Hydroxylation index of 1-methoxyanthraquinone

$$= \frac{C}{100-\text{1-methoxyanthraquinone excreted in feces (\% of dose)}}$$

$$= \frac{7.45}{100-13.46} = 0.086$$

Hydroxylation index of 2-methoxyanthraquinone

$$= \frac{C}{100-\text{2-methoxyanthraquinone excreted in feces (\% of dose)}}$$

$$= \frac{3.18}{100-27.21} = 0.044$$

A: Alizarin and 1-hydroxyanthraquinone excreted in urine (free+conjugated, % of dose).
B: Alizarin and 2-hydroxyanthraquinone excreted in urine and feces (free+conjugated, % of dose).
C: Alizarin excreted in urine (free+conjugated, % of dose).

It is conjectured from those indices that 2-methoxyanthraquinone is easily demethylated at the double rate of 1-methoxyanthraquinone in opposition to usual chemical reaction, and the hydroxylation of the latter compound would be occurred at double speed as easily as that of the former.

The authors wish to express their thanks to Miss H. Ueda for her cooperation in a part of this work.

Summary

Each of 1-methoxy- and 2-methoxyanthraquinones was demethylated in rats to be metabolized to the 1-hydroxy compound and they were finally hydroxylated to alizarin. Every form in conjugation of their metabolites was determined using a densitometer and an ultraviolet spectrophotometer.

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UDC 615.782-012

150. Noboru Shigematsu: Studies on the Synthetic Analgesics. XVI.[1] Synthesis of 1-(2-*tert*-Aminoalkyl)-3,4-dihydrocarbostyrils.

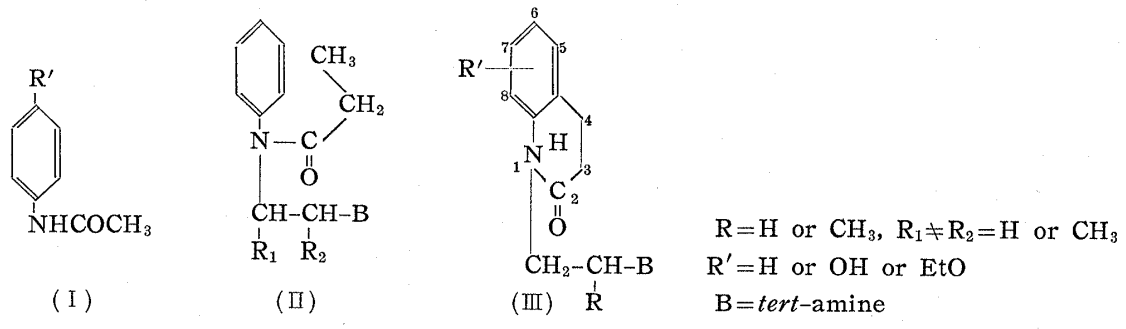
(*Osaka Research Laboratory, Tanabe Seiyaku Co., Ltd.*[*1])

Acetanilide (I: R′=H) and acetophenetidine (I: R′=EtO) have been regarded as a nonnarcotic antipyretic-analgesic for a long time. Boréus[2] recently reported that 4′-hydroxyacetanilide (I: R′=OH) showed the same antipyretic-analgesic action as acetophenetidine with less toxicity and diminished degree of methohemoglobin formation.

It is also noted that Wright[3] reported strong analgesic effect of a new series of propionanilide derivatives (II), the structure of which had likely been hinted by those of Methadone and Isomethadone.

*1 Kashima-cho, Higashiyodogawa-ku, Osaka (重松 遹).

1) Part XV: Yakugaku Zasshi, **81**, 815 (1961).
2) L.O. Boréus, F. Sandberg: Acta Physiol. Scand., **28**, 261 (1953).
3) W.B. Wright, H.J. Brabander, R.A. Hardy: J. Am. Chem. Soc., **81**, 1518 (1959).



(I) (II) (III)

Chart 1.

A great interest was therefore felt in the synthesis of a new type of compounds, 1-(2-*tert*-aminoalkyl)-3,4-dihydrocarbostyril (III : R′=H, R′=6-OH) in which a combination of the structural features of the above two compounds (I) and (II) may be considered. The compounds (III) with a hydroxyl group in 7-position were also prepared because analgesic effect was definitely favored by the introduction of a hydroxyl group into a position *meta* to the nitrogen substituent.[1] Effectiveness of these compounds would be of interest in terms of nonnarcotic antipyretic-analgesic.

