THE USE OF ACTIVATED DOUBLE BOND SYSTEMS IN HETEROCYCLIC SYNTHESES

By
Ez-el-din M. KANDEEL*, Ibrahim A. EL-GHAMRY and Abd-el-Rahman H. ABD-EL-RAHMAN

DEPARTMENT OF CHEMISTRY, FACULTY OF SCIENCE, MANSOURA UNIVERSITY, MANSOURA, A.R. EGYPT

Abstract: *The synthesized 2,3-diphenyl-6-methoxy-5-indolylidene-malononitrile, ethyl α-cyano-β-(2,3-diphenyl-6-methoxy-5-indolyl)acrylate, α-cyano-β-(2,3-diphenyl-6-methoxy-5-indolyl)acrylamide and diethyl 2-[(2`,3`-diphenyl-6`-methoxy-5`-indolyl)methylene]-malonate are used to yield new heterocyclic compounds of expected biological activities. Structural assignments of the new products were based upon the analytical and the spectral data (IR and ^1H NMR).*

Several patents and papers dealing with pharmacological studies on various indoles have recently been published [1-5]. In the light of these reports, and knowing a high biological activity of some pyridine [6], pyridone [7] and benzopyrone [8,9] derivatives we were encouraged to synthesize several new compounds of these classes.

Syntheses and results

α-Cyano-β-(2,3-diphenyl-6-methoxy-5-indolyl)-acrylonitrile 1 is easily accessible through the Knovenagel condensation of 2,3-diphenyl-5-formyl-6-methoxyindole [10] with malononitrile, in the presence of piperidine. The α-cyanoacrylonitrile derivative 1 reacts readily with p-hydroxyacetophenone, in the presence of ammonium acetate, to give 2-amino-3-cyano-6-p-hydroxyphenyl-4-(2`,3`-diphenyl-6`-methoxy-5`-indolyl)-pyridine 2.

Compound 1 was also reacted with 2-cyanoethanoic acid hydrazide, in ethanol containing piperidine, to give 1,6-diamino-3,5-dicyano-4-(2`,3`-

diphenyl-6`-methoxy-5`-indolyl)-2-pyridone 3. The reaction may be assumed to proceed through the Michael addition of the reagent to compound 1 and the resulting adduct undergoes a cyclization, in situ, via a nucleophilic attack at the cyano group to give a six-membered ring which, on aromatization, gives the N-amino-2-pyridone derivative.

Refluxing the indolylidenemalononitrile 1 with benzenethiol and malononitrile, in the presence of triethylamine, affords 2-amino-6-phenylthio-4-(2`,3`-diphenyl-6`-methoxy-5`-indolyl)-3,5-dicyanopyridine 4.

Compound 1 was reacted with cyanoacetamide, in the presence of piperidine, to give 6-amino-3,5-dicyano-4-(2`,3`-diphenyl-6`-methoxy-5`-indolyl)-3,4-dihydro-2-pyridone 5.

The reaction of 1 with hydrazine hydrate, in ethanol, yields 4-[(2`,3`-diphenyl-6`-methoxy-5`-indolyl)methylene]-3,5-diaminopyrazole 6.

Condensation of 2,3-diphenyl-5-formyl-6-methoxyindole with ethyl cyanoacetate or cyanoacetamide, using piperidine as a catalyst, gives ethyl α-cyano-β-(2,3-diphenyl-6-methoxy-5-indolyl) acrylate 7 and α-cyano-β-(2,3-diphenyl-6-methoxy-5-indolyl)acrylamide 8, respectively.

The action of pyridine hydrochloride on compounds 1,7 and 8 was investigated in order to synthesize some substituted pyrrolobenzopyrones. Thus, these compounds on fusion with the reagent at 150°C for two hours, furnished 2,3-diphenyl-6-substituted-7H-pyrrolo[3,2-g] [1] benzopyran-7-ones 9, 10 and 11, respectively.

