Tetrahedron Vol 24, pp 2645 to 2652 Pergamon Press 1968 Printed in Great Britain

SYNTHESIS OF A STRUCTURALLY DEFINITIVE INDOLE DERIVED FROM TUBEROSTEMONINE

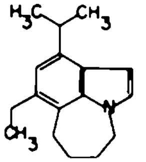
G. M. Strunz

Department of Chemistry, University of New Brunswick, Fredericton, New Brunswick, Canada

(*Received in USA* 12 *June* 1967; *accepted for publication* 17 *October* 1967)

Abstract Synthesis of the indole (I), a key degradation product of the alkaloid tuberostemonine, is described.

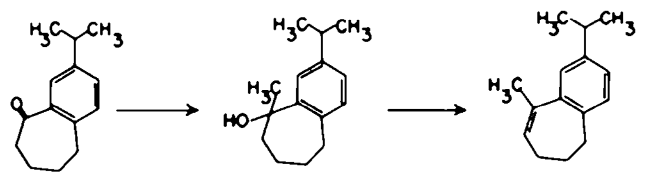
Isolation of the indole (I), a degradation product of the alkaloid tuberostemonine, has been reported in the preceding communication.[1] The structure of the indole was rigorously established by comparison with an authentic synthetic sample. This was instrumental in defining clearly the structure of the alkaloid.



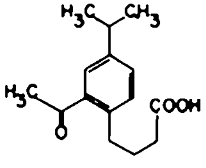
I

We now wish to describe the synthesis of I. γ-(*p*-isopropylbenzoyl)butyric acid (II) was prepared by the reaction of cumene and glutaric anhydride, in the presence of aluminium chloride. The keto acid (II) displayed characteristic IR, UV and NMR spectroscopic properties. Removal of the ketone function was effected by the Clemmensen reduction,[2] and gave rise to δ-(*p*-isopropylphenyl)valeric acid (III), which again exhibited predictable spectroscopic behaviour. Quantitative conversion to the benzosuberone (IV) was brought about by cyclization of III with hydrogen fluoride. The product, a colourless oil, showed IR absorption at 1680 cm^{-1}, and UV maxima at 249 mμ (ε 9500) and 292 mμ (ε 2000), in excellent agreement with an aromatic ketone. IV was characterized as its 2,4-dinitrophenylhydrazone, $C_{20}H_{22}O_4N_4$.

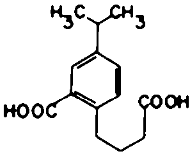
Prolonged treatment of IV with methyl magnesium iodide in tetrahydrofuran yielded the alcohol (V), the resulting change in functionality being manifested in the IR spectrum. Dehydration of V with acetic anhydride and sodium acetate furnished a mixture of endocyclic and exocyclic olefins, in a roughly 1:1 ratio, as determined by NMR spectroscopy. On equilibration with *p*-toluenesulphonic acid in benzene a virtually quantitative conversion to the endocyclic olefin (VI) was effected.[3] The latter, a colourless oil whose homogeneity was determined by VPC, displayed UV absorption at λ_{max} 245 mμ (ε 10,800). IR and NMR spectra also support the assigned structure.



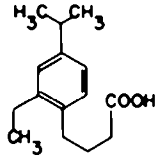
IV V VI



VII



VIII



X

The acidic material obtained from ozonolysis of VI after oxidative work-up (hydrogen peroxide) was a mixture of the keto acid (VII), and a dibasic acid, tentatively assigned the structure VIII on the basis of its spectroscopic properties.*

Separation was effected by a countercurrent distribution between ether and a phosphate–citric acid buffer, with the latter as moving phase. VII was isolated as a pale yellow oil, showing IR absorption at 1710 and 1690 cm^{-1}, corresponding to carboxylic acid and aromatic ketone, respectively; UV maxima were at 246 mμ (ε 9100) and 288 mμ (ε 1900). In the NMR spectrum, a one-proton singlet at 2·55 τ and a two-proton signal at 2·82 τ correspond to the hydrogens *ortho* to the acetyl group, and the other two aromatic protons, respectively. The three benzylic hydrogens appear as a multiplet at 7·16 τ. A singlet at 7·46 τ represents the three hydrogens of the methyl ketone, and the Me protons of the isopropyl group appear as superimposed doublets centered at 8·74 τ (J = 7·9 c/s).

