$-132°$; $\nu_{max}$ 3355, 3290, 1751, 1730 (sh), and 1718 $cm^{-1}$. *Anal.* ($C_{24}H_{34}O_4Cl_2$) C, H, Cl.

**6β-Chloro-16-methylene-17α-hydroxy-4-pregnene-3,20-dione 17-Acetate (21).**—To a slurry of 7.8 g of $CrO_3$ in 78 ml of pyridine at 15° was added **19** (7.8 g, 0.0171 mole) in 78 ml of pyridine. After 42 hr at room temperature, the reaction mixture was added to 1.6 l. of ice–water and 160 ml of concentrated HCl. The crude product obtained by $CH_2Cl_2$ extraction was chromatographed on 700 g of silica gel (100–200 mesh). Elution with $Et_2O$–$C_6H_{14}$ (3:7) afforded 3.38 g of **21**. Crystallization from $Et_2O$ yielded 2.25 g (31.5%); mp 145° dec; $[\alpha]D$ −110°; $\lambda_{max}$ 240 mμ (ε 15,000) [lit.[2b] mp 151–153°, $[\alpha]^{20}D$ −113° (*c* 1.0, $CHCl_3$), $\lambda_{max}$ 240 mμ (log ε 4.18)]; nmr, δ 4.74 (6-H, t, $J_{H_6H_{7ax}} = J_{H_6H_{7eq}}$ = 2 Hz), and 5.88 (4-H) ppm. *Anal.* ($C_{24}H_{31}O_4Cl$) C, H, Cl.

**3-Ethoxy-6-chloro-16-methylene-17α-hydroxy-3,5-pregnadien-20-one 17-Acetate (22).**—To a solution of **21** (5.76 g, 0.0137 mole) in 115 ml of dioxane was added 1.72 ml of EtOH, 17.2 ml of triethyl orthoformate, and 17.2 ml of a solution of $H_2SO_4$–dioxane (1:19). After 15 min at 25°, 35 ml of pyridine was added, and the solution was concentrated to a thick paste *in vacuo*. Addition of 10 ml of MeOH and cooling at 5° gave crystalline **22**, 4.32 g (70.2%), mp 173° dec, $[\alpha]D$ −234°, $\lambda_{max}$ 252 mμ (ε 21,650) [lit.[2b] mp 177–178°, $[\alpha]^{20}D$ −238° (*c* 1.0, $CHCl_3$), $\lambda_{max}$ 251 mμ (log ε 4.55)]. *Anal.* ($C_{26}H_{35}O_4Cl$) C, H, Cl.

**6-Chloro-16-methylene-17α-hydroxy-1,4,6-pregnatriene-3,20-dione 17-Acetate (23).**—A solution of **22** (11.34 g, 0.0254 mole) in 1.14 l. of $C_6H_6$ was added to 17.30 g (0.0762 mole) of DDQ in 1.14 l. of $C_6H_6$ and stirred at 25° for 6 hr. The reaction mixture was filtered, and the filtrate was evaporated to a residue *in vacuo*. The residue was dissolved in 3 l. of EtOAc–$Et_2O$ (1:1), which was washed with 1% NaOH, then with $H_2O$, dried ($MgSO_4$), and evaporated to a residue. Since the product appeared by tlc [silica gel, $CHCl_3$–EtOAc (9:1)] to be a mixture of approximately 4 parts of $\Delta^{1,4,6}$-triene to 1 part of $\Delta^{4,6}$-diene, dehydrogenation was carried out again, as follows. The product (10.56 g) was refluxed in 525 ml of dioxane with 5.72 g of DDQ for 4 hr. Evaporation *in vacuo* gave a residue to which was added 500 ml of $C_6H_6$. The $C_6H_6$ solution was separated from insolubles and evaporated *in vacuo* to a residue which was taken up in EtOAc–$Et_2O$ and washed as previously described. Evaporation of the solvent gave a crude product, 10.5 g, and two crystallizations from MeOH yielded **23**: 5.39 g (51%); mp 220° dec; $[\alpha]D$ −173°; $\lambda_{max}$ 228 mμ (ε 10,830), infl at 235, 258 (10,450), 297 (11,080) [lit.[2b] mp 228–230°; $[\alpha]^{20}D$ −217° (*c* 1.0, $CHCl_3$); $\lambda_{max}$ 229 mμ (log ε 4.01), 258 (4.00), 297 (4.03)]. *Anal.* ($C_{24}H_{27}O_4Cl$) C, H, Cl.

