# Potential Antineoplastic Agents Derived from 1,2-Epoxyindan

By JOSEPH SAM and THOMAS C. SNAPP, JR.*

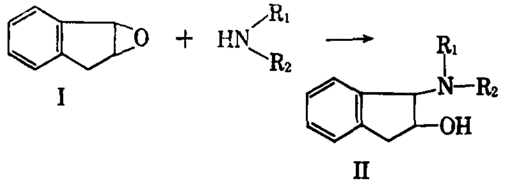
**The reaction of a number of amines and aminoacid derivatives with 1,2-epoxyindan provided 1-substituted amino-2-indanols. Preliminary tests, which are not complete, have not demonstrated pronounced antineoplastic activity in the compounds.**

As part of a broad program involving the investigation of potential antineoplastic agents it was desirable to investigate the preparation of a number of ring opening derivatives of epoxyindan.

Indan compounds recently have become of interest as antineoplastic agents. Connors and associates (1) observed that 1-amino-1-indancarboxylic acid possesses antitumor activity, while Leushina and co-workers (2) noted similar activity in 5-[bis(2-chloroethyl)amino]indan hydrochloride.

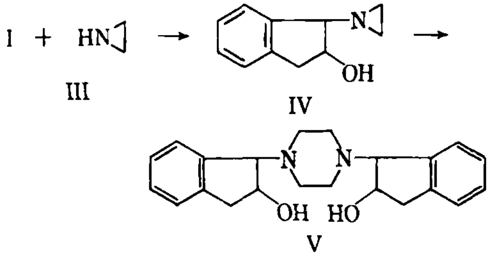
Although extensive investigations have been reported on cyclopentane-, cyclohexane-, and tetralin-1,2-epoxides, only a limited amount of information is available for 1,2-epoxyindan (3–6).

The work described in this paper involves the reaction of 1,2-epoxyindan (I) with amines to yield compounds (II) which may be considered either as potential alkylating agents and antimetabolites *per se* or which may be readily converted to potential alkylating agents.


I II

For example, the reaction of 1,2-epoxyindan (I) with aziridine (III) afforded 1-aziridinyl-2-indanol (IV) which was readily converted to 1,4-bis(2-hydroxy-1-indanyl)piperazine (V).

The latter also was prepared by the direct action of piperazine with 1,2-epoxyindan as described by Mousseron (6). The indanamines derived from 1,2-epoxyindan are listed in Table I. The nitrogen mustards (VII) were prepared by the chlorination of the corresponding alcohol (VI) whereas the potential antimetabolites were prepared from 1,2-epxoyindan by the reaction with amino acid derivatives. The folic acid relative (IX) was prepared in this manner. The intermediate, ethyl *N*-(*p*-nitrobenzoyl)glutamate (X), was prepared in good yield from *p*-nitrobenzoic acid and ethyl glutamate *via* the mixed anhydride reaction utilized for the preparation of peptides. The nitro group was readily reduced with platinum oxide catalyst at low hydrogenation pressures.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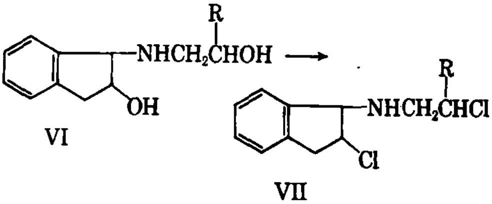
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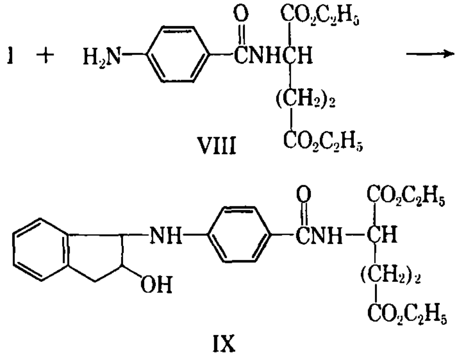
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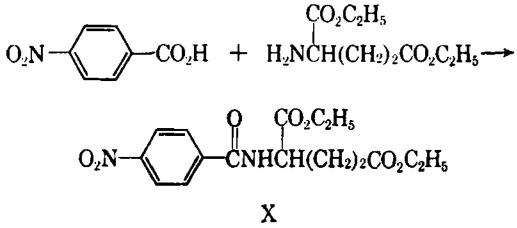
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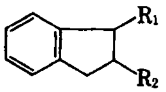
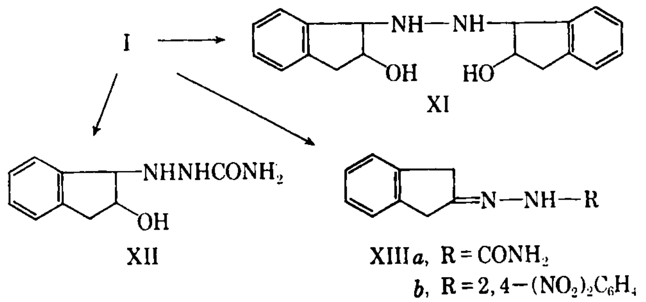
* Present address: Texas Eastman Co., Division of Eastman Kodak Co., Longview, Tex.

