Synthesis and Reactions of 3-Indolyl β Ketones

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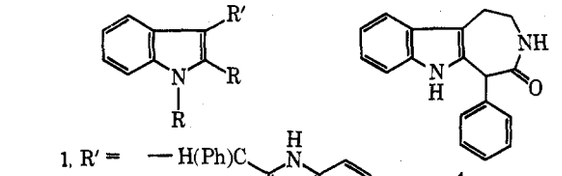
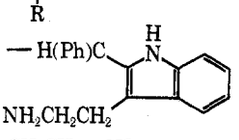
Reaction of indoles with free 3 position (**5**) with α-halo ketones (**6**) in acidic solutions affords 3-indolyl ketones (**7**). This novel reaction conveniently offers versatile starting materials for indolylcyclohexyl oximes (*e.g.*, **16**), amines (*e.g.*, **23**), alcohols (*e.g.*, **25**), indolylazabicycloheptanes ((*e.g.*, **21**), and indolyl fatty acids (*e.g.*, **19**), as well as pyrano[3,4-*b*]indoles (*e.g.*, **12**).

Alkylation of indoles in aqueous acid with phenylindolylcarbinols,[1] allyl bromide,[2] and ethyl bromoacetate,[3] and, intramolecularly, of haloacyltryptamines[4] has led to the facile formation of compounds **1–4**, respectively.



1, R′ = —H(Ph)C



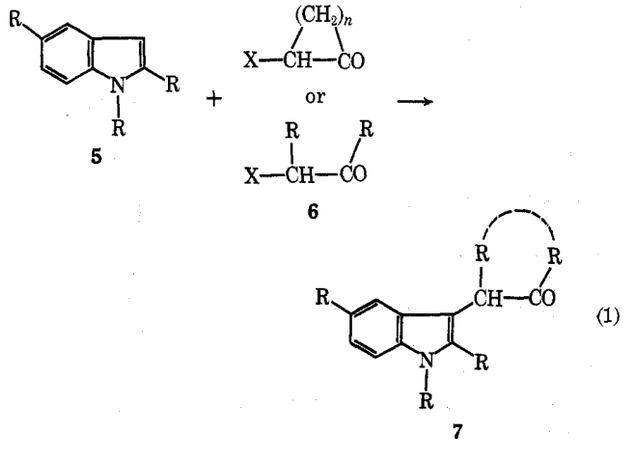
2, R′ = $-CH_2CH{=}CH_2$

3, R′ = $-CH_2COOC_2H_5$

4

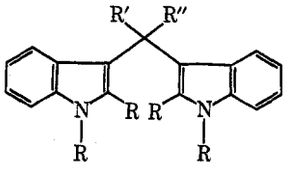
We wish to report the extension of this reaction to α-halo ketones leading to indolyl ketones. A number of these novel indole derivatives are convenient starting materials for a variety of tryptamine and serotonin related compounds of potential biological interest.

Synthesis.—On heating of an indole **5** and an α-halogen ketone **6** in a mixture of glacial acetic acid and phosphoric acid (2 *N*), a variety of substituted indolyl ketones **7** was obtained according to eq 1. Many of these compounds **7**, listed in Tables I–III, may be difficult to obtain by conventional indole synthesis. (For a review see ref 5a; also *e.g.*, ref 6.)



5 6 7 (1)

The dimerization to diindolylmethane derivatives (**8**), well documented for the reaction of indoles with aldehydes and ketones under acidic conditions,[5b] was observed as a minor side reaction only in a few cases, and as main reaction only, when the indole was unsubstituted (see **9** below). Also, when ω-bromoacetophenone was employed, the diindolylmethane **8** (R_1 = C_6H_5, R_2 = CH_2Br) was the sole reaction product and no ketone **7** was observed.

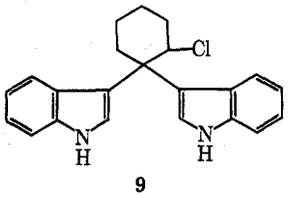


8

Bromoacetone, 2-bromo-3-butanone, and 2-chlorocyclohexanone proved to be suitable examples for **6** in this reaction.

With bromoacetoacetate, bromocyanoacetate, and bromomaleate no carbonyl-containing reaction products could be isolated. It appeared as if these compounds acted as brominating agents on the indoles.

A variety of substituted indoles was subjected to the above procedure. Generally, best results were achieved with 1,2-disubstituted indoles; with indoles unsubstituted in the 1 position the yields were lower. Indole itself reacted differently: on treatment with chlorocyclohexanone the diindolylchlorocyclohexane **9** was obtained (see Experimental Section).



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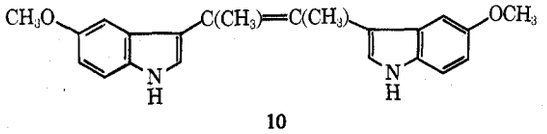
The reaction of 5-methoxyindole with 2-bromo-3-butanone proceeded in a different manner, yielding a diindolylbutene (**10**), according to spectral and analytical data.

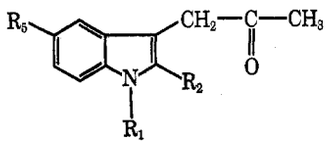


10

The heating of 1-*p*-chlorobenzyl-5-methoxy-2-methylindole with ethyl bromopyruvate did not give the expected indolyl pyruvate according to eq 1, but the

(1) K. Freter, H. H. Hübner, H. Merz, H. Detlef Schroeder, and K. Zeile, *Justus Liebigs Ann. Chem.*, **684**, 159 (1965).
(2) K. R. Freter, *Can. J. Chem.*, **45**, 2628 (1967).
(3) K. R. Freter, German Patent Application P1,963,845.0.
(4) K. Freter, *Justus Liebigs Ann. Chem.*, **721**, 101 (1969).
(5) R. J. Sundberg, "The Chemistry of Indoles," Academic Press, New York, N. Y., 1970: (a) p 412; (b) p 39; (c) p 47.
(6) P. Rosenmund, D. Sauer, and W. Trommer, *Chem. Ber.*, **103**, 496 (1970).