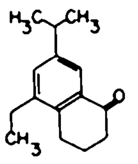
Reduction of the acetyl side chain of VII to an Et group was best achieved in two steps: treatment with sodium borohydride afforded the corresponding alcohol (IX), which was hydrogenolized in acetic acid with a Pd–C catalyst, furnishing X in good yield. The spectroscopic properties of these intermediates confirmed that the reactions had proceeded as anticipated.

Compound X was cyclized in excellent yield to the tetralone (XI), through the agency of hydrogen fluoride. The colourless oily product showed an IR band at 1685 cm^{-1}, and UV absorption at λ_{max} 255 mμ (ε 11,900) and 303 mμ (ε 2500), in complete accord with the assigned structure. The NMR spectrum displays one-proton singlets at 2·35 and 2·91 τ for the aromatic hydrogens *ortho* and *para*, respectively, to the carbonyl. The seven deshielded protons appear in a multiplet at 7·04–7·58 τ, and a multiplet with sharp peaks at 8·65 and 8·76 τ represents the three Me groups. The tetralone (XI), on treatment with hydroxylamine hydrochloride in the presence of sodium acetate, was converted to its oxime (XII), $C_{15}H_{21}ON$, further characterized by IR, UV and NMR spectroscopy.

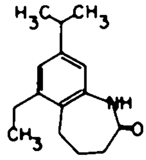
---

* The yield of VII was improved when the ozonation was followed by catalytic reduction, and subsequent mild permanganate oxidation of the resulting keto-aldehyde.

When the oxime was heated with polyphosphoric acid at 125–130°, Beckmann rearrangement occurred, affording the lactam (XIII), $C_{15}H_{21}ON$. IR absorption at 3400 and 3200 cm^{-1} can be attributed to N—H bond stretching, and a band at 1675 cm^{-1} is due to the lactam carbonyl; the UV spectrum shows maxima at 240 mμ (ε 13,800) and 282 mμ (sh, ε 1200). In the NMR spectrum, the two aromatic hydrogens appear as a single peak at 3·27 τ. The five benzylic protons give rise to a multiplet centered at 7·31 τ, and the protons α to the amide carbonyl are included in a multiplet at 7·75 τ. A multiplet with sharp peaks at 8·70 and 8·81 τ represents the three Me groups.



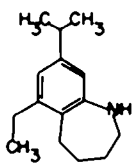
XI



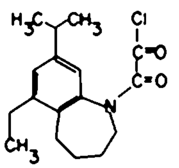
XIII

Reduction of XIII with LAH effected a smooth conversion to the oily amine XIV, whose IR spectrum showed N—H absorption at 3400 cm^{-1} and the absence of a CO band. The UV spectrum showed maxima at 238 mμ (sh, ε 8000) and 282 mμ (ε 1600); in acidic medium maxima were at 265 mμ (ε 1100) and 275 mμ (ε 1000).

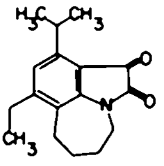
Oxalyl chloride was selected as the reagent for the introduction of the remaining two C atoms, since it was anticipated that its reaction with XIV would furnish an intermediate which could be cyclized with facility under the mildest possible conditions.[4,5] XIV was treated with a large excess of oxalyl chloride, which afforded the amorphous oxanilic acid chloride (XV) showing IR bands at 1785 and 1680 cm^{-1}.



XIV



XV



XVI

XV was not isolated, but was subjected immediately to Friedel Crafts cyclization with aluminium chloride in carbon disulphide. Trituration of the resulting red gum with pentane–ether gave blood red crystals of the isatin (XVI), $C_{17}H_{21}O_2N$. XVI displayed IR absorption at 1735 cm^{-1}, and its UV spectrum showed maxima at 253 mμ (ε 24,000) and 327 mμ (ε 7200).

Reduction of XVI to the indole (I) was effected in two steps. Treatment of the isatin with sodium dithionite[6] converted it to the corresponding dioxindole (XVII), which displayed IR absorption at 3600 and 3360 cm^{-1} for the OH group, and a lactam band at 1720 cm^{-1}. Finally, reduction of XVII to the indole (I) was effected in about 50% yield by means of LAH,[7] and the pure product was isolated by chromatography on alumina. The synthetic material was found to be completely identical with the "natural" indole (I) by comparison of IR, UV, NMR and mass spectra, and by mixed m.p.

