METHOXYCARBOSTYRILS

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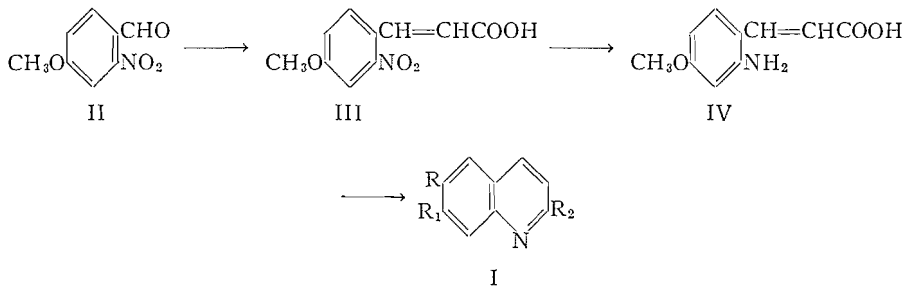
The central nervous sytem activity occasionally displayed by carbostyrils (1) led us to prepare several methoxy-substituted 2-hydroxyquinolines (cf. I) and a number of 2-quinolyl esters (Table I) for pharmacological evaluation. In general, the quinoline derivatives were based on structural features[2] of the hypotensive and sedative *Rauwolfia* alkaloids reserpine and resinnamine (2). Certain other 2-quinolyl esters (Table I), ethers, and 2-chloroquinolines were synthesized for comparison purposes.

Initially, it was considered necessary to prepare 6-methoxy-(I*a*), 7-methoxy-(I*b*), and 6,7-dimethoxy-carbostyril (I*c*). Of these, only 7-methoxycarbostyril was previously undescribed and synthesis was accomplished by the following reaction scheme (II → I).[3]

Chromyl chloride oxidation of 2-nitro-4-methoxytoluene (5) gave 2-nitro-4-methoxybenzaldehyde (II) as described by Boon (6). Condensation of benzaldehyde II with malonic acid led to 2-nitro-4-methoxycinnamic acid (III). Ferrous sulphate reduction of nitrobenzene III afforded 2-amino-4-methoxycinnamic acid (IV), which cyclized to 7-methoxycarbostyril (I*b*) in hot 2-propanol – hydrochloric acid solution. Phosphorus oxychloride readily converted carbostyril I*b* to 2-chloro-7-methoxyquinoline (I*d*).



II III IV

I

I*a*. R = OCH_3, R_1 = H, R_2 = OH
b. R = H, R_1 = OCH_3, R_2 = OH
c. R = R_1 = OCH_3, R_2 = OH
d. R = H, R_1 = OCH_3, R_2 = Cl
e. R = R_1 = OCH_3, R_2 = Cl
f. R = R_2 = R_2 = OCH_3
g. R = R_1 = OCH_3, R_2 = $OCH_2(CH_2)_2CH_3$
h. R = R_1 = OCH_3, R_2 = $OCH_2CH_2N(CH_3)_2$
i. R = R_1 = R_2 = OH

Preparation of 2-chloroquinoline I*d* illustrates the general reaction sequence employed for synthesis of 6,7-dimethoxycarbostyril (7) from 6-nitroveratraldehyde and subsequent conversion to 2-chloro-6,7-dimethoxyquinoline (I*e*). Dimethylformamide was found a superior solvent for effecting facile transformation of chloroquinoline I*e* to 2,6,7-trimethoxyquinoline (I*f*) with sodium methoxide. With methanol, Diglyme, or xylene as

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[2]*A number of recent investigations, directed toward preparation of useful ataractic agents, have been inspired by various aspects of the reserpine molecule: see for example, reference 3.*

[3]*Three years after the present investigation was completed, Sidhu (ref. 4) and colleagues reported a similar route to 7-methoxycarbostyril.*

solvent, extended reaction periods were necessary.[4] The butyl (I*g*) and dimethylaminoethyl (I*h*) ethers of dimethoxycarbostyril I*c* were prepared in an analogous manner. In addition, 2,6,7-trihydroxyquinoline (I*i*) was obtained by treating carbostyril I*c* with 48% hydrobromic acid.