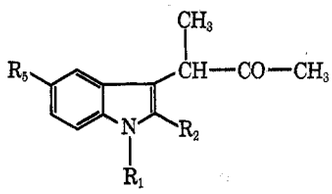
TABLE I



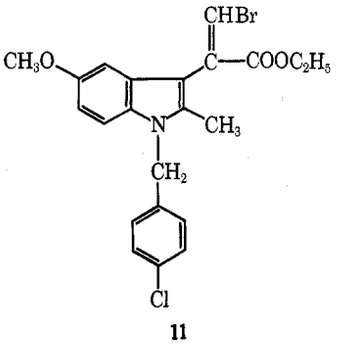
7	R_1	R_2	R_5	Time, min	Temp, °C	Yield, %	Empirical formula		C, %	H, %	N, %	Mp, °C	Mp, oxime, °C	Mp, thiosemicarbazone, °C
a	CH_3	CH_3	H	30	20	33	$C_{13}H_{15}NO$	Calcd	77.58	7.51	6.96	44	137	219
								Found	77.84	7.63	6.92			
b	H	CH_3	CH_3O	10	20	30	$C_{13}H_{15}NO_2$	Calcd[a]	57.92	6.25	19.30	Oil		203
								Found	58.10	6.35	19.31			
c	p-$ClC_6H_4CH_2$	CH_3	CH_3O	30	60	20	$C_{20}H_{20}ClNO_2$	Calcd	70.27	5.90	4.10	111		
								Found	69.98	5.66	4.19			

[a] Calculated for the thiosemicarbazone $C_{14}H_{18}N_4OS$.

TABLE II



7	R_1	R_2	R_5	Time, min	Temp, °C	Yield, %	Empirical formula		C, %	H, %	N, %	Mp, °C	Mp, oxime, °C	Mp, thiosemicarbazone, °C
d	CH_3	CH_3	H	30	60	70	$C_{14}H_{17}NO$	Calcd	78.10	7.96	6.51	70	183	209
								Found	78.10	8.29	6.69			
e	H	CH_3	OCH_3	25	90	65	$C_{14}H_{17}NO_2$	Calcd	72.70	7.41	6.06	79	140	165
								Found	72.48	7.30	6.10			
f	CH_3	CH_3	CH_3	45	80	79	$C_{15}H_{19}NO_2$	Calcd	73.44	7.81	5.71	85	177–185	195–201
								Found	73.79	8.06	5.40			
g	CH_3	C_6H_5	H	40	80	35	$C_{19}H_{19}NO$	Calcd	82.28	6.91	5.05	106	177	205
								Found	81.96	7.29	5.30			
h	p-$ClC_6H_4CH_2$	CH_3	OCH_3	90	100	58	$C_{21}H_{22}ClNO_2$	Calcd	70.87	6.24	3.93	110	169	134
								Found	71.11	6.10	4.09			



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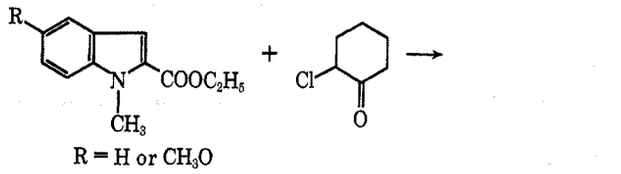
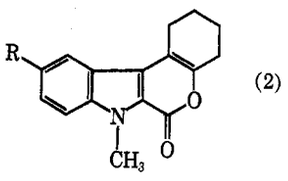
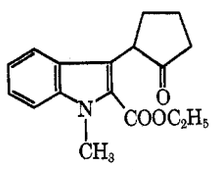


R = H or CH_3O



12, R = H
13, R = CH_3O

(2)



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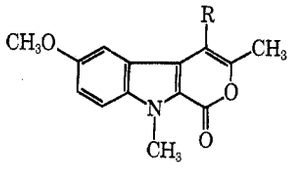


15a, R = H
b, R = CH_3

bromoacrylate **11** instead. This is in agreement with the reported reaction of 1,2-dimethylindole with ethyl pyruvate.[7]

The reaction of indolyl-2-carboxylates with, *e.g.*, chlorocyclohexanone produced the pyrone derivatives **12** and **13** (eq 2) in reasonable yields.

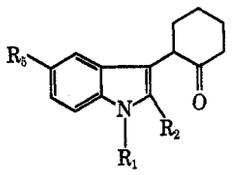
The interesting reactions of these compounds are discussed below. With chlorocyclopentanone, the expected keto ester (**14**) did not ring close and could be isolated in 63% yield. The pyrones resulting from the reaction with bromoacetone or bromobutanone were obtained only in small amounts (**15a** and **b**).

(7) S. H. Zee, Ph.D. Thesis with W. E. Noland, University of Minnesota, 1966; *Diss. Abstr.*, **27**, 123 (1967). See also ref 5c.

Reactions.—The ketones **7** form oximes and thiosemicarbazones in the usual manner in yields ranging from 70 to 90%.

