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1,2-DIHYDROISOQUINOLINES—II

BERBINE SYNTHESES[1]

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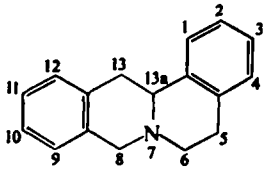
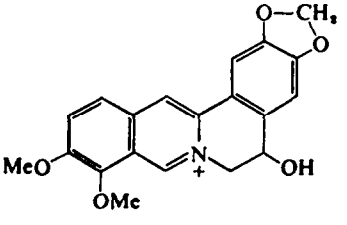
Abstract—If an N-β-arylethylisoquinolinium halide is treated with concentrated aqueous alkali the initially formed pseudobase undergoes a disproportionation reaction to yield the 1,2-dihydroisoquinoline and the isocarbostyril. When this mixture is treated with concentrated mineral acid ring-closure occurs to yield a mixture of the berbine and 8-oxoberbine systems. This procedure constitutes both a simplification and an improvement on existing methods for the synthesis of berbines, and it is the first reported example of a ring-closure of this type with an isocarbostyril.

IN PART I[2] of this series a brief review was given of the chemistry of 1,2-dihydroisoquinolines, and a second example of a benzyl migration in such systems was described. In this paper a simplification of a berbine ring-skeleton synthesis is reported, and also a novel ring-closure reaction of isocarbostyrils is described.

The 5,6,13,13a-tetrahydro-8H-dibenzo[a,g]quinolizine skeleton (1) is the fundamental structural unit of the tetrahydroberberine (or protoberberine) alkaloids.[3] The trivial name "berbine" has been suggested[4] for this ring system, and is often used for compounds other than the natural products, each one of which has its own trivial name. Our knowledge of the chemistry of this ring system is derived mainly



I



II

from the structural work on the individual alkaloids, and almost all synthetic efforts have been directed towards these natural products. Current interest in the berberine alkaloids centres around (a) the elucidation of structure of new members, recent examples being berberastine (II)[5] and steponine (III),[6] (b) their use as intermediates

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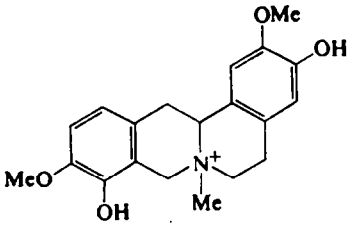
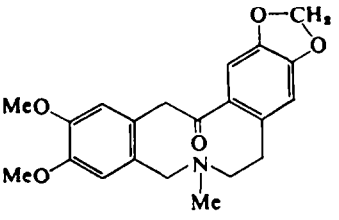
[1] A preliminary account; D. W. Brown and S. F. Dyke, *Tetrahedron Letters* 3587 (1964).
[2] S. F. Dyke and M. Sainsbury, *Tetrahedron* **21**, 1907 (1965).
[3] R. H. F. Manske and W. R. Ashford in *The Alkaloids* (Edited by R. H. F. Manske and H. L. Holmes) Vol. 4; Chap. 29. Academic Press, New York (1954).
[4] W. Awe, *Arch. Pharm.* **270**, 156 (1932).
[5] M. M. Nijland, *Pharm. Weekblad.* **98**, 301 (1963).
[6] M. Tomita, Y. Watanabe and M. Fuse, *J. Pharm. Soc. Japan*, **77**, 274 (1957); Y. Watanabe, *Ibid.*, 77, 278 (1957).

in the synthesis of the cryptopine-type ring skeleton, for example, fagarine-II[7] (IV), and (c) the biosynthesis of members of the group.[8–12]

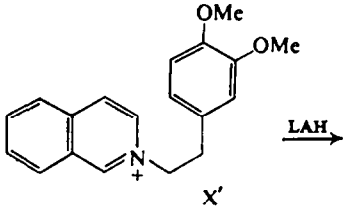


III

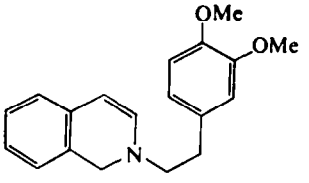


IV

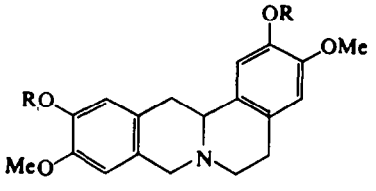
The more important methods of synthesis of the berbine ring system have been well reviewed by Pelz;[13] probably the simplest and most direct of these is that due to Huffman and Miller,[14] who reduced the quaternary isoquinolinium bromide (V, X = Br) with LAH, and cyclized the resultant 1,2-dihydroisoquinoline (VI) with mineral acid. 2,3-Dimethoxyberbine (VII) was obtained in an overall yield of 18%, upon basification. This method was extended by Battersby *et al.*[15] who obtained



