Prostaglandins and Congeners.† Synthesis of Simplified Prostaglandins. Inhibition of Gastric Acid Secretion by 2-(ω-Carboxyalkyl)-3-alkylcycloalkanones

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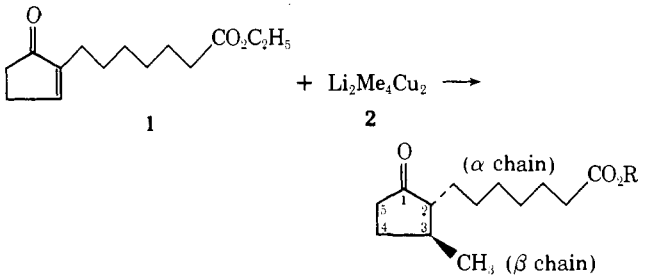
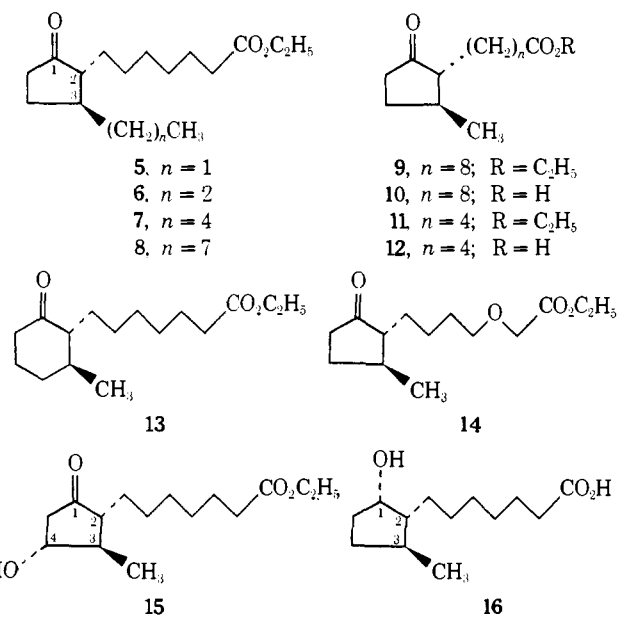
Simplified prostaglandin analogs were prepared and tested for inhibition of gastric acid secretion. An alkyl moiety of 1-8 carbon atoms was substituted for the C-13 to C-20 chain of the PG's. Analog variations included shortened and lengthened acid side chains, β-oxidation blockage, β-ketol, F_α-hydroxyl, and cyclohexanone substitution. Maximal inhibitory activity was obtained with the shorter alkyl moieties.

For some time we have investigated the possibilities of a convenient synthesis of the prostaglandins *via* the conjugate addition of an elaborated β chain to a cyclopentenone nucleus bearing the ω-carboxyalkyl α chain.[1] In the course of these studies we had occasion to perform some model experiments involving the treatment of cyclopentenone **1** with lithium methylcopper (**2**). This reaction proceeded smoothly to provide the 3-methylcyclopentanone **3**, which upon saponification produced the acid **4**.



3, R = C_2H_5
4, R = H

Since **4** retains several of the key features found in the prostaglandins, it was of interest to determine whether any prostaglandin-like activity was associated with it. Indeed, **4** produced a short-acting hypotensive effect upon intravenous administration in the anesthetized normotensive rat,[2]



5, n = 1
6, n = 2
7, n = 4
8, n = 7

9, n = 8; R = C_2H_5
10, n = 8; R = H
11, n = 4; R = C_2H_5
12, n = 4; R = H

13 14 15 16

similar to that produced by prostaglandin E_1, but manifested only at a much larger dose (MED ~2 mg/kg). Further studies with **4** revealed an ability to diminish gastric acid secretion in the pylorus-ligated (Shay) rat.[3] This latter observation was of sufficient interest to warrant the preparation and testing of a series of related compounds to elucidate further structure–activity relationships. Variations included homologation of the 3-methyl group to ethyl, propyl, pentyl, and octyl, **5–8**, as well as a two-carbon lengthening and shortening of the α chain, **9–12**. In addition, the cyclopentyl ring was enlarged to cyclohexyl, **13**. Since prostaglandins and fatty acids in general undergo metabolism by β-oxidation, we prepared the oxa derivative **14**, wherein such a course is not possible. The homolog **10** bearing the C-9 α chain was also of interest in this respect, since one β-oxidation sequence would provide the C-7 derivative **4**. We also prepared the 4-hydroxy derivative **15** embracing the β-ketol feature of the prostaglandin E series, and the 1α-ol, **16**, analogous to the prostaglandin F_α series.

