Derivatives of 2-Pyrazolin-5-one. III. The Preparation and Properties of Some 1′-Phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-ones[1]

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The choice of solvent has a great influence on the nature of the products obtained when suitably substituted aromatic nitro-compounds are reduced by means of sodium borohydride in the presence of palladium–charcoal. When derivatives of 4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one are reduced by this reagent in dioxane, three products are obtained. They are identified as derivatives of 1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, of 1-hydroxy-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, and of 4-(2-aminobenzyl)-1-phenyl-2-pyrazolin-5-one. The 1-hydroxyspiro[indolinepyrazolones] are very reactive compounds. The products of their oxidation, reductions with various reagents, and reactions with chemical nucleophiles have been isolated and identified. Some preliminary pharmacological properties of four of the synthesized compounds are reported.

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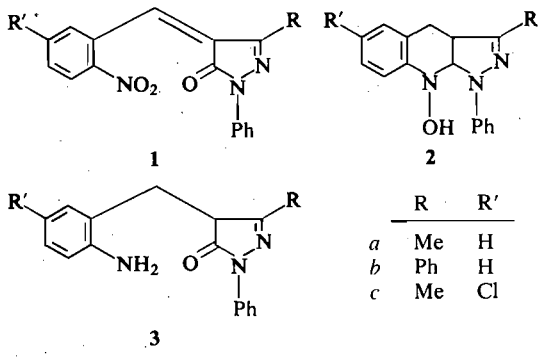
Le choix du solvant a une grande influence sur la nature des produits obtenus lors de la réduction, par $NaBH_4$ en présence de Pd–C, de composés nitro-aromatiques substitués de façon appropriée. Quand on réduit la (nitro-2 benzylidène)-4 phényl-1 pyrazoline-2 one-5 par ce réactif dans le dioxanne, on obtient trois produits: la phényl-1′ spiro[indoline-2,4′-[2]-pyrazoline]-one-5′, l'hydroxy-1 phényl-1′ spiro[indoline-2,4′-[2]-pyrazoline]-one-5′ et la (amino-2 benzyl)-4 phényl-1 pyrazoline-2 one-5. Les hydroxy-1 spiro[indolinepyrazolones] sont des composés très réactifs. On a isolé et identifié les produits de leur oxydation, de leur réduction avec divers réactifs et de leurs réactions avec des nucléophiles chimiques. On rapporte quelques propriétés pharmacologiques préliminaires pour quatre des composés synthétisés.

[Traduit par le journal]

When 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one, **1***a*, and the 3-phenyl analog **1***b* were reduced by sodium borohydride in the presence of 10% palladium–charcoal and using an ethanol–methanol mixture as solvent, two products were obtained in each instance (1). The major products were concluded initially to be cyclic hydroxylamines, **2**, but are now known (2) to be the aminobenzyl compounds, **3**; the minor products were left unidentified because of difficulties in purification.

It is well known that metal hydride reductions are often influenced by the nature of the solvent used (3, 4). This fact led to a repeat of the sodium borohydride – palladium–charcoal reductions just described, in another solvent, to determine whether this might facilitate cyclization to the desired *N*-hydroxy compounds, **2**, and whether previously unidentified products could be obtained in pure form. We have found dioxane to be a suitable solvent for catalytic sodium borohydride reductions (1, 5, 6) so this solvent was selected for the present investigation.



	R	R′
a	Me	H
b	Ph	H
c	Me	Cl

3-Methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one, **1***a*, therefore, was reduced with sodium borohydride and palladium–charcoal in dioxane. When hydrochloric acid was used to decompose the surplus hydride and precipitate the acidic products, a yellow impure

[1]For part II see ref. 2.

solid was obtained. Replacing hydrochloric acid with acetic acid produced a white solid which was easily separated by fractional crystallization into three compounds. The major product is identified as the cyclic *N*-hydroxy compound, 1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***a*. The other two products are shown to be 3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***b*, and the previously described amphoteric amine **3***a*.

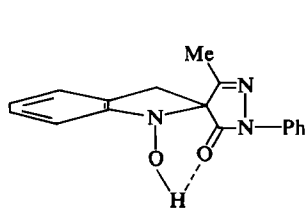
4

	R	R^1	R^2
a	OH	Me	H
b	H	Me	H
c	OH	Ph	H
d	H	Ph	H
e	OH	Me	Cl
f	H	Me	Cl
g	H	Me	OMe
h	H	Me	OH
i	H	Me	OAc

The identity of the *N*-hydroxy compound **4***a* was first suspected from its analysis ($C_{17}H_{15}N_3O_2$; M^+ *m/e* 293) and from the observations that it reduced Tollen's reagent, and gave a purple-red color with triphenyltetrazolium chloride, a reaction which is claimed to be specific for hydroxylamine derivatives (7, 8). That the pyrazolone ring still remained intact was suspected from the i.r. spectrum which showed a C=O absorption band at 1690 cm^{-1}. This C=O is present at a lower frequency than that usually demonstrated in 5,5-disubstituted pyrazolone derivatives. However, an intramolecular hydrogen bonding with the N—OH group is possible in such a structure **5** in which the donor and the acceptor groups are in *peri* positions. Katritzky and Lagowski (9) described a similar effect in 8-hydroxyquinoline 1-oxide and its azo derivative. Support for hydrogen bonding in **4***a* is the position of the i.r. O—H stretching band which was broad and centered at 3275 cm^{-1}.

All pyrazolones which have a hydrogen atom at C-4 are soluble in dilute sodium hydroxide solution. The product, $C_{17}H_{15}N_3O_2$, obtained by reduction of **1***a*, was not soluble in aqueous alkali, which was indicative of the absence of a hydrogen atom at C-4, and consistent with the cyclic hydroxylamine structure **4***a*.

The p.m.r. spectrum of the compound suspected to be **4***a* was consistent with that structure. When recorded in DMSO-d_6, the spectrum displayed, in addition to the aromatic and methyl



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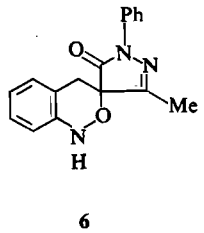

