Some Unusual Transformations in the Papaverine Series

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Summary Some novel azaberbinone heterocycles have been prepared starting from 6′-nitropapaverine and its dihydro-derivative and the presumed reductive rearrangement product obtained from 6′-nitropapaverine has been reassigned an azaberbinone structure.

THE dehydrogenation of tetrahydroberbines to the corresponding berbine alkaloids by iodine is a well known reaction.[1] While attempting to extend this reaction to the dehydrogenation of 3,4-dihydroisoquinolines, we encountered an unusual transformation leading to a novel heterocyclic system.

The reaction of 6′-nitro-3,4-dihydropapaverine (**1**) with hot ethanolic iodine solution containing sodium acetate afforded, not the expected 6′-nitropapaverine (**2**), but the isomeric bright red dihydroazaberbinone *N*-oxide (**3**), m.p. 240—241°, (54%); λ_{max} (dioxan) 238, 277, 341, 408, 480 sh, and 506 nm (log ϵ 4·38, 4·38, 4·14, 3·65, 4·16, and 4·26).† The n.m.r. spectrum of (**3**) showed in addition to four methoxy-groups and four aromatic singlets, only the two

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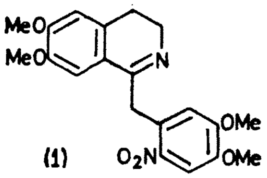
† Satisfactory analyses and spectral data were obtained for all new compounds.

adjacent methylenes of ring B [apparent triplets centred at δ ($CDCl_3$) 3·14 and 5·00]. Compound (**3**) was readily reduced (Pd and H_2, or $NaHSO_3$ in acetic acid) to the corresponding orange-yellow azaberbinone (**4**), m.p. 283—285°; λ_{max} (dioxan) 238, 249, 267, 313, 339, 357, 411, and 433 nm (log ϵ 4·46, 4·45, 4·42, 4·02, 3·90, 3·91, 4·11, and 4·33). Dehydrogenation of (**4**) with dichlorodicyanoquinone (DDQ) in refluxing benzene gave the fully aromatic yellow azaberbinone (**5**), m.p. 278—280°; λ_{max} (dioxan) 247 sh, 265, 280, 298, 322, 369 sh, 388, 408, 429, and 506 nm (log ϵ 4·35, 4·51, 4·36, 4·90, 3·95, 3·77, 3·99, 4·03, 4·33, and 4·45); the n.m.r. spectrum of (**5**) showed only six aromatic protons in addition to the four OMe signals.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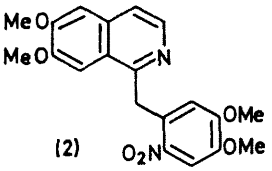
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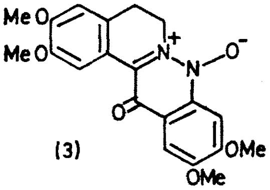
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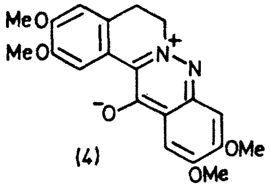
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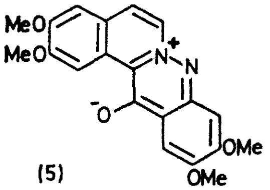
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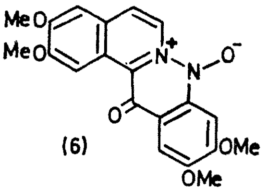
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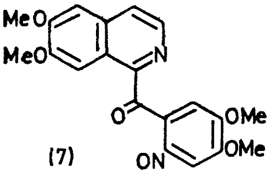
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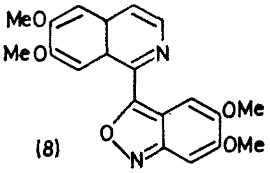
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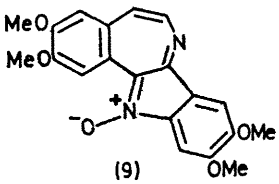
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Similarly, iodine oxidation of 6′-nitropapaverine gave the dark red azaberbinone *N*-oxide (**6**), m.p. 115—118°, (39%); λ_{max} (dioxan) 232, 252, and 349 nm (log ϵ 4·59, 4·51, and 4·10). Treatment of (**6**) with hot ethanol converted it into the open-chain green isomer, 6′-nitrosopapaveraldine (**7**), m.p. 198—199·5°; (**7**) was reconverted into (**6**) by dissolving it in acetic acid and diluting with water. Compound (**6**) was reduced rapidly by $NaHSO_3$ in acetic acid to give the azaberbinone (**5**) which was distinctly different from the isomeric yellow anthranilopapaverine (**8**) of Pschorr.[2] We obtained the latter compound in 85% yield by heating (**2**) under reflux with methanolic KOH.

According to a recent paper 6′-nitropapaverine (**2**) reacts with triethyl phosphite under reflux, to give, in low yield, a compound assigned the remarkable indolobenzazepine *N*-oxide structure (**9**).[3] Re-examination of this reaction has shown that the product is identical with azaberbinone (**5**). The mechanism of this transformation may involve the dehydration of (**2**) to anthranil (**8**), followed by a phosphite ester catalysed isomerization of (**8**) into (**5**). In support of this hypothesis, the conversion of (**8**) into (**5**) could be achieved under the reaction conditions employed.

We suggest that the conversion of (**2**) into (**6**) involves iodination of the benzylic carbon of (**2**), followed by a neighbouring group displacement of iodine by the adjacent nitro-group and subsequent ring-opening to give the open nitroso-ketone structure (**7**). A related mechanism has been suggested for the conversion of *o*-nitrobenzhydrol into *o*-nitrosobenzophenone by tosyl chloride in pyridine.[4]

We thank the National Institutes of Health for a grant in support of this work.

(*Received, September 7th*, 1970; *Com.* 1511.)

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[2] R. Pschorr, *Ber.*, 1904, **37**, 1926.

[3] T. Kametani, T. Yamanaka, K. Ogasawara, and K. Fukumoto, *J. Chem. Soc.* (*C*), 1970, 380.

[4] W. B. Dickinson, *J. Amer. Chem. Soc.*, 1964, **86**, 3580.