# 2-(4-Alkylamido-2-hydroxyphenyl)benz-X-azoles as Intermediates for the Synthesis of Dyes [1]



Ermanno Barni*, Piero Savarino, Mario Marzona and Marco Piva

Istituto di Chimica Organica Industriale, Università di Torino,
10125 C.so M. D'Azeglio 48, Torino, Italy

Received February 21, 1983

Nineteen substituted 2-phenylbenz-X-azoles, which are intermediates for the synthesis of dyes, were prepared from *p*-aminosalicylic acid (PAS). Substituents in the phenyl ring are 2'-hydroxy and/or 4'-amino and 4'-alkylamido with alkyl chains ranging from $C_1$ to $C_{15}$. The preferred route of the synthesis is discussed. The melting points and the $R_f$ values are correlated with the structure. An extensive discussion of the electronic absorption spectra, involving other compounds with the same general structure, is reported.

*J. Heterocyclic Chem.*, **20**, 1517 (1983).

The reaction of carboxylic groups or of their derivatives with aromatic *ortho* bisubstituted compounds to achieve benz-X-azole derivatives [2] was frequently employed with the aim of obtaining dye intermediates [3-5]. Recently we investigated micellar properties of 4-alkylamido-2-hydroxybenzoic acids III [6] and we used these intermediates in the synthesis of a series of weighted monazo dyes [7]. In order to extend the investigation on similar couplers and dyes we prepared the compounds of general formula IV, in which the carboxylic group is replaced by hetaryls. Such a substitution should reasonably involve significant variations of the acid-base character, of the steric effects and of the stabilization of the molecule towards the uv induced degradation [8], while minor changes should be expected on the possibility of complex formation and on the electronic effects [9,10].

The synthesis of compounds IV starting from 4-amino-2-hydroxybenzoic acid I (PAS) can be performed by two different routes: several reasons indicate route A as the

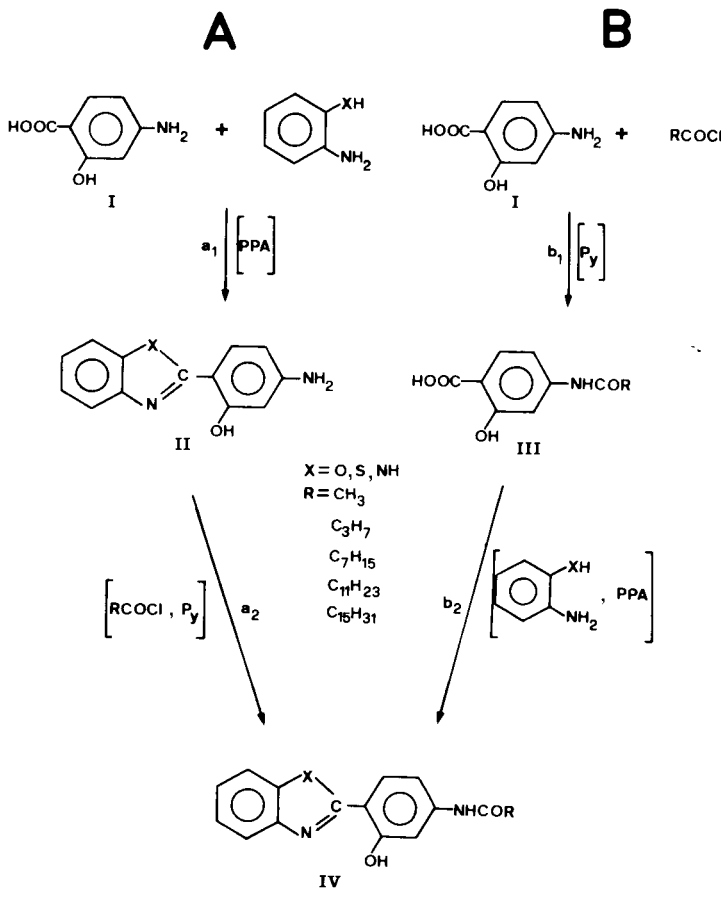
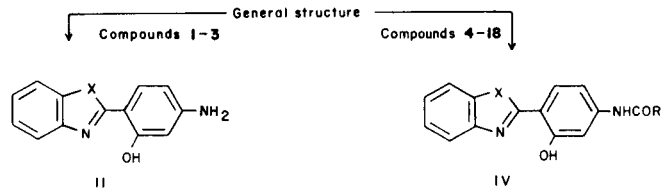