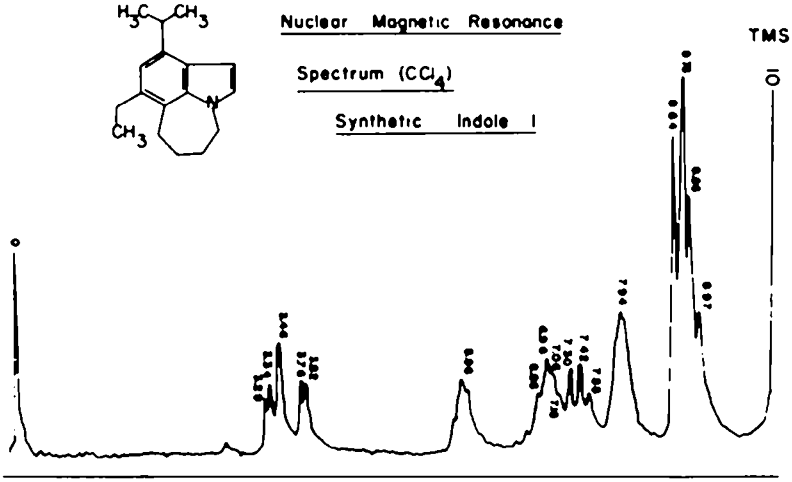


FIG. 1 NMR spectrum.

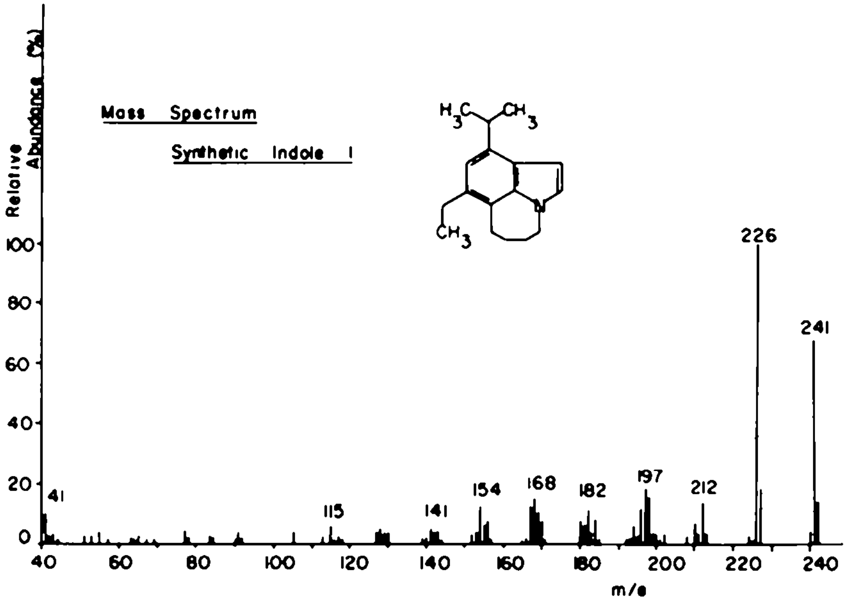


FIG. 2 Mass spectrum.

EXPERIMENTAL

M.ps were determined on a hot stage apparatus and are uncorrected. IR spectra were determined on a Perkin-Elmer Infracord Model 137B spectrophotometer. UV spectra were obtained in 95% EtOH soln on a Beckman DK-2 spectrophotometer. NMR spectra were measured in CCl_4 soln with a Varian Associates 56·4 Mc/s spectrometer. The mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6D mass spectrometer. Microanalyses were performed by Dr. F. Pascher, Mikroanalytisches Laboratorium, Bonn, West Germany and by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

γ-(p-*Isopropylbenzoyl*)*butyric acid* (II)