The 2-quinolyl esters (Table I) were prepared by warming the respective carbostyril and acyl chloride in pyridine. The infrared spectrum of each ester revealed a single strong band in the 5.78–5.82 μ region, compatible with O-alkylation. Evidence in favor of N-alkylation was not demonstrated.[5]

EXPERIMENTAL[6]

6-Methoxycarbostyril (Ia)

A solution of 6-methoxyquinoline-N-oxide (37.0 g, ref. 11) in 300 ml of acetic anhydride was heated at reflux for 5 h before removal of excess solvent *in vacuo*. The dark residue was warmed (steam bath) for 1 h with 200 ml of 2 *N* sodium hydroxide. After cooling, the product was collected and washed with dilute hydrochloric acid and water. The grayish-brown colored crystals weighed 12.6 g (33%) and melted at 208–216°. Recrystallization from ethanol (Darco) afforded colorless crystals of 6-methoxycarbostyril melting at 220–221°. The product was shown to be identical with an authentic sample (12) by mixture melting point determination and infrared spectral comparison.

2-Nitro-4-methoxycinnamic Acid (III)

To a solution of malonic acid (224 g) in 750 ml of pyridine were added piperidine (20 ml) and 2-nitro-4-methoxybenzaldehyde (127 g, ref. 5 and 6). After a 3-hr period of heating (steam bath), evolution of carbon dioxide appeared to be complete and the solution was poured into 3.2 l of 10% hydrochloric acid. The tan-colored crystalline product weighed 120 g (77%) and melted at 245–247° (with sintering from 190°). Recrystallization from ethanol (Darco) gave pale yellow needles, m.p. 246–248°. A melting point of 240° has been reported (4) for this substance. Anal. Calc. for $C_{10}H_9NO_5$: C, 53.81; H, 4.06; N, 6.28. Found: C, 53.90; H, 3.97; N, 6.56.

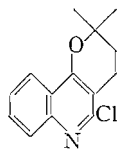
7-Methoxycarbostyril (Ib)

A solution of 2-nitro-4-methoxycinnamic acid (120 g) in 1.3 l of 28% aqueous ammonia was added, with stirring, to a warm solution of ferrous sulphate heptahydrate (1.3 kg) in 2 l of water. After the mixture was heated to 80° for 10 min, it was allowed to cool and was filtered through Celite. The filtrate was acidified to pH 6.5 with glacial acetic acid to furnish 44 g (43%) of light brown crystalline product (IV), m.p. 238–242° (dec.). A solution of the amino acid (44 g) in 500 ml of isopropyl alcohol containing concentrated hydrochloric acid (200 ml) was heated at steam bath temperature for 15 min, cooled, and filtered. The greyish-brown crystalline product was dissolved in 2 *N* sodium hydroxide (500 ml) and precipitated with 2 *N* hydrochloric acid. The tan-colored microcrystals weighed 18.3 g (45%) and melted at 198–200° (with sintering from 170°). Recrystallization from ethylene chloride gave colorless needles, m.p. 204–205.5°. An elemental analysis for nitrogen and a melting point of 199° has been reported (4) for carbostyril I*b*. Anal. Calc. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; H, 8.00. Found: C, 68.30; H, 4.91; N, 7.96.

2-Chloro-7-methoxyquinoline (Id)

A solution of 7-methoxycarbostyril (1.9 g) in 20 ml of phosphorus oxychloride was heated at reflux 3 h. The remaining phosphorus oxychloride was removed *in vacuo*. After addition of ice and aqueous ammonia, the basic mixture was extracted with chloroform. Removal of solvent from the dry (sodium sulphate) extract afforded 1.2 g (59%) of crystalline product; m.p. 96–97°, following recrystallization from benzene

[4]*The unexpected resistance displayed by chlorodeoxydihydroflindersine (ref. 8) (i) to nucleophilic attack by methoxide in methanol or xylene may be cited as another example: cf. also ref. 9.*



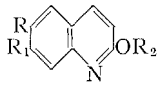
(i)

[5]*An imide structure, arising from N-alkylation, would be expected to exhibit a second band due to carbonyl absorption in the 5.85–6.00 μ region (ref. 10).*

[6]*Unless otherwise indicated, melting points were determined with a Fisher–Johns apparatus and are uncorrected. Elemental analyses were provided by the microanalytical laboratory of Eaton Laboratories. Infrared spectra were measured in chloroform solution using a Perkin–Elmer model 21 infrared spectrophotometer.*