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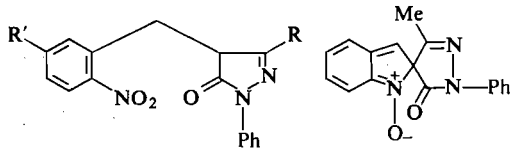
signals, a broad methylene signal at δ 3.28, and a one-proton signal at δ 9.67 which exchanged with deuterium. Assignment of this D-exchangeable signal to the N—OH function is consistent with the conclusions reached by other investigators of hydroxylamines (10–12). The appearance of the two methylene protons as a broad singlet was not expected since these two protons are non-equivalent. However, this appears to be only a solvent effect since the p.m.r. spectrum repeated in pyridine displayed, for these methylene protons, a doublet of doublets with a geminal coupling constant of 16 Hz. Also, in pyridine, the N—OH signal appeared further downfield as a broad peak centered at δ 12.1. Most of the data so far presented are also compatible with the reduction product, $C_{17}H_{15}N_3O_2$, being the isomeric structure **6**. This was considered, but the fact that the product isolated was neutral suggested that such a structure was not appropriate. Compound **6** would be expected to be basic since it is known that the related isoxazolidines (cyclic 5-membered-NH—O-compounds) are strong bases (13). Interpretation of the mass spectrum of the reduced product and its chemical reactivity confirmed that structure **6** was not tenable and that structure **4***a* was indeed the appropriate one. The mass spectrum contained an abundant molecular ion and diagnostic $(M-1)^+$, $(M-16)^+$ and $(M-17)^+$ ions. The last two fragments correspond to the loss of an oxygen atom and a hydroxyl radical from the molecular ion. A strong metastable ion of appropriate *m/e* value in the spectrum indicated that the transition $M^+ \rightarrow (M-17)^+$ was direct. No literature studies have been reported on the mass spectra of cyclic hydroxylamines, but these findings are consistent with our previous study (14) on aromatic hydroxylamines which were found to fragment by expelling an oxygen atom and a hydroxyl radical.

Some speculation on a possible mechanism to explain this unexpected formation of spiro-compound **4***a* by reduction of **1***a*, is warranted.

If the initial stage in the reduction of **1***a* is the hydrogenation of the benzylidene double bond to produce 3-methyl-4-(2-nitrobenzyl)-1-phenyl-2-pyrazolin-5-one, **7***a*, (*cf* 2), this intermediate might be expected to undergo base-catalyzed cyclization to the indoline **8**, which, on subsequent reduction and dehydration, would be converted to the 1-hydroxyspiro[indolinepyrazolone], **4***a*. Such a mechanism is in keeping with the one suggested to explain the formation of 1-hydroxyindoles by base-catalyzed cyclization of a variety of *o*-nitrobenzyl derivatives. A similar intermediate (**9**, in which R^1 and R^2 are electron-withdrawing groups) was proposed for that reaction (15, 16).



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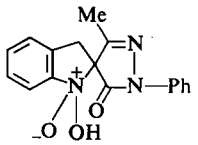
	R	R′
a	Me	H
b	Ph	H
c	Me	Cl

10



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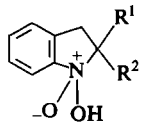

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When the *N*-hydroxy compound **4***a* was reduced catalytically it gave an almost quantitative yield of a product, $C_{17}H_{15}N_3O$, which is identified as the previously mentioned spiroamine **4***b*. The same product was also isolated when the reduction was carried out using iron and ferrous ammonium sulfate or zinc and ammonium chloride. The base peak in the mass spectrum of this compound was the molecular ion (*m/e* 277) which fragmented initially by the expulsion of a CO molecule to a fragment ion of *m/e* 249. In the mass spectrum of the deuterated reduced compound, these two ions appeared at *m/e* 278 and 250 respectively, consistent with a compound with one D-exchangeable hydrogen atom (**4***b*, NH → ND). The i.r. and p.m.r. spectra were also consistent with structure **4***b*.

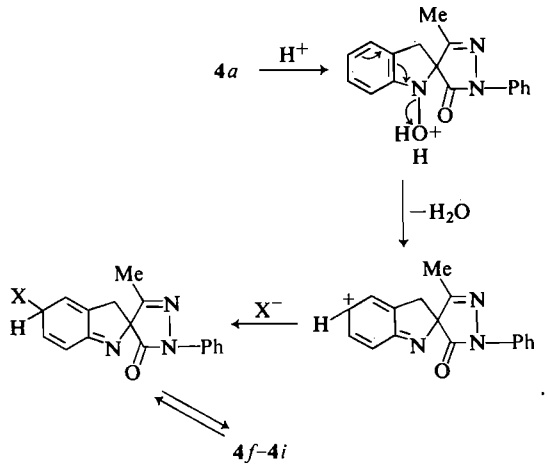
4-(2-Nitrobenzylidene)-1,3-diphenyl-2-pyrazolin-5-one, **1***b*, was then reduced with sodium borohydride and palladium–charcoal in a manner similar to that described for the methyl analog **1***a*. In this case, only two products were obtained. For reasons similar to those presented to identify the products obtained in the reduction of the methyl analog **1***a*, the major product obtained from the reduction of **1***b* is identified as 1′,3′-diphenyl-1-hydroxyspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***c*, while the minor product was found to be the amphoteric amine **3***b* (2).

Reduction of this hydroxylamine **4***c* either catalytically or using iron and ferrous ammonium sulfate as just described for the methyl analog **4***a*, yielded a compound $C_{22}H_{17}N_3O$, which gave i.r., p.m.r., and mass spectra consistent with this compound being the phenyl analog of **4***b*, *i.e.* 1′,3′-diphenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***d*. Zinc and ammonium chloride reduction of 1,3-diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one, **7***b*, was an alternative way of preparing the spiro(indoline)pyrazolone **4***d*. The precursor **7***b* is readily obtained by sodium borohydride reduction of the nitrobenzylidene compound **1***b* (2).

Relatively mild oxidation will convert some cyclic *N*-hydroxy compounds to the corresponding nitrones. Frequently, this is done in the absence of any catalyst by simply bubbling air through solutions of the *N*-hydroxy compound. Often, however, a catalyst is required before oxidation occurs, and copper sulfate – ammonia has been used extensively for this purpose (17, 18). It was also used in the present study to oxidize **4***a*. Crystallization of the crude product gave a dark brown solid which, despite difficulty in getting a pure sample for elemental analysis, is believed to consist mainly of the cyclic *N*-oxide **10**. The mass spectrum of this compound displayed a molecular ion at *m/e* 291 ($C_{17}H_{13}N_3O_2$). It liberated iodine from potassium iodide solution, a property common to *N*-oxides (19). Its i.r. spectrum was devoid of any amine or hydroxy absorption, and it displayed a carbonyl band at 1728 cm^{-1} which was located at a higher frequency than that of the *N*-hydroxy compound **4***a* due to the lack of any hydrogen bonding. The p.m.r. spectrum showed no D-exchangeable protons; it displayed only two signals, a methyl singlet and an aromatic 10-proton multiplet.