Table 1

Substituted 2-Phenyl-benz-X-azoles




II IV

| Compound number | Structure X = | R = | Mp °C | Crystallization solvent [a] | Empirical formula | Elemental Analyses Calcd./Found C | H | N | Electronic absorption spectra λ max nm (log ε) [b] | $R_f$ |
|---|---|---|---|---|---|---|---|---|---|---|
| **1** | O | — | 227-228 | A | $C_{13}H_{10}N_2O_2$ | 69.02<br>69.13 | 4.46<br>4.47 | 12.38<br>12.29 | 337 (4.58) | 0.88 |
| **2** | S | — | 215-216 | B | $C_{13}H_{10}N_2OS$ | 64.44<br>64.28 | 4.16<br>4.25 | 11.56<br>11.62 | 357 (4.57) | 0.89 |
| **3** | NH | — | 241-242 | C | $C_{13}H_{11}N_3O$ | 69.32<br>69.25 | 4.92<br>5.01 | 18.66<br>18.67 | 338 (4.53) | 0.86 |
| **4** | O | $CH_3$ | 232-233 | D | $C_{15}H_{12}N_2O_3$ | 67.16<br>67.08 | 4.51<br>4.55 | 10.44<br>10.37 | 330 (4.56) | 0.88 |
| **5** | O | $n$-$C_3H_7$ | 250-252 | C | $C_{17}H_{16}N_2O_3$ | 68.90<br>68.79 | 5.44<br>5.60 | 9.45<br>9.33 | 330 (4.56) | 0.92 |
| **6** | O | $n$-$C_7H_{15}$ | 174-175 | B | $C_{21}H_{24}N_2O_3$ | 71.57<br>71.48 | 6.86<br>6.83 | 7.95<br>8.04 | 330 (4.56) | 0.94 |
| **7** | O | $n$-$C_{11}H_{23}$ | 137-138 | C | $C_{25}H_{32}N_2O_3$ | 73.50<br>73.38 | 7.90<br>7.95 | 6.86<br>6.85 | 330 (4.56) | 0.96 |
| **8** | O | $n$-$C_{15}H_{31}$ | 131-132 | C | $C_{29}H_{40}N_2O_3$ | 74.96<br>75.02 | 8.68<br>8.76 | 6.03<br>5.95 | 330 (4.56) | 0.97 |
| **9** | S | $CH_3$ | 241-242 | D | $C_{15}H_{12}N_2O_2S$ | 63.36<br>63.43 | 4.25<br>4.34 | 9.85<br>9.81 | 344 (4.52) | 0.89 |
| **10** | S | $n$-$C_3H_7$ | 220-221 | D | $C_{17}H_{16}N_2O_2S$ | 65.36<br>65.38 | 5.16<br>5.21 | 8.97<br>8.97 | 344 (4.52) | 0.93 |
| **11** | S | $n$-$C_7H_{15}$ | 180-182 | D | $C_{21}H_{24}N_2O_2S$ | 68.45<br>68.34 | 6.56<br>6.40 | 7.60<br>7.74 | 344 (4.51) | 0.95 |
| **12** | S | $n$-$C_{11}H_{23}$ | 181-183 | B | $C_{25}H_{32}N_2O_2S$ | 70.72<br>70.60 | 7.60<br>7.73 | 6.60<br>6.51 | 344 (4.53) | 0.97 |
| **13** | S | $n$-$C_{15}H_{31}$ | 169-170 | D | $C_{29}H_{40}N_2O_2S$ | 72.46<br>72.41 | 8.39<br>8.47 | 5.83<br>5.89 | 343 (4.51) | 0.98 |
| **14** | NH | $CH_3$ | >350 | D | $C_{15}H_{13}N_3O_2$ | 67.40<br>67.43 | 4.90<br>4.99 | 15.72<br>15.68 | 327 (4.56) | 0.86 |
| **15** | NH | $n$-$C_3H_7$ | 321-322 | C | $C_{17}H_{17}N_3O_2$ | 69.13<br>69.18 | 5.80<br>5.73 | 14.23<br>14.20 | 327 (4.56) | 0.88 |
| **16** | NH | $n$-$C_7H_{15}$ | 275-276 | C | $C_{21}H_{25}N_3O_2$ | 71.77<br>71.81 | 7.17<br>7.09 | 11.96<br>11.94 | 327 (4.57) | 0.92 |
| **17** | NH | $n$-$C_{11}H_{23}$ | 264-265 | C | $C_{25}H_{33}N_3O_2$ | 73.68<br>73.65 | 8.16<br>8.23 | 10.31<br>10.35 | 327 (4.58) | 0.93 |
| **18** | NH | $n$-$C_{15}H_{31}$ | 248-250 | B | $C_{29}H_{41}N_3O_2$ | 75.12<br>75.03 | 8.91<br>9.02 | 9.06<br>9.17 | 327 (4.56) | 0.96 |