Diethyl 2-[(2`,3`-diphenyl-6`-methoxy-5`-indolyl)methylene]-malonate 12 was also prepared and used as follows. The reaction of 12 with methyl magnesium bromide gives ethyl α-carbethoxy-β-(2,3-diphenyl-6-methoxy-5-indolyl)butanoate 13. Allyl bromide was used as to effect the alkylation [11,12] of 13. Thus, when allyl bromide is added to compound 13, in the presence of sodium ethoxide, and the reaction mixture was refluxed for

several hours, ethyl α-allyl-α-carbethoxy-β-(2,3-diphenyl-6-methoxy-5-indolyl)butanoate 14 is obtained. Compound 14 was cyclized, using polyphosphoric acid, to give 6,6-diethoxycarbonyl-4,7-dimethyl-8-methoxy-4,5,6,7-tetrahydrobenzo[e]indole 15.

Experimental

All m.p's are uncorrected and were taken in a Gallenkamp electric m.p. apparatus. IR spectra were recorded with a Pye Unicam SP 2000 spectrophotometer, in KBr. ^{1}H NMR spectra were run with Varian (60 MHz or 250 MHz) spectrometers, in $CDCl_3$ or DMSO, using TMS (δ = 0 ppm) as an internal standard.

2,3-Diphenyl-6-methoxy-5-indolylidenemalononitrile 1

To a mixture of 2,3-diphenyl-5-formyl-6-methoxyindole (3.27 g, 0.01 mol) and malononitrile (0.66 g, 0.01 mol) in ethanol (30 ccm), 3 drops of piperidine were added, and the mixture was refluxed for 2 h, then left to cool down. The solid thus obtained was recrystallized from ethanol-acetone mixture yielding red crystals (90%), m.p. > 300°C, IR (cm^{-1}) : 3330 (NH), 2210 (C≡N).

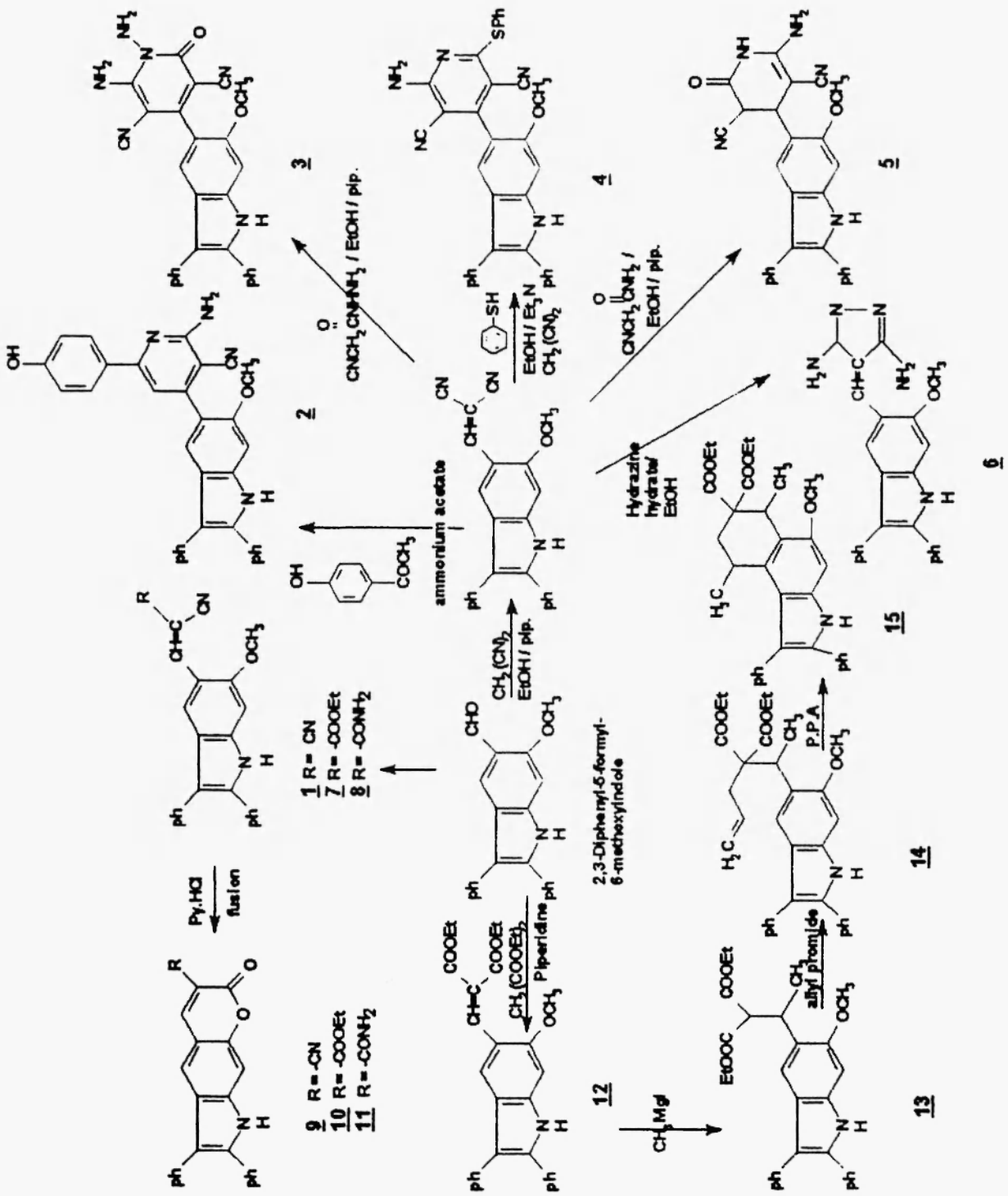
For $C_{25}H_{17}N_3O$ (375.4)