3,4-Dihydrocarbostyril (IV) and 6-hydroxy-3,4-dihydrocarbostyril (V) were prepared by the Friedel-Crafts reaction of 3-chloropropionanilide and 3-chloro-4′-ethoxypropionanilide, respectively.[4] 6-Hydroxy-3,4-dihydrocarbostyril (V) was derived to its benzyloxyl analog (VI).

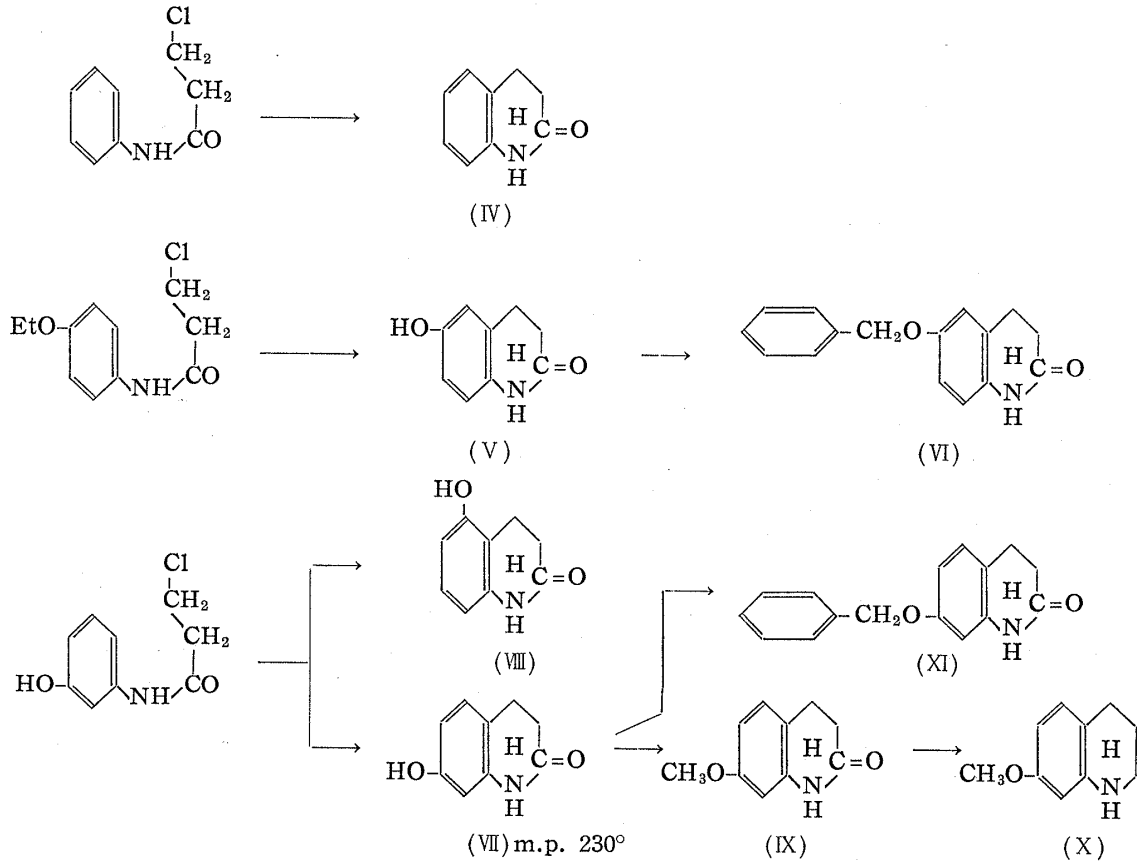


Chart 2.

4) F. Mayer, L. Zütphen, H. Philipps : Ber., **60**, 858 (1927).