Various nucleophilic reagents are known to react with aromatic hydroxylamines and hydroxamic acids. Reactions in which the nucleophile is a halogen (20, 21), oxygen (22), sulfur (23, 24), nitrogen (25), or carbon (26) species have been

reported. Few of these reactions involved cyclic hydroxylamines. Therefore, in the present study, different nucleophilic species, *i.e.* chloride ion, water, methanol, and acetic acid, were reacted, in acidic media, with the *N*-hydroxy compound **4***a*. In each case, it was deduced that a 5-substituted indoline derivative (**4***f*–**4***i*) was obtained, possible by an S_NI' mechanism (Scheme 1) such as that proposed by Heller *et al.* (27) for nucleophilic attack on phenylhydroxylamine. Thus, when hydrogen chloride was bubbled through a cold solution of the *N*-hydroxy compound **4***a* in tetrahydrofuran, a black semisolid product was obtained. Chromatography of this product on a silica gel column yielded 5-chloro-3′-methyl-5′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***f*, as a crystalline solid. This compound was identified by its elemental analysis ($C_{17}H_{14}ClN_3O$) as well as its spectral (i.r., n.m.r.) properties. The location of the chlorine atom in the position *para* to the nitrogen atom (**4***f*) was suggested from the ample literature evidence which has revealed that when hydrochloric acid and other nucleophilic reagents react with aromatic hydroxylamines, *p*-substituted amines are the major products isolated (20, 28, 29). Confirmation of this assignment could not be obtained from the p.m.r. spectrum of the product since the aromatic signal was complex and could not be easily interpreted. Proof of the location of the chlorine atom became necessary when another isomeric chlorinated compound was obtained by the action of acetyl chloride on the hydroxylamine **4***a*. Both chloro compounds displayed very similar mass spectra but their melting points, i.r. and p.m.r. spectra were different. Therefore, it was found necessary to prepare an authentic sample of **4***f* for comparison purposes.



SCHEME 1

3-Chloro-6-nitrobenzaldehyde was condensed with 3-methyl-1-phenyl-2-pyrazolin-5-one and the product **1***c* (1) was reduced with sodium borohydride and palladium–charcoal in dioxane. 5-Chloro-1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one **4***e*, $C_{17}H_{14}ClN_3O_2$, was the main product isolated, as well as a small amount of 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one, **3***c*. The major product, **4***e*, was identified from its physical and chemical properties which were similar to those of the other *N*-hydroxyindolines, **4***a* and **4***c*. Catalytic hydrogenation of **4***e* over platinum yielded the 5-chloroindoline **4***f*. Comparison of the spectral data and melting points of this compound with those of the product obtained by treating **4***a* with hydrogen chloride proved that both were identical. The 5-chloroindoline **4***f* and the *N*-hydroxy derivative **4***e* were also both obtained when 4-(5-chloro-2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one **7***c* (2) was reduced by means of zinc and ammonium chloride in ethanol.

Heating the *N*-hydroxy compound **4***a* with methanol in the presence of a catalytic amount of sulfuric acid, resulted in decomposition. When this reaction was repeated at 0 °C, a dark green solution was obtained from which was isolated a colorless compound which was identified as 5-methoxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***g*, since it analyzed correctly for $C_{18}H_{17}N_3O_2$ and its mass spectrum displayed a molecular ion at *m/e* 307, and showed, with minor differences, fragmentation patterns similar to those of the 5-chloroindoline **4***f*. The i.r. and p.m.r. spectra were consistent with structure **4***g*. The complexity of the n.m.r. aromatic signal did not allow deduction of the exact location of the OCH_3 group but the pattern displayed for this signal was very similar to that in the spectrum of the 5-chloroindoline **4***f*.

A better yield of this compound was obtained when methanolic sulfuric acid was replaced with a solution of boron trifluoride in methanol. This observation was the result of an attempt to methylate the *N*-hydroxy function by the use of diazomethane in methanol, with boron trifluoride as a catalyst. Acid catalyzed nucleophilic attack

by methanol occurred rather than methylation of the *N*-hydroxy function, and the only product isolated was the 5-methoxy compound **4***g*.

When the *N*-hydroxy compound **4***a* was reacted with a mixture of dioxane and water in the presence of catalytic amounts of sulfuric acid, an alkali-soluble product, $C_{17}H_{15}N_3O_2$, was isolated. A comparison of its i.r., p.m.r., and mass spectra with those of **4***f* and **4***g* indicated that this phenolic product was 5-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***h*.

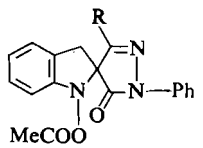
The related 5-acetoxy derivative **4***i* was obtained by heating **4***a* with glacial acetic acid for 1 h. This compound was identified by its elemental analysis ($C_{19}H_{17}N_3O_3$), mass spectrum (M^+ at *m/e* 335), i.r., and p.m.r. spectra.

Previous studies have shown that the cyclic *N*-acetoxy carbonyl function gives rise to an i.r. absorption band in the region of 1800 cm^{-1} and the presence of this absorption band is very diagnostic (30, 31). It was desirable, therefore, to acetylate the cyclic *N*-hydroxy compounds (**4***a* and **4***c*) as a means of confirming their structures and to study the chemical behavior of these *N*-acetyloxy products. A number of conventional procedures were attempted but most of them led to the formation of rearrangement and decomposition products. The only successful method was to react the *N*-hydroxy compound in pyridine at -10 °C with excess acetic anhydride. The *N*-acetyloxy products thus obtained were stable for several weeks at 0 °C but decomposed rapidly on standing at room temperature.

The acetylated product, ($C_{19}H_{17}N_3O_3$; M^+, *m/e* 335), obtained from the *N*-hydroxy compound **4***a* was identified as 1-acetyloxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **11***a*. That *O*-acetylation had occurred was confirmed by the presence of an *N*-acetyloxy C=O absorption band at 1790 cm^{-1}. In addition a lactam C=O band was located at 1723 cm^{-1} and the spectrum was devoid of any O—H or N—H bands. The p.m.r. spectrum showed two methyl signals (C—CH_3 and $OCOCH_3$), an aromatic multiplet (9 protons) and the methylene group signal as a doublet of doublets (J = 16.5 Hz). This spectrum had to be measured directly after dissolving in cold solvent because, in both solvents used, the compound decomposed and/or rearranged very rapidly; the *N*-acetyloxy signal disappeared with the appearance of some new signals and the spectrum became very complicated.

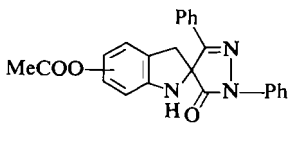
Heating the *N*-acetyloxy compound **11***a* in methanol or ethanol yielded two different crystalline products. One was identical to the 5-acetyloxy derivative **4***i* obtained earlier by the nucleophilic attack of acetic acid at C-5. The other product remains unidentified, although it is known from its elemental analysis ($C_{17}H_{13}N_3O$) and its mass spectrum (M^+, *m/e* 275) that it is a result of the loss of an acetic acid molecule from the parent *N*-acetoxy compound **11***a*. The same compound was also isolated, as described later, during attempts to methylate the *N*-hydroxy compound **4***a*.