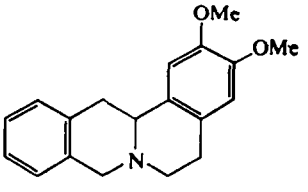
V



VI



VIII

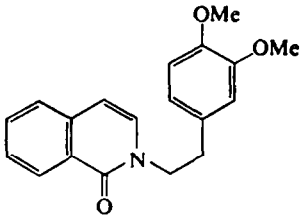


VII

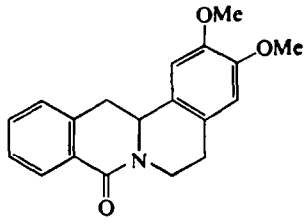
norcoralydine (VIII, R = Me) in 40% yield, and (±)-coreximine (VIII, R = H) in 13% yield from the corresponding isoquinolinium salts.

[7] D. Giacopello, V. Deulofeu and J. Comin, *Tetrahedron* **20**, 2971 (1964).
[8] I. D. Spenser and J. R. Gear, *Proc. Chem. Soc.* 228 (1962).
[9] D. H. R. Barton, R. H. Hesse and G. W. Kirby, *Proc. Chem. Soc.* 267 (1963).
[10] A. R. Battersby, R. J. Francis, M. Hirst and J. Staunton, *Proc. Chem. Soc.* 268 (1963).
[11] I. Monkovic and I. D. Spenser, *Proc. Chem. Soc.* 223 (1964).
[12] A. R. Battersby, R. J. Francis, E. A. Ruveda and J. Staunton, *Chem. Comm.* 89 (1965).
[13] K. Pelz, *Chem. Listy* **57**, 1107 (1963).
[14] J. W. Huffman and E. G. Miller, *J. Org. Chem.* **25**, 90 (1960).
[15] A. R. Battersby, D. J. LeCount, S. Garratt and R. I. Thrift, *Tetrahedron* **14**, 46 (1961).

It is well known[16] that when alkali is added to isoquinolinium salts, for example (V), the pseudobase is formed, and this may, in the presence of excess alkali, disproportionate to a mixture of a 1,2-dihydroisoquinoline (VI) and an isocarbostyril (IX), and it occurred to us that a further simplification of the Huffman–Miller berbine synthesis may be possible by simply treating an isoquinolinium salt successively with strong alkali and strong mineral acid. In the event, when an aqueous solution of V, (X = I) was treated, at room temperature, with cold aqueous sodium hydroxide solution an oil was immediately formed. This was quickly extracted with



IX



X

methylene chloride and the solvent was removed under reduced pressure. Concentrated aqueous hydrochloric acid was added to the residue, and after some time the white crystalline hydrochloride salt that had formed was collected. This was shown, by comparison with an authentic sample, to be identical with the 2,3-dimethoxyberbine hydrochloride described by Huffman and Miller. The yield was 24%.

