The Behavior of 2-Carbomethoxy- and 2-Acetyl-1,4-benzoquinone in the Nenitzescu Indole Synthesis

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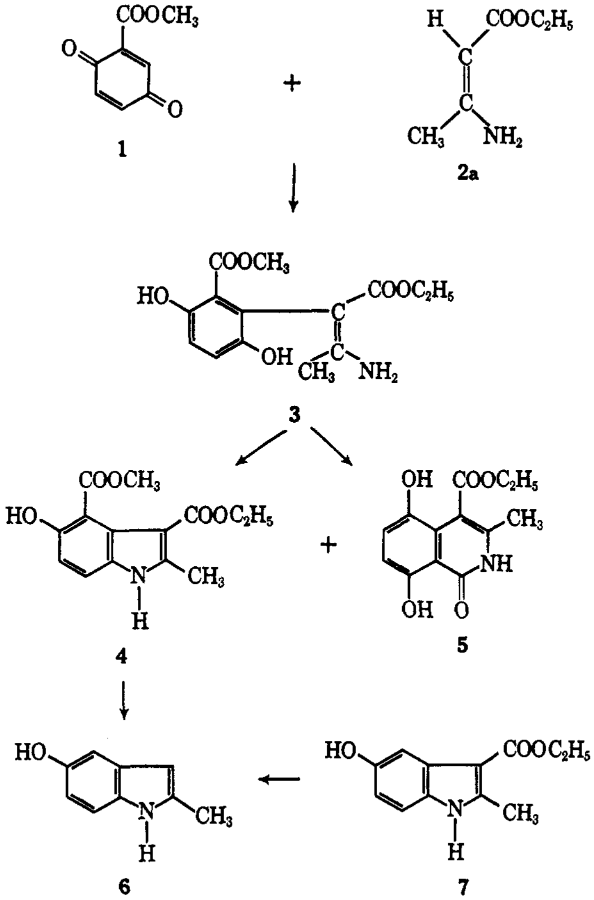
Reaction of 2-carbomethoxy-1,4-benzoquinone (**1**) with ethyl 3-aminocrotonate (**2a**) gave ethyl *trans*-3-amino-2-(2-carbomethoxy-3,6-dihydroxyphenyl)crotonate (**3**). This Michael-type adduct was transformed into ethyl 4-carbomethoxy-5-hydroxy-2-methylindole-3-carboxylate (**4**) and ethyl 5,8-dihydroxy-3-methylisocarbostyril-4-carboxylate (**5**) when treated with **1** under equilibrating conditions. 2-Acetyl-1,4-benzoquinone (**8**) reacted with **2a** and *t*-butyl 3-aminocrotonate (**2b**) to give the ethyl (**9a**) and *t*-butyl (**9b**) esters, respectively, of 5,8-dihydroxy-1,3-dimethylisoquinoline-4-carboxylic acid.

The utilization of the Nenitzescu reaction,[1] involving condensation of a *p*-benzoquinone with an aminocrotonate, for the preparation of indoles in the important 5-hydroxy series is well documented.[2a] Hitherto, with one exception,[3] condensations with monosubstituted benzoquinones have been reported to give only the 6-substituted 5-hydroxy isomer, although the mechanism[2] of this reaction suggests that the 4 and 7 isomers are also possible. Inasmuch as a quinoid acyl substituent is known to activate the *ortho* position to nucleophilic attack, it appeared reasonable that the use of such a quinone in this procedure would lead to a 4-substituted 5-hydroxyindole. In this paper we describe our studies with 2-carbomethoxy-1,4-benzoquinone (**1**) and 2-acetyl-1,4-benzoquinone (**8**).

Reaction of 2-carbomethoxy-1,4-benzoquinone (**1**)[4] with an equimolar quantity of ethyl 3-aminocrotonate (**2a**) gave 59% of the Michael adduct **3** (see Scheme I). This structure was indicated by analyses, the ultraviolet spectrum (λ_{max} 282 mμ), and the nmr spectrum (two essentially equivalent proton resonances at δ 6.66 and 6.67, a C-methyl proton resonance at 1.57,[5] and two hydroxyl proton resonances at 8.18 and 8.91).