Calcd. : C 80.0 H 4.6 N 11.2

Found : C 79.8 H 4.6 N 11.3

2-Amino-3-cyano-6-p-hydroxyphenyl-4-(2`,3`-diphenyl-6`-methoxy-5`-indolyl)pyridine 2:

A mixture of 1 (3.75 g, 0.01 mol), p-hydroxyacetophenone (1.36 g, 0.01 mol) and ammonium acetate (1.2 g, 0.015 mol) in 20 ccm of ethanol was refluxed for 4 h then left to cool down. The solid thus obtained was recrystallized from ethanol yielding pale brown crystals (70%); m.p. 179°C. IR (cm^{-1}): 3600 (OH), 3330 (NH), 3100-3020 (NH_2), 2190 (C≡N), 1630 (C=N). ^{1}H NMR (ppm): 1.75 (s, 2H, NH_2), 3.9 (s, 3H, OCH_3), 5.3 (s, 1H,



OH), 6.8 (s, 1H, C_5-pyridine), 7.0 (s, 1H, C`-4), 7.3-7.5 (m, 14H, aromatic), 7.7 (s, 1H, C`-7), 8.3 (s, 1H, NH).

For $C_{33}H_{24}N_4O_2$ (508.6)

Calcd. : C 77.9 H 4.7 N 11.0

Found : C 77.7 H 4.9 N 11.1

1,6-Diamino-3,5-dicyano-4-(2`,3`-diphenyl-6`-methoxy-5`-indolyl)-2-pyridone 3:

A mixture of 1 (3.75 g, 0.01 mol) and 2-cyanoethanoic acid hydrazide (0.99 g, 0.01 mol) was suspended in ethanol (50 ccm), with a magnetic stirring. When few drops of piperidine were added, the reactants dissolved in full, then a yellow precipitate was formed, which was recrystallized from ethanol-acetone mixture (85% yield). M.p.> 300°C. IR (cm^{-1}): 3330 (NH), 3480, 3200 (NH_2), 2210 (C≡N). 1650 (C=O, N-aminopyridone).