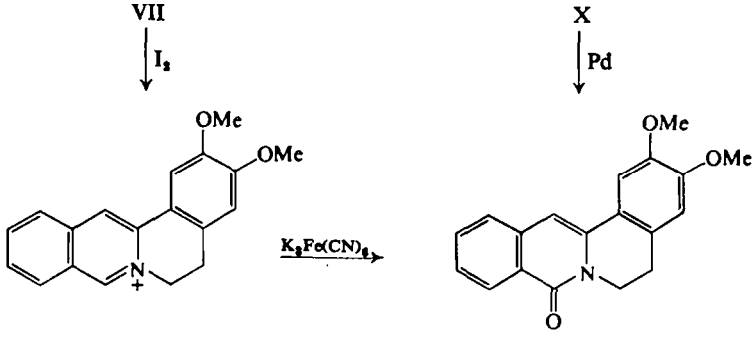
A white, neutral compound, m.p. 142° was obtained in 20% yield (based upon V, X = I) from the filtrate. A band at 1650 cm^{-1} in the IR spectrum indicated the presence of an amide group, but the substance was not identical with the expected isocarbostyril (IX). Elemental analysis indicated an empirical formula of $C_{19}H_{21}NO_3$, and the NMR spectrum (taken in $CDCl_3$ on a Varian A.60 spectrometer) revealed only two hydrogen atoms attached to the dimethoxy benzene ring. The suggested structure 2,3-dimethoxy-8-oxoberbine (X) was supported by the reduction of the compound with LAH to 2,3-dimethoxyberbine (VII). Dehydrogenation of the amide with Pd-black yielded an isocarbostyril (XII), which was shown to be identical with the product obtained from (VII) by dehydrogenation with iodine to (XI), followed by oxidation with potassium ferricyanide. The isocarbostyril (XII) was also described by Huffman and Miller[14] in their unambiguous synthesis of (VII).

It seemed, then, that the pseudobase of V had undergone disproportionation, as expected, to VI and IX and that HCl had caused a normal ring-closure of VI to VII, and further, that the isocarbostyril (IX) had been cyclised to X, perhaps as shown in XIII → XIV → X; none of IX could be detected in the reaction mixture. This interpretation was strongly supported when it was found that an authentic sample of IX, prepared by oxidation of V with potassium ferricyanide, was converted into X (in 77% yield) by treatment, at room temperature, with conc HCl solution.

Since a good yield of VII was readily achieved by this simple procedure, and since the ring-closure of the isocarbostyril (IX) was a novel one, the reaction was studied further. It was quickly found that concentrated hydrochloric acid gave better yields than HBr, which in turn was better than concentrated hydroiodic acid;

[16] R. C. Elderfield, *Heterocyclic Compounds* Vol. 4; p. 361. Wiley, New York, (1952).

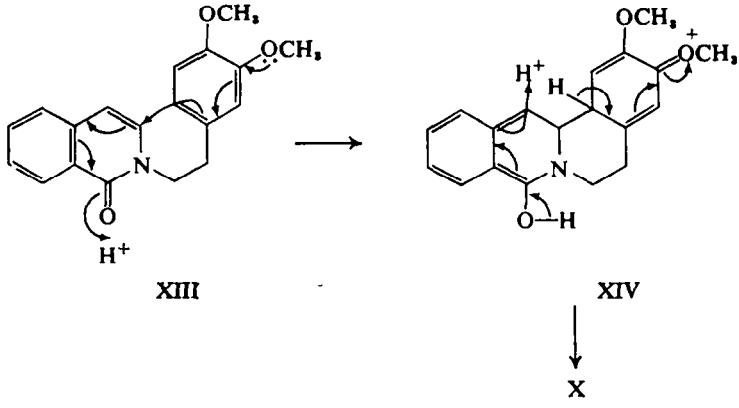
the use of perchloric acid had no advantage over HCl. By converting V (X = Br), via the pseudobase, to the mixture of VII and X, and then reducing with LAH,



XI XII

a 50% yield of VII was obtained—a distinct improvement over that obtained by Huffman and Miller.[14]

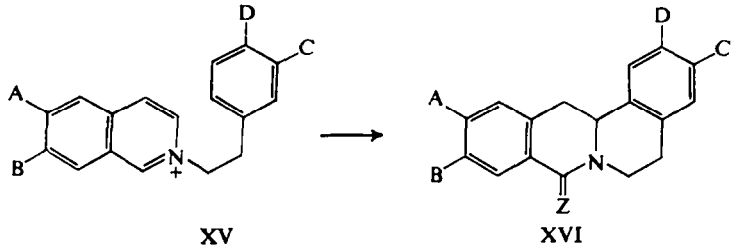
The ring-closure reaction was then studied with a number of isoquinolinium salts,



XIII XIV

X

and this work together with the above example, is summarized in Table 1. With XV (A = C = D = OMe, B = H and with A = B = C = D = OMe), disproportionation of the quaternary bromide occurred only after heating an aqueous alcoholic solution of it under reflux with sodium hydroxide. Norcoralydine (XVI, A = B = C = D = OMe, Z = H_2) could easily be isolated in 78% yield based upon the 1,2-dihydroisoquinoline formed in the disproportionation. All attempts to ring-close the corresponding tetramethoxyisocarbostyril failed.



