added 47.5 ml. of 0.2 *M* acetate buffer (pH 5.0). After about 10 min., a fine white precipitate began to form. After 6 days, 0.039 g. of a cream-colored solid was removed by filtration, but upon drying in a desiccator the solid decomposed to a dark brown solid. The filtrate was concentrated and the white precipitate was isolated by centrifugation. The solid was mixed with water and centrifuged, the clear solution was decanted, and the tan solid was dried in a desiccator. The product melted from 230–270° with gradual decomposition. The ultraviolet spectrum showed $\lambda_{\max}^{\mathrm{EtOH}}$ 252 mμ; the infrared, $\lambda_{\max}^{\mathrm{KBr}}$ 2.88, 3.1–3.2, 5.78 μ.

Polymer from Oxindole and Paraformaldehyde.—A mixture of 1.00 g. (7.5 mmoles) of oxindole, 0.23 g. of paraformaldehyde (equivalent to 8 mmoles of formaldehyde), 4 drops of piperidine, and 20 ml. of absolute ethanol was refluxed for 24 hr. A tan solid (0.02 g.) was removed by filtration and the filtrate was evaporated to dryness at room temperature. The residue was dissolved in tetrahydrofuran (THF), and benzene was added to the saturation point. Two crops of a cream solid, m.p. 211–213° dec., totaling 0.28 g., were obtained with $\lambda_{\max}^{\mathrm{EtOH}}$ 207 and 251 mμ. The infrared spectrum resembled that of the polymeric product from the decomposition of 3-bromooxindole-3-acetic acid.

A sample of the polymer, m.p. 220–221° dec., which had been recrystallized from tetrahydrofuran–benzene, had the following analysis: C, 67.89; H, 5.99; N, 9.00 ± 1.00.

Notes

The Synthesis and Infrared Spectrum of 3-Deuterioindole

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Whereas exchange of deuterium for hydrogen on the indole nitrogen can be effected in neutral solution by repeated evaporation of solutions of indole and D_2O in a common solvent,[1] exchange at the 3-position requires acid catalysis.[2,3] We have applied this method for convenient syntheses of 1,3-dideuterio- and 3-deuterioindole.[4] Recognition of pronounced differences between the infrared spectra of indole and its 3-deuterio derivatives enabled us to follow the exchange readily and to characterize the isolated products.

Previous work from this laboratory[5] has shown that very rapid exchange of the NH of skatole occurs in dioxane solutions containing 5×10^{-5} *M* sulfuric acid. Very little exchange of the indole NH occurred under comparable conditions during a 2-hr. period. In the presence of 10^{-4} *M* acid, NH exchange occurred but was still slower than exchange in skatole. At this acid concentration no evidence of deuterium at the 3-position of the isolated product was found.[6]

By refluxing a solution of indole in D_2O containing 5×10^{-3} *M* sulfuric acid, exchange of the β-proton was accomplished, yielding 1,3-dideuterioindole. This in turn was converted to 3-deuterioindole by refluxing with water. The last product had an isotopic purity of 87%, as determined by n.m.r. Although the 1,3-dideuterioindole also had a high per cent of deuterium at the 3-position, the nitrogen seldom held more than 60% deuterium, as determined by infrared. Exchange from the nitrogen is a more facile process, and attempts to raise this level by repeated treatments with D_2O were not effective. The same problem was encountered in a recent synthesis of 1,3-dideuterioindole *via* the indole Grignard reagent.[1b] In this case, however, the β-carbon was also only 50% deuterated. The work-up of the Grignard reagent involved basic conditions, which may have promoted exchange[2c] with traces of water inadvertently admitted.

Although the introduction of deuterium produced no visible changes in the CH or CD stretching region near 3.3 μ of the infrared spectrum, probably because the bands are too weak to see with standard equipment, in the C–H bending region deuterium had a very marked effect similar to that reported for other substituents at the 3-position.[7] Of the three characteristic strong peaks at 13.05, 13.45, and 13.85 μ in the indole spectrum, that at 13.05 μ disappeared completely in the deuterated material, and that at 13.85 μ, associated with indoles bearing no substituents at the 2- and 3-positions,[7] was reduced to a weak absorption at 13.70 μ. Had it been possible to obtain isotopically pure product, the last peak would probably have disappeared completely. The band at 13.45 μ, characteristic of indoles unsubstituted in the benzene ring,[7] was unchanged in 3-deuterioindole. New peaks in the deuterated material included a band of moderate intensity at 12.1 μ (830 cm.$^{-1}$), a strong band at 12.4 (808), and what appeared to be an overtone of the former at 6.05 (1660). The absorption at 12.4 μ is in the region characteristic of indoles bearing a substituent at the 3-position.[7]

Thus, the presence of deuterium at the 3-position can be detected by the band at 12.4 μ, and residual C–H at that position can be estimated quantitatively from the

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(1) (a) L. A. Cohen J. W. Daly, H. Kny, and B. Witkop, *J. Am. Chem. Soc.*, **82**, 2184 (1960); (b) R. V. Jardine, and R. K. Brown, *Can. J. Chem.*, **41**, 2067 (1963).