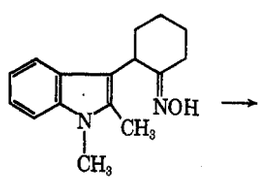
The oximes, on treatment with benzenesulfonyl

TABLE III

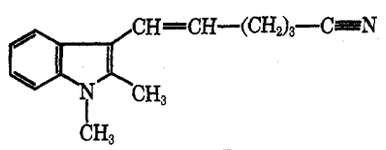


7	R_1	R_2	R_5	Time, min	Temp, °C	Yield, %	Empirical formula		C, %	H, %	N, %	Mp, °C	Mp, oxime, °C	Mp, thiosemicarbazone, °C
j	H	CH_3	H	90	60	27	$C_{15}H_{17}NO$	Calcd	79.26	7.54	6.16	139		
								Found	79.38	7.65	6.32			
k	CH_3	CH_3	H	60	100	50	$C_{16}H_{19}NO$	Calcd	79.63	7.94	5.80	161	226–232	192
								Found	79.75	7.67	5.78			
l	H	CH_3	CH_3O	240	20	32	$C_{16}H_{19}NO_2$	Calcd	74.68	7.44	5.44	163	187	196
								Found	74.39	7.23	5.71			
m	CH_3	CH_3	CH_3O	30	100	36	$C_{17}H_{21}NO_2$	Calcd	75.24	7.80	5.16	138		213
								Found	75.04	8.04	5.24			
n	CH_3	*p*-C_6H_4Cl	CH_3O	30	100	45	$C_{22}H_{22}ClNO_2$	Calcd	71.83	6.03	3.81	196		179
								Found	71.48	6.22	3.84			
o	*p*-$ClC_6H_4CH_2$	CH_3	CH_3O	30	100	36	$C_{23}H_{24}ClNO_2$	Calcd	72.40	6.33	3.67	157	202	
								Found	72.59	6.17	3.84			

chloride in pyridine, underwent a Beckmann rearrangement of the second order.[8] From the oxime **16**, for example, the unsaturated nitrile **17** was obtained in good yield.

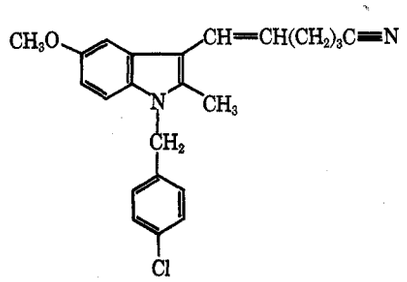


16



17

The nitrile **18** was obtained analogously from the oxime of ketone **7o**.

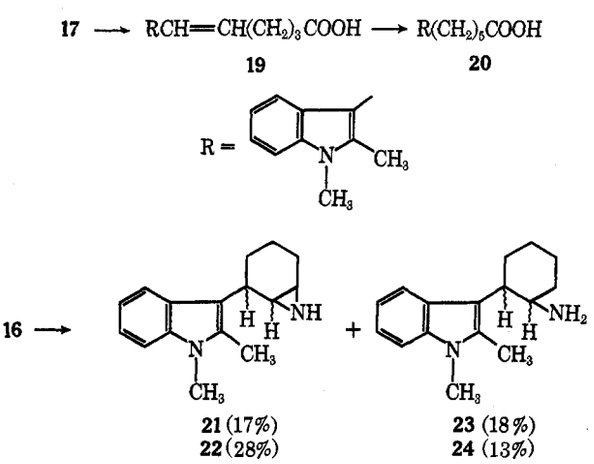


18

Saponification of the nitrile **17** followed by hydrogenation led to the ω-(1,2-dimethyl-3-indolyl)hexenoic acid (**19**) and -caproic acid (**20**), respectively.

The reduction of **16** with $LiAlH_4$ resulted in the formation of four basic compounds, which were separated by chromatography.

The analytical data indicate that **21** and **22** are the isomeric indolylazabicycloheptanes with regard to the relative position of the aziridine ring to the indolyl substitutent and **23** and **24** the corresponding isomeric cyclohexylamines.

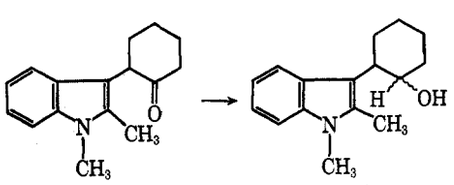


19 **20**

21 (17%) **22** (28%) **23** (18%) **24** (13%)

The formation of aziridines as result of oxime reductions has been recorded.[9] Since both aziridines and amines were obtained, it seems likely that the oxime **16** was a mixture of the syn and anti forms.[10]

The reduction of the ketones **7** with $LiAlH_4$ proceeded normally. In the case of **7k** the two isomeric cyclohexanols **25** and **26** were obtained in equal amounts.



7k **25, 26**

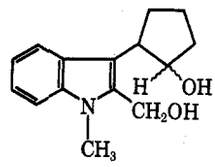
Two products, also, were obtained as expected after reduction of **14** with $LiAlH_4$ (**27**, **28**).

The situation was different when the lactones **12** or **13** were subjected to treatment with excess lithium aluminum hydride. Here the reduction stopped at the stage of the semiketals (**29**, **30**). Their structures were

(8) Houben-Weyl, "Methoden der Organischen Chemie," Vol. X-4, Georg Thieme Verlag, Stuttgart, 1968, p 229.

(9) K. Kitahonoki, Y. Takano, A. Matsuura, and K. Kotera, *Tetrahedron*, **25**, 335 (1969).

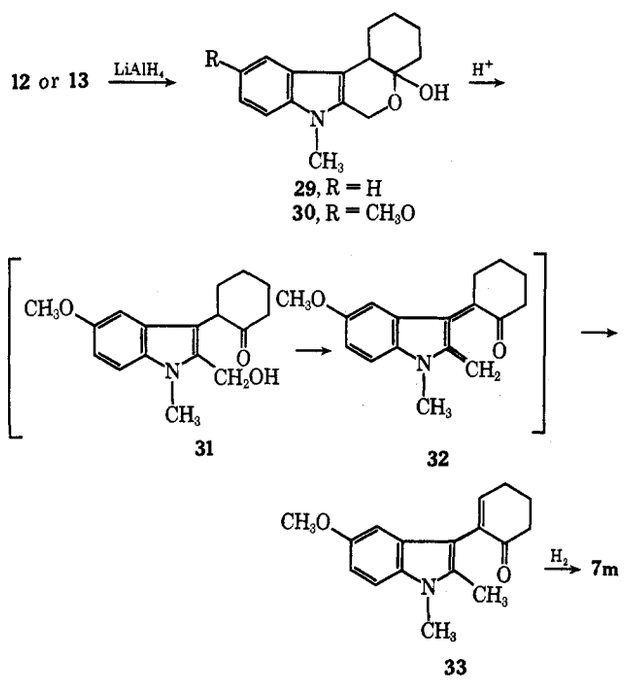
(10) J. L. M. A. Schlatmann, J. G. Korlsloot, and J. Schut, *ibid.*, **26**, 949 (1970).