Mayer[4] reported the Friedel-Crafts reaction of 3-chloro-3′-hydroxypropionanilide to give a reaction product of m.p. 230°, the position of the hydroxyl group of which remained ambiguous, whether in 5- or 7-position. A smooth reaction was observed by the modification of this Meyer's method, by heating a mixture of 3-chloro-3′-hydroxypropionanilide, aluminium chloride, sodium chloride, and potassium chloride (in a ratio of 1:5:0.6:0.6) at an elevated bath temperature of 170°, resulting in an improved yield of the reaction product. The infrared spectral data suggested the structure of 7-hydroxy-3,4-dihydrocarbostyril (Ⅶ) to the reaction product by the presence of out-of-plane vibrations of 1,2,4-trisubstituted benzene ring at 11.55 and 11.91 μ. The reaction product was then methylated to the methoxyl derivative (Ⅸ), followed by reduction with lithium aluminium hydride to the known compound, 7-methoxy-1,2,3,4-tetrahydroquinoline hydrochloride,[5] m.p. 188~189°, whose data agreed with those in the literature and confirmed the structure of the reaction product (Ⅶ). The hydroxyl derivative (Ⅶ) was converted to the benzyloxyl derivative (Ⅺ).

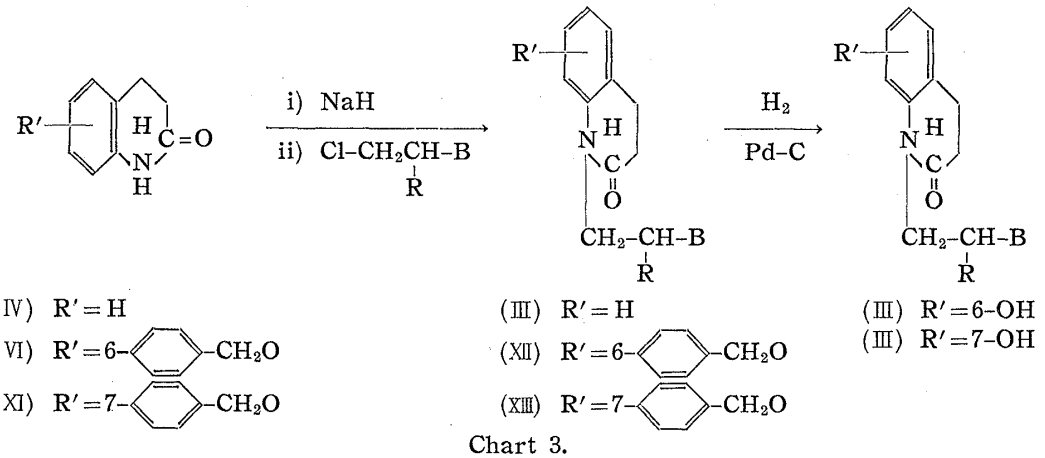
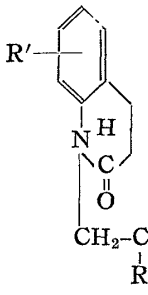


Chart 3.

Table I.



R′=H or 6-OH or 7-OH
R=H or CH_3
B=*tert*-amine

Compd. No.	B	R′	R	LD_{50} (mg./kg.)	Compd. No.	B	R′	R	LD_{50} (mg./kg.)
1	$N(CH_3)_2$	H	H	176.9	7	NH	6-OH	H	228
2	$N(Et)_2$	H	H	224.9	8	NH	6-OH	CH_3	307
3	NH	H	H	427.7	9	NH	7-OH	H	205
4	NHO	H	H	648.1	10	NH	7-OH	CH_3	103
5	NH	H	CH_3	648.5	11	$N(CH_3)(CH_2-CH_2-C_6H_5)$	7-OH	CH_3	316
6	$N(CH_3)(CH_2-CH_2-C_6H_5)$	H	CH_3	432.2					

5) P. Bratesi, G. Castorina : Il Farmaco (Pavia), Ed. Sci., **9**, 205 (1954) (C. A., **49**, 6258 (1955)).

Introduction of a basic substituent into the nitrogen atom of the carbostyrils (IV, VI, and XI) was carried out by the reaction of their sodium salt with appropriate 2-*tert*-aminoalkyl chloride in xylene and yielded 1-(2-*tert*-aminoalkyl)-3,4-dihydrocarbostyril (III: R′=H) and their 6-benzyloxy derivatives (XII) and 7-benzyloxy derivatives (XIII). The benzyloxy derivatives (XII and XIII) were debenzylated by catalytic reduction over palladium-carbon to the hydroxyl derivatives, 1-(2-*tert*-aminoalkyl)-6-hydroxy-3,4-dihydrocarbostyril (III : R′=6-OH) and 7-hydroxyl derivatives (III : R′=7-OH).