Chemistry. Compounds **3**, **9**, **11**, **13**, **14**, and **15** were prepared by conjugate addition of lithium methylcopper (**2**)[4] to their respective cycloalkenones.‡ Compounds **5**, **6**, and **8** were prepared by the copper(I) ion[4] catalyzed conjugate addition[1b] of the appropriate alkylmagnesium halide to cyclopentenone **1**. Catalytic hydrogenation of 2-(6-carbethoxyhexyl)-3-(*trans*-1-pentenyl)cyclopentanone§ produced **7**. Lithium tri-*sec*-butylborohydride reduction[6] of **4** gave alcohol **16**.

A point worthy of note concerns the relative configuration of the α and β side chains in the cycloalkanones prepared. The reaction mixture obtained by treatment of cyclopentenone **1** with cuprate **2** was quenched by addition to cold aqueous ammonium chloride solution. The α/β-chain configuration of the product thus obtained was 85% trans and 15% cis as determined by pmr and glc analyses. Treatment of this product under conditions which would be expected[7] to equilibrate 2,3-dialkylcyclopentanones, *i.e.*, refluxing with ethanolic potassium acetate or saponification with potassium hydroxide, failed to change the trans/cis ratio. It is apparent that kinetic protonation of the intermediate enolate obtained by the reaction of **1** with **2** takes place from the more hindered face and gives what is also the product of thermodynamic control. The thermodynamic trans/cis ratios for the various products described are given in Table I.

Biological Evaluation. Inhibition of gastric acid secretion (GAS) was determined by the usual Shay procedure[3] (pylorus-ligated rat) using a 3-hr end point and administer-

†Prostaglandins and Congeners. 7. For the previous paper in this series, see M. B. Floyd.[12]

‡The cycloalkenones used to synthesize compounds **3**, **5**, **6–9**, **11**, and **13** were prepared from their corresponding cycloalkanones by the sequence of enol acetylation, bromination, and dehydrobromination. The cyclopentenone precursor to compound **14** was prepared from 2-(3-carbethoxypropyl)-cyclopent-2-en-1-one, also derived *via* the above scheme, by the sequence methoxime formation, diisobutylaluminum hydride reduction of the ester to the alcohol, alkylation of the lithium alkoxide with lithium chloroacetate, deblocking, and esterification. The synthesis of these cycloalkenones is the subject of a paper in preparation; see also ref 5.

§2-(6-Carbethoxyhexyl)-3-(*trans*-1-pentenyl)cyclopentanone was prepared by conjugate addition[1a] of lithium diisobutylmethyl-*trans*-1-pentenylalanate to cyclopentenone **1**. We thank Dr. M. B. Floyd for a supply of this substance.

Table I

Compd	Method of prepn[a]	Yield, %	Trans/cis isomer ratios: Pmr[b]	Glc[c]: % trans	Column[d]	Temp, °C	RT[e]	% cis	RT[e]
3	A	92	85/15	85	A	180	10.0	15	12.0
4	–[f]	95	85/15	–[g]	–	–	–	–[g]	–
5	B	39	–[g]	89	B	170	7.4	11	8.0
6	B	44	–[g]	89	B	170	8.1	11	9.9
7	–[f]	93	–[g]	94	A	180	25.8	6	28.0
8	B	17	–[g]	–[g]	–	–	–	–[g]	–
9	A	75	85/15	87	B	180	5.7	13	6.5
10	–[f]	88	85/15	–[g]	–	–	–	–[g]	–
11	A	58	85/15	87	A	180	4.9	13	6.1
12	–[f]	95	85/15	–[g]	–	–	–	–[g]	–
13	A	66	65/35	67	B	180	4.3	33	5.0
14	A	31	80/20	87	A	180	16.1	13	19.9

[a]Method A, lithium methylcopper addition; Method B, copper(I) ion-catalyzed Grignard addition. [b]Ratios (±5%) determined by integration of the 3-methyl signals. [c]Ratios (±3%) determined by integration of glc peak areas. [d]Columns (see Experimental Section) operated isothermally at indicated temperature. [e]Minutes. [f]Miscellaneous method. [g]Not determinable.

