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SYNTHESIS OF FUSED ETHYLENEIMINES FROM CYCLIC OLEFINS[1]

A. HASSNER and C. HEATHCOCK
Department of Chemistry, University of Colorado, Boulder, Colorado

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Abstract—The stereospecific addition of iodine isocyanate to cyclic olefins leads via *trans* iodo isocyanates to *trans* iodo carbamates in good yields. The latter are converted by reaction with base into ethyleneimines. In this manner the following conversions were accomplished: cyclohexene to cyclohexeneimine, dihydronaphthalene to 1,2,3,4-tetrahydronaphthalene(1,2)imine, indene to indene(1,2)imine, 2-cholestene to cholestene(2β,3β)imine, styrene to α-phenylethyleneimine. A mechanistic interpretation of the reactions involved is given.

AMONG organic compounds, which were found to show some degree of carcinostatic activity, the aziridine (or the related β-haloethylamine) functional grouping has maintained an outstanding place.[2] The extensive work of Fanta *et al.* has made available ethyleneimines fused to 5–10 membered rings.[3] The preferred route has been the ring closure of *trans* 2-aminocycloalkanols, which are generally obtained by ring opening of the corresponding epoxide with ammonia.[3,4] However, epoxide opening as well as the cyclization step sometimes proceeds in low yields.[3d] *Trans* 2-halo amines would be preferred starting materials for ethyleneimines but such compounds are difficult to obtain.

Recently it has been shown that iodine isocyanate adds to cyclic olefins and the resulting 2-iodo isocyanates can be hydrolyzed to 2-iodo amine salts which cyclize to yield fused ethyleneimines.[5–7] In the synthesis of cholestene(2β,3β)imine, the first fused steroidal ethyleneimine reported,[6] we had observed that the ring closure to the aziridine takes place much more smoothly and in higher yield if one proceeds via a 2-iodo carbamate instead of a 2-iodo amine salt. When iodine isocyanate is added to cyclohexene, 2-cholestene, indene, 1,2-dihydronaphthalene and styrene, the resulting *trans* 2-iodo-1-isocyanates can be converted, without isolation, to *trans* 2-iodo-1-carbamates on treatment with alcohol. That the addition of iodine isocyanate to olefins takes place in a *trans* manner has already been demonstrated.[5–7] We are able to show

[1] [a] Paper III on the Chemistry of Urethanes. For paper II see ref. 7.
[b] This investigation was supported by Public Health Service Grant CY-4474, from the National Cancer Institute.

[2] For some examples see G. R. Pettit and J. A. Settepani, *J. Org. Chem.* **27**, 2962 (1963); N. H. Cromwell and R. A. Wankel, *J. Amer. Chem. Soc.* **70**, 1320 (1948); P. Brookes and P. D. Lawley, *Biochem. J.* **80**, 496 (1961); International Cancer Congress, Moscow, *Angew. Chem.* Intern. Ed. **1**, 600 (1962); D. V. Lefemine, M. Dann, F. Barbatschi, W. K. Hausmann, V. Zbinovsky, P. Monnikendam, J. Adam and N. Bohonos, *J. Amer. Chem. Soc.* **84**, 3184 (1962).

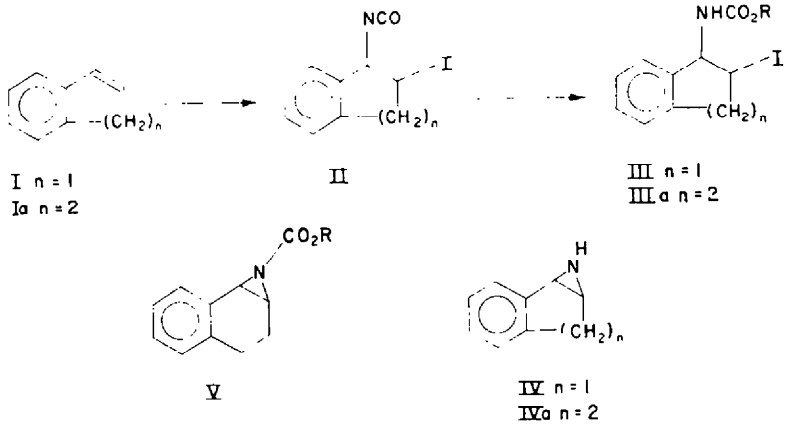
[3] [a] O. E. Paris and P. E. Fanta, *J. Amer. Chem. Soc.* **74**, 3007 (1952);
[b] P. E. Fanta, *J. Chem. Soc.* 1441 (1957);
[c] D. V. Kashelikar and P. E. Fanta, *J. Amer. Chem. Soc.* **82**, 4927 (1960);
[d] P. E. Fanta, L. J. Pandya, W. R. Groskopf and H. J. Su, *J. Org. Chem.* **28**, 413 (1963).