The values of LD_{50} of these compounds are presented in Table I.

Evaluation of analgesic effect was carried out by the hot-plate method[6] and the d'Amour Smith method. Introduction of a hydroxyl group into 7-position generally produced a much stronger effect. Pharmacological examination revealed depression of body temperature of a rat in compounds No. 1 and 3, and especially in No. 11. No. 11 was almost the same as aminopyrine both in its analgesic action and on body temperature. It was also noted that Nos. 10 and 11 showed an antitussive action in the same order as codeine. A more detailed report will be presented elsewhere.

Experimental

6-Benzyloxy-3,4-dihydrocarbostyril (VI)——6-Hydroxy-3,4-dihydrocarbostyril (10.9 g.) and KOH (3.75 g.) were dissolved in 250 cc. of EtOH. To this solution, benzyl chloride (8.45 g.) was added and heated for 5 hr. under reflux. After evaporation of EtOH (200 cc.), 1% NaOH solution (200 cc.) was added to the residue. The separated crystals were collected, washed with H_2O and dried. Yield, 14.4 g. (85.5%). The crude product was recrystallized from EtOH to colorless plates, m.p. 160～162°. *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found : C, 76.16; H, 6.12; N, 5.64.

7-Hydroxy-3,4-dihydrocarbostyril (VII)——A mixture of 3-chloro-3′-hydroxy propionanilide (40.3 g.), $AlCl_3$ (201.5 g.), NaCl (24.0 g.), and KCl (24.0 g.) was stirred and heated at 155～165° (oil bath temp. 170°) for 1 hr. After cool, the reaction mixture was poured into ice water, the separated crystals were collected, washed with H_2O, and dried. Yield, 26.3 g. (80%) of m.p. 225～228°. The crude product was recrystallized from hydr. EtOH to colorless plates, m.p. 228～230°.

7-Methoxy-1,2,3,4-tetrahydroquinoline (X)——7-Hydroxy-3,4-dihydrocarbostyril (VII) (3.3 g.) and KOH (1.2 g.) were dissolved in MeOH (30 cc.) to prepare potassium salt of 7-hydroxy-3,4-dihydrocarbostyril. MeI (2.9 g.) was added to this solution and heated for 6 hr. in a sealed tube at 100°. After cool, the reaction mixture was poured into dil. NaOH solution, the separated crystals were collected, washed with H_2O and dried. 7-Methoxy-3,4-dihydrocarbostyril (IX) (2.7 g., 75.7%), m.p. 146～148° (from EtOH), was obtained.

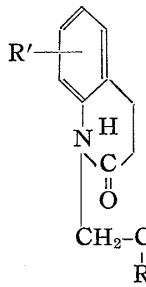
To a solution of $LiAlH_4$ (1.7 g.) in tetrahydrofuran (50 cc.), the methoxy derivative (IX) was added and heated for 8 hr. under reflux. After cool, the remaining $LiAlH_4$ was decomposed by addition of H_2O and inorganic substance was removed. The organic layer was dried, evaporated and the residue was distilled in a reduced pressure to yield 1.8 g. (72.6%) of a yellow liquid, $b.p_9$ 155～157°. The hydrochloride of this compound[5] melted at 188～189° (from EtOH).

7-Benzyloxy-3,4-dihydrocarbostyril (XI)——Benzyl chloride (9.2 g.) was added to a solution of 7-hydroxy-3,4-dihydrocarbostyril (VII) (11.8 g.) and KOH (4.5 g.) in EtOH (100 cc.) with stirring and refluxed for 5 hr. The reaction mixture was concentrated in a reduced pressure to about one-half the original volume. The residue was poured into dil. NaOH solution, the separated crystals were collected, washed with H_2O, and dried. Yield, 16.5 g. (90.1%), m.p. 147～150°. Recrystallization from EtOH yielded colorless needles, m.p. 153～154°. *Anal.* Calcd. for $C_{16}H_{15}O_2N$: C, 75.87; H, 5.97; N, 5.53. Found : C, 75.63; H, 5.84; N, 5.69.