**1α,2α-(4,3,1-Pyrazolino)-6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (24).**—Into a solution of 6.0 g of **23**, in 60 ml of $CH_2Cl_2$, maintained at approximately 5°, was distilled 600 ml of an $Et_2O$ solution of $CH_2N_2$ [prepared from bis(N-methyl-N-nitroso)terephthalamide by adding to 96 g of EXR-101[20] suspended in 1.2 l. of $Et_2O$ and 192 ml of $H_2O$, a solution of 48 g of KOH, 192 ml of EtOH, and 96 ml of $H_2O$]. The closed reaction flask was then allowed to remain at 25° for 48 hr. Excess $CH_2N_2$ was removed by air entrainment. An additional 6 g of **23** was similarly allowed to react with $CH_2N_2$, and the combined reaction products were chromatographed on silica gel (1200, 964, and 487 g, successive portions, 100–200 mesh) three times, eluting with $Me_2CO$–$C_6H_{14}$ (1:3) to obtain 2.80 g of impure **24**: $[\alpha]D$ −152°; $\lambda_{max}$ 227 mμ (ε 5560) and 287 mμ (ε 13,900); $\nu_{max}$ 1754, 1739, 1672, 1615, and 1562 $cm^{-1}$. A satisfactory analysis was not obtained for this substance.

**1,2α-Cyclomethylene-6-chloro-16-methylene-17α-hydroxy-4,6-pregnadiene-3,20-dione 17-Acetate (25).**—A solution of impure **24** (2.6 g) in 515 ml of $Me_2CO$ and 5.2 ml of 70% $HClO_4$ was allowed to react at 25° for 20 min. An equal volume of $H_2O$ was then added, and the pH was adjusted to about 7 with $NaHCO_3$. $Me_2CO$ was removed *in vacuo*, and after extraction with $CH_2Cl_2$, the crude product of 2.51 g was chromatographed on 250 g of silica gel (100–200 mesh). Elution with $Me_2CO$–$C_6H_{14}$ (3:17) gave 760 mg, principally **25**. Crystallization from $Et_2O$ yielded 452 mg (19.3%); mp 250° dec; $[\alpha]D$ +12°; $\lambda_{max}$ 282 mμ (ε 17,000); $\nu_{max}$ 1754, 1724, 1666, 1612, and 1589 (vw) $cm^{-1}$; nmr, δ 0.80 (13-$CH_3$), 1.23 (10-$CH_3$), 2.07 (17-OCO$CH_3$), 2.17 (20-$CH_3$), 5.50 and 5.63 (16-=$CH_2$), and 6.20 (4-H, 7-H) ppm. The recovered rotation sample was used for microanalysis and for mass spectroscopic determination. *Anal.* ($C_{25}H_{29}O_4Cl$·0.5-dioxane) C, H, *m/e* 428.

**Acknowledgments.**—We are indebted to Mrs. H. M. Marigliano and Mr. M. D. Yudis for interpretation of the nmr spectra, Mrs. F. E. Carlon for technical assistance, and Dr. T. Traubel for the mass spectra.

(20) A mixture of the amide with 30% mineral oil. E. I. du Pont de Nemours and Co., Inc., Explosives Department, Wilmington, Del.

# Tricyclic Analogs of Melatonin

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The angular tricyclic analog of melatonin, 8-methoxy-6-oxo-3,4,6,7-tetrahydro-1H,5H-azocin[4,5,6-*cd*]indole (IV) as well as the linear "dehydromelatonin," *viz.*, 5-methoxy-1-acetyl-2,3-dihydropyrrolo[2,3-*b*]indole (VI) had retained only tiny fractions of the activity of melatonin. The lactam IV and the corresponding amine V showed no major CNS effects in mice and cats.