[4] F. Winternitz, M. Mousseron and R. Dennilauler, *Bull. Soc. Chim. Fr.* 382 (1956).

[5] G. Drefahl and K. Ponsold, *Chem. Ber.* **93**, 519 (1960).

[6] A. Hassner and C. Heathcock, *Tetrahedron Letters* (No. 6), 393 (1963).

[7] C. Heathcock and A. Hassner, *Angew. Chem.* **75**, 344 (1963).



I n = 1
Ia n = 2

II

III n = 1
IIIa n = 2

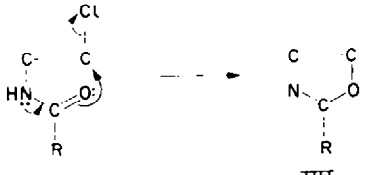
V

IV n = 1
IVa n = 2

that the reaction of these *trans* iodocarbamates with base constitutes a transformation of general utility leading in good yields to ethyleneimines.

For instance, methyl (*trans*-2-iodo-1-tetralin)carbamate IIIa (R:CH_3) obtained in 80% yield from 1,2-dihydronaphthalene is converted in 70% yield by warming with alcoholic potassium hydroxide to ethyleneimine IVa isolated as the phenylurea derivative or as the free imine IVa m.p. 51–53°. By contrast, IVa could be obtained only as a liquid when prepared by base treatment of 2-iodo-1-aminotetralin hydrochloride.[5] 2-Cholestene was transformed to cholestene(2β,3β)imine in an overall yield of 70% via methyl (3α-iodo-2β-cholestane)carbamate. Similarly, warming of methyl (*trans*-2-iodocyclohexane)carbamate or of ethyl (*trans*-2-iodo-1-indane) carbamate (III) with methanolic potassium hydroxide gave cyclohexene(1,2)imine (52%) or indene(1,2)imine (IV, 65%) respectively, both isolated as the phenylurea derivative. Alternatively, *trans*-2-chlorocyclohexylamine hydrochloride is obtained in 71% from methyl (*trans*-2-iodocyclohexane)carbamate by base hydrolysis followed by treatment with hydrochloric acid, without isolation of the intermediate cyclohexeneimine.

The ready conversion of *trans*-2-iodo carbamates, e.g. III, to ethyleneimines, e.g. IV, in the presence of base at room temperature or under mild heat is surprising in view of the well-known fact that *trans*-2-halo-N-acylamines (VI) cyclize to oxazolines (VII) rather than to ethyleneimines.[8] An exception to oxazoline formation is the isolation of an ethyleneimine (IX) from the diaxial N-benzoyl *trans*-β-mesyloxyamine VIII but not from the corresponding diequatorial isomer.[9] In our case the diaxial

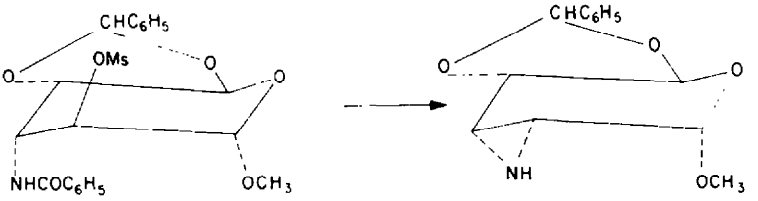


VI VII

[8] J. Sicher, M. Tichy, F. Sipos and M. Pankova, *Coll. Czech. Chem. Comm.* **26**, 2418 (1961); S. Winstein and R. Boschan, *J. Amer. Chem. Soc.* **72**, 4669 (1950).