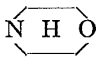
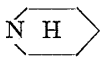
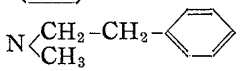
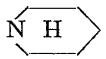
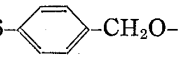
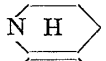
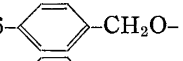
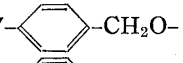
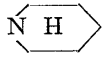
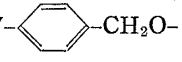
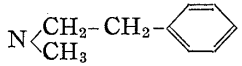
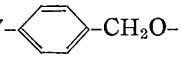
1-(2-*tert*-Aminoalkyl)-3,4-dihydrocarbostyril (III : R′=H), 1-(2-*tert*-Aminoalkyl)-6-benzyloxy-3,4-dihydrocarbostyril (XII) and 1-(2-*tert*-Aminoalkyl)-7-benzyloxy-3,4-dihydrocarbostyril (XIII)——N,N-Dimethyl-2-chloroethylamine hydrochloride,[7] 2-chlorotriethylamine hydrochloride,[8] 1-(2-chloroethyl)piperidine hydrochloride,[8] 4-(2-chloroethyl)morpholine hydrochloride,[9] and 1-(1-methyl-2-chloroethyl)piperidine hydrochloride[10] were prepared by adaptation of the procedure of Blicke.[8]

6) N.B. Eddy, D. Leimbach : J. Pharmacol. Exptl. Therap., **107**, 385 (1953).
7) L.A.R. Hall, V.C. Stephens, J.H. Burckhalter : Org. Syntheses, **31**, 37 (1951).
8) F.F. Blicke, C.E. Maxwell : J. Am. Chem. Soc., **64**, 429 (1942).
9) J.P. Mason, H.W. Block : *Ibid.*, **62**, 1443 (1940).
10) E. Rajner, E. Cerkovnikov, P. Stern : Arch. Pharm., **281**, 78 (1943).

TABLE II.



(III : R′=H), (XII), (XIII)

Compd. No.	B	R	R′	b.p. (°C/mm. Hg)	Derivatives	m.p. (°C)		Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1	$N(CH_3)_2$	H	H	135～139/0.40	Hydrochloride	colorless prisms	193～195 (EtOH–Et_2O)	[11]						
2	NEt_2	H	H	133～137/0.08	Picrate	yellow needles	122～124 (MeOH)	$C_{21}H_{25}O_8N_5$	53.05	5.30	14.73	53.27	5.23	14.71
3		H	H	153～158/0.08	Picrate	yellow needles	135～137 (EtOH)	$C_{22}H_{25}O_8N_5$	54.20	5.17	14.37	54.37	5.35	14.06
4		H	H	165～168/0.08	Picrate	yellow prisms	160～162 (dioxane–EtOH)	$C_{21}H_{23}O_9N_5$	51.53	4.74	14.31	51.52	4.91	14.16
5		CH_3	H	150～153/0.03	Oxalate	colorless prisms	177～179 (EtOH)	$C_{23}H_{28}O_5N_2$	66.97	6.84	6.79	66.55	7.04	6.69
6[a]		CH_3	H	195～198/0.08	Oxalate	colorless prisms	179～181 (EtOH)	$C_{19}H_{26}O_5N_2$	62.96	7.23	7.73	62.58	7.28	7.54
7		H		230～233/0.06	Oxalate	colorless prisms	172～174 (EtOH)	$C_{25}H_{30}O_6N_2$	66.06	6.65	6.16	65.98	6.50	6.53
8		CH_3		230～235/0.05	Oxalate	colorless needles	178～180 (EtOH)	$C_{26}H_{32}O_6N_2$	66.65	6.88	5.98	66.41	6.75	6.07
9		H		235～240/0.08	Oxalate	colorless needles	150～152 (EtOH)	$C_{25}H_{30}O_6N_2 \cdot \frac{1}{2}H_2O$	64.77	6.74	6.04	64.87	7.03	6.09
10		CH_3		225～230/0.03	Picrolonate	yellow needles	153～155 (EtOH)	$C_{34}H_{38}O_7N_6$	63.54	5.96	13.08	63.57	5.71	13.41
11[a]		CH_3		[b]										

Notes : *a*) N-(1-Methyl-2-chloroethyl)-N-methylphenethylamine hydrochloride, the starting material for Nos. 6 and 11, was prepared by adaptation of the procedure of Blicke[8] from 2-(N-methylphenethylamino)-1-propanol[12] (0.36 moles). The mixture was concentrated, and used for the following step.

b) The extracted benzene solution was dried and evaporated. The residue was dissolved in EtOH, filtered with charcoal, and used in the following reduction.