XV XVI

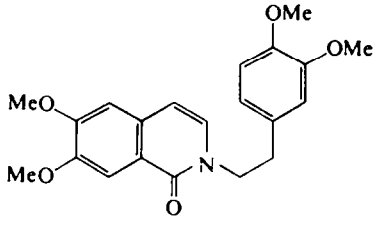
TABLE 1

Expt. No.	XV A	B	C	D	Yield* (16, Z = H_2)	Yield* (16, Z = O)
1	H	H	H	OMe	31	21
2	H	H	OMe	OMe	25	25
3	OMe	H	OMe	OMe	30†	24
4	H	OMe	OMe	OMe	27	17
5	OMe	OMe	OMe	OMe	39	0

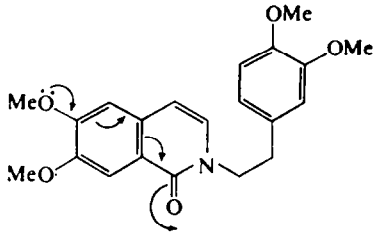
* based upon the isoquinolinium salt XV

† this compound has also been described by Kakac and Protiva.[18]

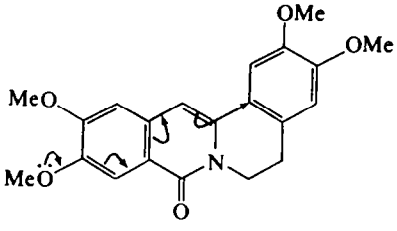
Since the isocarbostyrils derived from XV (A = C = D = OMe, B = H and B = C = D = OMe, A = H) can be ring-closed to the corresponding 8-oxoberbines (XVI, Z = O), the failure of the tetramethoxyisocarbostyril (XVII) may be due to the combination of adverse electronic effects of the 6- and the 7-methoxyl groups, as indicated in XVIII and XIX.



XVII



XVIII



XIX

EXPERIMENTAL

M.ps are uncorrected.

N-β-(3-Methoxyphenyl)ethylisoquinolinium iodide XV, A = B = D = H; C = OMe). A mixture of isoquinoline (8·0 g), *m*-methoxyphenylethyl bromide (14·5 g) and MeOH (15 ml) was heated under reflux for 12 hr. The residue from the MeOH was leached with ether and then treated with a sat NaIaq (12·0 g) in water. The quaternary iodide (10·7 g) was precipitated by the addition of acetone and crystallized from EtOH. *N-β-(3-methoxyphenyl)ethylisoquinolinium iodide* (XV, A = B = D = H; C = OMe) was obtained as pale yellow plates m.p. 196–197°. (Found: C, 55·6; H, 4·8; N, 3·6; I, 32·05: $C_{18}H_{18}NOI$ requires: C, 55·25; H, 4·63; N, 3·6; I, 32·4%.)

N-β-(3,4-Dimethoxyphenyl)ethylisoquinolinium bromide (XV, A = B = H; C = D = OMe) was prepared as described by Huffman and Miller.[14]

[17] C. K. Bradsher and N. L. Dutta, *J. Org. Chem.* **26**, 2231 (1961).

[18] B. Kakac and M. Protiva, *Coll. Czech. Chem. Comm.* **29**, 251 (1964).

N-β-(3,4-*Dimethoxyphenyl*)*ethyl*-6-*methoxyisoquinolinium bromide* (XV, A = C = D = OMe; B = H). A solution of 6-methoxyisoquinoline[19] (2·0 g) and 3,4-dimethoxyphenylethyl bromide (3·1 g) in dry benzene (10 ml) was left for 2 days, then evaporated to dryness. The residue was triturated with acetone to yield yellow crystals (3·2 g) of N-β-(3,4-dimethoxyphenyl)ethyl-6-methoxyisoquinolinium bromide, m.p. 182–186°. The iodide was obtained from EtOH, m.p. 188–189°. (Found: 53·35; H, 5·05; N, 2·9; I, 27·75. $C_{20}H_{22}NO_3I$ requires: C, 53·2; H, 4·9; N, 3·1 and I, 28·1%.)