Acetylation of the cyclic *N*-hydroxyindoline **4***c* with acetic anhydride and pyridine at -10 °C also yielded an *N*-acetoxy derivative identified as 1-acetyloxy-1′,3′-diphenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one **11***b* by its elemental analysis ($C_{24}H_{19}N_3O_3$) and by similarities of its spectral data with those of the methyl analog **11***a*. It was noted that the acetyloxy derivative **11***b* was relatively stable at room temperature



11

	R
a	Me
b	Ph



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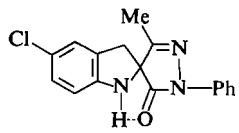
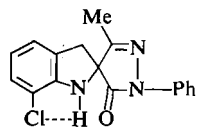


4*f*



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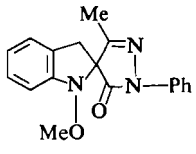

14

and in cold solvents. Rearrangement still occurred in solution but at a much slower rate than that demonstrated by the methyl analog **11***a*. Heating **11***b* in ethanol produced only one re-

arrangement product of formula $C_{24}H_{19}N_3O_3$. Infrared evidence supported the presence of an NH and two C=O groups (lactam and ester) in the molecule. The p.m.r. spectrum had signals which could be ascribed to $COCH_3$, CH_2, NH, and thirteen aromatic protons. Based on these data this compound was identified as *x*-acetyloxy-1′,3′-diphenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one **12**. Although it is most likely that **12** is substituted at the 5-position as was the case with the methyl analog **4***i*, the exact position of the substituent was not determined due to the complex nature of the aromatic signal in the p.m.r. spectrum and due to the lack of an authentic sample.

When 1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***a*, was treated with acetyl chloride at room temperature it failed to react. When this mixture was heated in dry benzene for several hours, a reddish solution was formed which on evaporation and crystallization yielded two compounds, neither of which was the *N*-acetyloxy derivative **11***a*. The minor product $C_{19}H_{15}N_3O_3$, was dark red in color and was shown by mass spectrometry to be a monoacetate (M^+, *m/e* 333; $M-CH_2=C=O$, *m/e* 291). It readily hydrolyzed to give a phenol, $C_{17}H_{13}N_3O_2$ (M^+, *m/e* 291) which was yellow in color. Insufficient quantities of this acetate were isolated to permit identification. Its dark color, however, is indicative of a highly conjugated system.

The elemental analysis ($C_{17}H_{14}ClN_3O$) as well as the mass spectrum (M^+, *m/e* 311) of the major product confirmed the presence of a chlorine atom in its molecular formula. The possibility of this compound being the same 5-chloroindoline, **4***f*, obtained earlier was ruled out by comparing i.r. and p.m.r. spectra and by the depression of a mixture melting point. However, the similarities of the spectral data of this product and that of **4***f* suggested that they were isomeric. The p.m.r. spectrum was essentially similar to that of the 5-chloroindoline derivative **4***f* except in the aromatic area where the substitution pattern differed. Again, this pattern was complex and could not be resolved. Since the chlorine atom in isomer **4***f* was known to be located at the 5-position, it was considered likely that the other isomer was a 7-chloro derivative, **13**. These two positions are more susceptible than any other position to attack by nucleophilic reagents. Accordingly, this product is tentatively identified as 7-chloro-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **13**. Support for this conclusion was found in its i.r. spectrum which had an NH absorption band at 3295 cm^{-1} and a C=O band at 1728 cm^{-1}. Compared to the corresponding absorption bands (3365 and 1710 cm^{-1}) in the related 5-chloroindoline, **4***f*, the N—H absorption showed a bathochromic shift of 70 cm^{-1} and the C=O a hypsochromic shift of 18 cm^{-1}. Intramolecular hydrogen bonding between the chlorine atom at C-7 and the amine hydrogen may be responsible for these shifts. In addition to the effect on the NH absorption, this also could affect the C=O absorption which is now located near the normal value ($\sim$1725 cm^{-1}) for compounds which do not display intramolecular hydrogen bonding. Hydrogen bonding between chlorine and hydrogen is now accepted (32) and the large frequency shift demonstrated here for the NH absorption may indicate that chlorine is a stronger electron donor than oxygen in this molecule.

The formation of a chlorinated product as a result of treating the *N*-hydroxy compound **4***a* with acetyl chloride was not unexpected due to the availability, in the reaction mixture, of chloride ions for nucleophilic attack. An explanation as to why a C-7 (**13**) and not a C-5 (**4***f*) chlorinated product, was obtained in the reaction with acetyl chloride is not possible although it may be due in part to the different solvents used (tetrahydrofuran for C-5 substitution and benzene for C-7 attack).

An attempt to react the 1-hydroxyindoline **4***a* with diazomethane, in the absence of any catalyst, failed to yield a methoxy derivative. When this reaction was carried out in methanol using boron trifluoride as catalyst, it produced the 5-methoxyindole **4***g*. The reaction was repeated in dioxane, and alcohol-free diazomethane and boron trifluoride-ether complex were used. This produced initially a dark-green product which was converted to a high melting pale yellow solid when treated with cold ethanol. This latter compound analyzed for $C_{17}H_{13}N_3O$ (M^+, *m/e* 275) and gave i.r. and mass spectra which were identical to the dehydrated product obtained when the *N*-acetyloxy compound **11***a* was treated with ethanol, as described earlier. A mixture melting point of both compounds showed no depression. The desired *N*-methoxyindoline, **14**, was obtained by methylating **4***a* with methyl iodide in the presence of sodium methoxide.

Identification of this compound was based on its elemental analysis ($C_{18}H_{17}N_3O_2$) as well as its i.r. (ν C=O at 1719 cm^{-1}) and p.m.r. (N—OH signal absent; N—OCH_3 at δ 3.80) spectra. The mass spectrum of this compound was also informative; it displayed a molecular ion at *m/e* 307 and strong $(M - 30)^+$ and $(M - 31)^+$ ions resulting from the expulsion of a CH_2O molecule and a CH_3O radical respectively from the molecular ion. The expulsion of a methoxy radical is not normally observed in the mass spectra of methyl ethers other than aromatic ethers where an *ortho*-effect operates (33, 34).

Pharmacology

A preliminary pharmacological screening of four of the compounds described above was undertaken. An observational technique similar to that described by Irwin (35, 36) was employed in an attempt to detect any behavioral neurological or autonomic changes after administering each compound to mice. Since the synthesized compounds possess a [2]pyrazolin-5-one nucleus and thus bear some chemical similarity to the known analgesics, antipyrine, aminopyrine, and nifenazone, selected compounds were also evaluated for their analgesic activity by means of the phenylquinone writhing test (37).

The two 1-hydroxyspiro[indolinepyrazolones] (**4***a* and **4***c*) were virtually devoid of pharmacological activity showing only a small decrease in motor activity and orientating movements when a 200 mg/kg oral dose of each was given to mice. On the other hand the spiro[indolinepyrazolones] (**4***b* and **4***d*) possessed some pharmacological activity. At an oral dose of 100 mg/kg or an intraperitoneal dose of 50 mg/kg, compound **4***b* caused a marked decrease in motor activity and orientating movements, and some muscle relaxation. Similar signs were observed with chlordiazepoxide (50 mg/kg intraperitoneally) in mice except that with this latter compound, ptosis and more marked muscle relaxation were evident.