ing the test compounds by the intraduodenal route at the time of ligation. The results, which are summarized in Table II, indicate that maximal potency is obtained with a methyl or perhaps also an ethyl substituent at the cyclopentanone 3 position and is consistent with lengthened and shortened carboxylic acid side chains as well as the reduction of the keto function to an α-hydroxyl group. Activity appears to be diminished by insertion of a β-oxa feature in the acid side chain, **14**, and by homologation of the ring to a cyclohexanone. When compared by this assay, several of the 3-methyl-*d,l* racemates, notably **3, 4, 9, 12,** and **16,** appear to have retained to a significant degree (approximately 10–30%) the GAS inhibitory activity of *l*-PGE_1.

Experimental Section

All organometallic reactions were performed under an inert atmosphere of argon or nitrogen. The standard isolation procedure employed, *i.e.*, "worked-up with," involved extracting the aqueous phase with the indicated solvent, washing the organic phase with water and then saturated brine, drying the extract with anhydrous $MgSO_4$, and evaporating the solvent at reduced pressure. Pmr spectra were measured (Varian A-60 or HA-100D) in $CDCl_3$, unless otherwise stated, using $(CH_3)_4Si$ as internal standard. Peak multiplicity is depicted as s for singlet, d for doublet, t for triplet, q for quartet, and m for multiplet. All compounds had ir and pmr spectra compatible with their assigned structures. Glc analyses were determined upon an F&M 720 gas chromatograph at a 75 ml/min flow rate of helium and isothermally at the indicated temperature. Stainless steel columns packed with diethylene glycol succinate on 60–80 mesh H.P. Chromosorb G were used: column A, 6-ft 3% DEGS; column B, 34-in. 3% DEGS. A Du Pont 310 curve resolver was employed to determine glc peak areas. Analytical results indicated by symbol only of an element were within ±0.4% of their calculated values. Melting points were determined in an open capillary tube with a Mel-Temp apparatus and are uncorrected.

2-(6-Carbethoxyhexyl)-3-methylcyclopentanone (3). To a slurry of 38.08 g (0.200 mol) of CuI in 60 ml of ether was added 238 ml (0.390 mol) of 5.07% methyllithium in ether dropwise to maintain the temperature at −10 to −5°. To the resulting solution was then added 23.8 g (0.100 mol) of 2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (1)[1,&] over 10 min and the mixture was stirred at −10° for 1 hr. The mixture was poured into excess cold saturated NH_4Cl solution, stirred for 1 hr, worked up with ether, and distilled to yield 23.43 g (92%) of a colorless oil, bp 112–115° (0.075 Torr). Pmr analysis indicated this oil to contain 85% of the trans isomer, δ 1.17 (d, J = 5.5 Hz, $CHCH_3$)[7] and 15% of the cis isomer, δ 0.90 (d, J = 7.0 Hz, $CHCH_3$).[7] *Anal.* ($C_{15}H_{26}O_3$) C, H.

&For the methyl ester of cyclopentenone 1, see ref 8.

2-(6-Carboxyhexyl)-3-methylcyclopentanone (4). A mixture of 15.20 g (0.0598 mol) of 2-(6-carbethoxyhexyl)-3-methylcyclopentanone (3) and 10.0 g (0.180 mol) of KOH in 400 ml of 1:1 aqueous methanol was stirred at ambient temperatures for 3 hr. The solvent was partially evaporated and the residue was poured into water and extracted with ether. The aqueous phase was acidified with HCl and worked up with ether to yield an oil. Distillation gave 12.87 g (95%) of an oil, bp 137–140° (0.05 Torr). Pmr analysis integrated for 85% of the trans isomer, δ 1.17 (d, J = 5.5 Hz, $-CHCH_3$),[7] and 15% of the cis isomer, δ 0.89 (d, J = 7.0 Hz. $-CHCH_3$).[7] *Anal.* ($C_{13}H_{22}O_3$) C, H.