$AlCl_3$ (587 g, 4·5 moles) was added during 7 hr under anhydrous conditions, with mechanical stirring and ice-cooling, to a soln of glutaric anhydride (228 g, 2·0 moles) in cumene (240·4 g, 2·0 moles) and tetrachloroethane (970 ml). The mixture was set aside at 25° for 12 hr, and was then warmed at 50° for 3 hr. After the resulting complex had been decomposed by addition of ice and conc HCl, the tetrachloroethane was removed by steam distillation. Organic material was extracted with ether from the distillation residue, and the acidic product was separated by extraction of the ether soln with saturated Na_2CO_3. The aqueous extracts were washed with ether until the washings were almost colourless, and then were treated with decolourizing charcoal. Acidification of the aqueous soln and subsequent extraction with ether furnished 196·6 g (42%) of pale brown crystalline acid. Recrystallization from n-hexane–ether afforded II as colourless prisms, m.p. 93–95°; IR bands (KBr) at 1705 and 1675 cm^{-1}. The NMR spectrum shows a 4-proton quartet with peaks at 2·11, 2·27, 2·74 and 2·91 τ for the aromatic protons which comprise two equivalent AB systems. The isopropyl methyls give rise to a 6-proton doublet centered at 8·93 τ (J = 6·8 c/s).

δ-(p-*Isopropylphenyl*)*valeric acid* (III)

The keto acid II (73 g, 0·31 moles) was reduced by the Clemmensen method, using essentially the procedure described in Organic Reactions[2] for reduction of β-benzoylpropionic acid. Work-up yielded 66·7 g (97%) of pale yellow crystalline material, containing a trace impurity which was insoluble in n-hexane. Recrystallization of the major product from n-hexane yielded III, colourless crystals, m.p. 49–52°; IR absorption (CCl_4), 1710 cm^{-1}; UV maxima: 257 mμ (ε 900), 264 mμ (sh, ε 850) and 272 mμ (ε 600). In the NMR spectrum, the 4 aromatic protons appear as a single peak at 3·33 τ.

3-*Isopropyl-5-oxo-6,7,8,9-tetrahydrobenzocycloheptene* (IV)

The acid III (46·84 g, 0·212 moles) was, for convenience, divided into three equal portions, and each was treated with HF (ca. 500 ml) in a polyethylene container. The resulting clear red-brown solns were set aside in the fume hood for 45 hr. After removal of the residual HF with the aid of a stream of N_2, water was added, and the mixture was made alkaline by the careful addition of solid Na_2CO_3. A heavy white ppt separated, and the mixture was extracted exhaustively with benzene and ether. The extracts, after washing and drying, yielded 40·8 g (95%) of pale yellow oil. Distillation at 188–212°/3 mm (bath temp) afforded 37·4 g of the colourless oily IV. The product was characterized as its 2,4-dinitrophenylhydrazone, m.p. 153–157°. (Found: C, 62·77; H, 5·87. $C_{20}H_{22}O_4N_4$ requires: C, 62·81; H, 5·80%).

Reaction of IV *with methyl magnesium iodide*

The benzosuberone IV (22·1 g, 0·109 moles) in anhyd THF (100 ml) was added dropwise during 15 min under anhydrous conditions, with stirring, to an ethereal soln of methyl Grignard reagent, prepared from Mg turnings (13·3 g, 0·547 g atoms) and MeI (77·4 g, 0·545 moles). Additional THF (400 ml) was added to replace 200 ml of ether-rich distillate which was removed. The mixture was heated under reflux with stirring for 48 hr (bath temp 70–80°), after which it was poured onto ice. Sat NH_4Cl aq was added until the precipitated salts had dissolved. Extraction with ether, followed by washing and drying of the extracts, yielded 23·78 g of V, a pale yellow viscous oil. The IR spectrum (CCl_4) showed OH absorption at 3624 and 3490 cm^{-1}, and the absence of CO absorption.

2-*Isopropyl-9-methyl-6,7-dihydro-5*H*-benzocycloheptene* (VI)

The Grignard product V (12·0 g, 0·055 moles) was dissolved in Ac_2O (120 ml), and fused NaOAc (12·0 g) was added. The mixture was heated under reflux for 24 hr, after which it was set aside at 25° for 65 hr. It was then poured into 1500 ml ice-water. Extraction with ether, followed by thorough washing of the extracts and drying over anhyd K_2CO_3 yielded, after removal of solvent, 11·13 g of a mobile brown oil. A signal centered at 5·12 τ in the NMR spectrum of the product, in addition to other spectral properties, demonstrated the presence of the exocyclic olefin.