In light of previous studies[3] it appeared that equilibration of **3** to the corresponding *cis* isomer in the presence of an appropriate oxidizing agent would allow completion of the Nenitzescu synthesis with the formation of the 4-carbomethoxy-5-hydroxyindole **4**. Indeed, when Michael adduct **3** was treated in acetic acid with 0.18 equiv of 2-carbomethoxy-1,4-benzoquinone (**1**), there was obtained a 30% yield of ethyl 4-carbomethoxy-5-hydroxy-2-methylindole-3-carboxylate (**4**) as well as 23% of ethyl 5,8-dihydroxy-3-methylisocarbostyril-4-carboxylate (**5**).

Scheme I



The assignment of indolic structure **4** to the major product was indicated by its ultraviolet spectrum (λ_{max} 220, 254, 305 mμ) which is in accord with spectra recorded for a variety of alkyl 5-hydroxy-2-methylindole-3-carboxylates.[3b,6] Moreover, the nmr spectrum of **4** revealed two nonequivalent aryl proton resonances at δ 6.71 and 7.03 possessing a typical *ortho* coupling constant of 9.0 cps and a methoxyl proton resonance at 3.63 in addition to the expected[5] 2-methyl (2.50) proton resonance. Chemical evidence for the indole ring system was afforded by acid decarbalkoxylation of **4** to the known 2-methylindol-5-ol (**6**).[1,7]

The 4-carbethoxy-5,8-dihydroxyisocarbostyril structure **5** was assigned to the coproduct as a result of the following evidence. The multiplicity of absorption bands in the ultraviolet spectrum (λ_{max} 242, 271, 306, 360 mμ) appeared to preclude an indolic structure, and this spectrum reasonably approximated those recorded for certain isocarbostyrils and their 3-carboxy deriva-

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(1) C. D. Nenitzescu, *Bull. Soc. Chim. Romania*, **11**, 37 (1929); *Chem. Abstr.*, **24**, 110 (1930).

(2) (a) G. R. Allen, Jr., C. Pidacks, and M. J. Weiss, *J. Am. Chem. Soc.*, **88**, 2536 (1966). (b) D. Raileanu and C. D. Nenitzescu, *Rev. Roumaine Chim.*, **10**, 339 (1965); *Chem. Abstr.*, **63**, 9903 (1965).

(3) Alkylquinones normally also afford the 7 isomer, but usually in only negligible amounts.[2a]

(4) J. Cason, *Org. Reactions*, **4**, 354 (1948).

(5) The 2-methyl proton resonance in the spectra of a variety of ethyl 5-hydroxyindole-3-carboxylates is observed at δ 2.62–2.70. However, the vinyl methyl proton resonance for four *trans* (ring/amine) Michael adducts such as **3** occurs at 1.61–1.88;[2a] see also G. O. Dudek and G. P. Volpp, *J. Am. Chem. Soc.*, **85**, 2697 (1963).

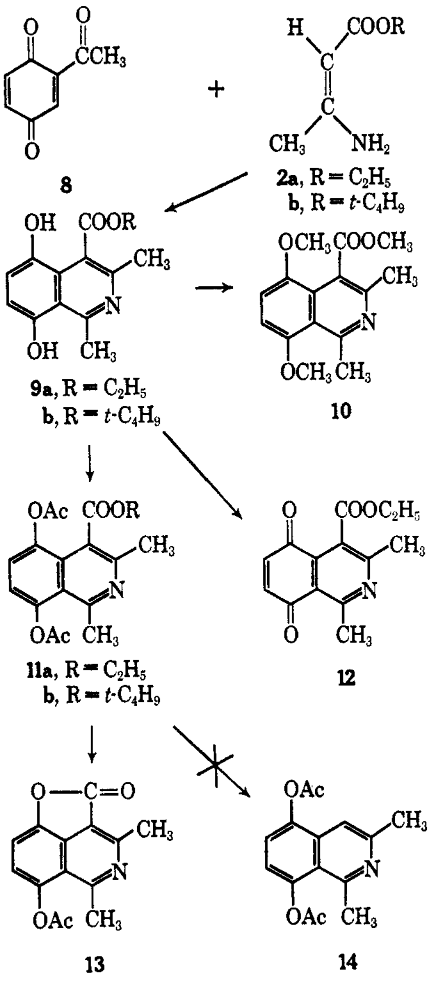
(6) For reproductions of certain typical spectra, see H. J. Teuber and G. Thaler, *Ber.*, **91**, 2264 (1958).

