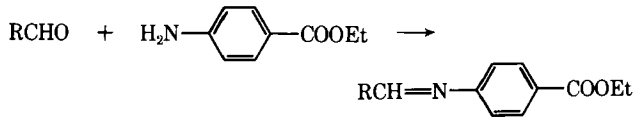
Table VII—Calculation of Effects in C Study

Factor	Estimated Effect, × 4
Citric acid	−1.13[a]
Corn syrup	−1.49[a]
F.D.C. Red No. 2	+0.19
Natural cherry flavor	−3.45[a]

[a] Significant.

Natural cherry flavor is incompatible with benzocaine probably because of the presence of natural reducing sugars (glucose, *etc.*) and aldehydes. The latter react with benzocaine to produce Schiff bases (16, 17) as illustrated in Scheme III.



Scheme III

SUMMARY AND CONCLUSIONS

Benzocaine in a throat lozenge formulation with 11 excipients was found to be unstable. Fractional factorial experiments identified three excipients, citric acid, corn syrup, and natural cherry flavor, as the causes of the incompatibility. The primary aromatic amine grouping instead of the ester linkage of benzocaine was involved in the stability problem. The standard pharmaceutical literature reference sources do not usually list the extent of benzocaine's incompatibility with commonly used pharmaceutical excipients.

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Synthesis and Antitussive Activity of *N*-[Indenyl(3)]ureas

T. GEORGE, R. TAHILRAMANI, C. L. KAUL, and R. S. GREWAL

Abstract □ Starting from indene, a variety of *N*-[indenyl(3)] ureas were synthesized and their pharmacological properties investigated. Several members of the series showed potent antitussive properties but also were found to possess a high order of toxicity.

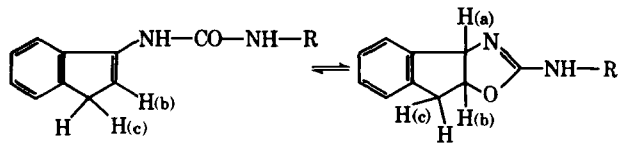
Keyphrases □ *N*-[Indenyl(3)]ureas—synthesis □ Antitussive activity—*N*-[indenyl(3)] ureas □ UV spectrophotometry—structure □ IR spectrophotometry—structure □ NMR spectroscopy—structure

Iodine isocyanate has been used successfully in recent years for the stereospecific synthesis of β-iodo isocyanates from olefins (1–3). Hassner and Heathcock (4,5) have shown that the addition of iodine isocyanate occurs in a stereospecific fashion and that iodine and the isocyanate functions are introduced *trans* to each other and diaxially in rigidly fused cyclohexanes. The above authors have also shown that methyl-*N*-[*trans*-2-iodo-1-indanyl] carbamate could be pyrolyzed to *cis*-indano [2,1-*b*]-2-oxazolidone. It was also shown that the above carbamate, in presence of base at room temperature or at slightly elevated temperature, is cyclized to an aziridin derivative with concomitant formation of indan-1-one as byproduct (6). *trans*-2-Iodocyclohexyl isocyanate was prepared by Wittekind *et al.* (2), converted to the corresponding urea by treatment with ammonia, and cyclized in presence of base to *cis*-2-amino-3*a*,4,5,6,7,7*a*-hexahydrobenzoxazole. This aminooxazoline was found to be a long-acting sympathomimetic agent. It is also known that some 2-amino indane derivatives synthesized by Huebner *et al.* (7) show analgesic activity. The possibility of synthesis of compounds of pharmacological interest prompted the authors to examine the prod-

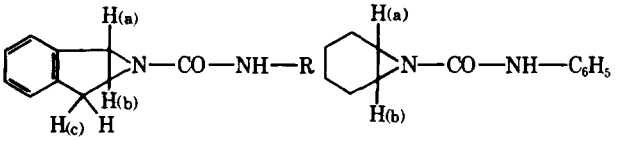
ucts of the reaction of *trans*-2-iodo-1-indanyl isocyanate with various amines and to study their behavior in presence of alkali.

RESULTS AND DISCUSSION

trans-2-Iodo-1-indanyl isocyanate was prepared using the procedure followed by Drefahl and Ponsold (1). Reaction of the above compound with primary and secondary amines gave the corresponding ureas. A solution of *N*-[*trans*-2-iodo-1-indanyl] urea in methanol was treated in the cold with aqueous alkali for 3–4 hr. The precipitated *N*-[indenyl(3)]ureas were filtered and recrystallized.