N-β-(3,4-*Dimethoxyphenyl*)*ethyl*-7-*methoxyisoquinolinium bromide* (XV, A = H, B = C = D = OMe). A mixture of 7-methoxyisoquinoline[20] (8·0 g) and 3,4-dimethoxyphenylethyl bromide (12·3 g) was heated on a steam-bath for 2 hr, then at 140° for 10 min. Acetone and NaI (8·0 g) were added and the quaternary iodide (9·0 g) was collected. The substance was characterized as the perchlorate, m.p. 214–215° from EtOH. (Found: C, 56·4; H, 5·4; N, 3·5; Cl, 8·4. $C_{20}H_{22}NO_7Cl$ requires: C, 56·65; H, 5·2; N, 3·3; Cl, 8·4%.)

N-β-(3,4-*Dimethoxyphenyl*)*ethyl*-6,7-*dimethoxyisoquinolinium bromide* (XV, A = B = C = D = OMe) was prepared as described previously.[15]

The Disproportionation and cyclization

General procedure. The salt XV (3·0 g) was dissolved in water (20 ml) and 40% NaOHaq (20 ml) was added. The resultant oil (which was obtained from XV (A = C = D = OMe; B = H) and XV (A = B = C = D = OMe) only after heating the mixture under reflux for 30 min, was extracted into CH_2Cl_2, the combined extracts were then evaporated, and the residue was dissolved in conc HCl or in 50% ethanolic HCl (20 ml). After 5 days at room temp, the mixture was concentrated under reduced press and acetone was added to the residue. The hydrochloride salt of XVI (Z = H_2) that separated was collected after 1 hr. The physical constants and analytical data are collected in Table 2; the yields are stated in Table 1.

The acetone filtrate was evaporated, and the residue dissolved in a large volume of ether. The ethereal solution was washed with water, dried (Na_2SO_4) and evaporated to dryness. The residue of XVI (Z = O) was crystallized from aqueous MeOH or ether. The yield obtained is indicated in Table 1, and Table 3 summarises the analytical data.

TABLE 2

Expt. No.	m.p.* hydrochloride	m.p.* perchlorate	Found C	Found H	Found N	Found Cl	Molecular Formula	Required C	Required H	Required N	Required Cl
1	208–210	209–211	59·25	5·55	4·05	9·35	$C_{18}H_{19}NO{\cdot}HClO_4$	59·1	5·5	3·8	9·65
2	237–238†										
3	214–216	251–253	56·8	5·8	3·1	8·35	$C_{20}H_{23}NO_3{\cdot}HClO_4$	56·4	5·7	3·3	8·3
4‡	214–215		66·0	6·7	3·6	9·5	$C_{20}H_{23}NO_3{\cdot}HCl$	66·4	6·7	3·9	9·8
5	212–213§										

* Crystallized from EtOH.
† literature[14] m.p. 237–238.
‡ Bradsher and Dutta[17] quote m.p. 214–215°, but quote a formula of $C_{20}H_{23}NO_3{\cdot}HCl{\cdot}H_2O$.
§ literature[21] m.p. 213.

2,3-*Dimethoxyberbine* VII *by reduction of* X. 2,3-Dimethoxy-8-oxoberbine (1·1 g) was dissolved in dry ether (50 ml), and LAH (0·27 g) was added portionwise, with stirring. The mixture was heated under reflux for 1·5 hr, then left at room temp overnight. Excess hydride was decomposed with water and the ether decanted. The solid material was extracted several times with ether and the combined ether extract was dried and evaporated to leave an oil (1·0 g) HCl and acetone were added and 2,3-dimethoxyberbine hydrochloride was collected. This material was shown to be identical with that described by Huffman and Miller.

[19] J. M. Gulland and C. J. Virden, *J. Chem. Soc.* 1791 (1929); R. A. Robinson, *J. Amer. Chem. Soc.* **69**, 1939 (1947).
[20] P. Fritsch, *Liebigs Ann.* **286**, 10 (1895).
[21] I. M. Heilbron and H. M. Bunbury, *Dictionary of Organic Compounds* Vol. 3. Eyre and Spottiswoode, London (1937).