Melatonin, N-acetyl-5-methoxytryptamine (I),[2] has been isolated from extracts of pineal glands and identified in peripheral nerves of mammals and man. It is conveniently assayed by its lightening effect on frog melanocytes.[3] Its biological properties are different from those of other known lightening agents.[4]

We have now applied the photocyclization of N-chloroacetyltryptophan (yielding the lactam II[5]) to the synthesis of the tricyclic dehydromelatonin IV and its reduction product V (Scheme I). On irradiation with a low-pressure mercury lamp in aqueous THF buffered with NaOAc, N-chloroacetyl-5-methoxytryptamine (III) afforded a 46% yield of the cyclized product IV. Reduction of the eight-membered lactam IV with diborane at room temperature gave 8-methoxy-3,4,6,7-tetrahydro-1H,5H-azocin[4,5,6-*cd*]indole (V), after decomposition of an intermediary, stable borane complex by refluxing in ethanolic KOH.

Tryptamine and tryptophan derivatives are con-

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(2) A. B. Lerner, J. D. Case, and R. V. Heinzelman, *J. Am. Chem. Soc.*, **81**, 6084 (1959).

(3) M. R. Wright and A. B. Lerner, *Endocrinology*, **66**, 599 (1960).

(4) A. B. Lerner, J. D. Case, W. Mori, and M. R. Wright, *Nature*, **183**, 1821 (1959).

(5) O. Yonemitsu, P. Cerutti, and B. Witkop, *J. Am. Chem. Soc.*, **88**, 3941 (1966).