(2) (a) M. Koizumi and T. Titani, *Bull. Chem. Soc. Japan*, **13**, 307 (1938); (b) M. Koizumi, *ibid.*, **14**, 453 (1939). (c) The possibility of base-catalyzed exchange at the 3-position is suggested by recent work with 2-methylindole [B. C. Challis and F. A. Long, *J. Am. Chem. Soc.*, **85**, 2524 (1963)].

(3) The occurrence of considerable exchange at the 3-position upon evaporation of solutions of D_2O and indole or 2-methylindole in acetone or ethanol has been reported.[1b] Although this result would be expected in the latter case,[2b] it is difficult to reconcile the indole result with the earlier studies[2a,b] and our own.

(4) The only reported syntheses of C-deuterated indoles are those for 1,3-dideuterioindole (50% isotopic purity at C-3),[1b] 5-deuterioindole, and 2,3,4,5,6,7-hexadeuterioindole [H. Plieninger, R. Fischer, G. Keilich, and H. D. Orth, *Ann.*, **642**, 214 (1961)].

(5) R. L. Hinman and E. B. Whipple, *J. Am. Chem. Soc.*, **84**, 2534 (1962).

(6) Indole is considerably more basic than skatole in equilibrium protonation where 3-protonation predominates [R. L. Hinman and J. Lang, *Tetrahedron Letters*, **No. 21**, 12 (1960)]. The differences in exchange rates of the NH proton may reflect differences in basicity of the 1-position.

(7) "Physical Methods in Heterocyclic Chemistry," Vol. II, A. R. Katritsky, Ed., Academic Press, New York, N. Y., 1963, pp. 211,212.

absorption at 13.85 μ. Moreover, these effects afford additional proof that deuterium is bonded to carbon. The intense N–D band in N-deuterioindole appeared at 3.95 μ, but no other significant change in the spectrum was observed.

Experimental

3-Deuterioindole.—A mixture of 10 g. of indole and 5 ml. of 0.005 *N* sulfuric acid in D_2O was refluxed under nitrogen for 12 hr., the minimum time required for complete exchange. The solution was cooled and then was extracted with dry benzene. The extract was washed twice with D_2O and once with a saturated solution of sodium chloride in D_2O, then was dried over anhydrous calcium sulfate and evaporated. The residual white solid contained about 60% 1,3-dideuterioindole; as indicated by the intensities of the NH and ND peaks in the infrared, the balance was 3-deuterioindole. The mixture was refluxed with 50 ml. of water under nitrogen for a minimum of 3 hr. The mixture was cooled and extracted with benzene. The benzene extract was washed with a saturated salt solution, dried over calcium sulfate, and evaporated. The residual solid was recrystallized twice from a benzene–hexane mixture and then was dissolved in warm hexane. The clear solution, which was decanted from the oil that formed upon standing, was concentrated and cooled. White crystals (0.70 g.) of 87% pure 3-deuterioindole were obtained, m.p. 50.5–51.5°. The purity of the product was determined from the integrated n.m.r. spectrum in carbon tetrachloride by comparison of the areas of the β- and α-H peaks.

The principal peaks of the infrared spectra of indole and 3-deuterioindole, determined in KBr, are given below. Italic values are those which do not appear in the other spectrum. The presence of deuterium on nitrogen made little difference in the spectrum, except for the NH and ND peaks.

Indole.—*2.92 (vs)*, 3.18 (vw), 3.23 (w), 5.15 (w), 5.25 (w), 5.33 (w), 5.47 (w), 5.58 (w), *5.82 (w)*, 5.89 (w), 6.16 (m), 6.30 (w), *6.61 (w)*, 6.68 (w), 6.83 (s), 7.03 (s), *7.35 (s)*, 7.45 (s), 7.80 (m), 8.00 (s), *8.27 (w)*, 8.69 (w), 8.82 (m), 9.15 (s), *9.40 (s)*, 9.87 (w), 9.93 (w), 10.70 (m), *11.13 (m)*, 11.45 (m), *11.60 (m)*, *13.05 (s)*, 13.43 (vs), 13.85 (vs).

Additional Peaks in 3-Deuterioindole.—*6.05 (w)*, *8.49 (w)*, *12.05 (m)*, *12.40 (s)*, *13.72 (s)*.