TABLE I.—INDANAMINE DERIVATIVES



| No. | $R_1$ | $R_2$ | Method | Recryst. Solvent | M.p., ° C. | Yield, % | Formula | Anal. C Calcd. | C Found | H Calcd. | H Found | N Calcd. | N Found |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | $N(CH_2)_2$ | OH | *A* | Toluene | 149–150 | 61 | $C_{11}H_{13}NO$ | 75.40 | 75.41 | 7.48 | 7.69 | 8.00 | 8.12 |
| 2 | *p*-$NHC_6H_4CN$ | OH | *F* | Ethanol | 196–197 | 54 | $C_{16}H_{14}N_2O$ | 76.77 | 76.59 | 5.64 | 5.36 | . . . | . . . |
| 3 | $NHCH_2CHOHCH_3$ | OH | *A*(*B*) | Ethyl acetate | 111–112 | 64(27) | $C_{12}H_{17}NO_2$ | 69.53 | 69.67 | 8.27 | 8.26 | 6.76 | 6.66 |
| 4 | *p*-$NHC_6H_4COOH$ | OH | *C* | Acetic acid | 238–239 | 85 | $C_{16}H_{15}NO_3$ | 71.36 | 71.26 | 5.61 | 5.38 | . . . | . . . |
| 5 | *p*-$NHC_6H_4CO_2CH_2CH_3$ | OH | *F* | Ethanol-water | 146–147 | 56 | $C_{18}H_{19}NO_3$ | 72.71 | 72.77 | 6.44 | 6.20 | . . . | . . . |
| 6 | *p*-$NHC_6H_4CON(CH_3)_2$ | OH | *C* | Ethanol-water | 177–178 | 46 | $C_{18}H_{20}N_2O_2$ | 72.95 | 73.18 | 6.80 | 6.64 | 9.45 | 9.71 |
| 7 | $NHCH_2CH_2OH$ | OH | *E* | Ethanol-acetone | 183–184 | 41 | $C_{11}H_{16}ClNO_2$[a] | 57.51 | 57.70 | 7.02 | 6.94 | 6.10 | 5.98 |
| 8 | *p*-$NHC_6H_4CONHCH(CH_3)_2$ | OH | *F* | Ethanol | 254–255 | 44 | $C_{19}H_{22}N_2O_2$ | 73.52 | 73.51 | 7.15 | 6.97 | 9.03 | 9.04 |
| 9 | *p*-$NHC_6H_4COC_9H_{16}NO_4$[b] | OH | *E* | Ethanol-water | 184–185 | 32 | $C_{25}H_{30}N_2O_6$ | 66.05 | 66.60 | 6.65 | 6.73 | 6.16 | 6.15 |
| 10 | *m*-$NHC_6H_4CF_3$ | OH | *C* | Ethanol | 108–109 | 53 | $C_{16}H_{14}F_3NO$ | 65.52 | 65.94 | 4.81 | 4.91 | . . . | . . . |
| 11 | $NHCH_2CO_2CH_2CH_3$ | OH | *C* | Toluene | 113–114 | 62 | $C_{13}H_{17}NO_3$ | 66.36 | 66.05 | 7.28 | 7.10 | 5.95 | 6.11 |
| 12 | $N(CH_2CH_2OH)_2$ | OH | *D* | Ethanol-ethyl acetate | 154–155 | 42 | $C_{19}H_{22}N_4O_{10}$[c] | 48.93 | 48.90 | 4.76 | 4.53 | 12.01 | 12.32 |
| 13 | $NHNHC_9H_9O$[d] | OH | *D* | Ethanol | 194–196 | 58 | $C_{18}H_{20}N_2O_2$ | 72.95 | 72.57 | 6.80 | 6.75 | 9.45 | 9.39 |
| 14 | $NHCH_2CHClCH_3$ | OH | *H* | Ethanol-ethyl acetate | 203–204 | 70 | $C_{12}H_{17}Cl_2NO$[a] | 54.97 | 54.78 | 6.54 | 6.57 | . . . | . . . |