(7) R. J. S. Beer, K. Clarke, H. F. Davenport, and A. Robertson, *J. Chem. Soc.*, 2029 (1951).

tives.[8] The infrared spectrum (λ_{max} 3.10 broad, 5.86, 6.05, 6.40 μ) indicated the presence of a bonded hydroxyl group, as well as ester and amide functions. The first two structural features were also indicated by the nmr spectrum, which had a single proton resonance at δ 12.4 (bonded hydroxyl) and ethoxyl proton resonances at δ 1.28 and 4.26 (J = 7 cps). In addition to these resonances a methyl proton resonance is evident at δ 2.18 and nonequivalent, *ortho*-coupled (J = 8.5 cps) aryl proton resonances are observed at δ 6.66 and 7.00. Presumably, **5** results from the cyclization of the *cis* Michael adduct while still in the hydroquinone state. Thus, treatment of **3** with acetic acid in the absence of an oxidant gave only isocarbostyril **5** (25%).

With 2-acetyl-1,4-benzoquinone (**8**),[9] no 4-substituted 5-hydroxyindole was obtained, the only product being the isoquinoline **9a** or **9b**[10] (67–71%) (see Scheme II). Thus, in this instance for a reason that is not apparent the Michael adduct is formed predominantly, if not exclusively, in the *cis* form.[11] The structural assignments for isoquinoline esters **9** are based on the following considerations. The solubility of these products in dilute acid, as well as the ultraviolet spectra (λ_{max} 248–250, 345–355 mμ), precluded an indolic or Michael adduct structure. The nmr spectrum of the ethyl ester **9a** showed ethoxyl (δ 1.33, 4.31; J = 7.5 cps), two C-methyl (2.42, 3.05), two essentially equivalent aryl (6.85), and two hydroxyl (9.70) proton resonances. The presence of two hydroxyl groups was also indicated by formation of a diacetate **11a** and a dimethyl ether **10**. The *para* relationship of these groups was suggested by the oxidation of **9a** to quinone **12** with ferric chloride. Attempts to effect decarbomethoxylation of dimethyl ether **10** to the known[12] 5,8-dimethoxy-1,3-dimethylisoquinoline proved unsuccessful, presumably as a result of the hindered environment of the ester function. Thus, treatment of **10** with alkali, acid, or even lithium iodide in collidine was ineffective, **10** being recovered in each instance. Attempts to effect decarbalkoxylation in the t-butyl ester series also proved unsuccessful. Thus, pyrolysis of diacetate **11b** furnished the 4,5-lactone **13** rather than the desired isoquinoline **14**.

SCHEME II



Experimental Section

General.—Melting points were determined in open capillary tubes on a Mel-Temp apparatus and are uncorrected. Ultraviolet spectra were determined in methanol solution with a Cary recording spectrophotometer, and infrared spectra were measured in pressed potassium bromide disks with a Perkin-Elmer Model 21 spectrophotometer. Nmr spectra were determined in deuteriochloroform, unless otherwise specified, with a Varian A-60 spectrometer using tetramethylsilane as an internal standard.

Ethyl *trans*-3-Amino-2-(2-carbomethoxy-3,6-dihydroxyphenyl)-crotonate (3).—A solution of 830 mg (5.0 mmoles) of 2-carbomethoxy-1,4-benzoquinone (**1**) and 645 mg (5.0 mmoles) of ethyl 3-aminocrotonate (**2a**) in 10 ml of ethanol was heated at reflux temperature for 2 hr. The solvent was removed and trituration of the residue with ether gave 871 mg (59%) of crystals, mp 132.5–134.5°. A specimen prepared in a similar experiment was recrystallized from dilute methanol to give crystals: mp 131–134°; λ_{max} 282 mμ (ϵ 13,100); λ 2.94, 3.02, 6.01, 6.07, 6.56, 7.84, 8.16 μ.

Anal. Calcd for $C_{14}H_{17}NO_6$: C, 56.94; H, 5.80; N, 4.74. Found: C, 57.18; H, 6.22; N, 4.70.