A B



C D

The possible structures which can be envisaged for the product of alkali treatment of the iodoindanyl ureas are represented as Structures A, B, and C. Structure A can be considered to arise from the *cis* elimination of hydrogen iodide by base whereas the oxazoline Structure B can be assigned to the product by analogy with the reported formation of *cis*-2-amino-3*a*,4,5,6,7,7*a*-hexahydrobenzoxazole from *N*-[*trans*-2-iodo-1-cyclohexanyl]urea (2). Strict analogy with the behavior of methyl *N*-[*trans*-2-iodo-1-indanyl]carbamate toward alkali would favor the Structure C.

NMR data on the products of treatment of *N*-(*trans*-2-iodo-1-indanyl)ureas with alkali give valuable evidence in favor of Structure A. The NMR spectrum of the product (R = H) in deuteriochloroform showed the H(b) proton in conjunction with an NH proton as a 2-proton band centered at δ = 5.25. Addition of trifluoroacetic acid showed a 2-proton band as a doublet centered at δ = 5.55 (J = 7 c.p.s.) overlapping with a sextet centered at δ = 5.75 (J = 3 c.p.s.). The authors ascribe the doublet at δ = 5.55 to H(*a*) and the sextet at δ = 5.75 to H(*b*). [JH(*b*) H(*a*) = 7 c.p.s. and J H(*b*) H(*c*) = 3 c.p.s.] This change in the pattern of the above 2-proton band can be attributed to acid-catalyzed cyclization of Structures A and B. In the presence of base it is conceivable that the equilibrium would shift overwhelmingly in favor of A. In the *N*-(phenylcarbamoyl) cyclohexane (1, 2) imine of Structure D, the ring-junction protons (*a*) and (*b*) appear as a doublet at δ = 2.73 (6). The absence of such a peak in the NMR spectrum of the product rules out the aziridine Structure C.

In contrast with the formation of aziridines as the major products of treatment of methyl *N*-[*trans*-2-iodo-1-indanyl]carbamate with alkali, *cis* elimination of hydrogen iodide occurs as the predominant reaction for *N*-[*trans*-2-iodo-1-indanyl]ureas. The stereochemical requirements of ring closure to aziridine are best satisfied when the groups involved are *trans* and diaxial (8). In five-membered rings where such a stereochemical arrangement of groups is not possible, the *cis* elimination of hydrogen iodide competes with the ring closure to ethylene imine as is illustrated in the case of methyl *N*-[*trans*-2-iodo-1-indanyl]carbamate which gave a 16% yield of indan-1-one as a minor product. It was not possible to establish the formation of aziridine C to any extent in the treatment of *N*-[*trans*-2-iodo-1-indanyl]ureas with alkali.

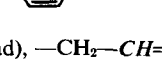
PHARMACOLOGICAL RESULTS

Of the eleven analogs tested, Compound II was the most potent in the series. The activity of this compound compares favorably with that of codeine and dextromethorphan when given intravenously (Table I). However, the oral activity of this compound was less when compared to the intravenous route indicating poor absorption of the compound. Compound II was slightly less toxic than dextromethorphan but it was one and one-half times more toxic than codeine when given intravenously. Next in order of potency were Compounds V, VII, VIII, and XI. Except for Compound VIII, all the other three compounds were more toxic than codeine or dextromethorphan although the activity was much less than these two compounds. Compounds I, III, IV, IX, and X were inactive up to 9 mg./kg. (i.v.) in reducing the cough reflex.

EXPERIMENTAL[1]

Preparation of trans-2-Iodo-1-indanyl Isocyanate—An ethereal solution of *trans*-2-iodo-1-indanyl isocyanate was prepared according to the method of Drefahl and Ponsold (1), starting from 23.2 g. (0.2 mole) of indene and made up to 800 ml. One hundred-milliliter aliquots of the above solution were used in each of the following experiments. The synthesis of *N*-[indenyl(3)] ureas is illustrated by the following examples.

N-[Indenyl(3)]urea (I)—Using the procedure outlined by Drefahl and Ponsold (1), 100 ml. of an ethereal solution of *trans*-2-iodo-1-indanyl isocyanate gave 3.05 g. of *N*-(*trans*-2-iodo-1-indanyl) urea as colorless crystals, m.p. 215° [lit. (1), m.p. 214–215°].