| 15 | $N(CH_2)_4NCH_2CH_2Cl$[e] | Cl | *D* | Ethanol-ethyl acetate | 188–189 | 83 | $C_{15}H_{22}Cl_4N_2$[e] | 48.47 | 48.24 | 5.96 | 6.26 | 7.53 | 7.25 |
| 16 | *p*-$NHC_6H_4CN$ | H | *J* | Ethanol-cyclohexane | 87–88 | 41 | $C_{16}H_{15}ClN_2$[a] | 70.98 | 71.11 | 5.58 | 5.48 | . . . | . . . |
| 17 | *p*-$NHC_6H_4COOH$ | Cl | *H* | Acetic acid | 202–203 | 64 | $C_{16}H_{14}ClNO_2$ | 66.78 | 67.45 | 4.90 | 5.15 | . . . | . . . |
| 18 | $NHCH_2CH_2Cl$ | Cl | *H* | Ethanol-ethyl acetate | 192–193 | 62 | $C_{11}H_{14}Cl_3N$[a] | 49.56 | 49.62 | 5.29 | 5.30 | 5.26 | 5.41 |
| 19 | $NHCH_2COOH$ | OH | *K* | Ethanol | 233–234 | 64 | $C_{11}H_{13}NO_3$ | 63.75 | 64.38 | 6.32 | 6.42 | 6.76 | 6.74 |
| 20 | $NCH_2CHCH_3$[f] | OH | *K* | Toluene | 136–137 | 53 | $C_{12}H_{15}NO$ | 76.15 | 76.60 | 7.99 | 8.12 | 7.40 | 7.32 |
| 21 | H[g] | O | *M* | Isopentanol | 218–219 | 77 | $C_{10}H_{11}N_3O$[h] | . . . | . . . | . . . | . . . | . . . | . . . |
| 22 | H[i] | O | *M* | Ethanol | 203–204 | 70 | $C_{15}H_{12}N_4O_4$[j] | . . . | . . . | . . . | . . . | . . . | . . . |
| 23 | $N(CH_2)_4C_9H_9O$[k,l] | OH | *C*(*L*) | Isopentanol | 252–253 | 72(80) | $C_{22}H_{26}N_2O_2$ | . . . | . . . | . . . | . . . | . . . | . . . |
| 24 | $NHNHCONH_2$ | OH | *C* | Methanol-water | 206–208 | 60 | $C_{10}H_{13}N_3O_2$ | 57.96 | 58.67 | 6.32 | 6.86 | 20.28 | 19.62 |

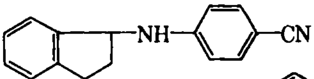
[a] Hydrochloride. [b] Ethyl *N*-[4-(2-hydroxy-1-indanylamino)benzoyl]-*dl*-glutamate. [c] Picrate. [d] Bis-(2-hydroxy-1-indanyl)hydrazine. [e] Dihydrochloride. [f] 1-(2-Methylaziridinyl)-2-indanol. [g] *Reference 14.* [h] Semicarbazone. [i] *Reference 15.* [j] 2,4-Dinitrophenylhydrazone. [k] 1,4-Di-(2-hydroxy-1-indanyl)piperazine. [l] *Reference 6.*



Several attempts were unsuccessful in the synthesis of the folic acid relative (IX) from 4-(2-hydroxy-1-indanylamino)benzoic acid and ethyl glutamate *via* the mixed anhydride reaction. Glutamic acid, morpholine, and piperidine were substituted for ethyl glutamate in this reaction, but the desired product was not obtained. In each reaction the starting materials were recovered.