For $C_{28}H_{20}N_6O_2$ (472.5)

Calcd. : C 71.2 H 4.3 N 17.8

Found : C 71.3 H 4.3 N 17.7

2-Amino-6-phenylthio-4-(2`,3`-diphenyl-6`-methoxy-5`-indolyl)-3,5-dicyanopyridine 4:

A mixture of 1 (1.87 g, 0.005 mol), benzenethiol (0.5 ccm, 0.005 mol) and malononitrile (0.33 g, 0.005 mol) in ethanol (20 ccm), containing 3 drops of triethylamine, was refluxed, with stirring, for 2 h, then left to cool down. The solid separated was recrystallized from diluted ethanol yielding pale brown crystals (85%); m.p. 110°C. IR (cm^{-1}): 3330 (NH), 3380, 3290 (NH_2), 2210 (C≡N), 1630 (C=N). ^1H NMR, (ppm): 1.58 (s, 2H, NH_2), 3.9 (s, 3H, OCH_3), 6.9 (s, 1H, C`-4), 7.3-7.5 (m, 15H, aromatic), 7.7 (s, 1H, C`-7), 8.3 (s, 1H, NH).

For $C_{34}H_{23}N_5OS$ (549.6)

Calcd. C 74.3 H 4.2 N 12.7

Found C 73.9 H 4.4 N 12.7

6-Amino-3,5-dicyano-4(2`,3`-diphenyl-6`-methoxy-5`-indolyl)-3,4-dihydro-2-pyridone 5:

To a mixture of 1 (3.75 g, 0.01 mol) and cyanoacetamide (0.84 g, 0.01 mol) in ethanol (30 ccm), 3 drops of piperidine were added, and the mixture was refluxed for 5 h. The solid thus obtained after cooling was recrystallized from ethanol, yielding orange crystals (80%); m.p. 115°C, IR (cm^{-1}): 3300 (NH), 2210 (C≡N), 1650 (CONH). ^1H NMR. (ppm): 1.6 (s, 2H, NH_2), 3.89 (s, 3H, OCH_3), 6.9 (s, 1H, C`-4), 7.3-7.5 (m, 12H; 10 aromatic, 2H, C-3, C-4 of pyridine), 7.8 (s, 1H, C`-7), 8.3 (s, 1H, NH).

For $C_{28}H_{21}N_5O_2$ (459.5).

Calcd. : C 73.2 H 4.6 N 15.2

Found : C 73.1 H 5.0 N 15.2

4-[(2`,3`-Diphenyl-6`-methoxy-5`-indolyl)methylene]-3,5-diaminopyrazole 6:

A mixture of 1 (3.75 g, 0.01 mol) and hydrazine hydrate (99%, 0.3 ccm) in ethanol (40 ccm) was refluxed for 3 h. The solid thus obtained after cooling, was recrystallized from ethanol-acetone mixture yielding yellow crystals (85%); m.p. > 300°C. IR (cm^{-1}): 3400 (NH_2), 3330 (NH), absence of -C≡N group.

For $C_{25}H_{21}N_5O$ (407.5)

Calcd. : C 73.7 H 5.2 N 17.2

Found : C 73.3 H 5.7 N 16.9

Ethyl α-cyano-β-(2,3-diphenyl-6-methoxy-5-indolyl)-acrylate 7 and α-cyano-β-(2,3-diphenyl-6-methoxy-5-indolyl)-acrylamide 8:

A mixture of 2,3-diphenyl-5-formyl-6-methoxyindole (3.27 g, 0.01 mol) and the active methylene nitrile (ethyl cyanoacetate or cyanoacetamide, 0.01 mol), in 20 ccm of ethanol containing two drops of piperidine, was refluxed

for 2 h. The solids thus obtained, after cooling, were recrystallized from ethanol to give:

Compound 7: as orange crystals (80%); m.p. 280°C. IR (cm^{-1}): 3330 (NH), 2220 (C≡N), 1700 (C=O, ester).

For $C_{27}H_{22}N_2O_3$ (422.4)

Calcd. : C 76.8 H 5.2 N 6.6

Found : C 76.7 H 5.3 N 6.7

Compound 8: as yellow crystals (75%); m.p. 220°C. IR (cm^{-1}): beside the characteristic bands of NH and C≡N, it displayed a band at 1670 (C=O, amide).