The olefin mixture was refluxed in anhyd benzene (100 ml) with *p*-toluenesulphonic acid (5·3 g, 0·031 moles) for 2 hr. The resulting soln was washed successively with sat $NaHCO_3$ aq and water, and after drying over anhyd K_2CO_3, removal of solvent yielded 10·67 g of brown oil. The pure olefin VI was collected as a colourless oil from distillation of the product at 120–130°/0·2 mm (bath temp). UV spectrum: λ_{max} 245 mμ (ε 10,800). The NMR spectrum shows signals at 3·04 (s, 3-H), 4·20 (m, 1-H), 7·94 (s, 3-H), and 8·76 τ (d, J = 6·8 c/s, 6-H).

Ozonolysis of VI

An O_3–O_2 mixture was passed by means of a sintered-glass bubbler into a soln of IV (9·34 g, 0·0465 moles) in EtOAc (160 ml) cooled in a dry ice-acetone bath. (Welsbach Model T-23 ozonator, operating at 90 V, 8 lb press, flow rate 0·03 cu ft/min). The end-point was detected when the emerging gas liberated I_2 from acidified KI soln, whereupon the system was immediately flushed with N_2. The soln was then shaken under H_2 at atm press with a prehydrogenated 10% Pd/C catalyst (745 mg), until the calculated amount of H_2 had been taken up. The catalyst was removed by filtration, and the solvent removed under reduced press.

The resulting keto aldehyde, a clear colourless oil, was dissolved in acetone (400 ml) and the soln cooled in an ice-bath. $KMnO_4$ (7·35 g, 0·0465 moles) in distilled water (400 ml) was added slowly with stirring during 1 hr, and the reaction mixture was set aside at 0° with stirring for an additional hr. SO_2 gas was then passed in until a clear soln resulted; this was extracted several times with ether. Evaporation of the extracts to dryness removed acetone, and the residue was redissolved in ether. Acidic material was then separated in the usual manner, and 9·26 g of yellow gum was isolated.

The combined products of 3 runs, performed as above, (23·0 g) were subjected to an 11 funnel counter-current distribution; the stationary phase was ether and a disodium phosphate-citric acid buffer (pH 8·0) was the moving phase. (The volume of each phase was 900 ml). The contents of funnels 3–7 were combined to yield 11·70 g of pure VII, a pale yellow gum. Funnels 10–11 contained 5·36 g of yellow crystalline material; recrystallization from pet. ether afforded colourless crystals. m p 128–133. Titration results suggested that this product is a dibasic acid, and structure VIII was tentatively assigned to it on the basis of its spectroscopic behaviour. The IR spectrum (CCl_4) shows absorption at 1710 and 1695 (sh) cm^{-1} (acids). UV spectrum: λ_{max} 231 mμ (sh, ε 8600), and 280 mμ (ε 1700); in alkaline soln no maxima, λ 220 mμ (ε 10,000), λ 340 mμ (ε = 0). In the NMR spectrum, a two-proton signal at − 2·02 τ represents the two acid protons. A one-proton singlet at 2·20 τ is in agreement with an aromatic hydrogen *ortho* to a CO group, and the other two benzenoid hydrogens appear at 2·85 τ. There is no evidence of methyl ketone hydrogens at 7·46 τ. The superimposed doublets arising from the 6 methyl hydrogens of the isopropyl group are found at 8·69 and 8·80 τ.

Sodium borohydride reduction of VII

To a soln of $NaBH_4$ (124 mg, 3·28 mmoles) in 0·1N NaOH (10 ml) was added dropwise, with magnetic stirring, a soln of VII (1·63 g, 6·56 mmoles) in 0·1N NaOH (90 ml). The mixture was set aside with stirring at 25° for 22 hr. After dilution with water to ca. twice the original volume, the soln was cooled to 0°, and the pH brought to approximately 3 by the addition of 5% HCl. Ether extraction and work-up yielded 1·60 g of IX, a pale yellow gum. IR absorption (CCl_4): 1710 cm^{-1} (acid).