The reaction of 1,2-epoxyindan with hydrazine, semicarbazide, and 2,4- dinitrophenylhydrazine also was investigated. Hydrazine and semicarbazide gave normal reaction products (XI, XII, respectively). However, 2,4-dinitrophenylhydrazine did not yield a product which could be identified. Both semicarbazide and 2,4-dinitrophenylhydrazine in the presence of 20% alcoholic sulfuric acid solution containing 30% water gave derivatives (XIII*a*, XIII*b*, respectively) of 2-indanone. The latter two products were identified by comparing melting points and infrared spectra to known samples derived from 2-indanone.

Included also in this paper is a description of the preparation of 4-(1-indanylamino)benzonitrile (XIV) and 2-indanylmethanesulfonate (XV).



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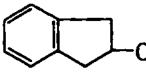

XV

## EXPERIMENTAL[1]

### Syntheses

The methods utilized for the preparation of the compounds in Table I are described below. Most of the amines were purchased from commercial sources; 4-amino-*N*,*N*-diethylbenzamide (7) was prepared according to the procedure described in the literature.

**Indanamines.**—*Method A.*—A solution of 13.2 Gm. (0.1 mole) of 1,2-epoxyindan (8) and 0.2 mole of amine in 80 ml. of dry benzene was refluxed for 48 hours. The benzene was evaporated *in vacuo*. The residue was dissolved in ether and washed with five 100-ml. portions of water. The ether portion was dried over anhydrous sulfate and then evaporated to dryness. (In the preparation of similar compounds, the extraction in ether, washing with water, and drying may be omitted.) The residue was recrystallized from a suitable solvent.

*Method B.*—A mixture of 0.2 mole of amine, 0.1 mole of 2-bromo-1-indanol (8), and 80 ml. of dry benzene was refluxed for 24 hours. The solution was cooled, washed with water, dried over anhydrous sodium sulfate, and evaporated *in vacuo* to dryness. The residual solid was recrystallized from a suitable solvent

*Method C.*—The procedure described in *Method A* was followed, except that ethanol was used as the solvent; the reflux period was 5–10 hours.

*Method D.*—The procedure described in *Method A* was followed, except that no solvent was used; the mixture was heated at reflux or at 120–125° for 4 hours.

*Method E.*—The procedure described in *Method A* was followed, except that *n*-amyl alcohol was used as the solvent; the reflux period was 5–10 hours.

*Method F.*—The procedure described in *Method C* was followed, except that 0.2 Gm. of phenylacetylene /0.1 mole of epoxide was added to catalyze the reaction.

**4-(2-Hydroxy-1-indanylamino)benzoic Acid.**—*Method G.*—To a solution containing 75 ml. of ethanol and 30 ml. of 12 *N* aqueous sodium hydroxide was added 8.5 Gm. (0.03 mole) of 4-(2-hydroxy-1 indanylamino)benzonitrile. The mixture was refluxed until a negative test for evolution of ammonia was observed. The ethanol was evaporated *in vacuo;* the residual sodium salt was acidified with dilute hydrochloric acid. The solid was removed by filtration and recrystallized from glacial acetic acid to give 6.8 Gm. (86%) of product, m.p. 238–239°.