The two spiro[indolinepyrazolones] (**4***b* and **4***d*) showed weak analgesic activity in mice. At oral doses of 200 mg/kg, these two compounds caused 45–48% protection as compared with 94% protection when the same dose of aminopyrine was administered.

Experimental

Melting points (capillary tube) are uncorrected. Infrared spectra were recorded as Nujol mulls, unless stated otherwise, using a Beckman IR-10 spectrophotometer, and p.m.r. spectra were obtained using a Varian A-60D spectrometer with DMSO-d_6 as solvent and TMS as internal standard. Mass spectra were measured on an A.E.I. MS-9 or MS-12 mass spectrometer at an ionization potential of 70 eV by Dr. A. M. Hogg and his associates, Department of Chemistry, University of Alberta, using the direct probe technique. Elemental analyses were performed by Mr. W. Dylke of our faculty. Deuterated **4***b* was prepared by repeatedly crystallizing **4***b* from dioxane–D_2O.

Reduction of 3-Methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one, 1a

(*a*) A solution of sodium borohydride (1.5 g) in water (20 ml) was added to a suspension of palladium–charcoal (10%, 0.15 g) in water (10 ml), followed by dioxane (20 ml). A solution of 3-methyl-4-(2-nitrobenzylidene)-1-phenyl-2-pyrazolin-5-one (1) (3.0 g) in dioxane (50 ml) was added dropwise to this mixture over a period of 30 min. Nitrogen was bubbled through the reaction mixture during the addition of the nitro-compound and for a further 15 min. The mixture was filtered and acidified with dilute hydrochloric acid then flooded with water (300 ml). It yielded a dark yellow precipitate (2.8 g). Attempts to purify the crude product by crystallization proved difficult. Chromatography on a silica gel column using chloroform–ether (9:1) followed by evaporation of eluate gave a yellowish crystalline compound (1.2 g), m.p. 187–188 °C dec. (ethanol) which was identified as 1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***a*. This compound reduced Tollen's reagent and gave, in the presence of alkali, a purple-red color with triphenyltetrazolium chloride. Infrared ν_{max} 1690 (C=O) and 3275 br (N—OH) cm^{-1}; p.m.r. δ 1.97 (3H, s, CH_3), 3.28 (2H, br, CH_2), 9.67 (1H, br, exchanged with D_2O, N—OH), and 6.70–8.10 (9H, m, aromatic protons); p.m.r. (pyridine) δ 2.10 (3H, s, CH_3), 3.44 (2H, doublet of doublets, J = 16 Hz, CH_2), 12.11 (1H, br s, D-exchangeable, N—OH), and 7.10—7.80 (9H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 293 (M^+, 70), 292 (18), 277 (55), 276 (32), 249 (35).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.16; N, 14.33. Found: C, 69.62; H, 5.07; N, 14.29.

Further elution of the column with a more polar solvent yielded only small amounts of dark brown oils which were not investigated.

(*b*) The above reaction was repeated but this time the filtrate was diluted with ice-cold water until a precipitate formed. The white solid (1.6 g) had m.p. 192–193 °C dec. (from ethanol). Infrared and p.m.r. spectra were identical to those of the *N*-hydroxyindoline **4***a* described in preparation *a*.

The filtrate remaining was acidified with glacial acetic acid to give a white precipitate (0.5 g) which was crystallized from ethanol to a small amount (0.08 g) of colorless crystals identified as 3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***b*, m.p. 126–127 °C. Infrared ν_{max} 1725 (C=O) and 3305 (NH) cm^{-1}; p.m.r. ($CDCl_3$) δ 2.09 (3H, s, CH_3), 3.33 (2H, d of d, J = 16.5 Hz, CH_2), 5.57 (1H, br s, D-exchangeable, NH), and 6.56–8.10 (9H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 277 (100), 276 (18), 260 (7), 249 (33).

Anal. Calcd. for $C_{17}H_{15}N_3O$: C, 73.63; H, 5.45; N, 15.15. Found: C, 73.93; H, 5.49; N, 14.94.

The mother liquor remaining after the removal of the above product was concentrated to yield a third product (0.33 g), m.p. 153–154 °C. This was 4-(2-aminobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one, **3***a*, (lit. (2) m.p. 153–154 °C); i.r., p.m.r., and mass spectrum were identical to literature spectra (2).

Anal. Calcd. for $C_{17}H_{17}N_3O$: C, 73.09; H, 6.13; N, 15.04. Found: C, 73.18; H, 6.18; N, 14.98.

Reduction of 1,3-Diphenyl-4-(2-nitrobenzylidene)-2-pyrazolin-5-one, 1b

The title compound (1) (3.0 g) was reduced in the same manner as the analog **1***a*, using method *a*. The reaction mixture was filtered free of palladium–charcoal and acidified with dilute acetic acid (300 ml).

The precipitate formed was crystallized from ethanol to an off-white solid (1.2 g), m.p. 178–179 °C dec. which was identified as 1′,3′-diphenyl-1-hydroxyspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***c*. This compound reduced Tollen's reagent and gave a positive test with triphenyltetrazolium chloride (7, 8) for an *N*-hydroxy compound. Infrared ν_{max} 1696 (C=O) and 3347 (N—OH) cm^{-1}; p.m.r. δ 3.47 (2H, br s, CH_2), 9.80 (1H, br s, D-exchangeable, N—OH), and 6.70–8.32 (14H, m, aromatic protons). Mass spectrum *m/e* (% relative abundance) 355 (42), 354 (4), 339 (100), 338 (24), 323 (9), 311 (50).

Anal. Calcd. for $C_{22}H_{17}N_3O_2$: C, 74.35; H, 4.79; N, 11.82. Found: C, 74.23; H, 4.87; N, 11.89.

Concentration of the mother liquors after the removal of the above product gave 0.35 g of a second compound, 4-(2-aminobenzyl)-1,3-diphenyl-2-pyrazolin-5-one, **3***b*, m.p. 151–153 °C (lit. (2) m.p. 151–153 °C). Infrared, p.m.r., and mass spectrum were identical to literature spectra (2).

Anal. Calcd. for $C_{22}H_{19}N_3O$: C, 77.40; H, 5.61; N, 12.31. Found: C, 77.46; H, 5.76; N, 12.26.