Ethyl 4-Carbomethoxy-5-hydroxy-2-methylindole-3-carboxylate (4) and Ethyl 5,8-Dihydroxy-3-methylisocarbostyril-4-carboxylate (5).—A solution of 1.96 g of (6.65 mmoles) ethyl *trans*-3-amino-2-(2-carbomethoxy-3,6-dihydroxyphenyl)crotonate (**3**) and 200 mg (1.2 mmoles) of 2-carbomethoxy-1,4-benzoquinone (**1**) in 30 ml of glacial acetic acid was heated on the steam bath for 15 hr and then evaporated. The residue was dissolved in ethyl acetate and this solution was washed three times with water, dried, treated with activated charcoal, and evaporated. The residue was triturated with about 25 ml of methylene chloride and filtered to give 383 mg (23%) of **ethyl 5,8-dihydroxy-3-methylisocarbostyril-4-carboxylate** (**5**) as cream-colored crystals, mp 253–254° dec. Material from a similar experiment was recrystallized from acetone–hexane to give crystals: mp 256–258° dec; λ_{max} 242, 271, 306, 360 mμ (ϵ 12,900, 6580, 5790, 9210); λ 3.10 broad, 5.85, 6.05, 6.20, 6.39, 7.92 μ.

Anal. Calcd for $C_{13}H_{13}NO_5$: C, 59.31; H, 4.98; N, 5.32. Found: C, 59.47; H, 4.75; N, 4.62.

The methylene chloride filtrate was chromatographed on a magnesia–silica absorbent; the material eluted by methylene chloride–acetone (95:5) was recrystallized from acetone–hexane to furnish 550 mg (30%) of **ethyl 4-carbomethoxy-5-hydroxy-2-methylindole-3-carboxylate** (**4**) as white crystals, mp 141–143°. Material from a similar experiment was obtained as white plates: mp 146–147°; λ_{max} 220, 254, 305 mμ (ϵ 26,400, 13,200, 7700); λ 3.10, 5.95 shoulder, 6.02, 6.21, 6.31, 8.37 μ.

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[8] J. N. Chatterjea, H. C. Jha, and B. K. Banerjee, *J. Indian Chem. Soc.*, **43**, 633 (1966).

[9] M. C. Kloetzel, R. P. Dayton, and B. Y. Abadir, *J. Org. Chem.*, **20**, 38 (1955).

[10] The utility of t-butyl 3-aminocrotonate in Nenitzescu condensations was first demonstrated by Mr. R. Littell of these laboratories.

[11] A referee has suggested that exclusive isoquinoline formation may result from initial Schiff base formation with the acetyl carbonyl group.

[12] T. R. Govindachari and B. R. Pai, *J. Org. Chem.*, **18**, 1253 (1953).

Anal. Calcd for $C_{14}H_{15}NO_5$: C, 60.64; H, 5.45; N, 5.05. Found: C, 60.71; H, 5.56; N, 4.83.

Ethyl 5,8-Dihydroxy-3-methylisocarbostyril-4-carboxylate (5).—A solution of 590 mg (2.0 mmoles) of ethyl *trans*-3-amino-2-(2-carbomethoxy-3,6-dihydroxyphenyl)crotonate (**3**) in 10 ml of glacial acetic acid was heated on the steam bath 15 min and then allowed to stand at room temperature for 24 hr. The solution was distributed between ethyl acetate and water, and the aqueous phase was extracted further with ethyl acetate. The combined extracts were washed with water, dried, and evaporated. The residue was recrystallized from acetone–hexane to give 132 mg (25%) of crystals, mp 249–251° dec. An additional recrystallization gave material with mp 255–257° dec. The infrared spectrum of this material was identical with that of the material prepared above.

Anal. Found: C, 59.31; H, 5.21; N, 4.75.

2-Methylindol-5-ol (6).—Ethyl 4-carbomethoxy-5-hydroxy-2-methylindole-3-carboxylate (**4**) (210 mg, 0.76 mmole) and 25 ml of 20% hydrochloric acid were stirred under argon at reflux temperature for 2 hr. The cooled solution was rendered alkaline to litmus by addition of a potassium hydroxide solution and was then slightly acidified with hydrochloric acid. The resulting solution was extracted with ethyl acetate, and the dried extracts were evaporated. The residue was dissolved in methylene chloride, and this solution was passed through a short magnesia-silica column, using methylene chloride as the eluting solvent. The solid contained in the initial 200 ml of effluent was recrystallized from methylene chloride–hexane to give 70 mg (60%) of white needles, mp 132–134° (lit.[7] mp 134°).