**4-(2-Chloro-1-indanylamino)benzoic Acid.**—*Method H.*—A solution of 12 Gm. (0.1 mole) of purified thionyl chloride in 50 ml. of dry chloroform was gradually added to a cooled mixture of 2 Gm. (0.1 mole) of 4-(2-hydroxy-1-indanylamino)benzoic acid and 50 ml. of dry chloroform. The mixture was refluxed for 4 hours. The solvent was distilled *in vacuo*, and the residue was neutralized with 10% aqueous sodium carbonate. Removal of the solid by filtration and recrystallization from glacial acetic acid yielded 1.7 Gm. (80%) of product, m.p. 202–203°.

**1-(2-Chloroethyl)amino-2-chloroindan Hydrochloride.**—*Method I.*—The procedure in *Method H* was followed, except that the reaction mixture was not neutralized; the product was isolated as the hydrochloride

**4-(1-Indanylamino)benzonitrile Hydrochloride.**—*Method J.*—A solution of 15.3 Gm. (0.1 mole) of 1-chloroindan (9) and 12.0 Gm. (0.1 mole) of 4-aminobenzonitrile in 100 ml. of dioxane was refluxed for 1.5 hours in an oil bath. The solution was cooled; the tan solid was isolated by filtration and recrystal-

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[1] All melting points were taken on a Fisher-Johns apparatus and are uncorrected; boiling points are uncorrected. Infrared spectra were determined on a Perkin-Elmer model 137 infracord spectrophotometer.

lized from an ethanol-cyclohexane mixture to yield 4 Gm. (15%) of product, m.p. 87–88°.

**N-(2-Hydroxy-1-indanyl)aminoacetic Acid.**—*Method K.*—A mixture of 2 Gm. (0.01 mole) of ethyl *N*-(2-hydroxy-1-indanyl)aminoacetate and 25 ml. of 0.1 *N* aqueous sodium hydroxide was stirred at room temperature for 24 hours. The resulting solution was chilled and acidified with concentrated hydrochloric acid to pH 2.5. The solid was isolated by filtration and recrystallized from ethanol to yield 1.3 Gm. (64%) of product, m.p. 233–234°.

**2-Indanyl Methanesulfonate.**—The general method described by Berti (10) was followed. A mixture of 4 Gm. (0.03 mole) of 2-indanol (8) and 4 Gm. (0.05 mole) of pyridine was placed in a dry 100-ml. three-necked flask fitted with a thermometer, stirrer, and dropping funnel. The mixture was cooled to 0° in an ice-salt bath, and treated with 4.6 Gm. (0.04 mole) of methanesulfonyl chloride over a 1-hour period. After stirring for 3 hours at 0°, the mixture was allowed to warm to room temperature with stirring. On addition of 50 ml. of water, a brown solid precipitated which was recrystallized from either hexane or an ethanol-water mixture to yield 4.4 Gm. (70%) of 2-indanyl methanesulfonate, m.p. 74–75°.

**Ethyl N-(4-nitrobenzoyl)-dl-glutamate.**—The mixed anhydride method generally utilized for the preparation of peptides was followed (11). To a stirred and cooled solution of 33.4 Gm. (0.2 mole) of *p*-nitrobenzoic acid in 250 ml. of diglyme, 20.2 Gm. (0.2 mole) of triethylamine was added dropwise. The yellow solution was maintained at 0° during the addition of 27.3 Gm. (0.22 mole) of ethyl chloroformate. The mixture was stirred at 0° for an additional hour and maintained at this temperature while a solution of 40.6 Gm. (0.2 mole) of ethyl *dl*-glutamate in 150 ml. of diglyme was added. The mixture was allowed to warm to room temperature and stirred for 12 hours. The triethylamine hydrochloride was removed by filtration, and the filtrate diluted with 1.5 L. of ice water. After refrigeration for 24 hours, the product was isolated by filtration. Recrystallization from an ethanol-water mixture gave 45 Gm. (56%) of product, m.p. 96–97° [lit. m.p. 97–98° (12)].

**Ethyl N-(4-aminobenzoyl)-dl-glutamate.**—Seventeen grams (0.05 mole) of ethyl 4-nitrobenzoyl-*dl*-glutamate in 200 ml. of ethanol was hydrogenated over 0.2 Gm. of platinum oxide catalyst at 40-50 p.s.i. at room temperature. Hydrogenation required 1 hour. The catalyst was removed by filtration, and the solvent evaporated *in vacuo*. Recrystallization of the residual solid from dilute ethanol yielded 13.6 Gm. (83%) of product, m.p. 142–143° [lit. m.p. 139–141° (12)].