TABLE I

2-Quinolyl esters



R	R_1	R_2	Yield,[a] %	Solvent[b]	M.p.,[c] °C	Formula	Calculated, % C	Calculated, % H	Calculated, % N	Found, % C	Found, % H	Found, % N
H	H	Nicotinyl	29	1	111–112	$C_{15}H_{10}N_2O_2$	71.99	4.03	11.20	72.14	3.94	11.22
H	H	3,4,5-Trimethoxybenzoyl	65	2	129.5–130.5	$C_{19}H_{17}NO_5$	67.25	5.05	4.13	67.00	4.65	4.09
OCH_3	H	3,4,5-Trimethoxybenzoyl	35	1	177–178.5	$C_{20}H_{19}NO_6$	65.03	5.19	3.79	65.20	4.88	3.66
OCH_3	H	3,4,5-Trimethoxycinnamoyl	32	2	120–121	$C_{22}H_{21}NO_6$	66.82	5.35	3.54	66.80	5.42	3.43
OCH_3	OCH_3	Benzoyl	50	2	133–134	$C_{18}H_{15}NO_4$	69.89	4.89	4.53	69.90	4.82	4.40
OCH_3	OCH_3	Nicotinyl	31	2	153–154	$C_{17}H_{14}N_2O_4$	65.80	4.55	9.03	66.00	4.60	8.88
OCH_3	OCH_3	3,4,5-Trimethoxybenzoyl	60	1	221–223	$C_{21}H_{21}NO_7$	63.15	5.30	3.51	63.10	5.01	3.31
CH_3	OCH_3	3,4,5-Trimethoxycinnamoyl	38	1	166–167.5	$C_{23}H_{23}NO_7$	64.93	5.45	3.29	65.10	5.25	3.10

[a]Yield based on a pure specimen.
[b]The ester was recrystallized from benzene (1), or benzene – petroleum ether (2).
[c]Melting point of the analytical sample.

(Darco)–hexane. The analytical sample crystallized as colorless needles from benzene–hexane, m.p. 97–98°. Anal. Calc. for $C_{10}H_8ClNO$: C, 62.02; H, 4.16; Cl, 18.31. Found: C, 62.20; H, 4.14; Cl, 18.05.

2-Chloro-6,7-dimethoxyquinoline (Ie)

A suspension of 6,7-dimethoxycarbostyril (100 g, ref. 7) in 300 ml of refluxing phosphorus oxychloride was stirred 3 h. Excess phosphorus oxychloride was removed *in vacuo* before the residue was cautiously added to an ice – aqueous ammonia mixture. The gray-colored crystalline product was collected and washed with water; yield 104.5 g (96%), m.p. 118–120°. Recrystallization from benzene (Darco) – petroleum ether gave colorless needles melting at 122–124°. Anal. Calc. for $C_{11}H_{10}ClNO_2$: C, 59.07; H, 4.51; Cl, 15.85. Found: C, 59.40; H, 4.50; Cl, 15.82.

2,6,7-Trimethoxyquinoline (If)

To a solution of 2-chloro-6,7-dimethoxyquinoline (I*e*, 5 g) in 100 ml of dimethylformamide was added 6.2 g of sodium methoxide. Before pouring the hot reaction mixture into 1 l of water, the resulting suspension was stirred and heated at reflux for 15 min. Collecting the colorless needles afforded 4.1 g (84%) of product melting at 116–117°. After further recrystallization from petroleum ether, the melting point remained at 116–117°. Anal. Calc. for $C_{12}H_{13}NO_3$: C, 65.74; H, 5.98; N, 6.39. Found: C, 65.75; H, 5.60; N, 6.24.

A fair yield (68%) in Diglyme was obtained after 24 h at reflux, while 48 h in refluxing xylene was needed to obtain a comparable yield (77%). The reaction in refluxing methanol, at periods up to 24 h, gave only crude starting material and was not further investigated. When a methanol solution of 6,7-dimethoxycarbostyril was treated with ethereal diazomethane and allowed to stand at room temperature for 24 h, only starting material was recovered.

2-Butoxy-6,7-dimethoxyquinoline (Ig)

Dimethylformamide (150 ml) and 20 g of 2-chloro-6,7-dimethoxyquinoline (I*e*) were added to solid sodium butoxide, prepared by adding sodium (12.4 g) to 200 ml of refluxing *n*-butyl alcohol (excess alcohol was removed *in vacuo*). Before the mixture was poured into 1.5 l of water, heating was maintained at 110–120° for 15 min. Heating the mixture to reflux caused excessive foaming. The crystalline product weighed 22.9 g and melted at 74–78° (with sintering from 65°). Distillation through a Claisen flask afforded 17.5 g (75%) of viscous oil, b.p. 175–179° (0.02 mm), which crystallized from benzene–petroleum ether as colorless crystals melting at 83–85°. An analytical sample, m.p. 85–86°, was crystallized from the same solvent. Anal. Calc. for $C_{15}H_{19}NO_3$: C, 68.74; H, 7.33; N, 5.36. Found: C, 68.74; H, 6.98; N, 5.08.