Ethyl 5-hydroxy-2-methylindole-3-carboxylate[1] (**7**) (2.00 g) was treated similarly with 100 ml of 20% hydrochloric acid to give 0.81 g (60%) of white needles, mp 132–134°. A mixture of the two preparations melted at 132–134°.

Ethyl 5,8-Dihydroxy-1,3-dimethylisoquinoline-4-carboxylate (9a).—A solution of 870 mg (5.8 mmoles) of 2-acetyl-1,4-benzoquinone (**8**) and 750 mg (5.8 mmoles) of ethyl 3-aminocrotonate (**2a**) in 10 ml of chloroform was heated at reflux temperature for 2 hr. A precipitate began forming after 20 min. The solvent was removed from the mixture, and the residue was recrystallized from acetone–hexane to give 1.071 g (71%) of crystals which slowly decomposed above 267°. One additional recrystallization from acetone–hexane and then one from ethyl acetate with the aid of activated carbon gave 658 mg of pale yellow crystals, which were soluble in dilute hydrocloric acid solution: λ_{max} 210, 248, 345 mμ (ε 30,600, 19,200, 7020); λ 212, 261, 340, 410 mμ (ε 34,600, 21,000, 5500, 5200) (0.1 *N* HCl); λ 3.10, 3.90 broad, 5.75 shoulder, 5.91, 6.19, 6.37, 7.86 μ.

Anal. Calcd for $C_{14}H_{15}NO_4 \cdot 0.5CH_3COOC_2H_5$:[13] C, 62.94; H, 6.27; N, 4.59. Found: C, 63.32; H, 6.49; N, 4.92.

When treated with acetic anhydride and sodium acetate the diol furnished diacetate **11a** which was obtained from ether–petroleum ether (bp 60–70°) as white crystals: mp 118–119°; λ_{max} 223, 282, 330 mμ (ε 44,500, 6490, 4860); λ 5.66, 5.78, 6.15, 6.39, 8.04, 8.30–8.50 μ; nmr, δ 1.40 (three, triplet, $J = 7.5$ cps), 2.32 (three, singlet), 2.38 (three, singlet), 2.58 (three, singlet), 2.98 (three, singlet), 4.45 (two, quartet, $J = 7.5$ cps), 7.21 (one, doublet), 7.45 (one, doublet) ($J = 8.0$ cps).

Anal. Calcd for $C_{18}H_{19}NO_6$: C, 62.60; H, 5.55; N, 4.06. Found: C, 62.52; H, 5.53; N, 4.40.

Methyl 5,8-Dimethoxy-1,3-dimethylisoquinoline-4-carboxylate (10).—A stirred solution of 3.05 g of ethyl 5,8-dihydroxy-1,3-dimethylisoquinoline-4-carboxylate (**9a**) in 20 ml of ethanol and 35 ml of 2 *N* sodium hydroxide solution was heated to reflux temperature and treated by dropwise addition with 6.00 g of methyl sulfate. Heating was continued for 1 hr, after which an additional 6.00 g of methyl sulfate was added. The solution was then heated an additional 1 hr, whereafter it was cooled, and the resulting mixture was filtered to give 0.84 g of crystals that was recrystallized from dilute alcohol to furnish 0.66 g of crystals: mp 79–81°; λ_{max} 251, 330 shoulder, 350 mμ (ε 12,600, 5500, 6340); λ 265, 335, 400 mμ (ε 16,100, 3580, 6060) (0.1 *N* HCl); λ 5.76, 5.82, 6.15, 6.39, 7.90, 8.05 μ; nmr, δ 2.57 (three singlets), 3.03 (three, singlet), 3.82, 3.83, 3.92 (nine, three singlet), 6.67 (one, doublet), 6.84 (one, doublet) ($J = 7.5$ cps).

Anal. Calcd for $C_{15}H_{17}NO_4$: C, 65.44; H, 6.22; N, 5.09. Found: C, 64.92; H, 6.79; N, 5.37.

This substance was soluble in dilute hydrochloric acid and recovered (96%) unchanged after treatment with 5% potassium hydroxide at reflux temperature for 2.5 hr.