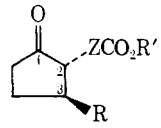
2-(6-Carbethoxyhexyl)-3-ethylcyclopentanone (5). To an ice-cold solution of 4.766 g (0.020 mol) of 2-(6-carbethoxyhexyl)cyclopent-2-en-1-one (1) and 0.330 g of copper(I) iodide–tri-*n*-butylphosphine[4,9] in 40 ml of THF was added dropwise a solution of ethylmagnesium iodide in toluene prepared at 40–45° from 0.535 g (0.022 g-atom) of magnesium, 3.44 g (0.022 mol) of ethyl iodide, 1.89 g (0.022 mol) of tetrahydrofuran, and 8 ml of toluene.[1b,10] The reaction mixture was then stirred at room temperature for 1 hr, poured into cold dilute HCl, and worked up with ether. The residue was dissolved into ether and treated with 4 molar equiv of aqueous $KMnO_4$ for 10 min to oxidize residual starting cyclopentenone. The mixture was filtered; the filtrate yielded an oil, which was purified by chromatography upon silica gel using 9:1 benzene–ether as eluent to yield 2.1 g (39%) of an oil. *Anal.* ($C_{16}H_{28}O_3$) C, H.

2-(6-Carbethoxyhexyl)-3-propylcyclopentanone (6). In the manner described for the preparation of **5**, treatment of 2.38 g (0.010 mol) of 1 with a Grignard reagent prepared from 1.55 g (0.0125 mol) of 1-bromopropane and 0.304 g (0.0127 g-atom) of magnesium gave, after purification upon 10% silver nitrate impregnated alumina with 19:1 hexane–ethyl acetate, 1.213 g (44%) of a colorless oil. *Anal.* ($C_{17}H_{30}O_3$) C, H.

2-(6-Carbethoxyhexyl)-3-pentylcyclopentanone (7). A solution of 2.00 g (0.0065 mol) of 2-(6-carbethoxyhexyl)-3-(*trans*-1-pentenyl)cyclopentanone[8] in 50 ml of ethanol was hydrogenated with 1 g of 10% Pd-on-carbon catalyst at 30 psi until hydrogen uptake ceased. The mixture was filtered, evaporated, and worked up with ether to yield 1.94 g (93%) of an oil. *Anal.* ($C_{19}H_{34}O_3$) C, H.

2-(6-Carbethoxyhexyl)-3-octylcyclopentanone (8). In the manner described for the preparation of **5,** treatment of 3.00 g (0.0126 mol) of 1 with a Grignard reagent prepared from 3.32 g (0.0138 mol) of 1-iodooctane and 0.332 g (0.0138 g-atom) of magnesium gave, after purification on Florisil using 9:1 hexane–ether, 0.737 g (17%) of an oil. Glc analysis did not resolve the isomers. *Anal.* ($C_{22}H_{40}O_3$) C, H.

Table II. Inhibition of Gastric Acid Secretion[a]



Compd	R	Z	R′	Dose, mg/kg	Inhibn of control GAS, %
3	CH_3	$(CH_2)_6$	C_2H_5	100	92
				50	58
				25	11
4	CH_3	$(CH_2)_6$	H	100	84
				50	62
				25	37
5	C_2H_5	$(CH_2)_6$	C_2H_5	100	81
6	n-C_3H_7	$(CH_2)_6$	C_2H_5	100	54
7	n-C_5H_{11}	$(CH_2)_6$	C_2H_5	100	61
9	CH_3	$(CH_2)_8$	C_2H_5	50	67
				25	39
10	CH_3	$(CH_2)_8$	H	100	91
				25	1
11	CH_3	$(CH_2)_4$	C_2H_5	100	88
12	CH_3	$(CH_2)_4$	H	50	86
				12.5	7
13	CH_3 (cyclohexanone ring)	$(CH_2)_6$	C_2H_5	100	60
14	CH_3	$(CH_2)_4OCH_2$	C_2H_5	200	55
16	CH_3 (1α-ol)	$(CH_2)_6$	H	50	53
l-Prostaglandin E_1				10	57
				5	41
				1	Nil

[a] Determined with the pylorus-ligated rat, essentially as per ref 3. Singly caged male CFE rats were fasted for 48 hr before each test. Water was supplied *ad libitum*. Body weights at the time of experiment ranged between 200 and 250 g, and the animals were sorted into comparable weight groups. Control groups consisted of seven animals, treated groups of five each. Test compounds were injected into the duodenum just after ligation. Three hours after surgery the rats were decapitated and exsanguinated, the gastric contents were collected, and the acidity was determined by titration with 0.04 *N* NaOH to pH 8.4.