Reduction of 4-(5-Chloro-2-nitrobenzylidene)-3-methyl-1-phenyl-2-pyrazolin-5-one, 1c

The title compound (1) (2.0 g) was reduced in the same manner as the analog **1***a*, using method *a* except that the filtrate was acidified with dilute acetic acid, followed by water. This yielded a white solid (1.3 g), m.p. 143–145 °C (from ethanol) which reduced Tollen's reagent and gave a purple-red color with triphenyltetrazolium chloride, and is identified as 5-chloro-1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***e*. Infrared ν_{max} 1685 (C=O), 3280 br (N—OH), and 1605 (C=N) cm^{-1}; p.m.r. δ 2.20 (3H, s, CH_3), 3.46 (2H, s, CH_2), 6.90–8.10 (8H, m, aromatic protons), and 8.60 (1H, br s, D-exchangeable, N—OH); mass spectrum *m/e* (% relative abundance) 329 (12), 327 (32), 313 (44), 312 (23), 311 (76), 310 (33), 285 (14), 283 (35).

Anal. Calcd. for $C_{17}H_{14}ClN_3O_2$: C, 62.29, H, 4.30, N, 12.82. Found: C, 62.13; H, 4.48; N, 13.09.

Concentration of the mother liquors after removal of the above product gave 4-(2-amino-5-chlorobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one, **3***c*, (0.18 g), m.p. 118–120 °C (lit. (2) m.p. 119–121 °C). Infrared, p.m.r., and mass spectra were identical to those reported (2).

Anal. Calcd. for $C_{17}H_{16}ClN_3O$: C, 65.06; H, 5.14. Found: C, 65.08; H, 5.12.

3′-Methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4b

(*a*) This compound was a minor product of the reduction of **1***a*, method *b*, as described above.

(*b*) A solution of 1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one (**4***a*, 0.5 g) in ethanol (70 ml) was hydrogenated over platinum oxide (0.05 g) at atmospheric pressure and room temperature. After the theoretical amount of hydrogen was absorbed, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*, then cooled, and a white crystalline product (0.43 g) separated. This was recrystallized from ethanol giving 3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***b*, as white crystals, m.p. 129–130 °C, identical to the product obtained by method *a*.

(*c*) To a heated solution of the 1-hydroxyspiro[indolinepyrazolone] (**4***a*, 0.5 g) in ethanol (30 ml) was added reduced iron (1.0 g) followed by a solution of ferrous ammonium sulfate (0.3 g) in water (25 ml) and the mixture was heated, under reflux, for 10 h then filtered. The filtrate was evaporated to dryness and the residue was dissolved in hot ethanol and refiltered. Cooling of this filtrate yielded the spiro(indoline)pyrazolone **4***b* as white crystals (0.44 g), m.p. 128–129 °C, identical to the product obtained by method *a*.

(*d*) Ammonium chloride (0.1 g) in water (5 ml) was added to a stirred solution of the *N*-hydroxy compound (**4***a*, 0.5 g) in 60% ethanol (25 ml). Zinc powder (0.5 g) was added in small portions and the mixture was refluxed for 1 h. After removal of the excess zinc and zinc oxide, the solution was concentrated *in vacuo* and extracted with chloroform (50 ml). Evaporation of the dried ($CaCl_2$) chloroform gave a white solid (0.41 g) which crystallized from ethanol as colorless crystals of **4***b*, m.p. 127–129 °C, identical to the product obtained by method *a*.

1,3′-Diphenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4d

(*a*) 1-Hydroxy-1′,3′-diphenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one (**4***c*, 0.5 g) was hydrogenated in a manner similar to that described for the preparation of **4***b*, method *b*. This gave the pale yellow title compound (**4***d*, 0.38 g), m.p. 193–194 °C. Infrared ν_{max} 1728 (C=O) and 3390 (NH) cm^{-1}; p.m.r. δ 3.51 (2H, br s, CH_2), 4.60 (1H, br s, D-exchangeable, NH), and 6.60–8.30 (14H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 339 (100), 338 (22), 322 (9), 311 (49).

Anal. Calcd. for $C_{22}H_{17}N_3O$: C, 77.85; H, 5.05; N, 12.38. Found: C, 77.69; H, 5.14; N, 12.41.

(*b*) Reduction of the 1-hydroxyspiro[indolinepyrazolone] (**4***c*, 0.4 g) with iron and ferrous ammonium sulfate in the manner described for the preparation of compound **4***b*, method *c*, gave the title compound (**4***d*, 0.29 g) as pale yellow crystals, m.p. 192–194 °C.

(*c*) 1,3-Diphenyl-4-(2-nitrobenzyl)-2-pyrazolin-5-one (2) (**7***b*, 1.0 g), dissolved in 50% ethanol (40 ml), was added to a solution of ammonium chloride (0.2 g) in water (10 ml). Zinc dust (0.5 g) was added and the mixture was heated under reflux for 2 h under nitrogen, then filtered. The filtrate was evaporated and the residue was recrystallized from ethanol to give the title compound (**4***d*, 0.78 g), m.p. 193–194 °C, as pale yellow crystals identical to the product obtained by method *a*.

5-Chloro-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4f

(*a*) A stream of hydrogen chloride was passed through a solution of 1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one (**4***a*, 0.5 g) in tetrahydrofuran (10 ml) for 30 s at 0 °C. The solution was left

standing at 0 °C for 12 h then evaporated *in vacuo* to dryness. The resulting black semisolid was chromatographed on a silica gel column using petroleum ether (30–60 °C, 100 ml) then benzene (100 ml) as solvent. Evaporation of the benzene eluate gave a dark yellow solid which crystallized from ethanol yielding the title compound **4***f* as white crystals (0.26 g), m.p. 153–154 °C. Infrared ν_{max} 1710 (C=O) and 3365 (N—H) cm^{-1}; p.m.r. ($CDCl_3$) δ 2.04 (3H, s, CH_3), 3.33 (2H, d of d, J = 16 Hz, CH_2), 4.00 (1H, br s, D-exchangeable, N—H), and 6.40–8.10 (8H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 313 (34), 312 (23), 311 (100), 310 (13), 294 (6), 285 (20), 283 (57).

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.06; H, 4.67; N, 13.21.

(*b*) Catalytic hydrogenation of 5-chloro-1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one (**4***e*, 0.35 g) in the way described for the preparation of **4***b*, method *b*, gave the title compound **4***f* (0.21 g) as colorless crystals, m.p. 152–153 °C, identical to the product obtained by method *a* immediately above.

(*c*) 4-(5-Chloro-2-nitrobenzyl)-3-methyl-1-phenyl-2-pyrazolin-5-one (2) (1.0 g) was reduced with zinc and ammonium chloride in the manner described for the preparation of the analog **4***d*, method *c*. This gave the title compound **4***f* (0.41 g) m.p. 153–154 °C with identical properties to the product obtained by method *a* immediately above.

Concentration of the mother liquors remaining after the removal of the above product yielded a second product (0.15 g), m.p. 144–145 °C which was identical (i.r., mass spectrum) to 5-chloro-1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***e*.

