Notes

β-Adrenergic Blocking Agents of the Chromone and Xanthone Groups

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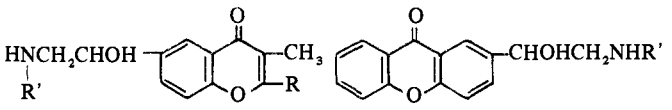
The search for new β-adrenergic blocking drugs with enhanced therapeutic properties is still very active[1] and there has recently been an increasing interest in heterocyclic (*e.g.*, benzodioxane,[2,3] indole,[4,5] benzofuran,[6] dibenzofuran,[7] quinoline, etc.[8]) derivatives. We now report the preparation of some new β-adrenergic blocking derivatives of the chromone and flavone group, with which we wish to illustrate further the versatility of the benzo-γ-pyrone molecule as a carrier moiety in medicinal research. We have also prepared 2 analogous xanthone derivatives (**19**, **20**) on the basis of the results obtained among the CNS stimulants of the same group.[9,10] The basic chain was located, according to the synthetic possibilities, in position 6 for **4**, **6**, **10**, and **12**



4, R = CH_3; R' = *i*-C_3H_7
6, R = C_6H_5; R' = *i*-C_3H_7
10, R = CH_3; R' = *tert*-C_4H_9
12, R = C_6H_5; R' = *tert*-C_4H_9

19, R' = *i*-C_3H_7
20, R' = *tert*-C_4H_9

and in the 2 position for **19** and **20**. The synthesis of these compds was carried out from the corresponding Ac derivatives, prepared by standard methods, by bromination, amination, and reduction of the final amino ketone intermediates. As an alternative, the reductive amination of the glyoxalyl derivatives (obtained by SeO_2 oxidation of the same starting materials) according to Fodor and Kovacs[11] gave unsatisfactory results. In Table I all the chromone and flavone derivatives prepared are shown, while the xanthone analogs are described in detail in the Experimental Section for illustrative purposes.

Compds **4**, **6**, **10**, **12**, **19**, and **20** have been evaluated for their β-adrenergic blocking activity in a number of tests at the Institute of Pharmacology of the University of Padua. The *N*-isopropyl derivatives were significantly more active than the *tert*-Bu analogs; the activity of the former group decreases in the order **4** > **19** > **10**. In this group, 6-[1-hydroxy-2-isopropylaminoethyl]-2,3-dimethylchromone (**4**), was the most active in all tests employed.

(a) Lipomobilizing Activity.[12] The norepinephrine-induced lipid mobilization in rats is competitively blocked by equimolecular doses of **4**, down to $2 \times 10^{-5} M$.

(b) Isolated Short-Circuited Frog Skin.[13,14] The increase of the short-circuited current in isolated frog skin is antagonized (60%) by **4** at $10^{-6} M$.

(c) Contraction Rates of Isolated Right Atrial Strips.[15] The chronotropic effect of 0.001 μg/ml of isoproterenol is reduced to about half and completely abolished with doses of 5 and, respectively, 10 μg/ml of **4**.

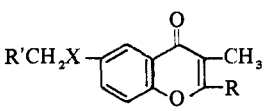
(d) Lengthening of the Refractory Period of the Isolated Guinea Pig Auricles.[16] An average 20% (EC_{20}) reduction in the maximal driven rate (MDR) at which the isolated guinea pig auricles respond to electrical stimulation is produced by 10 μg/ml of **4**. On the basis of the EC_{20} values, propranolol is approximately 10 times more active.

(e) Isolated Guinea Pig Tracheal Chain.[17] The isoproterenol reduction of the contraction of the isolated guinea pig tracheal chain caused by carbachol (0.5 μg/ml) is antagonized by very small doses of **4**. Figure 1 reports cumulative log concn response curves for the agonist (isoproterenol) in the presence of various concns of the antagonist (**4**).

(f) Blood Pressure in Anesthetized Dogs.[15] Iv administration of **1** and 5 mg/kg of **4** causes a 100% and 87% reduction of the hypotensive response to 0.2 and, respectively, 1 μg/kg of iv isoproterenol. The same doses of **4** cause a slight and transient hypotensive response of the order of −5 and −10 mm.