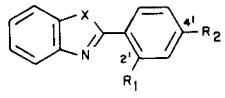
[a] A = xylene, B = dioxane/water, C = ethanol/water, D = acetic acid/water. [b] The λ max and log ε values correspond to the most intense peak of the long-wave band.

most probable. First of all, as the Schotten-Baumann acylation (steps $a_2$ or $b_1$) is more suitable in laboratory practice than the condensation with polyphosphoric acid (steps $a_1$ and $b_2$), the most reasonable way is to prepare large amounts of 2-(4-amino-2-hydroxyphenyl)benz-X-azoles II which are common intermediates for the synthesis of a series of compounds IV *via* acylation (step $a_2$). Furthermore, route A allows one to prepare the previously unknown 2-(4-amino-2-hydroxyphenyl)benzothiazole (No. 2 in Table I). Finally during step $b_2$, decarboxylation or deacylation occurred to some extent in several cases. The acylation of thiazole derivatives was more difficult than that of the benzoxazole and benzimidazole counterparts and required more drastic reaction conditions and a large excess of acyl chloride. This behaviour is quite surprising on the grounds of the lower electron-withdrawing effect of the benzothiazolyl group which should make less difficult the nucleophilic attack of the amino group to the carbon atom of the carbonyl group.

Analytical and spectroscopic data of the compounds II and IV are reported in Table I.

Table II

Electronic Absorption Spectra [a,b]




| | 1<br>$R_1$ = H,<br>$R_2$ = H | 2<br>$R_1$ = OH,<br>$R_2$ = H | 3<br>$R_1$ = H,<br>$R_2$ = $NH_2$ | 4<br>$R_1$ = H,<br>$R_2$ = $NHCOCH_3$ | 5<br>$R_1$ = OH,<br>$R_2$ = $NH_2$ | 6<br>$R_1$ = OH,<br>$R_2$ = $NHCOCH_3$ |
|---|---|---|---|---|---|---|
| X = S | 297 (4.29) [c] | 333 (4.20) [c] | 356 (4.56) [c] | 325 (4.50) [d] | 357 (4.57) | 344 (4.52) |
| X = O | 299 (4.35) [e] | 319 (4.23) [e] | 327 (4.50) [e] | 316 (4.51) [e] | 337 (4.58) | 330 (4.56) |
| X = NH | 304 (4.41) [f] | 316 (4.39) [g] | 318 (4.49) [h] | 316 (4.58) [i] | 338 (4.53) | 327 (4.56) |

[a] In each column λ max (nm) and, in parenthesis, log ε are given. [b] The λ max and log ε values correspond to the most intense peak of the long-wave band. [c] Taken from lit 11. [d] Taken from lit 12. [e] Taken from lit 13. [f] Taken from lit 14. [g] Taken from lit 15. [h] Taken from lit 16. [i] Taken from lit 17.