Oxidation of 1-Hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4a

Air was bubbled for 3 h through a solution of the 1-hydroxyspiro[indolinepyrazolone] (**4***a*, 0.3 g) in aqueous (60%) ethanol (25 ml) containing ammonia (1 ml) and copper sulfate (5 mg). Water (50 ml) was added and the dark brown precipitate which formed was extracted into chloroform (20 ml). The dried ($CaCl_2$) chloroform solution was concentrated *in vacuo* and the residue was crystallized from aqueous ethanol as a dark brown solid (0.18 g), m.p. 121–124 °C. This compound was tentatively identified as 3′-methyl-1′-phenylspiro[[2*H*]indole-2,4′-[2]pyrazoline]-5′-one-1-oxide (**10**); i.r. ν_{max} 1728 (C=O) cm^{-1}, NH and OH absorption absent; p.m.r. ($CDCl_3$) δ 2.07 (3H, s, CH_3) and 6.70–8.20 (10H, m, aromatic protons; mass spectrum M^+ *m/e* 291 ($C_{17}H_{13}N_3O_2$).

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: N, 14.42. Found: N, 14.22. (Satisfactory C, H analyses could not be obtained.)

5-Methoxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4g

(*a*) Concentrated sulfuric acid (0.5 ml) was added dropwise to a suspension of 1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one (**4***a*, 0.5 g) in methanol (15 ml) at 0 °C, and the mixture was left overnight at 0 °C. The solution was made alkaline with dilute sodium hydroxide then reacidified with glacial acetic acid and extracted with chloroform. The dried ($MgSO_4$) chloroform solution was evaporated to dryness to give a dark green oil which solidified when triturated with methanol. This was crystallized from ethanol as white crystals (0.37 g), m.p. 135–137 °C and is identified as the title compound **4***g*. Infrared ν_{max} 1710 (C=O) and 3310 (NH) cm^{-1}; p.m.r. ($CDCl_3$) δ 2.03 (3H, s, C—CH_3), 3.77 (3H, s, O—CH_3), 3.33 (2H, d of d, J = 16.5 Hz, CH_2), 4.28 (1H, br s, D-exchangeable, NH), and 6.50–8.40 (8H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 307 (100), 306 (34), 290 (9), 279 (26).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.21; H, 5.49; N, 13.70.

(*b*) Excess diazomethane in ether was added to a stirred solution of 1-hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one (**4***a*, 0.8 g) in methanol (80 ml) containing a catalytic amount (2 ml) of boron trifluoride (14% solution in methanol). The resulting green solution was allowed to stand for 24 h at room temperature then evaporated under reduced pressure leaving a green solid. Crystallization of this crude product from ethanol yielded a white crystalline solid (0.68 g), m.p. 137–138 °C, which was identical (i.r., p.m.r.) to the product **4***g* obtained by method *a* immediately above.

5-Hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4h

1-Hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2*H*]pyrazoline]-5′-one (**4***a*, 0.5 g) was dissolved in an ice-cold mixture of dioxane (8 ml) and water (7 ml). Concentrated sulfuric acid (0.5 ml) was added dropwise and the reaction mixture was allowed to stand at room temperature for 12 h. Dilute sodium hydroxide (10 ml) was added, and the solution was reacidified with glacial acetic acid and extracted with chloroform. Evaporation of the dried ($MgSO_4$) chloroform extract yielded the title compound **4***h* as a pale brown solid which crystallized from aqueous ethanol to an off-white alkali-soluble solid (0.19 g), m.p. 114–116 °C. Infrared ν_{max} 1709 (C=O) and 3100–3500 (NH, OH) cm^{-1}; p.m.r. δ 2.10 (3H, s, CH_3), 3.29 (2H, br s, CH_2), 4.70 (1H, br s, D-exchangeable, NH) 11.10 (1H, br s, D-exchangeable, OH), and 6.70–8.35 (8H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 293 (M^+, 19), 265 (26).

Anal. Calcd. for $C_{17}H_{15}N_3O_2$: C, 69.61; H, 5.16. Found: C, 70.09; H, 4.73.

5-Acetyloxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4i

A solution of the 1-hydroxyspiro[indolinepyrazolone] (**4***a*, 0.5 g) in glacial acetic acid (10 ml) was heated under reflux for 1 h. The resulting red solution was added to cold water (100 ml) and the pale brown precipitate formed was extracted with ether. The ethereal extract was washed with a saturated solution of sodium bicarbonate then with water and dried (Na_2SO_4). Evaporation of this extract yielded a pale yellow solid (0.38 g) which crystallized from ethanol to off-white crystals of the title compound **4***i*, m.p. 120–121 °C. Infrared ν_{max} 1712 (lactam C=O), 1744 (ester C=O), and 3380 (NH) cm^{-1}; p.m.r. ($CDCl_3$) δ 2.06 (3H, s, C—CH_3), 2.23 (3H, s, $COCH_3$), 3.36 (2H, d of d, J = 15 Hz, CH_2), 4.52 (1H, br s, D-exchangeable, NH), and 6.50–8.50 (8H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 335 (59), 293 (80), 292 (25), 277 (37), 265 (33), 249 (36), 91 (100).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 67.95; H, 5.17; N, 12.31.

1-Acetyloxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 11a

Cold acetic anhydride (3.0 ml) was added to a solution

of the 1-hydroxyspiro[indolinepyrazolone] (**4***a*, 0.3 g) in cold pyridine (3.0 ml) and the mixture was kept for 24 h at −10 °C. The title compound **11***a* separated as a colorless crystalline solid (0.26 g), m.p. 92–93 °C. Infrared ν_{max} 1790 (*N*-acetyloxy C=O) and 1723 (lactam C=O) cm^{-1} (NH and OH absorption bands absent); p.m.r. (measured directly after dissolving in cold $CDCl_3$ or DMSO-d_6) δ 2.05 (3H, s, CH_3), 2.14 (3H, s, CH_3), 3.38 (2H, d of d, J = 16.5 Hz, CH_2), and 6.50–8.20 (9H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 335 (55), 307 (7), 293 (56), 275 (66), 265 (60).

Anal. Calcd. for $C_{19}H_{17}N_3O_3$: C, 68.05; H, 5.11; N, 12.53. Found: C, 68.31; H, 5.23; N, 12.81.

Attempts to crystallize **11***a* (0.25 g) from ethanol or methanol resulted in the formation of an off-white crystalline solid (0.09 g), m.p. 306–308 °C; i.r. ν_{max} 1640 br (C=O) and 3410 (NH) cm^{-1}; p.m.r. δ 2.63 (3H, s, CH_3), 4.00–5.10 (1H, br s, D-exchangeable), and 7.20–8.30 (9H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 275 (100), 274 (81), 260 (5), 115 (16), 77 (15).

Anal. Calcd. for $C_{17}H_{13}N_3O$: C, 74.19; H, 4.76; N, 15.27. Found: C, 74.49; H, 4.57; N, 14.98.

When the mother liquor remaining after removal of the above compound was concentrated and allowed to stand, a pale yellow solid (0.13 g), m.p. 117–118 °C deposited and was identified (i.r., p.m.r.) as 5-acetyloxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***i*.