Compd **4** is therefore a selective β-adrenergic blocking

Table I. Chromone and Flavone Derivatives

Compd[d]	R	R'	X	Mp, °C	Formula	Analyses
						
1	CH_3	H	CO	136-138[a]	$C_{13}H_{12}O_3$	C, H
2	CH_3	Br	CO	143-146[b]	$C_{13}H_{11}BrO_3$	C, H, Br
3	CH_3	NH-*i*-$C_3H_7 \cdot$ HCl	CO	220-223[c]	$C_{16}H_{20}ClNO_3$	C, H, Cl, N
4	CH_3	NH-*i*-$C_3H_7 \cdot$ HCl	CHOH	233-235[c]	$C_{16}H_{22}ClNO_3$	C, H, Cl, N
5	CH_3	NH-*tert*-$C_4H_9 \cdot$ HCl	CO	200-202[c]	$C_{17}H_{22}ClNO_3$	C, H, Cl, N
6	CH_3	NH-*tert*-$C_4H_9 \cdot$ HCl	CHOH	244-247[c]	$C_{17}H_{24}ClNO_3$	C, H, Cl, N
7	C_6H_5	H	CO	154-156[a]	$C_{18}H_{14}O_3$	C, H
8	C_6H_5	Br	CO	216-217[b]	$C_{18}H_{13}BrO_3$	C, H, Br
9	C_6H_5	NH-*i*-$C_3H_7 \cdot$ HCl	CO	137-139[c]	$C_{21}H_{22}ClNO_3$	C, H, Cl, N
10	C_6H_5	NH-*i*-$C_3H_7 \cdot$ HCl	CHOH	202-204[c]	$C_{21}H_{24}ClNO_3$	C, H, Cl, N
11	C_6H_5	NH-*tert*-$C_4H_9 \cdot$ HCl	CO	257-259[c]	$C_{22}H_{24}ClNO_3$	C, H, Cl, N
12	C_6H_5	NH-*tert*-$C_4H_9 \cdot$ HCl	CHOH	269-270[c]	$C_{22}H_{26}ClNO_3$	C, H, Cl, N

Crystn solvent: [a]ligroin, [b]EtOAc, [c]MeOH-Et_2O. [d]The bases corresponding to compds 4, 6, 10, and 12 melted respectively (ligroin) at 105-107°, 157-159°, 121-122°, 146-148°.

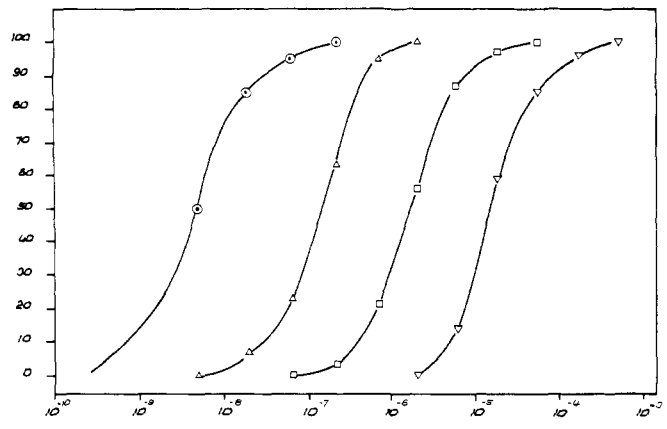


Figure 1. Cumulative log concentration-response curves for isoproterenol in the presence of various concns (⊙, 0 M; △, $3.2 \times 10^{-7} M$; □, $3.2 \times 10^{-6} M$; ▽, $3.2 \times 10^{-5} M$) of 6-[1-hydroxy-2-isopropylaminoethyl]-2,3-dimethylchromone. Abscissa: molar concns of isoproterenol. Ordinate: per cent of maximal release.

agent of the propranolol type,[18] with membrane activity (test d) and devoid of intrinsic sympathomimetic activity (test f). In comparison with propranolol, 4 has a potency ratio of 0.1 (test d), but its LD_{50} [223 mg/kg (205.5-242.0) iv in albino mice] is 2.5 times lower.

The data reported seem to confirm the pharmacological potentialities of the benzo-γ-pyrone molecule also in this field of medicinal chemistry.

Experimental Section

All melting points were detd in open glass capillaries, using a Büchi apparatus, and are uncor. Where analyses are indicated only by symbols of the elements, analytical results obtained for those elements were within ±0.4% of the theoretical values.

The general methods of synthesis described are illustrative of those of analogous compounds.

2-Propionyl-4-acetylphenol (13). To a soln of 25 ml of *o*-hydroxypropiophenone and 25 ml of AcCl in 100 ml of CS_2, 95 g of $AlCl_3$ was added in 1 hr, and the mixt was kept at 50-60° for 1 hr. After removal of the solvent the residue was treated with ice and HCl and extd with $CHCl_3$. The $CHCl_3$ layer was dried and filtered, and the solvent was evapd. The residue was distd at 175-180° (4-5 mm); the collected oil solidified on cooling. On crystg from ligroin, 23 g of white product (mp 64-65°) was obtd. *Anal.* ($C_{11}H_{12}O_3$) C, H.