27, 28

established on grounds of ir (no carbonyl absorption, OH at 3440 cm^{-1}), nmr spectra (distinct CH_2 singlet, one exchangeable OH proton), analyses, and mass spectra. Compounds **29** and **30** belong to a group of 8a-hydroxyhexahydrochromans, which are usually prepared from and are in equilibrium with the open-chain hydroxy alkyl ketones.[11] The formation of hydroxyisochromans on lithium aluminum hydride reduction of comparable enol-lactones has been recorded and discussed recently.[12]

The ring-open keto alcohol **31** could not be isolated. On treatment of **30** with dilute acid at room temperature, rearrangement to **33** took place. A possible mechanism may involve elimination of water from **31** *via* **32**, but this question was not pursued further.



29, R = H
30, R = CH_3O

31 **32** **33**

The structure of **33** followed from the spectral data and was confirmed by hydrogenation, which led to the indolyl ketone **7m**, identical with the ketone arrived at according to eq 1.

Experimental Section

Melting points were determined on a Fisher–Johns block and are uncorrected. Microanalyses were performed by Dr. A. B. Gygli, Toronto, or Dr. C. Daesslé, Montreal. Mass spectra were recorded on an RMU-6D instrument by Morgan Schaffer Corp., Montreal, and nmr spectra were taken on a Varian T-60 instrument, except for the 220-MHz study, kindly performed by Dr. A. A. Grey of the Canadian 220 MHz NMR Centre, Toronto.

(11) J. Colonge, J. Dreux, and M. Thiers, *Bull. Soc. Chim. Fr.*, 1459 (1959).

(12) J. Schneckenburger and R. Kaufmann, *Arch. Pharm. (Weinheim)*, **303**, 760 (1970).

The preparation of oximes and thiosemicarbazones is not recorded in the Experimental Section. Their melting points are included in Tables I–III. Satisfactory analyses were obtained for these compounds.

General Procedure for the Preparation of β-(3-Indolyl) Ketones (7).—The indole (0.1 mol) and the halo ketone (0.25 mol) were heated in 300 ml of acetic acid and 100 ml of 2 *N* phosphoric acid for the time and at the temperature indicated in Tables I–III. The mixture was poured on 1.5 l. of ice and 500 ml of ammonia. The resulting precipitate was either filtered and recrystallized or extracted with ethyl acetate, dried, and evaporated to dryness and then crystallized. In some cases, notably for the open-chain ketones **7a–h**, purification *via* chromatography on silica was advantageous.

2,2-(Di-3-indolyl)-1-chlorocyclohexane (9).—A mixture of indole (5 g), chlorocyclohexanone (6 ml), acetic acid (90 ml), and 2 *N* H_3PO_4 (30 ml) was stirred at 100° for 2 hr. After cooling, the crystals were collected, washed, and recrystallized from dimethylformamide–ether: yield 2.6 g (35%); mp 220–235°; ir, no carbonyl absorption.

Anal. Calcd for $C_{22}H_{21}ClN_2$: C, 75.71; H, 6.08; Cl, 10.18; N, 8.03. Found: C, 75.73; H, 6.28; Cl, 10.46; N, 8.30.

2,3-Di(5-methoxy-3-indolyl)-2-butene (10).—A mixture of 5-methoxyindole (10 g), 2-bromo-3-butanone (12 ml), glacial acetic acid (200 ml), and 2 *N* phosphoric acid (100 ml) was heated in an oil bath of 110° for 4 hr. It was poured on ice–ammonia and extracted with ethyl acetate, and the extract was washed, dried, and evaporated. The residue was chromatographed on silica with benzene–methanol (97:3). The main fraction crystallized from ethanol: yield 5.5 g (47%); mp 205–208°; nmr ($CDCl_3$) δ 8.1–7.9 (m, 2), 7.5–6.7 (m, 6), 3.99 (s, 3), 3.81 (s, 3), 3.25 (s, 2, exchangeable), 2.90 (s, 3), 2.26 (s, 3).

Anal. Calcd for $C_{22}H_{22}N_2O_2$: C, 76.27; H 6.40; N, 8.09. Found: C, 75.98; H, 6.72, N, 8.17.

Ethyl β-Bromo-α-(1-*p*-chlorobenzyl-5-methoxy-2-methyl-3-indolyl)acrylate (11).—1-*p*-Chlorobenzyl-5-methoxy-2-methylindole (5 g), 10 ml of ethyl bromopyruvate, 150 ml of acetic acid, and 10 ml of 2 *N* phosphoric acid were stirred at 40° for 5 min. The reaction mixture was poured on excess ice–ammonia and extracted with ether, and the extracts were washed, dried, and evaporated to dryness. The residue was chromatographed on silica, using benzene–methanol (99.5:0.5) as eluent. The fraction corresponding to an R_F of 0.6 on tlc plates using the same eluent was crystallized from methanol: yield 2 g (25%) of **11**; mp 105–107°; nmr ($CDCl_3$) δ 7.4–6.8 (m, 7), 6.70 (s, 1), 5.22 (s, 2), 4.34 (q, 2, J = 7.5 Hz), 3.83 (s, 3), 2.27 (s, 3), 1.32 (*t*, 3, J = 7.5 Hz).

Anal. Calcd for $C_{22}H_{21}BrClNO_3$: C 57.20; H, 4.57; Br, 17.27; Cl 7.66; N, 3.03. Found: C, 57.45; H, 4.43; Br, 16.95; Cl 7.95; N, 3.14.