[9] R. D. Guthrie, D. Murphy, D. H. Buss, L. Hough and A. C. Richardson, *Proc. Chem. Soc.* 84 (1963); see also J. E. Christensen and L. Goodman, *J. Amer. Chem. Soc.* **82**, 4738 (1960) and W. Meyer zu Reckendorf and W. A. Bonner, *Chem. Ber.* **95**, 1917 (1962).

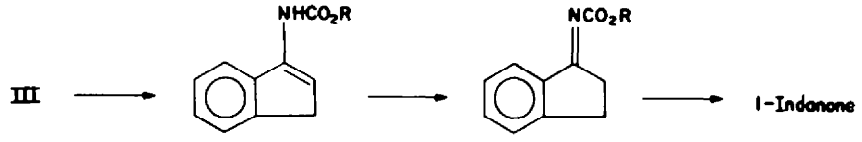
(cholestane) and diequatorial (cyclohexane), as well as the indane and open chain (phenylethyl) 2-iodo carbamates are converted only to ethyleneimines by base.[10]



VIII IX

In contrast to the behavior of the iodo urethanes mentioned above, simple urethanes are notoriously slow to hydrolyze in basic medium.[11] For instance ethyl cyclohexanecarbamate resists hydrolysis after 100 hr refluxing in 0·85N methanolic potassium hydroxide.[12] It can be shown that the ring closure of the 2-iodo carbamates e.g. III, proceeds by abstraction of the NH proton by base followed by immediate ring closure to an N-carbalkoxyethyleneimine of type V which is hydrolyzed to the free ethyleneimine.[12] Since arylsulfonamides of 2-halo amines may be cyclized by base to give the sulfonamide of the corresponding ethyleneimine,[13] it appears that the acidity of the NH of urethanes parallels that of the NH of sulfonamides and is greater than the acidity of a carboxamide NH. In basic medium, the anionic nitrogen of the urethane group can then displace a *trans* halogen on the β-carbon, the result being ring closure to an ethyleneimine. This proceeds in preference to displacement by oxygen to form a five-membered ring (cf. VII).

In the indene and styrene case, ethyleneimine production was found to be accompanied by the formation of 1-indanone and acetophenenone in 16% and 9% yields respectively. The presence of ketone by-products from certain of the *trans*-2-iodo carbamates can be accounted for on the basis of the following considerations. The stereochemical requirements of ring closure to an aziridine or an epoxide are best met when the groups involved are *trans* and diaxial.[14] In five membered rings where such a stereochemical arrangement is not possible, ring closure to an ethyleneimine is



X

accompanied by *cis* elimination of hydrogen iodide[15] to give an intermediate vinyl amine, which tautomerizes to an imine X. The latter is then hydrolyzed to 1-indanone.

[10] For oxazolidone formation from these iodo urethanes under different reaction conditions see ref. 7.

[11] S. Rovira, *Ann. Chim.* **20**, 660 (1945).

[12] A. Hassner, C. Heathcock and G. Nash to be reported in a separate paper.

[13] M. S. Kharash and H. M. Priestly. *J. Amer. Chem. Soc.* **61**, 3425 (1939); R. Adams and T. L. Cairns, *Ibid.* **61**, 2464 (1939).

[14] D. H. R. Barton and R. C. Cookson, *Quart. Rev.* **10**, 44 (1956).

[15] It has been shown that *cis* eliminations are much more favorable in five-membered than in six-membered rings, C. H. DePuy, R. E. Thurn and G. F. Morris, *J. Amer. Chem. Soc.* **84**, 1314 (1962).

In the acyclic ethyl 2-iodo-1-phenylethanecarbamate, as in the indane urethane III, elimination of hydrogen iodide, with concomitant ketone production, competes with the cyclization reaction.

EXPERIMENTAL

All m.p.s are uncorrected and were determined on a Fisher–Johns melting block. IR spectra were determined in KBr pellets using a Perkin–Elmer 21 IR spectrometer and NMR spectra were obtained using a Varian A-60 spectrometer and dilute solutions (ca. 10% by weight) in CCl_4 or $CDCl_3$. Tetramethylsilane was used as an internal standard and chemical shifts are expressed on the "tau" scale. UV spectra were determined in methanol on a Cary 14 instrument. Micro-analyses were performed by A. Bernhardt, Mikroanalytisches Laboratorium, Muelheim, Germany.

trans-2-*Iodo carbamates, general procedure*

The olefin to be used (0·1 mole) was dissolved in 200 ml anhydrous ether and freshly prepared silver cyanate (20 g, 0·133 mole) added. The slurry was stirred vigorously while being cooled in an ice-salt bath. Solid iodine (25·4 g, 0·1 mole) was added in one portion. The slurry was stirred 2 hr in the cold and then at room temp until the iodine color faded. At the end of the reaction, the mixture had a bright canary-yellow color.