Ethyl 1,3-Dimethyl-5,8-dioxo-5H,8H-isoquinoline-4-carboxylate (12).—A solution of 1.00 g of ethyl 5,8-dihydroxy-1,3-dimethylisoquinoline-4-carboxylate (**9a**) and 2.00 g of ferric chloride in 100 ml of methanol was allowed to stand at room temperature for 4 hr. The solution was diluted with water and extracted with ethyl acetate, and the dried extracts were evaporated. The residue was recrystallized from ether–petroleum ether to give 593 mg (59%) of yellow crystals: mp 103.0–103.5°; λ_{max} 230, 350 mμ (ε 14,800, 2850); λ 5.78, 6.00, 6.20, 6.36 μ.

Anal. Calcd for $C_{14}H_{13}NO_4$: C, 64.86; H, 5.05; N, 5.40. Found: C, 65.29; H, 5.78; N, 5.38.

***t*-Butyl 5,8-Dihydroxy-1,3-dimethylisoquinoline-3-carboxylate (9b).**—A solution of 1.50 g (10 mmoles) of 2-acetyl-1,4-benzoquinone (**8**) and 1.57 g (10 mmoles) of *t*-butyl 3-aminocrotonate (**2b**) in 25 ml of chloroform was heated at reflux temperature for 2 hr to give 1.93 g (67%) of crystals that slowly decomposed above 212°. This product was freely soluble in dilute hydrochloric acid solution and was recrystallized from ethyl acetate to give cream-colored crystals: λ_{max} 213, 250, 355 mμ (ε 21,200, 9780, 4450); λ 214, 262, 340, 410 mμ (ε 18,900, 12,100, 2760, 3600) (0.1 *N* HCl); λ 3.10 broad, 3.88 broad, 5.90, 6.18, 6.38, 7.80, 8.60 μ; nmr, δ 1.58 (nine, singlet), 2.46 (three, singlet), 3.03 (three, singlet), 6.86 (two, singlet), 9.67 (two, singlet) (erased by methanol-d_4).

Anal. Calcd for $C_{16}H_{19}NO_4$: C, 66.42; H, 6.62; N, 4.84. Found: C, 66.34; H, 6.71; N, 4.58.

On treatment with sodium acetate and acetic anhydride this substance gave diacetate **11b**, obtained from ether–petroleum ether as crystals: mp 137–138°; λ_{max} 226, 285, 298, 330, 338 mμ (ε 46,000, 5600, 5220, 5600); λ 5.63, 5.79, 6.15, 6.38, 7.93, 8.40, 8.64 μ.

Anal. Calcd for $C_{20}H_{23}NO_6$: C, 64.33; H, 6.21; N, 3.75. Found: 64.09; H, 6.51; N, 3.97.

8-Acetoxy-5-hydroxy-1,3-dimethylisoquinoline-4-carboxylic Acid 4 → 5 Lactone (13).—A mixture of 100 mg of *t*-butyl 5,8-diacetoxy-1,3-dimethylisoquinoline-4-carboxylate (**11b**) and 20 mg of powdered porous plate was heated at 170–175° for 90 min. The cooled melt was extracted with acetone, and the resulting mixture was filtered. The filtrate was evaporated, and the residue was recrystallized from methylene chloride–hexane to give 38 mg (58%) of yellow crystals: mp 189–191°; λ_{max} 248, 315 shoulder, 346 mμ (ε 22,600, 3180, 5140); λ 212, 262, 373 mμ (ε 28,600, 21,100, 4660) (0.1 *N* HCl); λ 5.55, 5.67, 6.09, 6.23, 8.27 μ; nmr, δ 2.45 (three, singlet), 2.93 (three, singlet), 3.02 (three, singlet), 7.18 (two, singlet).

Anal. Calcd for $C_{14}H_{11}NO_4$: C, 63.67; H, 4.52; N, 5.71. Found: C, 64.05; H, 4.48; N, 5.25.

Registry No.—**1**, 3958-79-0; **3**, 14949-31-6; **4**, 14949-32-7; **5**, 14949-33-8; **6**, 13314-85-7; **7**, 7598-91-6; **8**, 1125-55-9; **9a**, 14949-37-2; **9b**, 14949-38-3; **10**, 14949-39-4; **11a**, 14949-40-7; **11b**, 14949-41-8; **12**, 14949-42-9; **13**, 14949-43-0.

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[13] Ethyl acetate indicated by the nmr spectrum.