7-Methyl-1,2,3,4-tetrahydroindolo[2,3-*c*]coumarin (12).—Ethyl 1-methylindole-2-carboxylate (10 g), 40 ml of 2-chlorocyclohexanone, 80 ml of glacial acetic acid, and 20 ml of 2 *N* H_3PO_4 were heated for 2 hr at 130°. The mixture was poured on ice–ammonia, and the resulting precipitate was filtered, washed with water and cold ethanol, and then crystallized from chloroform–ether: yield 6.5 g (52%); mp 217–218°; ir (KBr) 1710 cm^{-1} (C=O); nmr ($CDCl_3$) δ 8.1–7.1 (m, 4), 4.13 (s, 3) 3.1–2.4 (m, 4), 2.1–1.5 (m, 4); mass spectrum (70 eV) *m/e* (rel intensity) 253 (100), 225 (93), 196 (85).

Anal. Calcd for $C_{16}H_{15}NO_2$: C, 75.87; H, 5.97; N, 5.53. Found: C, 76.13; H, 6.21; N, 5.42.

10-Methoxy-7-methyl-1,2,3,4-tetrahydroindolo[2,3-*c*]coumarin (13).—Ethyl 5-methoxy-1-methylindole-2-carboxylate (15 g), 60 g of 2-chlorocyclohexanone, 120 ml of glacial acetic acid, and 30 ml of 2 *N* H_3PO_4 were heated for 2 hr in an oil bath of 120°. The mixture was worked up as described for **12**, and the residue was purified on silica, using chloroform as eluent: yield 8.5 g (46%); mp 145–148°; ir (KBr) 1700 cm^{-1} (C=O); nmr ($CDCl_3$) δ 7.4–7.1 (m, 3), 4.00 (s, 3), 3.88 (s, 3), 3.0–2.4 (m, 4), 2.0–1.7 (m, 4).

Anal. Calcd for $C_{17}H_{17}NO_3$: C, 72.06; H, 6.05; N, 4.94. Found: C, 72.03; H, 5.97; N, 4.99.

Ethyl 3-(Cyclopentanon-2-yl)-1-methylindole-2-carboxylate (14).—Ethyl 1-methylindole-2-carboxylate (17 g), 2-chlorocyclopentanone (30 ml), glacial acetic acid (140 ml), and 2 *N* H_3PO_4 (35 ml) were heated for 150 min at 90–100°. The mixture was worked up as usual, and the crude reaction product was slurried with ethanol and crystallized from chloroform–petroleum ether (bp 30–60°): yield 15 g (63%); mp 181–184°; nmr

($CDCl_3$) δ 7.6–6.9 (m, 4), 4.36 (q, J = 7.0 Hz, 2), 3.94 (s, 3), 3.0–1.7 (m, 7), 1.32 (t, 3); ir (KBr) 1724, 1675 cm^{-1}.

Anal. Calcd. for $C_{17}H_{19}NO_3$: C, 71.56; H, 6.71; N, 4.91. Found: C, 71.67; H, 6.83; N, 5.00.

The thiosemicarbazone of **14** was obtained, mp 193°.

Anal. Calcd for $C_{18}H_{22}N_4O_2S$: C, 60.32; H, 6.19; N, 15.63; S, 8.93. Found: C, 60.09; H, 6.33; N, 15.53; S, 8.96.

6-Methoxy-3,9-dimethylpyrano[3,4-*b*]indol-1-one (15a).—Ethyl 5-methoxy-1-methylindole-2-carboxylate (10 g), 80 ml of acetic acid, 20 ml of 2 N H_3PO_4, and bromoacetone (15 ml) were heated to 100° for 5 hr. The mixture was worked up as usual and chromatographed on silica with chloroform as eluent. The above reaction product was obtained in 5% yield (0.5 g), after crystallization from ethanol: mp 135–137°; ir (KBr) 1700 cm^{-1}; nmr ($CDCl_3$) δ 7.6–7.2 (m, 3), 7.1 (m, 1), 4.16 (s, 3), 3.92 (s, 3), 2.42 (d, J = 1.0 Hz, 3). The latter signal of the 3-methyl group is split, possibly because of long-range coupling with the C^4 proton.

Anal. Calcd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.39; N, 5.76. Found: C, 69.34; H, 5.63; N, 5.91.

6-Methoxy-3,4,9-trimethylpyrano[3,4-*b*]indol-1-one (15b).—The preparation was identical with that of **15a**, replacing bromoacetone by 2-bromobutanone (**3**): yield 7%; mp 123–126°; ir (KBr) 1710 cm^{-1}; nmr ($CDCl_3$) δ 7.5–7.0 (m, 3), four methyl singlets at 4.03, 3.89, 2.34, and 2.30.

Anal. Calcd for $C_{15}H_{15}NO_3$: C, 70.02; H, 5.88; N, 5.44. Found: C, 70.09; H, 5.76; N, 5.39.

1,2-Dimethyl-3-(5-cyanopenten-1-yl)indole (17).—2-(1,2-Dimethyl-3-indolyl)cyclohexanone oxime (**16**) (14 g, 0.055 mol), prepared from **7k** and hydroxylamine hydrochloride, ethanol, and $NaHCO_3$ in the usual manner, was dissolved in 140 ml of dry pyridine. Benzenesulfonyl chloride (14 ml, 0.11 mol) was added under stirring and cooling. After standing at room temperature for 16 hr, the mixture was poured on ice and 6 N hydrochloric acid, and the reaction product was extracted with ethyl acetate. The residue after drying and evaporation was slurried with cold methanol and filtered, yield 10.6 g (81%), mp 97–100°. This product was sufficiently pure for further reactions.