For $C_{25}H_{19}N_3O_2$ (393.0)

Calcd. : C 76.3 H 4.8 N 10.7

Found : C 76.1 H 4.7 N 10.7

Substituted pyrrolobenzopyrones 9, 10 and 11:

A mixture of 1.0 g of each of compounds 1,7,8 with an excess of pyridine hydrochloride was fused at 150°C, for 2 h, and then left to cool down. The whole was decomposed with water (20 ccm), followed by acidification with dil. HCl which gave solids recrystallized from ethanol to give:

Compound 9: as brown crystals (75%); m.p. 245°C. IR (cm^{-1}): 3330 (NH), 1720 (C=O, coumarin), 2220 (C≡N).

For $C_{24}H_{14}N_2O_2$ (362.4)

Calcd. : C 79.5 H 3.9 N 7.7

Found : C 79.6 H 4.0 N 7.6

Compound 10: as pale green crystals (78%); m.p. 260°C, IR (cm^{-1}): 3330 (NH), 1720 (C=O, coumarin), 1740, (ester).

For $C_{26}H_{19}NO_4$ (409.4)

Calcd. : C 76.3 H 4.7 N 3.4

Found : C 76.1 H 4.5 N 3.4

Compound 11: as brown crystals (73%), m.p. 243°C. IR (cm^{-1}): 3330 (NH), 1700 (C=O, coumarin), 1640 (C=O, amide). ^1H NMR (ppm): absence of the OCH_3 group.

For $C_{24}H_{16}N_2O_3$ (380.4)

Calcd. : C 75.8 H 4.2

Found : C 75.8 H 4.1

Diethyl 2[(2`,3`-diphenyl-6`-methoxy-5`-indolyl)methylene]-malonate 12:

A mixture of 2,3-diphenyl-5-formyl-6-methoxyindole (3.27 g, 0.01 mol), diethylmalonate (1.6 ccm, 0.01 mol), and 2 drops of piperidine in 30 ccm of ethanol was refluxed for 2 h. The solid thus obtained after cooling, was recrystallized from ethanol, yielding yellow crystals (95%), m.p. 210°C. IR (cm^{-1}): 3330 (NH), 1680 (C=O, α,β-unsaturated ester). ^1H NMR (ppm): 1.1 (t, 3H, CH_3), 1.3 (t, 3H, CH_3), 3.8 (s, 3H, OCH_3), 4.1 (q, 2H, CH_2), 4.3 (q, 2H, CH_2), 6.7 (s, 1H, C-4), 7.2-7.4 (m, 11H; 10 aromatic protons + 1 olefmic proton), 7.6 (s, 1H, C-7), 8.7 (s, 1H, NH).

For $C_{29}H_{27}NO_5$ (469.5)

Calcd. : C 74.2 H 5.8 H 3.0

Found : C 74.2 H 5.6 N 3.1

Ethyl α-carbethoxy-β-(2,3-diphenyl-6-methoxy-5-indolyl)-butanoate 13:

A suspension of 12 (4.69 g, 0.01 mol) in dry diethyl ether (50 ccm) was added to an ethereal solution of methyl magnesium bromide (0.03 mol), and the reaction mixture was refluxed for 5 h, then left overnight at room temperature and poured into ice-cold water. Both the organic layer and the ethereal extract of the aqueous layer were collected together, washed with water, dried, and the solvent was removed to give an oily residue which solidified and then this was crystallized from dil. ethanol, yielding pale yellow crystals (70%); m.p. 121°C, IR(cm^{-1}): 3330 (NH), 1725 (C=O, ester).

For $C_{30}H_{31}NO_5$ (485.6).