TABLE 3

Expt. No.	m.p. Solvent	Mol. form	Found			Required		
			C	H	N	C	H	N
1	111–112° ether	$C_{18}H_{17}NO_3$	77·20	6·35	5·30	77·43	6·09	5·02
2	142° ether	$C_{19}H_{19}NO_3$	73·80	6·35	4·50	73·79	6·15	4·55
3	158–159° methanol	$C_{20}H_{21}NO_4$	70·70	6·20	4·35	70·78	6·24	4·13
4	161–162° methanol	$C_{20}H_{21}NO_4$	71·00	6·20	4·05	70·78	6·24	4·13

3-Methoxy-8-oxoberbine was similarly reduced to give a 92% yield of 3-methoxyberbine.

2,3-*Dimethoxyberbine by cyclization followed by reduction.* The disproportionation reaction was conducted as described above using 3·0 g of N-β-(2,3-dimethoxyphenyl)ethylisoquinolinium bromide. After leaving for 5 days in contact with HCl, the mixture was poured into water (100 ml) basified with ammonia and extracted with CH_2Cl_2. The combined organic extracts were dried (Na_2SO_4), evaporated to dryness and the resulting oil was dissolved in anhydrous ether (100 ml). LAH (0·8 g) was added in portions, and the mixture was then heated under reflux for 30 min. The excess LAH was decomposed with a saturated solution of sodium potassium tartrate and the basic product isolated in the usual way. 2-3,Dimethoxyberbine was obtained as the hydrochloride (1·33 g); 50% from acetone, m.p. 237–238°.

N-β-(3,4-*Dimethoxyphenyl)ethylisocarbostyril* IX. The bromide V, (X = Br; 4·4 g) was dissolved in water (80 ml) and heated under reflux whilst a solution of $K_3Fe(CN)_6$ (10 g) and KOH (2·4 g) in water (40 ml) was added dropwise. The resultant mixutre was heated for a further 5 min, then cooled and extracted with ether to yield a brown solid (3·0 g) m.p. 104–107°. After purification with charcoal IX was obtained as white needles, m.p. 111–112° from aqueous MeOH. (Found: C, 73·9; H, 6·4; N, 4·3; $C_{19}H_{19}NO_3$ requires: C, 73·8; H, 6·15; N, 4·55%.)

N-β-(3,4-*Dimethoxyphenyl)ethyl*-6,7-*dimethoxyisocarbostyril* was obtained similarly from XV, (A = B = C = D = OMe), as white needles m.p. 123–124° from MeOH or $CHCl_3$. (Found: C, 68·2; H, 6·2; N, 3·6. $C_{21}H_{23}NO_5$ requires: C, 68·3; H, 6·3; N, 3·8%.)

Ring-closure of IX. Compound IX (2·6 g) was dissolved in conc HCl (100 ml) and left at room temp. After 48 hr the crystalline material formed was washed with conc HCl and dried at 100° to give off-white crystals (2·0 g) m.p. 137–139°. Recrystallization from ether yielded white needles, m.p. 142° of X.

2,3-*Dimethoxyberberinium iodide* XI. Compound VII (0·7 g) was dissolved in EtOH (25 ml), and AcOK (1·0 g) was added. The solution was heated under reflux whilst a solution of I_2 (1·25 g) in EtOH (60 ml) was gradually added (15 min). Heating was continued for 30 min; the mixture was cooled and the yellow crystalline solid periodide collected, suspended in water and saturated with SO_2. The solid material was collected, washed with water and dried (0·85 g), m.p. 293–295°. Recrystallization from water gave yellow needles, m.p. 294–295° of XI. (Found: C, 54·4; H, 4·4; N, 3·15; I, 30·55. $C_{19}H_{18}NO_3I$ requires: C, 54·5; H, 4·29; N, 3·3; I, 30·3%.)

2,3-*Dimethoxy*-13, 13a-*dehydro*-8-*oxoberbine* XII. (a) Compound XI (0·22 g) was heated under reflux with water (4 ml) whilst a solution of $K_3Fe(CN)_6$ (0·45 g) and KOH (0·1 g) in water (2 ml) was added slowly. The mixture was then boiled for 1½ hr, cooled, and the product collected (0·15 g) m.p. 182–184°. Recrystallization from AcOEt raised the m.p. to 189–190°. (Huffman and Miller[14] quote m.p. 189–190°.) (b) Compound X (0·05 g) was mixed with Pd- black (0·03 g) and heated at 240° for 2½ hr. After cooling, the mixture was extracted with hot EtOH and filtered. Concentration of the filtrate yielded yellow plates (0·02 g) m.p. 189–190° undepressed on mixing with the sample of XII, prepared above.

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