The above product was dissolved in hot ethanol (5 ml.). To the solution so obtained and kept cooled in an ice bath was added a solution of 0.60 g. (0.015 mole) of sodium hydroxide in 10 ml. of water and the resulting solution stirred for 4 hr. The product obtained was filtered and recrystallized from ethanol to give 1.65 g. (38%) of *N*-[indenyl(3)]urea as colorless crystals, m.p. 202°. IR spectrum (mineral oil) showed bands at 3460, 1690, 1030, and 755 cm.$^{-1}$. UV spectrum showed $\lambda_{max.}^{EtOH}$ 275 mμ (log ϵ 3.04); 268 mμ (log ϵ 2.99); 212 mμ (log ϵ 3.72). NMR spectrum[2] ($CDCl_3$) showed bands at δ 3.25 (d,  , 2H), 4.55 (s, CO—NH_2, 2H), 5.25 [s (broad), —CH_2—CH=C, CO—NH, 2H], and 7.20 (m, aromatic, 4H). After addition of a few drops of trifluoroacetic acid and standing for 4 hr., the spectrum showed bands at δ = 3.45 (d, , 2H), 5.45–5.86 (m, —CH_2—CH—C—H, 2H), and 7.4 (m, aromatic, 4H).

Anal.—Calcd. for $C_{10}H_{10}N_2O$: C, 68.95; H, 5.79; N, 16.08. Found: C, 68.88; H, 5.77; N, 15.92.

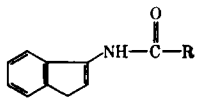
N-(Morpholinocarbonyl) Indenyl-3-amine (III)—A solution of 2 g. of morpholine in 10 ml. of anhydrous ether was added dropwise to 100 ml. of an ethereal solution of *trans*-2-iodo-1-indanyl isocyanate kept cooled in an ice bath. The stirring was continued for 0.5 hr. after the addition was completed. The precipitate formed was filtered to give 3.13 g. of *N*-(morpholinocarbonyl) *trans*-2-iodo-1-indanyl amine which was used directly for cyclization. To a solution of the above product in 10 ml. of ethanol and stirred in the cold was added dropwise a solution of 0.60 g. of sodium hydroxide in 10 ml. of water. The solution was stirred for 4 hr. and diluted with ice water. The precipitate was filtered to give 1.81 g. (29%) of colorless crystals which on recrystallization from aqueous methanol melted at 132°.

IR spectrum (mineral oil) showed bands at 1630, 1265, 1120, and 775 cm.$^{-1}$. UV spectrum showed $\lambda_{max.}^{EtOH}$ 275 mμ (log ϵ 3.02), 268 mμ (log ϵ 3.03), and 210 mμ (log ϵ 4.21). NMR spectrum ($CDCl_3$)

[1] Melting points were taken in glass capillary tubes and are uncorrected. IR spectrum was taken in mineral oil on a Perkin-Elmer model 237B spectrophotometer. NMR measurements were done on Varian Associates A-60 spectrophotometer in deuteriochloroform or deuteriochloroform to which a few drops of deuterated dimethyl sulfoxide was added, using tetramethylsilane as internal standard. UV measurements were recorded on a Beckmann DB model spectrophotometer.

[2] s = singlet, d = doublet, t = triplet, q = quartet, and m = multiplet in the NMR spectrum.

Table I—Antitussive Activity and Toxicity of *N*-[Indenyl(3)]ureas



Compd.	R[a]	M.p., °C.	Yield, %[b]	Antitussive Activity Expressed as Degree of Inhibition of Cough Reflex, Approx. ED_{50} mg./kg.	LD_{50} (i.v.) in Mice	Other Effects
I	$-NH_2$	205	38	[c]	—	
II	$-NH-CH_2-CH_2-OCH_3$	68	36	1.5–2	43.55 ± 3.19	
III		132	29	[c]	—	
IV	$-NHCH_2-CH_2-OH$	168	33	[c]	—	
V	$-NHCH_2-CH_2-CH_3$	91	22	3	18.21 ± 3.04	
VI	$-NHCH_2-CH_2-CH_2-OCH_3$	90	27	3.4	28.0 (approx.)	
VII		115	29	3	22.0 (approx.)	
VIII		85	36	3	37.41 ± 4.41	
IX		122	38	[c]	25.70 ± 1.37	
X		131	26	[c]	21.78 ± 1.59	
XI	$-NHCH_2-CH_2-CH_2-CH_3$	112	8	3	20.70 ± 1.35	
	Codeine	—	—	1.5	74.82 ± 4.29	
	Dextromethorphan hydrobromide	—	—	1.5	37.30 ± 4.45	