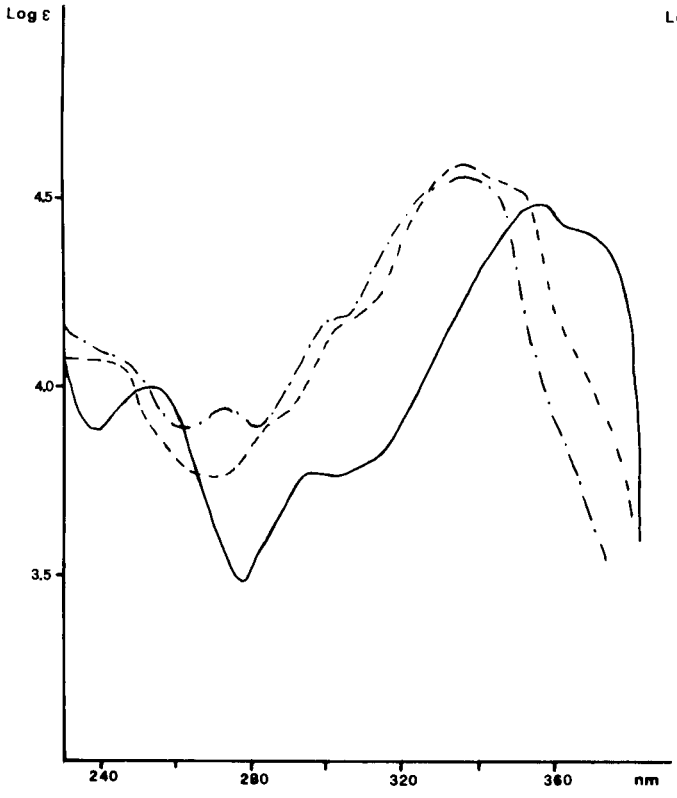



Figure 1. Electronic absorption spectra in ethanol of compounds: No. 2 — 2-(4-amino-2-hydroxyphenyl)benzothiazole; No. 1 - - - 2-(4-amino-2-hydroxyphenyl)benzoxazole; No. 3 - - - - - 2-(4-amino-2-hydroxyphenyl)benzimidazole.

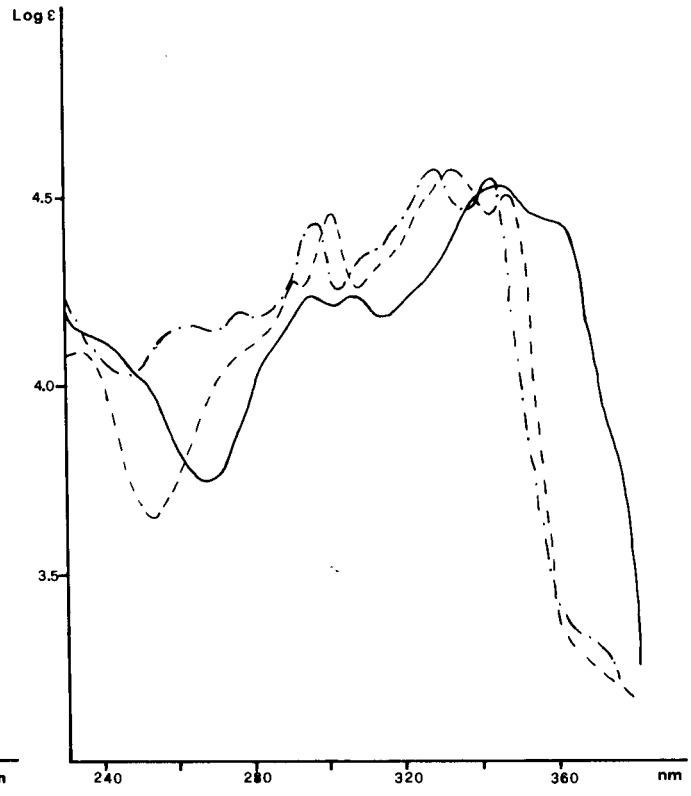


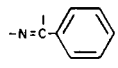

Figure 2. Electronic absorption spectra in ethanol of compounds: No. 9 — 2-(4-acetylamino-2-hydroxyphenyl)-benzothiazole; No. 4 - - - 2-(4-acetylamino-2-hydroxyphenyl)benzoxazole; No. 14 - - - - - 2-(4-acetylamino-2-hydroxyphenyl)benzimidazole.

As previously observed [4,5], the melting points of the benzimidazole derivatives are higher than those of their benzothiazole and benzoxazole counterparts probably because of intermolecular hydrogen bonding in benzimidazoles. Furthermore a general decrease in the melting points as the chain lengths increase is ascribed to the negative effect of weighted hydrophobic structures towards the accomodation into a crystalline lattice.

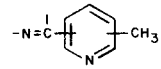
The $R_f$ data show an opposite behaviour because the hydrophobic chain lengthening decreases the polar character of the molecules, lowering the interactions with the polar substrate. The behaviour in the three series is in agreement with these statements: the imidazole derivatives systematically have lower $R_f$ values than the corresponding oxazoles and thiazoles.