The inorganic salts were filtered off through a layer of filter cel. At this point, the resulting ether solution occasionally had a degree of iodine color remaining. The solution was concentrated to ca. ½ volume and 200 ml of the appropriate alcohol added.

After the alcoholic solution had refluxed for 2–3 hr, the condenser was removed and the solution concentrated to ca. ½ volume, then poured into water containing a little Na_2SO_3. Work up was carried out by filtration if the product was solid, or by ether extraction if an oil was obtained.

Methyl (trans-2-*iodo*-1-*tetralin*)*carbamate* (IIIa). Prepared from 1,2-dihydronaphthalene; yield 78%; m.p. 129–131 (from methanol). (Found: C, 43·68; H, 4·18; I, 38·34. Calc. for $C_{12}H_{14}NO_2I$: C, 43·52; H, 4·26; I, 38·33%). ν_{max}: 3220, 3030, 1705 sh, 1685, 1530, 1260 cm^{-1}. $\nu_{max}^{CHCl_3}$: 3410, 3300, 1715, 1490, 1325 cm^{-1}. λ_{max}: 274 mμ (ε, 900), 267 mμ (ε, 1100).

Ethyl (trans-2-*iodo*-1-*indane*)*carbamate* (III). Prepared from indene. A 5-fold excess of silver cyanate was used but the reaction did not go to completion, even after several days; yield, 25–56%; m.p. 139–140 (from ether, lit.,[5] m.p. 139–140). ν_{max}: 3340, 1708, 1540, 1295, 1050 cm^{-1}. λ_{max}: 273 mμ (ε, 2060), 268 mμ (ε, 2040), 261 mμ (ε, 1580).

Methyl (trans-2-*iodo-cyclohexane*)*carbamate*. Prepared from cyclohexene; yield, 77%; m.p. 130–131° (from methanol, lit.,[16] m.p. 135°). ν_{max}: 3300, 3100, 3020, 1725 sh, 1700, 1563, 1270, 1053, 1033 cm^{-1}. $\nu_{max}^{CHCl_3}$: 3400, 3300, 1710, 1505, 1310, 1260 cm^{-1}. λ_{max}: 260 mμ (ε, 760).

Ethyl (2-*iodo*-1-*phenylethane*)*carbamate*. Prepared from styrene; yield, 62%; m.p. 86·5–87·5° (from ether-pentane). (Found: C, 41·75; H, 4·40; N, 4·47. Calc. for $C_{11}H_{14}NO_2I$: C, 41·40; H, 4·42; N, 4·39%). ν_{max}: 3350, 3100, 1700, 1542, 1258, 1049 cm^{-1}. $\nu_{max}^{CCl_4}$: 3420, 3310, 1720, 1495, 1330, 1225, 1047 cm^{-1}.

Basic hydrolysis of methyl (trans-2-*iodocylohexane*)*carbamate*

a. *Isolation of* N-(*phenylcarbamoyl*)*cyclohexane*(1,2)*imine*. A solution of 4·34 g methyl urethane in 50 ml 1·0N methanolic KOH was refluxed 30 min. Approximately ½ the solvent was removed (red. press.) and 50 ml sat. NaCl aq. added. The heterogeneous mixture was extracted with hexane (4 × 20 ml), the hexane solution washed with water (2 × 20 ml.) and sat. NaCl aq. (50 ml) and dried (Na_2SO_4). The drying agent was removed and 2 ml phenyl isocyanate added. After 30 min, the white precipitate was filtered off and washed with hexane. The air-dried product, 1·72 g (52%) had m.p. 150–156·5°.

