone of 2-Benzoyl-3-*p*-toluenesulfonylamidobenzofuran (XVIb).

Compound XIIb (1 g) and *N,N*-dimethylhydrazine (1 g) were refluxed 3 hours in ethylene glycol monomethyl ether (10 ml). The residue resulting from solvent evaporation was chromatographed on an alumina column eluting with an ethyl acetate-*n*-hexane (1:4) mixture, 0.7 g of product (68%) was thus obtained, which crystallized from cyclohexane and melted at 131-133°; nmr (deuteriochloroform): δ 9.73 (s, $-NH-SO_2$, 1H), 8.10 (m, aromatics, 1H), 7.13 (m, aromatics, 12H), 2.72 (s, $-N(CH_3)_2$, 6H), 2.07 (s, tosyl CH_3 , 3H). The nmr spectrum in DMSO- d_6 solution shows two peaks for the tosyl- CH_3 at 2.33 [*Z*]-isomer] and 2.08 [*E*]-isomer] in a ratio of about 1:3.

Anal. Calcd. for $C_{24}H_{23}N_3O_3S$: C, 66.50; H, 5.35; N, 9.70. Found: C, 66.54; H, 5.40; N, 9.68.

 α -Azine XXa.

a) From Hydrazone XIIIa.

To a solution of XIIIa (0.5 g) in ethanol (20 ml) a few drops of hydrochloric acid were added and a red solid immediately separated. The mixture was evaporated to dryness, the residue obtained suspended in water (40 ml) and the insoluble red material filtered and rinsed with water, 0.46 g (97%) azine XXa was thus obtained, mp 305° dec, practically insoluble in most organic solvents. Evaporation of the aqueous phase gave a white solid which was identified as hydrazine dihydrochloride, from which hydrazine picrate and picrolonate were prepared and shown to be identical with authentic samples. When the azine XXa (0.2 g) was heated at 120° for 15 minutes in nitrobenzene (20 ml) with 98% hydrazine hydrate (1 ml) a rapid decolorization of the red solution occurred and the hydrazone XIIIa was formed again. Steam distillation of nitrobenzene and crystallization of the resulting residue from ethanol gave 0.1 g XIIIa (48%).

b) From the *N*-Methylhydrazone XVa.

A solution of XVa (0.5 g) in ethanol (50 ml), added with a few drops of hydrochloric acid, was allowed to stand for 4 weeks at room temperature. The red solid which separated was filtered and rinsed with ethanol, 0.2 g (43%) XXa was thus formed as shown by ir (nujol) and ms. Evaporation of ethanol gave a residue which was suspended in water, filtered from the insoluble matter and the water distilled. The resulting white solid gave a picrate, a picrolonate and a benzoyl derivative identical with authentic samples prepared from *N*-methylhydrazine; ms: 655 ($M+1$, 21), 654 (M^+ , 38), 653 (16), 499 (12), 345 (32), 344 (99), 343 (52), 303 (23), 184 (37), 173 (31), 172 (31), 159 (45), 158 (39), 146 (26), 139 (19), 132 (22), 130 (46), 104 (24), 103 (34), 102 (17), 92 (23), 91 (100), 77 (29), 76 (15), 65 (29).

Anal. Calcd. for $C_{24}H_{23}N_4O_6S_2$: C, 62.38; H, 4.62; N, 8.55. Found: C, 62.15; H, 4.62; N, 8.43.

The following α -azines were obtained in the same manner from acidified solutions (hydrochloric acid) of the related hydrazones.

Compound XXb.

This compound was obtained from XIV (0.3 g) dissolved in acetonitrile

(30 ml), 0.13 g (45%) of orange prisms, mp 245-247° (from acetonitrile); ms: 778 (M⁺, 10), 623 (41), 469 (30), 468 (52), 467 (27), 439 (12), 365 (18), 246 (24), 236 (28), 235 (64), 234 (43), 221 (59), 220 (65), 219 (28), 190 (20), 165 (22), 155 (16), 139 (16), 132 (19), 118 (12), 105 (18), 104 (34), 103 (24), 92 (29), 91 (100), 90 (32), 77 (35), 76 (16), 65 (28).

Anal. Calcd. for C₁₄H₁₄N₂O₅S₂: C, 76.86; H, 4.40; N, 7.19. Found: C, 76.70; H, 4.36; N, 7.25.

Compound XXIIa.

a) This compound was obtained from Xa (0.5 g) in ethanol (20 ml) as yellow needles, mp 163-164° (lit [7] 167°), yield practically quantitative.

b) This compound was also obtained from the *N*-methylhydrazone of 2-acetylbenzofuran. 2-Acetylbenzofuran (IXa) (1.5 g) and 98% *N*-methylhydrazine (2 ml) were refluxed 2 hours in ethanol (20 ml), the mixture evaporated to dryness and the resulting viscous residue taken into ether, washed with water and dried with anhydrous sodium sulfate. The ether was then evaporated and the pale yellow crude viscous XXI (1.7 g, 97%) obtained was dissolved in ethanol (15 ml), a few drops of concentrated hydrochloric acid added and the mixture allowed to react at room temperature for one week, 0.2 g, (6%) of the azine XXIIa was thus obtained; ms: 317 (M + 1, 22), 316 (M⁺, 95), 301 (47), 299 (49), 273 (13), 158 (35), 144 (47), 143 (37), 131 (17), 115 (100), 89 (81), 63 (35).