For a more extensive discussion on electronic absorption spectra, Table II summarizes the spectroscopic data from Table I together with the data of similar compounds. Figures 1 and 2 show the spectral patterns of typical II and IV compounds. Spectra in Figure 2 are also representative of longer chain derivatives due to the insignificant changes connected with the chain length. In the following discussion the region above 250 nm is considered.

The broad and intense band in the high wavelength region was ascribed to the benzylidene-imine chromogen V which involves the phenyl ring and the >C=N- share of



V



VI

the five-membered ring [11,13,14]. The same assignment has been made about the spectra of nine methylpyridylbenz-X-azoles (chromogen VI) [4]. These compounds, together with those reported in the first column of Table II, show absorption bands in a narrow range (λ max 297-313 nm, log ε 4.26-4.41) irrespective of the nature of the X heteroatom.

The values of the absorption intensities allow us to collect the compounds listed in Table II in two groups, the former ($R_2$ = H) having lower values in a wider (4.20-4.41) range, the latter ($R_2 \neq$ H), higher values in a narrower (4.49-4.58) range. Moreover, all the substituted compounds, except the hydroxy derivatives in the second column, show a slight hyperchromic effect with respect to the corresponding unsubstituted compound.

The *para* amino group gives rise to a significant bathochromic shift due to the ability of this substituent to enter strongly into conjugation with the benzylidene-imine group. Where the conjugative ability of the nitrogen is almost suppressed by acetylation, the band is moved to lower wavelengths, yet being bathochromic in comparison with unsubstituted compounds. These effects have a different weight in the three series and the susceptibility order S>O>N is observed.

The derivatives with an *ortho* hydroxy group have a different spectral pattern [11,13], including the appearance of benzenoid $B_{2\mu}$ bands and the attenuation of the long-wave band. This was ascribed to the formation of N-heterocyclic-H-O hydrogen bonds.

The properties of the compounds described in this paper suggest some general considerations: a. When both the *para* amino group and *ortho* hydroxy group are present (column 5) the strongest bathochromic shifts occur. The spectral patterns in Figure 1 indicate that the benzenoid bands are almost obscured by the broad band of the benzylidene-imine chromogen conjugated to the amino group; b. Acetylation (or acylation) of the amino group, shifts the long-wave band (Figure 2) to lower values (yet being bathochromic *vs* acyl derivatives without the *ortho* hydroxy group (column 4)) and a fine structure is shown together with the appearance of the benzenoid transitions; c. The spectral data of the bis-acetyl derivative of the oxazole series (X = O, $R_1$ = $OCOCH_3$, $R_2$ = $NHCOCH_3$) (see Experimental) are identical with those of the acetylamino derivative (X = O, $R_1$ = H, $R_2$ = $NHCOCH_3$) (column 4), indicating the negligible effect of the *ortho* acetyloxy group in which the conjugative ability and the aptitude to form hydrogen bonds are forbidden; d. The Δλ values, *i.e.* the difference between the band wavelengths of the substituted compounds (columns 2-6) and of the corresponding unsubstituted compounds (column 1) indicate an appreciable (12-60 nm) bathochromic effect due to the substitution. The magnitude of this effect, in the order S>O>N for a given substitution, indicates that the main chromogen is differently affected by the X heteroatom.

The compounds described in this paper are useful intermediates for the synthesis of dyes. Compounds **4-18** can be employed as coupling components, compounds **1-3** as coupling and diazo components. Investigations on this topic are in progress. Other interesting applications arise from their ability to coordinate transition metal ions (already checked on a qualitative level) and from possible pharmacological properties due to their resemblance with other heterocyclic systems (*i.e.* 8-quinolinol) which form coordination compounds.

## EXPERIMENTAL

Electronic spectra were recorded, in ethanol, on a Pye Unicam SP 8-100 spectrophotometer. $R_f$ data were obtained on silica gel 60 F-254 tlc plates (Merck), using BAW 4:1:5 as eluent.

Commercial *p*-aminosalicylic acid (PAS), acylchlorides, *o*-aminophenol, *o*-aminothiophenol and *o*-phenylenediamine were employed.

Compounds 1-3 were prepared condensing *p*-aminosalicylic acid, 1 mole, with *o*-aminophenol (or *o*-aminothiophenol or *o*-phenylenediamine) 1 mole, in polyphosphoric acid (85% phosphorus pentoxide) over a period of three hours at 200°, following the general procedure indicated in reference [1]. The reaction mixture was poured into distilled water (to avoid complex formation with cations), the precipitate was collected and slurried in dilute sodium carbonate. The base was finally collected by filtration, dried and crystallised. Compounds **1** and **3** are also cited in [18] and [19] respectively.