Calcd. : C 74.1 H 6.4 N 3.0

Found : C 74.3 H 6.2 N 3.1

Ethyl α-allyl-α-carbethoxy-β-(2,3-diphenyl-6-methoxy-5-indolyl)-butanoate 14:

To a solution of sodium ethoxide in ethanol (0.1 g, i.e. 0.04 mol of sodium in 50 ccm of absolute ethanol) compound 13 (4.85 g, 0.01 mol) was added, with stirring, within 15 min. A solution of allyl bromide (0.9 ccm, 0.01 mol) in absolute ethanol (5 ccm) was added within 30 min, then the reaction mixture was refluxed, with stirring, for 24 h. The solid thus obtained after cooling, was washed with water, then recrystallized from ethanol, giving yellowish needles (65%); m.p. 178°C. IR (cm^{-1}): 3330 (NH), 1420 ($CH=CH_2$), 1725 (C=O, ester). ^1H NMR (ppm): 0.85 (t, 3H, CH_3 of ester), 1.25 (t, 3H, CH_3 of ester), 3.46 (s, 3H, CH_3), 3.64 (s, 3H, OCH_3), 3.75 (q, 2H, CH_2 of ester), 3.89 (q, 2H, CH_2 of ester), 7.1-7.3 (m, 12H, aromatic), 8.2 (s, 1H, NH).

For $C_{33}H_{35}NO_5$ (525.6)

Calcd. : C 75.4 H 6.7 N 2.7

Found : C 75.3 H 6.7 N 2.6

6,6-Diethoxycarbonyl-4,7-dimethyl-8-methoxy-4,5,6,7-tetrahydrobenzo-[e]indole 15:

Compound 14 (1.0 g) was added to polyphosphoric acid (20 ccm), warmed upto 70°C while stirring, and the temperature was raised slowly up, and then maintained at about 95°C for 6 h. After cooling down, the reaction mixture was decomposed with a stirred mixture of 50 ccm of ice-cold water and 100 ccm of $CHCl_3$. The chloroform extract was washed with water, dried, and the solvent was distilled off to give a solid which on recrystallization from ethanol gave brown crystals (50%); m.p. 145°C. IR (cm^{-1}): 3330 (NH), 1720 (C=O, ester), absence of -$CH=CH_2$-.

For $C_{33}H_{35}NO_5$ (525.6)

Calcd.: C 74.4 H 6.7 N 2.7

Found: C 73.9 H 6.5 N 2.7

REFERENCES

[1] T. Yu, Il'yuchenok V.P. Lepekhin, K.S. Shadurskii, Tezisy Dokl. Nauchn. Sesii, Inst. Med. Radiol. Akad. Nauk SSSR, 1st, Sb., Obninsk 1965, p. 67; Chem. Abs. 65, 17569 (1966)

[2] US Patent 3, 551, 451 (1970); Chem. Abs. 74, 141523 (1971).

[3] Netherland Patent 5, 511, 253 (1967); Chem. Abs. 68 , 39469 (1968).

[4] Hungarian Patent 6, 608 (1973); Chem. Abs. 80, 47835 (1974)

[5] W. Dekker, H.A. Selling, J.C. Overeem, J. Agric. Food Chem. 23, 785 (1975).

[6] E.P. Feofilova, M.N. Bekhtereva, Yu.I. Kozlova, Microbiologiya, 39, 457 (1970).

[7] J.F. Reinhard, O.J. Plekss, J.V. Scudi, Proc. Soc. Exptl. Biol. Med. 104, 480 (1960)

[8] C. Fest, K.J. Schmidt, The Chemistry of Organophosphorous Pesticides, Springer-Verlag, Berlin, 1973

[9] M. Eto, Organophosphorus Pesticides, Organic and Biological Chemistry, CRC Press, Cleveland, Ohio, USA, 1974

[10] O.H. Hishmat, A.H. Abd-el-Rahman, S.M.Sh. Atta, M.M.F. Ismail, Bull. of Pharmac. Cairo Univ. 26, 73 (1987)

[11] E.P. Kohler, Am. Chem. J. 33, 21 (1905)

[12] E.P. Kohler, Am. Chem. J. 34, 132 (1906)

Received on May 13, 1997