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Reduction of Some Oxindolylidene Derivatives to 3-Substituted Oxindoles by Sodium Borohydride[1]

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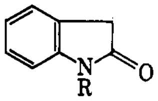
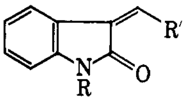
The 3-position of oxindole possesses distinct anionoid character. In 1909, Wahl and Bagard[2a] reported that base- or acid-catalyzed condensation of oxindole (**1**, R = H) with carbonyl compounds led to the formation of oxindolylidene derivatives (**2**). The trivial name "isoindogenides" has been given to the class of compounds with structure **2**. The isoindogenide 3-α-picolylideneoxindole (**2a**) first attracted our attention as a synthetic intermediate for spirooxindole derivatives (**3**).[3] Compounds with the proposed structure **2a** were previously reported by Abramovitch and Hey[4] and by Akkerman and Veldstra.[5] In both cases **2a** was prepared by condensation of isatin with α-picoline, but the two groups gave different melting points for their products.

A reaction between oxindole and 2-pyridinecarboxaldehyde, catalyzed by piperidine, gave a compound whose elemental analysis and spectra accord with constitution **2a**, and the melting point of this compound agrees with the value given by Akkerman and Veldstra. More recently 3-α-picolylideneoxindole (**2a**), which is described as exhibiting strong cholinergic effects, was included in a hydrogenation study of pyridine derivatives, but the method for preparing **2a** was not given.[6] When oxindole and the pyridinealdehyde were condensed in methanol, or when diethylamine was used as the basic catalyst in an open container, the major product was the carbinol (**4**).

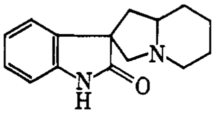
Some additions to the class of isoindogenides are reported in Table I and in the Experimental section. In some cases, both oxindole and N-methyloxindole were used. The carbonyl compounds employed (and the products formed) were 2-pyridinecarboxaldehyde (**2a** and **b**), 2-pyrrolecarboxaldehyde (**2c** and **d**), furfural (**2e**), and cyclohexanone.[7]



1



2



3

The scope of sodium borohydride reductions has been greatly expanded beyond the original conception that this reagent was limited to the reduction of carbonyl or imine groups. In particular, there are several reports in which carbon–carbon double bonds of enamines and α,β-unsaturated esters are reduced.[8,9] We found adventitiously that sodium borohydride reduces the 3-*exo* double bond in several isoindogenides.[10] The reaction occurs with a wide variation of substituents. For example, α-picolylideneoxindole (**2a**) is reduced to α-picolyloxindole (**5**)[11] by sodium borohydride, and 3-benzylideneoxindole (**2**, R′ = phenyl) is converted to 3-benzyloxindole (**6**). The proof of structure in the latter case was accomplished by comparing the product of the borohydride reduction with a sample of 3-benzyloxindole prepared by catalytic hydrogenation of benzylideneoxindole.[12] Even with an aliphatic

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(1) We gratefully acknowledge a grant in support of this research from the Tennessee Heart Association.

(2) (a) A. Wahl and P. Bagard, *Compt. rend.*, **148**, 716 (1909); (b) W. B. Wright and K. H. Collins, *J. Am. Chem. Soc.*, **78**, 221 (1956); (c) P. L. Julian, E. W. Meyer, and H. C. Printy, "Heterocyclic Compounds," Vol. 3, R. C. Elderfield, Ed., John Wiley and Sons, Inc., New York, N. Y., 1952, p. 185; (d) W. C. Sumpter and F. M. Miller, "Heterocyclic Compounds," Vol. 8, A. Weissberger, Ed., Interscience Publishers, Inc., New York, N. Y., 1954, p. 142.

(3) R. G. Mason, M. A. Thesis, Fisk University, 1962.

(4) R. A. Abramovitch and D. H. Hey, *J. Chem. Soc.*, 1697 (1954).

(5) A. M. Akkerman and H. Veldstra, *Rec. trav. chim.*, **73**, 629 (1954).

(6) G. N. Walker, *J. Org. Chem.*, **27**, 2967 (1962).

(7) 3-Furfurylideneoxindole has already been described: J. Staněk and D. Rybář, *Chem. Listy*, **40**, 173 (1946).

(8) I. W. Elliott and J. O. LeFlore, *J. Org. Chem.*, **25**, 3181 (1963); J. Szmuszkovicz, "Advances in Organic Chemistry," Vol. 4, R. A. Raphael, E. C. Taylor, and H. Wynberg, Ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 82.

(9) J. A. Meschino and C. H. Bond, *J. Org. Chem.*, **28**, 3129 (1963); M. S. Brown and H. Rapoport, *ibid.*, **28**, 3261 (1963); H. LeMoal, R. Carrié, and M. Bargain, *Compt. rend.*, **251**, 2541 (1960).

(10) These reductions were initiated with the hydrochloride salt of **2a** to establish the structure. The chemistry of these salts will be the subject of a separate communication.

(11) α-Picolyloxindole (**5**) has also been prepared by Walker (ref. 6).

(12) E. Kircher, *Nachr. kgl. Ges. Wiss. Gottingen Math.-Physik. Kl.*, 154 (1921); *Chem. Abstr.*, **17**, 1012 (1923).