1-Acetyloxy-1′,3′-diphenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 11b

When 1′,3′-diphenyl-1-hydroxyspiro[indoline-2,4′-[2]-pyrazoline]-5′-one (**4***c*, 0.3 g) was acetylated in the same manner as described above in the preparation of compound **11***a*, no product separated from the cooled solution. It was then diluted with ethanol (3 ml) and poured into ice-cold water with stirring. The title compound (**11***b*, 0.32 g) precipitated, m.p. 90–91 °C. Infrared ν_{max} 1792 (*N*-acetyloxy C=O), 1725 (lactam C=O) cm^{-1} (NH and OH absorption bands absent); p.m.r. (measured rapidly) δ 2.00 (3H, s, $OCOCH_3$), 3.61 (2H, d of d, J = 16.0 Hz, CH_2), and 6.90–9.30 (14H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 397 (24), 369 (9), 355 (22), 354 (14), 339 (13), 337 (10), 327 (38), 311 (15).

Anal. Calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.81; N, 10.57. Found: C, 72.19; H, 4.83; N, 10.26.

Heating the above compound (**11***b*, 0.3 g) in ethanol produced a reddish solution. This was added, with stirring, to ice-cold water (100 ml) and the brown precipitate formed was collected and dried. Crystallization twice from benzene–petroleum ether (40–60 °C) gave a yellow solid (0.12 g), m.p. 115–117 °C, which is partially identified as *x*-acetyloxy-1′,3′-diphenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **12**. Infrared ν_{max} 1723 (lactam C=O), 1750 (ester C=O), and 3340 (NH) cm^{-1}; p.m.r. ($CDCl_3$) δ 2.23 (3H, s, $COCH_3$), 3.58 (2H, d of d, J = 15.5 Hz, CH_2), 5.70 (1H, br s, D-exchangeable, NH), and 6.70–8.30 (13H, m, aromatic protons).

Anal. Calcd. for $C_{24}H_{19}N_3O_3$: C, 72.53; H, 4.81; N, 10.57. Found: C, 72.11; H, 4.99; N, 10.29.

Action of Acetyl Chloride on 1-Hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4a

To a solution of the title compound (**4***a*, 0.5 g) in hot dry benzene (10 ml), acetyl chloride (1.0 ml) was added and the mixture heated under reflux for 10 h. The resulting red solution was evaporated to dryness, leaving a dark oil which was dissolved in hot ethanol. Cooling gave a small quantity (0.07 g) of a product as red needles, m.p. 209–210 °C. This compound remains unidentified (its hydrolysis is described below). Infrared ν_{max} 1688 and 1712 (C=O) cm^{-1}; p.m.r. ($CDCl_3$) δ 2.44 (3H, s, CH_3), 2.48 (3H, s, CH_3), 7.00–8.20 (8H, m, aromatic protons), and 9.80 (1H, d, J = 8 Hz, unassigned); mass spectrum *m/e* (% relative abundance) 333 (47), 291 (70), 186 (7), 158 (24), 77 (100).

Anal. Calcd. for $C_{19}H_{15}N_3O_3$: C, 68.46; H, 4.54; N, 12.61. Found: C, 68.74; H, 4.95; N, 12.75.

After the above product was collected, the filtrate was concentrated and from it pale orange crystals (0.30 g), m.p. 188–189 °C separated. This was 7-chloro-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **13**; i.r. ν_{max} 1728 (C=O) and 3295 (NH) cm^{-1}; p.m.r. ($CDCl_3$) δ 2.10 (3H, s, CH_3), 3.46 (2H, d of d, J = 16 Hz, CH_2), 4.58 (1H, br s, D-exchangeable, NH), and 6.55–8.10 (8H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 311 (M^+, 100), 294 (9), 283 (60).

Anal. Calcd. for $C_{17}H_{14}ClN_3O$: C, 65.49; H, 4.53; N, 13.48. Found: C, 65.31; H, 4.66; N, 13.11.

A sample (60 mg) of the unidentified acetate, m.p. 209–210 °C described above was suspended in 10% aqueous sodium hydroxide (5.0 ml) and stirred for 2 h. The resulting yellow solution was filtered, acidified with dilute hydrochloric acid and extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract yielded a yellow solid (40 mg), m.p. 179–180 °C (ethanol). Infrared ν_{max} 1637 (C=O) and 2000–3300 (OH) cm^{-1}; p.m.r. δ 2.58 (3H, s, CH_3), 4.00–5.20 (1H, br s, D-exchangeable, OH), 8.62 (1H, d, J = 8 Hz, unassigned), and 6.70–8.10 (8H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 291 (M^+, 72), 205 (8), 200 (8), 186 (10), 178 (10), 158 (59), 130 (24), 120 (100).

Anal. Calcd. for $C_{17}H_{13}N_3O_2$: C, 70.09; H, 4.50; N, 14.42. Found: C, 69.73; H, 4.51; N, 14.02.

Methylation of 1-Hydroxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, 4a

(*a*) See preparation of 5-methoxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **4***g*, method *b*.

(*b*) Reaction *a* was repeated in dioxane (80.0 ml) using alcohol-free ethereal solution of diazomethane and boron trifluoride – ether complex (1 ml). Solvents were removed under reduced pressure leaving a green residue which was extracted with chloroform. Evaporation of the chloroform solution yielded a green solid, i.r. ν_{max} 1720 (C=O) cm^{-1}, NH and OH absorption absent, which recrystallized from ethanol as a yellow solid (0.21 g), m.p. 306–308 °C, identical to the unidentified product obtained by crystallizing **9***a* from ethanol.

(*c*) Methyl iodide (1.0 g) in methanol (5.0 ml) was added to a solution of the 1-hydroxyspiro[indolinepyrazolone] (**4***a*, 0.5 g) in methanol (15.0 ml) containing 0.2 g of sodium. The mixture was heated under reflux for 3 h during which time a yellow color developed. The solvent was evaporated and the residue extracted with ether. Evaporation of the dried (Na_2SO_4) ethereal extract gave a yellow solid which was crystallized from methanol to give 1-methoxy-3′-methyl-1′-phenylspiro[indoline-2,4′-[2]pyrazoline]-5′-one, **14**, as pale yellow crystals (0.39 g), m.p. 112–114 °C. Infrared ν_{max} 1719 (C=O) cm^{-1} (NH,

OH absorption absent); p.m.r. ($CDCl_3$) δ 1.96 (3H, s, C—CH_3), 3.80 (3H, s, O—CH_3), 3.27 (2H, d of d, J = 17 Hz, CH_2), and 6.80–8.30 (9H, m, aromatic protons); mass spectrum *m/e* (% relative abundance) 307 (80), 276 (61), 248 (28), 233 (7), 207 (7).

Anal. Calcd. for $C_{18}H_{17}N_3O_2$: C, 70.34; H, 5.58; N, 13.67. Found: C, 70.41; H, 5.38; N, 13.29.

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