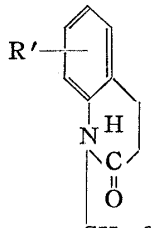
11) S. Ohki : Yakugaku Zasshi, **70**, 92 (1950).

12) Part XIV : *Ibid.*, **81**, 423 (1961).

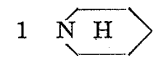
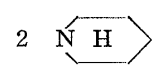
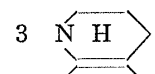
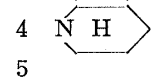
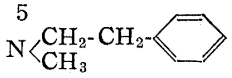
Xylene (50 cc.) was added to a solution of 2-*tert*-aminoalkyl chloride hydrochloride (0.033 moles) in H_2O (10 cc.) and the resulting mixture was basified with a dil. NaOH solution with cooling. The organic layer was separated and dried over K_2CO_3 for the next step. On the other hand, NaH (0.033 moles) was added to a solution of the corresponding 3,4-dihydrocarbostyril (0.03 moles) in xylene (100 cc.) with cooling, the mixture was heated slowly to the boiling point, and heating was continued at this temperature for 3~4 hr. to complete the formation of sodium salt of 3,4-dihydrocarbostyril. To this solution the xylene solution of 2-*tert*-aminoalkyl chloride was added drop by drop and the mixture was heated for 3~4 hr. under reflux. After cool, the reaction mixture was poured into ice water, the separated organic layer was shaken with 5% HCl, the acid layer was basified with K_2CO_3 and extracted with benzene. The benzene layer was dried, evaporated, and the residue was distilled in a reduced pressure. Yield, 85~90%.

1-(2-*tert*-Aminoalkyl)-6-hydroxy-3,4-dihydrocarbostyril (III : R′=6-OH) and 1-(2-*tert*-Aminoalkyl)-7-hydroxy-3,4-dihydrocarbostyril (III : R′=7-OH)——A solution of the benzyloxyl compound (XII or XIII) (0.02 moles) in EtOH (60 cc.) was reduced at atmospheric pressure in the presence of 10% Pd-C. About 1 mole of H_2 was smoothly absorbed. The filtrate from the catalyst was evaporated *in vacuo*, the residue was dissolved in NaOH solution, the alkaline solution was washed with benzene, treated with charcoal, filtered, and acidified with HCl. The acid solution was basified with an excess of K_2CO_3, the separated crystals were collected, and purified by recrystallization. Yield, 80~85%.

Table III.



CH_2-CH-B (III : R′=6-OH),
R (III : R′=7-OH)

Compd. No.	B	R	R′		m.p. (°C)	Formula	Analysis (%) Calcd. C	H	N	Found C	H	N
1		H	6-OH	colorless needles	132~134 (EtOH +H_2O)	$C_{16}H_{22}O_2N_2$	70.04	8.08	10.21	70.32	8.16	10.68
2		CH_3	6-OH	colorless needles	178~179 (EtOH +H_2O)	$C_{17}H_{24}O_2N_2$	70.80	8.39	9.71	70.55	8.38	9.74
3		H	7-OH	colorless needles	140~141 (EtOH)	$C_{16}H_{22}O_2N_2$	70.04	8.08	10.21	70.04	8.07	10.61
4		CH_3	7-OH	colorless prisms	178~180 (EtOH)	$C_{17}H_{24}O_2N_2$	70.80	8.39	9.71	70.74	8.62	9.79
5		CH_3	7-OH	Oxalate	colorless needles	153~155 (EtOH)	$C_{23}H_{28}O_6N_2$	64.47	6.59	6.54	64.49	6.62	6.74

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Summary

As a part of studies on nonnarcotic antipyretic-analgesic, 1-(2-*tert*-aminoalkyl)-3,4-dihydrocarbostyril (III : R′=H), 1-(2-*tert*-aminoalkyl)-6-hydroxy-3,4-dihydrocarbostyril (III : R′=6-OH), and 1-(2-*tert*-aminoalkyl)-7-hydroxy-3,4-dihydrocarbostyril (III : R′=7-OH) were synthesized. Analgesic, antitussive, and antipyretic action of these compounds were examined and some of these compounds showed anticipated activity.

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