**1,4-Di-(2-hydroxy-1-indanyl)piperazine.**—*Method L.*—A mixture of 25 ml. of 50% aqueous ethanol, 2.4 Gm. (0.015 mole) of sodium iodide, and 1 Gm. (0.006 mole) of 1-aziridinyl-2-indanol was refluxed on a steam bath for 24 hours. After cooling, the solid was isolated by filtration and recrystallized from isoamyl alcohol to yield 0.75 Gm. (80%) of product, m.p. 252–253° [lit. m.p. > 220° dec.(6)].

The infrared spectra of the products from *Methods C* and *L* were identical; a mixed melting point determination showed no depression.

**4-Amino-N-isopropylbenzamide.**—A solution of 10.4 Gm. (0.05 mole) of 4-nitro-*N*-isopropylbenzamide (13) in 200 ml. of ethanol was treated with 0.3 Gm. of 5% palladium-on-carbon catalyst and reduced in a Parr hydrogenator at 3 atm. The catalyst was removed by filtration, and the solvent was distilled *in vacuo*. Recrystallization of the residue from dilute ethanol yielded 8.1 Gm. (90%) of product, m.p. 95–96°.

*Anal.*—Calcd. for $C_{10}H_{14}N_2O$: C, 67.38; H, 7.92; N, 15.72. Found: C, 67.19; H, 8.21; N, 15.43.

**2-Indanone Semicarbazone and 2,4-Dinitrophenylhydrazone.**—*Method M.*—The procedure described in *Method A* was followed, with the exception that 20% ethanolic sulfuric acid solution containing 30% water was used as the solvent.

## Pharmacological Results[2]

Compounds 1–8, 10, 11, 14, 15, 16, 18, 19, 20, and 23 of Table I have been submitted for testing for antineoplastic activity. Although the tests are not complete, pronounced antineoplastic activity has not been observed in the compounds tested so far.

## REFERENCES

(1) Connors, T. A., *et al.*, *Biochem. Pharmacol.*, **5**, 108 (1960).

(2) Leushina, K. V., Kolodkina, I. I., and Servievskaya, S. I., *Zh. Obshch. Khim.*, **32**, 464(1962).

(3) Sam, J., Plampin, J. N., and Alwani, D. W., *J. Org. Chem.*, **27**, 4543(1962).

(4) Boeseken, J., and Van Loon, C., *Proc. Acad. Sci. Amsterdam*, **20**, 1186(1918); through *Chem. Abstr.*, **13**, 314 (1919).

(5) Goldschmidt, S., and Schussler, H., *Ber.*, **58**, 566 (1925).

(6) Mousseron, M., *Bull. Soc. Chim. France*, **51**, 782 (1932).

(7) Wenker, H., *J. Am. Chem. Soc.*, **60**, 1081(1938).

(8) Whitmore, W. F., and Gebart, A. I., *ibid.*, **64**, 912 (1942).

(9) Pacaud, R. A., and Allen, C. F. H., "Organic Syntheses," Coll. Vol. II, John Wiley & Sons, Inc., New York, N. Y., 1959, p. 336.

(10) Berti, G., *J. Am. Chem. Soc.*, **76**, 1213(1954).

(11) Albertson, N. F., *Org. Reactions*, **12**, 157(1962).

(12) Wright, W. B., *et al.*, *J. Am. Chem. Soc.*, **71**, 3014 (1949).

(13) Fusco, R., and Canonica, L., *Chim. Ind. Milan*, **32**, 208(1950); through *Chem. Abstr.*, **45**, 4645(1951).

(14) Thorpe, J. F., *Proc. Chem. Soc.*, **27**, 128(1911).

(15) Suter, S. M., and Milne, H. B., *J. Am. Chem. Soc.*, **62**, 3473(1940).

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