An analytical sample was prepared by recrystallization from acetone–water: mp 97–100°; ir ($CHCl_3$) 2230 cm^{-1}; nmr ($CDCl_3$) δ 8.0–7.7 (m, 1), 7.3–7.0 (m, 3), 6.64 (d, J = 16 Hz, 1), 5.96 (d, J = 16 Hz, split further to t, J = 7 Hz, 1), 3.50 (s, 3), 2.7–1.2 (m, 6), 2.30 (s, 3).

Anal. Calcd for $C_{16}H_{18}N_2$: C, 80.63; H, 7.61; N, 11.76. Found: C, 80.41; H, 8.01; N, 11.55.

1-*p*-Chlorobenzyl-5-methoxy-2-methyl-3-(5-cyanopenten-1-yl)indole (18).—This nitrile was prepared from the oxime of **7o** in the same manner as **17**, yield 30%, mp 101°.

Anal. Calcd for $C_{23}H_{23}ClN_2O$: C, 72.90; H, 6.12; Cl, 9.36; N, 7.40. Found: C, 72.58; H, 6.12; Cl, 9.40; N, 7.19.

6-(1,2-Dimethyl-3-indolyl)-5-hexenoic Acid (19).—The nitrile **17** (4 g) was heated to reflux in 50 ml of ethanol and 5 ml of 50% KOH for 14 hr. About 100 g of ice were added and the mixture was acidified with dilute hydrochloric acid. The precipitate was recrystallized from ethanol, yield 3.2 g (75%), mp 154–158°.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 74.49; H, 7.70; N, 5.20.

ε-(1,2-Dimethyl-3-indolyl)caproic Acid (20).—The unsaturated acid **19** (1 g) was hydrogenated in 100 ml of ethanol with palladium/charcoal at room temperature and atmospheric pressure in the usual way. The residue after filtration and evaporation crystallized from ethanol–water, yield 0.9 g (90%), mp 74°.

Anal. Calcd for $C_{16}H_{21}NO_2$: C 74.10; H, 8.16; N, 5.40. Found: C, 74.12; H, 8.13; N, 5.76.

$LiAlH_4$ Reduction of 2-(1,2-Dimethyl-3-indolyl)cyclohexanone Oxime (16).—Lithium aluminum hydride (4 g, 0.11 mol) was added under nitrogen to a stirred solution of the oxime **16** (20 g, 0.078 mol) in 500 ml of anhydrous tetrahydrofuran. The mixture was refluxed for 4 hr and worked up in the usual manner. The residue after evaporation was transferred to a silica column (30 × 10 cm, approximately 1 kg of silica gel) and chromatographed with chloroform–methanol–concentrated ammonia (97:2.8:0.2). Four major fractions were obtained which corresponded to the four spots with basic character (blue with iodo plateate[13]) of the R_f values 0.6, 0.5, 0.2, and 0.1 on thin layer silica plates, using the same eluent.

2-(1,2-Dimethyl-3-indolyl)-7-azabicyclo[4.1.0]heptane (21, *cis*- or *trans*-).[14]—The fraction of the above column, corresponding to R_f 0.6, was evaporated to dryness, yielding 3.2 g (17%) and crystallized from ethanol: mp 173°; nmr ($CDCl_3$) δ 8.2–8.0 (m, 1), 7.3–6.9 (m, 3), 3.62 (s, 3), 3.5–3.0 (m, 1), 2.49 (s, 3), 2.4–1.0 (m, 8), 0.8–0.4 (s, 1, exchangeable); mass spectrum (70 eV) m/e (rel intensity) 240 (76), 223 (100), 208 (57), 197 (49), 182 (68).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 80.07; H, 8.31; N, 11.30.

2-(1,2-Dimethyl-3-indolyl)-7-azabicyclo[4.1.0]heptane (22, *trans*- or *cis*-).—The fraction of the above column, which corresponded to R_f 0.5, was evaporated to dryness, yielding 5.2 g (28%), and crystallized from ether–petroleum ether (bp 30–60°): mp 153°; nmr ($CDCl_3$) δ 7.8–7.5 (m, 1), 7.3–6.9 (m, 3), 3.61 (s, 3), 3.5–2.8 (m, 1), 2.40 (s, 3), 2.5–1.1 (m, 8), 0.6–0.5 (s, 1, exchangeable); mass spectrum (70 eV) m/e (rel intensity) 240 (100), 223 (19), 212 (37), 197 (81), 182 (80).

Anal. Calcd for $C_{16}H_{20}N_2$: C, 79.95; H, 8.39; N, 11.66. Found: C, 80.25; H, 8.59; N, 11.33.

2-(1,2-Dimethyl-3-indoyl)cyclohexylamine (23, *cis*- or *trans*-).—The fraction corresonding to R_f 0.2 was evaporated to dryness and dissolved in ether and the hydrochloride was precipitated with ethereal HCl, yielding 3.8 g (18%). Recrystallization from ethanol gave mp 250–255°; nmr (free base in $CDCl_3$) δ 7.9–7.6 (m, 1), 7.3–6.9 (m, 3), 3.55 (s, 3), 3.3–1.3 (m, 10), 2.34 (s, 3) 1.19 (s, 2, exchangeable); mass spectrum (free base) (70 eV) m/e (rel intensity) 242 (95), 184 (100), 171 (99), 158 (100), 145 (96).

Anal. Calcd for $C_{16}H_{22}N_2 \cdot HCl$: C, 68.89; H, 8.32; N, 10.04. Found: C, 68.91; H, 8.22; N, 9.57.

2-(1,2-Dimethyl-3-indolyl)cyclohexylamine (24, *trans*- or *cis*-).—The fraction corresponding to R_f 0.1 was converted to the hydrochloride as described for **23**: yield 2.7 g (13%); mp 310–320° (from ethanol); nmr (free base in $CDCl_3$) δ 7.8–7.5 (m, 1), 7.3–6.8 (m, 3), 3.60 (s, 3), 3.5–0.8 (m, 10), 2.39 (s, 3), 1.15 (s, 2, exchangeable); mass spectrum (free base) (70 eV), m/e (rel intensity) 242 (100), 184 (82), 171 (65), 158 (100), 145 (95)

Anal. Calcd for $C_{16}H_{22}N_2 \cdot HCl$: C, 68.89; H, 8.32; N, 10.04. Found: C, 68.42; H, 8.25; N, 9.93.