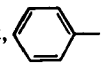
[a] Satisfactory elemental analyses were obtained for all the compounds described herein. [b] Yields are calculated on the basis of the indene used for the preparation of indene isocyanate. [c] No activity up to 9 mg./kg. [d] Compounds caused slight fall of blood pressure at a dose level of 3–9 mg./kg.

showed bands at δ = 3.24 (m, N—*CH*$_2$—C— and =CH—*CH*$_2$, 6H), 3.55 (m, O—*CH*$_2$—C, 4H), 5.35 (m = *CH*—CH$_2$— and —*NH*—C, 2H), 7.22 (m, aromatic, 4H).

Anal.—Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.83; H, 6.60; N, 11.47. Found: C, 68.75; H, 6.60; N, 11.28.

N-[Indenyl(3)]-N′-(n-propyl) Urea (V)—A solution of 2 g. of *n*-propylamine in 10 ml. of anhydrous ether was added dropwise to 100 ml. of an ethereal solution of *trans*-2-iodo-1-indanyl isocyanate and the solution stirred for 0.5 hr. The precipitate obtained was filtered and washed with ether to yield 2.22 g. of *N*-[*trans*-2-iodo-1-indanyl]-*N′*-(*n*-propyl) urea as a hygroscopic solid which was used directly for cyclization. To a solution of the above product in 6 ml. of ethanol kept cooled in an ice bath was added dropwise a solution of 0.6 g. of sodium hydroxide in 10 ml. of water and the solution was stirred for 3 hr. Filtration gave 1.17 g. (22%) of product, m.p. 91°. IR spectrum (mineral oil) showed bands at 1695, 1460, and 1020 cm.$^{-1}$. UV spectrum showed $\lambda_{max.}^{EtOH}$ 275 mμ (log ϵ 3.06), 268 mμ (log ϵ 3.03), and 210 mμ (log ϵ 4.07). NMR spectrum ($CDCl_3$) showed bands at δ = 0.80 (t, C—*CH*$_3$, 3H), 1.38 (q, =C—*CH*$_2$—CH$_3$, 2H), 3.01 (t, N—*CH*$_2$—CH$_2$, 2H), 3.20 (d,  —*CH*$_2$—CH, 2H), 5.1 (s, *NH*—CO—, 2H), 5.25 (m, —C—*CH*=C, 1H), and 7.22 (m, aromatic, 4H).

Anal.—Calcd. for $C_{13}H_{16}N_2O$: C, 72.19; H, 7.46; N, 12.95. Found: C, 71.87; H, 7.58; N, 13.01.

N-Indenyl(3)-N′-(p-fluorophenethyl) Urea (X)—A solution of 2.4 g. of *p*-fluorophenethyl amine in 20 ml. of anhydrous ether was added dropwise to 100 ml. of ethereal solution of *trans*-2-iodo-1-indanyl isocyanate and the solution was stirred for 0.5 hr. The precipitate of *N*-[*trans*-2-iodo-1-indanyl]-*N′*-(*p*-fluorophenethyl) urea which was obtained (3.6 g.) was collected on a filter, dissolved in hot ethanol, and cooled in an ice bath. To the above solution was added 0.6 g. of sodium hydroxide in 10 ml. of water and the solution was stirred for 4 hr. Filtration gave 1.92 g. (26%) of product as colorless crystals which on recrystallization from ethanol melted at 131°. IR spectrum (mineral oil) showed bands at 1695, 1460, and 1020 cm.$^{-1}$. UV spectrum showed $\lambda_{max.}^{EtOH}$ 275 mμ (log ϵ 3.27), 268 mμ (log ϵ 3.29), and 210 mμ (log ϵ 4.10). NMR spectrum ($CDCl_3$) showed bands at δ = 2.75 (t,  —*CH*$_2$—CH$_2$— CH$_2$—, 2H), 3.2 (m, NH—*CH*$_2$— and  —*CH*$_2$—C=, 4H), 4.86 (s, C—*NH*, 1H), 5.25 (m, *CH*—CH$_2$— and *NH*—C—, 2H), and 7.15 (m, aromatic, 4H).

Anal.—Calcd. for $C_{18}H_{17}FN_2O$: C, 72.96; H, 5.78; N, 9.46. Found: C, 72.97; H, 5.90; N, 9.27.