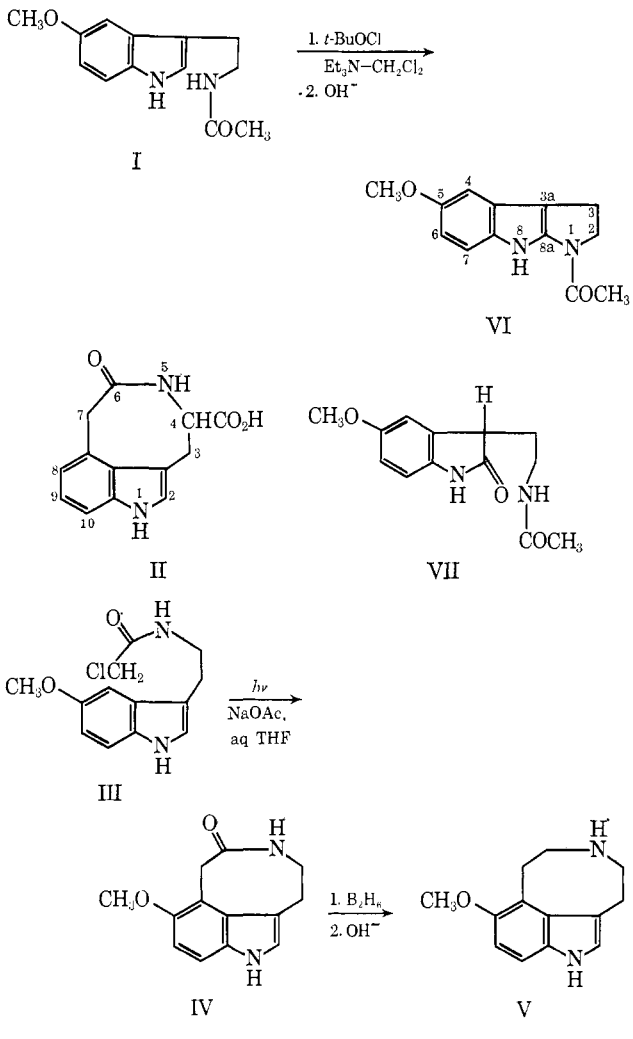
TABLE I

SUMMARY OF DATA FOR DEHYDROMELATONIN IV AND AMINE V

| Compd | Spontaneous p ychomotor act. test[a] in mice (oral) Dose, mg/kg | Cumulative mean ± SE | Reserpine ptosis tests[b] in mice (ip) | Overt behavioral test[c] in cats (iv) |
|---|---|---|---|---|
| IV | 0.5 | 451 ± 34.8 | Inactive at 0.125, 0.5, 2, and 8 mg/kg on both prevention and reversal tests. | Inactive at 4 mg/kg in three cats. |
| | 1.0 | 476 ± 32.4 | | |
| | 2.0 | 418 ± 71.1 | | |
| | 4.0 | 418 ± 57.0 | | |
| | 8.0 | 380 ± 30.8 | | |
| Control | | 358 ± 23.0 | | |
| V | 0.5 | 354 ± 45.4 | Inactive at 0.125, 0.5, 2, and 8 mg/kg on both prevention and reversal tests. | Increased viciousness[d] in one cat; no effects in two cats at 4 mg/kg. |
| | 1.0 | 370 ± 48.8 | | |
| | 2.0 | 345 ± 61.7 | | |
| | 4.0 | 469 ± 52.6 | | |
| | 8.0 | 317 ± 56.0 | | |
| Control | | 388 ± 56.1 | | |

[a] Four groups of four mice per dose were medicated (drug suspended in 1% gum tragacanth and volume administered was 0.1 ml/10 g) 30 min before being placed in photocell activity cages. Digital counters recorded the number of times that a beam of light impinging on a photocell was broken during a 30-min test period. Results were compared with those obtained with appropriate vehicle or solvent controls. [b] M. D. G. Aceto and L. S. Harris, *Toxicol. Appl. Pharmacol.*, **7**, 329 (1965). [c] Cats were medicated (drug was dissolved in 100% polyethylene glycol and volume injected was 1 cc/kg) and observed at hourly intervals (for 6 hr) and at 24 hr. [d] Viciousness was manifested by increased spitting, hissing, and vocalization.

SCHEME I




verted to linear tricyclic compounds by *t*-butyl hypochlorite, a method which provides an easy entry into the family of the natural products, to which physostigmine, the sporidesmins, and chimonanthine[6] belong.

Melatonin by this method gave a 62% yield of the sparingly soluble dehydromelatonin (VI) which was obtained directly from the reaction mixture by filtration. The product shows all the properties expected from a 2-acetamidoindole derivative and, under mildly acidic (pH <6) conditions, hydrolyzes rapidly to the oxindole VII. Attempted hydrogenation of the 3a,8a double bond with Pd–C or Rh–$Al_2O_3$ in THF regenerated melatonin.

Lactam IV and amine V were tested for CNS effects (Table I).[7] Both compounds were inactive in mice in two different tests. The amine V was also inactive when tested intravenously in the cat for effects on overt behavior. Increased viciousness lasting approximately 8 hr was noted in one cat out of three at 4 mg/kg.

The lightening effect of dehydromelatonin IV on frog melanocytes was about one millionth of that of melatonin.[8] Likewise, the linear dehydromelatonin VI had only a small fraction of the activity of melatonin (see Experimental Section).

## Experimental Section

**N-Chloroacetyl-5-methoxytryptamine (III).**—To a suspension of 3.0 g of 5-methoxytryptamine in 30 ml of THF was added a solution of 4 g of chloroacetic anhydride in 5 ml of THF with cooling in a MeOH–Dry Ice bath. After complete solution (2 hr), 20 g of ice was added and the reaction mixture was placed in the deep freezer overnight. The solvent was removed under reduced pressure and the residue was treated with small volumes of $Et_2O$ and $H_2O$. The insoluble crystalline product was collected to yield 3.86 g (90%) of colorless prisms, mp 122–123°. Recrystallization from aqueous MeOH raised the melting point to 124–125°.

*Anal.* ($C_{13}H_{15}ClN_2O_2$) C, H, N.

**Photocyclization of N-Chloroacetyl-5-methoxytryptamine (III) to 8-Methoxy-6-oxo-3,4,6,7-tetrahydro-1H,5H-azocin[4,5,6-*cd*]-indole (IV).**—The light source was a low-pressure mercury discharge tube, Hanovia type SC 2537, 5000 V, Hanovia Lamp Division, Engelhard Hanovia, Inc., Newark, N. J.

A solution of 400 mg of III and 500 mg of NaOAc in 90 ml of THF and 40 ml of $H_2O$ was irradiated for 5 hr inside two semicircular quartz chambers placed 16 cm from the light source (cooling jacket).