2-(1,2-Dimethyl-3-indolyl)cyclohexanol, *cis*- and *trans*- (25 and 26).—2(1,2-Dimethyl-3-indolyl)cyclohexanone (**7k**) (11.5 g) was dissolved in 150 ml of dry tetrahydrofuran and this solution was added dropwise under stirring and cooling and in an atmosphere of nitrogen to a suspension of 4 g of $LiAlH_4$ in 50 ml of tetrahydrofuran. After refluxing for 3 hr the mixture was worked up as usual and the residue after evaporation (11.0 g) was applied on a silica column and chromatographed with chloroform.

Cis Isomer (25).—The fraction corresponding to a tlc R_f of 0.4 crystallized from ethanol: yield 4.0 g (35%); mp 143–146°; ir (KBr) 3570 cm^{-1}; nmr ($CDCl_3$) δ 8.0–7.7 (m, 1), 7.3–6.9 (m, 3), 3.95 (s, broad, no splitting pattern discernible, 1), 3.62 (s, 3), 2.94 (s, broad, slight indication of a triplet, 1), 2.39 (s, 3), 2.2–1.2 (m, 9).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C 79.26; H, 8.57; N, 5.63.

Trans Isomer (26).—The second fraction (R_f 0.2) yielded 4 g (35%) after crystallization from ethanol: mp 190–193°; ir (KBr) 3450 cm^{-1} (broad); nmr ($CDCl_3$) δ 7.8–7.5 (m, 1), 7.4–6.8 (m, 3), 4.02 (t, J = 10 Hz, further split into doublets, J = 4.8 Hz, 1), 3.57 (s, 3), 2.70 (pattern is like signal at δ 4.02, 1), 2.35 (s, 3), 2.3–0.9 (m, 9).

Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 79.33; H, 8.83; N, 5.62.

2-(2-Hydroxymethyl-1-methyl-3-indolyl)cyclopentanols (27 and 28).—The keto ester **14** (15 g) was reduced with $LiAlH_4$ (5 g) analogously to the preparation of **25** and **26**. After the same work-up, the mixture of the two isomers was separated on silica, using chloroform–methanol (97:3) as eluent. The stereochemistry was not established. Fraction 1 (R_f 0.55), 9 g crude, was crystallized from ethanol–petroleum ether: yield 6.5 g (50%); mp 93–94°; nmr ($CDCl_3$) δ 7.8–7.5 (m, 1), 7.4–6.9 (m, 3), 4.68 (s, 2), 4.2–3.9 (m, 1), 3.62 (s, 3), 3.6–3.0 (m, 1), 2.8–1.0 (m, 2 + 6).

(13) "Anfärbereagenzien für Dünnschicht und Papierchromatographie," E. Marck, Darmstadt, p 29.

(14) A definite assignment of the stereochemistry could not be made with the data available. A 220-MHz nmr study, kindly performed by the Canadian 220-MHz NMR Centre, Director Dr. A. A. Grey, could not solve the problem either; it was possible in compound **21** to decouple the C_1 H signal (1.94 ppm) wiping out a 4-Hz coupling at the C_2 H signal (3.25 ppm) but the equivalent decoupling in **22** could not be performed due to experimental limitations.

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 73.88; H, 7.70; N, 5.87.

Fraction 2 (R_f 0.35), 2.7 g crude, was crystallized as above: yield 1.2 g (9%); mp 133–134°; nmr ($CDCl_3$) δ 7.7–7.4 (m, 1), 7.3–6.8 (m, 3), 4.60 (d, J = 3 Hz, 2), 4.6–4.1 (m, 1), 3.80 (s, 2, exchange with D_2O), 3.55 (s, 3), 3.1–2.6 (m, 1), 2.3–1.3 (m, 6).

Anal. Calcd for $C_{15}H_{19}NO_2$: C, 73.44; H, 7.81; N, 5.71. Found: C, 74.05; H, 7.77; N, 5.79.

4a-Hydroxy-7-methyl-1,2,3,4,4a,11c-hexahydro[1]benzopyrano[3,4-*b*]indole (29).—A suspension of 8 g of the lactam **12** in 100 ml of tetrahydrofuran was added under stirring and cooling in an atmosphere of nitrogen to a mixture of $LiAlH_4$ (3.6 g) and 20 ml of tetrahydrofuran. After stirring for 2 hr at 0°, the reaction products were worked up as usual and separated on a silica column, using $CHCl_3$–MeOH (97:3) as eluent. The main fraction, corresponding to an R_f of 0.5 on tlc, was crystalline after evaporation (5 g). Recrystallization from ethanol–petroleum ether yielded 4 g (50%) of **29**: mp 135–139°; ir (KBr) 3440 cm^{-1}; nmr ($CDCl_3$) δ 7.7–7.0 (m, 4), 4.95 (s, 2), 3.55 (s, 3), 3.2–1.5 (m, 10); mass spectrum (70 eV) parent 257.

Anal. Calcd for $C_{16}H_{19}NO_2$: C, 74.68; H, 7.44; N, 5.44. Found: C, 75.01; H, 7.69; N, 5.65.

4a-Hydroxy-10-methoxy-7-methyl-1,2,3,4,4a,11c-hexahydro-[1]benzopyrano[3,4-*b*]indole (30).—The reduction of **13** was performed analogously to the one described for the preparation of **29**. In this case, the reaction was carried out at room temperature and the reaction product was crystallized without chromatography in 68% yield from chloroform: mp 165–168°; nmr (DMSO-d_6) δ 7.4–6.6 (m, 3), 5.70 (s, 1, exchange), 4.85 (s, 2), 4.55 (broad s, 1), 3.73 (s, 3), 3.48 (s, 3), 3.0–0.9 (m, 8).