γ-*(2-Ethyl-4-isopropylphenyl)butyric acid* (X)

The alcohol IX (1·60 g, 6·4 mmoles), dissolved in glacial AcOH (55 ml), was shaken under H_2 at atm press in the presence of prehydrogenated 10% Pd/C catalyst (200 mg). When the calculated volume of H_2 had been taken up, the catalyst was removed by filtration. The AcOH was evaporated under reduced press, removal of the last traces of acid being facilitated by repeated evaporations with benzene. The product X was a pale brown oil (1·42 g): IR maximum (CCl_4) 1710 cm^{-1}. In the NMR spectrum the 3 aromatic protons give rise to a sharp signal at 3·10 τ. A multiplet at 7·50 τ accounts for the 7 deshielded protons, and a multiplet with sharp peaks at 8·72 and 8·83 τ represents the 3 Me groups. The two remaining hydrogens appear as a multiplet at 8·17 τ.

5-*Ethyl*-7-*isopropyl*-1-*tetralone* (XI)

The acid X (3·7 g) was treated in a polyethylene bottle with HF (200 ml). After 115 hr, most of the HF had evaporated. Work-up as for IV yielded 3·16 g of red oil. On distillation of the product, XI was collected as a colourless oil, b.p. 150–160°/4 mm (bath temp).

Oxime of XI

To a soln of XI (2·36 g, 10·9 mmole) in 70% aqueous EtOH (110 ml) was added $NH_2OH \cdot HCl$ (1·36 g, 19·6 mmole) and anhyd NaOAc (1·79 g, 21·8 mmoles). The resulting soln was refluxed for 13 hr (oil bath at 112°), after which the volume was reduced by distilling off ca. 35 ml of solvent. After standing at 25° for 36 hr, the white crystalline solid which had separated was filtered at the pump, and washed with several portions of water; 2·15 g of colourless plates resulted, m.p. 141–146°; IR spectrum (CCl_4): 3600 and 3260 (OH), 1600 cm^{-1} (weak). UV spectrum: λ_{max} 256 (ε 11,500), 293 mμ (sh, ε 2100) and 304 mμ (sh, ε 1400).

The aromatic protons show in the NMR as singlets at 2·48 and 3·12 τ. An analytical sample of XII was prepared by recrystallization from EtOH-water, m.p. 145–146°. (Found: C, 77·87; H, 9·19; O, 7·02; N, 6·09. $C_{15}H_{21}ON$ requires: C, 77·88; H, 9·15; O, 6·92; N, 6·05%.)

6-Ethyl-8-isopropyl-2,3,4,5-tetrahydro-2-oxo-1-benzazepine (XIII)

The oxime XII (585 mg) was heated with polyphosphoric acid (19·3 g) with stirring at 125–130° for 30 min. When cool, water (20 ml) was added, and after stirring the mixture was poured onto ice (ca. 200 g). The white solid which separated was extracted with ether, and after washing and drying of the extracts, removal of solvent furnished 562 mg of pale yellow crystalline XIII. An analytical sample, m.p. 108–110°, was prepared by recrystallization from ether–cyclohexane. (Found: C, 77·43; H, 9·29; O, 7·08; N, 6·36 $C_{15}H_{21}ON$ requires: C, 77·88; H, 9·15; O, 6·92; N, 6·05%).

Reduction of the lactam (XIII)

LAH (1·64 g, 43·2 mmoles) was added to a soln of XIII (1·0 g, 4·32 mmoles) in anhyd ether (200 ml), and the mixture was heated under reflux for 16 hr. Water was added cautiously, dropwise, until vigorous reaction ceased, and the mixture was then diluted with water to about 150 ml. Organic material was isolated by exhaustive extraction of the resulting suspension with ether. Separation of the desired basic material was effected by extraction of the ether soln with 10% HCl. Work-up in the usual manner afforded 887 mg of colourless oily amine (XIV).

Preparation of the oxanilic acid chloride (XV)

A soln of XIV (580 mg, 2·66 mmoles) in dry ether (100 ml) was added dropwise during 15 min with stirring under anhydrous conditions to ice-cooled oxalyl chloride (44·6 g, 0·35 mole). Following the addition, the ice-bath was removed and the clear, almost colourless solution was stirred for 12 hr at 25°. Excess oxalyl chloride was then distilled off under reduced press, removal of the last traces being facilitated by repeated evaporations with anhyd benzene. 788 mg of pale brown amorphous material was obtained in this manner. IR maxima (CCl_4): 1785 and 1680 cm^{-1}. XV was subjected immediately to the Friedel–Crafts reaction.