An analytical sample, m.p. 158–159°, was obtained by two crystallizations from acetone–hexane, followed by recrystallization from methanol and finally, recrystallization from acetone–water. (Found: C, 72·54; H, 7·27; N, 13·21. Calc. for $C_{13}H_{16}N_2O$: C, 72·19; H, 7·46; N, 12·95%). ν_{max}: 3300, 3000, 2860, 2700, 1650, 1590, 1530, 1403, 753, 697 cm^{-1}.

The NMR spectrum, in $CDCl_3$, had bands at 2·7τ (complex multiplet, aromatic protons), 7·27τ ($W^{1/2}$ = 5 cps, C_1—H and C_2—H), 8·17τ ($W^{1/2}$ = 14 cps, C_3—H and C_6—H) and 8·67τ (complex multiplet, $W^{1/2}$ = 13 cps, C_4—H and C_5—H).

[16] L. Birckenbach and M. Lindhard, *Ber. Dtsch. Chem. Ges.* **64B**, 1076 (1931).

b. *Isolation of* trans-2-*chlorocyclohexylamine hydrochloride*. A solution of 2·83 g urethane in 100 ml 1·0N methanolic KOH was refluxed 30 min, then poured into 100 ml sat. NaCl aq. Water was added until the precipitated NaCl all dissolved and the solution was extracted with ether (3 × 50 ml). The combined ether extracts were washed with water, 10% HCl aq. and sat. NaCl aq., then dried ($MgSO_4$). Evaporation of the ether left 42 mg oil which gave a negative Beilstein test. The IR spectrum of this oil showed typical urethane absorption and probably was methyl (*trans*-2-methoxycyclohexane)carbamate.

The above hydrochloric acid extracts were evaporated to dryness to yield 1·21 g (71%) of *trans*-2-chlorocyclohexyl amine hydrochloride. m.p. 209–210·5 (sealed capillary). The reported[4] m.p. is 205–207°. ν_{max}: 2750 (broad), 2020, 1600, 1515, 1450, 732 cm^{-1}.

Basic hydrolysis of ethyl (trans-2-*iodo*-1-*tetralin*)*carbamate*

A solution of 1·0 g carbamate and 3 g KOH in 30 ml absolute ethanol was refluxed 2 hr. The solution was diluted with water and worked up by ether extraction, yielding 362 mg of oil which solidified on standing; m.p. 40–45°.

A portion of this material (160 mg) was recrystallized from hexane to give 128 mg of the imine, m.p. 51·5–53 . The yield of purified imine being 69%.

Another recrystallization from hexane furnished an analytical sample, m.p. 52–52·5°. (Found: C, 82·32; H, 7·76; N, 9·81. Calc. for $C_{14}H_{11}N$: C, 82·71; H, 7·64; N, 9·38%).

The IR spectrum of this material was identical with that of the authentic imine prepared by the method of Drefahl and Ponsold,[5] who report b.p. 108–110°/5 torr but give no m.p.

N-(*Phenylcarbamoyl*)-1,2,3,4-*tetrahydronaphthalene*(1,2)*imine*. The phenylurea derivative of 1,2,3,4-tetrahydronaphthalene(1,2)imine, was prepared in the following manner. Phenyl isocyanate (5 drops) was added to 120 mg of the imine in 5 ml hexane. The precipitate which formed was filtered off and washed with hexane. The dried product, 165 mg (76%) and m.p. 161–162·5°.

An analytical sample, m.p. 161–162°, was obtained by recrystallization from ether–hexane. (Found: C, 77·45; H, 6·22; N, 10·72. Calc. for $C_{17}H_{16}N_2O$: C, 77·25; H, 6·10. N, 10·60%). ν_{max}: 3270, 3130, 3090, 3050, 1670, 1610, 1600 cm^{-1}.

Basic hydrolysis of ethyl (trans-2-*iodo*-1-*indane*)*carbamate*

a. *Isolation of* N-(*phenylcarbamoyl*)*indene*(1,2)*imine*. A solution of 3·31 g urethane in 80 ml 1·5N methanolic KOH and 20 ml water was stirred 5 hr at room temp and was then poured into 200 ml water. Extraction of the slurry with methylene chloride (4 × 50 ml) gave an organic phase which was dried (Na_2SO_4), filtered, and evaporated. Phenyl isocyanate (2 ml) was added and the mixture heated on a steam bath for a few minutes. The resulting crystalline mass was placed on a funnel and washed well with hot hexane and then air-dried, yield, 1·375 g (65%), m.p. 138–141°.