Nine runs were combined and evaporated under reduced pres-

(6) M. Ohno, T. F. Spande, and B. Witkop, *J. Am. Chem. Soc.*, **90**, 6521 (1968).

(7) We are greatly indebted to Drs. S. Archer and M. D. Aceto, Sterling Winthrop Research Institute, for carrying out these tests.

(8) *Cf.* H. Yajima, K. Kawasaki, Y. Okada, and S. Lande, *Biochim. Biophys. Acta*, **107**, 141 (1965).

sure. The crystalline residue was washed with 30 ml of MeOH to yield 1.45 g (46.6%) of colorless prisms, mp 286–288° dec. The melting point was not raised by recrystallization from EtOH. *Anal.* ($C_{19}H_{11}N_2O_2$) C, H, N; mol wt: calcd, 230; found, 211 (osmometric measurement on a 0.091 m*M* solution in dioxane).

**8-Methoxy-3,4,6,7-tetrahydro-1H,5H-azocin[4,5,6-*cd*]indole (V).**—To a suspension of 638 mg of IV in 30 ml of THF was added gradually 10 ml of a 1.0 *M* solution of $B_2H_6$ in THF (ice cooling, stirring). After standing for 1 day at room temperature, excess $B_2H_6$ was decomposed by the addition of 10 g of ice. Evaporation under reduced pressure gave a B-containing crystalline residue, mp 268–270° dec. This complex was refluxed on a steam bath for 10 hr in 10 ml of EtOH containing 2 g of alkali. After removal of the EtOH, the mixture was extracted three times with 50-ml portions of hot $C_6H_6$. The combined extracts were evaporated under reduced pressure and dissolved in 0.1 *N* HCl. This solution was treated with a small amount of charcoal and filtered. To the clear filtrate was added a 1% aqueous solution of picric acid. The insoluble microcrystalline yellow picrate resulting was collected, washed ($H_2O$), and dried. The crude picrate was extracted with 30 ml of hot MeOH, filtered, and dried to yield 1.08 g. This material was suspended in a mixture of 20 ml of 2.0 *N* HCl and 100 ml of EtOAc and shaken with $C_6H_6$ to remove a small amount of picric acid. After addition of excess alkali, the $H_2O$ layer was extracted three times with 50 ml of hot benzene. The combined benzene extracts were dried with KOH pellets and evaporated under reduced pressure to yield 483 mg (80%) of colorless crystals, mp 152–153°. Recrystallization from MeOH–$H_2O$ gave colorless prisms, mp 153–154°. *Anal.* ($C_{13}H_{16}N_2O$) C, H, N.

The uv spectrum revealed typical indole absorption, $\lambda\lambda_{max}$ 279 nm (ε 6070), 289 (5010); the ir spectrum showed no carbonyl absorption.

**5-Methoxy-1-acetyl-2,3-dihydropyrrolo[2,3-*d*]indole (VI).**—To 132 mg of melatonin (0.57 mmole, Regis Lot P5-581) and 0.32 ml of $Et_3N$ (2.28 mmoles, dried over KOH) in 25 ml of $CH_2Cl_2$ at −10° (ice–acetone bath) was added dropwise with stirring over 20 min, 10 ml of a 0.084 *M* solution of *t*-BuOCl (Nutritional Biochem. Corp., Cleveland, Ohio) in $CH_2Cl_2$. The reaction mixture was allowed to warm to 0° over 20 min. A solution of 0.96 ml of 1.0 *N* NaOH, diluted to 8 ml with absolute EtOH, was added dropwise with stirring at 0°. The turbid solution was stirred for several minutes, then filtered to afford a crop of microcrystalline material (81 mg after washing and drying, 61.8% yield), mp 250° dec. Tlc (silica gel G, 4% $CH_3OH$ in $CHCl_3$) revealed very little dehydromelatonin ($R_f$ 0.67, pink spot with *p*-dimethylaminocinnamaldehyde spray) in the filtrate. The compound was recrystallized from dichloroethane–hexane to give material of mp 250–255° dec. After sublimation (145–160°, high vacuum) material of mp 255–260° was obtained. Biological assays were run using this material: uv, $\lambda\lambda_{max}$ 318 nm (ε 20,800), 223 (16,400). *Anal.* ($C_{13}H_{14}N_2O_2$) H, N; mol wt: calcd, 230; found, parent peak ($M^+$) at *m/e* 230 in the mass spectrometer, with principal peaks at 188 ($M^+ - CH_2CO$), 187 ($M^+ - CH_3CO$), 173 ($M^+ - CH_2CO - CH_3$), and 145 ($M^+ - CH_2CO - CH_3 - CO$).