2-(8-Carbethoxyoctyl)-3-methylcyclopentanone (9). In the manner described for the preparation of **3**, treatment of 2.519 g (0.00947 mol) of 2-(8-carbethoxyoctyl)cyclopent-2-en-1-one[4] with lithium methylcopper prepared from 3.60 g (0.0190 mol) of Cu[I]I and 21.8 ml of 1.7 *M* (0.037 mol) methyllithium in ether gave, after purification on silica gel using 9:1 benzene–ether, 2.078 g (75%) of a colorless oil. Pmr analysis integrated for 85% of the trans isomer, δ 1.15 (d, J = 5.5 Hz, $CHCH_3$), and 15% of the cis isomer, δ 0.88 (d, J = 7.0 Hz, $CHCH_3$). *Anal.* ($C_{17}H_{30}O_3$) C, H.

2-(8-Carboxyoctyl)-3-methylcyclopentanone (10). In the manner described for the preparation of **4**, 1.80 g of ester **9** was saponified to yield 1.43 g (88%) of an oil. Pmr analysis integrated for 85% of the trans isomer, δ 1.15 (d, J = 5.5 Hz, $CHCH_3$), and 15% of the cis isomer, δ 0.88 (d, J = 7.0 Hz, $CHCH_3$). *Anal.* ($C_{15}H_{26}O_3$) C, H.

2-(4-Carbethoxybutyl)-3-methylcyclopentanone (11). In the manner described for the preparation of **3**, treatment of 4.20 g (0.0199 mol) of 2-(4-carbethoxybutyl)cyclopent-2-en-1-one[4] with lithium methylcopper, prepared from 7.60 g (0.0399 mol) of Cu[I]I and 33.8 ml of 2.29 *M* (0.0770 mol) methyllithium in ether, gave after purification on 10% silver nitrate–impregnated alumina using 19:1 hexane–ethyl acetate 2.44 g (58%) of a colorless oil. Pmr analysis integrated for 85% of the trans isomer, δ 1.15 (d, J = 5.5 Hz, $-CHCH_3$), and 15% of the cis isomer, δ 0.87 (d, J = 7.0 Hz, $CHCH_3$). *Anal.* ($C_{13}H_{22}O_3$) C, H.

2-(4-Carboxybutyl)-3-methylcyclopentanone (12). In the manner described for the preparation of **4**, 1.90 g (0.0084 mol) of ester 11 was saponified to yield 1.65 g (95%) of an oil. Pmr analysis integrated for 85% of the trans isomer, δ 1.14 (d, J = 5.5 Hz, $CHCH_3$), and 15% of the cis isomer, δ 0.86 (d, J = 7.0 Hz, $CHCH_3$). *Anal.* ($C_{11}H_{18}O_3$) C, H.

2-(6-Carbethoxyhexyl)-3-methylcyclohexanone (13). In the manner described for the preparation of **3**, treatment of 3.78 g (0.0150 mol) of 2-(6-carbethoxyhexyl)cyclohex-2-en-1-one[4] with lithium methylcopper, prepared from 5.70 g (0.030 mol) of Cu[I]I and 28 ml of 2.1 *M* (0.0588 mol) methyllithium in ether, gave 2.60 g (66%) of a colorless oil, bp 117–118° (0.12 Torr). Pmr analysis integrated for 65% of the trans isomer, δ 1.02 (d, J = 5.5 Hz, $CHCH_3$),[7] and 35% of the cis isomer, δ 0.80 (d, J = 7.0 Hz, $CHCH_3$).[7] *Anal.* ($C_{16}H_{28}O_3$) C, H.

2-(6-Carbethoxy-5-oxahexyl)-3-methylcyclopentanone (14). In the manner described for the preparation of **3**, treatment of 2.40 g (0.0100 mol) of 2-(6-carbethoxy-5-oxahexyl)cyclopent-2-en-1-one[4] with lithium methylcopper, prepared from 3.81 g (0.020 mol) of Cu[I]I and 18.6 ml of 2.1 *M* (0.039 mol) of methyllithium in ether, gave after purification upon silica gel using 9:1 benzene–ether 0.829 g (31%) of an oil. Pmr analysis integrated for 80% of the trans isomer, δ 1.16 (d, J = 5.5 Hz, $CHCH_3$), and 20% of the cis isomer, δ 0.88 (d, J = 7.0 Hz, $CHCH_3$), 4.08 (s, 2 H, OCH_2CO_2). *Anal.* ($C_{14}H_{24}O_4$) C, H.