Anal. Calcd for $C_{17}H_{21}NO_3$: C, 71.05; H, 7.37; N, 4.87. Found: C, 71.02; H, 7.35; N, 5.07.

2-(5-Methoxy-1,2-dimethyl-3-indolyl)cyclohex-2-enone (33).—A solution of the semiketal **30** (8 g) in dioxane (80 ml) containing 4 ml of 4 N HCl was allowed to stand for 30 min at room temperature. It was diluted with 100 ml of 2 N Na_2CO_3 and extracted with two 200-ml portions of ethyl acetate. The residue after washing, drying, and evaporation (8 g) was chromatographed on silica using $CHCl_3$–CH_3OH (99:1) as eluent. A main fraction was obtained crystalline in 50% yield (4 g). After recrystallization from ethanol, 1.9 g (25%) of the unsaturated ketone **33** was obtained analytically pure: mp 107–108°; ir (KBr) 1675 cm^{-1}; nmr ($CDCl_3$) δ 7.3–6.6 (m, 4), 3.78 (s, 3), 3.57 (s, 3), 2.8–2.0 (m, 6), 2.22 (s, 3).

Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H 7.11; N, 5.20. Found: C, 75.65; H, 7.17; N, 5.20.

2-(5-Methoxy-1,2-dimethyl-3-indolyl)cyclohexanone (7m).—The unsaturated ketone **33** (0.5 g) was hydrogenated in ethanol (50 ml) with palladium (5%) on carbon at room temperature and atmospheric pressure in the usual way. The residue after filtration and evaporation yielded crystals from ethanol, which were identical (melting point, ir, nmr, tlc) with the material obtained according to eq 1 (see Table III).

Registry No.—**7a,** 32544-44-8; **7a** oxime, 32500-86-0; **7a** thiosemicarbazone, 32500-87-1; **7b,** 32500-88-2; **7b** thiosemicarbazone, 32500-89-3; **7c,** 32500-90-6; **7d,** 32500-91-7; **7d** oxime, 32500-92-8; **7d** thiosemicarbazone, 32500-93-9; **7e,** 32500-94-0; **7e** oxime, 32500-95-1; **7e** thiosemicarbazone, 32500-96-2; **7f,** 32500-97-3; **7f** oxime, 32500-98-4; **7f** thiosemicarbazone, 32500-99-5; **7g,** 32544-45-9; **7g** oxime, 32501-00-1; **7g** thiosemicarbazone, 32501-01-2; **7h,** 32500-28-0; **7h** oxime, 32500-29-1; **7h** thiosemicarbazone, 32500-30-4; **7i,** 32605-77-9; **7k,** 32544-46-0; **7k** oxime, 32500-31-5; **7k** thiosemicarbazone, 32500-32-6; **7l,** 32500-33-7; **7l** oxime, 32500-34-8; **7l** thiosemicarbazone, 32500-35-9; **7m,** 32500-36-0; **7m** thiosemicarbazone, 32500-37-1; **7n,** 32500-38-2; **7n** thiosemicarbazone, 32500-39-3; **7o,** 32500-40-6; **7o** oxime, 32500-41-7; **9,** 32500-42-8; **10,** 32500-43-9; **11,** 32500-44-0; **12,** 32500-45-1; **13,** 32500-46-2; **14,** 32544-47-1; **14** thiosemicarbazone, 32500-47-3; **15a,** 32500-48-4; **15b,** 32500-49-5; **17,** 32500-50-8; **18,** 32500-51-9; **19,** 32500-52-0; **20,** 32500-53-1; *cis*-**21, -22,** 32500-54-2; *trans*-**21, -22,** 32500-55-3; *cis*-**23, -24,** 32500-56-4; *trans*-**23, -24,** 32500-57-5; *cis*-**25,** 32500-58-6; *trans*-**26,** 32500-59-7; *cis*-**27, -28,** 32500-60-0; *trans*-**27, -28,** 32500-61-1; **29,** 32500-62-2; **30,** 32500-63-3; **33,** 32500-64-4.

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Synthesis of Dinitroxides

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The synthesis of seven stable nitroxide biradicals has been completed. Five of these compounds, namely, *N*-(1-oxyl-2,2,6,6-tetramethylpiperidyl)-*N'*-(1-oxyl-2,2,6,6-tetramethyl-4-methoxycarbonylpiperidyl)urea, 1-oxyl-2,2,5,5-tetramethylpyrrolyl-4-*N*-(1-oxyl-2,2,5,5-tetramethylpyrrolidyl-3-methylene)carboxamide, 1-oxyl-2,2,5,5-tetramethylpyrrolidine-3-*N*-(1-oxyl-2,2,6,6-tetramethylpiperidyl-4)carboxamide, 1,2-bis(1-oxyl-2,2,6,6-tetramethyl-4-methoxycarbonylpiperidyl-4)oxalic acid diamide, and 1,2-bis(1-oxyl-2,2,6,6-tetramethylpiperidyl-4)-succinic acid diamide, fulfill the two conditions which are postulated for their application as a flexible strain gauge in biological material: a distance of 7–11 Å between the two radical units in order to guarantee an interaction between the two unpaired electrons and a certain rigidity in the connecting chain in order to achieve a high resolution of the esr spectrum.

In this paper we describe the synthesis of new stable biradicals in the class of nitroxides of pyrrolines, pyrrolidines, and piperidines. Stable biradicals have been proposed as a flexible strain gauge, which would be attached to a biological sample (membrane or macromolecule) at two points, deform together with the support, and transduce the strain into the interaction-dependent features of the esr spectrum.[4,5]

***N,N'*-Bis(1-oxyl-2,2,6,6-tetramethyl-4-cyano-4-piperidyl)diaminoethane (I).**—This biradical in the class of the bis(α-imino acid nitriles) was obtained by a

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