Two recrystallizations from acetone–hexane furnished the analytical sample, m.p. 144–146°. (Found: C, 77·27; H, 5·50; N, 11·08. Calc. for $C_{16}H_{14}N_2O$: C, 76·68; H, 5·64; N, 11·19%). ν_{max}: 3230, 1660, 1534, 1500, 1315, 1248 cm^{-1}.

b. *Identification of* 1-*indanone*. A solution of the ethylcarbamate III (7·5 g) in 100 ml 1N methanolic KOH was refluxed 2·5 hr. The solution was poured into water, worked up as usual and the resulting crude pale-green oil distilled (red. press.). The fraction distilling at 90–120°/2·5 mm weighed 1·0 g.

This clear oil was analyzed by vapor phase chromatography on a Perkin–Elmer Vapor Fractometer, using a 2 meter, 5 mm ID column packed with 20% Silicone Dow 710 on 60–80 mesh Chromosorb W. The helium flow rate was 50 ml/min. At both 210° and 290°, the fractogram contained a peak with exactly the same retention time as authentic 1-indanone (3.9 min at 210°, 1·25 min at 290°). The area of this peak was calibrated against the area given by the same volume of known mixtures of 1-indanone and acetone.

It was then calculated that the material analyzed contained 50% 1-indanone and 50% of another component, which would not emerge from the column. This corresponds to a 16% overall yield of 1-indanone.

Basic hydrolysis of ethyl(2-*iodo*-1-*phenylethane*)*carbamate*

A solution of 10 g carbamate and 10 g KOH in 70 ml methanol and 30 ml water was refluxed 1 hr. The solution was cooled to room temp and poured into 250 ml water. A pale-green oil weighing 2·77 g was obtained by ether extraction in the normal manner.

The NMR spectrum of this material showed that it consisted of 12·5 ± 0·5% acetophenone and 85·5 ± 0·5% 2-phenylaziridine. The yields of the product were thus: acetophenone, 9·2%; 2-phenylaziridine, 61·2%.

A portion of the oil (2·09 g) was dissolved in ether and washed with 10% HCl aq. The dried solution was evaporated on a steam bath to obtain crude acetophenone. The ketone was converted into its 2,4-dinitrophenylhydrazone derivative by the normal procedure. After recrystallization from acetone–methanol, the compound had m.p. 240–245° (sealed capillary) and a mixed m.p. with authentic acetophenone 2,4-dinitrophenylhydrazone (m.p. 240–245°) of 241–245°.

In a similar experiment, using 1·5 g carbamate, the crude product was distilled (red. press.) to obtain 500 mg (88%) 2-phenylaziridine, b.p. 90–95°/2 mm (reported,[17] 94–95°/10 mm). The NMR spectrum, in CCl_4, was identical to that reported for this compound.

Cholestene(2β,3β)imine. Methyl (3α-iodo-2β-cholestane)carbamate[8] (2·45 g) was dissolved in 100 ml ethanol containing 10 ml water and 10 g KOH. The resulting solution was refluxed on a steam bath for 1¾ hr and then poured into 250 ml water. The suspension was extracted with ether and the extracts washed well with water and then dried ($MgSO_4$). Evaporation of the ether on a steam bath yielded a clear oil which solidified on standing, yield 1·46 g (90%) m.p. 103–105°.

An analytical sample was prepared in the following way: 600 mg imine was dissolved in ether and the solvent allowed to evaporate completely at 5°. The resulting crystalline mass was placed on a filter and washed well with cold ether leaving 35 mg colorless prisms, m.p. 105–106·5°. (Found: C, 84·00; H, 12·19; N, 3·76. Calc. for $C_{27}H_{47}N$: C, 84·08; H, 12·28; N, 3·63%). ν_{max}: 3300, 1418, 797, 733 cm^{-1}.

The NMR spectrum, in CCl_4, has broad bands at 7·9τ and 8·1τ (C_2—H and C_3—H), 9·13τ (C_{26} and C_{27}, doublet, J = 6·5 cps), 9·18τ (C_{19}, singlet) and 9·37τ (C_{18}, singlet).

[17] S. J. Brois, *J. Org. Chem.* **27**, 3532 (1962).