2-(2′-Dimethylamino)ethoxy-6,7-dimethoxyquinoline (Ih)

Sodium (12.4 g) was added in small portions to 150 ml of refluxing dimethylaminoethyl alcohol. Excess solvent was removed *in vacuo* and to the crystalline residue was added dimethylformamide (200 ml) and 20 g of 2-chloro-6,7-dimethoxyquinoline (I*e*). Before the mixture was poured into 2 l of cold water, stirring and heating at reflux was continued for 15 min. The aqueous solution was saturated with sodium chloride and extracted with chloroform. Removal of solvent from the dry (sodium sulphate) organic extract left a dark brown mobile oil. A portion of the oily residue (1.7 g) in benzene–hexane (1:1) was chromatographed on 50 g of activated alumina (Merck "Suitable for Chromatography"). Elution with 750 ml of the same solvent gave 0.42 g of colorless crystals. Further elution with 1 l of benzene afforded 0.28 g. After recrystallization from benzene – petroleum ether, the two crystalline fractions melted, respectively, at 108–110° and 112–114°. An analytical sample crystallized as colorless platelets from benzene – petroleum ether, m.p. 113–114°. Anal. Calc. for $C_{15}H_{20}N_2O_3$: C, 65.19; H, 7.30; N, 10.14. Found: C, 65.65; H, 7.23; N, 10.05.

The remaining reaction product was distilled through a Claisen flask. The main fraction boiled at 184-186° (0.01 mm) and separated from benzene – petroleum ether as colorless crystals (8.8 g), m.p. 100–107°. Several additional recrystallizations from benzene – petroleum ether raised the melting point to 109–111°. A mixture melting point determination with the chromatographed product showed no depression. The total yield of crystalline material amounted to 9.5 g (38%).

6,7-Dihydroxycarbostyril (Ii)

A stirred suspension of 6,7-dimethoxycarbostyril (I*c*, 30 g, ref. 7) in 600 ml of 48% hydrobromic acid was heated at reflux 24 h. The dark-colored solution was cooled and the brown needles (27.6 g) collected, washed with water, and recrystallized from glacial acetic acid (Darco). The straw-colored crystalline salt weighed 19.5 g and melted at 268–270° (with sintering from 260°). Precipitation from 450 ml of 2 *N* sodium hydroxide solution, with 2 *N* hydrochloric acid, gave 13 g of tan-colored *6,7-dihydroxycarbostyril*, m.p. 330–334° (dec.) with sintering from 315° .The yield was increased to 17.5 g (68%) by diluting the hydrobromic acid filtrate with ca. 100 ml of water and converting the second crop of hydrobromide to 6,7-dihydroxycarbostyil as previously described. An analytical sample was obtained as colorless crystals from glacial acetic acid, m.p. 338–340° (dec.) with darkening from 315°.[7] Anal. Calc. for $C_9H_7NO_3$: C, 61.01; H, 3.98; N, 7.91. Found: C, 60.90; H, 3.90; N, 7.82.

2-Quinolyl Esters (Table I)

Details for the preparation of 2-quinolyl-3′,4′,5′-trimethoxybenzoate will illustrate the general procedure

[7]*Capillary tube melting point.*

(13). To a warm solution of carbostyril (263 g) in 1.2 l of pyridine was added 418 g of 3,4,5-trimethoxybenzoyl chloride (14). Before pouring the solution into 13 l of water, heating was maintained at steam bath temperature for 1 h. The crude product was collected, dissolved in 2 l of chloroform, and washed successively with five 300 ml portions of 2 *N* sodium hydroxide and then with water. After removal of solvent from the dry organic extract, the residue was recrystallized (Table I).

Nicotinyl chloride was prepared as described by Clark-Lewis and Thompson (15). The following method was employed for preparation of *3,4,5-trimethoxycinnamoyl chloride*. Oxalyl chloride (35 ml) was added to 3,4,5-trimethoxycinnamic acid (39 g) and, after the initial reaction had subsided, the mixture was heated at reflux 1 h. Removal of excess oxalyl chloride *in vacuo* left a dark-colored crystalline residue which recrystallized from benzene – petroleum ether as yellow-colored crystals; yield 37 g (88%), m.p. 88–90°.

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SYNTHESIS OF TRYPTOPHAN-CARBOXYL-^{14}C[1]

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Tryptophan labelled in the carboxyl group with carbon 14 was required for studies on the biosynthesis of a fungal metabolite, but was not commercially available. The synthesis was achieved from indole-3-aldehyde and hydantoin-4-^{14}C* using a modification of the procedure described by Bond (1) for the corresponding ^{13}C-labelled compound.

In the modified method, the indolylidenehydantoin (I) was reduced by the action of Raney nickel alloy in dilute sodium hydroxide solution, instead of using Raney nickel catalyst in sodium hydroxide (2). The reduction product, indolylmethylhydantoin (II),

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