Preparation of the isatin (XVI)[5]

Freshly sublimed $AlCl_3$ (500 mg, 3·75 mmoles) was added in 3 portions during 5 min under anhydrous conditions to an ice-cold soln of XV (780 mg, ca. 2·53 mmoles) in freshly distilled CS_2 (100 ml). The mixture was set aside with stirring at 25° for 5 min; it was then warmed at 50° for 10 min, and finally was allowed to stand at 25° with stirring for 16 hr. The resulting complex was decomposed by addition of ice-water (60 ml), followed by slow addition of conc HCl (20 ml). The organic layer was separated, and the aqueous phase extracted several times with CH_2Cl_2. The extracts were washed successively with $NaHCO_3$aq and water. After drying over $MgSO_4$, removal of solvent afforded 619 mg of deep red gum. Recrystallization from pet. ether afforded blood red crystals of XVI, m.p. 79–82°. (Found: C, 75·40; H, 7·78; N, 5·12 $C_{17}H_{21}O_2N$ requires: C, 75·25; H, 7·80; N, 5·17%).

Preparation of dioxindole (XVII)

The isatin XVI (250 mg, 0·922 mmoles) was dissolved in dioxan (8·0 ml, freshly distilled from Na). Water (ca. 12 ml) was added until the isatin began to separate as an oil. The mixture was heated to boiling, and solid $Na_2S_2O_4 \cdot 2H_2O$ (330 mg, 1·57 mmoles) was added in 4 portions during 15 min, each portion being washed in with water, so that the total volume finally was 40 ml. The resulting pale yellow soln was refluxed for 1 hr, and was then set aside for 12 hr at 25°. The soln was diluted to 100 ml by addition of water, and was then extracted several times with EtOAc. The extracts, after washing and drying, furnished 242 mg of pale yellow crystalline XVII, m.p. (crude) 149–162°.

Reduction of XVII *to the indole* (I)

LAH (376 mg, 9·9 mmoles) was added to a soln of XVII (242 mg, 0·885 mmoles) in anhyd ether (200 ml), and the mixture was refluxed for 15 hr. Water was added cautiously, dropwise, until vigorous reaction ceased, and the mixture was then diluted with water to 250 ml. The organic layer was separated, and the aqueous phase extracted exhaustively with ether. Basic material was removed from the combined extracts by washing with 5% HCl, and after washing with water and drying, the extracts furnished 165 mg of neutral green-brown gum. Chromatography of the product on Woelm grade I basic alumina yielded from the pet. ether eluates more than 100 mg of the pure I (47% from dioxindole). On standing for several days below 10° in the absence of air, I was obtained in crystalline form, m.p. 49–53°.

Acknowledgements—The author wishes to thank Drs. M. Götz and Z. Valenta for their interest in this work. Grateful acknowledgement is made to the Shell Oil Co. of Canada, and the National Research Council of Canada for financial support.

REFERENCES

[1] M. Götz, T. Bögri, A. H. Gray and G. M. Strunz, *Tetrahedron* Ref.

[2] *Organic Reactions* (Edited by Roger Adams) Vol. I; p. 166. Wiley, New York (1942). Also: E. L. Martin, *J. Am. Chem. Soc.* **58**, 1438 (1936).

[3] H. Christol and F. Plenat, *Bull. Soc. Chim* 1325 (1962) cf. also: R. B. Turner and R. H. Garner, *J. Am. Chem. Soc.* **80**, 1424 (1958).

[4] For a summarizing reference see: *Heterocyclic Compounds* (Edited by Robert C. Elderfield) Vol. 3, Ch. I. John Wiley and Sons Inc. New York (1952).

[5] R. Stolle, *J. prakt. Chem.* **128**, 1 (1930).

[6] C. Marschalk, *J. prakt. Chem.* **88**, 227 (1913).

[7] P. L. Julian and H. C. Printy, *J. Am. Chem. Soc.* **71**, 3206 (1949).