Compounds 5-8 and 15-18 were prepared by dropwise addition under stirring of acyl chloride (1 mole) to a pyridine solution of compounds **1-3** (1 mole) at 15-20°. The reaction mixture was kept overnight, then poured

into a large volume of distilled water. The solid was collected by filtration, dried and crystallised.

Compounds **9-13** were prepared as before, with the following variations: a. 1.5 moles of acyl chloride were employed; b. after the addition of the acyl chloride, the temperature was maintained at 100° for 4 hours; c. the reaction mixture was kept 72 hours before working up.

Compound **14** was prepared as **5-8** and **15-18**, adding acetic anhydride (2.4 moles) to a pyridine solution of **3** (1 mole).

Compound **4** was prepared in two steps. Reacting **1** (1 mole) with acetyl chloride (2 moles) under the same conditions as **9-13**, 2-(2-acetyloxy-4-methylamidophenyl)benzoxazole **19** was obtained, mp 223-224° after crystallization from acetic acid/water, $R_f$ 0.91; λ max 316 nm, log ε 4.51.

*Anal.* Calcd. for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03. Found: C, 65.92; H, 4.76; N, 8.86.

The bis-acetyl derivative **19** was selectively hydrolysed by dissolving 1 mole in a 2% aqueous solution of sodium hydroxide (4 moles) and heating until complete dissolution. After cooling, the solution was acidified with acetic acid and the crude precipitate of **4** was collected, dried and crystallised.

## REFERENCES AND NOTES

[1] This work was supported by Ministero della Publica Istruzione.

[2] D. W. Hein, R. J. Alheim and J. J. Leavitt, U. S. Patent, 2,985,661 (1961); *Chem. Abstr.*, **57**, 11203 (1962).

[3] E. Barni and G. Di Modica, *Ann. Chim. (Rome)*, **66**, 379 (1976).

[4] E. Barni and P. Savarino, *J. Heterocyclic Chem.*, **14**, 937 (1977).

[5] E. Barni and P. Savarino, *ibid.*, **16**, 1579 (1979).

[6] E. Pelizzetti, E. Pramauro, E. Barni, P. Savarino, M. Corti and V. Degiorgio, *Ber. Bunsenges. Phys. Chem.*, **86**, 529 (1982).

[7] E. Barni, P. Savarino, G. Di Modica, R. Carpignano, S. S. Papa and G. Giraudo, *Dyes Pigm.*, in press.

[8] D. L. Williams and A. Heller, *J. Phys. Chem.*, **74**, 4473 (1970).

[9] V. F. Bystrov, Zh. N. Belaya, B. E. Gruz, G. P. Syrova, A. I. Tolmachev, L. M. Shulezhko and L. M. Yagupol'skii, *Zh. Obshch. Khim.*, **38**, 1001 (1968); *Chem. Abstr.*, **69**, 96568q (1968).

[10] E. Barni, P. Savarino and G. Di Modica, *Atti Accad. Sci. Turin*, **107**, 63 (1972).

[11] A. Cerniani and R. Passerini, *J. Chem. Soc.*, 2261 (1954).

[12] A. Brembilla and P. Lochon, *C. R. Acad. Sci. Paris, Ser. C*, **286**, 557 (1978).

[13] R. Passerini, *J. Chem. Soc.*, 2256 (1954).

[14] M. Gelus and J. M. Bonnier, *J. Chim. Phys.*, 1602 (1967).

[15] P. Grammaticakis and H. Texier, *C. R. Acad. Sci. Paris, Ser. C*, **274**, 878 (1972).

[16] G. Leandri, A. Mangini, F. Montanari and R. Passerini, *Gazz. Chim. Ital.*, **85**, 769 (1955).

[17] H. Mc. Nab and D. M. Smith, *J. Chem. Soc., Perkin Trans. I*, 1310 (1973).

[18] Ciba Ltd, Belgian Patent 634,193; *Chem. Abstr.*, **60**, 14525g (1964).

[19] L. P. Nagorskaya, E. D. Samartseva, L. I. Rudaya and I. Ya. Kvitko, Deposited Doc. 1977, VINITI 543; *Chem. Abstr.*, **90**, 105598n (1979).