PHARMACOLOGICAL METHODS

Cough was induced in anesthetized cats (pentobarbitone 40–50 mg./kg. i.p.) by mechanical irritation of the trachea by a soft polythene tube which was pushed in and out of the trachea two or three times (9). The interval between the two stimuli was about 5 min. All the responses were recorded from the abdomen (just below the sternum) to which was attached a lightly sprung lever writing on a smoked kymograph. All the drugs were given intravenously. In one or two cases oral activity of the compound was also tested in which case the compound was given in the loop of the intestine. Codeine and dextromethorphan hydrobromide[3] were used as standard drugs to inhibit the cough reflex.

[3] Romilar, Sauter Laboratories, Inc., Nutley, N. J.

CONCLUSIONS

The yields of *N*-[indenyl (3)] ureas varied from 8–38% as can be seen from the table. With increase in the chain length of the alkyl group as the substituent on the urea nitrogen atom, the yield decreased. β-Methoxyethyl substituent on the urea gave maximum antitussive activity. *n*-Propyl and isopropyl substituents imparted activity of a lower order. 3,4-Dimethoxybenzyl-substituted urea showed some activity. Other compounds showed no activity at all. The compounds, however, do not warrant any further studies as regards the mechanism of action, because of low oral absorption and high toxicity.

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Aryloxyacetamidines of Medicinal Interest

WILLIAM J. HAGGERTY, JR.* and WILLIAM J. ROST

Abstract □ The synthesis of new aryloxyacetamidines of potential medicinal interest as antihypertensives was undertaken. The preparation of the unsubstituted, *N*-methyl and *N,N*-dimethyl amidines was carried out by the Pinner synthesis or a modification of this process. The *N,N,N'*-trimethylaryloxyacetamidines necessitated preparation by another procedure. Fifteen amidines and nine intermediates not previously reported in the literature have been prepared and characterized. 2-Thymoloxyacetamidine, 2-(2,6-xylyloxy)acetamidine, 2-(2,6-dichlorophenoxy)acetamidine, 2-(2,6-dimethoxyphenoxy)acetamidine, 2-benzyloxyacetamidine, and their *N*-methyl and *N,N*-dimethyl derivatives were evaluated for their potential cardiovascular effects. None of these compounds showed any potent pharmacological activities in a general screen or when tested as norepinephrine-depleting agents or as adrenergic neuron-blocking agents.

Keyphrases □ Aryloxyacetamidines—synthesis □ NMR spectroscopy—identity, structure □ Pharmacological screening—aryloxyacetamidines

Although the literature describes the adrenergic neuron-blocking effects of guanidines, aminoguanidines, amidoximes, and quaternary ammonium compounds with bulky substituents, it appears that aryloxyamidines have received little attention as potential antihypertensive agents (1). Previous research has shown that molecules consisting of a strongly basic group attached to a suitable ring by a short alkylene or oxyalkylene chain can give rise to compounds with considerable hypotensive effects (2).

The purpose of this research was to investigate the synthesis of variously substituted aryloxyacetamidines and to have them screened as potential adrenergic neuron-blocking agents and anticholinergics. The synthesis of the amidines and substituted acetamidines of the thymoloxy, 2,6-xylyloxy, 2,6-dichlorophenoxy, 2,6-dimethoxyphenoxy, and the 2-benzyloxy series would provide structural analogs of active compounds and provide new information for the design of drugs which act on the autonomic nervous system.

Although there are many synthetic methods for preparing amidines, the most versatile method for preparing these compounds appeared to be the well-known Pinner synthesis (3). This method was used for the preparation of the amidines and *N,N*-dimethyl amidines. However, it was noted that yields were lowered unless the intermediate imidate salts were freshly prepared. In one case, the 2-(2,6-dimethoxyphenoxy)acetimidate hydrochloride could not be obtained, but instead 2-(2,6-dimethoxyphenoxy)acetamide was isolated. It has been reported that some acetimidate salts which contain electronegative groups on the β carbon will decompose to an amide and alkyl halide at room temperature (4, 5). Because of this difficulty, an alternate synthetic approach to the desired amidine was tried. Schaefer has noted that many electronegatively substituted nitriles may be converted to the imidates by alcohol in the presence of catalytic amounts of sodium. Reaction of the imidates with amine salts or ammonium chloride yielded the amidine salts (6). This method was also used and proved superior to the Pinner synthesis in both yields and facility.