2α-(6-Carbethoxyhexyl)-4α-hydroxy-3β-methylcyclopentanone (15). In the manner described for the preparation of **3**, treatment of 1.69 g (0.00500 mol) of 2-(6-carbethoxyhexyl)-4-tetrahydropyranyloxycyclopent-2-en-1-one** with lithium methylcopper, prepared from 1.90 g (0.010 mol) of Cu[I]I and 7.7 ml of 2.1 *M* (0.016 mol) of methyllithium in ether, gave 1.46 g of 2α-(6-carbethoxyhexyl)-3β-methyl-4α-tetrahydropyranyloxycyclopentanone. This material was heated at 45° for 1 hr with 85 ml of 2:1:1 acetic acid–tetrahydrofuran–water, cooled, diluted with 150 ml of H_2O, and worked up with ether. The residue was chromatographed upon SilicAR CC-4 eluting with 4:1 hexane–ethyl acetate to yield 0.30 g (22%) of **15** as an oil: pmr (1:1 $CDCl_3$–C_6D_6) δ 0.98 (d, 3 H, J = 5.5 Hz, $-CHCH_3$), 1.08 (t, 3 H, J = 7 Hz, OCH_2CH_3), 1.95 (dd, 1 H, J_{gem} = 18 Hz, $J_{4,5\text{-}cis}$ = 8.5 Hz, C-5β), 2.18 (t, 2 H, CH_2CO_2), 2.43 (dd, 1 H, J_{gem} = 18 Hz, $J_{4,5\text{-}trans}$ = 7 Hz, C-5α), 3.54 (m, 1 H, $J_{3,4} \approx$ 7.0 Hz, C-4), 4.01 (q, 2 H, OCH_2CH_3). *Anal.* ($C_{15}H_{26}O_4$) C, H.

1α-Hydroxy-2α-(6-carboxyhexyl)-3β-methylcyclopentane (16). To a solution of 15.7 ml of 1.0 *M* (0.0157 mol) lithium tri-*sec*-butylborohydride[6] in 1:1 pentane–THF at −78° was added dropwise 1.5 g (0.0066 mol) of **4** in 5 ml of THF. The mixture was stirred at −78° for 30 min and was then treated with 9 ml of 2.5 *M* NaOH followed by 9 ml of 30% H_2O_2. The mixture was allowed to warm to 15°, then diluted with 20 ml of ether, acidified with 10% HCl, and worked up with ether. The residue was dry column chromatographed[11] upon 200 g of silica gel eluting with 80:20:2 cyclohexane–ethyl acetate–acetic acid. The product, **16**, was found along the column at R_f 0.27–0.44 and was crystallized from ether–hexane: mp 46–47°; 1.08 g (71%); pmr δ 0.97 (d, 3 H, J = 6 Hz, $CHCH_3$), 2.34 (t, 2 H, CH_2CO_2), 4.22 (m, 1 H, $-CHOH-$), 6.15 (br m, 2 H, exchangeable, CO_2H,OH). *Anal.* ($C_{13}H_{24}O_3$) C, H.

Acknowledgments. The authors wish to thank Dr. M. B. Floyd for supplying the precursors to compounds **13** and **15**, Mr. R. E. Schaub for the preparation of compound **8**, and Dr. P. J. Kohlbrenner, Mr. D. Moran, Mr. J. Nocera, and Mr. P. Mirando for the preparation of the cyclopentenone starting materials. We thank Mr. W. Fulmor and Mr. G. Morton for the ir and pmr spectra determinations and Mr. L. Brancone and staff for elemental analyses. We also thank Miss Lillian Lipchuck for the hypotensive testing results.