**Lightening Effects on Frog Skin.**[9]—Frog skin is removed and lightened by washing with several changes of Ringers solution. It is then darkened with a predetermined amount of MSH (in these experiments, 10 units of standard MSH). At 60 min the lightening agent is added, and the degree of lightening (increase in reflectance) is measured. The data indicate that 0.01 or 0.02 mg of dehydromelatonin (VI) has approximately the same lightening activity as $0.2 \times 10^{-6}$ mg of melatonin; $0.2 \times 10^{-7}$ mg of dehydromelatonin has very little lightening activity.

The total volume of the buffer, which contains the skin, is 20 ml. By dividing these numbers by 20 one gets the concentration of melatonin or dehydromelatonin that produces effective reversal of MSH darkening. The experiments indicate that 0.1 and 0.2 mg of dehydromelatonin is as effective a lightening agent as $0.2 \times 10^{-6}$ mg of melatonin; $0.2 \times 10^{-5}$, $0.2 \times 10^{-4}$, and $0.2 \times 10^{-3}$ mg of dehydromelatonin have no lightening effect on frog skin.

(9) We are greatly indebted to Dr. J. McGuire, School of Medicine, Yale University, New Haven, Conn., for carrying out these evaluations.

# β-Adrenergic Blocking Agents. V. 1-Amino-3-(substituted phenoxy)-2-propanols

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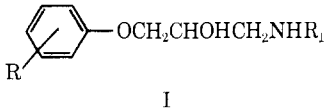
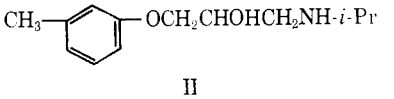
Several 1-amino-3-(substituted phenoxy)-2-propanols have been synthesized and tested against isoproterenol-induced tachycardia in anesthetized cats. Their β-adrenergic blocking activity proved in general to be similar to that of the propranolol analogs described in part II.[1a] Structure–activity relationships are discussed. Of the compounds tested, 1-isopropylamino-3-(3-methylphenoxy)-2-propanol was examined in detail in laboratory animals.

In our previous paper[1a] we described a series of 1-amino-3-naphthoxy-2-propanols which possessed potent β-adrenergic blocking properties. We now report the synthesis of a series of 1-amino-3-(substituted phenoxy)-2-propanols.[1b–e]




I

The biological evaluation of these compounds has shown that the ability to antagonize the effects of isoproterenol was widely spread over the series. From a large number of compounds synthesized the *m*-tolyl analog (II) was selected for further evaluation. It proved to be similar in potency to propranolol[2] in antagonizing the effects of isoproterenol in laboratory animals.[3] Evaluation of this compound in man has




II

been reported by Hahnel.[4]

**Chemistry.**—The compounds were prepared in a manner analogous to that for the 1-amino-3-naphthoxy-2-propanols[1a] using the 1,2-epoxy-3-(substituted phen-

(1) (a) A. F. Crowther and L. H. Smith, *J. Med. Chem.*, **11**, 1009 (1968); (b) A. F. Crowther, L. H. Smith, and T. M. Wood, U. K. Patent 1,069,341 (1967); (c) A. F. Crowther, L. H. Smith, and T. M. Wood, U. K. Patent 1,069,345 (1967); (d) D. J. Gilman and B. J. McLoughlin, U. K. Patent 1,128,052 (1968); (e) B. J. McLoughlin, U. K. Patent 1,123,258 (1968).

(2) Inderal®.

(3) R. G. Shanks and T. M. Wood, *Nature*, **212**, 88 (1966).

(4) J. Hahnel, *Z. Kreislaufforsch.*, **55**, 1023 (1966).