Compound XXIIb.

Compound XXIIb was obtained from either Xb or XI (0.5 g) dissolved in ethanol (15 ml) and 0.25 g of XXIIb (54%) mp 124-126° (cyclohexane) were obtained; ms: 441 (M + 1, 26), 440 (M⁺, 75), 412 (11), 364 (28), 363 (100), 337 (17), 323 (13), 297 (28), 296 (17), 220 (42), 206 (50), 205 (94), 178 (63), 177 (37), 176 (39), 165 (11), 152 (37), 151 (25), 126 (13), 89 (38), 77 (55), 63 (17).

Anal. Calcd. for C₂₀H₂₀N₂O₂: C, 81.80; H, 4.58; N, 6.36. Found: C, 81.63; H, 4.67; N, 6.32.

3-Aminobenzofuran-2-carboxylic Acid Hydrazone (XXIV).

3-Amino-2-ethoxycarbonylbenzofuran (XXIII) [2] (1 g) and 98% hydrazine hydrate (1.5 ml) were heated for 4 hours in refluxing ethylene glycol monomethyl ether (10 ml). The solvent was then evaporated and the resulting residue crystallized from benzene, 0.9 g of XXIV (97%) was thus obtained, mp 137-139°; nmr (DMSO-d₆): δ 9.06 (s, -CO-NH, 1H), 7.75 and 7.25 (m, aromatics, 1H and 3H respectively), 5.82 and 4.23 (two s, two -NH₂ groups, 2H each).

Anal. Calcd. for C₉H₉N₃O₂: C, 56.54; H, 4.75; N, 21.98. Found: C, 56.76; H, 4.80; N, 21.84.

2-Ethoxycarbonyl-3-*p*-toluenesulfonylamidobenzofuran (XXV).

Compound XXIII (4.1 g, 0.02 mole) and *p*-toluenesulfonylchloride (3.8 g, 0.02 mole) in anhydrous pyridine (20 ml) were allowed to react overnight at 0°. The reaction mixture was then poured into ice water, and the precipitate obtained crystallized from ethanol, yield 5.2 g (72%), mp 120-122°; nmr (deuteriochloroform): δ 8.40 (m, -NH-SO₂, 1H), 8.23 (m, aromatics, 1H), 7.33 (m, aromatics, 7H), 4.30 (q, -CH₂-CH₃, 2H), 2.30 (s, tosyl CH₃, 3H), 1.48 (t, -CH₂-CH₃, 3H).

Anal. Calcd. for C₁₄H₁₇NO₅S: C, 60.16; H, 4.77; N, 3.90. Found: C, 60.31; H, 4.60; N, 3.76.

3-Hydrazinobenzofuran-2-carboxylic Acid Hydrazone (XXVI).

Compound XXV (4 g) and 98% hydrazine hydrate (3.2 ml) were heated 1.5 hours in refluxing ethanol (20 ml). The reaction mixture was then kept overnight in a refrigerator, and the pale yellow prisms which separa-

ted were collected, yield 2 g (87%), mp 176-178° dec. The product was sensitive to light and temperature. It could be purified by dissolution in warm (no more than 60°) DMF and dilution with 2-3 volumes ethyl ether. From the reaction ethanolic mother liquor 1.8 g (95%) of *p*-toluenesulfonylamide could be isolated; nmr (DMSO-d₆): δ 9.38 (broad, CO-NH-, 1H), 8.25 (m, aromatics, 1H), 7.17 (m, three aromatics and the NH group of position 3, 4H), 4.52 (broad, two -NH₂ groups, 4H).

Anal. Calcd. for C₉H₁₀N₄O₂: C, 52.42; H, 4.89; N, 27.17. Found: C, 52.26; H, 4.86; N, 27.12.

Diacetyl Derivative of XXVI.

To a cooled (0°) suspension of XXVI (0.4 g) in anhydrous pyridine (5 ml) acetic anhydride (2 ml) was added and the clear solution obtained was kept overnight in a refrigerator. The reaction mixture was then diluted with 5 volumes of ethyl ether, and the resulting white solid collected, yield 0.3 g (53%), white silky needles mp 232-234° (from ethanol-ether); nmr (DMSO-d₆): δ 10.33 (d, -NH-CO of position 3, 1H), 10.30 and 9.90 (two s, -CO-NH-NH-CO- of position 2, 1H each), 8.03 (d, -NH of position 3, 1H), 7.97 (m, aromatics, 1H), 7.50 (m, aromatics, 3H), 1.93 (s, two -CO-CH₃, 6H); ms: 290 (M⁺, 41), 248 (55), 205 (15), 190 (12), 175 (68), 174 (56), 160 (29), 148 (20), 147 (29), 132 (15), 120 (18), 119 (19), 118 (16), 104 (18), 103 (29), 89 (38), 77 (20), 76 (17), 75 (27), 43 (100).

Anal. Calcd. for C₁₃H₁₄N₄O₄: C, 53.79; H, 4.86; N, 19.30. Found: C, 53.66; H, 4.89; N, 19.10.

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