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Synthesis and Pharmacology of Some 2-Aminotetralins. Dopamine Receptor Agonists†

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Received September 26, 1974

A series of 2-amino-1,2,3,4-tetrahydronaphthalene compounds bearing substituents on the nitrogen and in the aromatic ring was synthesized from β-tetralone intermediates. Compounds were screened *in vivo* for dopaminergic activity using tests in which apomorphine was especially active. It was found that apparent dopaminergic activity is inherent in 2-dialkylaminotetralins, the dipropylamine substitution being the most consistently productive amine group studied. Activity was greatly enhanced by proper substitution in the aromatic ring. The 5,6-dihydroxy group was the best potentiating group found. These data support the idea that the extended conformation for the phenylethylamine moiety of ampmorphine and dopamine is favorable for dopaminergic agonist activity. They also suggest that an unetherified catechol group may not be essential for such activity.

The report[1] of the marked anti-Parkinson activity of apomorphine (APM) has encouraged research in the development of drugs which mimic this agent. It is currently believed that APM is a dopaminergic agonist and presumably it is through this mechanism that this agent is effective clinically. Unfortunately, APM has a relatively short duration of action and is a particularly powerful emetic in man. Hence, it would be desirable to discover longer acting, nonemetic dopaminergic agonists.

By inspection of the structure of APM and dopamine, the 2-aminotetralins suggest themselves as candidates for possession of dopaminergic activity. This relationship has been noted by Cannon and coworkers[2,3] as the rationale for synthesis of some 5,6-dioxy-2-aminotetralins, and, indeed, agonist activity was found. We have expanded considerably this series of compounds by various substitutions on the nitrogen and the aromatic ring and have examined more fully the recent conclusion[4] that the emetic pharmacophore of APM necessarily includes an unetherified catechol group. It will be shown below that this requirement does not necessarily hold for properly modified fragments of APM, a finding which has significance in the characterization of central dopamine receptors.

Chemistry. Several general routes to 2-amino-5,6-dioxytetralins can be envisioned. The use of 5,6-dimethoxy-2-amino-1-tetralone as an intermediate has been reported.[3] For simplicity of introduction of as wide as possible a variety of amino groups into the 2 position we hoped that the β-tetralone **4** would offer greater versatility as an intermediate. Its synthesis had not been reported, but it was obtained easily from the known 1,2,6-trimethoxynaphthalene **3**. Our synthesis is shown in Scheme I. This route to **3** is somewhat shorter than the other pertinent schemes[5,6] which have been used.

The use of Fremy's radical for the oxidation of **1** to **2** gave very unpredictable results in the phosphate buffers employed by Teuber and Gotz[7] for this reagent. From our study of this reaction we have concluded that the pH must be controlled to the range 4.0–4.5 (litmus). For this purpose a phthalate buffer was effective. At lower pH the oxidation slowed and the radical decomposed rapidly. At higher pH a faster reaction occurred, but pure **2** could not be obtained from the complex products.

The trihydroxynaphthalene formed by reduction of **2** was very sensitive to air oxidation in solution, so the reduction–methylation of **2** to **3** was performed without isolation of this intermediate. Reduction of **3** to **4** was done by the method of Robinson and coworkers.[8] An identical route was used for 5,8-dimethoxy-2-tetralone and 7,8-dimethoxy-2-tetralone starting from 1,6-dihydroxynaphthalene and 2,7-dihydroxynaphthalene, respectively. Other 2-tetralones were available commercially or were made from commercial 2-methoxynaphthalenes.

These 2-tetralones proved convenient as intermediates and were used for reductive alkylation of primary amines by standard methods.[9] The less reactive secondary amines required forcing dehydration to intermediate enamines, which were subsequently reduced to the tertiary amines **6**. For introduction of secondary amines not commercially available, secondary amines **5** were alkylated by simple methods. Cleavage of the ether groups was generally successful using HI–acetic acid. Difficulty was frequently encountered in purifying the resulting hydroiodides, so these were converted to HCl salts, which were easier to obtain as colorless, crystalline solids.

An additional structural variation which at one point we decided to pursue was the homologation of one of the hydroxy groups in **7**, preferably the 5-hydroxy group. This attempt was prompted by persistent emesis in the tetralins, which we attributed initially to the presence of the catechol function. To this end we devised Scheme II.

In order to secure placement of the hydroxymethyl group in the 5 position rather than the 7 position, it was necessary

† Presented in part before the Division of Medicinal Chemistry at the 167th National Meeting of the American Chemical Society, Los Angeles, Calif., April 1974.