6-Acetyl-2,3-dimethylchromone (1). A mixt of 10 g of 2-propionyl-4-acetylphenol (13), 6 g of anhyd NaOAc, and 10 ml of Ac_2O was heated in an oil bath at 170-180° for 7 hr. The fused mixt was taken up in H_2O and the sepd solid was collected, washed (H_2O), and dried. On crystg from ligroin, 8 g of yellow product, mp 136-138°, was obtd. *Anal.* ($C_{13}H_{12}O_3$) C, H.

6-Acetyl-3-methylflavone (7). A mixt of 15 g of 2-propionyl-4-acetylphenol (13), 30 g of BzCl, and 45 g of PhCOONa was heated in an oil bath at 180-190° for 7-8 hr. The reaction mixt was taken up in H_2O, washed (NaOH-H_2O), and extd with $CHCl_3$. Removal of the solvent left a residue which on crystg from ligroin, gave 15 g of yellow solid, mp 154-156°. *Anal.* ($C_{18}H_{14}O_3$) C, H.

2-Carboxy-4'-acetyldiphenyl Ether (14). A mixt of 7.8 g of *o*-chlorobenzoic acid, 6 g of *p*-hydroxyacetophenone, 4 g of NaOH, and 0.5 g of Cu powder was heated in an oil bath at 200° for 0.5 hr. The mixt was poured into ice water and acidified with dil HCl, and the sepd product was isolated by filtration, dissolved ($NaHCO_3$), and repptd with dil HCl. The crude product, on crystg from EtOH-H_2O, gave 6 g of white cryst solid, mp 185-186°. *Anal.* ($C_{15}H_{12}O_4$) C, H.

2-Acetylxanthone (15). To a soln of polyphosphoric acid (from 100 g of P_2O_5 and 100 g of 85% H_3PO_4), 9.3 g of 14 was added in small portions. The reaction mixt was kept on a steam bath for 1.5 hr and then poured into ice H_2O. The sepd solid was collected, washed ($NaHCO_3$-H_2O), and dried. On crystg from EtOH, 5.5 g of white solid, mp 199-200°, was obtd. *Anal.* ($C_{15}H_{10}O_3$) C, H.

2-Bromoacetylxanthone (16). To a soln of 4.8 g of **15** in 300 ml of $CHCl_3$, a soln of 3.2 g of Br_2 in 75 ml of $CHCl_3$ was added, with stirring, in 2 hr. The reaction mixt was transferred to a separatory funnel, washed (dil NaOH-H_2O), and dried, and the solvent was evapd. The residue, after 2 crystns from EtOAc, gave 3 g of white solid, mp 194-196°. *Anal.* ($C_{15}H_9BrO_3$) C, H, Br.

2-Isopropylaminoacetylxanthone Hydrochloride (17). To a soln of 17 g of 16 in 1.5 l. of PhH, a slight excess of *i*-$PrNH_2$ was added, and the mixt was kept at room temp with stirring for 4 hr. The soln was washed (H_2O) and dried. The PhH layer, treated with HCl gas, gave the amino ketone as the HCl salt. On crystallg the crude product from MeOH-Et_2O, 8 g of white solid, mp 210-211°, was obtd. *Anal.* ($C_{18}H_{18}ClNO_3$) C, H, Cl, N.

2-*tert*-Butylaminoacetylxanthone Hydrochloride (18). In a similar manner, starting from 7.3 g of 2-bromoacetylxanthone (16), 3 g of the corresponding amino ketone hydrochloride (18), mp 189-193° dec (MeOH-Et_2O), was obtained. *Anal.* ($C_{19}H_{20}ClNO_3$) C, H, Cl, N.

2-[1-Hydroxy-2-isopropylaminoethyl]xanthone Hydrochloride (19). A soln of 4.1 g of 17 in 40 ml of MeOH was hydrogenated over 10% Pd/C until H_2 uptake ceased. The soln was filtered from the catalyst and evapd to dryness. The residue, on crystg from MeOH-Et_2O gave 2.5 g of white product, mp 224-226° [*Anal.* ($C_{18}H_{20}ClNO_3$) C, H, Cl, N]; base, white cryst solid, mp 108-110° (ligroin) [*Anal.* ($C_{18}H_{19}NO_3$) C, H, N].

2-[1-Hydroxy-2-*tert*-butylaminoethyl]xanthone Hydrochloride (20). With the same procedure 3 g of *tert*-butylaminoacetylxanthone hydrochloride (18) gave 1.7 g of the corresponding amino alcohol hydrochloride as a white solid, mp 230-233° (MeOH-Et_2O); [*Anal.* ($C_{19}H_{22}ClNO_3$) C, H, Cl, N]; base, white cryst solid, mp 112-114° (ligroin) [*Anal.* ($C_{19}H_{21}NO_3$) C, H, N].

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